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SUMÁRIO

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Hospital Santa Cruz

ORIGINAL ARTICLE

Consumption of antimicrobials during the period of the COVID-19 pandemic in specific macro-regions of Brazil

Consumo de antimicrobianos durante o período de pandemia de COVID-19 em macrorregiões específicas do Brasil

Consumo de antimicrobianos durante el período de la pandemia de COVID-19 en macrorregiones específicas de Brasil

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ABSTRACT

Background and Objectives: The main objective was to analyze the consumption of antimicrobials (ATMs) subjected to prescription retention, and with indication for the treatment of respiratory infections in Brazil, from 2014 to 2021. **Methods:** This is an ecological study of mixed design. Secondary data was obtained from the National System for the Management of Controlled Products (SNGPC). Data was presented following the equation: number of total consumption of ATMs for each macro-region of Brazil by year or trimester / number of residents for each macro-region per year *1.000 inhabitants. Annual data was analyzed by Prais-Winsten, and quarterly data was analyzed by automatic forward stepwise regression. **Results:** The Southern region showed the highest mean rates of consumption when compared to the other macro-regions. For annual analysis, the proportion of stability, increase and decrease of consumption of ATMs was similar among macro-regions. The quarterly period registered an increase in the consumption of Amoxicillin, Amoxicillin+Clavulanate, Azithromycin and Cephalexin altogether, in the Southern, Southeastern and Northern regions. **Conclusion:** Our data reveals an increased consumption of some ATMs during the pandemic period in specific macro-regions of Brazil. The five macro regions have shown different patterns of ATMs consumption.

Keywords: *Acute respiratory infections. Antimicrobials. Brazil. COVID-19. Pharmacovigilance.*

RESUMO

Justificativa e Objetivos: O objetivo principal foi analisar o consumo de antimicrobianos (ATMs) sujeito a retenção de receita e com indicações para tratamento de infecções respiratórias no Brasil de 2014 até 2021. **Métodos:**

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Trata-se de um estudo ecológico de desenho misto. Dados secundários foram obtidos do Sistema Nacional de Gerenciamento de Produtos Controlados (SNGPC). Dados foram apresentados conforme a seguinte equação: número total de consumo de ATMs por cada macrorregião do Brasil por ano ou trimestre/ número de residentes por cada macrorregião do Brasil por ano *1.000 habitantes. Dados anuais foram por Prais-Winsten, e dados trimestrais por regressão automática passo-a-passo. **Resultados:** Região Sul apresentou maiores taxas médias de consumo em comparação às demais macrorregiões. Para análise anual, a proporção de estabilidade, aumento e diminuição dos ATMs foi similar entre as macrorregiões. O trimestre registrou aumento no consumo de Amoxicilina, Amoxicilina+Clavulanato, Azitromicina e Cefalexina, juntas, nas regiões Sul, Sudeste e Norte. **Conclusão:** Nossos dados revelam um aumento no consumo de alguns ATMs durante o período de pandemia em macrorregiões específicas do Brasil, as cinco macrorregiões apresentaram padrões diferentes de consumo de ATMs.

Descritores: *Infecções respiratórias agudas. Antimicrobianos. Brasil. COVID-19. Farmacovigilância.*

RESUMEN

Justificación y Objetivos: El objetivo principal fue analizar el consumo de antimicrobianos (ATMs) sujetos a retención de ingresos con indicaciones para el tratamiento de infecciones respiratorias en Brasil de 2014 a 2021. **Métodos:** Se trata de un estudio ecológico de diseño mixto. Datos secundarios obtenidos del Sistema Nacional de Gestión de Productos Controlados (SNGPC). Los datos fueron presentados siguiendo la ecuación: número de consumo total de cajeros automáticos para cada macro región de Brasil por año o trimestre / número de residentes para cada macro región por año *1.000 habitantes. Los datos anuales fueron analizados por Prais-Winsten, y trimestralmente analizados por regresión paso a paso automática hacia adelante. **Resultados:** La región Sur mostró las mayores tasas medias de consumo en comparación con las demás macrorregiones. Para el análisis anual, la proporción de estabilidad, aumento y disminución de ATMs fue similar entre las macrorregiones. En el trimestre se registró aumento en el consumo de Amoxicilina, Amoxicilina+Clavulanato, Azitromicina y Cefalexina, en conjunto, en las regiones Sur, Sudeste y Norte. **Conclusión:** Nuestros datos revelan un mayor consumo de algunos ATMs durante el período de la pandemia en macro regiones específicas de Brasil, las cinco macro regiones han mostrado diferentes patrones de consumo de ATMs.

Palabras Clave: *Infecciones respiratorias agudas. Antimicrobianos. Brasil. COVID-19. Farmacovigilancia.*

INTRODUCTION

The COVID-19 pandemic has intensified the concern for the inappropriate use of antimicrobials, once the action of these drugs has been discussed and investigated regarding the prevention or treatment of this viral disease. In this context, pharmacovigilance monitoring becomes essential because these drugs have the potential effect of triggering antimicrobial resistance, which is an additional problem for the health system, with a prospective effect difficult to handle.[1] The SARS-CoV-2 virus, involved in the COVID-19 disease, weakens the host's immunity allowing the development of secondary or bacterial coinfections.[2] Although studies point out to a low rate of coinfections in patients with COVID-19, the use of antimicrobials for this condition was high.[3] Identifying the co-infection acquired after the confirmation of COVID-19 is essential for the development of appropriate antimicrobial prescribing policies for the treatment.[1,4]

The pharmacological approach was one of the first steps taken in the attempt to control the health crisis and, even though COVID-19 is a disease of viral origin, it also included empirical treatment with antimicrobial drugs with the use for this purpose being off-label.[1,5,6] In addition to antimicrobials, since the beginning of the pandemic, different pharmacological classes have been tested to prevent or treat COVID-19, including antiparasitic, antirheumatic and antiviral.[7] However, preclinical and clinical studies failed to prove the action of antimicrobials and others upon COVID-19. Only one antiviral treatment (remdesivir) was recently approved to treat COVID-19 for specific conditions.[8]

It is important to point out that Brazil is a large country with five macro-regions with distinct aspects regarding economic and social features. Socioeconomic and demographic factors are possibly interfering with the acquisition of drugs for the treatment of this viral disease and can influence the incidence and mortality by COVID-19.[9,10] In May 2020, Latin America was declared the epicenter of the COVID-19 pandemic, mainly because of Brazil.[11]

In this context, as COVID-19 is a disease that can influence the development of other respiratory tract infections,[12] the objective of this study was to analyze the sale of ATMs subject to prescription retention with indication for the treatment of respiratory infections in Brazil, from 2014 to 2021.

METHODS

Study design

This is a mixed ecological study design for temporal analysis of the consumption of ATMs subjected to pres-

cription retention to treat respiratory infection diseases in the pre-pandemic and pandemic periods considering the five macro-regions of Brazil, and considering the interference of COVID-19 pandemic.

Ethics

Secondary data was obtained from official open platforms regarding the consumption of medicines with prescription retention, such as ATMs. These medicines are under control of the Brazilian Sanitary Surveillance Agency (ANVISA). Research projects using this kind of data are exempt from submission to research ethics committees.

Study area

Brazil is the largest country in South America and the fifth largest in the world, with more than 210 million inhabitants and territorial extension approximately 8.5 million km^2. It comprises 5,570 municipalities and 27 federative units (26 states and the Federal District) that are divided into five macro-regions (North, Northeast, Midwest, Southeast and South) established based on different criteria such as natural, social, cultural, political, and economic coexisting in the national territory.

Data collection

Data was collected from official websites: *Sistema Nacional de Gerenciamento de Produtos Controlados* (SNGPC) (portal.anvisa.gov.br) and *Instituto Brasileiro de Geografia e Estatística*.[13] This system aims to monitor all movements of products subject to special control, in accordance with *Portaria* SVS/MS nº. 344, May 1998. The capture and analysis of data from the SNGPC was used, observing the effect of the COVID-19 pandemic on the use of these drugs. Secondary data was used considering the Brazilian macro-regions, since socioeconomic and demographic factors exert an influence on acquisition of medicines.

Time period collection

The data about consumption of these drugs was collected annually from 2014 to 2020, and it was characterized as the pre-pandemic period. Also, data was collected by each quarter (1st, 2nd, 3rd, 4th) from January of 2020 until June of 2021, characterizing only pandemic periods.

Variables

From SNGPC, data was collected as the total of antimicrobial presentations commercialized per year from 2014 to 2020. Also, for secondary analysis data was collected as the total number of antimicrobial consumptions per each quarter from 2020 to 2021. In addition, for the pandemic period, data from prescribers was collected.

From IBGE, population data and estimates were collected per year from 2014 to 2020. Brazil had an estimate of 211.755.692 inhabitants on 1st July of 2020 distributed in five macro-regions (South, Southeast, Midwest, Northeast and North).[13]

Data presentation

The dependent variable was the total consumption of ATMs with prescription retention with indication for the treatment of respiratory infection diseases, and it was presented as annual coefficients per 1.000 inhabitants, using the following equation: number of total consumption of ATMs for each macro-region of Brazil by year/ number of residents for each macro-region per year *1.000 inhabitants. In this study, the term "consumption" is used to describe the dispensing of medication to the population, however, it is pertinent to remember that not all medication distributed is consumed.

Statistical analysis

Data was extracted from websites; the database double entry and review were performed using Microsoft Excel 2010, the statistical software Stata 11.0 and SPSS, version 18.0. Quantitative variables were expressed as mean ± standard deviation (±SD) or median and interquartile range (IQR), defined by the normality test of Shapiro-Wilk. Qualitative variables were described by absolute (n) and relative (%) frequencies. Temporal analysis was performed using the Prais Winsten test from the STATA package for the data from 2014 to 2020. Additionally, automatic forward stepwise regression analyses were conducted considering ATMs consumption from January of 2020 until June of 2021, individually for each macro-region of Brazil. As a summary of the proportion of each variable explained by these models, the final regression standardized coefficient (β) and 95% confidence interval (95% CI) were calculated. The significance level adopted for all analysis was set at 5%.

RESULTS

Annual data analysis of ATMs consumption from 2014 to 2020

The annual mean rates and standard deviations of ATMs consumption for each macro-region of Brazil from 2014 to 2020 were described in table 1 regarding the 21 ATMs selected for this study. It is observed that the highest mean consumption rates of the 21 ATMs studied are in the Southern, Midwestern and Southeastern regions, with emphasis in the Southern region, which registered 71.43% of these highest rates, followed by the Midwestern region, with 23.81%, and from the Southeastern region, with 4.76%. On the other hand, the lowest average rates were recorded in the North, with 66.67%, and the Northeast, with the remaining 33.33%.

Table 2 shows the trend recorded in annual ATM consumption data for the period from 2014 to 2020, in each of the macro-regions of Brazil. Among the drugs analyzed, it is observed that Ampicillin and Erythromycin showed a reduction of sales over the period under study for all macro-regions. Such behavior was also registered for Amoxicillin+Sulbactam, except for the Northeastern macro-region, which showed stability in sales.

On the other hand, there was an increase in consumption of Cefuroxime, Clindamycin, Doxycycline and Moxifloxacin in most of the macro-regions. The exceptions were the stability observed in the Northern region

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for Cefuroxime, in the Midwest for Clindamycin, in the Southern region for Doxycycline, and in the Northeast for Moxifloxacin. There was also stability in consumption during the study period recorded for Amoxicillin, Azithromycin, Cephalexin, Ceftriaxone and Penicillin G, in all macro-regions of Brazil (table 2).

Considering the behavior of the 21 ATMs analyzed in the period from 2014 to 2020, it was observed that in all macro-regions there was stability in annual consumption for most of these medicines (47.6% for the Southeastern macro-region and 57.1% for the other four macro-regions) (table 3).

Trimestral data from 2020 to 2021 - during pandemic period

Trimestral consumption of ATMs from January of 2020 until June of 2021 is expressed as cumulative frequencies (consumption percentage (%) per 1,000 inhabitants) by ATMs in figure 1 (and figures in the supplementary material). Intentionally, there was no parametrization in the scale of the data on the y-axis to facilitate the graphical visualization of the linear regression results.

The summary report of automatic forward stepwise regression analysis considering ATMs consumption from January of 2020 until June of 2021, individually for each macro-region of Brazil, is displayed in table 4. Briefly, Amoxicillin, Amoxicillin+Clavulanate, Azithromycin, and Cephalexin consumption (% per 1,000 inhabitants), together, increased in the Southern (p≤0.0001), the Southeastern (p=0.022) and the Northern (p=0.035) regions, but decreased in the Midwestern (p≤0.0001) and Northeastern (p≤0.0001) regions. Erythromycin consumption (% per 1,000 inhabitants) reduced in the South (p=0.012), the Midwest (p≤0.0001) and the Northeast (≤0.0001) regions but increased in the Southeast (p≤0.0001) and the North (≤0.0001) regions. Cefuroxime, Cefadroxil, Ceftriaxone, Doxycycline, and Norfloxacin consumption (% per 1000 inhabitants), together, reduced in the Southern (p=0.002), the Southeastern (p=0.002), the Midwestern (p≤0.0001), and the Northeastern (p≤0.0001) regions, but increased in the Northern (p=0.001) region.

Table 1. Mean rates of total drug presentations in the macro-regions of Brazil from 2014 to 2020.

	South		Southeast		Midwest		Northeast		North	
Drugs	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Penicillin class										
Amoxicillin	100.82	29.36	74.80	13.86	58.26	11.07	34.43	10.66	27.26	2.12
Amoxicillin + Clavulanate	89.52	18.78	67.21	13.17	66.78	22.17	32.55	8.31	17.32	2.94
Amoxicillin + Sulbactam	0.74	0.31	1.08	0.50	1.10	0.39	0.84	1.14	0.20	0.07
Ampicillin	2.56	0.66	1.51	0.44	1.81	0.45	1.44	0.42	2.24	0.54
Penicillin G	5.17	1.03	2.65	0.62	4.12	1.33	3.41	0.94	2.42	0.67
Macrolides class										
Azithromycin	103.36	27.64	74.12	13.04	74.70	22.94	38.48	7.52	40.14	13.12
Clarithromycin	3.24	0.58	5.96	1.18	11.96	21.87	1.70	0.31	1.58	0.21
Erythromycin	0.91	0.82	0.71	0.67	0.60	0.56	0.46	0.46	0.48	0.50
Cephalosporin class										
Cefaclor	8.01	11.39	5.23	4.41	4.96	1.28	1.32	0.34	2.09	0.43
Cefadroxil	5.90	0.50	7.17	0.49	19.32	19.85	8.89	5.43	3.56	0.25
Cephalexin	90.51	17.90	77.38	8.48	63.82	6.40	43.46	8.33	40.29	2.79
Ceftriaxone	18.41	2.40	11.47	1.84	13.05	1.99	5.82	0.73	4.16	0.66
Cefuroxime	4.71	1.26	4.79	0.99	3.62	1.36	1.34	0.36	0.84	0.19
Quinolone class										
Ciprofloxacin	50.22	15.54	37.97	4.16	33.33	3.18	23.12	7.86	19.88	1.35
Levofloxacin	55.36	21.40	27.64	5.10	25.77	13.52	13.86	5.91	17.14	18.39
Moxifloxacin	6.69	9.10	4.34	0.54	4.00	0.81	2.11	0.32	1.42	0.48
Norfloxacin	14.32	8.73	8.61	1.96	12.57	18.57	4.51	5.00	2.10	0.57
Lincosamides class										
Clindamycin	3.90	0.80	5.00	1.22	6.76	5.69	1.89	0.74	1.38	0.46
Tetracycline class										
Doxycycline	6.26	1.19	5.13	1.07	5.55	1.51	2.20	0.53	2.48	0.52
Tetracycline	5.02	0.36	3.65	0.25	2.80	0.33	0.96	0.10	0.72	0.09
Sulfonamide class										
Sulfamethoxazole + Trimethoprim	17.92	1.51	14.00	0.94	24.29	22.06	11.08	5.30	12.39	6.08

SD: Standard Deviation.

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Table 2. Tendency coefficients of total drug presentations in the macro-regions of Brazil from 2014 to 2020.

	South		Southeast		Midwest		Northeast		North	
Drugs	**Coef. (CI 95%)**	***p-value**	**Coef. (CI 95%)**	***p-value**	**Coef. (CI 95%)**	***p-value**	**Coef. (CI 95%)**	***p-value**	**Coef. (CI 95%)**	***p-value**
Penicillin class										
Amoxicillin	-1.83 (-13.02 9.35)	0.691	-3.57 (-11.42 4.28)	0.295	-0.47 (-2.88 1.94)	0.638	0.01 (-6.95 6.97)	0.997	0.48 (-0.25 1.21)	0.141
Amoxicillin + Clavulanate	5.11 (-0.77 10.98)	0.076	2.85 (-3.88 9.59)	0.326	6.34 (-1.36 14.04)	0.088	2.60 (0.09 5.11)	0.045[a]	1.25 (0.68 1.82)	0.004[a]
Amoxicillin + Sulbactam	-0.13 (-0.19 -0.08)	0.001[b]	-0.16 (-0.28 -0.05)	0.016[b]	-0.13 (-0.22 -0.04)	0.012[b]	-0.03 (-0.56 0.50)	0.882	-0.03 (-0.04 -0.02)	≤0.001[b]
Ampicillin	-0.30 (-0.34 -0.27)	<0.001[b]	-0.19 (-0.25 -0.14)	≤0.001[b]	-0.20 (-0.26 -0.15)	≤0.001[b]	-0.20 (-0.22 -0.17)	≤0.001[b]	-0.25 (-0.37 -0.12)	0.004[b]
Penicillin G	-0.03 (-0.59 0.53)	0.887	0.10 (-0.22 0.42)	0.455	0.07 (-0.72 0.86)	0.824	0.18 (-0.24 0.60)	0.330	0.14 (-0.13 0.41)	0.246
Macrolides class										
Azithromycin	0.61 (-14.47 15.69)	0.921	3.93 (-0.26 8.11)	0.061	5.35 (-3.23 13.92)	0.170	-0.19 (-3.51 3.13)	0.891	1.13 (-5.54 7.79)	0.682
Clarithromycin	0.13 (0.01 0.24)	0.037[a]	0.11 (-0.07 0.30)	0.169	0.10 (-10.11 10.30)	0.982	0.03 (-0.08 0.14)	0.498	0.08 (0.01 0.14)	0.024[a]
Erythromycin	-0.36 (-0.49 -0.23)	0.001[b]	-0.30 (-0.39 -0.21)	≤0.001[b]	-0.26 (-0.32 -0.19)	≤0.001[b]	-0.20 (-0.26 -0.14)	≤0.001[b]	-0.21 (-0.30 -0.13)	0.001[b]
Cephalosporin class										
Cefaclor	-0.41 (-5.89 5.07)	0.854	-0.50 (-2.68 1.67)	0.579	-0.49 (-0.83 -0.15)	0.014[b]	-0.13 (-0.23 -0.03)	0.022[b]	-0.15 (-0.32 0.03)	0.080
Cefadroxil	0.25 (0.21 0.28)	<0.001[a]	0.20 (0.18 0.23)	≤0.001[a]	-1.76 (-10.47 6.95)	0.625	0.15 (-2.51 2.80)	0.892	0.07 (-0.01 0.16)	0.085
Cephalexin	2.18 (-5.04 9.39)	0.473	-1.80 (-5.61 2.02)	0.280	1.26 (-2.03 4.55)	0.369	-0.38 (-4.11 3.35)	0.804	0.66 (-0.77 2.09)	0.289
Ceftriaxone	-0.17 (-0.88 0.53)	0.558	-0.06 (-0.95 0.84)	0.874	0.07 (-0.99 1.14)	0.864	0.01 (-0.36 0.38)	0.947	0.08 (-0.27 0.44)	0.571
Cefuroxime	-0.17 (-0.88 0.53)	0.005[a]	0.45 (0.25 0.66)	0.003[a]	0.64 (0.45 0.84)	≤0.001[a]	0.16 (0.09 0.23)	0.002[a]	0.06 (-0.04 0.17)	0.184
Quinolone class										
Ciprofloxacin	-1.18 (-7.25 4.89)	0.638	-1.59 (-3.15 -0.03)	0.047[b]	0.34 (-1.70 2.37)	0.690	1.57 (-0.44 3.57)	0.101	-0.49 (-1.16 0.19)	0.123
Levofloxacin	-0.78 (-3.45 1.89)	0.488	0.01 (-2.66 2.68)	0.990	0.41 (-6.27 7.09)	0.880	1.85 (0.82 2.88)	0.006[a]	0.32 (-8.30 8.94)	0.928
Moxifloxacin	2.78 (0.57 4.99)	0.023[a]	0.20 (0.07 0.33)	0.010[a]	0.30 (0.03 0.56)	0.035[a]	0.09 (-0.04 0.22)	0.136	0.21 (0.14 0.29)	0.001[a]
Norfloxacin	-2.43 (-5.77 0.90)	0.120	-0.89 (-1.13 -0.65)	≤0.001[b]	4.99 (0.29 9.70)	0.041[a]	1.20 (-0.10 2.49)	0.063	-0.26 (-0.31 -0.22)	≤0.001[b]
Lincosamides class										
Clindamycin	0.43 (0.42 0.44)	≤0.001[a]	0.55 (0.45 0.66)	≤0.001[a]	0.47 (-2.19 3.12)	0.670	0.36 (0.33 0.39)	≤0.001[a]	0.22 (0.18 0.26)	≤0.001[a]
Tetracycline class										
Doxycycline	0.42 (-0.01 0.85)	0.055	0.42 (0.13 0.71)	0.014[a]	0.77 (0.65 0.88)	≤0.001[a]	0.24 (0.16 0.32)	0.001[a]	0.19 (0.03 0.36)	0.031[a]
Tetracycline	-0.09 (-0.27 0.09)	0.261	0.01 (-0.16 0.18)	0.892	0.12 (0.01 0.23)	0.040[a]	0.05 (0.03 0.06)	≤0.001[a]	0.03 (-0.01 0.07)	0.142
Sulfonamide class										
Sulfamethoxazole + Trimethoprim	0.51 (0.25 0.77)	0.005[a]	0.31 (0.18 0.44)	0.003[a]	0.60 (-9.86 11.05)	0.889	-0.34 (-2.71 2.03)	0.725	-1.12 (-3.85 1.61)	0.340

[a]Ascending tendency: positive coefficient and p-value < 0.05. [b]Decreasing tendency: negative coefficient and p-value < 0.05. Stable tendency: p-value ≥ 0.05 (Prais Winsten test).

Table 3. Summary of the analysis based on tendency coefficients of total drug presentations in the macro-regions of Brazil from 2014 to 2020.

Drugs	**South**	**Southeast**	**Midwest**	**Northeast**	**North**
Penicillin class					
Amoxicillin	-	-	-	-	-
Amoxicillin+Clavulanate	-	-	-	↑	↑
Amoxicillin+Sulbactam	↓	↓	↓	-	↓
Ampicillin	↓	↓	↓	↓	↓
Penicillin G	-	-	-	-	-
Macrolides class					
Azithromycin	-	-	-	-	-
Clarithromycin	↑	-	-	-	↑
Erythromycin	↓	↓	↓	↓	↓
Cephalosporin class					
Cefaclor	-	-	↓	↓	-
Cefadroxil	↑	↑	-	-	-
Cephalexin	-	-	-	-	-
Ceftriaxone	-	-	-	-	-
Cefuroxime	↑	↑	↑	↑	-
Quinolones class					
Ciprofloxacin	-	↓	-	-	-
Levofloxacin	-	-	-	↑	-
Moxifloxacin	↑	↑	↑	-	↑

Norfloxacin	-	↓	↑	-	↓
Lincosamides class					
Clindamycin	↑	↑	-	↑	↑
Tetracycline class					
Doxycycline	-	↑	↑	↑	↑
Tetracycline	-	-	↑	↑	-
Sulfonamide class					
Sulfamethoxazole+Trimethoprim	↑	↑	-	-	-

↑ increased consumption; ↓ decreased consumption; - no alteration.

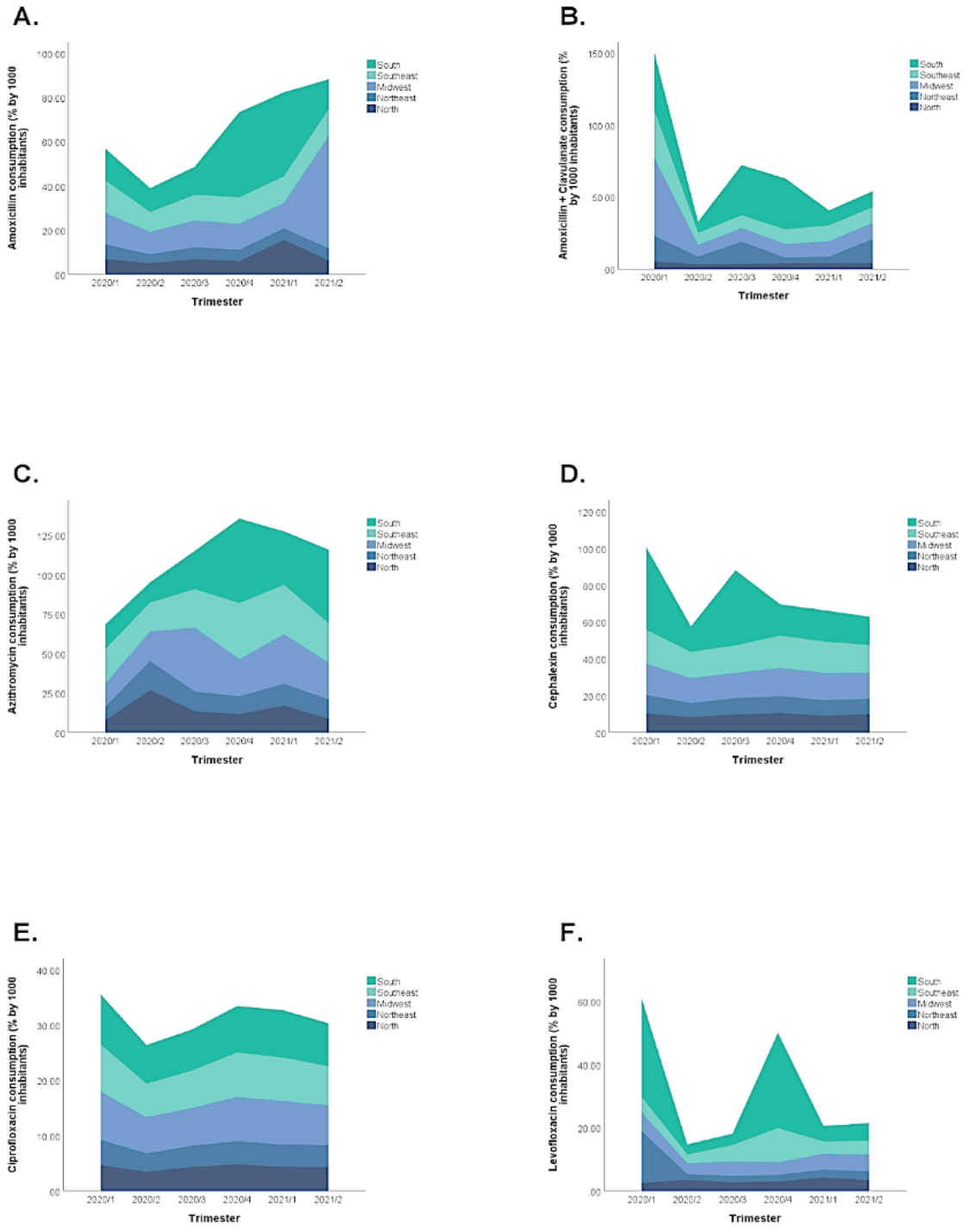

Figure 1. Trimestral consumption of ATMs from January 2020 until June 2021. Data expressed as cumulative frequencies (consumption % per 1,000 inhabitants).

Table 4. Summary of automatic forward stepwise regression analysis considering ATMs trimestral consumption from January 2020 until June 2021, individually for each macro-region of Brazil.

ATMs	Southern region (n=126) Standardized β (95%CI) (Adjusted R^2) = 0.631	*p-value
Amoxicillin + Sulbactam	-8.434 (-15.031 - -1.838)	0.013
Clarithromycin	-7.878 (-14.475 - -1.282)	0.020
Erythromycin	-8.499 (-15.095 - -1.902)	0.012
Ampicillin, Cefaclor	-8.146 (-13.361 - -2.931)	0.002
Cefuroxime, Cefadroxil, Ceftriaxone, Doxycycline, Norfloxacin	-6.760 (-10.932 - -2.588)	0.002
Amoxicillin, Amoxicillin + Clavulanate, Azithromycin, Cephalexin	16.728 (12.365 - 21.091)	≤0.0001
Clindamycin, Moxifloxacin, Penicillin G, Tetracycline	-7.466 (-11.830 - -3.103)	0.001
Ciprofloxacin, Levofloxacin, Sulfamethoxazole + Trimethoprim	0[a]	NA

F (7, 118) = 31.596, p≤0.0001. [a] It is redundant. NA: not applicable.

ATMs	Southern region (n=126) Standardized β (95%CI) (Adjusted R^2) = 0.860	*p-value
Amoxicillin + Sulbactam	-4.103 (-6.739 - -1.467)	0.003
Clarithromycin	-4.231 (-6.867 - -1.595)	0.002
Erythromycin	21.754 (19.118 - 24.390)	≤0.0001
Ampicillin, Cefaclor	-4.009 (-6.645 - -1.373)	0.003
Cefuroxime, Cefadroxil, Ceftriaxone, Doxycycline, Norfloxacin	-4.316 (-6.953 - -1.680)	0.002
Amoxicillin, Amoxicillin + Clavulanate, Azithromycin, Cephalexin	3.081 (0.445 - 5.717)	0.022
Clindamycin, Moxifloxacin, Penicillin G, Tetracycline	-3.693 (-6.329 - -1.057)	0.006
Ciprofloxacin, Levofloxacin, Sulfamethoxazole + Trimethoprim	-2.574 (-4.727 - -0.422)	0.020

F (12, 113) = 65.199, p≤0.0001.

ATMs	Southern region (n=126) Standardized β (95%CI) (Adjusted R^2) = 0.573	*p-value
Amoxicillin + Sulbactam	-18.568 (-23.773 - -13.363)	≤0.0001
Clarithromycin	-18.743 (-23.948 - -13.538)	≤0.0001
Erythromycin	-18.302 (-23.507 - -13.097)	≤0.0001
Ampicillin, Cefaclor	-17.506 (-22.711 - -12.301)	≤0.0001
Cefuroxime, Cefadroxil, Ceftriaxone, Doxycycline, Norfloxacin	-18.865 (-24.070 - -13.660)	≤0.0001
Amoxicillin, Amoxicillin + Clavulanate, Azithromycin, Cephalexin	-11.345 (-16.550 - -6.140)	≤0.0001
Clindamycin, Moxifloxacin, Penicillin G, Tetracycline	-17.228 (-22.433 - -12.023)	≤0.0001
Ciprofloxacin, Levofloxacin, Sulfamethoxazole + Trimethoprim	-17.911 (-23.116 - -12.706)	≤0.0001

F (12, 112) = 13.908, p≤0.0001.

ATMs	Southern region (n=126) Standardized β (95%CI) (Adjusted R^2) = 0.808	*p-value
Amoxicillin + Sulbactam	-0.147 (-1.733 - 1.438)	0.854
Clarithromycin	-0.535 (-2.120 - 1.050)	0.505
Erythromycin	13.599 (12.014 - 15.184)	≤0.0001
Ampicillin, Cefaclor	-0.563 (-2.149 - 1.022)	0.483
Cefuroxime, Cefadroxil, Ceftriaxone, Doxycycline, Norfloxacin	2.624 (1.038 - 4.209)	0.001
Amoxicillin, Amoxicillin + Clavulanate, Azithromycin, Cephalexin	1.708 (0.122 - 3.293)	0.035
Clindamycin, Moxifloxacin, Penicillin G, Tetracycline	0.192 (-1.394 - 1.777)	0.811
Ciprofloxacin, Levofloxacin, Sulfamethoxazole + Trimethoprim	-0.331 (-1.917 - 1.254)	0.680

F (12, 113) = 44.824, p≤0.0001.

β: final regression standardized coefficient. 95%CI: 95% confidence interval (lower and upper limits). R^2: corrected goodness-of-fit (model accuracy) measure for linear models.

DISCUSSION

The behavior observed in the consumption of ATMs in this study is quite variable considering the five macro-regions of Brazil. However, our data reveals an increased consumption of some ATMs during the pandemic period in specific macro-regions of Brazil. The Southern region (71.43% of the 21 ATMs) showed the highest mean rates of consumption compared to the other macro-regions. For annual analysis (2014 to 2020), the proportion of stability (10 or 12 of 21), increase (5 or 6 of 21) and decrease (3 to 5 of 21) of ATMs consumption was similar among macro-regions, with consumption stability exceeding 50% in all of them. On the other hand, we found an effect of the pandemic on the consumption of ATMs. The quarterly analysis revealed an increased consumption of amoxicillin, amoxicillin+clavulanate, azithromycin and cephalexin in the Southern, Southeastern and Northern macro-regions, with a decrease in the Midwest and Northeast.

ATMs mean rates of consumption from 2014 to 2020

The Southern macro-region presented the highest mean rates. This macro-region has different weather conditions linked to a more rigorous winter than the other regions of Brazil. It is the coldest region of the country, where, during the winter, there are frosts and even snow in some places. Due to the low temperatures, it is common for people to stay longer indoors, which facilitates the spread of respiratory diseases, increasing the incidence of these diseases, and consequently increasing the consumption of ATMs.[14] Often, this high ATMs consumption can be related to its inappropriate use in the treatment of viral respiratory infections.[15,16] High mean consumption rates were also concentrated in the Southeast. In contrast, the North and Northeast, in general, presented a record of lower mean rates of presentations sold of the 21 ATMs. A possible explanation for this could be the distribution of the mean income of the population among these macro-regions. The North and Northeast have low socioeconomic indices, such as income and schooling.[14] It is important to note that these regions concentrate 60% of the Brazilian territory and more than 35% of the population; however, they hold only 18.8% of the country's total Gross Domestic Product (GDP). The contrast with the South and Southeast macro regions is noticeable, which have only 17.7% of the territory, but concentrate more than half of the population and 70% of the national GDP; highlighting the inequalities throughout the Brazilian territory.[17] However, it was not possible to analyze and prove this hypothesis due the economic markers have not been updated.

Annual ATMs consumption from 2014 to 2020

As shown in table 2, it is possible to verify that amoxicillin, azithromycin, cephalexin, ceftriaxone and penicillin G were stable in all macro-regions. However, there was a noticeable increase in the number of ATMs consumption in specific classes: cephalosporins experienced a 40% increase, with cefuroxime increasing in 4 out of the 5 macro regions, except for the North where it remained stable; tetracyclines saw a 100% increase, with doxycycline increasing in 4 out of the 5 macro regions, except for the South where it remained stable; quinolones had a 75% increase, with moxifloxacin increasing in 4 out of the 5 macro-regions, except for the Northeast where it remained stable; and lincosamides had a 100% increase, with clindamycin being the only ATM in this class and increasing in 4 out of the 5 macro-regions, except for the Midwest where it remained stable.

Despite the variety of available ATMs, some are well established for the treatment of conditions. The stability and increase of these drugs consumption is not easy to explain. Here are three possibilities: 1. an already high consumption remained unchanged over the time evaluated; 2. they are classic drugs with a well-established prescription, regardless of whether they are older or newer drugs; 3. their clinical indications are not necessarily for respiratory , since these drugs are also indicated for the treatment of other infections such as urinary tract, skin and soft tissues. In addition, for the prophylaxis in surgeries, and allergies. It is not uncommon allergies to penicillin, for example, to require the choice of other classes of ATMs for treatment, such as Cephalosporins and Macrolides. Also, azithromycin showed a good activity against atypical bacteria (Mycoplasma *pneumoniae, Chlamydia pneumoniae,* and *Legionella species*).[18] Interesting to note that co-infection of *C. pneumoniae* and *M. pneumoniae* with SARS-CoV-2 is associated with more severe features.[19]

In the same analysis of the annual data, there was a reduction of total presentations commercialized of Ampicillin, of the Penicillin class, and Erythromycin, of the Macrolide class, in all macro-regions of Brazil (table 2). This behavior can be explained by the shortage of medicines caused by interruption and/or discontinuation in the production system, which makes access difficult. Brazil has an external dependence, mainly on China and India, and imports 70% of its demand. It affects the national production supply chain's dynamics, as production can be interrupted due to issues like acquiring active pharmaceutical ingredients, raw materials used to make medicines, due to supplier changes or import issues.[20] This was strongly observed during the pandemic period.

Trimestral ATMs consumption from 2020 to 2021 - during pandemic period

Despite the annual stability of azithromycin, during the pandemic period (table 4) there was an increase in consumption rates for the Southern, Southeastern and Northern macro-regions, with a reduction in the Midwest and Northeast. For Erythromycin, there was an increase in the Southeastern and Northern regions (table 4). Although this increase is statistically significant, it does not represent a relevant clinical impact, as the mean rates present very low values in relation to other ATMs, with rates lower than 1% (figure in the supplementary material 1S, 2S and 3S).

Along with azithromycin, an increase in consumption of amoxicillin, amoxicillin+clavulanate and cephalexin was also observed in this period in the Southern (around 16x), Southeastern (around 3x) and Northern (1.7x) macro-regions (Table 4). This higher consumption may be related to the seasonal variation of temperature in the Southern region, since this increase was around 16x, and the average income in the Southeast, which is the highest in the country, as already discussed. On the other hand, the Midwestern and Northeastern macro-regions registered a reduction in these ATMs. In agreement with this reduction registered in the two macro-regions, Buehrle and colleagues[21] corroborate the record of significant reductions in mean monthly data throughout 2020, in the United States, for amoxicillin, azithromycin and amoxicillin+clavulanate, which may be associated with medical perception that SARS-CoV-2 does not always require treatment.

Around the world, corroborating our data, it is possible to observe a trend of decreased ATMs consumption. In Portugal, an immediate decrease in the overall antibiotic prescription was noticed in outpatient care at the beginning of the pandemic, in particular classes

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(3rd-generation cephalosporins, fluoroquinolones, and clarithromycin).[22] In Australia, a reduction of 36% in antibiotic dispensing was observed from April 2020, with large reductions (range 51–69%) regarding antibiotics for respiratory tract infections.[23] In the US, significant reductions in mean monthly fills of the four commonly prescribed outpatient antibiotics (i.e., amoxicillin, azithromycin, amoxicillin-clavulanate, doxycycline) persisted throughout 2020.[21]

The reduction observed in the quarterly consumption for most ATMs during the pandemic may be associated with the period of social distance experienced, as this possibly hampered access to health services and consequently to ATMs prescriptions. Even after the regulation of electronic prescription issuance, in October 2021 in Brazil, also for antimicrobials.[24] Additionally, the use of masks and hygiene measures, such as washing hands and using alcohol gel, social distancing and the low mobility of the population also prevented other infections, especially those of the respiratory tract.[21,25] The reduction in ATMs consumption in the pandemic period was also recorded in other countries.[26,27] It is also noteworthy that the reduction in consumption may be linked to the economic crisis that worsened in the country with the arrival of the pandemic, which increased the vulnerability of the population with the reduction of its purchasing power.[28]

This study has some limitations. First, our intention was to use the Human Development Index (HDI), GDP and per capita income data, however they are not updated annually and 2018 was the latest record. Second, SGNPC was discontinued to uploading data after September 2021. Third, to define the mean rates presented, the total population of each macro-region was considered; however, part of this population has access to medicines by the public service, which was not included in the study by considering only data from private establishments. Fourth, it was not possible to assess if all private establishments have a registration with the SNGPC, considering distant cities in Brazil. Another important factor that should be considered is that it is impossible to evaluate the sale of the ATMs without prescription, and we are aware of an illegal market of these medicines. This fact may interfere with the current data, not showing the real frame of Brazil.

The data of the current study reveals an increased consumption of some ATMs during the pandemic in specific macro-regions of Brazil, such as South and Southeast, and in general, some stability in the North. It is noticeable that the five macro-regions of Brazil have shown different patterns of ATMs consumption related to macro-regional inequalities, both in terms of sociodemographic data and in relation to access and use of health services. Moreover, although the prescription of ATMs and the factors that involve it are widely discussed, so far there are no studies carried out that cover the period, all classes and macro-regions addressed in this research, making it difficult to compare with other results. Thus, further studies are encouraged to add information regarding ATMs prescription and pandemic periods seeking more assertiveness in the control of these drugs.

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AUTHORS' CONTRIBUTIONS

Gisele Paludo Polesello conception, article design, article writing and analysis; article planning and design, article review and final approval. **Iraci Lucena da Silva Torres** conception, article design, article writing and analysis; article planning and design, article review and final approval. **Charles Francisco Ferreira** conception, article design, article writing and analysis; article planning and design, article review and final approval. **Douglas Nunes Stahnke** conception, article design, article writing and analysis; article planning and design, article review and final approval. **Vera Maria Vieira Paniz** conception, article design, article writing and analysis; article planning and design, article review and final approval. **Liciane Fernandes Medeiros** conception, article design, article writing and analysis; article planning and design, article review and final approval.

All author have approved the final version to be published and are responsible for all aspects of the study, including the assurance of precision and integrity.

SUPPLEMENTARY MATERIAL

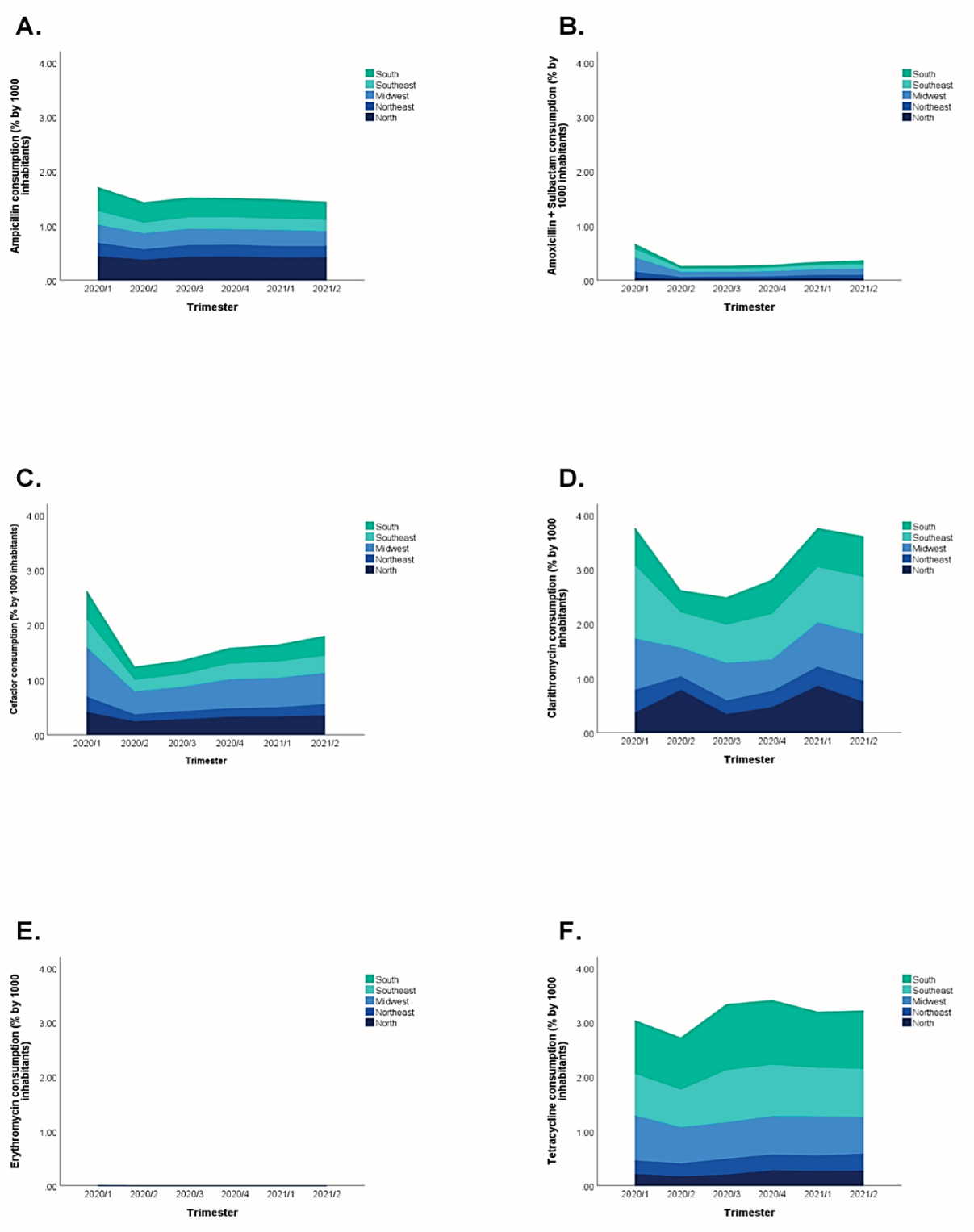

Figure 1S. Trimestral consumption for Ampicillin, Amoxicillin plus Sulbactam, Cefaclor, Clarithromycin, Erythromycin, and Tetracycline. Data expressed as cumulative frequencies (consumption % per 1,000 inhabitants)

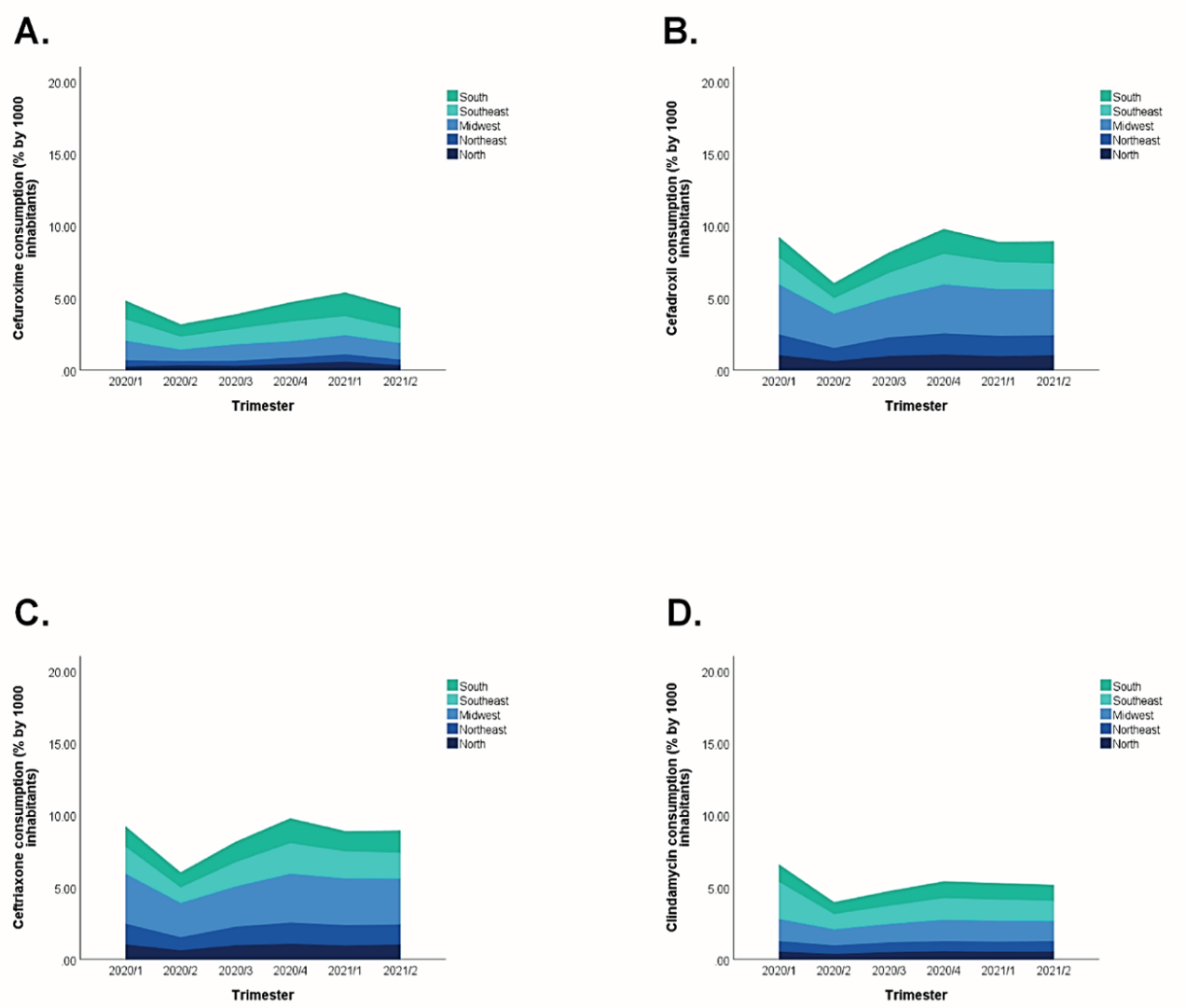

Figure 2S. Trimestral consumption for Cefuroxime, Cefadroxil, Ceftriaxone, and Clindamycin. Data expressed as cumulative frequencies (consumption % per 1,000 inhabitants)

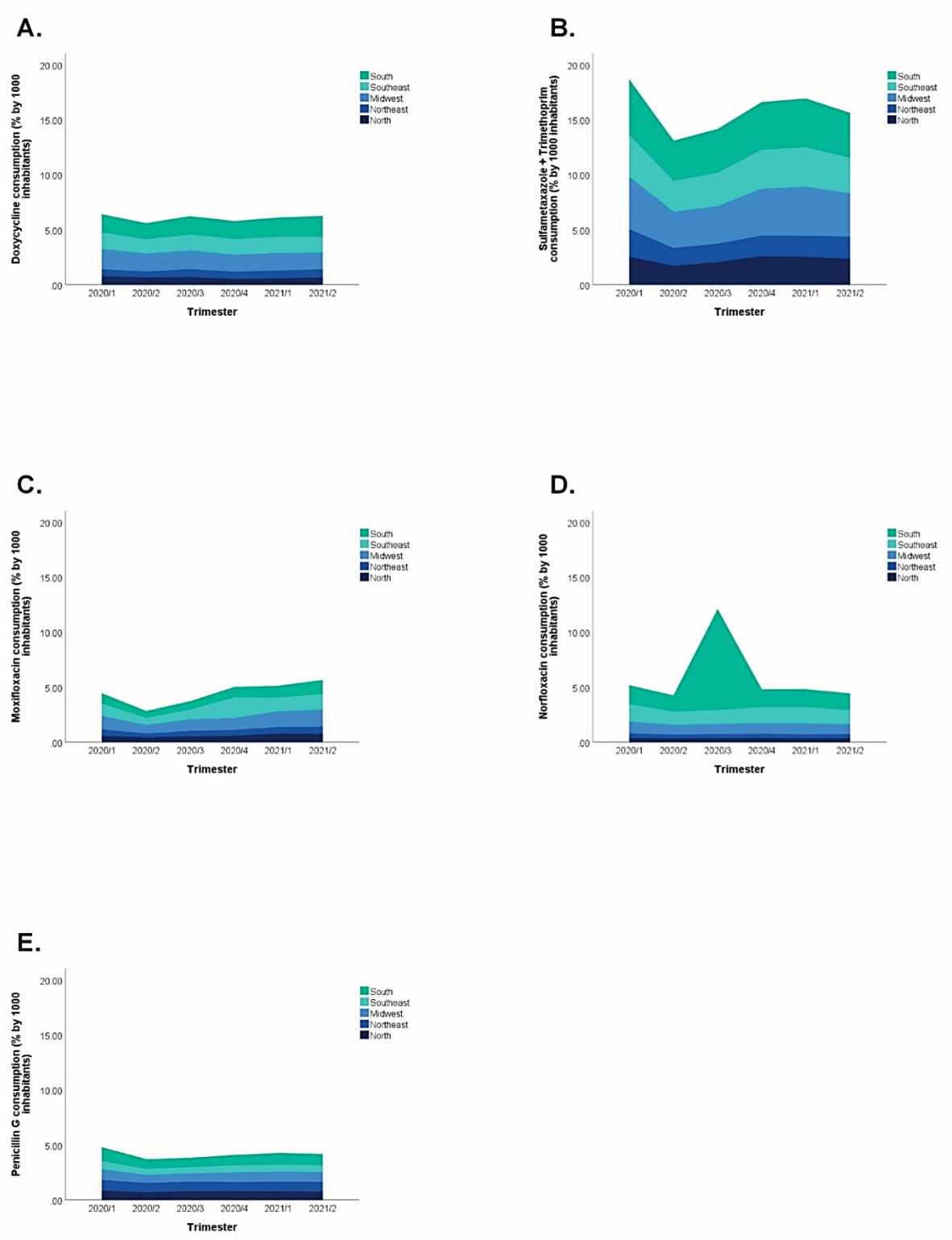

Figure 3S. Trimestral consumption for Doxycycline, Sulfamethoxazole plus Trimethoprim, Moxifloxacin, Norfloxacin, and Penicillin G. Data expressed as cumulative frequencies (consumption % per 1,000 inhabitants)

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ABSTRACT

Justification and Objectives: dengue is one of the serious public health concerns in the world, due to the severity of its infection, which can lead to serious cases and death. The study aimed to analyze the epidemiological profile of dengue cases as well as their temporal distribution in the municipality of Jaboatão dos Guararapes-PE before and during the COVID-19 pandemic. **Methods:** this is an ecological time series study, with a descriptive character of suspected cases of dengue in the Notifiable Diseases Information System, from 2018 to 2021. **Results:** it should be noted that 2018 had the lowest dengue incidence rate of the years analyzed. The other years had high incidence rates, however 2020 had a decline in cases when compared to 2019. The year 2021 was marked by the highest number of cases in the study period. **Conclusion:** it was possible to observe a seasonal pattern of dengue in 2020 that was different from other years, with a more pronounced decrease in dengue cases following the arrival of COVID-19 in the municipality.

Keywords: *Dengue. COVID-19. Temporal Distribution. Epidemiology.*

RESUMO

Justificativa e Objetivos: a dengue é um dos graves problemas de saúde pública no mundo, devido à gravidade de sua infecção, podendo evoluir para casos graves e a óbito. O estudo teve como objetivo analisar o perfil epidemiológico dos casos de dengue, bem como sua distribuição temporal no município do Jaboatão dos Guararapes-PE antes e durante a pandemia de COVID-19. **Métodos:** trata-se de estudo ecológico de série temporal, com caráter descritivo dos casos suspeitos de dengue no Sistema de Informação de Agravos de Notificação, de 2018 a 2021. **Resultados:**

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observou-se que o ano de 2018 apresentou a menor taxa de incidência de dengue dos anos analisados. Os demais anos tiveram altas taxas de incidência, no entanto 2020 teve um decréscimo dos casos quando comparado com o ano de 2019. Já o ano de 2021 foi marcado pela maior quantidade de casos do período temporal de estudo. **Conclusão:** foi possível observar um padrão de sazonalidade da dengue em 2020 diferente dos demais anos, com um decréscimo mais acentuado dos casos de dengue a partir da chegada da COVID-19 no município.

Descritores: *Dengue. COVID-19. Distribuição Temporal. Epidemiologia.*

RESUMEN

Justificación y Objetivos: el dengue se presenta como uno de los graves problemas de salud pública en el mundo, debido a la gravedad de su infección, que puede provocar casos graves y la muerte. El estudio tuvo como objetivo analizar el perfil epidemiológico de los casos de dengue, así como su distribución temporal en el municipio de Jaboatão dos Guararapes-PE antes y durante la pandemia de COVID-19. **Métodos:** un estudio de serie temporal ecológica, con carácter descriptivo de casos sospechosos de dengue en el Sistema de Información de Enfermedades de Declaración Obligatoria, del 2018 al 2021. **Resultados:** cabe señalar que el año 2018 tuvo la tasa de incidencia de dengue más baja de los años analizados. Los demás años tuvieron altas tasas de incidencia, sin embargo el 2020 tuvo una disminución de casos en comparación con el 2019. El año 2021 estuvo marcado por el mayor número de casos en el período de estudio. **Conclusión:** se pudo observar un patrón estacional del dengue en el año 2020 diferente a otros años, con una disminución más pronunciada de los casos de dengue tras la llegada del COVID-19 al municipio.

Palabras Clave: *Dengue. COVID-19. Distribución Temporal. Epidemiología.*

INTRODUCTION

Dengue is one of the most serious public health concerns in the world, due to the severity of its infection.[1] It is an infectious, acute and systemic disease, caused by the virus of the *Flaviviridae* family and spread mainly by the *Aedes aegypti* mosquito, with the female being responsible for this transmission.[1] Dengue can present as asymptomatic forms or more severe cases, with shock, intense bleeding and/or organ complications, which can lead to death.[1] Its transmission is related to numerous factors, such as climatic, social, urbanization, sanitation, environmental, economic and educational conditions.[2]

In the Northeast, the state of Pernambuco had its first dengue outbreak in 1987 and currently still has a high prevalence scenario.[4] In 2021, the state had an 89.4% increase in dengue cases compared to the previous year.[4] In the municipality of Jaboatão dos Guararapes, the scenario was no different, as it also showed an increase in dengue cases when compared to 2020 and 2021.[5] Furthermore, it is the second most populous municipality in the state and has marked socioeconomic and demographic differences,[6] in addition to a precarious basic sanitation system,[7] which have a strong influence on dengue.

During 2020, dengue notifications decreased in the country when compared to the same period in 2019, a fact that may be associated with the introduction of the COVID-19 virus in Brazil from 2020 onwards.[8]

Since they initially share similar signs and symptoms, dengue and COVID-19 can have difficult diagnoses as well as adequate notifications and management in the Brazilian healthcare system.[9] At the same time, the numerous cases of COVID-19 have had an impact on healthcare services and neglected the care of diseases present in the daily routine of the Healthcare Network.[10]

A better way to understand the distribution of dengue in the context of the COVID-19 epidemiological scenario is through temporal analysis techniques. These can identify non-random patterns and estimate the effect of external factors on the variation of a time series of interest, allowing seasonal variations to be detected.[11]

Therefore, this study aimed to describe the epidemiological profile of dengue cases, as well as to analyze the temporal distribution of these cases in the municipality of Jaboatão dos Guararapes before and during the COVID-19 pandemic, based on the hypothesis that there was a change in the scenario of this arbovirus after the introduction of the new coronavirus.

METHODS

This is an ecological time series study with a descriptive character. In the research, probable dengue cases (notified cases, excluding discarded cases) were selected in the period preceding the COVID-19 pandemic (2018 to 2019) and during the pandemic (2020 to 2021).

The study took place in Jaboatão dos Guararapes, located in the state of Pernambuco, northeastern Brazil, which makes up the metropolitan mesoregion of Recife, being the second most populous municipality in the state. It is divided into seven regions and 27 neighborhoods.[6] It has a territorial area of 258,724 km² and a population density of 2,491.82 inhabitants/km², with an estimated population of 711,330 people in 2021 and a Human Development Index of 0.71.[6]

The data used in this study were extracted from the Notifiable Diseases Information System (SINAN - *Sistema*

de Informação de Agravos de Notificação) of the Municipal Health Department of Jaboatão dos Guararapes, through notification forms. The database was subsequently cleaned to remove duplicates, inconsistencies and incompleteness. The population data for calculating the indicators were obtained from the Brazilian Institute of Geography and Statistics (IBGE - *Instituto Brasileiro de Geografia e Estatística*) for each year analyzed.

Concerning the completion of the fields from notification forms, those that were blank or filled in as "ignored" were considered incomplete. Therefore, only variables classified as excellent and regular were considered in this study, according to criteria of Oliveira *et al.* (2009),[12] being ≥90% and between 70% and 89%, respectively.

Thus, the variables used to describe the epidemiological profile of notified dengue cases were sex, age, clinical signs, preexisting diseases and final classification, which were described by means of absolute and relative frequency as well as organized in a table. Regarding the final classification of cases, for the notified cases that exceeded the 60-day deadline for closure, the system automatically categorizes them as inconclusive.

The incidence rate of dengue by year of onset of symptoms, used to calculate the time series of probable cases, was calculated as follows: number of probable cases in each year, divided by the study area population in the same year, multiplied by 100,000 inhabitants. The classification of dengue incidence according to the Brazilian National Dengue Control Program occurs as: low incidence: less than 100 cases/100,000 inhabitants; medium incidence: 101 to 299 cases/100,000 inhabitants; and high incidence: 300 or more cases/100,000 inhabitants.[13]

The analysis of the time series of dengue cases in the municipality was performed using the joinpoint regression model (version 4.9.1.0). This model allows us to observe whether a line with multiple segments is, according to statistics, better for developing a temporal evolution of a given event than a straight line or line with fewer segments.[14] This, in turn, allows us to observe and identify joinpoints of a time series with statistically significant changes.[14]

To carry out the study using this model, the Monthly Percent Change (MPC) was performed for each year of the study, where each joinpoint indicated a change in the line. The classification is made as follows: when positive, it shows growth; when negative, it shows reduction; when equal to zero, it represents maintenance.[14] The MPC was calculated considering a 95% Confidence Interval and a 5% significance level.

The study was carried out in compliance with ethical standards required by Resolutions 466/2012, 510/2016 and 580/2018 of the Ministry of Health, and was approved by the *Faculdade Tiradentes do Jaboatão dos Guararapes* (FTJG) Research Ethics Committee (REC), under Opinion 5,554,360 and CAAE (*Certificado de Apresentação para Apreciação Ética* - Certificate of Presentation for Ethical Consideration) 58177722.3.0000.872, on August 1, 2022.

RESULTS

During the study period, 18,427 probable cases of dengue were identified, 347 in 2018, 4,848 in 2019, 3,414 in 2020, and 9,818 in 2021.

It was observed that probable cases of dengue were more frequent in females (54.57%) and in the age group between 20 and 39 years (37.55%). The main signs and symptoms found were fever (87.61%), headache (67.32%), and myalgia (65.61%). As for preexisting diseases, the one that presented most frequently was hypertension (1.16%) (Table 1).

In relation to the incidence of probable dengue cases, the following rates were noted: 52.75 cases/100,000 inhabitants. In 2018, it could be classified as having a low incidence, while in the other years, they presented high incidence rates, being: 693.30 cases/100,000 inhabitants (in 2019); 481.99 cases/100,000 inhabitants (in 2020); and 1,375 cases/100,000 inhabitants (in 2021).

It is possible to observe a reduction in the incidence rate of dengue in 2020 from February onwards. This decrease intensified with the introduction of the new coronavirus in the municipality, represented by the red dot, as well as with the insertion of a contingency plan against COVID-19, represented by the green dot in April 2020, a period in which municipal services are subject to restrictions and their priorities are directed towards the new coronavirus pandemic (Figure 1).

It is possible to observe that, in May 2020, there was a 94% reduction in incidence (incidence rate = 6.37 cases/100,000 inhabitants) compared to May 2019 (incidence rate = 112.63 cases/100,000 inhabitants). In contrast, in May 2021, the incidence rate was 276.52 cases/100,000 inhabitants, which represents a growth of 97.7% compared to the same month in 2020.

Regarding the temporal trends in this study, it was observed that only 2018 did not present any statistically significant trend. Regarding the other years, only 2020 had a declining trend (MPC -31.5), whereas in other years these trends were positive compared to the first months of the year (January to May 2019 and January to April 2021), which represents an increase in dengue cases during this period. When analyzing all the years in this study (2018 to 2021), 2021 presented the greatest increasing trend of the years analyzed (MPC 226.2) and had two trends, initially increasing (January to April) and, subsequently, decreasing (July to December) (Table 2).

Figure 2 shows the trend in the incidence rates of probable dengue cases, observed and adjusted, in the years analyzed, and the joinpoints of the series. The year 2018 (Figure 2A), even though it did not present significant changes, had two joinpoints: June and September. As for 2019 (Figure 2B), the points were in May and October. In 2020 (Figure 2C), the points were in May and August, and in 2021 (Figure 2D), in April and July.

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Table 1. Epidemiological variables of probable dengue cases from 2018 to 2021. Jaboatão dos Guararapes, Pernambuco, Brazil.

Variables	2018 N (347)		2019 N (4,848)		2020 N (3,414)		2021 N (9,818)		TOTAL N (18,427)	
	N	%	N	%	N	%	N	%	N	%
Sex										
Male	168	48.41	2,259	46.60	1,516	44.41	4,400	44.82	8,343	42.28
Female	179	51.59	2,589	53.40	1,891	55.39	5,396	54.96	10,055	54.57
Ignored/blank	0	0.0	0	0.0	7	0.21	22	0.22	29	0.16
Age group										
0 to 9 years	69	19.88	594	12.55	374	10.95	1,084	11.04	2,121	11.51
10 to 19 years	91	26.22	1,179	24.32	370	10.84	1,408	14.34	3,048	16.54
20 to 39 years	118	34.01	1,840	37.95	1,420	41.59	3,542	36.08	6,920	37.55
40 to 59 years	53	15.27	895	18.46	908	26.60	2,681	27.31	4,537	24.62
60 years or older	14	4.03	312	6.44	304	8.90	977	9.95	1,607	8.72
Ignored/blank	2	0.58	28	0.58	38	1.11	126	1.28	194	1.05
Clinical signs										
Fever	344	99.14	4,413	91.03	2,871	84.09	8,516	86.74	16,144	87.61
Myalgia	270	77.81	3,221	66.44	2,035	59.61	6,564	66.86	12,090	65.61
Headache	259	74.64	3,267	67.39	2,155	63.12	6,724	68.49	12,405	67.32
Rash	67	19.31	1,039	21.43	706	20.68	3,288	33.49	5,100	27.68
Vomiting	115	33.14	1,263	26.05	614	17.98	1,471	14.98	3,463	18.79
Nausea	53	15.27	866	17.86	449	13.15	1,155	11.76	2,523	13.69
Back pain	11	3.17	226	4.66	242	7.09	869	8.85	1,348	7.32
Conjunctivitis	2	0.58	58	1.20	28	0.82	129	1.31	217	1.18
Arthritis	2	0.58	98	2.02	111	3.25	189	1.93	400	2.17
Severe arthralgia	73	21.04	923	19.04	907	26.57	4,919	50.10	6,822	37.02
Petechiae	7	2.02	180	3.71	94	2.75	401	4.08	682	3.70
Leukopenia	7	2.02	104	2.15	37	1.08	75	0.76	223	1.21
Positive tourniquet test	1	0.29	24	0.50	18	0.53	23	0.23	66	0.36
Retroorbital pain	57	16.43	856	17.66	534	15.64	2,568	26.16	4,015	21.79
Ignored/blank	0	0.0	96	1.98	98	2.87	215	2.19	409	2.22
Preexisting diseases										
Diabetes	0	0.0	39	0.80	25	0.73	48	0.49	112	0.61
Hematological diseases	0	0.0	10	0.21	10	0.29	24	0.24	44	0.24
Liver diseases	0	0.0	17	0.35	12	0.35	16	0.16	45	0.24
Chronic kidney disease	0	0.0	10	0.21	8	0.23	15	0.15	33	0.18
Hypertension	2	0.58	72	1.49	44	1.29	96	0.98	214	1.16
Acid-peptic disease	1	0.29	10	0.21	12	0.35	24	0.24	47	0.26
Autoimmune diseases	1	0.29	10	0.21	11	0.32	31	0.32	53	0.29
Ignored/blank	0	0.0	96	1.98	98	2.87	215	2.19	409	2.22
Final classification										
Dengue	303	87.32	557	11.49	60	1.76	115	1.17	1,035	5.62
Dengue with warning signs	40	11.53	33	0.68	6	0.18	8	0.08	87	0.47
Severe dengue	2	0.58	3	0.06	4	0.12	0	0.0	9	0.05
Inconclusive	2	0.58	4,203	86.70	3,312	97.01	9,581	97.69	17,108	92.84
Ignored/blank	0	0.0	52	1.07	32	0.94	104	1.06	188	1.02

Table 2. Analysis of temporal trend of incidence of probable dengue cases per 100,000 inhabitants between 2018 and 2021. Jaboatão dos Guararapes, Pernambuco, Brazil.

Year	Period	Trend 1 MPC	Trend 1 95% CI	Period	Trend 1 MPC	Trend 1 95% CI
2018	-	-	-	July-December	-	-
2019	January-May	99.1	38.1 to 187.1	July-December	-	-
2020	January-May	-31.5	-48.8 to -8.5	July-December		
2021	January-April	226.2	34.2 to 692.9	July-December	-36.4	-57.3 to -5.4

Note: MPC - Monthly Percent Change; CI - Confidence Interval.

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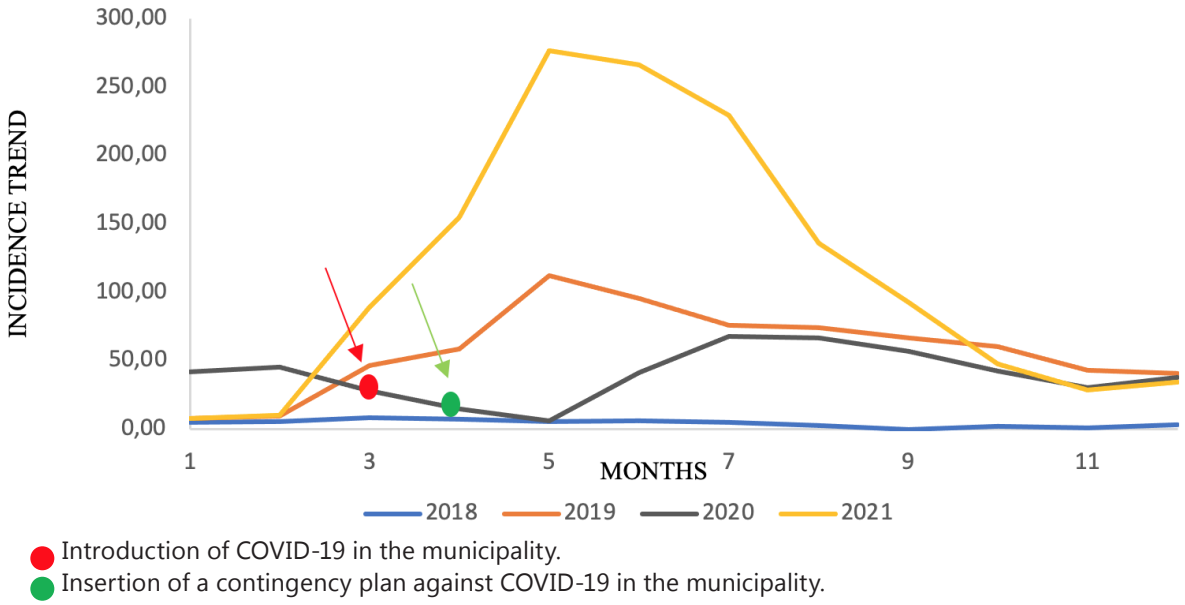

Figure 1. Incidence rate of probable dengue cases per 100,000 inhabitants, from 2018 to 2021. Jaboatão dos Guararapes, Pernambuco, Brazil.

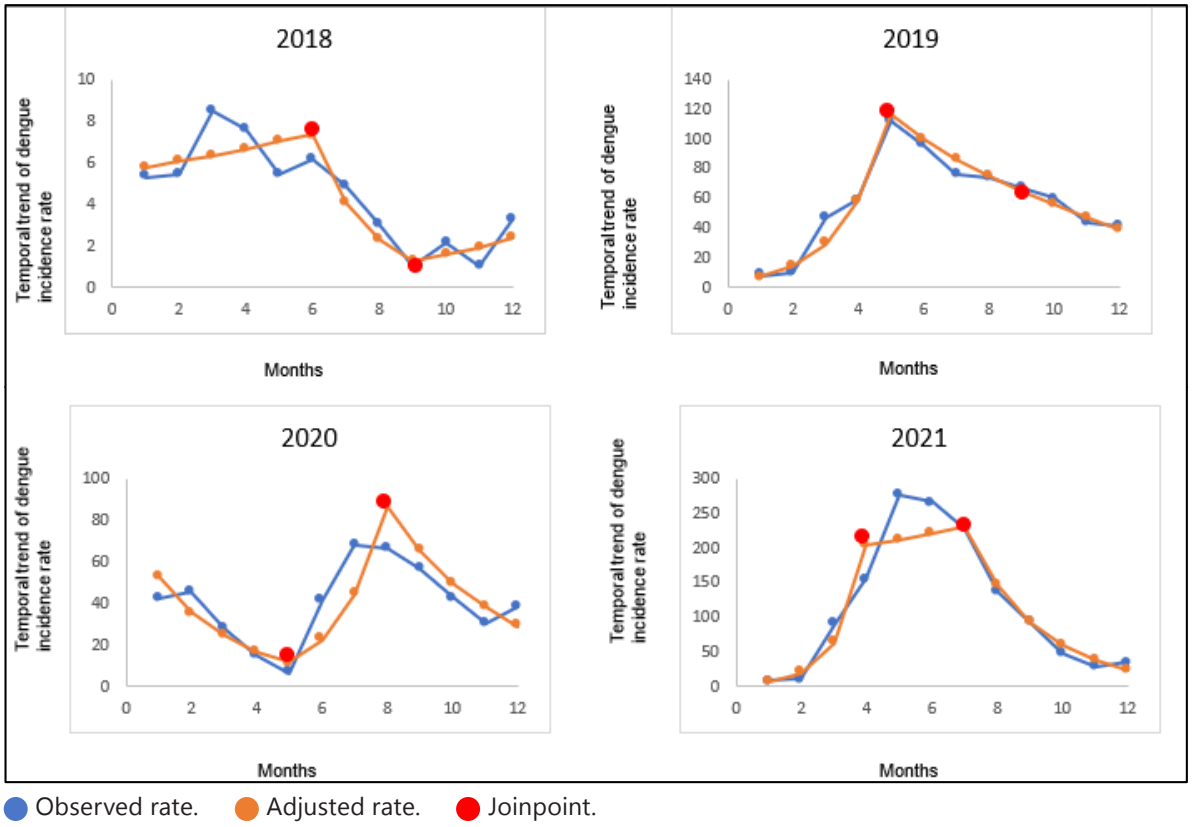

Figure 2. Time trend of observed and adjusted incidence rate of probable dengue cases per 100,000 inhabitants and joinpoints, from 2018 to 2021. Jaboatão dos Guararapes, Pernambuco, Brazil

DISCUSSION

In this study, we sought to analyze the temporal pattern of dengue cases from 2018 to 2022 to analyze the influence of COVID-19 in this period. When analyzed, the variables female gender and the age group between 20 and 39 years were the most affected by dengue. In a study carried out in the municipality of Primavera do Leste-MT, between 2014 and 2017, a higher occurrence was also observed in this population.[15] The predominance of cases in this population can be explained by the fact that they are the most economically active age group and

move around the most.

The greater incidence of the female population may be associated with a greater demand for healthcare services and more time spent in the home and peridomestic environment, places where there is a greater predisposition to mosquito dispersion.[16]

When analyzing clinical variables, the most prevalent preexisting disease was hypertension, which was also present in greater numbers in a study carried out in Goiânia. [7] the main signs and symptoms found were fever, headache and myalgia. These may also be present in other pathologies, including COVID-19,[18,19] since, in the initial stages, dengue and COVID-19 share similar signs and symptoms, allowing for erroneous diagnoses and, consequently, undernotification of arbovirus cases.

Moreover, the healthcare system was focusing its actions on the pandemic caused by the new coronavirus and its human resources were mainly directed towards combating COVID-19. Likewise, restrictions on services and transportation, as well as recommendations to stay at home, may have made it difficult for users to access healthcare services, especially primary care,[20,21] supporting the hypothesis of undernotification of dengue in 2020.

The aforementioned situations may have contributed to the scenario observed in the municipality under study. When analyzing the COVID-19 epidemiological bulletin version 275, from Jaboatão dos Guararapes,[22] it is possible to observe that the peaks of COVID-19 cases in 2020, in the municipality, occurred at the end of April and beginning of May as well as deaths, mostly caused by the new coronavirus that occurred in May of the same year, a time when there was a sharper decrease in dengue cases in the municipality.

The findings of this study also demonstrate increasing temporal trends in dengue cases in the first months of 2019 and 2021, represented by positive MPC. However, 2020 presented a different scenario from the others in relation to this problem, a fact that may also have been triggered by the consequences arising from the COVID-19 pandemic.

The year 2021 was marked by a considerable increase in dengue cases in Jaboatão dos Guararapes, similar to some findings of a study that analyzed cases of arboviruses in the state of Amazonas, between 2018 and 2022.[23] In this research, it was observed that the largest number of cases was also found in 2021, and they attributed this fact to COVID-19, associating it with the justification of a greater search by the population for testing for the coronavirus; with this, individuals ended up being considered suspects for dengue.

It is also possible to observe the seasonality pattern of dengue, since it showed increasing incidence curves in the first months of the year, with the exception of 2020, which presented an atypical scenario compared to the others. The first five months of the year are characterized by high temperatures and greater humidity, which favor an increase in the incidence of dengue.[15]

Studies report that, in addition to climatic conditions, other factors are associated with the emergence of dengue cases, such as disorderly population growth, poor sanitation conditions, inadequate housing, no running water, sanitation and open sewage, disorganization of cities, with inadequate infrastructure, deficiencies in garbage collection, in addition to cultural and educational factors.[24,25]

As it is one of the most populous municipalities in the state of Pernambuco and is a large urban center, it has peculiarities such as accelerated urbanization, social inequality, high consumption of industrialized and disposable products that consequently create conditions and environments favorable to outbreaks of the disease. The combination of these factors predisposes to a high incidence of dengue, as seen in most of the years analyzed in the study (2019, 2020 and 2021).

According to the *Instituto Trata Brasil* (2022),[7] the municipality also has a precarious sewage and basic sanitation system with around 79% of water supply in homes. A study carried out in northeastern Brazil found that the most populous municipalities had a higher incidence rate of dengue and also observed a correlation between lack of access to piped water and its incidence. [24] A population that does not have access to running water ends up storing this resource incorrectly, predisposing it to the emergence of arboviruses.

The present study made it possible to identify and associate its findings with the reality of Jaboatão dos Guararapes, and, therefore, contributed to greater epidemiological knowledge of dengue in the municipality and its presentation during the COVID-19 pandemic.

With the decrease in notified dengue cases in 2020 and their explosion in 2021, it is suggested that healthcare professionals, especially those involved in primary care, health surveillance, and municipal management, monitor this condition more closely. There is also a need for greater attention to timely closure of cases as well as an alert for municipal planning in interventions in the face of new syndemics.

Regarding limitations, since this is a study produced from a secondary database, there is the possibility of reporting bias, which may present inconsistencies in the quantity, quality and processing of information. There were also restrictions on the variables analyzed due to the low percentage of completion of notification forms. These variables include race/color, education, case classification, confirmation/discard criteria and case evolution. However, even with these circumstances, the study was able to analyze the temporal patterns of dengue in the municipality.

In fact, improving the socio-environmental conditions of a population and raising awareness is a path that can be effective against the spread of the mosquito and the occurrence of the disease. Finally, the knowledge provided in this study allows us to assess the health situation regarding dengue notifications before and during the COVID-19 pandemic, in order to subsidize healthcare professionals, with the aim of reducing the burden of dengue.

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AUTHOR'S CONTRIBUTIONS

Natália Ferreira de Sousa contributed to the bibliographic research, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Celivane Cavalcanti Barbosa** contributed to writing the manuscript, interpretation and description of results, conclusions, review and statistics. **Edivânia Felix dos Santos and Paulino José de Albuquerque Vasconcelos Neto** contributed to writing and critically reviewing the content of the manuscript. **Emília Carolle Azevedo de Oliveira** contributed to the conception and design of the study, writing and critically reviewing the content of the manuscript.

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ORIGINAL ARTICLE

Impact of COVID-19 on the epidemiology of respiratory viruses in southern Brazil

Impacto da COVID-19 na epidemiologia de vírus respiratórios no Rio Grande do Sul

Impacto epidemiológico de la COVID-19 sobre los virus respiratorios en sur de Brasil

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ABSTRACT

Background and objectives: During the SARS-CoV-2 pandemic, reduction in detection of other Respiratory Viruses (RV) was observed. Epidemiological studies are needed to understand the impact of the pandemic on the circulation of RV. The aim of this study is to analyze the epidemiological profile of cases of severe acute respiratory infection (SARI) associated with the main RV in hospitalized patients from Rio Grande do Sul, Brazil (RS), between 2010 and 2019 (period *A*) and between 2020 and 2021 (period *B*). **Methods:** Data related to SARI cases in RS were retrieved from SIVEP-Gripe. **Results:** In period *A* there were more infections with Influenza, Parainfluenza, Adenovirus and Respiratory Syncytial Virus, while in period *B* most cases were of SARS-CoV-2 infection. The most affected age groups were individuals <5 years old (67.1%) in period *A*, and >60 years old (50%) in period *B*. The main symptoms were fever and cough in period *A*, and dyspnea and O_2 saturation <95% in period *B*. The most reported comorbidities were lung diseases and chronic cardiovascular diseases in period *A*, and chronic cardiovascular diseases and diabetes mellitus in period *B*. Importantly, a higher fatality rate was observed in period *B*. Most cases occurred between May and July in period *A*, and in November and December 2021 in period *B*. **Conclusion:** This study reveals that the COVID-19 pandemic changed the epidemiological profile of SARI in RS, and most cases were in the elderly with chronic cardiovascular disease and diabetes mellitus.

Keywords: *Coronavirus Infections. Epidemiological Monitoring. Severe Acute Respiratory Syndrome.*

RESUMO

Justificativa e Objetivos: Durante a pandemia de SARS-CoV-2 foi observada redução na detecção de outros vírus respiratórios (VR). Estudos epidemiológicos são importantes para uma melhor compreensão dos impactos da pandemia sobre a circulação de VR. O objetivo deste estudo foi analisar o perfil epidemiológico dos casos de

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síndrome respiratória aguda grave (SRAG) associados aos principais VR em pacientes internados no Rio Grande do Sul, Brasil (RS), entre 2010 e 2019 (período *A*) e entre 2020 e 2021 (período *B*). **Métodos:** Dados relacionados a casos de SRAG no RS foram obtidos do SIVEP-Gripe. **Resultados:** No período *A* houve mais infecções por Influenza, Parainfluenza, Adenovírus e Vírus Sincicial Respiratório, enquanto no período *B* a maioria foi por SARS-CoV-2. Os grupos etários mais afetados foram de indivíduos <5 anos de idade (67,1%) no período *A*, e >60 anos (50%) no período *B*. Os principais sintomas foram febre e tosse no período *A*, e dispneia e saturação de O_2 <95% no período *B*. As principais comorbidades no período *A* foram pneumopatias e cardiopatias, enquanto no período *B* foram cardiopatias e diabetes mellitus. A mortalidade foi maior no período *B*. A maioria dos casos no período *A* foram entre maio e julho, e no período *B* entre novembro e dezembro de 2021. **Conclusão:** Este estudo revela que a pandemia de COVID-19 alterou o perfil epidemiológico de SRAG no RS, sendo a maioria dos casos em indivíduos idosos com doença cardiovascular e diabetes.

Descritores: *Infecções por Coronavirus. Monitoramento Epidemiológico. Síndrome Respiratória Aguda Grave.*

RESUMEN

Justificación y Objetivos: Durante la pandemia por SARS-CoV-2 se observó reducción en la detección de otros virus respiratorios (VR). Los estudios epidemiológicos son importantes para comprender los impactos de la pandemia en la circulación de VR. Este estudio analizó variables epidemiológicas asociadas al Síndrome Respiratorio Agudo Grave (SRAG) en Rio Grande do Sul (RS), Brasil, antes de la aparición del SARS-CoV-2 (período *A*, 2010-2019) y durante la pandemia (período *B*, 2020-2021). **Métodos:** Los datos relacionados con los casos de SRAG en RS se obtuvieron de SIVEP-Gripe. **Resultados:** En el período *A* hubo más infecciones por Influenza, Parainfluenza, Adenovirus y Virus Respiratorio Sincitial, mientras que en el período *B* la mayoría de los casos fueron causados por SARS-CoV-2. Los grupos de edad más afectados fueron <5 años (67,1%) en el período *A*, y >60 años (50%) en el período *B*. Los principales síntomas fueron fiebre y tos en el período *A*, y disnea y saturación de O_2 <95% en el período *B*. Las principales comorbilidades en el período *A* fueron enfermedades pulmonares y cardíacas, y en el período *B* fueron enfermedades cardíacas y diabetes mellitus. La mortalidad fue mayor en el período *B*. La mayoría de los casos en el período *A* fueron entre mayo y julio, y en el período *B* entre noviembre y diciembre. **Conclusiones:** Este estudio revela que la pandemia de COVID-19 cambió el perfil epidemiológico del SRAG en RS. La mayoría de los casos se dan en personas de edad avanzada con enfermedades cardiovasculares y diabetes.

Palabras Clave: *Infecciones por Coronavirus. Monitoreo Epidemiológico. Síndrome Respiratorio Agudo Grave.*

INTRODUCTION

Acute respiratory infections are a global health problem, with high morbidity and mortality.[1] Respiratory viruses (RVs) can infect the upper and lower respiratory tract, leading to symptoms such as fever, headache, cough, chills, among others. The clinical spectrum can vary from mild cases of acute respiratory infection (ARI) to cases of Severe Acute Respiratory Infection (SARI).[2]

Epidemiological surveillance of RVs is paramount for disease control and prevention. In Brazil, surveillance of RVs is based on case notification and collection of nasopharyngeal samples from patients for laboratorial analysis, which is performed in public laboratories throughout the country, including State Central Laboratories (LACEN) and the National Influenza Centers (NIC). Cases of SARI are notified in the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe) of Brazil.[2]

Rio Grande do Sul (RS) is one of the states with the highest incidence of viral respiratory infections in the country.[3-7] During the first two years of the coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the health network focused efforts for the identification and confirmation of COVID-19 cases, with detection of SARS-CoV-2 becoming a priority over other RV. Therefore, a lower number of SARI cases associated with other RV were reported;[5] noteworthy, pandemic control measures may also have impacted the circulation of other viruses. Moreover, the emergence of a given RV such as SARS-CoV-2 can affect the dynamics of other RVs in the population.[8-10] In this sense, analyses of the circulation of different RV during epidemic and pandemic events are important to better understand the epidemiology of viral respiratory infections in different scenarios and the factors that may contribute for differences in viral circulation. Such studies contribute to the prevention and control of outbreaks and epidemics.

The aim of this study was to analyze the epidemiological profile of cases of respiratory infection associated with the main RVs in hospitalized patients from RS, between 2010 and 2019 (period *A*) and between 2020 and 2021 (period *B*).

METHODS

This study evaluated data from laboratory analyses performed at the Central Public Health Laboratory of Rio Grande do Sul (LACEN-RS) for detection of RVs in respiratory secretion samples from patients with SARI hospitalized in RS between January 1, 2010 and June 30,

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2021. Laboratory data were provided by LACEN-RS, which is responsible for performing surveillance of RVs in RS and diagnosis of viral infection based on viral detection by RT-qPCR and immunofluorescence assays in samples collected from patients in public or affiliated hospitals in all 497 RS municipalities. All analyses are performed based on validated protocols as described elsewhere.[2-4,6,7] It is important to note that samples from period *A* were first tested for influenza viruses; when negative for influenza viruses, samples were tested for other RVs.

Demographic and clinical data related to each SARI case were retrieved from the SIVEP-Gripe system and provided by the State Health Surveillance Center (CEVS-RS). The following data were obtained for epidemiological analysis: sex, age, clinical symptoms, comorbidities, result of RV investigation, outcome, and length of stay in the hospital (LOS). The monthly averages of the maximum and minimum temperatures (in ºC) in RS were obtained from the National Institute of Meteorology (INMET) to associate seasonality with the peak period of each RV.

The databases used contain raw data, which passed inclusion and exclusion criteria, in addition to statistical analyses. The inclusion criteria were: a) total data on SARI cases for absolute numbers; b) data with laboratory examination by qPCR, RT-qPCR or immunofluorescence for any RV and with result "Detected", for analysis of RV; c) the respiratory viruses analyzed were: hPIV, HAdV, RSV, IAV/IBV, SARS-CoV-2; d) cases notified between January 1, 2010 and June 30, 2021. Data from individuals without SARI symptoms and from individuals that were tested only for influenza viruses were excluded.

The database was used for stratification and was later exported for data analysis in the R v.3.6.3 software statistical package. Data presentation was performed through Residual Analysis and Chi-square tests. Results were considered significant when $p<0.0001$ for Chi-square and >1.96 for Residual Analysis. Mean values, percentage or absolute data for quantitative variables were also used. To assess the existence of significant differences in LOS – number of days from date of admission in the hospital to date of evolution (cure or death) –, the Mann-Whitney test was performed for two independent samples; the significance level $\alpha=0.05$ was used.

This study is part of projects approved by the Ethics Committee of UFCSPA which are registered on Plataforma Brasil (CAAE 75118217.9.0000.5345; CAAE 75357417.1.0000.5345; CAAE 30714520.0.0000.5345). The research was conducted in accordance with the required ethical standards from Resolutions 466/2012, 510/2016 and 580/2018, from the Brazilian Ministry of Health.

RESULTS

Data from 29,902 SARI cases from period *A* and 128,642 cases from period *B* were analyzed. Table 1 presents the number of cases according to RV, showing the total number of cases and the percentage in relation to the total number of positive cases for the analyzed RV. The analysis of adjusted residues (res.adj) reveals that IAV/IBV, hPIV-1, hPIV-2, hPIV-3, HAdV and RSV were more detected in period *A* than period *B* (res.adj=196.81, 31.27, 14.91, 66.07, 62.62, 202.15), while SARS-CoV-2 was the main virus detected in period *B* (res.adj=307.69).

Regarding the sex of the individuals, 52.5% of SARI cases in period *A* and 53.8% in period *B* were male, with no differences between sexes. Table 2 shows the age profile of SARI cases caused by different respiratory viruses in RS in periods *A* and *B*. In period *A*, there were more cases among individuals aged <1, 1–5, 6–11 and 12–19 (res.adj= 199.19, 123.02, 42.32, 23.25, respectively), while in period B there were significantly more cases in the age groups 20–39, 40–59 and ≥60 (res.adj= 16.27, 50.33, 72.10, respectively). The Chi-square test reveals that there is an association between the age of the patients and the period (pre-pandemic and pandemic, $p<0.0001$).

As shown in Table 3, cough, fever, dyspnea, and sore throat were the symptoms analyzed in both periods, whereas other symptoms were evaluated separately because not all of them were reported in both periods. The frequency of cases with fever and cough was higher in period *A* (res.adj=24.67, 9.27 respectively), while dyspnea and sore throat were more reported in period *B* (res. adj=19.51, 21.26); our analysis revealed an association between patients' symptoms and period ($p<0.0001$). In period *B*, dyspnea was the most predominant symptom,

Table 1. Number of SARI cases caused by the respiratory viruses analyzed in this study.

Variable	Period A (2010-2019), N (%)	Period B (2020-2021), N (%)
Notified cases	29902	128642
Positive for respiratory viruses[a]	9310 (31.1)	89915 (69.9)
Influenza[b]	3875 (41.6)	18 (0.02)
hPIV[b]	581 (6.2)	6 (0.01)
hPIV-1	108 (18.6)	6 (100)
hPIV-2	23 (4.0)	0 (0)
hPIV-3	450 (77.5)	0 (0)
HAdV[b]	416 (4.5)	10 (0.01)
RSV[b]	4438 (47.7)	370 (0.4)
SARS-CoV-2[b]	0 (0)	89511 (99.6)

N: number of cases. [a] Percentage of positive cases in relation to the total number of notified cases. [b] Percentage of cases for the specified respiratory virus in relation to the total number of positive cases for respiratory viruses. In the case of influenza virus, IAV and IBV were not specified.

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Table 2. Age profile of SARI cases caused by different respiratory viruses in Rio Grande do Sul between 2010 and 2019 (Period A) and between 2020 and 2021 (Period B).

Age (years)	Influenza N (%)	hPIV-1 N (%)	hPIV-2 N (%)	hPIV-3 N (%)	HAdV N (%)	RSV N (%)	SARS-CoV-2 N (%)	All respiratory viruses, N (%)
PERIOD A								
<1	519 (13.6)	47 (43.5)	14 (60.9)	333 (74.0)	209 (50.2)	3290 (74.1)	0 (0)	4412 (47.6)
1-5	559 (14.6)	40 (37.0)	2 (8.7)	97 (21.6)	157 (37.7)	949 (21.4)	0 (0)	1804 (19.5)
6-11	217 (5.7)	7 (6.5)	1 (4.4)	4 (0.9)	8 (1.9)	34 (0.8)	0 (0)	271 (2.9)
12-19	177 (4.6)	1 (0.9)	1 (4.4)	2 (0.4)	14 (3.4)	12 (0.3)	0 (0)	207 (2.2)
20-39	589 (15.4)	3 (2.8)	2 (8.7)	1 (0.2)	10 (2.4)	27 (0.6)	0 (0)	632 (6.8)
40-59	868 (22.7)	3 (2.8)	0 (0)	5 (1.1)	12 (2.9)	43 (1.0)	0 (0)	931 (10.1)
≥60	899 (23.5)	7 (6.5)	3 (13.0)	8 (1.8)	6 (1.4)	83 (1.9)	0 (0)	1006 (10.9)
PERIOD B								
<1	2 (11.1)	3 (50.0)	0 (0)	0 (0)	8 (80.0)	253 (68.4)	219 (0.2)	485 (0.5)
1–5	2 (11.1)	3 (50.0)	0 (0)	0 (0)	1 (10.0)	89 (24.1)	169 (0.2)	264 (0.3)
6–11	1 (5.6)	0 (0)	0 (0)	0 (0)	0 (0)	7 (1.9)	91(0.1)	99 (0.1)
12–19	0 (0)	0 (0)	0 (0)	0 (0)	1 (10.0)	4 (1.1)	327 (0.4)	332 (0.4)
20–39	1 (5.6)	0 (0)	0 (0)	0 (0)	0 (0)	5 (1.4)	11327 (12.7)	11333 (12.6)
40–59	7 (38.9)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)	32347 (36.1)	32355 (36.0)
≥60	5 (27.8)	0 (0)	0 (0)	0 (0)	0 (0)	11 (3.0)	45031 (50.3)	45047 (50.1)

N: number of cases of the respective respiratory virus in the specified age group. %: Percentage of cases in the age group in relation to the total number of cases of the respective respiratory virus.

Table 3. Symptoms observed in SARI cases by different respiratory viruses in Rio Grande do Sul between 2010 and 2019 (Period A) and between 2020 and 2021 (Period B).

Symptom N/t[a] (%)	Influenza	hPIV-1	hPIV-2	hPIV-3	HAdV	RSV	SARS-CoV-2
PERIOD A							
Fever	3518/3852 (91.3)	99/108 (91.7)	22/23 (95.7)	424/449 (94.4)	401/415 (96.6)	4012/4423 (90.7)	0/0 (0)
Cough	3578/3849 (93.0)	102/108 (94.4)	23/23 (100)	430/447 (96.2)	398/414 (96.1)	4257/4425 (96.2)	0/0 (0)
Dyspnea	2959/3823 (77.4)	89/108 (82.4)	22/23 (95.7)	418/443 (94.4)	370/414 (89.4)	3977/4396 (90.5)	0/0 (0)
Sore throat	996/3364 (29.6)	13/77 (16.9)	2/12 (16.7)	12/151 (7.9)	37/200 (18.5)	173/2152 (8)	0/0 (0)
Myalgia	1349/2914 (46.3)	11/55 (20.0)	3/9 (33.3)	11/108 (10.2)	33/111 (29.7)	169/1681 (10.1)	0/0 (0)
PERIOD B							
Fever	14/18 (77.8)	6/6 (100)	0/0 (0)	0/0 (0)	10/10 (100)	225/335 (67.2)	50481/77738 (64.9)
Cough	13/18 (72.2)	6/6 (100)	0/0 (0)	0/0 (0)	4/10 (40)	326/357 (91.3)	61423/79717 (77.1)
Dyspnea	15/17 (88.2)	5/6 (83.3)	0/0 (0)	0/0 (0)	7/10 (70)	252/337 (74.8)	72180/83555 (86.4)
Sore throat	3/18 (16.7)	0/6 (0)	0/0 (0)	0/0 (0)	1/9 (11.11)	7/285 (2.5)	17103/67250 (25.4)
Respiratory distress	15/17 (88.2)	4/6 (66.7)	0/0 (0)	0/0 (0)	6/10 (60)	274/342 (80.1)	60140/78254 (76.9)
Saturation O^2 < 95%	11/17 (64.7)	2/6 (33.3)	0/0 (0)	0/0 (0)	5/9 (55.56)	203/331 (61.3)	67652/82115 (82.4)
Diarrhea	2/17 (11.8)	2/6 (33.3)	0/0 (0)	0/0 (0)	2/9 (22.22)	21/288 (7.3)	14208/67280 (21.1)
Vomiting	2/17 (11.8)	3/6 (50)	0/0 (0)	0/0 (0)	2/9 (22.22)	50/292 (17.1)	8146/65776 (12.4)
Fever	14/18 (77.8)	6/6 (100)	0/0 (0)	0/0 (0)	10/10 (100)	225/335 (67.2)	50481/77738 (64.9)

[a] Number of cases positive for the respective respiratory virus with a given symptom (N) in relation to the total of answers for that symptom (t).

observed in 86% of the cases. Other symptoms were included in the notification forms of SARI in period *B*, including respiratory distress (in 77% of the cases), O_2 saturation <95% (82%), diarrhea (21%) and vomiting (12%).

Table 4 presents comorbidities observed in SARI cases in periods *A* and *B*. Chronic cardiovascular disease, chronic kidney disease and immunodeficiency/immunosuppression were reported in all years between periods *A* and *B*. As revealed by the analysis of adjusted residuals, the percentage of cases that presented immunodeficiency/immunosuppression and chronic kidney disease was significantly higher in period *A* (res.adj=30.96, 6.42, respectively). There was no significant difference between the two periods regarding the frequency of patients with chronic cardiovascular disease (res.adj=0.02). The Chi-square test reveals that there is an association between the patients' comorbidities and the period (p<0.0001).

In period *A*, 6.7% of the patients with respiratory viral infection died, whereas in period *B* the fatality rate was higher, reaching 37%. In this sense, "cure" was associated with period *A* (res.adj=57.73), while "death" was associated with period *B* (res.adj=57.73). The chi-square test

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Table 4. Comorbidities observed in SARI cases by different RV in RS between 2010 and 2019 (Period A) and between 2020 and 2021 (Period B).

Comorbidity/Risk factor	Influenza	hPIV-1	hPIV-2	hPIV-3	HAdV	RSV	SARS-CoV-2
PERIOD A – N/t (%[a])							
Chronic cardiovascular disease	600/3552 (16.9)	7/99 (7.1)	2/20 (10.0)	14/393 (3.6)	12/348 (3.5)	122/3981 (3.1)	0/0 (0.0)
Chronic kidney disease	121/3545 (3.41)	1/99 (1.0)	1/20 (5.0)	1/393 (0.3)	2/349 (0.6)	13/3982 (0.3)	0/0 (0.0)
Immunodeficiency/immunosuppression	263/3534 (7.4)	4/98 (4.1)	1/20 (5.0)	4/393 (1.0)	12/346 (3.5)	55/3978 (1.4)	0/0 (0.0)
Chronic lung diseases (2010–2018)	734/3299 (22.3)	15/94 (16.0)	2/19 (10.5)	73/385 (19.0)	71/325 (21.9)	535/3878 (13.8)	0/0 (0.0)
Smoking (2010–2018)	1/49 (2)	0/10 (0.0)	1/6 (16.7)	0/36 (0)	1/42 (2.4)	10/717 (1.4)	0/0 (0.0)
Asthma (2019)	50/253 (19.8)	2/6 (33.3)	1/1 (100)	3/7 (42.9)	10/23 (43.5)	40/109 (36.7)	0/0 (0.0)
Other chronic lung diseases (2019)	42/253 (16.6)	0/5 (0)	0/1 (0)	2/7 (28.6)	3/23 (13.0)	7/109 (6.4)	0/0 (0.0)
Obesity (2019)	18/249 (7.2)	0/5 (0)	0/1 (0)	0/6 (0)	0/23 (0.0)	1/108 (0.9)	0/0 (0.0)
PERIOD B – N/t (%)							
Chronic cardiovascular disease	3/10 (30)	1/3 (33.3)	0/0 (0)	0/0 (0)	0/4 (0)	13/83 (15.7)	31524/51833 (60.8)
Chronic kidney disease	1/10 (10)	0/3 (0)	0/0 (0)	0/0 (0)	0/4 (0)	0/80 (0)	3397/42165 (8.1)
Immunodeficiency/immunosuppression	2/10 (20)	1/3 (33.3)	0/0 (0)	0/0 (0)	0/4 (0)	5/80 (6.3)	2953/42089 (7.0)
Chronic hematological disease	0/10 (0)	1/3 (33.3)	0/0 (0)	0/0 (0)	0/4 (0)	1/81 (1.2)	710/41536 (1.7)
Down's syndrome	0/10 (0)	1/3 (33.3)	0/0 (0)	0/0 (0)	0/4 (0)	4/82 (4.9)	246/41652 (0.6)
Chronic liver disease	0/10 (0)	0/3 (0)	0/0 (0)	0/0 (0)	0/4 (0)	1/80 (1.3)	1044/41564 (2.5)
Asthma	2/10 (20)	1/3 (33.3)	0/0 (0)	0/0 (0)	0/4 (0)	24/83 (28.9)	3735/42446 (8.8)
Diabetes mellitus	2/10 (20)	0/3 (0)	0/0 (0)	0/0 (0)	0/4 (0)	5/83 (6.0)	21893/48674 (44.9)
Chronic neurological disease	1/10 (10)	0/3 (0)	0/0 (0)	0/0 (0)	1/4 (25)	13/83 (15.7)	4784/42700 (11.2)
Other chronic lung diseases	2/10 (20)	0/3 (0)	0/0 (0)	0/0 (0)	1/4 (25)	4/81 (4.9)	4625/42730 (10.8)
Obesity	1/9 (11.1)	0/3 (0)	0/0 (0)	0/0 (0)	0/4 (0)	2/81 (2.5)	12593/44709 (28.2)
Puerperal	0/10 (0)	0/3 (0)	0/0 (0)	0/0 (0)	0/4 (0)	0/81 (0)	187/41506 (0.5)

[a] *Number of cases positive for the respective respiratory virus with a given symptom (N) in relation to the total of answers for that comorbidity (t).*

Table 5. SARI cases by RV according to the month in Period A (2019-2020) and Period B (2020 and 2021).

	Influenza	hPIV-1	hPIV-2	hPIV-3	RSV	SARS-CoV-2
PERIOD A 2010–2019						
January	16	4	3	10	4	-
February	10	2	1	2	8	-
March	89	17	2	3	62	-
April	682	19	4	4	253	-
May	799	17	2	7	972	-
June	786	10	2	23	1392	-
July	814	5	1	25	1193	-
August	372	6	6	70	428	-
September	167	9	0	114	101	-
October	54	7	2	109	18	-
November	59	6	0	59	4	-
December	26	6	0	24	3	-
Total	3874	108	23	450	4438	-
PERIOD B 2020						
January	5	0	0	0	2	0
February	3	2	0	0	3	0
March	2	4	0	0	3	230
April	2	0	0	0	0	648
May	0	0	0	0	0	1027
June	3	0	0	0	0	2644
July	0	0	0	0	0	4929
August	0	0	0	0	1	4468
September	0	0	0	0	0	3050
October	1	0	0	0	0	3323
November	0	0	0	0	0	5479
December	0	0	0	0	0	5698
Total	16	6	0	0	9	31496
PERIOD B 2020						
January	1	0	0	0	2	4642
February	1	0	0	0	5	13812
March	0	0	0	0	19	16671
April	0	0	0	0	137	8902
May	0	0	0	0	136	10912
June	0	0	0	0	62	3076
Total	2	0	0	0	361	58015

with Yates' correction showed that there is an association between patient outcomes and period (pre-pandemic or pandemic, p<0.0001).

The average length of stay in the hospital (LOS) was 11 days in both periods. Statistical analysis revealed a significant difference between periods (W = 1116421728, p-value < 2.2e-16). The mean LOS in period *A* was 11.21 days (± 0.127 days), and in period *B* 11.57 days (± 0.039 days) (data not shown).

The monthly number of SARI cases positive for each respiratory is shown in Table 5. Data related to period *B* was obtained until June 2021; to avoid bias when comparing period *B* with period *A* (which contains data from January to December of all years), period *B* was divided into two segments (period *B*-2020 and period *B*-2021).

In period *A*, most infections occurred between April and August. There was a predominance of Influenza and RSV between April and August (3,453 and 4,238 cases, respectively), with the number of cases decreasing in late winter and early spring (221 and 119 cases, respectively). HAdV circulated mainly in autumn (90 cases) and spring (282 cases). Regarding hPIV, the dominant type was hPIV-3, with peaks in spring (282 cases) and winter (118 cases); whereas most cases of hPIV-1 were observed during fall (53 cases), and of hPIV-2 in winter (9 cases) and autumn (8 cases).

In period *B*, no cases of hPIV-2 and hPIV-3 infection were reported, whereas six (6) cases of hPIV-1 were reported between February and March 2020. Nine (9) cases were positive for HAdV between January and April 2020, and one (1) case in May 2021. There were few cases of RSV in 2020 (9 cases), but in 2021 361 cases of RSV were reported between January and June. Regarding influenza viruses, there were only 18 confirmed cases as of June 2021.

DISCUSSION

The first cases of SARS-CoV-2 infection occurred in China in December 2019. The COVID-19 pandemic was declared in March 2020,[11] and RS had the first case on March 10, 2020.[12] This study analyzed SARI cases associated with RV infection in hospitalized patients along 10 years before the COVID-19 pandemic and during the first 18 months of the pandemic in the State of Rio Grande do Sul (RS), Brazil. Data related to cases notified in the SINAN and SIVEP-Gripe systems between January 2010 and June 2021 were assessed to build two databases, one with data of SARI cases before the COVID-19 pandemic (period *A*, 2010 to 2019: 29,902 cases), and the other with data of SARI cases during the first two years of the COVID-19 pandemic (period *B*, 2020 to 2021: 128,642 cases).

The most detected RVs among SARI patients in period *A* were IAV/IBV and RSV, which is in accordance with data from epidemiological bulletins in the state.[13] These RV were also detected in some cases in period *B*, with more cases of RSV than of Influenza (370 and 18 cases, respectively). In 2021, RSV was the only RV detected in samples of patients with SARI that were negative for SARS-CoV-2, and 335 of 361 RSV-positive cases occurred during autumn and winter, when temperatures are a little above 10ºC. Between September and December, when minimum and maximum temperatures in RS are around 15ºC–21ºC and 23ºC–29ºC, respectively, there were more cases of Influenza than RSV.

In period *A*, a significant number of SARI cases during spring was associated with hPIV-3 infection; hPIV-1, on the other hand, circulates mainly during the autumn. This finding corroborates a previous study that analyzed cases of hPIV-1, hPIV-2, and hPIV-3 along 28 years in RS that found hPIV-3 to be the most common type of parainfluenza virus among hospitalized individuals.[7]

HAdV had a peak in the number of cases in July and August, however with fewer cases than other RVs. Cases of HAdV were also reported in January, like other HAdV studies in RS in years prior to 2020.[4]

In 2020, the first year of the COVID-19 pandemic, a significant number of SARS-CoV-2 infections were observed during winter (July and August), however the months with the highest number of cases in 2020 were November and December, which may be associated with non-seasonal causes posed by the pandemic.

In period *B*, circulation of other RVs in RS was more common during autumn and winter, corroborating other studies.[4,6,7,14] The seasonal occurrence of RV diseases in temperate regions, with more respiratory diseases during colder seasons, as is the case of RS, may be related to factors such as higher replication of some RV at lower temperatures and higher transmission among individuals because of closed and less-ventilated environments.

Regarding the age of patients with SARI associated with RV infection, the most affected age group was <1 year in period *A*, and ≥60 years in period B. Additionally, in period *A* there were more patients aged <5 years (67.1%), while in period B most cases were in adults aged 20 to 59 years (48.6%) and elderly ≥60 (50.1%). Our results corroborate studies performed in RS and in other Brazilian regions.[3,8,15,16] In our study, only 0.54% of the individuals with SARI due to SARS-CoV-2 were children. As discussed in other studies, the prevalence of asymptomatic COVID-19 in children is likely to be underestimated.[17,18]

The most common symptom presented in period *A* was cough, reported by 95% of patients, followed by fever (91%). In period *B*, dyspnea and O_2 saturation <95% were the most common symptoms, corroborating other findings in Brazil.[19] Fever and cough are the most common symptoms in cases of RV infection, however dyspnea and low O_2 saturation are criteria for classification of SARI.[2] Therefore, the COVID-19 pandemic clearly caused an increase in cases of SARI.

Individuals with comorbidities such as cardiovascular disease and chronic respiratory diseases, and with other risk factors such as smoking, pregnancy and immunosuppression, are more susceptible to severity in case of respiratory viral infection.[1,4,6,20] In the present study, the most common comorbidities in period *A* were respiratory diseases (asthma, lung diseases and other chronic lung diseases), with 58% of the patients having at least

one of these comorbidities. In period *B*, the most common comorbidities were chronic cardiovascular disease, diabetes and obesity (present in 60.7%, 44.9% and 28.1% of the patients, respectively). The findings of the present study corroborate previous studies reporting chronic cardiovascular disease as the most common comorbidity associated with COVID-19, also being a risk factor for adverse prognosis.[20-22]

In period *A*, the percentage of individuals with a given comorbidity was similar among the SARI cases regardless of the viral type; in contrast, the most common comorbidities observed in period *B* were mainly in individuals infected by SARS-CoV-2. This might have contributed for a higher fatality in period *B* compared to period *A* (37% and 6.7%, respectively), considering that patients with some comorbidities are more susceptible to developing severe COVID-19.[15,20-24]

Positive cases for IAV/IBV, hPIV-1, hPIV-2, hPIV-3, HAdV and RSV viruses decreased significantly after the emergence of SARS-CoV-2, corroborating findings of another study in RS.[8,10] Studies conducted in other countries also found a decrease in the circulation of other respiratory viruses during the first months of the COVID-19 pandemic, which has been attributed to the effectiveness of the public health measures adopted to reduce SARS-CoV-2 transmission.[9,25]

This study analyzed data from the epidemiological surveillance of respiratory infection in Brazil. Prior to 2020, surveillance of respiratory viruses in Brazil, and globally, primarily focusing on detecting influenza viruses. This limited the ability to comprehensively analyze the epidemiology of other RVs and also hindered the identification of co-infection cases and their interactions.[2,13,16] The COVID-19 pandemic demanded health management and diagnosis efforts to control the spread of SARS-CoV-2, posing even more limitations to detection of other RVs in period *B*.[2,16] The fact that this study was based on the analysis of a few respiratory viruses and missed many cases of co-infections represents a limitation of the study and reinforces the need of a continuous surveillance of respiratory viruses for control and prevention of epidemics. Despite these limitations, the findings presented herein are important to support policies and guidelines for the continuous surveillance of different RVs along the year, to better plan prevention strategies according to viral seasonality and circulation.

In addition to actions aimed at preventing viral infections, it is crucial to strengthen the diagnostic and epidemiological structure to improve monitoring and control of RV in RS, including genomic surveillance, which provides information about circulating viral strains and even strains that might emerge in the region.[26-28] To achieve this, public policies and health planning and management actions need to be aligned with the population's needs. This would allow for greater accessibility to viral detection tests for suspected cases, along with the implementation of organized and standardized data recording systems.

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AUTHORS CONTRIBUTIONS

Fernanda P. S. Carpeggiani: data analysis and interpretation; writing the draft; writing the manuscript. **Thiago Menezes Cézar:** data analysis and interpretation; description of results; preparation of tables; writing the draft. **Tatiana Schäffer Gregianini:** concept of the study; collection of samples and molecular analyses in the laboratory; reviewing the manuscript. **Felipe Grillo Pinheiro:** statistical analysis and interpretation of results; writing the draft. **Letícia Garay Martins:** data acquisition. **Ana Beatriz Gorini da Veiga:** study design; project administration and acquisition of funds; data analysis; reviewing draft and writing the manuscript.

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ORIGINAL ARTICLE

Analysis of leprosy cases in the state of Pará between 2001 and 2020

Análise dos casos de hanseníase no estado do Pará entre 2001 e 2020

Análisis de los casos de lepra en el estado de Pará entre 2001 y 2020

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ABSTRACT

Background and Objectives: leprosy is a mycobacteriosis known for centuries and prevalent to this day and, despite the reduction in the number of cases, it still affects many Brazilians. To this end, this study aimed to assess the clinical forms of leprosy in the state of Pará between 2001 and 2020. **Methods:** an ecological study was carried out using data from the Notifiable Diseases Information System (SINAN) of patients with leprosy according to three classifications, such as notified clinical form, notified operational classification and notified degree of disability, collected between 2001 and 2020. **Results:** the milder forms of leprosy showed a greater decrease than the more severe form, combined with a greater drop in cases in the paucibacillary class compared to the multibacillary classification. Furthermore, grade zero disability showed a large reduction in cases, in contrast to grades one and two, which remained stationary. **Conclusion:** despite the evident decrease in leprosy in the state, the most serious forms of the disease, which are related to higher levels of disability and transmission, showed little reduction.

Keywords: *Leprosy. Health Information Systems. Epidemiology. Paucibacillary Leprosy. Multibacillary Leprosy.*

RESUMO

Justificativa e Objetivos: a hanseníase é uma micobacteriose conhecida há séculos e prevalente até os dias atuais e, apesar da diminuição dos números de casos, ainda atinge diversos brasileiros. Para tanto, este estudo tem como objetivo avaliar as formas clínicas da hanseníase no estado do Pará entre 2001 e 2020. **Métodos:** foi realizado estudo ecológico a partir de dados do Sistema de Informação de Agravos de Notificação (SINAN) de pacientes com hanseníase de acordo com três classificações, como forma clínica notificada, classificação operacional notificada, e grau de incapacidade notificado, coletados entre os anos de 2001 e 2020. **Resultados:** as formas mais brandas da hanseníase tiveram um decrescimento maior do que a forma mais grave, aliado a uma maior queda dos casos da classe paucibacilar em comparação com a classificação multibacilar. Além disso, o grau zero de incapacidade apresentou

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grande redução dos casos, em contraste aos graus um e dois, que se mantiveram estacionários. **Conclusão:** apesar do decréscimo evidente da hanseníase no estado, as formas mais graves da doença, que estão relacionadas a maiores níveis de incapacidade e transmissão, apresentaram pouca redução.

Descritores: *Hanseníase. Sistemas de Informação em Saúde. Epidemiologia. Hanseníase Paucibacilar. Hanseníase Multibacilar.*

RESUMEN

Justificación y Objetivos: la lepra es una micobacteriosis conocida desde hace siglos y prevalente hasta el día de hoy y, a pesar de la reducción del número de casos, todavía afecta a muchos brasileños. Para ello, este estudio tiene como objetivo evaluar las formas clínicas de lepra en el estado de Pará entre 2001 y 2020. **Métodos:** se realizó un estudio ecológico utilizando datos del Sistema de Información de Enfermedades de Declaración Obligatoria (SINAN) de pacientes con lepra según tres clasificaciones, tales como forma clínica notificada, clasificación operativa notificada y grado de invalidez notificado, recopiladas entre 2001 y 2020. **Resultados:** las formas más leves de lepra tuvieron una disminución mayor que la forma más grave, combinado con una mayor caída de casos en la clase paucibacilar, en comparación con la clasificación multibacilar. Además, la discapacidad de grado cero mostró una gran reducción de casos, en contraste con los grados uno y dos, que se mantuvieron estacionarios. **Conclusiones:** a pesar de la evidente disminución de la lepra en el estado, las formas más graves de la enfermedad, que se relacionan con mayores niveles de discapacidad y transmisión, mostraron poca reducción.

Palabras Clave: *Lepra. Sistemas de Información en Salud. Epidemiología. Lepra Paucibacilar. Lepra Multibacilar.*

INTRODUCTION

Leprosy is an infectious disease caused by the etiological agent *Mycobacterium leprae*, which mainly affects the skin and peripheral nerves, causing deformities and morphofunctional disabilities with relevant social, emotional and psychological repercussions for individuals affected by the pathology. In Brazil, it presents itself as an endemic, neglected disease, with unequal distribution linked to the condition of poverty, which maintains this ancient disease as a public health concern, especially in the North, Northeast and Midwest regions.[1-4]

Despite these general characteristics, leprosy has different clinical forms that are classified according to paucibacillary (PB) (presence of a low number of bacilli and lesions on the skin) and multibacillary (MB) characters (presence of a high number of bacilli and lesions on the skin), according to the Monitoring and Evaluation Guide, published by the World Health Organization. Within the spectrum of PB clinical forms, the initial type of the disease is indeterminate leprosy, characterized by hypochromic or erythematous-hypochromic macules, without variations in relief, with poorly defined limits and decreased local sensitivity (hypoesthesia). There is also the tuberculoid form at a milder end, characterized by skin lesions in plaques with well-defined, elevated, papular edges and recurrent hypoesthesia. There are MB forms, which can be moderate, such as dimorphic leprosy, which is characterized by a variable clinical presentation, with symptoms ranging from the mildest to the most severe. Finally, at the most serious end, there is Virchowian leprosy, with a high bacterial load, in which individuals present dry, red skin, papules, nodules, madarosis, cramps, tingling and loss of sensitivity.[2,5-6]

A diagnosis of leprosy can be made based mainly on clinical criteria, analyzing the presence of the main signs and symptoms characteristic of the disease, such as loss of local sensitivity, total or partial hair loss, presence of spots, papules and nodules. Furthermore, there may be a need to perform a histopathological and bacilloscopic examination, when clinical examinations alone do not make it possible to determine a final diagnosis. This exam consists of an intradermal scraping, used as a complement, to analyze cases of PB and MB leprosy. In this exam, the presence of bacilli in the tissue sample is verified, provided that *Mycobacterium leprae* is present in the sample, which may result in a positive sputum smear microscopy, common in MB types, whereas the opposite is characteristic of the PB form, with a negative smear microscopy.[2]

After diagnosing leprosy, it is necessary to assess patients' degree of disability, based on some criteria, based on the Eyes, Hands, Feet (EHF) score. In general, this assessment must be carried out at the time of diagnosis and after patients progress to cure. The final score is calculated from the sum of the grades of disability attributed to the right and left segments of EHF, varying on a scale from 0 (no loss of disability) to 12 (the highest grade of impairment of patients). This assessment makes it possible to analyze the loss of protective sensitivity as a consequence of a possible neural injury and serve as an epidemiological indicator used to assess the leprosy surveillance program in the country.[2]

In Brazil, many healthcare professionals have little periodic training for managing and diagnosing the different forms of leprosy. Thus, even with the availability of these complementary tests, the correlation of results

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with observed clinical signs becomes nonspecific and subjective, generalizing the diagnosis and classifying the type of disease only when there are very evident signs. Therefore, there is a need to understand the clinical forms of leprosy, which is an essential factor in the effective intervention of health actions to combat the progression and transmission of the disease in northern Brazil. Therefore, this study aims to assess the evolution of clinical forms of leprosy in the state of Pará between 2001 and 2020, with the purpose of presenting relevant information on the subject to the scientific community and healthcare professionals. Furthermore, the aim is to verify the prevalence of the disease, comparing its temporal progression with that of other locations, in addition to interpreting and indicating the implications that result from the epidemiological overview found in that state.[2,7] Therefore, this work is justified by the need to analyze the persistence of leprosy in its most serious forms in the state of Pará, which are related to higher levels of disability and transmission.

METHODS

This is an ecological study that used data made available by the Brazilian Health System Information Technology Department (DATASUS - *Departamento de Informática do Sistema Único de Saúde*) and e-SUS Primary Care (e-SUS AB - *e-SUS Atenção Básica*) in the category of the Notifiable Diseases Information System (SINAN - *Sistema de Informação de Agravos de Notificação*). The study was carried out in the state of Pará, which has a population of 8,074 million inhabitants and is 1,248,000 km² in length. New cases of patients reported with a diagnosis of leprosy in this state between 2001 and 2020 were considered.

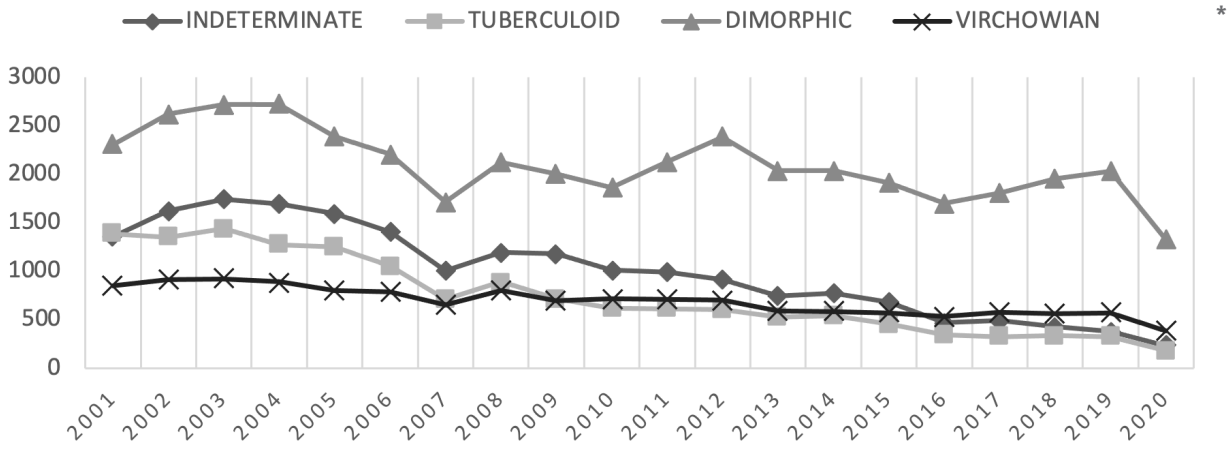
The data collected in DATASUS were acquired following the tabs "Health Information (Tabnet)", "Epidemiological and morbidity", in the group "Tuberculosis Cases "Leprosy Cases - since 2001 (Sinan)", with geographic coverage being the state of Pará. On the Tabnet 3.0 page, notified cases of leprosy were collected according to the municipality of residence, according to classifications: notified clinical form; notified operational classification; and notified degree of disability. As an inclusion criterion, cases reported and tabulated by date of diagnosis in the state of Pará that were diagnosed in 2001 and 2020 were used. As an exclusion criterion, the elimination of incomplete notifications was adopted.

Data were extracted in July 2022 and grouped in Excel 2016® software. After extraction, the data were analyzed by IBM SPSS Statistics 21® software, using the simple linear regression model, expressed in R^2, which means how much the dependent variable (number of cases) is explained by the independent variable (year of notification), with the maximum being 1, the highest association, and the minimum 0, the lowest association between the variables. In addition, the percentage variation (Δ) was calculated, calculated from the equation (*Final value −Initial value/Initial value*) *x* 100, which means, in percentage, the change in the number of cases between the years assessed. Only results with a p-value > 0.05 were considered significant, ensuring high statistical reliability. This criterion ensures that conclusions based on the results are robust and representative of the study population. To better visualize the data, Excel 2016® was used to create the graphs.

As it is information in the public domain, the study was not submitted for assessment by the Research Ethics Committee (REC), in accordance with CNS Resolution 510 of 2016, article 2, VI.

RESULTS

From 2001 to 2020, 99,205 cases of leprosy were recorded in Pará. The highest frequency was recorded in 2003 (n= 7,053), and the lowest, in 2020 (n = 2,277). The results indicated a decrease over the years in the detection rate of the disease, with a greater decrease in the indeterminate (R^2= 0.92; Δ= -0.83) and tuberculoid (R^2= 0.93; Δ= -0 .87) clinical forms instead of the dimorphic (R^2= 0.52; Δ= -0.42) and Virchowian (R^2= 0.87; Δ= -0.55) forms, which showed a smaller drop in the period, as indicated in Figure 1.



** p < 0.05*
Source: own elaboration.

Figure 1. New cases of leprosy according to clinical form in the state of Pará from 2001 to 2020.

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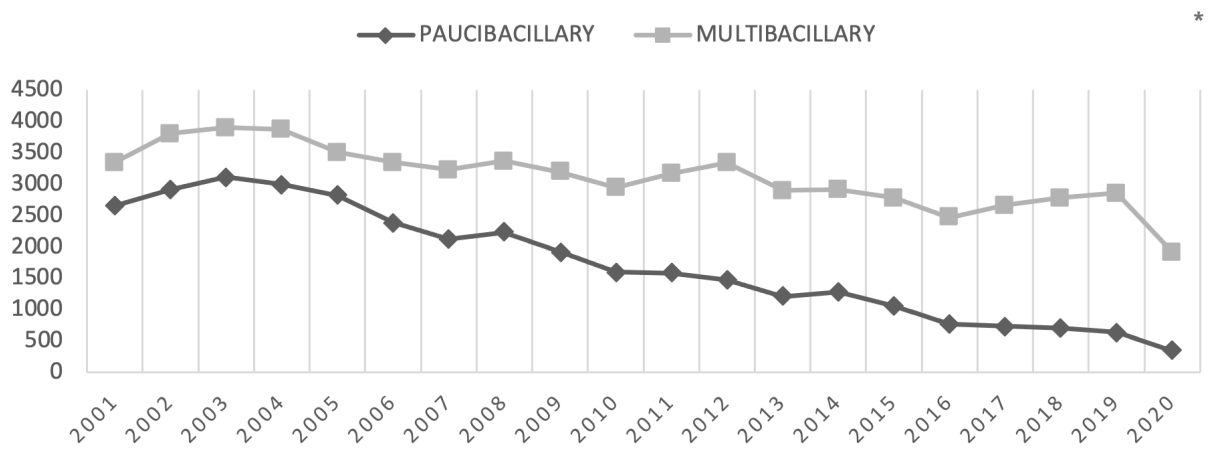
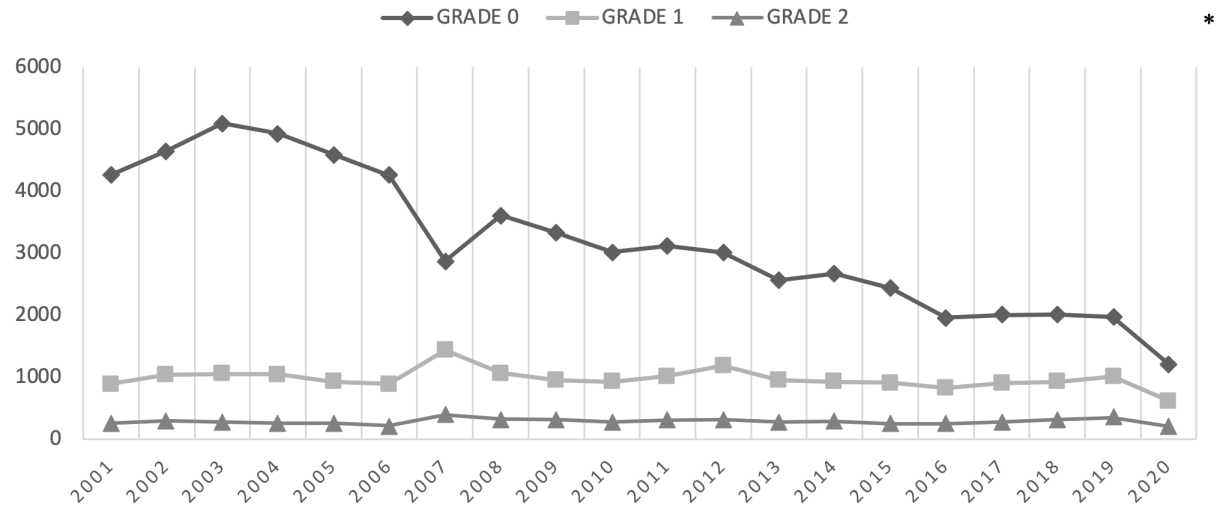


** p < 0.05*
Source: own elaboration.

Figure 2. New cases of leprosy according to the operational classification in the state of Pará from 2001 to 2020.



** p < 0.05*
Source: own elaboration.

Figure 3. New cases of leprosy according to the degree of disability in the state of Pará from 2021 to 2020.

As for distribution according to operational classification, the annual numbers of MB cases were higher than those of PB throughout the assessed period. Furthermore, a greater reduction was identified in PB form (R^2= 0.96; Δ= -87%) when compared to MB form (R^2= 0.77; Δ= -43%), although both modalities have a decreasing incidence, as seen in Figure 2. In relation to the grade of disability assessed, grade zero was the most prevalent and also had the greatest decline (R^2= 0.90; Δ= -72%); however, grades one and two showed inconsistent values and were not considered significant as they resulted in a p > 0.05, and were therefore considered stationary. These findings were summarized in Figure 3.

DISCUSSION

The drop in detection of new cases of leprosy in Pará, during the time interval assessed, suggests a reduction in the dimensions and strength of this endemic. This projection was also confirmed in studies carried out in the municipality of Sobral-CE and in the states of Alagoas, Amapá, Tocantins and Goiás, covering the last two decades. These indices are important for continuous monitoring of the elimination of leprosy as a public health concern; however, they should not be used in isolation, and need to be accompanied by other indicators, such as the number of cases in children under 15 years of age, to avoid possible misinterpretations, especially in endemic regions.[8-13]

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In this context, due to the long incubation period and the difficult control of leprosy, reduced detection may result in a lack of adequate diagnosis, which ideally should be early, with a comprehensive patient assessment, recording degree of disability (measured at zero, one or two), the operational (PB or MB) and clinical (indetermined, tuberculoid, dimorphic or Virchowian) types of the disease, and should encourage the active search for those infected, through analysis of the affected person's household and social contacts. Such measures are useful indicators to estimate the veracity of reported statistical data and, thus, better direct regional actions towards the correct management of the endemic. However, measures do not occur effectively in Brazil, allowing an increase in hidden prevalence, especially at home, late diagnosis, psychosocial impacts and active transmission of the disease, in addition to the lack of surveillance and continuing health education that qualifies professionals about leprosy.[8,10]

Decreases or increases in new recorded cases may be related to the various operational conditions of healthcare services, such as changes in management, professional turnover, decrease or increase in active search, presence or absence of specific projects and protocols for surveillance, among others. This information is proven in other studies. As an example, the project "Innovative Approaches to Intensify Efforts for a Leprosy-Free Brazil" was indicated as justification for the increase in the notification of new cases in Brazil in 2017 and 2018, as it trained Primary Healthcare professionals to diagnose, treat and prevent the disease.[8,10]

The study also concluded that leprosy case records in the general population of Tocantins were boosted between 2003 and 2008 due to the municipalization of disease control actions in this state, which increased the effectiveness of notification coverage by health programs. Furthermore, other research has highlighted the importance attributed to the Family Health Strategy in controlling and reducing the incidence of leprosy, with an important role in strategic planning, training and coordination of health teams in surveillance actions, by valuing diagnosis, treatment, monitoring and active search for new infected people.[8,11,12,14,15]

In the present study, the highest frequency was the dimorphic form, with values decreasing sequentially in Virchowian, indeterminate and tuberculoid, but this distribution pattern of the disease was different in other locations. In new cases of leprosy in the microregion of Crateús-CE, between 2001 and 2015, the indeterminate form prevailed (28.93%), then dimorphic (22.48%), and then tuberculoid, with 18.57%, and Virchowian, with 14.56%, noting that 15.44% of cases were not classified in clinical terms. In a spatio-temporal distribution of leprosy in the city of Belém-PA from 2006 to 2015, the most frequent clinical forms were dimorphic (39.56%), tuberculoid (26.17%) and Virchowian (21.42%), with a lower incidence in the indeterminate form.[14,15]

In relation to operational classification, in this study, the incidence of MB cases was higher and had a smaller decrease than that of PB. This reveals the vulnerability in controlling the disease, supporting the hidden prevalence, late diagnosis and contagion by leprosy in Pará, due to the active transmission chain linked to the MB form, which, by promoting a greater bacillary load in the dermis and mucous membranes, represents the most infectious, debilitating and segregating leprosy pattern. This slow reduction in severe forms demonstrates limitations in Primary Healthcare services, which should mitigate leprosy. In this regard, the precariousness in monitoring transmission is a major obstacle to controlling the disease, as there are failures in notifications and in filling out medical records, making it difficult to break the transmission cycle through early diagnosis and treatment. Late diagnosis also limits the epidemiological slowdown, with the active search for patients being a fundamental combat strategy, through examination of all contacts of the diagnosed case, especially those within households.[16-19]

This epidemiological configuration of MB sovereignty was also mentioned in investigations carried out in several locations: the proportions of MB remained higher and constant in Amapá between 2005 and 2018, but had significant growth in the municipalities of Sobral-CE, between 2001 and 2016, Ribeirão Preto- SP, between 2006 and 2016, and Aracaju-SE, between 2003 and 2017. There was also an increase in the microregion of Crateús-CE, between 2001 and 2015, as well as in the states of Tocantins, between 2001 and 2012, and Paraíba, between 2008 and 2012. This entire situation proves the sustained infection that prevails in Brazil, which is disguise by reducing notifications of the disease.[8,10,11,14,16,19]

The predominance of MB forms may also result in poor reporting of PB forms, as these represent less of a concern for the population when seeking healthcare services, except when accompanied by disabilities or leprosy reactions. Thus, the sudden reduction in the count of milder clinical forms (indeterminate and tuberculoid) tends to express less concern about the initial stages of the disease. The present study does not exclude such a possibility, since, in fact, there was a significant decrease in the registration of PB forms (Δ= -0.87) during the time interval investigated. Furthermore, the SARS-CoV-2 pandemic may have interfered with the 2020 numbers, as there was a general drop in notifiable diseases in the North, including leprosy, which saw a reduction in all states. Thus, two possible effects of the pandemic on the disease are suggested: reduction in contagion, due to restriction of human contact; population's difficulty in accessing healthcare services, which would result in greater underreporting.[19,20]

The greater presence of dimorphic and Virchowian clinical forms and the MB operational classification as well as their lower rates of reduction expresses concern regarding physical damage and neural involvement. A study carried out in a university hospital in northeastern Brazil, with 73 participants, showed that these more serious forms have a greater potential to cause grade one physical disabilities, related to reduced sensitivity in EHF. In this study, they were also the only ones that caused

grade two physical disability, related to visible deformities and motor deficiencies in these same organs.[21]

The present study assessed the progression of clinical forms of leprosy between 2001 and 2020 in Pará. The linear regression analysis allowed us to observe the total reduction of all clinical forms of leprosy in the period, noting a greater reduction in indetermined and tuberculoid clinical forms, accompanied by a greater reduction in cases identified as PB. The clinical forms considered more serious, such as dimorphic and Virchowian, showed a smaller downward trend, as did smear microscopies, identified as MB, concluding that the most contagious groups that cause more harm to patients remain in vogue in the state.

A limitation of this study is using secondary data, which is subject to underreporting or incorrect completion of notification forms, which may compromise the obtaining of reliable data. Finally, it is urgent to encourage community access to health information, in order to avoid a progression in the rate of infections. Hence, adequate management of affected people, combined with appropriate public knowledge about leprosy contagion, prevention, symptoms and treatment, is essential for early detection and combating the disease.

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AUTHORS' CONTRIBUTIONS

Lyncoln Eduardo Alves Silva contributed to study conception and design, as well as bibliographical research, writing the discussion and conclusion, interpreting and describing the results, drawing up conclusions, critical review of content, translation of abstract into English and Spanish, choice and translation of the five descriptors according to DeCS (Bireme Health Science Descriptors), and formatting of full text and references according to RECI standards - Journal of epidemiology and infection control. **Ewerton Lima da Silva** contributed to writing the summary, review and statistics. **Dyana Melkys Borges da Silva** collaborated in preparing the abstract, reviewing, statistical analysis and correcting the text. **João Claudio Paes Magno** contributed to project administration, bibliographic research, writing the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics. **Amanda Araujo Pereira** contributed to the bibliographical research, writing the introduction and critical review of content. **Athos Costa Pedroza** contributed to writing the introduction, objectives and formatting of references, critical review of content and bibliographical research.

All authors 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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Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

ORIGINAL ARTICLE

Musculoskeletal symptoms in Primary Health Care professionals

Sintomas osteomusculares em profissionais da Atenção Primária à Saúde

Síntomas musculoesqueléticos en profesionales de Atención Primaria de Salud

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ABSTRACT

Background and Objectives: musculoskeletal diseases affect the musculoskeletal system and have multifactorial causes, with a higher risk of developing in some work activities. This study aimed to analyze the occurrence of musculoskeletal symptoms in Primary Health Care professionals. **Methods**: a comparative study among healthcare professionals from two municipalities. A structured questionnaire containing sociodemographic and professional variables and the Nordic Musculoskeletal Questionnaire were applied. **Results:** a total of 429 healthcare professionals have participated; 85 (19.8%) from municipality A and 344 (80.2%) from municipality B. There was no difference in the percentage of professionals with musculoskeletal symptoms between the municipalities (p>0.05). The main pain complaints in the last 12 months were for the lumbar region (56.2%), neck/cervical (48.4%), shoulders (44.7%), back/thoracic region (35.3%) and ankles/foot (31.7%). The lowest rates of pain complaints were for elbows (10.5%) and forearms (14.6%). In the last 12 months, 203 (48.7%) professionals avoided their daily activities of working, at-home service or leisure/pastime due to musculoskeletal problems/symptoms. **Conclusion:** Primary Health Care professionals from the studied municipalities reported main complaints of musculoskeletal symptoms, in the last 12 months, in the lumbar region, neck/cervical, shoulders, dorsal/thoracic region and ankles/foot. The regions with the fewest complaint rates were elbows and forearms. There were no significant differences in the number of professionals with complaints of musculoskeletal symptoms between the municipalities. This study provides new knowledge by contributing with information that can guide the planning and implementation of actions to promote health and prevent musculoskeletal disorders in Primary Health Care workers.

Keywords: *Cumulative Trauma Disorders. Prevalence. Healthcare Personnel. Primary Health Care. Family Health Strategy.*

RESUMO

Justificativa e Objetivo: as doenças osteomusculares afetam o sistema osteomuscular e possuem causas multifatoriais, com maior risco de desenvolvimento em algumas atividades laborais. Este estudo objetivou analisar

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a ocorrência de sintomas osteomusculares em profissionais da Atenção Primária à Saúde. **Métodos:** estudo comparativo entre profissionais de saúde de dois municípios. Foi aplicado um questionário estruturado contendo variáveis sociodemográficas e profissionais, e o Questionário Nórdico de Sintomas Osteomusculares. **Resultados:** participaram 429 profissionais, sendo 85 (19.8%) do município de pequeno porte e 344 (80,2%) do município de grande porte. Não houve diferença nos porcentuais de profissionais com sintomas osteomusculares entre os municípios (p>0,05). As principais queixas de dor, nos últimos 12 meses, foram para a região lombar (56,2%), pescoço/cervical (48,4%), ombros (44,7%), região dorsal/torácica (35,3%) e tornozelos/pés (31,7%). Os menores índices de queixas de dor foram para os cotovelos (10,5%) e antebraços (14,6%). Nos últimos 12 meses, 203 (48,7%) profissionais evitaram as atividades diárias de trabalho, serviço doméstico ou lazer/passatempo, em decorrência de problemas/sintomas osteomusculares. **Conclusão**: os profissionais da Atenção Primária à Saúde relataram queixas de sintomas osteomusculares, nos últimos 12 meses, na região lombar, no pescoço/cervical, ombros, região dorsal/torácica e tornozelos/pés. As regiões com menores queixas foram os cotovelos e antebraços. Não houve diferenças significativas do número de profissionais com queixas de sintomas osteomusculares entre os municípios. O estudo agrega novos conhecimentos, ao contribuir com informações capazes de direcionar o planejamento e a implementação de ações de promoção da saúde e prevenção de lesões osteomusculares nos trabalhadores da Atenção Primária à Saúde.

Descritores: *Transtornos Traumáticos Cumulativos. Prevalência. Pessoal de Saúde. Atenção Primária à Saúde. Estratégia Saúde da Família.*

RESUMEN

Justificación y Objetivos: las enfermedades musculoesqueléticas afectan al sistema musculoesquelético y tienen causas multifactoriales, con un mayor riesgo de desarrollarse en algunas actividades laborales. Este estudio tuvo como objetivo analizar la aparición de síntomas musculoesqueléticos en profesionales de Atención Primaria de Salud. **Métodos**: un estudio comparativo entre profesionales de la salud de dos municipios. Se aplicó un cuestionario estructurado que contiene variables sociodemográficas y profesionales, y el Cuestionario Nórdico de Síntomas Musculoesqueléticos. **Resultados**: participaron 429 profesionales; 85 (19.8%) del municipio A y 344 (80,2%) del municipio B. No hubo diferencias en el porcentaje de profesionales con síntomas musculoesqueléticos entre los municipios (p>0,05). Las mayores quejas de dolor, en los últimos 12 meses, fueron para la región lumbar (56,2%), el cuello/cervical (48,4%), los hombros (44,7%), la espalda/región torácica (35,3%) y los tobillos/pies (31,7%). Las tasas más bajas de quejas de dolor se dieron en los codos (10,5%) y los antebrazos (14,6%). En los últimos 12 meses, 203 (48,7%) profesionales evitaron las actividades diarias de trabajo, servicio doméstico u ocio/pasatiempo debido a problemas/síntomas musculoesqueléticos. **Conclusión:** los profesionales de la Atención Primaria de Salud de los municipios estudiados relatan las mayores quejas de síntomas osteomusculares, en los últimos 12 meses, en la región lumbar, cuello/región cervical, hombros, región dorsal/torácica y tobillos/pies. Las regiones con menos quejas fueron los codos y los antebrazos. No hubo diferencias significativas en el número de profesionales con quejas de síntomas musculoesqueléticos entre los municipios. El estudio añade nuevos conocimientos al contribuir con información capaz de dirigir la planificación y la implementación de acciones para promover la salud y prevenir los trastornos musculoesqueléticos en los trabajadores de la Atención Primaria de Salud.

Palabras Clave: *Trastornos Traumáticos Acumulativos. Prevalencia. Personal de Salud. Atención Primaria de Salud. Estrategia de Salud Familiar.*

INTRODUCTION

The Brazilian National Primary Care Policy (PNAB - *Política Nacional de Atenção Básica*) establishes that Primary Health Care (PHC) or Primary Care (PC) is considered the first level of care, and encompasses individual and collective health actions, focused on the "promotion and protection of health, disease prevention, diagnosis, treatment, rehabilitation and health maintenance".[1]

In PHC services, the overload of worker activities to guarantee assistance based on care that is more articulated to the context of people's lives adds to the traditional occupational risks in the health field (chemical, physical, ergonomic and biological).[2] In this context, healthcare professionals' routine, which is normally tiring, becomes even more intense, leading workers to experience situations of pain, distress, illnesses and deaths in their work routine. Therefore, professionals can develop Burnout syndrome, characterized by physical and emotional signs and symptoms, which have implications for their health and can trigger mental illness and physical musculoskeletal problems.[2,3]

Musculoskeletal disorders are injuries that affect healthcare professionals, in the performance of their duties, as a consequence of movements and efforts to which they are subjected during the performance of their duties, especially those that require repetitiveness or continued efforts. Above all, they occur due to the im-

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position of positions that are not recommended on the body and that require spinal torsion, taking it away from the center of balance of the muscular system and causing strong pressure and twisting in its fibers. As a result of these efforts, more than one symptom may appear, characterizing musculoskeletal disorders.[2-4]

These disorders involve disorders of tendons, nerves, synovium (joint linings), ligaments, muscles and fascia (muscle envelope), in isolation or in combination, with tissue degeneration possible, and are associated with pain and paresthesia. These morbidities can also be defined as repetitive strain injuries (RSI), musculoskeletal disorders (MSD) and cumulative trauma injuries (CTI), generally affecting the upper limbs, the scapular region around the shoulder and the cervical region, causing tendinitis, low back pain, neck pain and back pain. They can also affect the lower limbs and are often responsible for temporary or permanent work disabilities.[2,5]

Musculoskeletal morbidities are among the main occupational diseases arising from the industrialization process. It is believed that this condition is among the main public health problems, causing several negative impacts on the social and economic environment of a country. In general, the symptoms gradually develop and, when they are noticed, they are already systematically installed, leading to loss of productivity and compromising workers' production capacity, who begin to present high rates of absenteeism.[2,6-7]

Healthcare professionals are very vulnerable and subject to musculoskeletal disorders, due to the high workload and lack of effort that goes beyond the work activity itself. Added to this is the lack of specific training to perform the role, incorrect physical postures, inappropriate lifting, repetitive movements and other issues related to body postures.[2,7-8]

Therefore, the work process and the work environment have a strong influence on the process of musculoskeletal illness in healthcare professionals, who perform repetitive activities and under overload conditions, capable of causing irreversible physical injuries.[2-3,9] In this context, this study aimed to analyze the occurrence of musculoskeletal symptoms in PHC professionals.

METHODS

This is a cross-sectional study, carried out in two municipalities in the state of São Paulo, with a non-probabilistic, convenience sample, which included 429 professionals from the Basic Health Units teams.

The first municipality (municipality A) is located in western state, 596 km from the capital, São Paulo. It is a small municipality, with a population of 33,707 inhabitants. The municipality is a reference center in health for municipalities in the *Nova Alta Paulista* region. When structuring the local health model, during the study period, PHC was carried out by four Basic Health Units, with ten Family Health teams and coverage of 100% of the municipality's population.[10]

The second municipality (municipality B) is in northwestern São Paulo, 452 km from the capital. It is a large municipality, with an estimated population of 438,354 inhabitants. The municipality is the headquarters of Regional Health Division XV, the largest in the state of São Paulo, in addition to being a reference in healthcare.[11]

During the study period, the municipality had a restructuring of its geographic division and began to be organized into ten health regions (previously there were five health regions), according to Decree 18,073 of June 29, 2018. PHC was responsible for 27 municipal services, three of which were Basic Health Units with teams from the Community Health Workers Strategy (EACS) and 24 Basic Health Units that comprised 58 Family Health teams and 21 Oral Health teams, responsible for covering 61.2% of the municipality's population.[12]

The study population was made up of all professionals who made up the minimum team of the Family Health Strategy (doctors, nurses, nursing assistants/technicians, community health workers), including professionals from oral health teams (dentists and dental assistants), from all Basic Health Units in both municipalities. This choice aimed to equate the professionals assessed in both municipalities. Professionals who were on vacation during the data collection period and/or away from professional activities for any other reason were excluded.

Data were collected in the first half of 2018 using two self-administered instruments: the first was a questionnaire containing closed questions about training, age, sex, marital status, income, education, type of employment (Consolidation of Labor Laws (CLT - *Consolidação das Leis do Trabalho*), statutory), type of care unit/service, if has other employment relationships, practice physical activity, smoke/drink, if is satisfied and/or if has thought about giving up the profession/function, if has been away in the last year (reasons and number of times); the second was the Nordic Musculoskeletal Questionnaire (NMQ), translated and adapted into Portuguese, which allowed assessing symptoms of work-related musculoskeletal disorders (WMSD) and their relationship with musculoskeletal morbidity, demographic and occupational variables and personal habits. This questionnaire is simple to apply, and the Portuguese version was validated in Brazil.[13] The NMQ contains two parts. The first has a human figure divided into nine anatomical regions, such as cervical, shoulders, arms, elbows, forearm, wrists/hands/fingers, dorsal region, lumbar region, hips/lower limbs. Participants identify, on this body map, the presence of pain, discomfort or numbness in the indicated regions, during the last 12 months. For symptomatic regions, participants indicate whether or not the symptoms are related to the work they perform.

Data collection was previously scheduled with nurses and managers of health units and carried out, preferably, during team meeting. After presenting the study to professionals from the team(s) and collecting signature on the Informed Consent Form, the researchers delivered the questionnaires to professionals, who were able to answer them immediately or within a week. After answering, the professionals delivered the questionnaires

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to the unit managers in sealed, unmarked envelopes. After receiving the completed instruments, managers contacted the researchers to collect the questionnaires.

The data obtained was stored in a database, using a Microsoft Excel® spreadsheet. Analysis was performed with Statistical Package for the Social Sciences (SPSS) version 23.0.

Sociodemographic and professional variables were used to characterize the study population. To assess the symptoms of musculoskeletal disorders, initially, the NMQ answers were categorized into occurrence and non-occurrence of musculoskeletal symptoms in the last 12 months. Different body parts were considered (neck/cervical, shoulders, dorsal/thoracic, lumbar, elbows, forearms, wrists/hands/fingers, hips/thighs, knees and ankles/feet). Then, the answers were grouped by body regions, considering the upper trunk (neck/cervical and dorsal/thoracic), lower trunk (lumbar region), upper limbs (shoulders, elbows, forearms, wrists/hands/ fingers) and lower limbs (hips/thighs, knees, ankles/feet). Finally, the answers were grouped considering body parts (neck/cervical, shoulders, back/thoracic, lumbar, elbows, forearms, wrists/hands/fingers, hips/thighs, knees and ankles/feet) to assess whether, during the last 12 months, professionals had to avoid daily activities (work, domestic service or leisure/hobby) due to musculoskeletal problems/symptoms. Comparisons were made using the chi-square test, considering a significance level of 5% ($p \leq 0.05$).

This study is part of a matrix project entitled "*Qualidade de vida, engagement, comprometimento e entrincheiramento com a carreira, estresse, estratégias de enfrentamento e queixas de distúrbios osteomusculares entre trabalhadores da Atenção Básica*". In compliance with current ethical aspects regarding research involving human beings (Resolutions 466/2012 and 510/2016 of the Ministry of Health), the project was approved by the *Faculdade de Medicina de São José do Rio Preto* (FAMERP) Research Ethics Committee on December 4, 2017, under Opinion 2,412,726 and Certificate of Presentation for Ethical Consideration (CAAE - *Certificado de Apresentação para Apreciação Ética*) 59604116.0.0000.5415.

RESULTS

The sample was defined by convenience and consisted of 429 professionals who answered the instruments, 85 (19.8%) from municipality A and 344 (80.2%) from municipality B. Among the professionals assessed, 41 (9.6%) were doctors, 92 (21.4%), nurses, 25 (5.8%), dentists, 83 (19.3%), nursing assistants/technicians, 177 (41.3%), community health workers, and 11 (2.6%), oral care assistants. Figure 1 shows the distribution of study professionals according to municipality and professional category. Professionals' mean age was 42.6 years, ranging from 20.9 to 75.4 years.

As shown in Table 1, there was a predominance of female professionals (79.7%), married (63.4%), aged between 36 and 50 years (42.9%), with a 40-hour work-

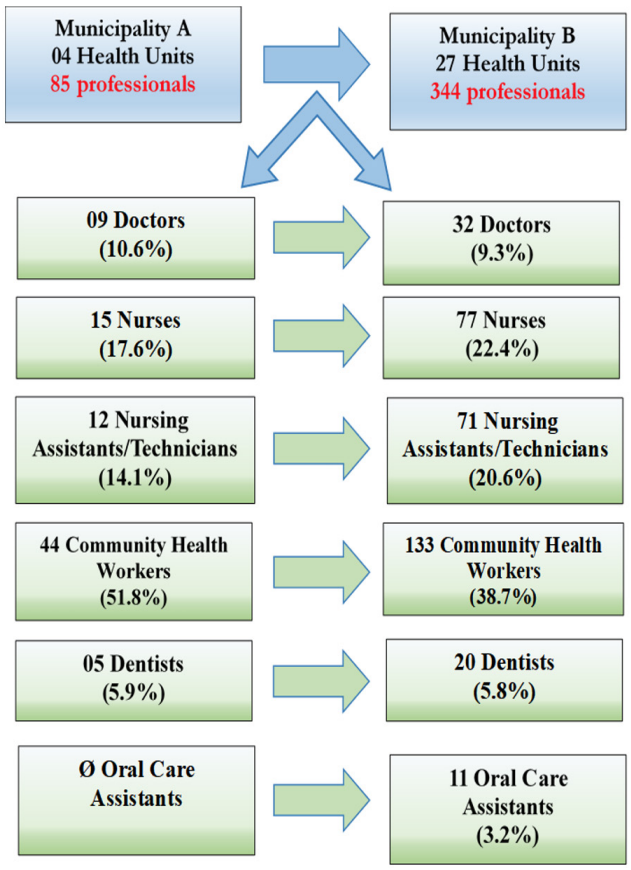

Figure 1. Study sample distribution.

ing day weekly (87.6%) and family income of two to five minimum wages (59.9%). It was observed that 34.7% of professionals were overweight; 60.4% did not practice physical activity; 60.1% had leisure activities; 80.7% had no other paid activity; and 79.7% slept six to eight hours a night. In relation to the length of professional experience, it is noteworthy that 40.3% of professionals had worked for five years or more in PHC services.

The results did not show statistically significant differences in the percentages of professionals with musculoskeletal symptoms between the municipalities (Table 2). It was observed that the main complaints of pain, in the last 12 months, involved the lumbar region (56.2%), neck/cervical (48.4%), shoulders (44.7%), dorsal/thoracic region (35.3%) and ankles/feet (31.7%). The lowest rates of pain complaints were for elbows (10.5%) and forearms (14.6%).

In municipality A, there was a slightly higher percentage of professionals complaining of musculoskeletal pain than in municipality B, but without statistical significance (Figure 2).

Table 3 shows that 203 (48.7%) professionals reported that, in the last 12 months, they had to avoid daily work, domestic service or leisure/hobby activities due to musculoskeletal problems/symptoms.

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Table 1. Distribution of sociodemographic and professional characteristics of Primary Health Care workers assessed in the study

Variables	Municipality A n (%)	Municipality B n (%)	Total n (%)
Total	**85 (100.0)**	**344 (100.0)**	**429 (100.0)**
Sex			
Male	23 (27.1)	60 (17.4)	83 (19.3)
Female	61 (71.8)	281 (81.7)	342 (79.7)
Did not answer	1 (1.2)	3 (0.9)	4 (0.9)
Marital status			
Married	51 (60.0)	221 (64.2)	272 (63.4)
Single	28 (32.9)	86 (25.0)	114 (26.6)
Separate	3 (3.5)	28 (8.1)	31 (7.2)
Widow	2 (2.4)	9 (2.6)	11 (2.6)
Did not answer	1 (1.2)	221 (64.2)	1 (0.2)
Age group			
From 21 to 35 years	28 (32.9	90 (26.2)	118 (27.5)
From 36 to 50 years	31 (36.5	153 (44.5)	184 (42.9)
From 51 to 65 years	20 (23.5	86 (25.0)	106 (24.7)
Over 65 years	6 (7.1)	3 (0.9)	3 (0.7)
Did not answer	-	12 (3.5)	18 (4.2)
Weekly workload			
20 hours	6 (7.1)	20 (5.8)	26 (6.1)
30 hours	15 (17.6)	8 (2.3)	23 (5.4)
36 hours	1 (1.2)	-	1 (0.2)
40 hours	62 (72.9)	314 (91.3)	376 (87.6)
Did not answer	1 (1.2)	2 (0.6)	3 (0.7)
Family income*			
Up to a minimum wage	14 (16.5)	23 (6.7)	37 (8.6)
From two to five minimum wages	57 (67.1)	200 (58.1)	257 (59.9)
Six to ten minimum wages	8 (9.4)	66 (19.2)	74 (17.2)
More than ten minimum wages	6 (7.1)	47 (13.7)	53 (12.4)
Did not answer	-	8 (2.3)	8 (1.9)
BMI classification			
Under weight	2 (2.4)	3 (0.9)	5 (1.2)
Normal weight	22 (25.9)	97 (28.2)	119 (27.7)
Overweight	35 (41.2)	114 (33.1)	149 (34.7)
Grade I obesity	14 (16.5)	56 (16.3)	70 (16.3)
Grade II obesity	2 (2.4)	20 (5.8)	22 (5.1)
Grade III obesity	3 (3.5)	6 (1.7)	9 (2.1)
Did not answer	7 (8.2)	48 (14.0)	55 (12.8)
Practices physical activity			
Yes	37 (43.5)	129 (37.5)	166 (38.7)
No	48 (56.5)	211 (61.3)	259 (60.4)
Did not answer	-	4 (1.2)	4 (0.9)
Has leisure activities			
Yes	55 (64.8)	205 (59.6)	258 (60.1)
No	28 (32.9)	132 (38.4)	160 (37.3)
Did not answer	2 (2.4)	7 (2.1)	11 (2.6)
Daily hours of sleep			
Less than six hours	14 (16.5)	64 (18.6)	78 (18.2)
Between six and eight hours	70 (82.4)	272 (79.1)	342 (79.7)
More than eight hours	-	5 (1.5)	5 (1.2)
Did not answer	1 (1.2)	3 (0.9)	4 (.9)
Length of experience in PHC			
Less than two years	21 (24.7)	126 (36.6)	147 (34.3)
From two to five years	30 (35.3)	61 (17.7)	91 (21.2)
Between five and ten years	12 (14.1)	69 (20.1)	81 (18.9)
More than ten years	20 (23.5)	72 (20.9)	92 (21.4)
Did not answer	2 (2.4)	16 (4.7)	18 (4.2)
Has another paid activity			
Yes	21 (24.7)	54 (15.7)	75 (17.5)
No	64 (75.3)	282 (82.0)	346 (80.7)
Did not answer	-	8 (2.3)	8 (1.9)

**Minimum wage value: R$937.00; BMI – Body Mass Index; PHC – Primary Health Care.*

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Table 2. Percentage of complaints of musculoskeletal symptoms by body parts among Primary Health Care professionals.

Variables	Municipality A n (%)	Municipality B n (%)	Total n (%)	p-value*
Occurrence of musculoskeletal symptoms				
Lumbar region	54 (63.5)	181 (54.4)	235 (56.2)	0.080
Neck/cervical	46 (54.8)	157 (46.9)	203 (48.4)	0.195
Shoulders	40 (47.1)	148 (44.0)	188 (44.7)	0.352
Dorsal/thoracic region	25 (29.8)	121 (36.7)	146 (35.3)	0.146
Ankle/feet	25 (29.8)	115 (34.4)	140 (33.5)	0.249
Knees	27 (32.1)	105 (31.6)	132 (31.7)	0.512
Wrist/hands/fingers	29 (34.5)	92 (27.5)	121 (28.9)	0.127
Hip/thighs	15 (17.9)	56 (17.2)	71 (17.3)	0.498
Forearms	10 (12.0)	51 (15.2)	61 (14.6)	0.294
Elbows	7 (11.0)	37 (8.4)	44 (10.5)	0.320

**Chi-square test.*

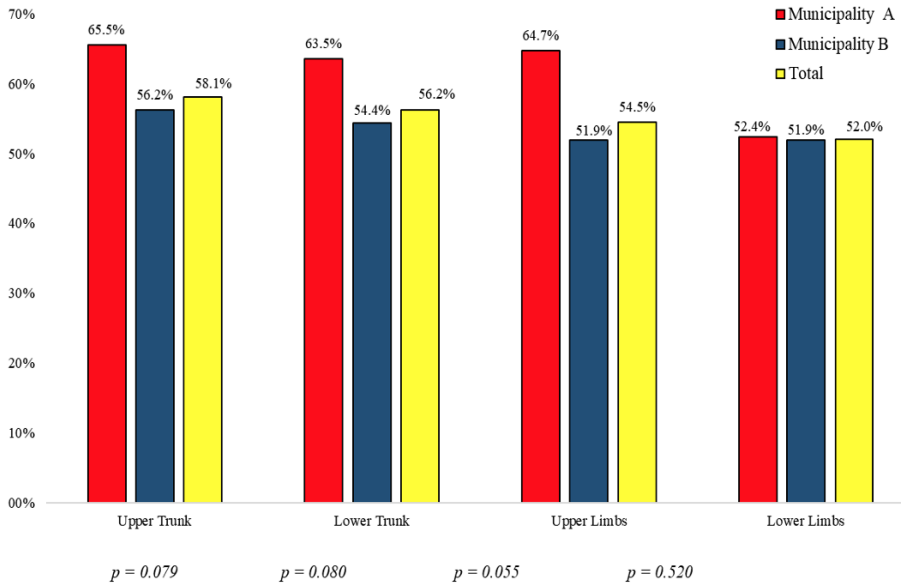

Figure 2. Distribution of percentages of complaints of musculoskeletal symptoms by body regions among Primary Health Care professionals (chi-square test).

Table 3. Distribution of professionals who, in the last 12 months, reported having avoided daily activities due to musculoskeletal symptoms.

	Municipality A	Municipality B	Total	p-value*
Avoided daily activities in the last 12 months				
Yes	43 (51.2)	160 (48.0)	203 (48.7)	0.347
No	41 (48.8)	173 (52.0)	214 (51.3)	

**Chi-square test.*

DISCUSSION

The profile of the participants in this study is consistent with other studies carried out with PHC workers,[2-3,14-16] and the professional structure of the teams complies with PNAB regulations in relation to the composition of the Family Health Strategy minimum teams.[1]

The percentage of PHC professionals with complaints of musculoskeletal symptoms found in this study is much higher than that reported in the Brazilian population, whose prevalence of musculoskeletal diseases is approximately 2.5%.[16] The appearance of these symptoms in healthcare professionals is due to several factors and is generally related to work characteristics, such as strenuous working hours, double employment, inadequate furniture and posture.[2,3]

In the case of community health workers, long

distances covered, often with excessive weight, in strong heat or inadequate postures, are risk factors for the emergence of injuries and musculoskeletal symptoms.[3] Among nursing professionals, doctors and oral healthcare professionals, risk factors for the appearance of musculoskeletal symptoms can be considered: double shift work or night work, common among these professionals; performing repetitive movements; the adoption of inappropriate postures; lack of breaks, due to high demand or demands for productivity; exposure to work stressors, such as lack of training and professional autonomy; and insufficient time to carry out work activities.[17-19]

In addition to work overload and inadequate professional sizing, emotional involvement also leads to dissatisfaction that can cause health problems for team professionals,[20] showing that social and psychological factors can contribute to worsening the clinical condition of workers affected by musculoskeletal injuries/symptoms.[21] A study with Family Health Strategy professionals showed that workers with high levels of perceived stress were more likely to develop musculoskeletal diseases.[22]

The predominance of complaints of musculoskeletal symptoms in the lumbar region, neck/cervical region, shoulders, dorsal/thoracic region and ankles/feet, observed among the PHC professionals studied, is reported in other studies,[2-3,19] showing that the work process in PHC services can cause illness among professionals, compromising the physical conditions of workers, who begin to present musculoskeletal symptoms.

A study with nursing professionals from a Basic Health Unit pointed out heavy loads, postural problems and uncomfortable chairs as the main ergonomic risks for these workers. Lack of foot support and work overload were also indicated as factors associated with the prevalence of musculoskeletal symptoms. The authors associated work overload with a reduction in the quality of care, considering that overworked professionals are not able to offer care in accordance with the time and quality required expected by users.[23]

Another important consequence related to musculoskeletal symptoms is absenteeism or absence from work, which causes discontinuity in care processes and the relationship with the patient, in addition to staff being absent due to frequent leaves of absence. Furthermore, pain makes it difficult to carry out work efficiently, directly affecting the quality of care provided to patients.[20]

The high rates of professionals complaining of musculoskeletal symptoms in the thoracic region support the literature, which indicates the existence of a high role and work overload among healthcare professionals, the consequences of which are the high prevalence of back pain and ergonomic problems.[24] Given this scenario, it is necessary to implement regular training, with programs aimed at worker health and safety and that seek to prevent complications caused by work overload, such as workplace gymnastics, training courses on ergonomic issues at work, implementation of pre-established breaks and weight control programs.[20]

Regular physical activity is seen as a great ally in improving or maintaining professionals' health conditions and quality of life. The inclusion of physical activity practices, such as workplace gymnastics, in the workplace has contributed significantly to improving physical health and the perception of quality of life. Therefore, simple and low-cost measures, such as assessing the level of physical activity and monitoring workers, can contribute to preventing musculoskeletal problems and reducing absenteeism, favoring an increase in work performance and the quality of service provided to the population.[25]

In this context, it is essential that managers monitor and to know their teams, understand their needs and encourage actions to prevent damage (physical and/or mental) professionals, i.e., it is important that they identify factors that lead to imbalances in workers' health and act on them.[20] Encouraging physical activity by PHC workers is an important prevention and health promotion strategy, seeking to minimize or avoid the illness of these healthcare professionals.

This study has limitations related to convenience sampling, which reduces the potential for generalizing the results and restricts the representativeness of the population, and data analysis, which does not allow inferring the existence of a direct relationship between musculoskeletal symptoms and the current work activity of assessed professionals. However, the results contribute important information for planning and implementing actions to promote health and prevent musculoskeletal injuries in PHC workers.

As demonstrated, PHC professionals in the municipalities studied reported complaints of musculoskeletal symptoms, mainly in the lumbar region, neck/cervical region, shoulders, dorsal/thoracic region and ankles/feet in the last 12 months. The regions with the lowest rates of complaints were the elbows and forearms. There was no significant difference in the number of professionals complaining of musculoskeletal symptoms between the municipalities. However, there was a slightly higher percentage of professionals with complaints of musculoskeletal symptoms in the small municipality (municipality A) compared to the large municipality (municipality B). These results show that musculoskeletal symptoms are an important problem for PHC workers' health, since almost half of the professionals studied reported having avoided daily work, domestic service or leisure/hobby activities in the last 12 months, due to musculoskeletal problems/symptoms. For this reason, it is necessary to implement actions to promote PHC workers' health, especially the prevention of work-related injuries and treatment/rehabilitation of professionals suffering from musculoskeletal injuries/complaints.

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AUTHORS' CONTRIBUTIONS

Luciano Garcia Lourenção and **Cláudia Eli Gazetta** contributed to the project design and administration. **Luciano Garcia Lourenção**, **Cláudia Eli Gazetta** and **Fabio Ribeiro da Silva** contributed to writing the manuscript and approving the final version. **Carlos Leonardo Figueiredo Cunha**, **Natália Sperli Geraldes Marin dos Santos Sassaki**, **Vagner Ferreira do Nascimento** and **Daniele Alcalá Pompeo** contributed to the critical review of the manuscript and approval of the final version.

All authors are responsible for all aspects of the work, including ensuring its accuracy and integrity.

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ORIGINAL ARTICLE

Epidemiological profile of leptospirosis in Minas Gerais State, Brazil 2012-2022

Perfil epidemiológico da leptospirose em Minas Gerais, 2012-2022

Perfil epidemiológico de la leptospirosis en el estado de Minas Gerais, Brasil 2012-2022

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ABSTRACT

Justificativa e Objetivos: A D

Background and Objectives: Leptospirosis is an infectious disease caused by the bacterium *Leptospira spp.* and its epidemiology is not well known in Minas Gerais State, which makes its prevention and control more difficult. The objective of this study is to outline the epidemiological profile of leptospirosis in the State of Minas Gerais from 2012 to 2022. **Methods:** An ecological epidemiological study was carried out by collecting data from the Information System for Notifiable Diseases, the secondary database was made available by the Department of Informatics of the Unified Health System. Data regarding the disease cases notified in the selected place and period were collected and descriptive statistical analyses were carried out based on sociodemographic and clinico-epidemiological variables. **Results:** 1,728 cases of leptospirosis were reported. The highest number of notifications was in 2020 and the lowest in 2015. There is a higher occurrence of the disease in the white population (46.30%), in males (81.66%) and in the age group 40 to 59 years (38.77 %). As for education, the highest number of registered cases was ignored/blank, with 814 (47.11%). Observing the evolution of the disease, from 2012 to 2022, the aggravation of leptospirosis leading to death occurred in 9.29% of the cases. Cure was the most frequent outcome: 1,415 discharges in that decade (81.89%). **Conclusion:** Based on the results obtained, we concluded that there is a predominance of male patients, white, aged between 40 and 59 years, in relation to education, the largest number of registered cases was ignored/blank and more than 80% of the cases notified resulted in the recovery of the patient's health.

Keywords: *Leptospirosis. Epidemiology. Public health.*

RESUMO

Justificativa e Objetivos: A leptospirose, doença infecciosa causada pela bactéria *Leptospira spp.*, tem a epidemiologia pouco conhecida em Minas Gerais, o que dificulta sua prevenção e controle. O objetivo deste estudo é traçar

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o perfil epidemiológico da leptospirose no estado de Minas Gerais no período de 2012 a 2022. **Métodos:** Estudo epidemiológico ecológico, realizado pela coleta de dados no Sistema de Informações de Agravos de Notificações, disponibilizado pelo banco de dados secundários do Departamento de Informática do Sistema Único de Saúde. Foram coletados dados referentes aos casos da doença notificados no local e período selecionados e realizadas análises estatísticas descritivas a partir das variáveis sociodemográficas e clínico-epidemiológicas. **Resultados:** Foram notificados 1.728 casos de leptospirose. O maior número de notificações foi em 2020 e menor em 2015. Há maior ocorrência da doença na população branca (46,30%), no sexo masculino (81,66%) e na faixa etária de 40 a 59 anos (38,77%). Observando a evolução da doença, nota-se que, de 2012 a 2022, foram registrados óbitos pelo agravo da leptospirose em 9,29% dos casos. A cura se manteve com maior ocorrência: 1,415 altas nessa década (81,89%). **Conclusão:** Com base nos resultados obtidos conclui-se que há predomínio de pacientes do sexo masculino, raça branca, faixa etária entre 40 e 59 anos e mais de 80% dos casos notificados resultaram na recuperação do quadro de saúde do paciente.

Descritores: *Leptospirose. Epidemiologia. Saúde pública.*

RESUMEN

Justificación y Objetivos: La leptospirosis, una enfermedad infecciosa causada por la bacteria *Leptospira spp.*, tiene su epidemiología poco conocida en el estado de Minas Gerais, lo que dificulta su prevención y control. El objetivo de este estudio es delinear el perfil epidemiológico de la leptospirosis en el estado de Minas Gerais del 2012 al 2022. **Métodos:** Estudio epidemiológico ecológico, realizado a partir de la recolección de datos del Sistema de Información de Enfermedades de Declaración Obligatoria, disponibles en la base de datos secundaria. del Departamento de Informática del Sistema Único de Salud. Se recolectaron datos sobre los casos de la enfermedad notificados en el lugar y período seleccionado y se realizaron análisis estadísticos descriptivos con base en variables sociodemográficas y clínico-epidemiológicas. **Resultados:** Se reportaron 1.728 casos de leptospirosis. El mayor número de notificaciones fue en el 2020 y el menor en el 2015. Hay una mayor ocurrencia de la enfermedad en la población blanca (46,30 %), en el sexo masculino (81,66 %) y en el grupo de edad de 40 a 59 años (38,77 %). En cuanto a la educación, el mayor número de casos registrados fue ignorado/blanco, con 814 (47,11%). Al observar la evolución de la enfermedad, se destaca que, de 2012 a 2022, se registraron 9,29% de muertes por agravamiento de la leptospirosis. La cura quedó con la mayor ocurrencia: 1.415 altas en esa década (81,89%). **Conclusión:** Con base en los resultados obtenidos se concluye que existe predominio de pacientes masculinos, blancos, con edades entre 40 y 59 años, con relación a la escolaridad, el mayor número de casos registrados fue ignorado/blanco y más del 80% de los casos notificados resultó en la recuperación de la salud del paciente.

Palabras Clave: *Leptospirosis. Epidemiología. Salud pública.*

INTRODUCTION

Leptospirosis is an infectious disease caused by *Leptospira spp*. It occurs all over the world, however, it is more common in tropical and subtropical areas.[1] Usually it is transmitted by the urine of infected animals, such as rats, dogs, cattle, and other rodents, which contaminate the water, soil or foods.[2]

Brazil is the country with the highest number of cases in Latin America.[2] Leptospirosis is an important public health problem in Brazil because it finds in the country a favorable environment for its spread, due to geographical factors as well as the population characteristics, in urban and rural areas, and it presents a high epidemic potential.[3] For this reason, leptospirosis is a mandatory notification disease in Brazil since the year 2000 and the surveillance is carried out in the whole country by the Ministry of Health.[2]

But, despite its mandatory notification, the disease is still neglected. It mainly affects vulnerable populations such as rural and urban workers, people living in slums, people who do not have full access to drinking water and basic sanitation. On top of that, there are those cases that occur because of the high volumes of rain during the rainy season, which floods the urban centers and contributes to the transmission of the bacteria.[4]

Low-resource populations in tropical regions, especially in low and middle-income countries, present the highest burden of diseases.[5] Globally, it is estimated that leptospirosis is responsible for 1.03 million cases and 58,900 deaths yearly. In the Americas region, it is estimated that 10,000 cases occur every year, the majority (95%) occurring in Latin America, and Brazil accounts for 40% of the cases notified.[2]

Clinical manifestations of leptospirosis can vary from mild to severe, depending on the inoculum, serovar or strain, as well as the age and the health condition of the individual.[6] The initial symptoms of the disease such as fever, muscle aches and pain, and headache may be unspecific and similar to other diseases. In more severe cases, leptospirosis may cause jaundice, kidney or liver failure, in addition to pulmonary and neurological complications.[7]

Early diagnosis is important to prevent severe

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complications and even death. The diagnosis is based on laboratory tests such as blood tests for the detection of antibodies against *Leptospira spp*., and blood or urine cultures for the identification of the bacteria.[3] Leptospirosis treatment entails the use of antibiotics and other types of support care such as hydration and symptoms control. In severe cases, hospital admission may be necessary.[6]

Despite of the several studies on leptospirosis in Brazil, yet there are gaps about the disease epidemiology focusing specifically determined locations of the country, namely Minas Gerais State, and its behavior over the years. Understanding the dynamics of the disease makes it possible to implement public policies for prevention and control that take into account factors such as population characteristics and socioeconomic conditions from the location, the presence of host animals, and the disease behavior, with the objective of developing effective strategies against leptospirosis.[8]

Therefore, the aim of the present study is to analyze the epidemiological profile of leptospirosis in Minas Gerais State, from 2012 to 2022.

METHODS

This is an ecological epidemiological study. Data from notified cases of leptospirosis in the State of Minas Gerais, in the period between January 2012 and December 2022, were collected. The State comprises an area of 586,13,983 km² and the population is estimated to be 21,411,923 inhabitants.[9]

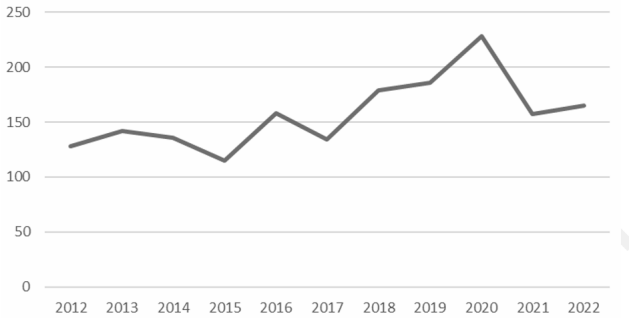
Information about the epidemiological profile of patients was obtained from the Information System for Notifiable Diseases (SINAN), made available by the Ministry of Health. Data was obtained from the notification files filled out by the local health service and stored in the software TABNET, a public domain system, made available by the Department of Informatics of the Unified Health System (DATASUS), which was accessed on the 27th of March, 2023.

After data collection, the following variables were analyzed: sociodemographic (sex, race, age group and schooling), and clinico-epidemiological (notification number and the evolving of the disease). Following, descriptive stratified statistical analyses with a quantitative approach were carried out and presented as proportions and variables frequencies, using the software Microsoft Excel Professional Plus 2021.

This study was conducted using secondary data sources from the Health Surveillance Board from Minas Gerais State, which are of public domain and the individual's identities were not displayed. Therefore, it is not required to be submitted to the Research Ethics Committee, according to the resolution nº 510/16 of the Brazilian National Health Council (2016).

RESULTS

In the period between 2012 and 2022, 1,728 cases of leptospirosis were registered in Minas Gerais State. The highest number of cases occurred in 2020, 228 cases, and the lowest number of cases occurred in 2015, 115 cases. From 2012 to 2020 a trend of increase in the cases was observed. After the peak, there was a decrease in the years 2021 and 2022 (figure 1).



Source: Ministry of Health/Sanitary Surveillance Secretariat - Information System for Notifiable Diseases - Sinan Net.

Figure 1. Cases confirmed in the Information System for Notifiable Diseases (SINAN) in Minas Gerais State, 2012-2022 (n= 1,728).

Table 1. Sociodemographic and clinical characteristics of the confirmed cases of leptospirosis in Minas Gerais State, 2012-2022 (n=1,728).

Characteristics	N=1,728	%
Race/Skin color		
Ignored/Blank	163	9.43%
White	800	46.30%
Black	118	6.83%
Yellow/Asian	7	0.41%
Brown/mixed	638	36.92%
Indigenous	2	0.12%
Sex		
Male	1,411	81.66%
Female	317	18.34%
Age group		
Ignored/blank	1	0.06%
<1 year	4	0.23%
01-4	1	0.06%
05-9	19	1.10%
10-14	44	2.55%
15-19	92	5.32%
20-39	660	38.19%
40-59	670	38.77%
60-64	93	5.38%
65-69	70	4.05%
70-79	65	3.76%
80 e +	9	0.52%
Outcome		
Ignored/blank	128	7.41%
Cure	1,415	81.89%
Death caused by the disease notified	159	9.20%
Death by another cause	26	1.50%

Source: Ministry of Health/Sanitary Surveillance Secretariat - Information System for Notifiable Diseases - Sinan Net.

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The racial profile of the cases notified presented white people as the most affected group, with 800 cases (46.3%). The most frequent occurrence of leptospirosis was among male patients, 1,411 (81.66%) cases, and when we assessed the patients diagnosed with the disease by age group, 40 to 59 years of age was the most frequent group with 670 (38.77%) patients. As for the evolving of the disease, in the majority of the cases, 1,415 (81.89%), the outcome was cure (table 1).

DISCUSSION

From the analysis of DATASUS platform, we observed a total of 1,728 cases of leptospirosis notified between the years 2012 and 2022 in Minas Gerais State. In 2020 there was a peak of notifications, 228 cases of the disease, and in 2015 the lowest number of cases of leptospirosis for the period was notified (115 cases). It was observed that after the increase in the number cases that occurred up until the year 2020, there was a decrease in the period 2021-2022. It can be a result of the sub-notifications that occurred during the COVID-19 pandemic period, and from repeated infection of the most exposed population to the etiologic agent – people living in flooded areas, lack of basic sanitation and/or areas with garbage accumulation – which can acquire immunity to the disease due to milder presentation of the disease.[10]

Leptospirosis is considered a mimetic disease, in other words, this disease, in its milder form, is harder to diagnose because it is similar to other illnesses such as dengue fever, bacterial sepsis and malaria. The signs and symptoms of leptospirosis can vary from a limited and mild fever to many organs malfunction, which can cause death. Most of the cases do not evolve to any complications, only around 10% do. Weil's syndrome is an example of a complication of leptospirosis, which is characterized by acute renal damage, jaundice, and conjunctival suffusion. In addition to that, another common cause of death by this infection is pulmonary haemorrhage.[3]

Leptospirosis is a disease which major risk factor is related to floods and inundation, and because of that, in years with higher volumes of rainfall there is a higher occurrence of epidemic outbreaks of human leptospirosis. The State of Minas Gerais is characterized by these occurrences due to its geographic location.[11] In 2020, the high number of cases detected in the Southeastern region of Brazil can be justified by the intensification of the South Atlantic convergence zone with the sub-tropical cyclone Kurumí above the Atlantic ocean, which boosted the humidity in the whole region[12], demonstrating that there is a need for natural disasters monitoring and alert as a support to the public health management. The drop in the notifications in the years 2021 and 2022 can be explained by the COVID-19 pandemic and the mobilization to tackle it, which prioritized COVID-19 to the detriment of diseases with a lower incidence, such as leptospirosis. This factor impacted on the detection of the disease, caused sub-notification and worsened the clinical outcomes.[13]

Brazil has the highest number of leptospirosis cases among the Latin American countries.[14] That is due to the hot and humid climate of countries located in the tropical and sub-tropical regions, which fosters the survival of the bacteria, as well as the intense rainfall regime found, mainly in the Southeastern region, which favours the transmission of leptospirosis because it causes floods and inundation in the area.[15] For that reason, it is important to outline the epidemiological profile of the disease in the country, mainly in the regions where there are gaps in the tracking of the disease, basic infrastructure and neglect – namely Minas Gerais State – in order to implement public policies to prevent and fight the disease, once it is a highly prevalent disease related to climate, socioenvironmental and socioeconomic factors.[16]

As for the ethnic profile of the population from Minas Gerais State that was affected by the disease, 800 (46.3%) cases occurred in white people, followed by 638 (36.92%) cases that occurred in brown/mixed, 163 (9.43%) were ignored/blank, 118 (6.83%) in black people, 7 (0.40%) in yellow/Asian, and 2 (0.11%) cases in indigenous people.

Regarding gender, a higher number of cases was reported in male, 1,411 (81.66%) cases, whist 317 (18.34%) in females. For this parameter, there is no difference in the susceptibility to the disease, once infection can occur in both genders when they are exposed to the same infectious sources equally. However, men usually are more exposed due to the type of work performed such as work in areas with inundation, plantations and places with garbage accumulation, and consequently, present a higher risk of being affected by leptospirosis.[17]

With respect to the age group of patients diagnosed with leptospirosis, we observed that 4 (0.23%) cases reported were under one year of age, 20 (1.16%) were from 1 to 9 years old, 136 (7.87%) cases were from 10 to 19 years old, 660 (38.19%) from 20 to 39 years old, 670 (38.77%) from 40 to 59 years old, 228 (13.19%) from 60 to 79 years old, 9 (0,52%) cases were 80 or older, and ignored/blank 1 (0.06%). The highest number of cases occurred within the age group 40 to 59 years old, which shows that this age group is more likely to be exposed to the disease's risk factors, such as crowded and flooded spaces, than children and the elderly.[18]

As for schooling, in the majority of the cases, 814 (47.11%), the information was ignored/blank, followed by completed high school for 222 (12.85%) cases, and from 5th to incomplete 8th grade of elementary school for 164 (9.49%). The high number of missing information may be related to errors in the filling out of the patient's notification files or the sending of inadequate records in the system, making the information unavailable.[19] In addition, less schooling may contribute to a poor understanding of prevention methods and the adoption of unhealthy practices, such as the inadequate accumulation of materials that should be forwarded to recycling, and garbage.[20]

Regarding the evolving of leptospirosis illness, from 2012 to 2022, 159 (9.29%) deaths by the complications of the disease were registered, and 2016 was the year with the highest number of deaths. Cure was the most frequent outcome with 1,415 (81.89%) patients discharged

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during the decade. The low number of deaths when compared to the cure occurs due to the early and appropriate diagnosis of the disease in its early stages, slowing down its progression.[21] Furthermore, the appropriate treatment with penicillin G benzathine, ampicillin, and ceftriaxone is another factor that contributes to the high cure rates.[22]

Although the disease presents a low fatality rate due to the early diagnosis and correct treatment, it cause high costs to the public health sector with medication and hospital stays, mainly because it affects the lower income populations more frequently, once they are more exposed to precarious living conditions and sanitation.[23]

Thus, leptospirosis is an endemic infectious and contagious disease, mainly associated to the rainfall regimes, floods and inundation.[24] In addition to that, disease outbreaks are attached to social and living conditions, basic sanitation, rodent infestation, and floods.[25] In this perspective, transmission is boosted by socioenvironmental vulnerability, once the infection occurs by direct or indirect contact with the urine of contaminated animals and is facilitated by the hydric component.[26]

Thus, it is necessary to maintain the disease under control and to increase the effectiveness of early diagnoses, and for that, it is important to adopt preventive and health promotion measures in order to assure the decrease in the transmission and health loss.[27]

The present study outlined the epidemiological profile and mapped leptospirosis in the State of Minas Gerais, from 2012 to 2022, despite of the typical limitations of an ecological study, namely the availability and quality of data.

The study results pointed out that the resources used provided an epidemiological panorama of leptospirosis cases in the State of Minas Gerais, and they can be an useful tool for the healthcare professionals to rethink their practices and direct more investments in this area of knowledge, in addition to create an opportunity to public managers to plan preventive strategies specific to this population.

To delineate the epidemiological profile of leptospirosis cases in the State of Minas Gerais is very important because this is a region with favorable climate and sociogeographic conditions to the disease, also, it is a location where there are gaps in studies about the epidemiology of leptospirosis and its characterization over the years.

Hence, it is necessary to understand the disease dynamics, in order to make possible the implementation of public measures for its prevention and control, taking into account factors such as population characteristics and the socioeconomic conditions of the location, so that more effective strategies against leptospirosis can be developed.

In accordance to the study results, we concluded that among the leptospirosis cases in the State of Minas Gerais, from 2012 to 2022, there is a predominance of male patients, white, from 40 to 59 years old. In the period of the study, 1,728 cases of leptospirosis were notified, and more than 80% resulted in the full recovery of patient's health status.

As demonstrated above, the objective of the study was achieved by the use of quantitative analyses, making possible to follow the number of cases and sociodemographic and clinico-epidemiological variables, which may contribute to the development of public policies for the reduction and prevention of the disease, which requires strategies for health education together with the development of infrastructure.

We highlight that studies using public domain databases can minimize the costs and time, and at the same time constitute reliable sources for research and organization of public services and policies.

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AUTHOR'S CONTRIBUTION

Fernanda Carvalho Camargos Vieira, Yanca Cristina Parreira e Karina Raasch Jacobsen contributed to the conception and design of the study and writing of the manuscript. **Letícia Lima da Silva, Nathany Martello Eich e Leonardo Augusto Ferraz** contributed to the conception of the study, data analysis and interpretation, and writing of the manuscript. **Guilherme de Andrade Ruela** contributed to the planning and design of the study, review and final approval of the manuscript.

All authors approved the final version of the manuscript to be published and are responsible foe all aspects of the study, including the assurance of its precision and integrity.

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ORIGINAL ARTICLE

Staphylococcus aureus: changes in antimicrobial sensitivity profile and its relationship with SCC*mec* among clinical isolates

Staphylococcus aureus: alterações no perfil de sensibilidade antimicrobiana e sua relação com SCCmec entre isolados clínicos

Staphylococcus aureus: cambios en el perfil de sensibilidad antimicrobiana y su relación con SCCmec entre aislados clínicos

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ABSTRACT

Background and Objectives: *Staphylococcus aureus* is a pathogen of great clinical relevance, especially those resistant to methicillin, called MRSA. Over the years, *S. aureus* antimicrobial resistance patterns have changed. Understanding such changes is essential to update protocols and propose efficient therapeutic approaches. This study aimed to characterize the temporal distribution of *S. aureus* antimicrobial resistance in patients admitted to the hospital as well as to assess its relationship with SCC*mec* typing. **Methods:** a total of 9,949 cultures of clinical materials were analyzed, between January 2000 and October 2019, from patients admitted to a university hospital in southern Brazil. All isolates had their identification and antimicrobial sensitivity profile analyzed using manual and automated techniques. Furthermore, 86 isolates were selected for *mec*A gene research and SCC*mec* typing using conventional and multiplex PCR techniques, respectively. **Results**: when assessing the temporal distribution of *S. aureus* over 20 years, it was possible to observe a drop in the proportion of MRSA compared to methicillin-sensitive *S. aureus* (MSSA). Between 2000 and 2002, the frequency of MRSA was 58.5%, whereas that of MSSA was 36.7%. However, from 2003 onwards, there was a reversal of these percentages. At the end of the analyzed period, 55.2% of infections were caused by MSSA, whereas 36.2% contained MRSA isolates. Furthermore, in the period analyzed, the highest prevalence was of SCC*mec* type II. **Conclusion**: these data suggest an epidemiological change in *S. aureus* from clinical materials, with a change in the prevalent type of SCC*mec* and changes in the antimicrobial sensitivity profile exhibited by the isolates. Such facts must be considered by the clinical staff with a focus on effective patient management, the choice of appropriate antimicrobial therapy so that effective infection control measures are implemented.

Keywords*: S. aureus. Clinical Epidemiology. MRSA. MSSA.*

RESUMO

Justificativa e Objetivos: *Staphylococcus aureus* é um patógeno de grande relevância clínica, especialmente aqueles resistentes à meticilina, denominados MRSA. Ao longo dos anos, os padrões de resistência antimicrobiana dos *S. aureus* têm apresentado modificações. Compreender tais mudanças é fundamental para atualizar protocolos e propor abordagens terapêuticas eficientes. O objetivo do estudo foi caracterizar a distribuição temporal da resistência antimicrobiana de *S. aureus* proveniente de pacientes internados no hospital, bem como avaliar sua relação com a tipagem SCC*mec*. **Métodos**: foram analisadas 9.949 culturas de materiais clínicos, entre janeiro de 2000 e outubro de 2019, de pacientes internados em um hospital universitário no sul do Brasil. Todos os isolados tiveram sua identificação e perfil de sensibilidade aos antimicrobianos analisados por técnicas manuais e automatizadas. Ainda, 86 isolados foram selecionados para a realização da pesquisa do gene *mec*A e tipagem SCC*mec*, utilizando a técnica de PCR convencional e multiplex, respectivamente. **Resultados:** avaliando a distribuição temporal dos *S. aureus* ao longo de 20 anos, foi possível observar queda na proporção de MRSA em comparação com o *S. aureus* sensível à meticilina (MSSA). Entre 2000 e 2002, a frequência de MRSA foi de 58,5%, enquanto que a de MSSA foi de 36,7%. No entanto, a partir de 2003, houve uma inversão desses percentuais. Ao final do período analisado, 55,2% das infecções foram ocasionadas por MSSA, enquanto que 36,2% continham isolados de MRSA. Ainda, no período analisado, a prevalência maior foi do SCC*mec* tipo II. **Conclusão**: esses dados sugerem uma alteração epidemiológica em *S. aureus* provenientes de materiais clínicos, com alteração do tipo SCC*mec* prevalente e modificações do perfil de sensibilidade aos antimicrobianos exibidos pelos isolados. Tais fatos devem ser considerados pelo corpo clínico, focando para que haja um manejo efetivo dos pacientes, escolha da terapia antimicrobiana adequada e para que medidas de efetivas de controle de infecção sejam implementadas.

Descritores*: S. aureus. Epidemiologia Clínica. MRSA. MSSA.*

RESUMEN

Justificación y Objetivos: *Staphylococcus aureus* es un patógeno de gran relevancia clínica, especialmente los resistentes a meticilina, denominado MRSA. Con el paso de los años, los patrones de resistencia a los antimicrobianos de *S. aureus* han cambiado. Comprender tales cambios es esencial para actualizar los protocolos y proponer enfoques terapéuticos eficientes. El objetivo del estudio fue caracterizar la distribución temporal de la resistencia antimicrobiana de *S. aureus* en pacientes ingresados en el hospital, así como evaluar su relación con la tipificación de SCC*mec*. **Métodos:** se analizaron 9.949 cultivos de materiales clínicos, entre enero de 2000 y octubre de 2019, de pacientes ingresados en un hospital universitario del sur de Brasil. Se analizó la identificación y el perfil de sensibilidad antimicrobiana de todos los aislados mediante técnicas manuales y automatizadas. Además, se seleccionaron 86 aislados para la investigación del gen *mec*A y la tipificación de SCC*mec*, utilizando técnicas de PCR convencional y múltiple, respectivamente. **Resultados**: al evaluar la distribución temporal de *S. aureus* durante 20 años, fue posible observar una caída en la proporción de MRSA en comparación con *S. aureus* sensible a meticilina (MSSA). Entre 2000 y 2002, la frecuencia de MRSA fue del 58,5%, mientras que la de MSSA fue del 36,7%. Sin embargo, a partir de 2003, se produjo una reversión de estos porcentajes. Al final del período analizado, el 55,2% de las infecciones fueron causadas por MSSA, mientras que el 36,2% contenía aislados de MRSA. Además, en el período analizado, la mayor prevalencia fue de SCC*mec* tipo II. **Conclusión:** estos datos sugieren un cambio epidemiológico en *S. aureus* a partir de materiales clínicos, con un cambio en el tipo prevalente de SCC*mec* y cambios en el perfil de sensibilidad antimicrobiana exhibido por los aislados. El personal clínico debe considerar estos hechos, centrándose en el tratamiento eficaz del paciente, la elección del tratamiento antimicrobiano adecuado y la implementación de medidas eficaces de control de infecciones.

Palabras Clave*: S. aureus. Epidemiología Clínica. MRSA. MSSA.*

INTRODUCTION

Staphylococcus aureus is a versatile pathogen, present in a wide variety of infections. These can be localized, both in soft tissues and in systemic infections, such as bacteremia. Due to the high potential to acquire antimicrobial resistance genes and high number of virulence factors, *S. aureus* has been prominent as a causative agent of infection in both hospital and community settings.[1]

Among *S. aureus* isolates, those with methicillin resistance (Methicillin-Resistant *S. aureus* - MRSA) are the one that, so far, are prevalent in infectious processes. Methicillin resistance occurs by the acquisition of the *mec*A gene, located in a mobile genetic element called the Staphylococcal Chromosome Cassette *mec* (SCC*mec*), which encodes a Penicillin-Binding Protein (PBP) with low affinity for beta-lactams called PBP2a.[2]

Multicenter studies have shown that the frequency and epidemiology of *S. aureus* has currently been changing in several geographic regions. Allied to this fact, MRSA isolates, commonly found in community settings, and called community-acquired Methicillin-resistant *S.*

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aureus (CA-MRSA), have been described in hospital settings. Similarly, isolates described as Hospital-Acquired Methicillin-resistant *S. aureus* (HA-MRSA) have been found in community settings. This interchange and emergence of infections caused by CA-MRSA and HA-MRSA has significantly altered therapeutic management.[3,4,5]

MRSA isolates, related to nosocomial infections, have often been described as multidrug resistant, i.e., besides to beta-lactam resistance, they are resistant to several other classes of antimicrobial agents, including macrolides, lincosamines, fluoroquinolones and aminoglycosides. In addition to the characteristic resistance profile, these isolates usually contain SCC*mec* elements types I, II or III. CA-MRSA, on the other hand, is routinely described as susceptible to most non-beta-lactam antimicrobial agents and carriers of SCC*mec* types IV and V.[6]

In Brazil, there are few data on the molecular epidemiology of MRSA and its relationship to antimicrobial susceptibility. Therefore, this study aimed to assess the distribution of *S. aureus* from these infections over the last 20 years according to antimicrobial resistance patterns and to establish a relationship with the SCC*mec* types circulating in a hospital in southern Brazil.

METHODS

A retrospective, observational, cross-sectional study was carried out with patients from a 431-bed Sentinel Network tertiary university hospital located in southern Brazil.

From January 2000 to October 2019, 9,949 cultures of blood, skin and soft tissues, bone fragments, respiratory secretions, cavitary fluids, urine, among others, positive for *S. aureus*, were assessed using the AGTA Healthcare Information System database, LABHOS® module, of the microbiology sector of the hospital's clinical analysis laboratory.

The identification of all isolates, as well as their antimicrobial sensitivity profile, and Minimum Inhibitory Concentration (MIC), according to Clinical & Laboratory Standard Institute (CLSI), was performed using the MicroScan WalkAway® (Beckman Coulter), Phoenix® (Becton, Dickinson) or Vitek2® (bioMérieux- Durham, NC, USA) automated systems, according to the study period, following the manufacturer's guidelines.

Vancomycin's MIC, for *S. aureus*, was determined by the Etest® method, using plastic strips containing the antimicrobial in a concentration gradient from 0.16 to 256 µg/mL, according to the manufacturer's recommendations.

Isolates that showed a MIC for oxacillin ≥ to 4 µg/mL were designated MRSA, whereas those with a MIC for oxacillin ≤ 2 µg/mL were considered MSSA. Isolates that showed a MIC for benzylpenicillin < 0.12 µg/mL were categorized as PSSA.

After phenotypic analysis, for convenience, 100 *S. aureus* isolates, from clinical materials, previously stored in the bacteria bank of the microbiology department, were selected for molecular testing.

Total DNA was extracted using alkaline method protocol,[7] and the genetic identification of *S. aureus* was confirmed using the coagulase (*coa*) and thermonuclease (*nuc*) genes.[8,9]

The *mec*A gene research as well as the typing of SCC*mec* elements was performed using a multiplex PCR protocol.[10]

MRSA strains type I (NCTC10442), type II (N315), type III (85/2082), type IV (JCSC4744), and type V (WIS) were used as quality control.

The most frequent MIC50 and MIC90 for antimicrobial agents, which correspond to 50 and 90% of the isolates, were calculated and a comparison between MRSA and MSSA was traced. Of the 9,949 isolates, for convenience, 2,904 isolates were selected for data analysis relating to MIC 50 and MIC 90.

Results of MICs for oxacillin, benzylpenicillin, ceftaroline, erythromycin, clindamycin, ciprofloxacin, daptomycin, levofloxacin, prulifloxacin, gentamicin, sulfamethoxazole-trimethoprim, rifampicin, linezolide, fusidic acid, teicoplanin and tigecycline, and for *S. aureus* were assessed by the Vitek2®, MicroScan WalkAway® or Phoenix® systems, depending on period, using panel for gram-positive microorganisms, obtained using the Observa® data management system.

Statistical Package for the Social Sciences (SPSS - IBM Corp., New York, USA) version 20.0 for Windows was used for statistical analysis. MRSA annual trend as well as MSSA prevalence were studied by linear regression using GraphPad Prism v.6.01 (GraphPad Software Inc., La Jolla, CA). Chi-square test was used for categorical variables, and Fishers Exact test, for continuous variables, when appropriate. Value ≤ 0.05 was considered statistically significant.

The study was submitted to the *Universidade Estadual de Londrin*a (CEP/UEL) Research Ethics Committee, under Certificate of Presentation for Ethical Consideration (CAAE - *Certificado de Apresentação para Apreciação* Ética) 78657317.0.0000.5231, The study was approved under Opinion 2.344.065 and respected all the ethical precepts of Resolutions 466/2012, 510/2016 and 580/2018 of the Ministry of Health.

RESULTS

The results of 9,949 cultures positive for *S. aureus*, performed from January 2000 to October 2019, were analyzed. It was found that the frequency of *S. aureus* was higher in male patients (6,128/9,949; 61.6%). About age, there was a range from 0 to 98 years, with a median of 45 years.

As for material collection, *S. aureus* was isolated most frequently in skin and soft tissues (3,392/9,949; 35%), respiratory secretions (1,698/9,949; 17%), and blood (1,575/9,949; 16%). The majority of patients, 6,696/9,949 (67%), were hospitalized, and of these, 23.2% (2,308/9,949) were in Intensive Care Units (ICU). As for the clinical outcome, 79% (7,860/9,949) of patients were discharged from the hospital, whereas 21% (2,089/9,949) eventually died.

The overall resistance to oxacillin was 45% (1,306/2,904), with MIC50 and MIC90 of 0.5 µg/mL and 4.0 µg/mL, respectively. For ceftaroline, although 100% of MSSA isolates were sensitive, 5% (145/2,904) of the MRSA showed resistance (MIC50/90, 1.0/1.0 µg/mL), as shown in Table 1.

Resistance to fluoroquinolones was found ranging from 4% (398/9,949), for ciprofloxacin, and 3% (298/9,949), for levofloxacin, in MSSA isolates, to 85% (8.456/ 9,949) and 89% (8,854/9,949), respectively, for MRSA isolates. However, for prulifloxacin, a new fluoroquinolone, no resistance rates were found.

The macrolide, lincosamine and streptogramin B resistance phenotype (MLSB) was more frequent for MRSA (85% - MIC50/90, 8/8 µg/mL) than for MSSA (30% -MIC50/90, 0.25/0.25 µg/mL).

As for vancomycin, intermediate resistance was seen in 7.5% of MSSA isolates (MIC50/90 1.5/2.0 µg/mL) and in 5% of MRSA isolates (5% - MIC50/90, 1.5/3.0 µg/mL). All isolates were sensitive to linezolid (MIC50/90, 2.0/2.0 µg/mL), daptomycin (MIC50/90, 0.25/1.0 µg/mL) and tigecycline (MIC50/90, 0.12/0.12 µg/mL) (Table 1).

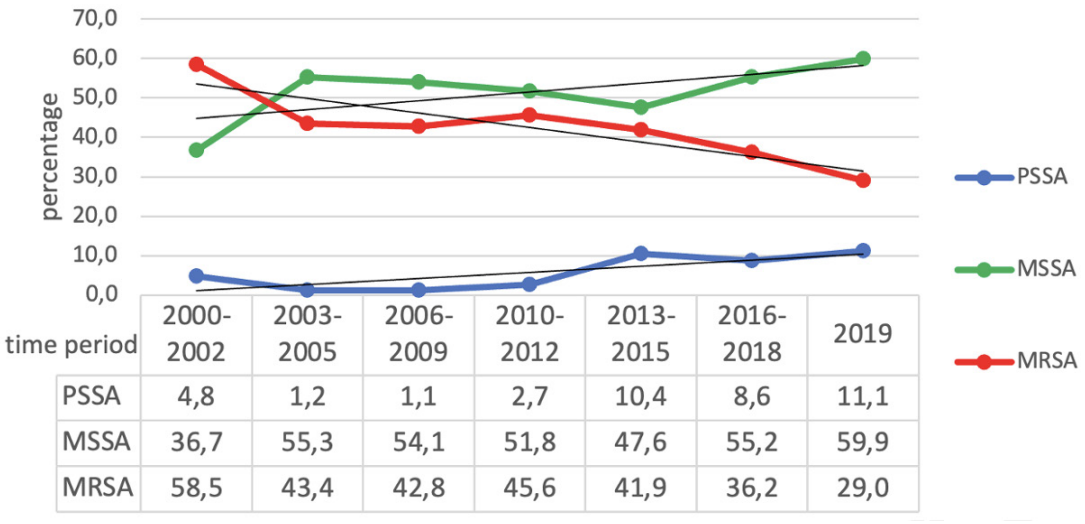
Between 2000 and 2002, a higher percentage of MRSA (58.5%) causing infectious processes was found in MSSA (36.5%). However, starting in 2003, a reversal in the frequency of *S. aureus* with respect to methicillin susceptibility was observed. MSSA infections increased to 59.9% in 2019, whereas those caused by MRSA reduced to 29%. Another important fact was the positive trend of PSSA isolates as promoters of the infectious process, which increased from 4.8% in 2000 to 11.1% in 2019 (Figure 1).

Between 2000 and 2002, a large proportion of isolates (88%) belonged to antibiotypes A and B. However, there was a significant reduction in microorganisms be-

Table 1. Minimum Inhibitory Concentration (MIC50 and MIC90) and percentage of resistance to antimicrobial agents of 2,904 S. *aureus* and vancomycin from 303 isolates identified in a hospital in southern Brazil from March 2012 to October 2019.

	MSSA (1.638)		MSSA (1.266)		
	MIC_{50}/ MIC_{90} (µg/mL)	R (%)	MIC_{50}/MIC_{90} (µg/mL)	R (%)	p-value
Benzylpenicillin	0.5/ 0.5	83	0.5/ 0.5	100	-
Oxacillin	0.25/ 0.5	00	4.0/ 4.0	100	< 0.05
Ceftaroline	0.25/ 0.25	00	1.0/ 1.0	5	< 0.05
Erythromycin	0.25/ 8.0	37	8.0/ 8.0	89	< 0.05
Clindamycin	0.25/ 0.25	30	8.0/ 8.0	85	< 0.05
Ciprofloxacin	0.5/ 0.5	4	8.0/ 8.0	85	< 0.05
Daptomycin	0.25/ 1.0	0	0.25/ 1.0	0	-
Levofloxacin	0.25/ 0.25	3	8.0/ 8.0	89	< 0.05
Prulifloxacin	0.5/ 1.0	0	0.5/ 0.5	0	-
Gentamicin	0.5/ 0.5	1	0.5/ 16.0	14	< 0.05
Rifampicin	0.5/ 0.5	1	0.5/ 0.5	8	< 0.05
Linezolid	2.0/ 2.0	0	2.0/ 2.0	0	-
Tigecycline	0.12/ 0.12	0	0.12/ 0.12	0	-
Fusidic acid	0.5/ 0.5	1	0.5/ 0.5	2	-
Teicoplanin	0.5/ 0.5	3	0.5/ 0.5	8	< 0.05
Sulfamethoxazole/trimethoprim	0.5/ 0.5	3	0.5/ 1.0	10	< 0.05
Vancomycin** (303)	1.5/ 2.0	7.5	1.5/ 3.0	5	-

*Caption: MSSA – methicillin-sensible Staphylococcus aureus; MRSA - methicillin-resistant Staphylococcus aureus; MIC - Minimum Inhibitory Concentration; R - antimicrobial resistance; **Minimum inhibitory concentration assessed by E-test® for 303 isolates.*



time period	2000-2002	2003-2005	2006-2009	2010-2012	2013-2015	2016-2018	2019
PSSA	4,8	1,2	1,1	2,7	10,4	8,6	11,1
MSSA	36,7	55,3	54,1	51,8	47,6	55,2	59,9
MRSA	58,5	43,4	42,8	45,6	41,9	36,2	29,0

Caption: PSSA – penicillin-susceptible Staphylococcus aureus; MSSA – methicillin-susceptible Staphylococcus aureus; MRSA – methicillin-resistant Staphylococcus aureus.

Figure 1. Temporal distribution of beta-lactam resistance for 9,949 *S. aureus* identified in cultures of clinical materials in a hospital in southern Brazil from January 2000 to October 2019.

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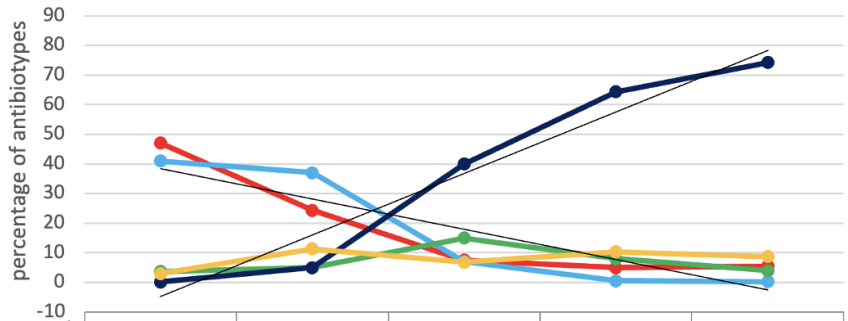
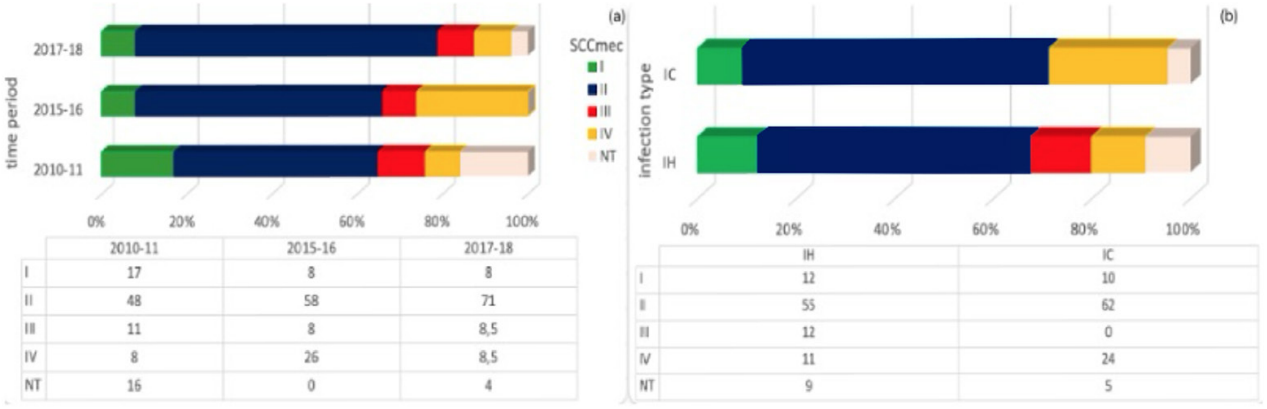


time period	2000-2002	2006-2009	2010-2012	2013-2015	2016-2018
MRSA A	47	24	7,5	5	6
MRSA B	41	37	7,1	0,6	0,3
MRSA C	4	5	15	8	4
MRSA D	0	5	40	64	74
MRSA G	3	11	6,8	10	9

Caption: A - sensitive to tigecycline and linezolid. Resistant to oxacillin, penicillin, erythromycin, clindamycin, ciprofloxacin, gentamicin, sulfamethoxazole–trimethoprim, rifampicin; B - sensitive to tigecycline, linezolid and rifampicin. Resistant to oxacillin, penicillin, erythromycin, clindamycin, ciprofloxacin, gentamicin, sulfamethoxazole–trimethoprim; C - sensitive to tigecycline, linezolid, rifampicin and sulfamethoxazole–trimethoprim. Resistant to oxacillin, penicillin, erythromycin, clindamycin, ciprofloxacin, gentamicin; D - sensitive to tigecycline, linezolid, rifampicin, sulfamethoxazole-trimethoprim, and gentamicin. Resistant to oxacillin, penicillin, erythromycin, ciprofloxacin and clindamycin; G - sensitive to tigecycline, linezolid, rifampicin, sulfamethoxazole-trimethoprim, gentamicin, erythromycin, ciprofloxacin and clindamycin. Resistant to oxacillin and penicillin.

Fugure 2. Temporal distribution of the most frequent antibiotypes for 3,517 clinical MRSA isolates from January 2000 to October 2019.



	2010-11	2015-16	2017-18
I	17	8	8
II	48	58	71
III	11	8	8,5
IV	8	26	8,5
NT	16	0	4

	IH	IC
I	12	10
II	55	62
III	12	0
IV	11	24
NT	9	5

Caption: HI - healthcare-related infection; CI - community-related infection; SCCmec types: I, II, III, IV; NT - non-typeable.

Fugure 3. Temporal distribution of SCCmec types identified among MRSA isolates from skin and soft tissues from January 2010 to May 2018 (a) and SCCmec elements identified among MRSA from healthcare-related infections and from community-acquired infection from January 2010 to May 2018 (b).

longing to these antibiotics, falling to 61% between 2006 and 2009 and just 1.2% in 2019 (Figure 2).

On the other hand, antibiotype D, which had not been identified before 2005, gradually started to increase in 2006, jumping from 5% to 74% in the last period of analyses, between 2016 - 2018. This antibiotype, currently, is the predominant.

Among the isolates selected for molecular analysis, the *mec*A gene was found in 86% (86/100) of assessed isolates. These were typed for SCC*mec* elements. Typing revealed SCC*mec* type II as the most frequent, being described in 48.8% (42/86) of the isolates. SCC*mec* types IV, I and non-typeable isolates were identified at lower frequencies, 13.9% (12/86), 11.6% (10/86) and 8.1% (7/86), respectively.

Comparing the types of SCC*mec* identified among MRSA related to hospital-acquired and community-acquired infections, type II was found to be the most frequent in both groups, with 36/65 (55.3%) and 13/21 (61.9%), respectively. The percentage of isolates with SCC*mec* type IV was higher in the group of community-origin infections (5/21; 23.8%) than in the group of hospital-origin infections (7/65; 10.7%). On the other hand, the proportions of SCC*mec* type I were very similar in both, community-origin infections (2/21; 9.5%) and hospital-origin infections (8/65; 12.3%).

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SCC*mec* type III was identified only in isolates from patients with hospital-origin infection (8/65; 12.3%) (Figure 3).

When assessing the distribution of identified SCC*mec* types over time, it is possible to see an upward trend in the frequency of isolates with cassette type II from 17/36 (48%) in the first period (2010-2011) to 15/26 (58%) in the second (2015-2016) and to 17/24 (71%) in the third (2017-2018) (Figure 3).

However, there was a decrease in the frequency of isolates carrying SCC*mec* type I from 16.6% (6/36), between 2010 and 2011, to 7.6% (2/26), between 2015 and 2016, and 8.3% (2/24), between 2017 and 2018. In the period analyzed, therefore, there is maintenance in the frequency of isolates carrying SCC*mec* type III and an increase in *S. aureus* carrying type IV from the first to the second period (8.3%; 3/36), in the first period (2010-2011) and (26.9%; 7/26) in the second period (2015-2016), decreasing to 8.3% (2/24) in the third period assessed (2017 to 2018).

A relationship was made between the antimicrobial resistance profile, antibiotypes, and SCC*mec* type presented by isolates from skin and soft tissues infections.

MRSA isolates that had SCC*mec* type I were characterized as belonging to antibiotype C in all samples analyzed (100%). Similarly, 90% of *S. aureus* with SCC*mec* type II belonged to antibiotype D, and 87.5% of type III belonged to antibiotypes A and B (Figure 4).

Among MRSA containing SCC*mec* type IV, this relationship was not so evident. Most strains were associated with antibiotype G (43%), which is characteristically sensitive to non-beta-lactam drugs; however, this genotype was also identified in more resistant isolates, such as antibiotypes A, B and C in 8% each, and D in 15% of the isolates analyzed.

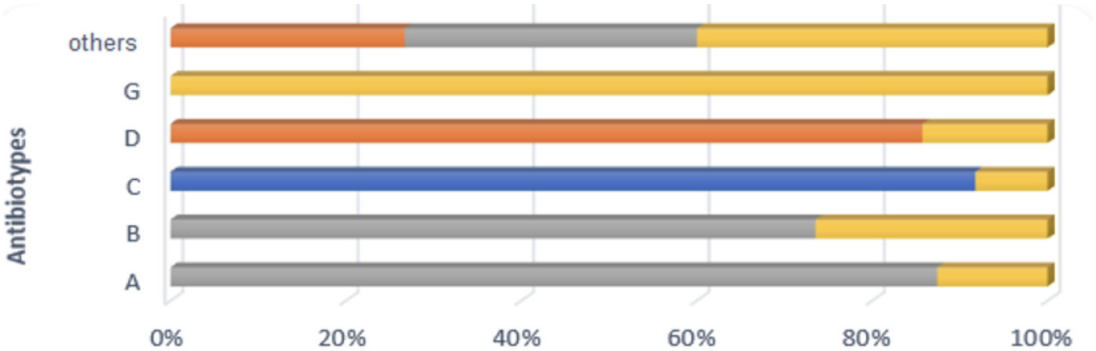
DISCUSSION

In this study, there was a change in the epidemiology of *S. aureus* over a 20-year period. Our data indicate a decline in the frequency of MRSA and a corresponding increase in MSSA as well as PSSA. In addition to this, there was evidence of a change in the SCC*mec* types of MRSA isolated from skin and soft tissues infections, and a relationship between the changing pattern of *S. aureus* resistance and molecular characteristics.

Studies have pointed to a change in the epidemiology of *S. aureus* in recent years.[11,12,13] Going against this statement, this paper reports a change, as it verified a decline in the proportion of MRSA, with a consequent increase in MSSA, which may indicate an important epidemiological change.

In a publication by the multicenter antimicrobial surveillance program, SENTRY, 191.460 *S. aureus* obtained from diverse sites were assessed over a 20-year period. The overall frequency of MRSA was 77,146 (40.3%) and ranged from 26.8% in Europe and 47.0% in North America. Methicillin resistance trend analysis over time showed that the proportion of MRSA among *S. aureus* isolates increased from 33.1% from 1997-2000 to 44.2% in 2005-2008 and then decreased to 42.3% from 2009-2012 and 39.0% from 2013-2016. Such data reinforce the results of this study and are in line with data from a study carried out in Germany with 146,561 isolates, whose data demonstrate a drop in the percentage of MRSA causing infectious processes.[12, 13.]

There was a reduction in the antimicrobial resistance profile exhibited by MRSA isolates between 2010 and 2015. Resistance to last-line antimicrobial agents,



	A	B	C	D	G	outros
I	0	0	100	0	0	0
II	0	0	0	90	0	10
III	62,5	25	0	0	0	12,5
IV	9	9	9	15	43	15

Caption: I, II, III, IV- types of SCCmec; A - sensible to tigecycline and linezolid. Resistant to oxacillin, penicillin, erythromycin, clindamycin, ciprofloxacin, gentamicin, sulfamethoxazole–trimethoprim, rifampicin; B - sensible to tigecycline, linezolid and rifampicin. Resistant to oxacillin, penicillin, erythromycin, ciprofloxacin, clindamycin, gentamicin, sulfamethoxazole–trimethoprim; C - sensible to tigecycline, linezolid, rifampicin and sulfamethoxazole–trimethoprim. Resistant to oxacillin, penicillin, erythromycin, ciprofloxacin, clindamycin, gentamicin; D - sensible to tigecycline, linezolid, rifampicin, sulfamethoxazole - trimethoprim, and gentamicin. Resistant to oxacillin, penicillin, erythromycin, ciprofloxacin and clindamycin; G - sensible to tigecycline, linezolid, rifampicin, sulfamethoxazole-trimethoprim, gentamicin, erythromycin, ciprofloxacin and clindamycin. Resistant to oxacillin and penicillin.

Fugure 4. Correlation between antibiotypes and SCCmec types for 86 MRSA isolates obtained from skin and soft tissues from January 2010 to May 2018.

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including ceftaroline, daptomycin, linezolid, tigecycline, vancomycin, and teicoplanin, remained almost non-existent.[12] Concerning the time trend of MRSA, we found higher resistance rates for clindamycin, ceftaroline, and vancomycin, which may be explained by sampling divergence.

In a study from Wisconsin state, USA, that assessed 309 clinical isolates of *S. aureus* collected from microbiology laboratories, as part of another multicenter surveillance study, resistance to penicillin was reported in 86% of isolates, to methicillin, in 56.8%, to levofloxacin, in 25%, and to clindamycin, in 20.5%. In addition, MRSA was found to have higher resistance rates for clindamycin, erythromycin and levofloxacin when compared to MSSA isolates.[14]

Almost all *S. aureus* demonstrated sensitivity to ceftaroline, dalbavancin, telavancin, and vancomycin (MIC90 of 1 µg/mL). The proportion of MRSA decreased continuously from 16% in 2010 to 10% in 2015. Interestingly, according to studies using *S. aureus* isolated from blood stream infections in Canada and Finland, there was a reduction in penicillin resistance and decrease in MRSA isolates, a fact also observed in this study.[15,16]

Also according to another study, treatment with penicillin in patients infected with penicillin-sensitive isolates has some advantages, such as low spectrum of action, low cost, and less association to secondary infections, as *Clostridium difficile* infection. They also offer advantages in terms of pharmacokinetics and pharmacodynamics, since they have a lower MIC compared to wild-type strains than cloxacillin and cefazolin, requiring a lower dose to reach an effective therapeutic concentration.[15]

On the other hand, MRSA carrying community-acquired SCC*mec* type IV (CA-MRSA) has been frequently reported in hospital-acquired infections. *Staphylococcus aureus* has been noted as a frequent infectious agent in outpatients; however, a modification in the epidemiology of these infections has been occurring in recent years.[17, 18]

With this epidemiological shift in mind and its relationship to the antimicrobial sensitivity profile in isolates from bloodstream infections, a study with 792 patients with MRSA infections, admitted in a hospital in Japan, between 2010 and 2016, was investigated. The authors found that isolates carrying SCC*mec* type II, characteristic of HA-MRSA, prevalent in 2010, were replaced by SCC*mec* type IV MRSA related to CA-MRSA. Moreover, according to them, there was a change in the sensitivity profile, supporting the molecular finding. Importantly, in this study, there was also an increase in the frequency of SCC*mec* type IV MRSA isolates.[19]

In another study, 45 MRSA isolated from patients admitted to ICUs between 2005 and 2010 were assessed. All isolates tested showed resistance to clindamycin, erythromycin, and levofloxacin. Regarding SCC*mec* elements, isolates showed types III (66.7%), II (17.8%), IV (4.4%), and I (2.2%). In this study, the isolates with SCC*mec* type III were related to the Brazilian endemic clone (ST239, CC8, SCC*mec* type III), predominant between 2005 and 2007, whereas the USA100/CC5/SCC*mec* II strain, which emerged in 2007, was more frequent in recent years.[20]

In our study, differently, SCC*mec* type II conductor isolates were the most frequent throughout the assessed period, with type III, throughout the assessed period, decreasing in frequency. This change in the prevalent clone as well as decrease in the frequency of isolates with SCC*mec* type III is in line with what was reported.[21]

Other authors have reported that similar events, such as emergence, expansion and decline of one MRSA clone with replacement by another clone, have occurred repeatedly in the MRSA evolutionary process. Furthermore, there is the report of CA-MRSA clones will likely become dominant in hospitals due to the fact that there is an expanding reservoir of MRSA in the community and its continued influx into the hospital.[22,23]

In a study conducted between 2014-2015, it was observed that 27% of *S. aureus* bloodstream infections were caused by isolates carrying SCC*mec* type IV related to the community ST80 clone. This finding indicates that clones of community origin, when within hospital settings, behave more like HA-MRSA and can cause more severe infections with more difficult treatment.[24,25]

Furthermore, the potential for these isolates to become multidrug resistant in healthcare settings is a worrisome factor. In fact, the authors identified an ST80-IV isolate resistant to seven different classes of antimicrobial agents, such as fluoroquinolones, macrolides, clindamycin, tetracyclines, fusidic acid, rifampin, and gentamicin.

With these 20-year analyses, we observed an increase in the population of PSSA and MSSA as a cause of infections, and a consequent reduction in MRSA. Moreover, the antimicrobial sensitive prefile has changed. Antimicrobial resistance is a life mechanism that needs constant monitoring and knowledge of local epidemiology for institutions of the best clinical therapies.

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AUTHOR'S CONTRIBUTIONS

Felipe Crepaldi Duarte: contributed to article conception, design, analysis and writing. **Livia Marina Finger:** contributed to article conception, design, analysis and writing. **Renan Hayami Obata:** contributed to article conception, design, analysis and writing. **Diogo Cesar Carraro**: contributed to article conception, design, analysis and writing. **Marcia Regina Eches Perugini:** contributed to article planning, design, review and final approval. **Philipe Quagliato Belinati** contributed to article planning, design, review and final approval.

All authors 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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Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

ORIGINAL ARTICLE

Analysis of testing for COVID-19 in Parnaíba city, state of Piauí, from march to December 2020

Análise da testagem para COVID-19 na cidade de Parnaíba, estado do Piauí, de março a dezembro de 2020

Análisis de pruebas de COVID-19 en la ciudad de Parnaíba, estado de Piauí, de marzo a diciembre de 2020

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ABSTRACT

Background and Objectives: it is extremely important and necessary to assess epidemiological events through the analysis of measures adopted at the time of crises, especially those with a health impact as a way of improving the system for future events, with testing being a gold standard to be assessed during an epidemic. This study aimed to analyze tests for COVID-19 diagnosis, with a view to detecting possible false negative results, in Parnaíba, Piauí, from March to December 2020. **Methods:** a statistical analysis of the data reported and made available by the Municipal Health Department using the IBM SPSS Statistics® 21.0 software, in which the variables type of test, date of symptom onset and date of material collection were crossed to obtain the results. **Results:** a total of 9,473 tests were negative, of which 11.1% were carried out using the RT-PCR methodology, 6.5% using rapid antigen tests, and 82.3% using a rapid antibody test. The analysis revealed that only 0.47% RT-PCR tests and 1.7% rapid antigen tests had been carried out within the ideal testing interval. On the other hand, the rapid antibody test had 0.14% performed outside the range. **Conclusion:** the most successful diagnostic test was the rapid antibody test, but it is the least specific and not suitable for determining health crisis management policies, especially for isolation measures for infected people, which suggests improvements in testing systems and development of tests with longer and more accurate testing intervals.

Keywords: *SARS-CoV-2. Epidemiology. Clinical Laboratorial Techniques. Public Health.*

RESUMO

Justificativa e Objetivos: é de suma importância e necessidade a avaliação dos eventos epidemiológicos por meio da análise das medidas adotadas no momento das crises, em especial aqueles de impacto sanitário como forma

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de melhor o sistema para eventos futuros, sendo a testagem um padrão-ouro a ser avaliado durante uma epidemia. O objetivo deste estudo foi analisar os testes para o diagnóstico de COVID-19, na perspectiva de detectar possíveis resultados falsos negativos, em Parnaíba, Piauí, de março a dezembro de 2020. **Métodos:** análise estatística dos dados notificados e disponibilizados pela Secretaria Municipal de Saúde a partir do *software* IBM SPSS® Statistics 21.0, em que as variáveis tipo de teste, data do início dos sintomas e data da coleta do material foram cruzadas para obtenção dos resultados. **Resultados:** 9.473 testes resultaram negativo, em que 11,1% foram realizados pela metodologia RT-PCR, 6,5%, pelos testes rápidos de antígeno, e 82,3%, por teste rápido de anticorpo. A análise revelou que apenas 0,47% testes por RT-PCR e 1,7% testes rápidos de antígeno haviam sido realizados dentro do intervalo ideal de testagem. Por outro lado, o teste rápido de anticorpo teve 0,14% realizados fora do intervalo. **Conclusão:** o teste com maior sucesso de diagnóstico foi o teste rápido de anticorpo, porém é o menos específico e não adequado para determinação de políticas de gerenciamento de crise sanitária, em especial para medidas de isolamento de infectados, o que sugere melhorias em sistemas de testagem e desenvolvimento de testes com intervalos de testagem maior e precisos.

Descritores: *SARS-CoV-2. Epidemiologia. Diagnóstico Laboratorial. Saúde Pública.*

RESUMEN

Justificación y Objetivo: es sumamente importante y necesario evaluar los eventos epidemiológicos a través del análisis de las medidas adoptadas en el momento de las crisis, especialmente aquellas con impacto en la salud, como una forma de mejorar el sistema para eventos futuros, siendo las pruebas un estándar de oro a ser evaluado durante una epidemia. El objetivo de este estudio fue analizar pruebas para el diagnóstico de COVID-19, con miras a detectar posibles resultados falsos negativos, en Parnaíba, Piauí, de marzo a diciembre de 2020. **Métodos:** análisis estadístico de los datos reportados y puestos a disposición por la Secretaría de Salud Municipal mediante el software IBM SPSS® Statistics 21.0, en el cual se cruzaron las variables tipo de prueba, fecha de inicio de síntomas y fecha de recolección del material para obtener los resultados. **Resultados:** un total de 9.473 pruebas resultaron negativas, de las cuales el 11,1% se realizaron mediante la metodología RT-PCR, el 6,5% mediante pruebas rápidas de antígenos y el 82,3% mediante prueba rápida de anticuerpos. El análisis reveló que sólo el 0,47% de las pruebas RT-PCR y el 1,7% de las pruebas rápidas de antígenos se habían realizado dentro del intervalo de prueba ideal. Por otro lado, la prueba rápida de anticuerpos tuvo un 0,14% realizado fuera del rango. **Conclusión:** la prueba diagnóstica más exitosa fue la prueba rápida de anticuerpos, pero es la menos específica y no adecuada para determinar políticas de gestión de crisis sanitarias, especialmente para medidas de aislamiento de personas infectadas, lo que sugiere mejoras en los sistemas de pruebas y desarrollo de pruebas con tiempos más largos y precisos. intervalos de prueba.

Palabras Clave: *SARS-CoV-2. Epidemiologia. Técnicas de Laboratório Clínico. Salud Pública.*

INTRODUCTION

COVID-19 was first reported in the Chinese province of Wuhan in 2019. From then on, the number of infected cases grew on a global scale, which is why it was classified by the World Health Organization (WHO) as a health emergency public interest of international concern.[1]

Caused by SARS-CoV-2, COVID-19 is a disease with a varied clinical appearance, and can present from asymptomatic to severe conditions leading to death. Depending on the emergence of the first and subsequent cases, approximately 80% of patients are asymptomatic and 20% of detected cases require hospital care.[1]

The clinical picture of the disease occurs after an incubation period of between two and 14 days, and the most common symptoms are dry cough, fever, dyspnea, headache, myalgia, fatigue and diarrhea.[2] Acute respiratory distress syndrome (ARDS) is one of the most serious complications, associated with prolonged hospitalization and high mortality.[3]

Moderate and severe cases require hospitalization with drug therapy with antipyretics, antivirals, antibiotics and steroids.[23] The advent of the vaccine and its complete progression in adults has meant that severe cases of COVID-19 tend to concentrate in unvaccinated populations.[4]

The gold standard diagnosis for identifying the SARS-CoV-2 virus is made using reverse transcription polymerase chain reaction (RT-PCR) with real-time amplification, and, for molecular identification of the variant, partial or total sequencing of the viral genome is necessary. RT-PCR depends on the reverse transcriptase enzyme, which specifically amplifies the fragment of interest. When testing for the virus, the first complementary DNA (cDNA) is synthesized using reverse transcriptase followed by polymerase chain reaction (PCR). This offers greater sensitivity and specificity than nucleic acid tests.[5]

Ideally, collection should be carried out after the appearance of symptoms, between the third and fifth day and up to seven days after the event, since in samples collected early or late, false negative results can be obtained, and the same may occur with insufficient material collection methodology from the nasopharynx or contaminated samples.[6]

Like all other viral infections, the body reacts to the presence of the virus by producing antibodies, initially of the immunoglobulin A (IgA) class, followed by immunoglobulin M (IgM) and immunoglobulin G (IgG). Sero-

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logical testing can be implemented using two different techniques: ELISA and immunochromatographic assays. Most COVID-19 patients begin producing antibodies between seven and 11 days after exposure to the virus, although some may develop antibodies sooner.[7] Rapid tests are the types of serological tests that detect antibodies produced upon exposure to the virus. Instead, they could also be based on the detection of antigenic viral proteins in patient samples. They are less sensitive than nucleic acid-based tests.[8]

The rapid antigen test, a test that emerged later, is an immunochromatographic assay that qualitatively detects SARS-CoV-2 antigens against the infection, and must be performed between the second and seventh day of the onset of symptoms. Its performance does not require complex structures or specialized devices, most of the time generating a rapid diagnostic response, which helps prevent vertical transmission of the disease.[9]

In addition to the availability and distribution of vaccines, local, social and demographic characteristics must be taken into account in response strategies to the epidemic, since the country has a large population, distributed unevenly across the territory, with cultural and cultural differences. geographical areas that can influence adherence to interventions, in addition to showing marked social inequalities and in access to health services. [9]

In cases of health crises, the priority is to establish the profile of the infection by recognizing the etiological agent and testing the population so that it is possible to outline combat and prevention measures. Analyzing testing is a way of assessing the combat measures adopted and generating knowledge on how to act in future situations. The study took place with the purpose of analyzing tests for COVID-19 diagnosis, with a view to detecting possible false negative results in the state of Piauí, with data reported to the Municipal Health Department through Epidemiological Surveillance, available for notification to the Ministry of Health (MoH).

METHODS

This is a descriptive epidemiological study. The research was carried out with epidemiological data from the city of Parnaíba, state of Piauí, Northeast region of the country, collected at the Municipal Health Surveillance Department, covering the period from March to December 2020, tabulated in Microsoft® Office Excel 2010 software. for Microsoft® Windows 10. These were transferred to the researchers in their original format in Microsoft® Office Excel 2010 and then exported to IBM SPSS® Statistics software. Data were described with sociodemographic (gender, age, city of residence) and clinical-epidemiological variables (date of notification, type and result of the test, date of onset of symptoms, date of testing, symptoms, associated disease conditions pre-existing conditions and description of symptoms).

In Microsoft® Office Excel 2010, the data was sorted, and those that were incomplete or had typing errors that compromised understanding for data analysis were excluded from the study. To have an overview of diagnosis, data confirmed by clinical-epidemiological criteria and diagnostic imaging were initially considered only as complementary information, being excluded in statistical analyses, as they are non-specific for diagnosis. Negative data were classified as discarded and non-specific flu-like syndromes, with those tested using RT-PCR or serology methods being selected, followed by import into IBM SPSS® Statistics 21.0, for statistical analysis and obtaining results through graphs and tables.

For data analysis, the time intervals from the onset of symptoms to the test were classified using the terms "adequate", when they comply with the test usage interval, or "inadequate", when they do not comply with, following the MoH recommendations based on the Epidemiological Surveillance guide, which recommends the ideal intervals and tests for an accurate diagnosis, with parameters for appropriate intervals after the onset of symptoms: RT-PCR test, for an interval of three to seven days; rapid antibody test, for intervals ≥ eight days; rapid antigen test, for an interval of two to seven days; ELISA IgM and IgG test, for intervals ≥ eight days. Tests performed outside these standards will be classified as inadequate.

After data analysis, 2,775 cases were excluded, with the exclusion criterion being the unavailability of complete data, making them invalid for the study. The remaining quantity was 16,880 suitable tests, of which 7,346 totaled positive results with a higher percentage of 36.84%, confirmed by laboratory criteria. On the other hand, 9,534 was the total number of negative cases, of which 3.29% were ruled out for COVID-19 and 45.2% were classified as non-specific flu-like syndrome (Figure 1).

After classification, the mean and standard deviation of the time intervals between the onset of symptoms and the tests were calculated according to adequacy classification. Variables were summarized as medians and interquartile ranges, while categorical variables were expressed as counts and percentages. Odds Ratios (OR) with 95% Confidence Intervals were calculated to identify risk factors in univariate logistic regression models. After obtaining statistical results, graphs and tables were generated in the present study.

All ethical precepts established by Resolution 466/2012 of the Brazilian National Health Council (CNS – *Conselho Nacional de Saúde*) were respected with regard to ensuring information legitimacy, privacy and confidentiality, making the results of this research public, when necessary. The research presents the substantiated opinion of the Research Ethics Committee, under the Certificate of Presentation for Ethical Consideration (CAAE - *Certificado de Apresentação para Apreciação Ética*) 52834021.0.0000.0192, approved on December 6, 2021, under Opinion 5.147.515.

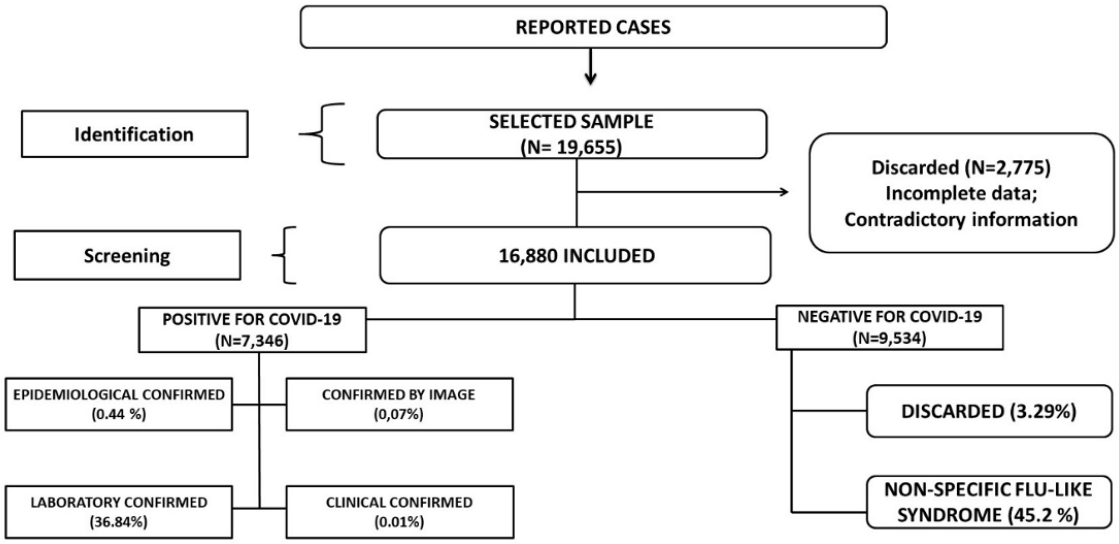

Figure 1. Representative scheme of reports for detecting positive cases for COVID-19 through clinical-laboratory confirmation during the second half of 2020 following the methodological sequence of the study.

RESULTS

Due to the initial challenges of the pandemic, which particularly hampered the notification and testing of cases, samples from the first half of 2020 were excluded and samples from the second half of 2020 were selected, as it is the interval in which knowledge of disease patterns and the establishment of procedures that constitute greater availability of complete and more solid data were better developed, totaling 19,655 cases reported in the city of Parnaíba, state of Piauí, in this period of time.

The tests used in diagnoses with negative results were 1,054 using the RT-PCR methodology, 621 using the rapid antigen test, and 7,798 using the rapid antibody test (IgG and IgM) (Figure 2).

Among the three main tests used in the period, it was observed that, among those tested using the RT-PCR methodology, representing approximately 11.1% of those tested with a negative result, 1,049 were carried out outside the recommended interval of three to seven days for testing, which represented 99.5% of tests using this methodology with possible false negatives (Table 1). The rapid antigen test presented a similar statistic, in which 610 of its 621 tests did not respect the ideal methodological intervals for testing, which characterizes a test with 98.2% of negative results with characteristics of possible false negatives, with these intervals being recommended as a basis for a more accurate diagnosis and with greater sensitivity and specificity of these methodologies.

The test performance and result vary depending on circumstances such as sample storage or transport, serum conversion and decline in antibody titer as well as testing interval. Therefore, obtaining diagnostic tests with high sensitivity and specificity, combined with appropriate analytical conditions for sample collection and treatment, avoids a high frequency of false negative

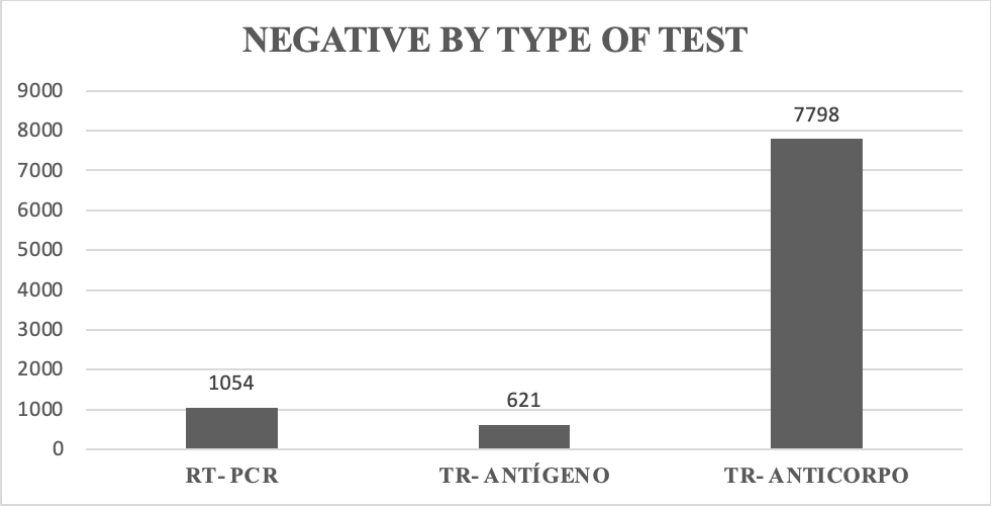

Figure 2. Results of negative cases tested by RT-PCR methodologies, and rapid antigen and antibody tests, referring to the second half of 2020.

results that can influence infection control strategies.

On the other hand, the rapid antibody test presented a result with interesting methodological errors, presenting only 11 of its 7,798 tested inappropriately, which elects it as one of the tests with the least false negatives, since the testing error was less than 1%, but its result is already expected when taking into account its applied methodology, discussed in this study.

An important point observed was that, according to the notification data, all tests carried out followed the same parameter. Most patients tested had more than ten days of symptoms.

Table 1. Quantity of tests during the study period and the list of total tests carried out outside the testing interval classified as inadequate following the Ministry of Health and test manufacturers recommendations.

TYPE OF TEST	FULLY TESTED N (%)	INADEQUATE TESTING N (%)
RT-PCR	1.054 (11.1)	1.049 (99.5)
RT-ANTIGEN	621 (6.5)	610 (98.2)
RT-ANTIBODY	7.798 (82.3)	11 (0.14)

DISCUSSION

The pandemic has highlighted variation in access to healthcare, healthcare infrastructure and preparedness across regions, and these in turn have significantly affected outcomes. The accuracy of official data in the first months of the pandemic was quite challenging, a moment that, despite the efforts of health services, which were overloaded, to notify, operational difficulties, laboratory diagnostic errors, asymptomatic cases and even difficulties in differentiating COVID-19 from other diseases coexisted.

The data from this research revealed that the majority of those tested who tested negative, after careful analysis, were led to believe that they were false negatives, based on the type of inappropriate test, taking into account the date of onset of symptoms recommended by health authorities.

The main challenges for carrying out the initial diagnosis of COVID-19 include ideal biological material for testing, definition of biological marker to be detected, the type of methodology used and ideal time of infection for sample collection.[10] In the case of the RT-PCR kit, distributed by the Centers for Disease Control and Prevention (CDC) in China, it was designed to detect the nucleocapsid and ORF1ab, and infection is confirmed when both are amplified. However, it is possible that the results are inconsistent due to amplification of only one of the targets.

The testing strategy must consider the accuracy of tests for detecting antibodies, as the sensitivity and specificity of tests approved in Brazil vary between commercial kits from different manufacturers. Among the tests approved in the country, sensitivity is at low to moderate levels, which may imply difficulty in detecting infected individuals, especially in tests for the detection of anti-SARS-CoV-2 antibodies of the IgM class in initial phase of infection.[10]

As of April 3, 2020, the Brazilian MoH had confirmed around 9,000 confirmed cases of COVID-19 (BRASIL, 2020). Detection of SARS-CoV-2 using real-time PCR test kits can be considered the gold standard for diagnosing COVID-19; however, this technique requires certified laboratories, more expensive equipment and trained technicians.[11] These characteristics were very far from the initial reality in the fight against COVID-19, being yet another in-depth demonstration of the statistics of a possible high number of false negatives.

Testing must respect the ideal interval recommended by manufacturers and the MoH; if this interval is not respected, these can be classified as negative when the patient is infected with the virus, generating false negatives.[12,13] Based on this assumption, taking into account the difficulties experienced at the beginning of the pandemic, it is expected that many negative tests will include positive patients. Adequate test management and effective patient clinical assessment, together with the correct completion of the notification instrument, were aspects considered relevant for the development of this study.

Analysis of these data suggests that the majority of discarded/negative tests may have been improperly analyzed, as they were performed outside the recommended time interval, based on the immunological window and manufacturer indications for each test. This indicates that the number of positive cases may be greater than the expected averages in the number of mobile cases reported by health units, not only related to analytical test errors, but also to epidemiological analysis, which includes the city's own demographics, which can make it difficult for patients to access health services, whether for geographic or economic and cultural reasons.

The limited scientific knowledge available, both for clarifying doubts and for training health professionals, had great significance, since, for hospital intervention and mass testing, a greater level of information would be necessary so that the results do not harm case management. Until patients meet the criteria according to pre-established protocols for reporting flu-like syndrome, they must be monitored as a suspected case of COVID-19.

Regarding the difficulty of clinical differentiation between the common cold and Influenza, these should be considered, with symptomatic cases and negative testing for COVID-19, suggesting the need for testing for other possible circulating viruses, considering that these patients classified as flu-like syndrome have not been diagnosed and confirmed for other syndromes.[14] Due to the totality of the sample and the epidemiological conditions of the pandemic, this percentage makes the chances of false negative results for COVID-19 questionable.

Furthermore, the high demand for tests, in some periods, caused their unavailability combined with the unpreparedness and lack of information on the part of professionals to face an emerging disease.[14] The immunochromatographic antibody test was the one that presented the best results in relation to the analytical phase of the test, as it was carried out in the appropriate period,

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since approximately 6.3% of tests were carried out outside the recommended range, and this is probably due to the longer period available for them to be carried out.

Data analysis and presentation in this study favor the adoption of integrated public policies and measures, aiming to reduce prevalence rates. Furthermore, these data can be used to develop future studies in the area. Exposing these results to the scientific community and health professionals can better assist in choosing the ideal technique and management for each suspected case.

Furthermore, disseminating the study to the general population disseminates knowledge of the symptomatological differences between those affected and the relevance of the data acquired regarding the health promotion strategy. Although Brazil does not have a reference population for standardizing rates, it is noteworthy that incidence rates are directly influenced by the testing strategies adopted in the country and in each Federative Unit.[15]

To implement initiatives that guarantee continuous transmission control actions for tracking and testing suspected cases, it is necessary to use diagnostic methods that are easily accessible to professionals. As is the case with rapid virus antigen tests which, despite their low specificity and sensitivity, compared to the molecular technique, allow rapid detection of those infected, enabling early identification of cases, contact tracing and taking the necessary measures to greater control of the spread of the virus.[16]

Diagnostic approaches such as nucleic acid amplification tests (NAAT) such as RT-PCR are most widely used for the detection of SARS-CoV-2 infection, followed by rapid antigen tests[17]. However, they tend to give false positive and false negative results respectively. Therefore, it is important, in crisis situations, to have the availability and application of sensitive and specific testing measures for the virus being investigated.

As a limitation of this study, there is a high number of incomplete notifications, with approximately 14% of the data. The recording of dates, especially regarding the onset of symptoms and possible errors in filtering data when using analytical tools, is a reflection of the reality of overload in the healthcare system currently experienced. It is believed that these factors cause harm to the occurrence of worsening of the pathology and, consequently, facilitate the spread of the disease, which may have favored the pandemic. However, it is concluded that this is also a result of the critical analysis of data from this research.

It was also noted that the data coming from an early period of the pandemic, where everything was uncertain and testing measures were precarious, meant that notifications and results were less precise, requiring a deeper analysis to obtain promising results. However, this is also characterized by having a direct implication on public health policies, as it proves that testing measures, when not precise and specific, can lead to an increase in infected people through asymptomatic false negatives.

In short, it is observed that, in outbreak situations, variations in incidence arising from suboptimal testing capacity must be differentiated from variations in real cases during monitoring. If the number of individuals reported as suspects is much higher than the testing capacity, this difference may lead to underdiagnosed cases.

It is important to highlight that inadequate testing implies unnecessary costs, with the acquisition of tests that do not provide specific results, in addition to influencing medical conduct, affecting the dynamics of infection containment, since case surveillance ends up being compromised.

Health policies must be based on testing systems and ensure their greater effectiveness, especially when dealing with infections that have an asymptomatic clinic, as this increases transmission, thus increasing the degree of epidemics and antigenic variations of the etiological agent, generating unwanted variants in a short period.

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AUTHORS' CONTRIBUTIONS

Anna Carolina Toledo da Cunha Pereira contributed to project administration, bibliographic research and review. **Dénis Miguel Rodrigues de Oliveira** contributed to bibliographical research, writing the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Deyseane Zacarias Freire de Sousa** contributed to bibliographic research, writing the abstract, discussion, interpretation and description of results, conclusions. **Gustavo Portela Ferreira** contributed to project administration, textual review of the abstract, methodology, results, conclusions, statistics. **Karliane de Araujo Lima** contributed to data availability, abstract writing, review and statistics. **Paloma Maria de Sousa Araujo** contributed to bibliographic research, introduction, methodology, discussion, interpretation and description of results, review and statistics. **Vanessa Poleana Silva** contributed to project administration, literature research, review and statistics.

All authors 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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ORIGINAL ARTICLE

Folate and vitamin B12 related to homocysteine and DNA damage in female university students

Folato e vitamina B12 relacionados com homocisteína e danos no DNA em estudantes universitárias

Folato y vitamina B12 relacionados con homocisteína y daño en el ADN en estudiantes universitarias

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ABSTRACT

Background and Objectives: It is not clear whether the increase in nutrition students' knowledge is associated with healthier eating behavior and fewer micronutrient deficiencies that can cause DNA damage. Deficiency in some vitamins can be a risk factor for increased homocysteine (Hcy) levels, a marker of cardiovascular risk. Therefore, this study aimed to verify whether dietary and serum folate and vitamin B12 are associated with Hcy levels and DNA damage in female university students. **Methods:** A cross-sectional study was conducted with female university students from southern Brazil. Folate, vitamin B12, and Hcy levels were determined in their diet or serum. DNA damage levels were assessed by the alkaline comet assay (index and frequency) and the buccal micronucleus assay (micronuclei frequency and binucleated cells frequency). **Results:** Correlation analyses did not show an association between Hcy levels and dietary or serum folate and vitamin B12 consumption. Dietary folate and vitamin B12 were associated with the index and frequency of damages; however, only serum folate was negatively associated with the index and frequency of damages. Additionally, the frequency of binucleated cells was negatively associated with dietary vitamin B12 and positively associated with serum levels. Serum folate was negatively associated with the frequency of micronuclei. Hcy levels were associated with the index and frequency of damages. **Conclusion:** These findings strengthen the role of healthier dietary patterns with adequate micronutrients as a preventive strategy to reduce the risk of cardiovascular diseases. This approach should play a pivotal role in shaping health policies and advocating for appropriate food choices.

Keywords: *Folic Acid. Vitamin B 12. Homocysteine. Genomic instability, Cardiovascular Diseases.*

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RESUMO

Justificativa e Objetivos: Não está claro se o aumento do conhecimento dos estudantes de nutrição está associado a um comportamento alimentar mais saudável, com menores deficiências de micronutrientes que podem induzir danos no DNA. A deficiência de algumas vitaminas pode ser um fator de risco para o aumento dos níveis de homocisteína (Hcy), um marcador de risco cardiovascular. Portanto, este estudo verificou se folato e vitamina B12 dietético e sérico estão associados aos níveis de Hcy e danos no DNA em estudantes universitárias. **Métodos:** Estudo transversal com universitárias do sul do Brasil. Determinou-se folato, vitamina B12 e Hcy dietético e séricos. Os níveis de danos no DNA foram avaliados pelo ensaio do cometa alcalino (índice e frequência) e pelo ensaio de micronúcleos bucais (frequência de micronúcleos e células binucleadas). **Resultados:** Análises de correlação não mostraram associação entre os níveis de Hcy com o consumo de folato e vitamina B12 dietético ou sérico. Folato e vitamina B12 dietéticos associou-se ao índice e frequência de danos, entretanto, somente folato sérico associou-se negativamente ao índice e frequência de danos. Ainda, a frequência de células binucleadas estava negativamente associada à vitamina B12 da dieta e positivamente associada aos níveis séricos. Folato sérico associou-se negativamente à frequência de micronúcleos. Os níveis de Hcy associou-se ao índice e frequência de danos. **Conclusão:** Esses achados fortalecem o papel de padrões alimentares mais saudáveis com micronutrientes adequados como estratégia preventiva visando a redução do risco de doenças cardiovasculares. Esta abordagem deve desempenhar um papel fundamental na formulação de políticas de saúde e na defesa de escolhas alimentares apropriadas.

Descritores: *Ácido Fólico. Vitamina B 12. Homocisteína. Instabilidade Genômica, Doenças Cardiovasculares.*

RESUMEN

Justificación y Objetivos: No está claro si el aumento del conocimiento de estudiantes de nutrición está asociado con un comportamiento alimentario más saludable, con menores deficiencias de micronutrientes que puedan inducir daños en ADN. La deficiencia de algunas vitaminas puede ser un factor de riesgo para el aumento de los niveles de homocisteína (Hcy), marcador de riesgo cardiovascular. Consiguiente, este estudio verificó si folato y vitamina B12 dietéticos y séricos están asociados con niveles de Hcy y daños en el ADN en estudiantes universitarias. **Métodos:** Estudio transversal con universitarias del sur de Brasil. Se determinaron folato, vitamina B12 y Hcy dietéticos y séricos. Los niveles de daño en el ADN se evaluaron por ensayo del cometa alcalino (índice y frecuencia) y el ensayo de micronúcleos bucales (frecuencia de micronúcleos y células binucleadas). **Resultados:** Los análisis de correlación no mostraron asociación entre los niveles de Hcy con folato y vitamina B12 dietéticos y séricos. Folato y vitamina B12 dietéticos se asociaron con índice y frecuencia de daños, pero, solo folato sérico se asoció negativamente con índice y frecuencia de daños. Además, la frecuencia de células binucleadas estaba negativamente asociada con la vitamina B12 de la dieta y positivamente asociada con los niveles séricos. Folato sérico se asoció negativamente con la frecuencia de micronúcleos. Los niveles de Hcy se asociaron con índice y frecuencia de daños. **Conclusión:** Estos hallazgos refuerzan el papel de patrones alimentarios más saludables con micronutrientes adecuados como estrategia preventiva para reducir el riesgo de enfermedades cardiovasculares. Este enfoque debería desempeñar un papel fundamental en la elaboración de políticas de salud y en la promoción de elecciones alimenticias apropiadas.

Palabras Clave: *Ácido Fólico. Vitamina B 12. Homocisteína. Inestabilidad Genómica, Enfermedades Cardiovasculares.*

INTRODUCTION

Nutritional behaviors are multifaceted, influenced by various factors, including individual choices, cultural influences, and education.[1] Nutrition education plays a crucial role in promoting healthier dietary choices, equipping individuals with the knowledge and awareness necessary to make informed decisions about their eating habits.[2] In the context of higher education, university students pursuing degrees in nutrition undergo comprehensive and detailed training in the subject, which ideally results in a higher level of nutrition knowledge compared to individuals not pursuing such degrees.[3] Additionally, it is expected that, as students advance in their academic journey, those in the final semesters would display a more profound understanding of nutrition compared to their peers in the initial semesters. Furthermore, this unique population of university students of nutrition is often presumed to have better eating habits compared to other individuals due to their educational background and training in this field.

However, despite their potential advantage in nutrition knowledge and eating behaviors, unhealthy dietary practices among university students, including those in nutrition programs, can still be prevalent and may contribute to increased health risks.[4] Unhealthy eating behaviors have been identified as risk factors for various diseases, particularly cardiovascular diseases (CVD),[5] which continue to be a significant public health concern. In the context of CVD risk assessment, Homocysteine (Hcy), a non-essential amino acid containing sulfur, has emerged as a potential marker. Elevated levels of Hcy, resulting from the demethylation of methionine, have

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been associated with an increased risk of CVD.[6]

Notably, Hcy levels are modulated by the availability of folate (vitamin B9) and vitamin B12 in the body. Deficiencies in these essential vitamins can lead to the accumulation of Hcy, further exacerbating the risk of cardiovascular complications.[7] Folate and vitamin B12 play crucial roles in numerous physiological processes, including their involvement in the synthesis of methionine and S-adenosylmethionine, acting as essential donors of methyl groups.[8] As a consequence, insufficient levels of these vitamins can induce DNA damage and disrupt DNA methylation processes, both of which are significant risk factors associated with elevated Hcy levels.[9]

While reference values for serum folate and vitamin B12 have been established based on disease prevention, their adequacy in minimizing chromosome damage and optimizing DNA methylation state remains a subject of inquiry.[8,10] Understanding the potential relationships between dietary intake, serum vitamin levels, Hcy concentrations, and DNA damage is essential in devising effective preventive strategies for CVD, particularly among university students of nutrition, who are vital in disseminating nutritional knowledge to the broader population.

Given the importance of nutrition in overall health and disease prevention, it is crucial to investigate factors influencing cardiovascular risk among university students of nutrition. This study aims to fill existing gaps in knowledge, focusing on the unique population of university nutrition students. Although these students are often assumed to have better eating habits due to their educational background, this study hypothesizes that poor eating practices may still be prevalent, contributing to health risks. Despite the existence of reference values for folate and B12 based on disease prevention, the adequacy of these levels in minimizing DNA damage remains an area of investigation. Therefore, this study proposes to explore the potential associations between dietary intake, serum folate and vitamin B12 levels, Hcy concentrations, and DNA damage in this specific population group. Due to the lack of studies in this area, this research will provide valuable insights into the consumption of folate and vitamin B12 and their potential relationship with cardiovascular risk and DNA damage among university students of nutrition, filling an important gap in the research. Therefore, this cross-sectional study aimed to verify whether dietary and serum folate and vitamin B12 are associated with Hcy levels and DNA damage in female university students.

METHODS

This is a descriptive cross-sectional study conducted from March to April 2016. The included subjects were female undergraduate students of nutrition, aged 19 to 50 years, enrolled in any semester at a community-university from Santa Cruz do Sul, Brazil. Exclusion criteria comprised subjects reporting atrophic gastritis, bariatric surgery, pregnancy or lactation, students taking drugs affecting folate and vitamin B12 metabolism, exposure to genotoxicants (e.g., cytotoxic drugs), and those with incomplete data or who did not sign the informed consent form were excluded. Participants were recruited by convenience sampling, with all nutrition course students invited via emails and/or other social media channels (including Instagram™ and Facebook™), and all efforts were made to avoid potential sources of bias in the study, such as selection bias or information bias.

Folate and vitamin B12 intake determination were obtained using three 24-hour food recalls. To estimate regular intake, three food recalls were performed on two weekdays and one weekend day, during the period of one week. To minimize potential memory errors and ensure consistency in the responses, the questionnaires were administered by a properly trained individual. Students completed food recalls, in which they reported all food intakes (type and amount of food and liquids) in the last 24 hours. The quantification of folate and vitamin B12 consumption was determined using the DietWin® software. For evaluating the adequacy of folate and vitamin B12 intake, reference values from the Dietary Reference Intake (DRI) were used, following the Estimated Average Requirements (EAR).[11]

A qualified professional performed blood collection on the day scheduled by a specialized professional. Students were requested to fast for at least four hours. The blood collected (5 mL) was used in the biochemical dosage of Hcy, folate, and vitamin B12, in addition to comet assay. At the same opportunity, oral mucosa cells were also collected to perform the Buccal Micronucleus Cytome (BMCyt) assay.

Blood quantifications of serum folate, vitamin B12, and Hcy were performed in a clinical analysis laboratory using the methodology of competitive chemiluminescent immunoassay on a Immulite 2000 Immunoassay System (Siemens Healthineers). Measurement of these blood parameters was conducted using commercial kits from Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA. All procedure was performed following the manufacturer's recommendations. The equipment was subjected to controls and limit of quantification as defined by the manufacturer's guidelines. Reference values used were: 4.44 to 13.56 µmol/L for Hcy, above 3.50 ng/mL for folate, and 174 to 878 pg/mL for vitamin B12, following laboratory standards. Moreover, another reference value for vitamin B12 (490 pg/mL) was considered as the safe lower threshold.[12]

The alkaline comet assay of blood cells was performed as described by Molz et al.[13] In total, 5 µL of whole blood (mixed with heparin) was embedded in 95 µL of low melting point agarose (LMP) (0.75%) over a slide precoated with agarose, and subsequently, a coverslip was gently placed over that slide. After the mixture solidified, the coverslips were removed and the slides were put in a freshly prepared lysis solution containing high salt and detergent concentrations (2.5 M NaCl, 100 mM EDTA, 10 Mm Tris, pH 10–10.5, with freshly added 1% Triton X-100 (v/v) and 10% DMSO) (v/v) for a minimum of 1 h under refrigeration. Subsequently, the slides were exposed for 20 min to an alkaline solution (300 mM NaOH and

1 mM EDTA, pH>13) for DNA unwinding and to express the alkali-labile sites as single-strand breaks. The slides were then immediately subjected to an electrical current (electrophoresis in the same solutions at 300 mA and 25 V (0.90 V/cm) for 15 min at 4 °C to induce the migration of DNA fragments in the direction of the current. After that, the slides were washed with neutralization buffer (Tris 0.40M, pH 7.5) and fixed. Silver nitrate was used in the staining process of DNA. All procedures were conducted under dim yellow light to prevent DNA damage induced by ultraviolet radiation.

For each individual, two slides were prepared and 100 cells were randomly selected and analyzed (50 per slide, two slides per individual) using an optical microscope. Slides were coded to allow a blinded analysis, making it impossible to identify the individual, and the coding was performed by two properly trained individuals. Damage was determined visually by cells classification (comet morphology) in five classes of DNA migration, ranging from 0 damage (no damage, circular morphology only head and no tail) to damage 4 (maximum damage, tail expressively larger than head). Thus, the damage index for 100 cells ranged from 0 (no damage) to 400 (all cells with maximum damage). Damage frequency (%) was calculated using the relationship between the number of cells with damage (classified from 1 to 4) and the total of 100 cells from the sample.

BMCyt assay was performed following the protocol by Thomas et al.[14] Firstly, oral mucosa cells were collected using a cervical brush, which was then shaken into a microtube containing 1 mL of methanol. The brush was discarded from the microtubes and 20 µL of DMSO were added for subsequent centrifugation at 3,500 g for 3 min. Then, 200 µL of supernatant were aspirated off and more 200 µL of methanol were added. A pipette tip was used to dissociate the cells (this procedure was repeated three times). Next, 400 µL of supernatant were discarded, and 100 µL of the remaining cell suspension were distributed onto clean microscope slides (two slides per individual). After that, the slides were treated with HCl and Schiff's reagent, let dry overnight, and then stained following the Feulgen method.[14] The slides were later analyzed using an optical microscope. A total of 2,000 differentiated cells were evaluated for the presence of DNA damage and the score from 1,000 cells was evaluated to determine the frequency of abnormal cells. They were classified according to the cytological and nuclear features in indicative of DNA damage (micronuclei and/or nuclear buds), cytokinetic defects (binucleated cells) and/or cell death (karyorrhexis, pyknotic and karyolytic cells), based on nuclear/cytoplasmic ratio, nuclear morphology, and texture.[14] Results are expressed as counts per 1,000 cells. Microscope slides were coded to allow a blinded analysis, making it impossible for the evaluator to know the subject identification. The analysis of slides was conducted by two examiners (two slides per subject).

The Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM, Armonk, USA) was used for data tabulation. Descriptive statistics was presented as means and standard deviations or frequencies and percentages. Numerical data were tested for normal distribution and equality of variances by the Shapiro-Wilk test. The evaluation of adequacy for folate, vitamin B12 intake, serum levels of folate, vitamin B12, and Hcy were classified into distribution percentiles. Pearson correlation analyses were performed to test the association between normal parameters, and Spearman correlation was applied for non-normal parameters. This aimed to assess the relationship between folate and vitamin B12 intake, serum levels of folate, vitamin B12, and Hcy. Additionally, it also investigated the association between the DNA damage index and frequency with folate and vitamin B12 intake, serum levels of folate, vitamin B12, and Hcy. The significance level used was $p<0.05$.

The study was approved by the research ethics committee from the University of Santa Cruz do Sul/UNISC (protocol no. 1.432.400/2016; CAAE: 52822115.8.0000.5343) and followed the guidelines established by 466/2012 - 510/2016 - 580/2018 Brazilian resolution. All participants singed an informed consent form, indicating their voluntary agreement to participate. Additionally, a unique identification code was assigned to each participant to guarantee unbiased examination of test outcomes and respect privacy.

RESULTS

In this study, 47 women with a mean age of 24.8±6.7 years were evaluated. Table 1 presents the folate and vitamin B12 inadequacy, evaluated via diet and blood. Our results showed that 100% of the women presented inadequate folate intake and 48.9% of vitamin B12, according to the EAR.[11] Regarding serum vitamins levels, 6.4% of women were deficient in serum folate. In addition, 10.6% of the women had vitamin B12 levels below 174 pg/mL and 93.6% of the women had levels below 490 pg/mL. None of the women had deficient Hcy levels (Table 1) nor had Hcy levels above 13.56 µmol/L.

Additional analyses showed that Hcy levels were not correlated with folate and vitamin B12 intake or serum levels ($p>0.05$; Supplementary Figure 1).

Correlation analyses identified important relationships between the index and the frequency of DNA damage with vitamins in diet and serum. Folate intake ($r=0.177$; $p=0.025$ and $r=0.302$; $p=0.026$, respectively; Figure 1a, c) and vitamin B12 intake ($r=0.364$, $p=0.015$ and $r=0.340$, $p=0.024$, respectively; Figure 1b, d) were significantly associated with the damage index and frequency in DNA.

In addition, only folate serum level was negatively associated with damage index and frequency ($r=-0.406$, $p=0.008$ and $r=-0.430$, $p=0.05$, respectively; Figure 2a, d). Hcy levels were significantly positively associated with damage index and frequency ($r=-0.273$, $p=0.038$ and $r=-0.342$, $p=0.027$, respectively; Figure 2c, f).

Regarding the BMCyt assay, only vitamin B12 intake was negatively associated with binucleated cells

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Table 1. Evaluation of folate, vitamin B12 intake, and serum levels of folate, vitamin B12, and homocysteine (n=47).

			Regular intake distribution percentiles									
Dietary	**EAR**	**Mean±SD**	10	20	30	40	50	60	70	80	90	**Evaluation comments**
Folate (µg/day)	320.0	103.7±46.3	54.0	60.0	70.8	82.7	93.9	109.7	122.4	143.0	171.2	Inadequacy prevalence of 100.0%
Vitamin B12 (µg/day)	2.0	2.0±1.3	0.8	1.0	1.4	1.6	1.8	2.1	2.2	2.5	3.6	Inadequacy prevalence of 48.9%
			Regular intake distribution percentiles									
Serum levels	**EAR**	**Mean±SD**	10	20	30	40	50	60	70	80	90	**Evaluation comments**
Folate (ng/mL)	Lower than 3.5	7.5±3.2	4.0	5.0	5.5	6.2	7.4	8.0	8.9	9.4	12.4	Inadequacy prevalence of 6.4%
Vitamin B12 (pg/mL)	Lower than 174.0[a]	249.7±100.5	111.8	176.6	197.2	213.4	224.0	255.0	292.2	312.0	362.2	Inadequacy prevalence of 10.6%
	Lower than 490.0[b]											Inadequacy prevalence of 93.6%
Homocysteine (µmol/L)	Lower than 4.4	8.0±1.8	5.7	6.5	6.7	7.4	8.1	8.5	8.8	9.5	9.9	Inadequacy prevalence of 0.0%

[a] *according to laboratory standards.*
[b] *considering 490 pg/mL as the safe lower threshold.*

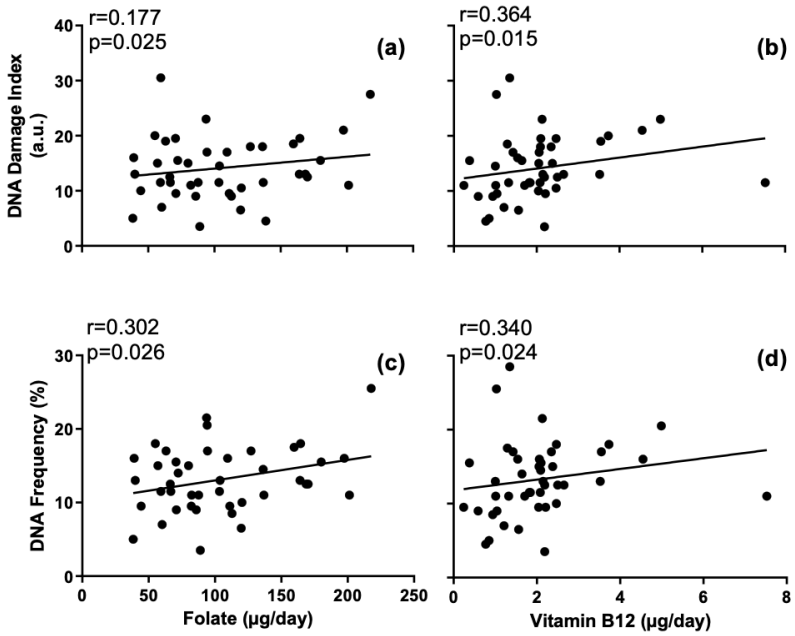

Figure 1. Association between DNA damage index and frequency with folate (a, c) and vitamin B12 (b, d) intake. r: correlation coefficient and p: significance level according to Pearson's or Spearman's tests.

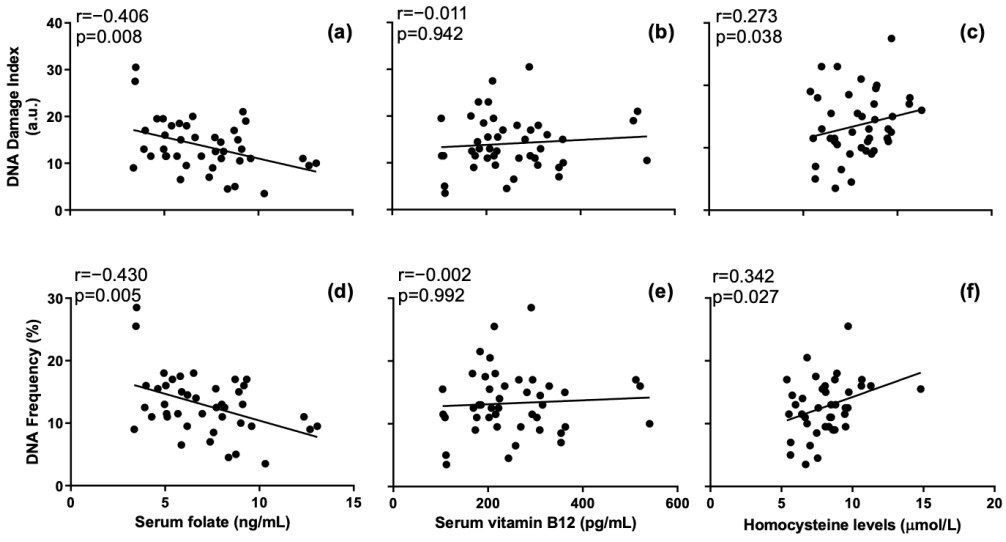

Figure 2. Association between DNA damage index and frequency with folate (a, d), vitamin B12 (b, e), and homocysteine (c, f) serum levels. r: correlation coefficient and p: significance level according to Pearson's or Spearman's tests.

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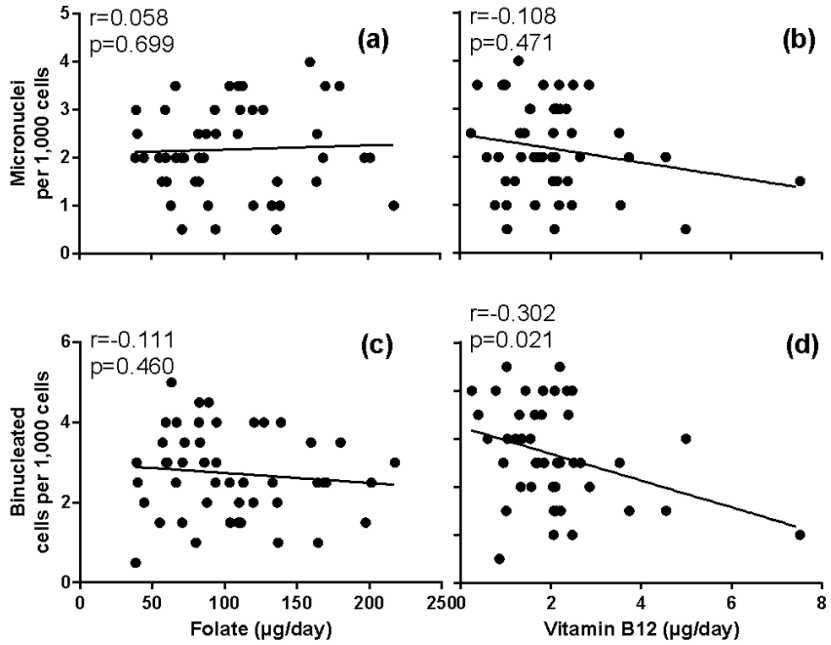

Figure 3. Association between micronuclei and binucleated cells frequency with folate (a, c) and vitamin B12 (b, d) intake. r: correlation coefficient and p: significance level according to Spearman's test.

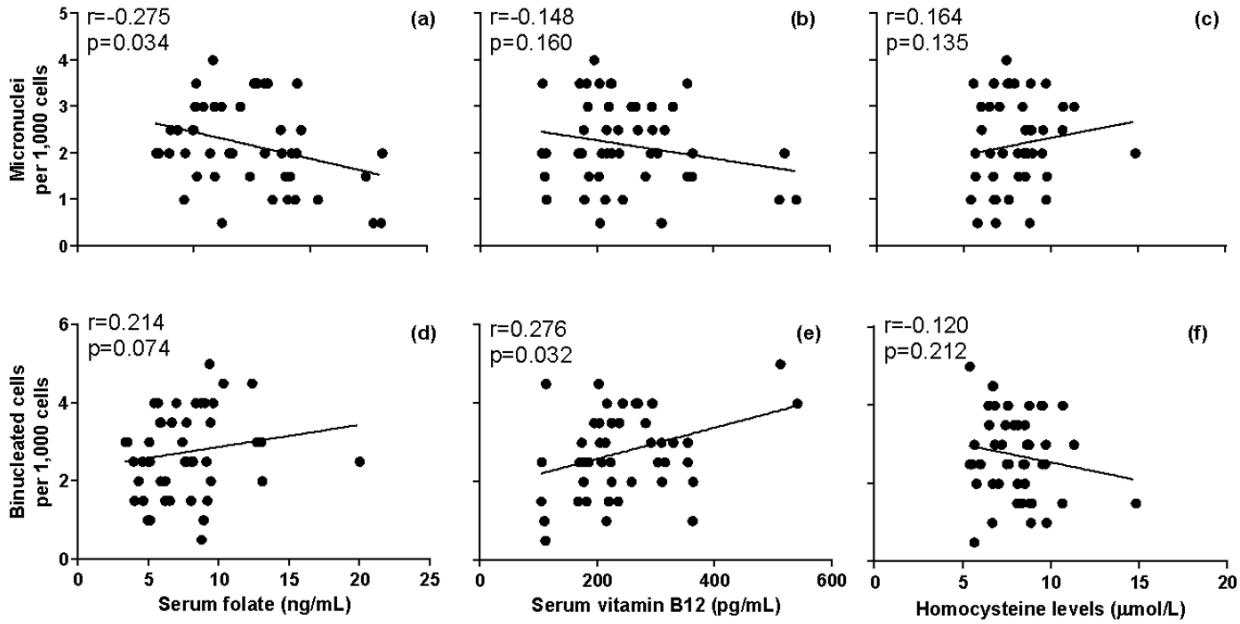

Figure 4. Association between micronuclei and binucleated cells frequency with folate (a, c) and vitamin B12 (b, d) serum levels. r: correlation coefficient and p: significance level according to Spearman's test.

frequency (r=−0.302, p=0.021; Figure 3d). In serum, there was a significant negative association between folate and the micronuclei frequency (r=−0.275; p=0.034; Figure 4a) and a significant positive association between vitamin B12 and binucleated cells frequency (r=0.276, p=0.032; Figure 4e). Hcy levels were not significantly associated with micronuclei frequency nor binucleated cells frequency (p>0.05).

DISCUSSION

This study evaluated the consumption and blood levels of both folate and vitamin B12 in female university students to assess whether there was an association with cardiovascular risk and/or genomic damage. It was expected that nutrition university students would present a low prevalence of folate inadequacy and vitamin B12 in diet and serum due to their knowledge on nutrition.

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However, our results showed that all female students had inadequate folate intake, with nearly half of them (48.9%) showing vitamin B12 inadequacy, following EAR values according to the DRI.[11] Pereira et al.[15] evaluated Brazilian undergraduate and graduate students aged 36.2±9.4 years and observed that 12% and 11.1% of the participants presented a possible insufficient intake of folate and vitamin B12, respectively, values smaller than the ones found in this study. Besides that, Manios et al.[16] also evaluated the coefficients of variation (CV) of food intake, finding 44.7% for folate and 65% for vitamin B12. The standard CV of DRI for healthy women is 62% for folate and 294% for vitamin B12 in the same age group of the population studied.[11] These values are much higher than ours (44.24% to folate intake and 61.8% to vitamin B12), showing that our subjects were more homogeneous than the subjects used by the DRI and similar to the study by Manios et al.[16]

In this study, the prevalence of folate serum levels inadequacy was lower than in the diet (6.4% vs. 100%). As for vitamin B12 serum levels, 10.6% of the individuals had levels below 174 pg/mL, and 93.6% of women had figures below 490 pg/mL. Those results were lower when compared to an Australian study that evaluated young adult women.[9]

Hcy is a metabolite of methionine (since humans do not acquire Hcy by food) and a key intermediate metabolite in the folate cycle-linked metabolic processes of remethylation and transsulfuration, producing L-methionine and L-cysteine, respectively.[17] Remethylation requires vitamin B12 and 5-methyltetrahydrofolate (active folate) as methyl donors. In the transsulfuration process, Hcy is irreversibly converted to cysteine and it can be utilized in protein synthesis and glutathione (GSH) production (beneficial antioxidant). In this context, lack of the various B-vitamins, such as B12 and folate could elicit an excessive level of Hcy (hyperhomocysteinemia), a modifiable risk factor for CVD.[8]

Hyperhomocysteinemia has been classified as moderate (16 to 30 µmol/L), intermediate (31 to 100 µmol/L), and severe (>100 µmol/L).[18] In this study, none of the women had Hcy above 16 µmol/L. Studies have also reported that Hcy levels above 10 µmol/L are associated with an increased risk of cardiovascular disease.[19] In our study, only 8.5% of women had Hcy levels above 10 µmol/L.

In addition, low folate intake or folate metabolism abnormalities, as well as vitamin B12 deficiency, can lead to Hcy elevation.[6] We did not observe an association between serum Hcy levels and folate or vitamin B12 intake. Nevertheless, only one subject (2.13%) presented an elevated level of Hcy (14.8 µmol/L) and none of them had it below 4.4 µmol/L. However, serum vitamin B12 above 490 pg/mL prevents functional deficiency more reliably.[12] Based on this criterion, 93.6% of the sample was at risk of vitamin B12 deficiency. Han et al.[20] also evaluated serum folate levels and found 10% inadequacy and, similarly to our study, found that 5% of the subjects had serum Hcy higher than 15 µmol/L. Besides that, they found that serum Hcy was negatively correlated with serum folate, which is contrary to our results. Folsom et al.[21] found a negative association between Hcy and vitamin B12, differing from our study, in which we did not find an association between these variables.

O'Keefe et al. evaluated only the folate intake, finding that among young women aged from 21 to 27 years, the intake of 200 µg/day of folate was negatively correlated with plasma Hcy,[22] being significantly higher than when compared with the ingestion of 300 to 400 µg/day of folate. These results show that elevated Hcy levels are associated with lower folate levels in the diet, possibly due to the need for this nutrient to prevent Hcy accumulation by converting Hcy into methionine. Another study, which evaluated university students in South Korea, found a negative correlation of folate with serum Hcy levels.[20] We did not evaluate folate supplementation; however, a meta-analysis assessing the effect of folic acid supplementation on the risk of cardiovascular disease found that it did not decrease the levels of Hcy in all the studies analyzed.[23] Thus, the authors did not recommend the supplementation of folic acid to decrease the risk of cardiovascular disease.

However, it has been reported that folate and vitamin B12 may present an important role in DNA metabolism.[24] These vitamins are required for the synthesis of methionine and S-adenosyl methionine, used for the maintenance of methylation patterns in DNA. Folate and Vitamin B12 deficiencies can lead to elevated DNA damage rate and altered DNA methylation, important risk factors for the increase of Hcy status.[3] Using comet assay, we found a significant association between folate and vitamin B12 in the diet with DNA damage (both index and frequency of damage). Regarding BMCyt assay, only vitamin B12 intake was negatively associated with binucleated cells. In addition, serum folate levels presented an inverse association with the index and frequency of DNA damage, as well as with the micronuclei frequency. No association was found between serum vitamin B12 levels and DNA damage by comet assay, but serum vitamin B12 was associated with binucleated cells frequency. Milić et al. found a significant association between serum vitamin B12 and increased DNA damage using the comet assay.[25] These authors also reported that a higher serum vitamin B12 concentration was associated with a lower frequency of micronuclei, corroborating our study, in which we found this tendency but without statistical significance (Figure 4). According to Fenech, the increased micronuclei frequency is an important biomarker associated with defects in the metabolic pathways that requires folate and vitamin B12.[9]

Increased or slightly increased Hcy might contribute to DNA damage induction. We observed a significant association between serum Hcy and DNA damage (both index and frequency of damage). Regarding DNA damage evaluated by the lymphocyte micronucleus assay, the study of Fenech found that elevated plasma Hcy was associated with increased micronucleus formation.[9] We did not find this association, possibly due to the low age range of our subjects and since only one subject had

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increased level of Hcy. Besides that, Fenech[9] also showed that the micronuclei frequency is lower when serum Hcy is below 7.5 µmol/L and when the plasmatic vitamin B12 is higher than 300 pmol/L.

Our study holds some limitations that should be highlighted. Firstly, the 24-hour food recall method, though widely acknowledged as the gold standard for assessing food intake, is dependent on respondents' full cooperation, memory, and honesty. As a result, it may lead to potential underestimation or overestimation of their actual intake. To mitigate this, efforts were made to ensure participants understood the importance of accurate reporting. Secondly, the cross-sectional design of this study limits its capacity to establish a causal relationship between the analyzed variables. To address this limitation, future research should consider employing longitudinal studies or experimental designs to explore causal associations more effectively. Despite these limitations, the study gains strength in evaluating nutrition course students, as there are only a few existing studies on this specific topic. This uniqueness adds value to the findings and offers valuable insights into an underexplored area of research.

In conclusion, the results from this study showed that Hcy levels were not associated with folate and vitamin B12 intake or serum levels in this population of female university students. However, folate and vitamin B12 intake were positively associated with damage index and frequency, whereas only folate serum was negatively associated with damage index and frequency. Furthermore, binucleated cells frequency was negatively associated with vitamin B12 intake and positively associated with serum levels. There was a significant negative correlation between micronuclei frequency and folate, but not serum levels. Additionally, Hcy levels were correlated with damage index and frequency, but not with micronuclei or binucleated cells frequency. Our findings strengthen the role of healthier eating patterns with adequate micronutrients, mainly folate and vitamin B12 intake.

Considering the results of this study, future research can deepen the understanding of the relationship between Hcy, folate, and vitamin B12 associated with genomic instability in the female university population. Consequently, further studies are necessary to investigate mechanisms related to the consumption of folate and vitamin B12, exploring direct influences on cellular processes or mediating factors and identifying protective or modulating mechanisms for these cellular events. Longitudinal and intervention studies are also recommended to assess dietary patterns over time, aiming to analyze the relationship with Hcy, folate, and vitamin B12, providing a more profound understanding of these biomarkers and whether adequately adjusting the intake of folate and vitamin B12 can positively impact cellular damage markers and Hcy levels.

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AUTHOR'S CONTRIBUTIONS

Luana Beatriz Limberger performed the experiment and wrote the manuscript. **Patrícia Molz** performed the experiment, analyzed the data, and wrote the manuscript. **Caio Fernando de Oliveira** and **Jane Dagmar Pollo Renner** performed the experiment and helped with constructive discussions. **Silvia Isabel Rech Franke** designed and guided the research.

All the authors read, critically evaluated, gave their feedback, and edited the manuscript.

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Hospital Santa Cruz

ORIGINAL ARTICLE

Epidemiological profile of patients with ventilation-associated pneumonia in a teaching hospital

Perfil epidemiológico de pacientes com pneumonia associada à ventilação mecânica de um hospital escola

Perfil epidemiológico de pacientes con neumonía asociada a ventilación mecánica en un hospital universitario

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ABSTRACT

Background and Objectives: Ventilator-associated pneumonia may occur within 48 to 72 hours after endotracheal intubation and mechanical ventilation, being the most frequent infection in intensive care units, linked to increased mortality. This research aims to identify the epidemiological profile of patients with ventilator-associated pneumonia in the intensive care unit of a teaching hospital. **Methods:** This is a cross-sectional, retrospective, documentary study with a quantitative approach. The data collection was carried out using a semi-structured instrument with data made available by the Hospital Infection Control Commission and in the electronic medical records of patients diagnosed with ventilator-associated pneumonia, from July to December 2022. Data were organized using the Excel software and subsequently analyzed with the program Statistical Package for Social Science for Windows, using descriptive statistics. **Results:** Most individuals were male (59.6%), aged 60 years or older (53.9%), retired (48.3%), nondrinkers (61.8%), nonsmokers (66.3%), with pre-existing comorbidities (62.9%), hospitalized due to trauma (23.6%), enteral nutrition (97.8%), Klebsiella pneumoniae pathogenic agent (15.7%), using endotracheal tube (91.7%), not requiring reintubation (67.4%), not presenting multidrug resistance (59.6%), and the clinical outcome was death (65.2%). **Conclusion:** There is still a need for specific interventions and measures for critically ill patients. It is expected that the variables found may contribute to promoting patient safety on mechanical ventilation and help to develop prevention strategies in order to reduce the incidence of ventilator-associated pneumonia.

Keywords: *Pneumonia, Ventilator-Associated. Intensive Care Units. Health Profile.*

RESUMO

Justificativa e Objetivos: A pneumonia associada à ventilação mecânica (PAV) ocorre a partir de 48 a 72 horas

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após a intubação endotraqueal e ventilação mecânica, sendo a infecção mais frequente nas unidades de terapia intensiva, vinculada ao aumento da mortalidade. Esta pesquisa tem como objetivo identificar o perfil epidemiológico de pacientes com PAV em Unidades de Terapia Intensiva de um hospital escola. **Métodos:** Trata-se de um estudo transversal, retrospectivo, documental, com abordagem quantitativa. A coleta foi realizada através de instrumento semiestruturado, com dados disponibilizados pela Comissão de Controle de Infecção Hospitalar e nos prontuários eletrônicos dos pacientes com diagnóstico de PAV, entre julho a dezembro de 2022. Os mesmos foram organizados no software Excel e, posteriormente, analisados através do programa SPSS®, versão 22, mediante estatísticas descritivas. **Resultados:** A maioria era do sexo masculino (59,6%), faixa de etária de 60 anos ou mais (53,9%), aposentados (48,3%), não etilistas (61,8%), não tabagista (66,3%), com comorbidades preexistentes (62,9%), diagnóstico de internação por trauma (23,6%), nutrição enteral (97,8%), agente patogênico *Klebsiella pneumoniae* (15,7%), em uso de tubo endotraqueal (91,7%), não precisaram de reintubação (67,4%), não tiveram multirresistência (59,6%), e apresentaram como desfecho clínico óbito (65,2%). **Conclusão:** O perfil epidemiológico se caracteriza pelo sexo masculino, com idade igual ou superior a 60 anos, com comorbidades, vítima de trauma e com desfecho clínico desfavorável ao óbito. Espera-se que as variáveis encontradas possam contribuir para promover a segurança do paciente em ventilação mecânica e ajudar a desenvolver estratégias de prevenção, a fim de reduzir a incidência de PAV.

Descritores: *Pneumonia Associada à Ventilação Mecânica. Unidades de Terapia Intensiva. Perfil de Saúde.*

RESUMEN

Justificación y Objetivos: La neumonía asociada a ventilación mecánica (NAVM) ocurre entre 48 y 72 horas después de la intubación endotraqueal y ventilación mecánica, por lo que es la infección más frecuente en las unidades de cuidados intensivos asociada al aumento de la mortalidad. Este estudio tiene como objetivo identificar el perfil epidemiológico de los pacientes con neumonía asociada a ventilación mecánica en la unidad de cuidados intensivos de un hospital universitario. **Métodos:** Se trata de un estudio transversal, retrospectivo, documental, con enfoque cuantitativo. La recogida de datos se realizó mediante un instrumento semiestructurado con datos facilitados por la Comisión de Control de Infecciones Hospitalarias y en los registros electrónicos de pacientes con diagnóstico de NAVM, en el período de julio a diciembre de 2022. Los datos se pusieron en *software* Excel para, posteriormente, pasar por un análisis mediante el programa *Statistical Package for Social Science para Windows*, versión 22, utilizando estadística descriptiva. **Resultados:** La mayoría de los participantes fueron hombres (59,6%), mayores de 60 años (53,9%), jubilados (48,3%), no bebedores (61,8%), no fumadores (66,3%), con comorbilidades preexistentes (62,9%), diagnóstico de hospitalización por traumatismos (23,6%), nutrición enteral (97,8%), agente patógeno Klebsiella pneumoniae (15,7%), en uso de tubo endotraqueal (91,7%), no requirieron nueva intubación (67,4%), no presentaron multirresistencia (59,6%) y tuvieron como desenlace clínico muerte (65,2%). **Conclusión:** El perfil epidemiológico se caracterizó por sexo masculino, de 60 años o más, con comorbilidades, víctima de traumatismos y desenlace clínico desfavorable de muerte. Se espera que las variables encontradas puedan contribuir a promover la seguridad del paciente en la ventilación mecánica y ayudar a desarrollar estrategias de prevención para reducir la incidencia de NAVM.

Palabras Clave: *Neumonía Asociada al Ventilador. Unidades de Cuidados Intensivos. Perfil de Salud.*

INTRODUCTION

Intensive care unit (ICU) is a continuous monitoring ward of hospitals that provides care to critically ill patients with hemodynamic instability and high risk of death. Due to this complexity and numerous invasive procedures performed, patients face a high risk of developing Healthcare-associated infections (HAIs).[1]

HAIs are characterized as adverse events that persist in health services, and are considered a serious public health issue, as they put patient safety at risk, in addition to negatively affecting the quality of health services. It is important to emphasize that most HAIs can be avoided.[2]

Ventilator-associated pneumonia (VAP) is one of the most common HAIs in an ICU, which may occur within 48 to 72 hours after endotracheal intubation, with a high mortality rate. This infection prolongs the duration of hospital stay and mechanical ventilation (MV), considerably increasing treatment costs.[3]

To obtain the diagnosis of VAP, clinical, radiological, and laboratory criteria should be used; the most important are: the presence of hyperthermia (temperature ≥ 37.8°C), with no other related cause; the change in secretion characteristics; worsening gas exchange with the need to increase oxygen supply or increase ventilatory parameters; and alteration in pulmonary auscultation. After diagnosis of underlying heart or lung diseases, medical imaging tests should be performed to obtain the following measurement: infiltration, opacification, and cavitation. Laboratory tests should

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show changes in blood culture without other points of infection, leukopenia (< 4,000 cel/mm^3) or leukocytosis (> 12,000 cells/mm^3), positive result for pleural fluid culture, positive result for culture of pulmonary secretions obtained by alveolar broncholavage lavage or tracheal aspirate.[4]

The literature indicates different mortality rates caused by VAP, but it is estimated that approximately 33% of patients with VAP died as a direct result of the infection, and the overall mortality associated with it varies from 20% to 60%, depending on associated risk factors.[5]

A study carried out in an ICU in Bueno Aires identified that some patients were diagnosed more than once with VAP and there was a predominance of the disease in male patients: 50% of them were aged over 70 years, and the mortality rates at 30 and 90 days after the infection diagnosis were 30% and 63.7%, respectively.[6] Therefore, it is necessary to identify the epidemiological profile of patients with VAP, since they involve possible risk factors.

This research is justified, for it may contribute to the hospitals awareness of these patients' profile, thus being able to develop strategies to improve the provided care, aiming at reducing VAP rates, implementing specific and intensive care, instructing the multidisciplinary team using protocols, training, continuing education, and continuous monitoring of these means. Moreover, it may also contribute to the emergence of new scientific research on VAP, which may help both professionals and lay people to better understand the disease, how it occurs, and why this infection affects more than one specific patient profile.

Thus, this study aimed to identify the epidemiological profile of patients with VAP in ICU of a teaching hospital.

METHODS

This is a cross-sectional, retrospective, documental study, with a quantitative approach, carried out in the ICU of a teaching hospital, which only hospitalizes patients via the Brazilian Unified Health System (SUS), provides 40 regular beds in the unit, and is a reference in trauma and orthopedics, serving 12 municipalities that make up the 3rd Regional Health District of Paraná.

The study population consisted of 89 patients who were hospitalized in the adult ICU of a teaching hospital and who were diagnosed with ventilator-associated pneumonia from July to December 2022. The inclusion criteria was patients aged 18 years or older, who were hospitalized and diagnosed with VAP during hospitalization. Patients aged under 18 years or those which medical records were not fully available were excluded from the study.

Data collection was carried out using a semi-structured instrument, with information provided by the Hospital Infection Control Committee (CCIH) of the institution and consultation of the patients' electronic medical records, using the Tasy information system. Following the variables of interest: sociodemographic (sex, age group, occupation) and clinical-epidemiological (alcoholism, smoking, preexisting comorbidity, hospitalization diagnosis, enteral nutrition, pathogen, airway management, reintubation, multidrug resistance, outcome, previous and total days of hospitalization, and ventilation).

The data collected in the medical records were organized and tabulated in Excel program and analyzed by the program Statistical Package for Social Science for Windows (SPSS®) version 22, using descriptive statistics of absolute and relative frequency.

This study was submitted to the Research Ethics Committee of Cesumar University, according to opinion No. 6,054,902 CAAE No. 69280823.9.0000.5539, respecting the recommendations contained in Resolutions No. 466/2012, No. 510/2016 and No. 580/2018 of the National Health Council (CNS), which provides for the guidelines and standards for research involving human beings.

RESULTS

Of the 89 patients hospitalized with VAP, 53 (59.6%) were male; 48 (53.9%) were aged 60 years or older, with a average age of 57.8 years; 43 (48.3%) were retired; 55 (61.8%) did not drink; 59 (66.3%) were nonsmokers; 56 (62.9%) had comorbidities such as systemic arterial hypertension (SAH), diabetes mellitus (DM), and chronic obstructive pulmonary disease (COPD) (Table 1).

Regarding hospitalization diagnoses, trauma was the most common cause, with 21 (23.6%) cases; followed by respiratory insufficiency (n = 15; 16.9%); stroke (n = 15; 16.9%); lowered level of consciousness (n = 11; 12.4%); and other causes (n = 27; 30.2%) (Table 1).

Regarding other variables, 87 (97.8%) were under enteral nutrition; pathogens were identified in 40.4% of the patients: *Klebsiella pneumoniae* in 14 (15.7%) patients; *Acinetobacter baumannii* in 9 (10.1%); *Staphylococcus aureus* in 7 (7.9%); *Pseudomonas aeruginosa* in 6 (6.7%) patients; and *Enterobacter cloacae* in 6 (6.7%) patients. Regarding the device, 81 (91.1%) used an endotracheal tube; 80 (67.4%) did not require reintubation; and 53 (59.6%) did not present multidrug resistance. Regarding clinical outcome, 58 (65.2%) of the patients died and 31 (34.8%) were discharged from the hospital (Table 1).

The average length of hospital stay was 30 days and average duration of MV was 19 days. The average length of hospital stay prior to VAP was 8.7 days and the average duration of ventilation prior to VAP was 9.1 days.

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Table 1. Epidemiological profile of patients diagnosed with ventilator-associated pneumonia (n=89). Ponta Grossa, Paraná, Brazil, 2023.

Parameter	N (%)
Sex	
Male	53 (59.6)
Female	36 (40.4)
Age group	
18 to 39 years old	20 (22.5)
40 to 59 years old	21 (23.6)
≥ 60 years old	48 (53.9)
Occupation	
Retired	43 (48.3)
Employed/Self-employed/Student	29 (32.6)
Unemployed	17 (19.1)
Alcoholism	
Yes	34 (38.2)
No	55 (61.8)
Smoking	
Yes	30 (33.7)
No	59 (66.3)
Pre-existing comorbidity	
Yes	56 (62.9)
No	33 (37.1)
Hospitalization diagnosis	
Trauma	21 (23.6)
Respiratory failure	15 (16.9)
Stroke	15 (16.9)
Lowered level of consciousness	11 (12.4)
Others	27 (30.2)
Enteral nutrition	
Yes	87 (97.8)
No	2 (2.2)
Pathogen	
Klebsiella pneumoniae	14 (15.7)
Acinetobacter baumannii	9 (10.1)
Staphylococcus aureus	7 (7.9)
Pseudomonas aeruginosa	6 (6.7)
Enterobacter cloacae	6 (6.7)
Others	10 (11.2)
Airway management	
Negative culture	37 (41.7)
Endotracheal tube	81 (91.1)
Tracheostomy	8 (8.9)
Reintubation	
Yes	29 (32.6)
No	80 (67.4)
Multi-resistance	
Yes	36 (40.4)
No	53 (59.6)
Outcome	
Discharge	31 (34.8)
Death	58 (65.2)

DISCUSSION

Most participants of this study were males. The Brazilian guidelines for treating hospital-acquired pneumonia and VAP indicate being male as an independent risk factor for the disease, i.e., it produces a change in health/disease status as a risk factor or exposure.[7] A descriptive and quantitative study in an ICU in the city of Teresópolis presented a similar result, but with a prevalence of 73% male patients in a sample of 52 people, which was even higher.[8]

A descriptive, cross-sectional, documental study with a quantitative approach including 20 medical records of patients hospitalized in an adult ICU of a medium-sized hospital, diverged with our study regarding age, in which the highest incidence of VAP occurred in those aged under 60 years.[9] Advanced age is a nonmodifiable risk factor for VAP diagnosis, since the body of older adults undergoes physiological changes due to aging, immunity decline, predisposition to chronic diseases, and invasive procedures, which can aggravate or increase the body response to the disease.[10] Therefore, due to the older adults' frailty and the need for an advanced airway management, the risk of complications due to this infection is increased.

An integrative literature review with articles published in the last 10 years in the Virtual Health Library and in the MEDLINE and LILACS databases, performing a descriptive analysis of 10 articles, found smoking as one of the main risk factors for acquiring PAV,[11] in accordance with the prevalence found in this study. Smokers face higher risks due to the harm of cigarette smoke to the functioning of immune system, degrading the lung cells, decreasing the immunoglobulins circulating in the blood, and presenting a high amount of altered leukocytes, which can cause recurrent infections.[12] We suggest a need for further anti-smoking programs to help people quit smoking, to show how harmful it is to health, and to discourage young people from starting to smoking cigarettes and/or e-cigarettes. Alcohol consumption can also interfere with the clinical recovery of hospitalized patients, by weakening the body.[13]

This study showed a predominance of patients with preexisting comorbidities, similar to a retrospective, documental study, with a quantitative approach developed in João Pessoa, Paraíba, including 59 medical records, which shows a prevalence of 74% patients with comorbidities.[14] Preexisting clinical manifestations are determining factors for the need for ICU admission, in addition to the predisposition to complications and increased difficulty in recovery when affected by new diseases, such as VAP. The increase of aging-related diseases and the difficult access to quality healthcare greatly impact the health of the population and place these diseases among the main causes of death worldwide.[15] Programs are needed to improve adherence to treatments related to comorbidities (SAH, DM, COPD), maintaining these morbidities under control and reducing damage to the patient's body.

Regarding the diagnosis for hospitalization, trauma was the most prevalent in patients with VAP. In a retrospective study, carried out at the Hamad General Hospital in Qatar, the highest rate of VAP was identified in patients who suffered severe injuries caused by trauma.[16] In this study, the main diagnosis for hospitalization is associated with the profile of the institution, which is a regional

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reference center in major trauma. It is understood that trauma patients are more susceptible to developing VAP due to the need for ventilatory support, severely injured patients may require an early advanced airway management and MV for longer than other patients.[17]

Most patients in this study were under enteral nutrition. A descriptive, documentary, retrospective study, with a quantitative approach, carried out in a public teaching hospital in the city of Cascavel, demonstrated that, of the 146 patients diagnosed with VAP, 54.1% of the patients used a nasoenteral tube (NET).[18] Malnourished and patients with obesity may develop greater vulnerability to infection and death.[14] The association of nutritional status with the clinical outcome of patients in a hospital environment still needs to be continuously monitored, since malnutrition considerably increases hospital mortality, both in critical and non-critical patients.[19]

Regarding pathogens, in this study, there was a prevalence of Gram-negative *K. pneumoniae Carbapenemase* KPC, responsible for several infections, especially nosocomial infections. Similar data were found in a descriptive, cross-sectional, retrospective, and quantitative study, carried out in an adult ICU of a medium-sized hospital, in which the predominant microorganism was *K. pneumoniae Carbapenemase* (45% of cases).[9] It can be observed that multidrug-resistant Gram-negative bacteria are present in most studies, corroborating our results. According to the Brazilian National Health Surveillance Agency (ANVISA), the dissemination of KPC-producing enterobacteriaceae is a serious clinical and epidemiological problem in several Brazilian health institutions. Moreover, the antimicrobial therapy applied in the treatment is based on the use of Polymyxin B or Polymyxin E, together with one or more antibiotics, such as aminoglycosides (gentamicin or amikacin), Carbapenems (meropenem or doripenem), and tigecycline.[20]

Endotracheal intubation is characterized as a medical emergency, since the patient requires invasive ventilation immediately. Regarding the device used in this study, endotracheal intubation was predominant, corroborating an analytical, cross-sectional, and retrospective study conducted in Piauí, which recorded 58.3% of use in a sample of 36 patients with VAP.[21] According to ANVISA, endotracheal intubation facilitates bacterial colonization of the tracheobronchial tree and aspiration of contaminated secretion from the upper airways, due to the decrease in the cough reflex, the accumulation of secretion above the cuff, and the contamination of the tube itself.[5]

In our study, there were few cases of reintubation, which corroborates a retrospective, documental study with a quantitative approach, developed in a teaching hospital, in which 34% of the patients required reintubation.[14] Early extubation is one of the predisposal factors to reintubation. This procedure favors reintubation in the first 24 hours after MV removal, causing an increased incidence of secondary VAP due to the risk of aspirating secretion from the upper airways.[5]

For microbial resistance, patients with VAP of our sample developed some type of microbial multidrug resistance. A retrospective cohort study conducted in the ICU of a medium-sized hospital located in the inland Rio Grande do Sul, Brazil, also demonstrated evidence of pathogenic microorganisms resisting to antibiotics.[22] The antibiotic resistance is a serious public health concern, as it interferes with infection control, increases the risk of morbidity and mortality, reduces therapeutic efficacy, poses a risk to patient safety, and causes high costs for health care.[23] Thus, to reduce resistant microorganisms in health services, it is necessary to implement strategies for the rational use of antimicrobials, to evaluate appropriate administration, and correct duration of antibiotic therapy.

In this study, the clinical outcome of 65.2% of the cases was death. In a descriptive study with a prospective approach, developed in the adult ICU of the Dr. Heitor Vieira Dourado Tropical Medicine Foundation, similar results were obtained in a sample of 30 patients, from which 63.3% died due to VAP.[24] Notably, some studies cited indicate the high mortality rate associated with VAP, reaffirming that this infection is a risk factor for death in ICUs. To reduce death figures associated with VAP, it is necessary to implement prevention actions in intensive care units, such as the use of a VAP prevention bundle, periodic training, as well as continuing and permanent training.[17]

The average length of hospitalization of patients diagnosed with VAP was 30 days in an observational, cross-sectional, and retrospective study conducted in a teaching hospital in the south of Minas Gerais. It corroborates our outcomes, which showed an average length of stay of 27 days.[25] This is an alarming data, because staying in the hospital environment increases the risk of infections and, as a consequence, hospital costs and the chances of an unfavorable outcome, such as death. The duration of MV in this study was longer than in a study conducted in an adult ICU with a MV time <10 days.[24] The increase in MV time is an important risk factor for acquiring VAP, since it compromises the body defense, favors the installation and multiplication of more resistant, aggressive, pathogenic microorganisms, and contributes to high mortality rates.[5]

The retrospective and documental design holds some limitations, as there is no direct contact with the patient, making it impossible to collect data in full and with real infection potentials. Some information about the living conditions of the people studied was unavailable. It is known that, the closer the disease occurs to the individual, the closer it is to biological explanations, in which professionals and managers have proportionally reduced success over the collective impact.

Despite the research limitations, numerous benefits may be provided not only to the studied institution, but also to other institutions, in addition to contributing to the emergence of new research on the subject, to improve the quality of care provided to patients. Based on the knowledge of the epidemiological profile that is most susceptible to the development of VAP and the variables with the highest prevalence of infection, the institution can elaborate management and care protocols along with patient safety and the Hospital Infection Control

Committee, as well as promote continuing training with professionals who work directly in the care of patients on MV, to avoid and minimize the VAP incidence.

According to the outcomes, it was found that the epidemiological profile of patients with VAP were male, aged 60 years or older, with preexisting comorbidities, mostly victims of trauma, with prolonged hospitalization and ventilation, and with a prevalent clinical outcome of death.

This study concludes that there is still a need for interventions, continuing education, and the development of specific measures for critically ill patients. Therefore, we hope that these variables can contribute to promoting patient safety in MV and improving the quality of care provided to them. Furthermore, it is expected to help in developing prevention strategies to reduce VAP incidence.

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AUTHORS' CONTRIBUTIONS

Iris Broggian Correa Nascimento, **Luciane Terezinha Ienke** and **Taís Ivastcheschen Taques** contributed to project administration, bibliographic research, writing of the abstract , introduction, methodology, discussion, interpretation, and description of results, conclusions, review, and statistics.

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ORIGINAL ARTICLE

Intestinal parasitosis in AIDS and/or HTLV patients: findings from an infectious disease reference hospital

Parasitoses intestinais em pacientes com AIDS e/ou HTLV: resultados de um hospital de referência em doenças infecciosas

Parasitosis intestinal en pacientes con SIDA y/o HTLV: hallazgos de un hospital de referencia en enfermedades infecciosas

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ABSTRACT

Background and Objectives: Human Immunodeficiency Virus (HIV) and Human T-Lymphotropic Virus (HTLV) infections precipitate immunological deficiencies, predisposing afflicted individuals to opportunistic diseases and exacerbating clinical symptoms. A prevalent health concern among these patients is enteroparasitosis. This research delineates the intestinal parasitosis profile in patients diagnosed with AIDS and/or HTLV at a specialized infectious disease hospital in Alagoas. **Methods**: this quantitative, cross-sectional analysis was conducted from August 2021 to May 2022, encompassing patients diagnosed with AIDS and/or HTLV. The study employed various coproparasitological assessments, including the Hoffman, Pons, and Janer, Baermann-Moraes, and Safranin-methylene blue techniques, complemented by macroscopic examination of fecal consistency. These assessments were carried out at the Infectious-Parasitic Diseases Laboratory of the *Universidade Estadual de Ciências da Saúde de Alagoas*. Data processing was performed utilizing the Statistical Package for the Social Sciences®. Ethical clearance was obtained from the *Universidade Estadual de Ciências da Saúde de Alagoas* Research Ethics Committee. **Results**: from the 77 participants recruited, 44 provided fecal specimens. All participants were HIV-positive, with a male predominance. Enteroparasites were detected in 27.27% of the samples. Notably, *Entamoeba histolytica/Entamoeba dispar* and *Strongyloides stercoralis* emerged as the most prevalent protozoan and helminth, respectively. The Hoffman, Pons, and Janer technique successfully identified parasites in all positive samples. Treatment was administered to all patients with positive findings. **Conclusion**: the significant prevalence of opportunistic parasites observed underscores the criticality of routine coproparasitological screening in immunocompromised patients. Such proactive measures are essential to mitigate the risk of heightened morbidity and mortality within this vulnerable population.

Keywords: *Acquired Immunodeficiency Syndrome. Human T-lymphotropic virus 1. Human T-lymphotropic virus 2. Opportunistic Infections. Parasitic Intestinal Disease.*

RESUMO

Justificativa e Objetivos: as infecções pelo Vírus da Imunodeficiência Humana (HIV) e pelo Vírus Linfotrópico T Humano (HTLV) desencadeiam deficiências imunológicas, predispondo os indivíduos afetados a doenças oportunistas e exacerbando sintomas clínicos. Uma preocupação de saúde prevalente entre esses pacientes é a enteroparasitose. Esta pesquisa delineia o perfil de parasitose intestinal em pacientes diagnosticados com AIDS e/ou HTLV em um hospital especializado em doenças infecciosas em Alagoas. **Métodos**: esta análise quantitativa e transversal foi realizada de agosto de 2021 a maio de 2022, abrangendo pacientes diagnosticados com AIDS e/ou HTLV. O estudo empregou diversas avaliações coproparasitológicas, incluindo as técnicas de Hoffman, Pons e Janer, Baermann-Moraes e azul de metileno safranina, complementadas por exame macroscópico da consistência fecal. Essas avaliações foram executadas no Laboratório de Doenças Infecto-Parasitárias da Universidade Estadual de Ciências da Saúde de Alagoas. O processamento dos dados foi realizado utilizando o Pacote Estatístico para as Ciências Sociais®. A aprovação ética foi obtida do Comitê de Ética em Pesquisa da Universidade Estadual de Ciências da Saúde de Alagoas. **Resultados**: dos 77 participantes recrutados, 44 forneceram amostras fecais. Todos os participantes eram HIV-positivos, com predominância masculina. Enteroparasitas foram detectados em 27,27% das amostras. Notavelmente, *Entamoeba histolytica/Entamoeba dispar* e *Strongyloides stercoralis* emergiram como o protozoário e helminto mais prevalentes, respectivamente. A técnica de Hoffman, Pons e Janer identificou com sucesso parasitas em todas as amostras positivas. Tratamento foi administrado a todos os pacientes com achados positivos. **Conclusão:** a significativa prevalência de parasitas oportunistas observada sublinha a criticidade da realização rotineira de exames coproparasitológicos em pacientes imunocomprometidos. Tais medidas proativas são essenciais para mitigar o risco de aumento da morbidade e mortalidade nessa população vulnerável.

Descritores*: Síndrome da Imunodeficiência Adquirida. Vírus Linfotrópico de Células T Tipo 1 Humano. Vírus Linfotrópico de Células T Tipo 2 Humano. Infecções Oportunistas. Doenças Parasitárias.*

RESUMEN

Justificación y Objetivos: las infecciones por el Virus de Inmunodeficiencia Humana (VIH) y el Virus Linfotrópico Humano de Células T (HTLV) provocan deficiencias inmunológicas, predisponiendo a los individuos afectados a enfermedades oportunistas y exacerbando los síntomas clínicos. Una preocupación sanitaria prevalente entre estos pacientes es la enteroparasitosis. Esta investigación delinea el perfil de parasitosis intestinal en pacientes diagnosticados con SIDA y/o HTLV en un hospital especializado en enfermedades infecciosas en Alagoas. **Métodos**: este análisis cuantitativo y transversal se llevó a cabo de agosto de 2021 a mayo de 2022, abarcando a pacientes diagnosticados con SIDA y/o HTLV. El estudio empleó diversas evaluaciones coproparasitológicas, incluyendo las técnicas de Hoffman, Pons y Janer, Baermann-Moraes y azul de metileno safranina, complementadas con el examen macroscópico de la consistencia fecal. Estas evaluaciones se realizaron en el Laboratorio de Enfermedades Infecto-Parasitarias de la *Universidade Estadual de Ciências da Saúde de Alagoas*. El procesamiento de datos se llevó a cabo utilizando el Paquete Estadístico para las Ciencias Sociales®. Se obtuvo la aprobación ética del Comité de Ética en Investigación de la *Universidade Estadual de Ciências da Saúde de Alagoas*. **Resultados**: de los 77 participantes reclutados, 44 aportaron muestras fecales. Todos los participantes eran VIH positivos, con una predominancia masculina. Se detectaron enteroparásitos en el 27,27% de las muestras. Notablemente, *Entamoeba histolytica/Entamoeba dispar* y *Strongyloides stercoralis* emergieron como el protozoo y helminto más prevalentes, respectivamente. La técnica de Hoffman, Pons y Janer identificó con éxito parásitos en todas las muestras positivas. Todos los pacientes con resultados positivos recibieron tratamiento. **Conclusión**: la prevalencia significativa de parásitos oportunistas observada subraya la importancia de la evaluación coproparasitológica rutinaria en pacientes inmunocomprometidos. Tales medidas proactivas son esenciales para mitigar el riesgo de aumentar la morbilidad y mortalidad en esta población vulnerable.

Palabras clave*: Síndrome de Inmunodeficiencia Adquirida. Virus Linfotrópico Tipo 1 de Células T Humanas. Virus Linfotrópico Tipo 2 de Células T Humanas. Infecciones Oportunistas. Enfermedades Parasitarias.*

INTRODUCTION

The Acquired Immunodeficiency Syndrome (AIDS) caused by the Human Immunodeficiency Virus (HIV) is considered a pandemic, with approximately one million cases detected in Brazil from 1980 to June 2018.[1] The definition of AIDS is associated with viral infection, high viral load, immunological deficiency, especially in CD4+ T-cells, which can lead to neoplasms and opportunistic infections.[2]

Another retrovirus that represents a public health concern is the Human T-Lymphotropic Virus (HTLV), which induces symptoms in a minority of patients (around 3% to 5% of infected individuals), whereas HIV causes clinical disease in all infected individuals.[3] Currently, two subtypes capable of infecting humans have been identified: HTLV I and HTLV II, both with tropism for T-lymphocytes.[4]

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Despite having a considerable national average prevalence (0.41%) and possessing immunosuppressive potential, HTLV infection is not subject to mandatory reporting, and the disease is neglected in the country.[1]

Among the opportunistic infections that can affect these immunocompromised patient groups, intestinal parasitosis stands out as one of the challenges faced by healthcare systems in developing countries like Brazil.[5] Controlling these parasitic infections requires widely available sanitation facilities, high access to clean water, and relatively adequate personal and domestic hygiene.[6] Furthermore, understanding the extent of intestinal parasitic infections in a community is crucial for planning efficient intervention programs.[7,8]

Understanding the prevalence of intestinal parasitosis in AIDS and/or HTLV patients is crucial to develop effective preventive measures and targeted treatments to improve their overall health outcomes. By exploring the presence and types of parasites in this vulnerable group, healthcare professionals can optimize diagnostic strategies and implement appropriate interventions, thereby reducing morbidity and mortality associated with enteroparasitosis.

Within the framework of this investigation, the primary objective is to delineate the epidemiological profile of intestinal parasitosis among patients hospitalized with AIDS and/or HTLV, specifically in a hospital renowned for its expertise in managing infectious diseases in the Alagoas State.

METHODS

The present study analyzes the prevalence of parasitic infections in immunocompromised patients. We specifically examined the hypothesis that there may be a correlation between parasitic infection and stool consistency in immunocompromised patients. To this end, the research adopted a quantitative and cross-sectional approach, utilizing medical records, questionnaires, and fecal samples from patients diagnosed with AIDS and/or HTLV. These patients were admitted to the *Hospital Escola Dr. Helvio Auto* (HEHA), a center of excellence for treating infectious diseases, located in Maceió, Alagoas. The timeframe for data collection spanned from August 2021 to May 2022.

Upon obtaining their consent to participate in the study, patients received a printed copy of the Informed Consent Form (ICF) from researchers, providing accessible and concise information about the purpose of the research and the manner in which they would participate. They were also informed that they could withdraw from the study at any stage.

Subsequently, a structured questionnaire related to socioeconomic and epidemiological aspects was administered to identify potential risk factors for parasitic infection, such as food preparation methods, hygiene habits, and living conditions.

Following this, fecal samples (approximately 25g) were collected from patients using wide-mouth containers with lids and examined using three parasitological methods: Hoffman, Pons, and Janer (HPJ); Baermann-Moraes (BM); and Safranin-methylene blue technique (SMBT).

The HPJ method aims to increase the concentration of eggs, larvae, or cysts and isolate fats from most of the debris through spontaneous sedimentation by gravitational or centrifugal force. As a result, the cysts, eggs, and larvae settle at the bottom of the container while the debris remains suspended at the surface.[9]

The BM technique identifies nematode larvae, particularly *Strongyloides stercoralis* and hookworms, based on the larvae's hydro- and thermotropism properties. It takes advantage of their attraction to warm water for isolation.[10]

The SBMT method uses differential staining to visualize oocysts separately from the rest of the fecal material. Consequently, the oocysts acquire a reddish color, whereas fecal artifacts appear blue under the microscope, allowing for a quick and easy diagnosis.[11]

These exams were performed at the Laboratory of Infectious-Parasitic Diseases (LaDIP), located in the Ib Gatto Research Pavilion within the headquarters of *Universidade Estadual de Ciências da Saúde de Alagoas* (UNCISAL). Biosafety measures were strictly observed for all these methods. Additionally, the data from the questionnaires, medical records, and coproparasitological sheets of each patient were individually entered into an Excel spreadsheet for subsequent tabulation.

The study included patients with confirmed diagnoses of AIDS and/or HTLV who were admitted to HEHA between August 2021 and May 2022. Only patients who willingly provided fecal samples for coproparasitological analysis were considered for inclusion. Patients with incomplete medical records or data on their AIDS/HTLV status, those who declined to participate, and individuals with known allergies or contraindications to the exam procedures were excluded from the study.

The data collected were subsequently tabulated and analyzed using the Statistical Package for the Social Sciences®. A percentage analysis of the results was performed and Fisher's exact test was applied, which assesses the association between two independent variables.[12] This test was used to establish the significance between stool consistency and presence of parasites as well as presence of mucus in stools and presence of parasites. A p-value of < 0.05 was used to determine significance between the two variables in question.

The study was approved by the UNCISAL Research Ethics Committee, under registration CAAE (*Certificado de Apresentação para Apreciação Ética* - Certificate of Presentation for Ethical Consideration) 70057017.2.00005011. Acceptance report 4.728.414 was approved on May 24, 2021. It included the main researcher's commitment statement and ethical statements as well as absence of conflicts of interest declarations from all researchers. The research was conducted in accordance with the ethical standards required - Ministry of Health Resolutions 466/2012, 510/2016, and 580/2018.

RESULTS

From August 2021 to May 2022, 111 patients with AIDS and/or HTLV admitted to HEHA were approached. Out of these, 77 agreed to participate in the research, granting access to their medical records and expressing interest in responding to the questionnaire and providing a fecal sample for intestinal parasite investigation. The reasons for refusal encountered were: a) discharge from the hospital; b) refusal to participate; c) bedridden patient without an accompanying person; d) psychiatric patient without isolation.

A total of 44 fecal samples were collected for coproparasitological examination. The numerical difference between the research participants and collected fecal samples occurred due to some patients either not providing the fecal sample for examination (due to hospital discharge or loss of the sample) or not being eligible for inclusion in the study. All participants in the research were HIV-positive, and none had HTLV infection.

Table 1 describes the sample socioeconomic profile. The majority of those infected with parasites were male (22.7%), aged between 35 and 39 years (9.1%), lived in the municipality of Maceió (15.9%), had incomplete elementary school (13.6%), had an income equal to or less than 2 minimum wages (25%) and were single (11.4%).

As shown in Table 2, parasitic infection was confirmed through coproparasitological exams in 27.27% (12) of patients. Among these, 83.33% (10) were infected with a single parasite species (monoparasitism), whereas 16.67% (2) were infected with multiple parasite species (polyparasitism).

Table 1. Independent variables related to sociodemographic data according to the presence or absence of intestinal parasites in HIV-positive patients admitted to a reference hospital for infectious diseases, Maceió, Alagoas.

Variable	Parasitized		Not parasitized	
	Absolute	%	Absolute	%
Sex				
Female	2	4.5	4	9.1
Male	10	22.7	28	63.6
Age range				
<18	0	0	0	0
18-24	1	2.3	1	2.3
25-29	0	0	1	2.3
30-34	0	0	4	9.1
35-39	4	9.1	6	13.6
40-44	0	0	6	13.6
45-49	2	4.5	8	18.2
50-54	1	2.3	1	2.3
55-60	2	4.5	3	6.8
>60	2	4.5	2	4.5
Municipality				
Maceió	7	15.9	19	43.2
Others	5	11.4	13	29.5
Income				
Up to 2 minimum wages	11	25	29	65.9
2-4 minimum wages	0	0	2	4.5
4-6 minimum wages	1	2.3	1	2.3
6-8 minimum wages	0	0	0	0
8 or more minimum wages	0	0	0	0
Education				
No education	3	6.8	5	11.4
Incomplete elementary school	6	13.6	22	50
Complete elementary school	0	0	0	0
Incomplete high school	0	0	0	0
Complete high school	1	2.3	3	6.8
Incomplete higher education	1	2.3	1	2.3
Complete higher education	1	2.3	1	2.3
Marital status				
Single	5	11.4	17	38.6
Married	4	9.1	4	9.1
Divorced	2	4.5	8	18.2
Widower	1	2.3	3	6.8

Table 2. Occurrence of enteroparasites in patients with AIDS assisted at a reference hospital for infectious diseases in Maceió, Alagoas, from August 2021 to May 2022.

Coproparasitological test		
Positive (%)	**Negative (%)**	**Total (%)**
12 (27.27)		
10 monoparasitized (83.33%)	32 (72.73)	44 (100)
2 polyparasitized (16.67)		

Table 3. Enteroparasites identified and quantity of positive results by parasitological technique performed in patients with AIDS assisted at a reference hospital for infectious diseases in Maceió, Alagoas, from August 2021 to May 2022.

Enteroparasites	HPJ*	BM**	SMBT ***
Protozoa			
Entamoeba histolytica/Entamoeba dispar	3	-	-
Endolimax nana	2	-	-
Cystoisospora belli	1	-	1
Giardia lamblia	1	-	-
Helminths			
Strongyloides stercoralis	4	4	1
Ancylostomatidae	2	-	-
Schistosoma mansoni	1	-	1

**Hoffman, Pons, and Janer; **Baermann-Moraes; ***Safranin-methylene blue technique.*

Table 3 shows the distribution of positive results for each parasite concerning the parasitological methods used: HPJ; BM; and SBMT. The findings revealed that under the protozoa category, *Entamoeba histolytica/ Entamoeba dispar* was identified in three instances exclusively through the HPJ method, whereas *Endolimax nana* was detected in two cases, also solely with HPJ. Additionally, *Cystoisospora belli* was observed in one case each by HPJ and SMBT, but not by BM. *Giardia lamblia* was detected in a single case, again only through HPJ. In

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Table 4. Relationship between stool consistency and the results of parasitological exams in patients with AIDS assisted at a reference hospital for infectious diseases in Maceió, Alagoas, from August 2021 to May 2022.

	Parasitological exam (N/%)			Odds Ratio	p-value
Stool consistency	**Negative**	**Positive**	**Total (N/%)**	1.1	1.0
Formed	22 (73.30)	8 (26.70)	30 (100)		
Diarrheic	10 (71.40)	4 (28.60)	14 (100)		
Total	32 (72.70)	12 (27.30)	44 (100)		

the helminths category, *Strongyloides stercoralis* showed a higher prevalence, being identified in four cases each with HPJ and BM, and in one case with SMBT. The family *Ancylostomatidae* was detected in two cases, but only through HPJ. Lastly, *Schistosoma mansoni* was identified in one case each by HPJ and SMBT, but not by BM.

These outcomes indicate that the HPJ method demonstrated a broader detection capability for a range of parasites in the sample. In contrast, the BM method showed a specific efficacy in identifying *Strongyloides stercoralis*. SMBT, while showing limited overall detection, was effective in identifying *Cystoisospora belli* and *Schistosoma mansoni*, highlighting its potential utility in diagnosing specific parasitic infections.

The macroscopic examination of the stools allowed the identification of 14 (31.81%) diarrheal samples, as shown in Table 4. Among them, only four (28.70%) were parasitized. Furthermore, mucus was found in five (35.71%) of the diarrheal samples and in seven (15.90%) out of the 44 samples collected. The relationship between the analyzed stool consistency and parasitized individuals, according to Fisher's exact test, was not statistically significant (p=1.0). The odds ratio of 1.1 suggests a slight, but not substantial, increase in the odds of testing positive for parasites in individuals with diarrheic stool compared to those with formed stool. However, this is not statistically significant.

DISCUSSION

Opportunistic infections by enteroparasites are found in 30-60% of HIV-positive patients in developed countries and 90% in developing countries. In particular, infections caused by agents such as *Cystoisospora belli*, *Cryptosporidium sp.*, and *Giardia duodenalis* have been frequently reported in individuals with AIDS.[13] For instance, *Cystoisospora belli* is an obligatory intracellular protozoan exclusive to humans, belonging to the phylum *Apicomplexa*, which leads to diarrhea, commonly reported in opportunistic infections, especially in individuals with CD4+ T lymphocyte count below 200 cells/ml.[14]

Cryptosporidium, on the other hand, is an intracellular extracytoplasmic protozoan that can cause diarrhea of varying severity in both immunocompetent and immunocompromised individuals. For instance, in individuals with AIDS or children with nutritional deficits, condition tends to be more severe.[15] Additionally, the protozoan *Giardia lamblia* and the nematode *Strongyloides stercoralis*, also found in immunocompetent individuals, are frequently identified in the parasitological profile of immunosuppressed individuals.[16]

Therefore, coproparasitological exams should be frequently requested for immunocompromised patients to determine the presence of any opportunistic agent or to ensure criteria for intestinal parasitic cure.[17]

The predominance of monoparasitized individuals among those with AIDS is consistent with findings in the literature,[18] although polyparasitism is more common in people with HIV than in immunocompetent individuals.[19] However, due to the small sample size, it is not possible to determine the relevance of this information. Nevertheless, it is necessary to mention that individuals with HIV/AIDS are 11.42 times more likely to develop parasitic infections than healthy individuals. In addition to environmental contamination, host nutritional and immunological factors are essential in the establishment of parasitic diseases.[20]

According to Table 1, the most frequently identified parasites in the exams were the protozoa species *Entamoeba histolytica/Entamoeba dispar* (25%) and the helminth species *Strongyloides stercoralis* (33.33%). Additionally, *S. stercoralis* is capable of causing severe gastroenteropathy and significant weight loss in HIV-positive individuals.[21] In immunocompromised individuals, hyperinfection syndrome may occur, with a mortality rate exceeding 80%.[22]

Two polyparasitized patients were detected, one infected with two species of protozoa (*Endolimax nana* and *Entamoeba histolytica/Entamoeba dispar*) and the other with two helminth species (*Ancylostomatidae* and *Schistosoma mansoni*). Polyparasitism can exacerbate the severity of infectious diseases, such as AIDS.[23] Moreover, in immunocompromised individuals, schistosomiasis is more likely to lead to portal hypertension, hepatic fibrosis, digestive bleeding, and severe liver failure in the chronic phase of the disease, resulting in death.[24]

Each fecal sample was analyzed using three different parasitological methods, as applying different techniques to the same individual's sample allows for greater accuracy and confidence in the results obtained. The BM technique, specific for identifying helminth larvae, only yielded positive results for *S. stercoralis* larvae. The Modified Ziehl-Neelsen technique identified *Cystoisospora belli* oocysts, *S. stercoralis* larvae, and *Schistosoma mansoni* eggs.

All parasites were detected using the HPJ method after analyzing the same fecal material. Thus, it is inferred

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that this technique was the most sensitive and comprehensive in diagnosing these enteroparasites, making it the most effective.[25]

Research participants are more vulnerable to opportunistic parasitic infections due to their immunocompromised status. Therefore, persistent symptoms, such as prolonged diarrhea, may be present, which, if not treated promptly, can lead to unfavorable outcomes for patients.[26]

All coproparasitological exams were performed promptly, and the reports were attached to patients' medical records so that positive cases could be treated by the hospital's technical staff. Treatment for HIV and/or HTLV-positive individuals is essential as symptoms can become chronic, given that the gastrointestinal tract is an organ significantly affected by HIV infection.[27]

A factor that can worsen parasitic infections affecting this population is poor adherence to antiretroviral therapy, which has significant implications for the immunosuppression of these individuals. Inadequate hygiene conditions, lack of basic sanitation, and consumption of contaminated water and food can also contribute to their increased vulnerability.[20]

Coccidia are also resistant to conventional water treatment.[20] This favors their viability and dissemination in the environment. Therefore, preventive measures for intestinal parasitic infections are the responsibility of both the individuals – through adherence to antiretroviral treatment and proper hygiene conditions – and the State, which should guarantee the constitutional right to basic sanitation.

The study has certain limitations that should be acknowledged. Firstly, the sample size of 77 participants, with only 44 providing fecal samples, may be considered relatively small, potentially affecting the study's statistical power and generalizability. Secondly, the cross-sectional design limits the ability to establish causal relationships between intestinal parasitosis and disease progression. Additionally, missing data on AIDS/HTLV status and other variables might introduce bias into the results. The sensitivity of the coproparasitological exam methods used could influence parasite detection accuracy.

Despite these limitations, the study provides valuable insights into the prevalence and profile of intestinal parasitosis in AIDS and/or HTLV patients, offering a foundation for further research and clinical implications while recognizing the need for cautious interpretation. At the end, it was possible to identify opportunistic parasites, which are frequently described in immunocompromised populations. As a result, measures to combat the transmission of these parasites should be implemented, and policies should encourage antiretroviral treatment maintenance. Among preventive measures is the performance of parasitological exams and immediate treatment for positive cases to avoid significant morbidity and mortality.

Based on the findings from the work, the recommendations include the need for frequent coproparasitological examinations in immunocompromised patients, particularly those with HIV/AIDS, to promptly identify and treat opportunistic parasitic infections. Emphasis should be placed on enhancing adherence to antiretroviral therapy and improving hygiene and sanitation conditions to mitigate the risk of parasitic infections. For future studies, it is suggested to expand the sample size and possibly employ a longitudinal study design to better understand the causal relationships between intestinal parasitosis and the progression of HIV/AIDS and HTLV infections. Further research could also explore the impact of varying antiretroviral adherence levels on the prevalence and severity of parasitic infections and the effectiveness of different water treatment methods in controlling the spread of resistant parasites.

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AUTHORS' CONTRIBUTIONS

Victória Christine de Almeida Santos contributed to bibliographical research, abstract writing, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review, statistics and final approval of the version to be published. **Fernando Luiz de Andrade Maia** contributed to project administration and supporting patients' medical treatment. **Lucas Emanuel de Oliveira Silva** contributed to article writing, review and final approval of the version to be published. **Anna Amélia de Paula Moraes** contributed to data collection and processing a in the laboratory. **Josenildo Francisco da Silva** contributed to data collection and processing in the laboratory. **Flaviana Santos Wanderley** contributed to project administration and supervision, interpretation of results, review and final approval of the version to be published.

All authors 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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ORIGINAL ARTICLE

Human anti-rabies post-exposure care in a city in Paraná - 2007 to 2022: demographic factors and causality

Atendimento antirrábico humano pós-exposição, Paraná - 2007 a 2022: fatores demográficos e causalidade

Atención antirrábica humana posterior a la exposición en ciudad de Paraná - 2007 hasta 2022: factores demográficos y causalidad

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ABSTRACT

Justificativa e Objetivos: Antropozoonose de relevância global, a raiva apresenta alta letalidade e requer atendimento qualificado, assim como atenção às espécies agressoras. Assim, o objetivo foi descrever o perfil sociodemográfico e a causalidade de atendimentos antirrábicos humanos pós-exposição notificados entre 2007 e 2022 no município de Ponta Grossa, Paraná. **Método:** Estudo epidemiológico descritivo e quantitativo realizado com dados secundários obtidos das fichas de notificação de atendimento antirrábico humano no município de Ponta Grossa, Paraná, entre janeiro de 2007 e dezembro de 2022. Os dados foram coletados do sistema de informação de Agravos de Notificação (SINAN) e tabulados no programa *Excel*. As variáveis analisadas foram: fatores sociodemográficos, data de atendimento, tipo de exposição e espécie do animal envolvido. Os dados foram analisados a partir de frequência absoluta e relativa. **Resultados:** A amostra foi composta por 16.668 casos. O perfil sociodemográfico dos usuários que buscaram atendimento antirrábico foi dividido em 51,93% do sexo masculino, 92,98% brancos e 4,55% pardos, 15,77% com idade entre 20 e 29 anos. Quanto à causalidade, 90,35% das notificações decorreram de mordeduras, e 95,60% destas foram causadas pela espécie canina e 4,43% pela felina. **Conclusão:** Apesar do predomínio de notificações decorrentes de acidentes envolvendo mordeduras, é necessário sensibilizar os profissionais da saúde e a população sobre a importância epidemiológica dos outros tipos de potenciais exposições ao vírus da raiva.

Descritores: *Raiva. Profilaxia Pós-Exposição. Causalidade. Epidemiologia.*

ABSTRACT

Background and Objectives: Rabies is an anthropozoonosis of global relevance and high lethality that requires qualified care and attention to the aggressor species. The objective was to describe the sociodemographic profile

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and causality of human anti-rabies care services reported between the years 2007 and 2022 in the city of Ponta Grossa, state of Paraná. **Method:** Descriptive and quantitative epidemiological study carried out from the notification forms of human anti-rabies care in the city of Ponta Grossa, Paraná, between January 2007 and December 2022. Data were collected from the Notifiable Diseases Information System (SINAN) and tabulated in the Excel program. The main variables addressed were: sociodemographic factors, date of care, type of exposure, and species of the animal involved. Data were analyzed from absolute and relative frequency. The project follows the ethical standards of the National Health Council. **Results:** The sample included 16,668 cases. The sociodemographic profile of users who sought anti-rabies care was made up of 51.93% male, 92.98% were White and 4.55% Brown race, 15.77% were aged between 20 and 29 years, 13.16% between 30 and 39 years old. As for causality, 90,35% of notifications were due to bites, of which 95.60% were caused by canines and 3,81% by felines. **Conclusion:** Despite the predominance of reports resulting from accidents involving bites, it is necessary to raise awareness among health professionals and the population regarding the epidemiological importance of other types of potential exposure to the rabies virus.

Keywords: *Rabies. Post-Exposure Prophylaxis. Causality. Epidemiology.*

RESUMEN

Justificación y Objetivos: Antropozoonosis de relevancia mundial, la rabia tiene una alta letalidad y requiere cuidados calificados, así como atención a la especie agresora. Así, el objetivo fue describir el perfil sociodemográfico y la causalidad de las visitas antirrábicas humanas notificadas entre los años 2007 y 2022 en el municipio de Ponta Grossa, Paraná. **Métodos:** Estudio epidemiológico descriptivo y cuantitativo realizado a partir de los formularios de notificación de atención antirrábica humana en el municipio de Ponta Grossa, Paraná, entre enero de 2007 y diciembre de 2022. Los datos fueron recolectados por el Sistema de Información de Enfermedades de Declaración Obligatoria (SINAN) y tabulados en el programa Excel. Las principales variables abordadas fueron: factores sociodemográficos, fecha de atención, tipo de exposición y especie de animal involucrada. Los datos se analizaron a partir de la frecuencia absoluta y relativa. El proyecto sigue las normas éticas del Consejo Nacional de Salud. **Resultados:** La muestra incluyó 16.668 casos. El perfil sociodemográfico de los usuarios que buscaron atención antirrábica estuvo conformado por 51,93% hombres, 92,98% eran blancos y 4,55% mestizos, 15,77% con edad entre 20 y 29 años, 13,16% entre 30 y 39 años. Cuánto a la causalidad, 90,35% de las notificaciones se debieron a mordeduras, de las cuales 95,60% fueron causados por caninos y el 3.81% por felinos. **Conclusiones:** A pesar del predominio de las notificaciones resultantes de accidentes con mordeduras, es necesario concientizar a los profesionales de la salud y la población sobre la importancia epidemiológica de otros tipos de exposición potencial al virus de la rabia.

Palabras Clave: *Rabia. Profilaxis Posexposición. Causalidad. Epidemiología.*

INTRODUCTION

Rabies is an infectious disease that affects all mammals. It is an anthropozoonosis of great global relevance characterized by an acute and progressive encephalomyelitis with a fatal course caused by the virus of the *rhabdoviridae* family, genus *Lyssavirus*.[1]

The virus can be transmitted mainly by bites and, in rarer cases, by licking or scratching mucous membranes. The epidemiological chain of the disease involves the urban (dogs and cats), rural (horses and cattle), wild aerial (bats) and wild terrestrial (monkeys, opossums, among others) cycles.[2-4] The incubation period of the virus can vary according to the animal involved and other criteria, such as the extent and location of the wound. In carnivorous and herbivorous species, the incubation period can vary from 15 days to four months, while in chiropterans, this period is longer.[5] In humans, the incubation period can vary from days to months.[2]

The classification of the accident depends on characteristics such as location, depth, extension and number of injuries. The use of anti-rabies vaccination is the most efficient action for controlling and eliminating the disease, which is highly preventable when appropriate immunization strategies are adopted for people at risk and animals, as they are the main source of transmission.[2]

Prophylaxis against human rabies can be done pre- or post-exposure. The former is indicated for people at risk of permanent exposure to the virus, during occupational activities performed by veterinarians, biologists, researchers, among others. The post-exposure prophylaxis (PEP) is indicated for people accidentally exposed to the virus and involves evaluation, careful cleaning of the wound and immunization with the rabies vaccine, alone or in combination with serum or human anti-rabies immunoglobulin.[2] The incorrect assessment of the wound can lead to the unnecessary use of already scarce therapeutic resources, in addition to exposing patients to unnecessary adverse effects.[6]

Rabies is a public health problem as it presents high risk of infection, high fatality rates, and high cost of treatment and prevention actions. As reliable sources in some endemic countries are lacking, the exact number

of human rabies cases worldwide is unknown, but the estimated number of deaths associated with the virus is close to 60,000 per year.[7,8] Rabies is considered endemic throughout Brazil, but occurs to different degrees depending on the geopolitical region analyzed.[2]

Despite the known importance of the disease and the large number of human anti-rabies treatments, the disease and its flows may still remain unclear to health professionals, and more information is needed to improve the actions developed in the control and prevention of rabies.[6] Thus, the objective of the present study was to describe the sociodemographic profile and causality of post-exposure human anti-rabies treatments reported between 2007 and 2022 in the municipality of Ponta Grossa, Paraná.

METHODS

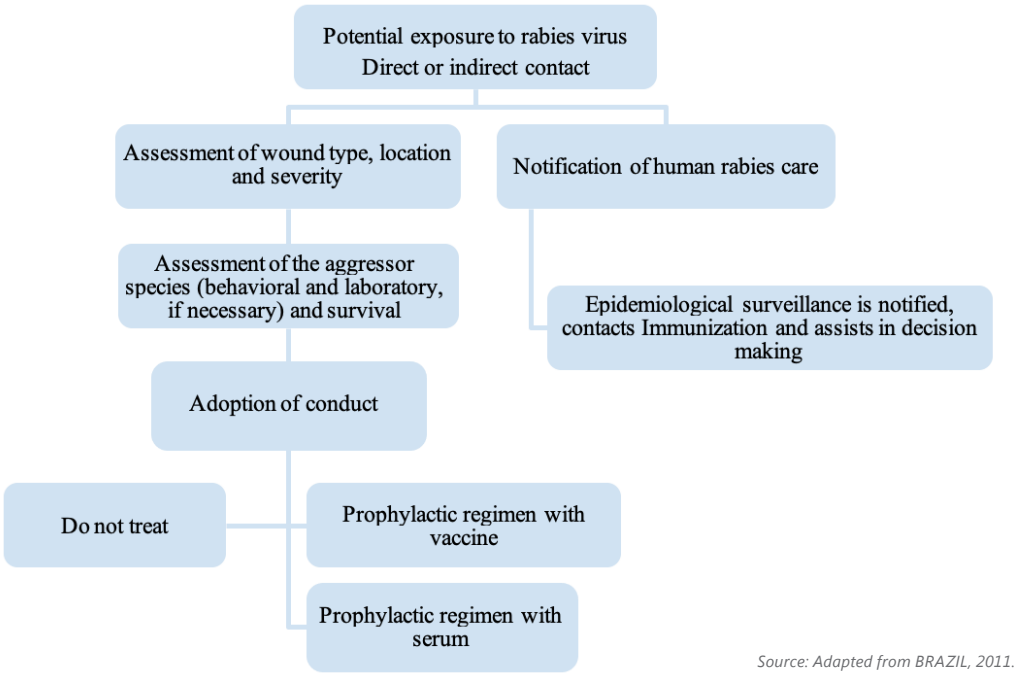
This is a quantitative, descriptive, observational, cross-sectional retrospective epidemiological study conducted through exploratory analysis of secondary data obtained from the Notifiable Diseases Information System (SINAN) processed by the Epidemiology Department of the Ponta Grossa Municipal Health Foundation, state of Paraná, in partnership with the Immunization Department, responsible for implementing the pre- and post-exposure prophylaxis.

The municipality of Ponta Grossa (25°05'41" S and 50°09'42" W) is located in the central region of the state of Paraná, on the second plateau of the Campos Gerais region of Paraná at approximately 117 km from Curitiba, the state capital. According to the most recent data from the Brazilian Institute of Geography and Statistics (IBGE), it is the fourth most populous municipality in Paraná with approximately 358,838 inhabitants in an area of 2,054,732 km^2 (population density of 150.72 inhabitants/km^2). The neighboring municipalities are Campo Largo, Carambeí, Castro, Ipiranga, Teixeira Soares and Tibagi.[9]

All human rabies care caused by different animal species in the last 15 years (2007 to 2022) reported to the Epidemiology Department of the city of Ponta Grossa, Paraná, were included and considered, without exclusion. The analysis compared absolute numbers, relative values and the average number of care services provided.

As the focus of this study is the rabies PEP, it is important to recognize and define the flow to be followed by an individual potentially exposed to the human rabies virus (Figure 1). The first step after seeking care is to define the type of exposure (indirect or direct contact through licking, scratching or biting), the site of contact (mucosa, head, trunk or limbs), the type of injury and its severity (superficial, deep or lacerated), as well as the species of animal involved.[2]

Along with the procedures for addressing the wound, the professional responsible for the care must complete the SINAN Human Anti-Rabies Care Form and forward it to the Epidemiology and Zoonosis service of the municipality responsible for observing and evaluating the animals involved. At the same time, the Immunization Department is notified and will contact the patient to begin PEP according to the criteria established by the municipal protocol and clinical evaluation. Several factors are taken into consideration to define the conduct, such as the possibility of observation and the behavior of the animal involved, its survival for the next ten days, in addition to the aforementioned factors related to the accident.



Source: Adapted from BRAZIL, 2011.

Figure 1. Approach to accidents with potential exposure to the human rabies virus.

Please cite this article as: *Pereira CCFA, Trupel LLL, Batista TD, Maia JFS, Stocco C, Kloster M. Atendimento antirrábico humano pós-exposição, Paraná - 2007 a 2022: fatores demográficos e causalidade. Rev Epidemiol Control Infect [Internet]. 19º de agosto de 2024 [citado 19º de agosto de 2024];14(2). Disponível em: https://online.unisc.br/seer/index.php/epidemiologia/article/view/18918*

Data collected by the Immunization and Epidemiology services date from January 1, 2007 to December 31, 2022 and involve all cases of accidents with application of the PEP reported by the health services of the municipality of Ponta Grossa.

The Anti-Rabies Care Form served as a subsidy for adopting the following variables: date of care, sociodemographic factors, type of exposure, number and location of wounds, history of rabies treatment, species and condition of the animal involved, treatment indicated for the accident, status of the rabies regimen and occurrence of adverse effects.

The information shared by the Epidemiology Department did not contain any type of patient identification, only the notification number, sociodemographic data and accident characteristics. The notification forms were transcribed by the department and coded into variables in the Excel program, where the average values for absolute and relative frequencies were also calculated. The descriptive analysis of data was performed based on these frequencies, which represent the prevalence of accidents requiring anti-rabies prophylaxis. In total, 16,668 notification forms for human anti-rabies care were analyzed.

The study project was exempted from consideration by the Research Ethics Committee, according to the regulations of the National Health Council (CNS) Resolution No. 510 of April 7, 2016, sub paragraph, item V.

RESULTS

1 - Sociodemographic profile

When analyzing the profile of the sample, composed of 16,668 cases, it was possible to observe that 48.06% (n=8,011) of the people who sought human anti-rabies care were women, 51.93% (n=8,656) were men and 0.01% (n=1) had their sex ignored when filling out the notification form.

Regarding race/color, 92.98% (n=15,498) of the sample was classified as White, 4.55% (n= 759) as Brown, 1.22% (n=209) as Black, 0.19% (n=31) as Yellow and 0.28% (n=46) as Indigenous, while 0.78% (n=130) was ignored.

The most predominant age groups (Figure 2) in the study were 20-29 years with 15.77% (n= 2,628), 30-39 years with 13.16% (n=2,192) and 40-49 years with 12.46% (n=2,077).

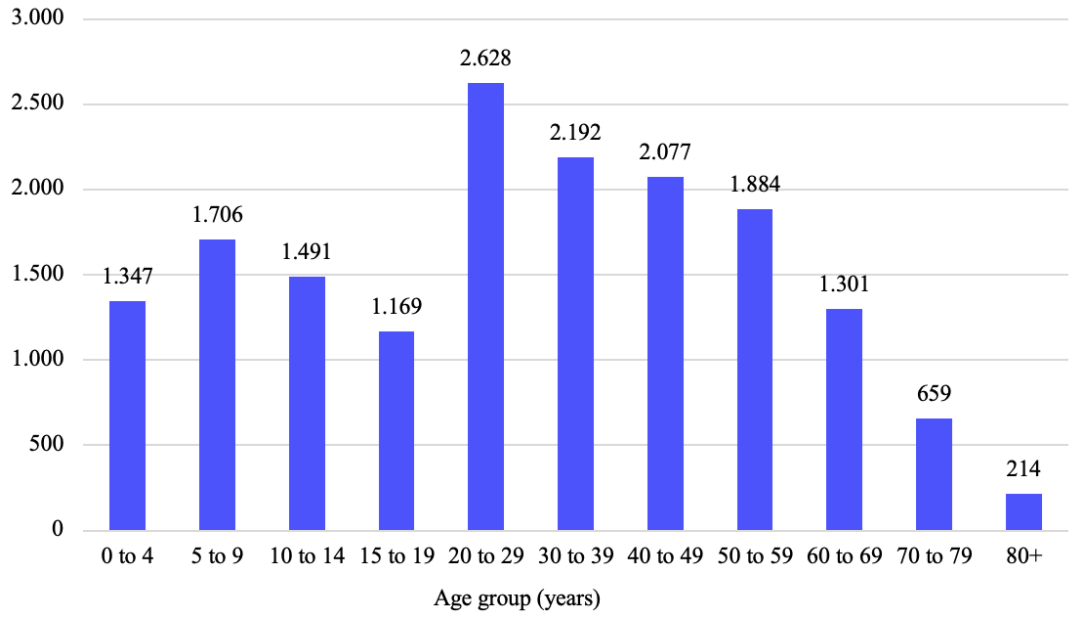
Older adults were the sample population with the lowest proportion of anti-rabies care services (n=2,174; 13.04% considering all age groups aged 60 or over). The frequency of notifications related to babies and children aged between 0 and 4 years is noteworthy with 8.08% (n=1,347), and between 5 and 9 years with 10.23% (n=1,706).

When considering education, some individuals had incomplete primary education (n=5,798; 34,78%;), complete secondary education (n=3,900; 23.40%) or incomplete secondary education (n=1,803; 10.82%), only 4.12% (n=686) had started higher education and 4.91% (n=818) had completed it.

2 - Causality

Among the 16,668 reports (Table 1) of exposure to the human rabies virus, the significant majority of accidents were due to bites (n=15,059; 90.35%), of which 95.60% (n=14,396) were caused by dogs and 3.81% (n=574) by cats.

Canines stood out as the most frequent aggressor species leading to anti-rabies care, accounting for 93.98% (n=15,665), followed by felines with 4.43% (n=739).



Source: the authors (2023).

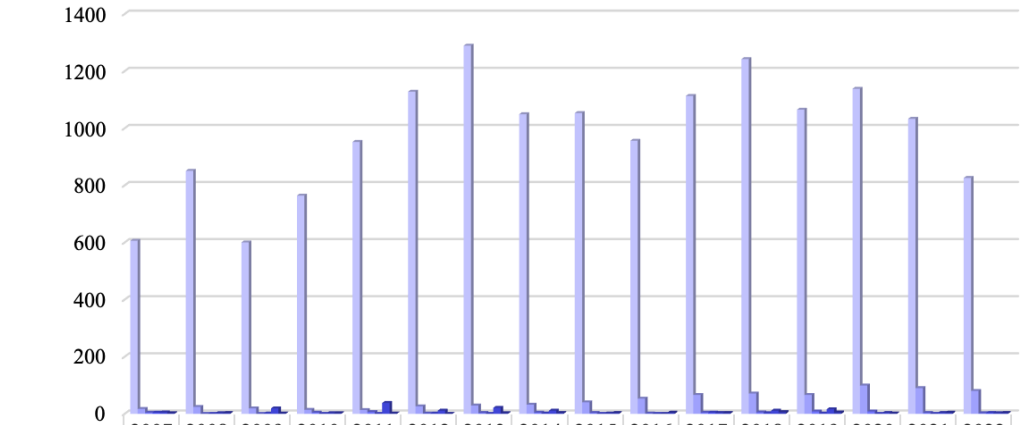
Figure 2. Distribution of human anti-rabies care provided between 2007 and 2022 in the municipality of Ponta Grossa, Paraná, according to age group. n=16,668.

Please cite this article as: *Pereira CCFA, Trupel LLL, Batista TD, Maia JFS, Stocco C, Kloster M. Atendimento antirrábico humano pós-exposição, Paraná - 2007 a 2022: fatores demográficos e causalidade. Rev Epidemiol Control Infect [Internet]. 19º de agosto de 2024 [citado 19º de agosto de 2024];14(2). Disponível em: https://online.unisc.br/seer/index.php/epidemiologia/article/view/18918*

Table 1. Distribution of post-exposure prophylaxis cases by type of exposure and animal species between 2007 and 2022. Ponta Grossa, 2023. (n=16,668).

	Type of exposure						
Species	**Indirect n (%)**	**Scratching n (%)**	**Licking n (%)**	**Biting n (%)**	**Combined** n (%)**	**Ignored n (%)**	**Total n (%)**
Canine	91 (43.13)	677 (88.27)	46 (74.20)	14,396 (95.60)	409 (83.81)	46 (56.80)	15,665 (93.98)
Feline	04 (1.90)	84 (10.95)	04 (6.45)	574 (3.81)	73 (14.96)	0 (0)	739 (4.43)
Chiroptera	19 (9.00)	01 (0.13)	0 (0)	26 (0.17)	02 (0.41)	08 (9.88)	56 (0.34)
Primate	01 (0.47)	0 (0)	0 (0)	16 (0.11)	0 (0)	0 (0)	17 (0.10)
Domestic herbivore	93 (44.08)	0 (0)	12 (19.35)	16 (0.11)	0 (0)	27 (33.32)	148 (0.89)
Other*	03 (1.42)	05 (0.65)	0 (0)	31 (0.20)	04 (0.82)	0 (0)	43 (0.26)
Total	211(1.26)	767 (4.60)	62 (0.37)	15,059 (90.35)	488 (2.93)	81 (0.49)	16,668 (100)

*Caption: *Other includes wild boars, opossums, coatis, otters, squirrels and wild cats. It also includes cases of more than one species at the same time, such as coati/dog and cat/dog.*
***Combined contact: more than one type of contact at the same time, such as scratching and licking, scratching and biting or licking and biting.*



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Canine	606	851	600	764	952	1.128	1.289	1.049	1.053	956	1.113	1.242	1.065	1.138	1.033	826
Feline	17	24	19	14	13	26	29	32	40	53	66	71	66	99	90	80
Quiroptera	4	0	0	4	6	1	3	4	3	1	4	5	8	8	3	2
Primate	4	0	1	0	0	1	0	1	0	0	4	2	1	0	0	3
Herbivore	5	2	19	2	38	11	21	11	1	0	3	11	16	3	3	2
Other	2	3	1	2	1	0	2	3	3	4	3	6	5	1	4	3

Source: The authors (2023).

Figure 3. Annual distribution of anti-rabies care services according to the aggressor species. Ponta Grossa, 2023. (n=16,668).

The prevalence of attacks caused by bats found in this study was 0.34% (n=56) and the frequency of bite cases involving bats was 0.17% (n=26).

Next, the most common cases were scratches (n=767; 4.60%), most of which were caused by canine and feline species, and combined exposures (n=488; 2.93%) caused by canines, domestic herbivores and felines. Contamination from indirect contact was (n=211; 1.26%).

Regarding the number of annual notifications (Figure 3), there was an average of 1,041 cases per year, and an increase of 21% in the number of notifications when comparing the year 2011 (n=1,003) to the previous year (n=786).

Another year in which the number of care services provided was significantly higher was 2018 (8.02%; n=1,337).

DISCUSSION

After performing the analysis, a predominance of the search for care by men was observed. This profile is corroborated by a study conducted in Brazil between 2014 and 2019 with data referring to notifications of anti-rabies care, in which the sample was composed mostly of men, probably due to their work activities, such as postmen, delivery men, garbage collectors, meter readers, among others, with greater exposure to animals that can potentially transmit rabies.[10-11]

The presence of a higher prevalence of one ethnicity over others can lead to debates such as the accuracy in the completion of notification forms, since the race must

be self-declared at the time of care and not inferred by the professional, which can lead them to automatically fill in a certain ethnic group, differing from other similar studies. Furthermore, according to the demographic census performed by the IBGE in 2022, 78.56% of the population of Ponta Grossa is of declared White, corroborating the number found in the present study.[9]

Individuals under 19 years of age were treated more frequently, which may be related to behavioral aspects of these age groups, such as playfulness and abrupt attitudes that may trigger an aggressive reaction in the animals involved.[10-12]

A descriptive study that used data from SINAN to evaluate anti-rabies care between 2014 and 2019 in Brazil highlighted similar findings: 81.9% of accidents were caused by bites.[10] Another study conducted in Belo Horizonte through the analysis of notification forms for human anti-rabies care from 2011 to 2012 also highlighted a higher prevalence of contact through bites when analyzing the canine species (n = 15,665; 93.0%).[13]

The high prevalence of care resulting from bites may be due to the fact that this act is a defense mechanism for most aggressor animals.[9] In addition, the population and the healthcare community recognize that this type of contact has a greater potential for contamination by the rabies virus, which leads to greater demand for health services and an increase in notifications.[10,13]

On the other hand, it is essential to highlight the importance of seeking health services in the most diverse types of contact, including minor accidents or indirect contact. Such search should be reinforced and intensified in cases of exposure to wild animals, considering the need to evaluate post-exposure behavior and the high lethality of human rabies.[10]

A study developed by Estima et al. (2022) in Brazil indicated that 81.5% of accidents were caused by dogs, while cats accounted for 15.2%.[10] This finding is corroborated by the systematic review conducted by Mshelbwala et al. (2021) with articles on rabies records between 1978 and 2020 in Nigeria, in which a large part of the attacks were related to dog bites, ranging from 36.4% to 97% of cases.[14]

Despite the high prevalence of care linked to the urban cycle of rabies transmission (canines and felines), with the adoption of strategies such as large-scale vaccination of dogs and cats and expanded access to prophylaxis, Brazil has undergone a transmission transition - where the latest records of the disease were related to exposure to wild animals, mainly bats - as observed in developed countries. A descriptive investigation of the epidemiological profile of human rabies in Brazil between 2000 and 2017 demonstrated that 45.9% of cases of the disease involved the chiropteran species.[10,15-16]

The lower number of notifications involving the species in the present study may be due to the profile of chiropterans in the region, where non-hematophagous bats predominate, with a low frequency of bites, considering the behavior of frugivorous and insectivorous bats.[17] In any case, it is necessary to remain alert to exposure to bats, as in 2017, the Central Laboratory (LACEN) of Paraná identified four insectivorous bats infected with the rabies virus.[18] Furthermore, bats have a good adaptive capacity to the conditions of cities and environments of human intervention, which favors contact with humans, domestic animals and herbivores.[19,20]

It is also important to highlight that most cases involving herbivores resulted from exposure to domestic herbivores, such as cattle and horses. In a study that evaluated epidemiological data on rabies cases in different species in Brazil between 2012 and 2017, Gonçalves, Soares & Santos (2018) highlighted that Paraná remains an endemic area for rabies in wild animals and herbivores, as does the municipality of Ponta Grossa.[17,18] Regarding serology, a descriptive observational study that used records of rabies cases diagnosed in herbivores between 1977 and 2012 in the state of Paraná identified a 28.1% positivity rate, with a higher occurrence in the central-eastern mesoregion, where Ponta Grossa is located.[19]

At the same time, the prevalence of different types of contact leads to reflections on the accuracy of the exposure classification, as well as the quality of the anamnesis and completion of the form. Furthermore, underreporting significantly impacts the reporting of suspected and confirmed cases and human anti-rabies care.[19] Several factors, such as work overload and ongoing and continuous health education, impact both the quality of the completion of notification forms and the search for health services and possible failures in epidemiological surveillance, and the control, prevention and diagnosis of zoonoses.[19,21]

Incomplete or erroneous completion of the form were also noted in similar studies regarding the analysis of care provided in the state of São Paulo, with a high frequency of incomplete fields and poor quality of completion.[12]

The increase in the search for human anti-rabies care may have been caused by the 13.5% increase in the number of confirmed cases of human rabies between 2017 and 2018.[22] This increase may also be related to the publication of information note No. 26-SEI/2017 by the Ministry of Health regarding changes in the PEP regimen of human rabies, promoting awareness among health professionals about the importance of disease prevention measures.[23]

The progressive increase in the number of notifications involving felines as aggressors may be related to the increase in the number of domesticated cats in the country.[24] A study conducted by Johann (2019) observed that the verticalization of cities brings with it the need for pets that adapt to environments with little space, causing an increase in the feline population in Brazilian homes.[24]

In the sample analyzed, a large part of the population that sought anti-rabies care was composed of white men with low education, between the ages of 20 and 29 years old. Most notifications analyzed were of dog bites, followed by those of cat bites. The number of notifications analyzed follows the trend shown by similar Brazilian studies, with 2013 and 2018 as the years with the highest records of human anti-rabies care.

It is important to raise awareness among the population to seek anti-rabies care in the event of any type of contact with a potential transmitter of the rabies virus,

and to assist in monitoring the animals involved in order to notify the competent authorities for better decision-making regarding the prophylactic protocol.

It is also necessary to properly train health professionals at the different levels of care responsible for providing care and completing the notification form, aiming at greater accuracy in epidemiological data and the reduction of underreporting of exposure cases.

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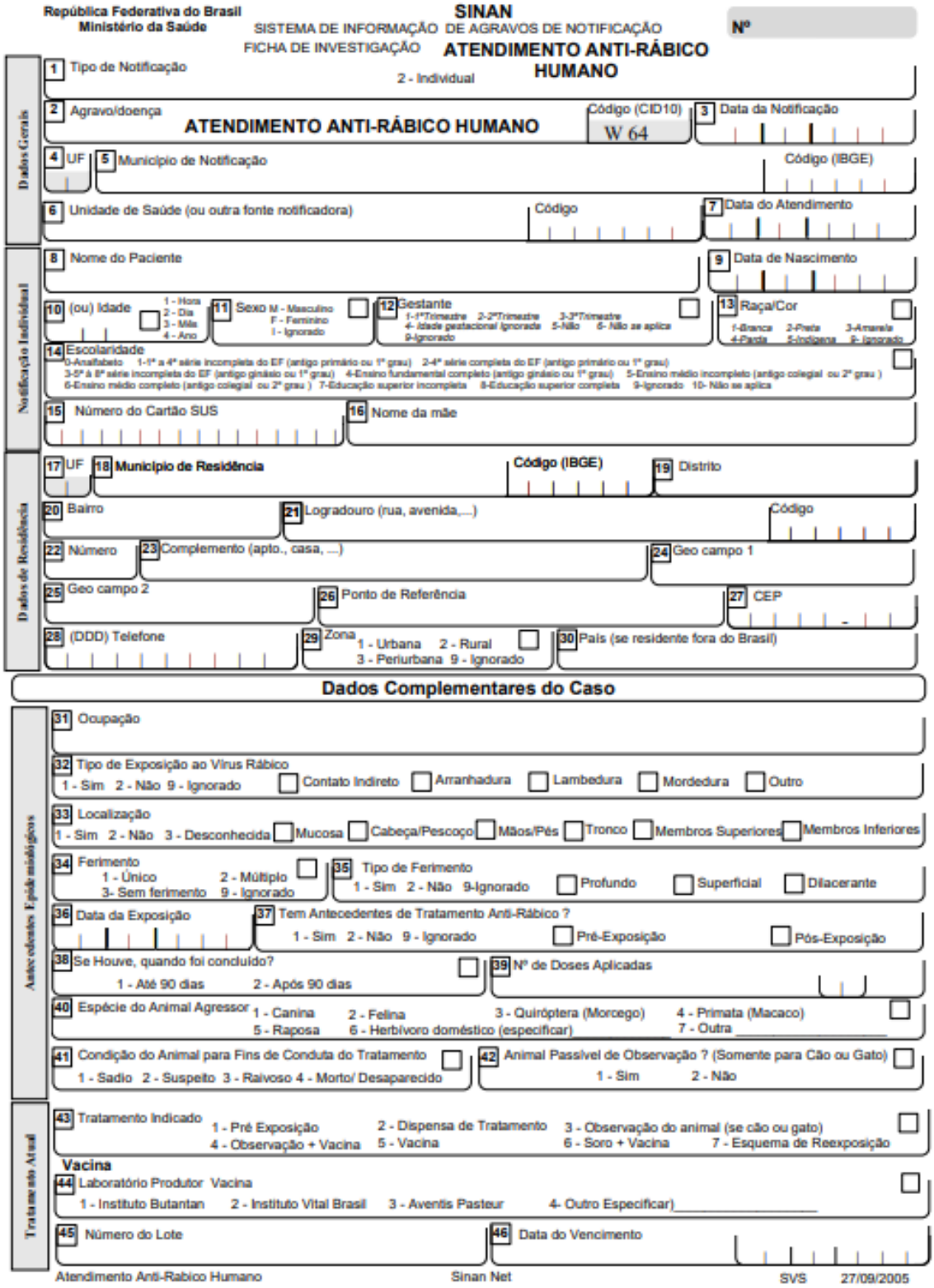
AUTHOR CONTRIBUTIONS

Lucas Lauriano Tremel Trupel contributed to the literature search, abstract writing, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Clara Caroline Ferrarezi Antunes Pereira** contributed to the literature search, abstract writing, introduction, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Tayane Diniz Batista** contributed to the discussion of results, conclusions and review. **Jisiane** Fátima **Sobczak Maia** contributed to the literature search, introduction and review. **Caroliny Stocco** contributed to the review and statistics. **Mônica Kloster** contributed to the project administration and review.

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

ANNEX A

Mandatory notification form for human anti-rabies care.



República Federativa do Brasil
Ministério da Saúde

SINAN
SISTEMA DE INFORMAÇÃO DE AGRAVOS DE NOTIFICAÇÃO
FICHA DE INVESTIGAÇÃO
ATENDIMENTO ANTI-RÁBICO HUMANO

Nº

Dados Gerais

1 Tipo de Notificação — 2 - Individual

2 Agravo/doença — ATENDIMENTO ANTI-RÁBICO HUMANO — Código (CID10) W 64

3 Data da Notificação

4 UF | 5 Município de Notificação | Código (IBGE)

6 Unidade de Saúde (ou outra fonte notificadora) | Código

7 Data do Atendimento

Notificação Individual

8 Nome do Paciente

9 Data de Nascimento

10 (ou) Idade — 1 - Hora 2 - Dia 3 - Mês 4 - Ano

11 Sexo M - Masculino F - Feminino I - Ignorado

12 Gestante — 1-1ºTrimestre 2-2ºTrimestre 3-3ºTrimestre 4- Idade gestacional ignorada 5-Não 6- Não se aplica 9-Ignorado

13 Raça/Cor — 1-Branca 2-Preta 3-Amarela 4-Parda 5-Indígena 9- Ignorado

14 Escolaridade — 0-Analfabeto 1-1ª a 4ª série incompleta do EF (antigo primário ou 1º grau) 2-4ª série completa do EF (antigo primário ou 1º grau) 3-5ª à 8ª série incompleta do EF (antigo ginásio ou 1º grau) 4-Ensino fundamental completo (antigo ginásio ou 1º grau) 5-Ensino médio incompleto (antigo colegial ou 2º grau) 6-Ensino médio completo (antigo colegial ou 2º grau) 7-Educação superior incompleta 8-Educação superior completa 9-Ignorado 10- Não se aplica

15 Número do Cartão SUS | 16 Nome da mãe

Dados de Residência

17 UF | 18 Município de Residência | Código (IBGE) | 19 Distrito

20 Bairro | 21 Logradouro (rua, avenida,...) | Código

22 Número | 23 Complemento (apto., casa, ...) | 24 Geo campo 1

25 Geo campo 2 | 26 Ponto de Referência | 27 CEP

28 (DDD) Telefone | 29 Zona 1 - Urbana 2 - Rural 3 - Periurbana 9 - Ignorado | 30 País (se residente fora do Brasil)

Dados Complementares do Caso

Antecedentes Epidemiológicos

31 Ocupação

32 Tipo de Exposição ao Vírus Rábico — 1 - Sim 2 - Não 9 - Ignorado — Contato Indireto | Arranhadura | Lambedura | Mordedura | Outro

33 Localização — 1 - Sim 2 - Não 3 - Desconhecida — Mucosa | Cabeça/Pescoço | Mãos/Pés | Tronco | Membros Superiores | Membros Inferiores

34 Ferimento — 1 - Único 2 - Múltiplo 3- Sem ferimento 9 - Ignorado

35 Tipo de Ferimento — 1 - Sim 2 - Não 9-Ignorado — Profundo | Superficial | Dilacerante

36 Data da Exposição

37 Tem Antecedentes de Tratamento Anti-Rábico ? — 1 - Sim 2 - Não 9 - Ignorado — Pré-Exposição | Pós-Exposição

38 Se Houve, quando foi concluído? — 1 - Até 90 dias 2 - Após 90 dias

39 Nº de Doses Aplicadas

40 Espécie do Animal Agressor — 1 - Canina 2 - Felina 3 - Quiróptera (Morcego) 4 - Primata (Macaco) 5 - Raposa 6 - Herbívoro doméstico (especificar)_____ 7 - Outra _____

41 Condição do Animal para Fins de Conduta do Tratamento — 1 - Sadio 2 - Suspeito 3 - Raivoso 4 - Morto/ Desaparecido

42 Animal Passível de Observação ? (Somente para Cão ou Gato) — 1 - Sim 2 - Não

Tratamento Atual

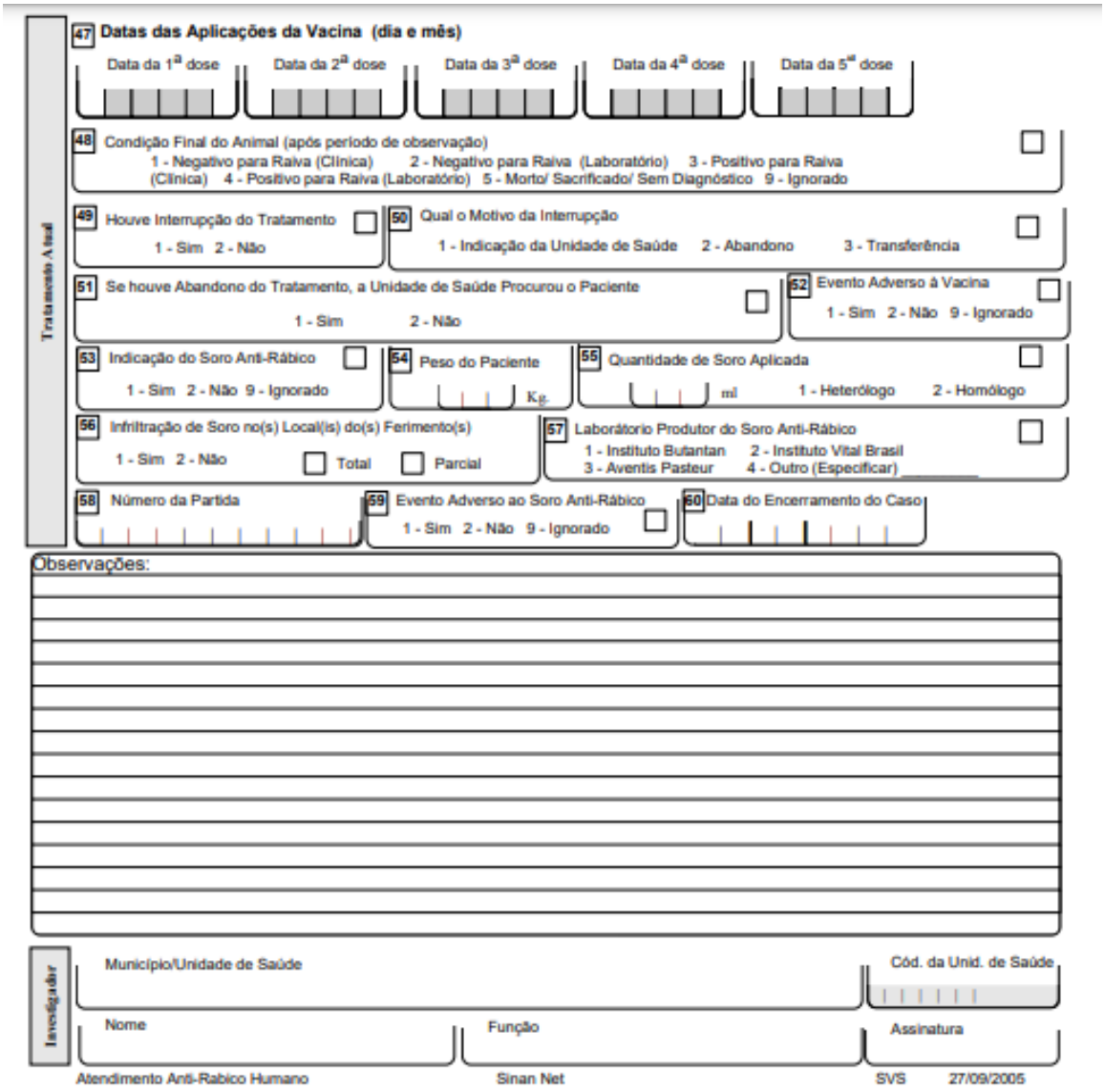
43 Tratamento Indicado — 1 - Pré Exposição 2 - Dispensa de Tratamento 3 - Observação do animal (se cão ou gato) 4 - Observação + Vacina 5 - Vacina 6 - Soro + Vacina 7 - Esquema de Reexposição

Vacina

44 Laboratório Produtor Vacina — 1 - Instituto Butantan 2 - Instituto Vital Brasil 3 - Aventis Pasteur 4- Outro Especificar)_____

45 Número do Lote | 46 Data do Vencimento

Atendimento Anti-Rabico Humano — Sinan Net — SVS — 27/09/2005


Tratamento Atual
47 Datas das Aplicações da Vacina (dia e mês)
Data da 1ª dose
Data da 2ª dose
Data da 3ª dose
Data da 4ª dose
Data da 5ª dose
48 Condição Final do Animal (após período de observação)
1 - Negativo para Raiva (Clínica) 2 - Negativo para Raiva (Laboratório) 3 - Positivo para Raiva (Clínica) 4 - Positivo para Raiva (Laboratório) 5 - Morto/ Sacrificado/ Sem Diagnóstico 9 - Ignorado
49 Houve Interrupção do Tratamento
1 - Sim 2 - Não
50 Qual o Motivo da Interrupção
1 - Indicação da Unidade de Saúde 2 - Abandono 3 - Transferência
51 Se houve Abandono do Tratamento, a Unidade de Saúde Procurou o Paciente
1 - Sim 2 - Não
52 Evento Adverso à Vacina
1 - Sim 2 - Não 9 - Ignorado
53 Indicação do Soro Anti-Rábico
1 - Sim 2 - Não 9 - Ignorado
54 Peso do Paciente
Kg.
55 Quantidade de Soro Aplicada
ml
1 - Heterólogo 2 - Homólogo
56 Infiltração de Soro no(s) Local(is) do(s) Ferimento(s)
1 - Sim 2 - Não
Total
Parcial
57 Laboratório Produtor do Soro Anti-Rábico
1 - Instituto Butantan 2 - Instituto Vital Brasil
3 - Aventis Pasteur 4 - Outro (Especificar)
58 Número da Partida
59 Evento Adverso ao Soro Anti-Rábico
1 - Sim 2 - Não 9 - Ignorado
60 Data do Encerramento do Caso
Observações:
Investigador
Município/Unidade de Saúde
Cód. da Unid. de Saúde
Nome
Função
Assinatura
Atendimento Anti-Rabico Humano
Sinan Net
SVS 27/09/2005

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ORIGINAL ARTICLE

Characterization of vancomycin resistance mechanisms in *Enterococcus faecium* isolates from a Brazilian tertiary hospital

Caracterização dos mecanismos de resistência à vancomicina em isolados de Enterococcus faecium de um hospital terciário brasileiro

Caracterización de los mecanismos de resistencia a la vancomicina en aislamientos de Enterococcus faecium de un hospital terciario brasileño

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ABSTRACT

Background and Objectives: Vancomycin-resistant *Enterococcus faecium* (VREf) is an opportunistic pathogen responsible for hospital infections, characterized by increasing prevalence and a lack of comprehensive epidemiological studies. We aimed to assess the occurrence of VREf and vancomycin resistance genetic elements *vanA* and *vanB* in strains isolated from clinical samples of patients treated at a tertiary hospital in Brazil. **Methods:** The isolates were obtained from convenience sampling according to routine medical requests for nine months. *Enterococcus faecium* strains were identified by routine biochemical tests, BD Phoenix® Automated Microbiology System and confirmed by MALDI-TOF Mass Spectrometry. The antimicrobial sensitivity profile was determined by disk-diffusion method and BD Phoenix® Automated Microbiology System. Vancomycin resistance was specially assessed and confirmed by the conventional microdilution technique. Molecular detection of *vanA* and *vanB* resistance genes was investigated by polymerase chain reaction (PCR) and confirmed by Sanger DNA sequencing. **Results:** A total of 8,376 cultures was performed, of which 19 (0.22%) were identified as *Enterococcus* sp. and nine (47%) as vancomycin-resistant *E. faecium*. The antimicrobial susceptibility testing analysis of *E. faecium* showed high resistance to antimicrobial agents. The analysis to determine the genetic profile of *E. faecium* isolates by PCR showed that all of them carried the *vanA* gene associated with vancomycin resistance. **Conclusion:** During the study period, there was low occurrence of *Enterococcus* species observed. However, all VREf isolates carried the *vanA* gene associated with vancomycin resistance and showed resistance to commonly used antimicrobial agents, highlighting concerns about the effectiveness of available antimicrobial treatments for infections caused by these isolates.

Keywords*: Enterococcus faecium. Epidemiological surveillance. Drug Resistance. Vancomycin Resistance.*

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RESUMO

Justificativa e Objetivos: *Enterococcus faecium* resistente à vancomicina (VREf) é um patógeno oportunista responsável por infecções hospitalares, caracterizado por crescente prevalência e falta de estudos epidemiológicos abrangentes. O objetivo foi avaliar a ocorrência de VREf e dos elementos genéticos de resistência à vancomicina *vanA* e *vanB* em cepas isoladas de pacientes atendidos em um hospital terciário no Brasil. **Métodos:** Os isolados foram obtidos por amostragem de conveniência de acordo com as solicitações médicas de rotina durante nove meses. As cepas foram identificadas por testes bioquímicos, Sistema de Microbiologia Automatizada BD Phoenix®, e confirmadas por MALDI-TOF. O perfil de sensibilidade aos antimicrobianos foi determinado por difusão em disco e pelo BD Phoenix®. A resistência à vancomicina foi avaliada e confirmada pela técnica de microdiluição. A detecção molecular dos genes de resistência *vanA* e *vanB* foi investigada por reação em cadeia da polimerase (PCR) e sequenciamento de DNA. **Resultados:** Um total de 8.376 culturas foi realizado, sendo 19 (0.22%) identificadas como *Enterococcus* sp., e nove (47%), como *Enterococcus faecium* resistente à vancomicina. A análise do teste de sensibilidade aos antimicrobianos do *E. faecium* mostrou alta resistência aos antimicrobianos. A análise para determinar o perfil genético dos isolados de *E. faecium* por PCR mostrou que todos eles carregavam o gene vanA associado à resistência à vancomicina. **Conclusão:** Durante o período de estudo, observou-se baixa ocorrência de espécies de *Enterococcus*. No entanto, todos os isolados de VREf apresentaram o gene *vanA* associado à resistência à vancomicina e mostraram resistência aos antimicrobianos comumente utilizados, alertando sobre a eficácia dos tratamentos antimicrobianos disponíveis para infecções causadas por esses isolados.

Descritores: *Enterococcus faecium. Vigilância Epidemiológica. Resistência a Medicamentos. Resistência à Vancomicina.*

RESUMEN

Justificación y Objetivos: *Enterococcus faecium* resistente a vancomicina (VREf) es un patógeno oportunista responsable de infecciones hospitalarias, caracterizado por su creciente prevalencia y la falta de estudios epidemiológicos exhaustivos. El objetivo fue evaluar la ocurrencia de VREf y los elementos genéticos de resistencia a vancomicina *vanA* y *vanB* en cepas aisladas de muestras clínicas de pacientes tratados en un hospital terciario en Brasil. **Métodos:** Los aislamientos se obtuvieron mediante muestreo de conveniencia según las solicitudes médicas de rutina durante nueve meses. Las cepas fueron identificadas mediante pruebas bioquímicas, utilizando el BD Phoenix® y MALDI-TOF. El perfil de sensibilidad a los antimicrobianos se determinó mediante difusión en disco y el BD Phoenix®. La resistencia a vancomicina se evaluó mediante microdilución. La detección molecular de los genes de resistencia *vanA* y *vanB* se investigó mediante reacción en cadena de la polimerasa (PCR) y secuenciación de ADN. **Resultados:** Se realizaron un total de 8,376 cultivos, identificándose 19 (0.22%) como *Enterococcus* sp., de las cuales 9 (47%) fueron VREf. El análisis de la sensibilidad a los antimicrobianos mostró una alta resistencia. El análisis para determinar el perfil genético de los aislados de *E. faecium* mediante PCR mostró que todos portaban el gen *vanA* asociado a la resistencia a la vancomicina. **Conclusión:** Durante el período de estudio, se observó una baja incidencia de especies de *Enterococcus*. Sin embargo, todos los aislamientos de VREf presentaron el gen *vanA* asociado con resistencia a la vancomicina y mostraron resistencia a los antimicrobianos comúnmente utilizados, lo cual alerta sobre la eficacia de los tratamientos antimicrobianos disponibles para infecciones causadas por VREf.

Palabras Clave: *Enterococcus faecium. Monitoreo Epidemiológico. Farmacorresistencia Bacteriana. Resistencia a la Vancomicina.*

INTRODUCTION

Enterococci, characterized as non-sporulated Gram-positive cocci, typically appear in short chains. They are facultative anaerobes, lack catalase activity, and exhibit dimensions spanning from 0.6 to 2.5 µm. These microorganisms are comprehensive components of the gastrointestinal microbiota in mammals and can also be encountered in the genitourinary tract and on the skin.[1] In the environment, *E. faecium* can be found in soil, water, and food, and it has the ability to survive on inanimate surfaces for long periods.[1]

Enterococci's remarkable capacity to swiftly acquire virulence traits, either through mutational events or by incorporating genetic material from other bacteria via plasmid and transposon transfer, is augmented by their intricate virulence mechanisms. These mechanisms encompass toxin secretion, stress response proteins, transport systems, and specific gene regulators. Collectively, these attributes enhance the microorganism's efficacy in causing infections, establishing colonization and persisting in both biotic and abiotic environments. This adaptability confers a selective advantage that aids in withstanding adverse conditions.[1]

The initial accounts of antimicrobial resistance among *Enterococci* surfaced during the 1970s, primarily involving isolates displaying high-level resistance to gentamicin.[2] Subsequently, strains exhibiting resistance traits associated with modifications of penicillin-binding proteins (PBPs) were reported.[1,2] In a pivotal development, in

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1986, the first instances of vancomycin-resistant strains were documented, marking a significant shift towards the prevalent isolation of *Enterococci* resistant to ampicillin, aminoglycosides, and vancomycin in hospital-acquired infections. [1,3] Notably, in Brazil, the inaugural case of vancomycin-resistant *Enterococci* (VRE) was identified in 1996, specifically in Curitiba, Paraná.[3]

Vancomycin (C66H75Cl2N9O24) is a tricyclic glycopeptide antibiotic developed in 1956 that inhibits peptidoglycan biosynthesis, altering cytoplasmic membrane permeability and RNA synthesis. Its mechanism of action occurs through the binding to D-Alanyl-D-Alanine of peptidoglycan pentapeptide, resulting in a destabilized cell wall caused by interference of transpeptidation and transglycosylation steps.[2,4,5]

Vancomycin resistance in *E. faecium* is associated with nine resistance genes, classified according to its gene sequence and organization, as follows: i) D-Ala-D-lac, including *vanA*, *vanB*, *vanD* and *vanM* genes; and ii) D-Ala-D-Ser, including *vanC*, *vanE*, *vanG*, *vanL* and *vanN* genes.[2,5]

Globally, the *vanA* and *vanB* genes hold paramount clinical significance, distinguished by their varying levels of resistance to vancomycin, transferability between organisms, and capacity to trigger resistance in the presence of an antimicrobial agent. [2,5,6]

Vancomycin-resistant *Enterococcus faecium* (VREf) is categorized as opportunistic pathogens and represents a significant etiology of healthcare-associated infections (HAI).[1] These infections predominantly originate from patients' indigenous microbiota or through direct or indirect contact.[1] Common clinical manifestations of VREf infections encompass urinary tract infections (UTI), wound infections, meningitis, infections associated with catheters and other implanted medical devices, bacteremia, and endocarditis. These infections primarily afflict hospitalized patients who are grappling with severe underlying conditions, including cancer, hematological disorders, chronic renal insufficiency, transplant recipients, and individuals with compromised immune systems.[7]

Given the escalating prevalence of VREf and the notable dearth of comprehensive epidemiological investigations pertaining to this microorganism, the primary aim of this study was to assess the frequency of VREf and the presence of genetic components associated with vancomycin resistance, specifically *vanA* and *vanB* genes, within strains obtained from clinical specimens of patients undergoing treatment at a tertiary healthcare facility in Brazil. The objective was to assess the occurrence of VREf and the presence of *vanA* and *vanB* genetic elements associated with vancomycin resistance in strains isolated from clinical samples of patients treated at a tertiary hospital in Brazil.

METHODS

Bacterial isolates and species identification

This is a descriptive cross-sectional study developed in a tertiary hospital from Recife-PE, Brazil. The isolates were obtained from convenience sampling according to routine medical requests sent to the Clinical Microbiology Laboratory during nine months (December 2020 – August 2021) and including samples from rectal swab (surveillance culture), urine and soft tissue from patients treated in the vascular, orthopedics and oncology clinics. For bacterial growth and isolation, samples from different anatomopathological sites were plated on Müeller-Hinton agar (Difco®), supplemented with 0.5% (v/v) defibrinated sheep blood and on CHROMagar™ (Becton, Dickinson and Company®). The plates were incubated at 35 ± 2° C for 18 to 24 hours, and the cultures were visually inspected to assess bacterial growth and identify the different morphologies of the colonies. At least one colony with characteristic morphology for *Enterococcus* sp. was selected for further identification by BD Phoenix® Automated Microbiology System. Additionally, the isolates identified were also submitted to species

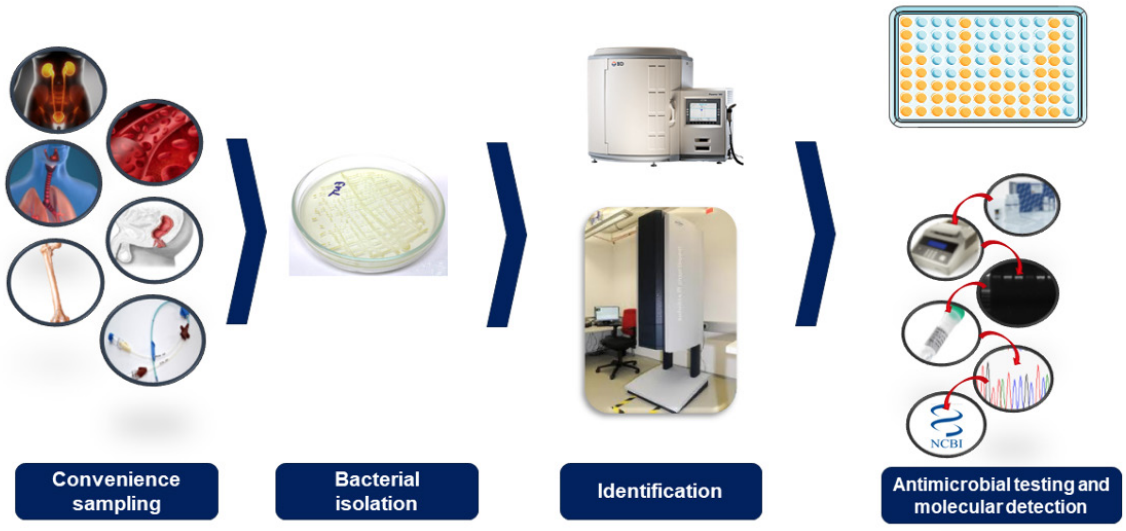

Figure 1. Schematic overview of methodology steps. Schematic representation detailing the sequential steps and procedures followed in the methodology, illustrating the key stages from sample collection to data analysis.

confirmation by the Matrix-Assisted Laser Desorption Ionization – Time of Flight (MALDI-TOF) mass spectrometry technique using the MALDI Biotyper system version 2.0 (Bruker Daltonics®). A summarized overview of the steps conducted during the methodology can be observed in a schematic diagram presented in Figure 1.

Antimicrobial susceptibility testing

The antimicrobial susceptibility test was performed using the broth microdilution technique, according to the Brazilian Committee on Antimicrobial Susceptibility Testing (BrCAST, 2022) (http://brcast.org.br) and Clinical Laboratory Standard Institute (CLSI, 2020) (http://www.clsi.org/) standardization and recommendations. The resistance profile to teicoplanin, gentamicin, streptomycin, daptomycin, linezolid and ampicillin was assessed using data extracted from the identification process by BD Phoenix® Automated Microbiology System NMIC panel (Biomerieux). The vancomycin resistance profile was specially assessed by using 96-well microdilution plates containing serial dilutions of vancomycin (0.5 µg/mL to 256 µg/mL) in Cation-adjusted Müeller Hinton II Broth (Oxoid). As quality control, strains from the American Type Culture Collection (ATCC®) of *Enterococcus faecalis* ATCC® 29212 and *Escherichia coli* ATCC® 25922 were used.

Molecular detection of vancomycin-resistance associated genes

Genomic DNA extraction was performed using the DNeasy Blood & Tissue Kit (Qiagen), following the manufacturer's recommendations, from an aliquot of 1,500 µL of culture grown in Luria-Bertani (LB) broth (Himedia) at 35 ± 2°C for 18 hours. For this, an aliquot of each sample of interest was previously plated on BHI agar (Himedia), which was incubated at 35 ± 2 °C for 18 hours. The extracted genomic DNA was quantified in NanoDrop 2000c (Thermo Fisher Scientific Inc.) with verification of the parameters used to estimate the extraction (A260/280) purity and yield. DNA amplification reactions were performed by polymerase chain reaction (PCR) containing 50 ng of genomic DNA, 20 pmol of each *vanA* (5'- CATGAATAGAATAAAAGTTGCAATA -3'; 5'- CCCCTTTAACGCTAATACGATCAA -3') or *vanB* (5'- GTGACAAACCGGAGGCGAGGA -3'; 5'- CCOGCCATCCTCCTGCAAAAAA -3') oligonucleotide pair, 200 mM of each dNTP, 50 mM of Tris-HCl (pH 9.0), 50 mM of NaCl, 5 mM of MgCl2 and 1U of Taq DNA polymerase (Promega). Amplification reactions were thermocycling in GeneAmp PCR System 9700 (Applied Biosystems), and PCR amplicons were submitted to 1% agarose gel electrophoresis (m/v), being visualized and photographed under UV. The amplicons were purified by ExoSAP-IT PCR Product Cleanup kit (Affymetrix) and sequenced by the Sanger method in 3,500 xL Genetic Analyzer (Applied Biosystems). The chromatograms were analyzed using Chromas Lite 2.1.1 (Technelysium), and the contigs were assembled using BioEdit Sequence Alignment Editor (Tom Hall) software. The assembled contigs were compared with DNA sequences available in GenBank (http://www.ncbi.nlm.nih.gov/genbank) by Basic Local Alignment Search Tool (BLAST) to confirm amplification reaction specificity and gene identification (Figure 1).

Ethical approval

This study is part of the Program for Surveillance and Study of Bacterial Resistance to Antimicrobial agents (HC/UFPE), of the Department of Microbiology of IAM/Fiocruz-PE and of the *Hospital das Clínicas* Hospital Infection Control Service (SCIH/HC/UFPE), for studying local epidemiology of bacterial resistance among samples of clinically important species. This study was appreciated by the Research Ethics Committee of FIOCRUZ, with the title "Microbiological Collection for the Implementation of a Surveillance Program and Study of Bacterial Resistance to Antimicrobial agents: Genetic Study of the Determinants of Antimicrobial Resistance Among Bacterial Clinical Isolates", and its execution was approved by Certificate of Presentation for Ethical Consideration (CAAE - *Certificado de Apresentação para Apreciação Ética*) 45080915.0.0000.5190/REC 1.190.837. This study was conducted in accordance with the ethical standards required by Resolutions 466/2012, 510/2016 and 580/2018 of the Ministry of Health, Brazil.

RESULTS

During the study period, a total of 8,376 cultures were conducted. Among the collected clinical samples, 19 were identified as *Enterococcus* species. Notably, within this group, nine isolates, designated as Ef_01 to Ef_09, displayed resistance to vancomycin, constituting 47% of the *Enterococcus* isolates. These VREf strains were then chosen for further comprehensive analysis, as detailed in Table 1.

Antimicrobial susceptibility testing analysis of *E. faecium* showed high resistant to antimicrobial agents commonly used in clinical practice and assessed in the present study. According to BD Phoenix® Automated Microbiology System data, all isolates showed resistance to teicoplanin, ampicillin and penicillin, exhibiting minimum inhibitory concentration (MIC) values of ≥ 16, 8 and 8 µg/mL, respectively. None showed resistance to linezolid and daptomycin (MIC ≤ 1 and ≤ 2 µg/mL for each antimicrobial, respectively). All isolates showed high resistance to vancomycin and to high concentrations of gentamicin (assessed by synergism test, 500 µg/mL). Only the Ef_04 isolate was not susceptible to streptomycin synergism test, exhibiting MIC of ≥ 1,000 µg/mL. Table 1 shows the MIC of each antimicrobial agent tested on different isolates.

The genetic profiling of *E. faecium* isolates via PCR analysis revealed that all of them harbored the vancomycin resistance-associated *vanA* gene. Furthermore, in silico analysis of the *vanA* gene and the predicted amino acid sequence of the *vanA* protein, conducted on the isolates from this study using Sanger DNA sequencing data, demonstrated complete coverage and identity, achieving 100% similarity with the d-alanine-d-lactate subfamily *vanA* sequence (GenBank accession number: WP_001079845.1). It is noteworthy that none of the isolates exhibited PCR amplification for the *vanB* gene.

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Table 1. Minimum inhibitory concentrations (MIC) of each antimicrobial agent tested to different *E. faecium* isolates.

Strain ID	VAN (µg/mL)	AMP (µg/mL)	PEN (µg/mL)	TEC (µg/mL)	LZD (µg/mL)	DAP (µg/mL)	GEN* (µg/mL)	STP* (µg/mL)
Ef_01	128	≥ 8	≥ 8	≥ 16	< 1	< 1	< 500	< 1000
Ef_02	128	≥ 8	≥ 8	≥ 16	< 1	< 1	< 500	< 1000
Ef_03	128	≥ 8	≥ 8	≥ 16	< 1	< 1	< 500	< 1000
Ef_04	≥ 256	≥ 8	≥ 8	≥ 16	< 1	< 1	< 500	> 1000
Ef_05	≥ 256	≥ 8	≥ 8	≥ 16	< 1	< 1	< 500	< 1000
Ef_06	≥ 256	≥ 8	≥ 8	≥ 16	< 1	< 1	< 500	< 1000
Ef_07	≥ 256	≥ 8	≥ 8	≥ 16	< 1	< 1	< 500	< 1000
Ef_08	≥ 256	≥ 32	≥ 8	≥ 16	< 1	< 1	< 500	< 1000
Ef_09	≥ 256	≥ 32	≥ 8	≥ 16	< 1	< 2	< 500	< 1000

*Caption: AMP – ampicillin; PEN – penicillin or benzylpenicillin; VAN – vancomycin; TEC – teicoplanin; LZD – linezolid; DAP – daptomycin; GEN – gentamicin; STP – streptomycin. The antimicrobial agents were tested using the corresponding MIC cut-offs (µg/mL) for classification into susceptible (S) or resistant (R) range: ampicillin, S≤4, R≥8; penicillin, S≤16, R≥16; vancomycin, S≤4, R≥4; teicoplanin, S≤2, R≥2; linezolid, S≤4, R≥4; daptomycin, S≤8, R≥8. *For gentamicin and streptomycin, synergism tests were performed. For gentamicin, the isolated were considered resistant when MIC was ≥ 128µg/mL and, for streptomycin, when MIC was ≥ 512µg/mL (EUCAST, 2020; BrCAST, 2021).*

DISCUSSION

VRE is classified as one of the main pathogens causing HAIs in the United States.[8] This microorganism has intrinsic resistance to several antimicrobial agents and progressive resistance to ampicillin and aminoglycosides. Vancomycin resistance, however, has been reported more recently by beta-lactamases enzymes, probably due to indiscriminate use in antimicrobial therapy.[8]

In *E. faecium*, vancomycin resistance has changed its clinical relevance worldwide, being among the main causes of HAI.[8] In Brazil, the isolation of these pathogens is increasingly frequent, considering that many studies have reported the rapid emergence of VRE.[9]

During the study period, 19 strains of *E. faecium* were isolated, of which 47% (9) were resistant to vancomycin. These results are similar to those found by a multicenter study conducted in Europe.[10] In Europe, the occurrence rate of VREf in tertiary hospitals varies between the different hospitals and countries.[11,12] In 2021, resistance percentages below 1% were observed in six (14%) of the 44 countries reporting data on this microorganism. Conversely, percentages equal to or exceeding 25% were found in 17 (39%) countries. Alarmingly, vancomycin resistance percentages equal to or above 50% were reported by five (11%) countries.[11] Infections by VREf can result in prolonged hospital stays and additional antimicrobial therapy, comprising an important public health concern. This allows colonization and infection of patients, favoring HAI outbreaks, and promotes a significant increase in hospital expenses.

The emergence of VRE has coincided with the increase of the incidence of *E. faecium* in several countries, which also presents a high level of resistance to penicillin and aminoglycosides.[13] It represents a major threat to public health, since the combination of an aminoglycoside with a beta-lactam agent is a pharmacological synergism strategy used to "bypass" some bacterial resistance mechanisms, especially in the treatment of bacteremia and severe endocarditis. Thus, considering this scenario, it is also necessary to monitor aminoglycoside resistance. All the VREf in this study showed susceptibility to high levels of gentamicin (500 µg/mL). [11,13] These results are similar to other studies developed in a tertiary hospital in Brazil, whose sensitivity to gentamicin was observed in the majority of the assessed isolates.[14,15]

In the present study, all VRE isolates showed resistance to ampicillin (MIC≥08 µg/mL). Studies suggest that point mutations in penicillin-binding protein 5 (PBP 5) may change the bacteria's affinity for beta-lactams, leading to resistance to this class of antimicrobial agents.[16]

All the isolates were resistant to vancomycin and teicoplanin, having the *vanA* gene with identical sequences. Isolates with this resistance profile were previously reported in multicenter studies that assessed more than 1,200 VREf isolates from 26 hospitals in southwestern Brazil.[17] In silico analysis performed in the same study confirmed the presence of the *vanA* gene in all strains assessed. Considering that most of the *vanA* genes are associated with a Tn1546-type resistance transposon that can be transported by plasmids, the presence of VREf isolates in the hospital cannot be neglect, since *vanA* can be transferred by conjugation between different species.[15] Multifactor studies developed in North America observed that, in the first seven cases of vancomycin-resistant *S. aureus* (VRSA) in the United States, the *vanA* gene was transferred from *Enterococci*, in addition to identifying that patients with VRSA were also infected with VRE.[18]

In our study, all strains were sensitive to linezolid and daptomycin, used as last-line antimicrobial agents for the treatment of VREf infections. Linezolid and daptomycin resistance to *Enterococci* is still uncommon, although cases have already been reported. [19-22] Multicenter studies developed with VREf isolates from 66 different countries observed that those isolates with the *vanA* genotype were sensitive to these two antimicrobial agents (MIC < 2 µg/mL).

It is important to highlight that the present study was developed during the COVID-19 pandemic, in a

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scenario where several hospitals had to adapt to receive a greater demand for medical and hospital care, in particular the lack/unequal distribution of healthcare professionals and medium/high complexity care infrastructure as well as limited capacity to produce and carry out diagnostic tests. Thus, all cases of VREf came from patients relocated from other hospitals of the Brazilian Health System (SUS - *Sistema Único de Saúde*) due to redistribution of beds. Transfer of patients between health units or even intra-hospital, associated with factors such as overcrowding, shortage of Intensive Care Unit beds, medical equipment and medicines, indiscriminate use of antimicrobial agents in COVID-19 treatment and improvisation of Intensive Care Unit beds in wards, contributes significantly to the worsening and dissemination of multidrug-resistant isolates in hospital settings.

It was observed that 50% of the isolates came from a surveillance culture sample. This fact has already been shown in Brazilian studies that VRE infection has a low prevalence; however, high rates of isolation are reported from intestinal colonization research by surveillance cultures of rectal swabs. Almost 67% of patients with positive cultures for VREf were hospitalized in the same ward, at different times, being exposed to the same healthcare professionals and medical devices. Previous studies have already highlighted the importance of healthcare settings and professionals as agents of cross-contamination, whether through transient or persistent colonization. In this scenario, non-colonized patients who share rooms or wards with patients colonized by VREf are exposed to contamination and possible infections.[23,24]

Studies indicates that the most common comorbidities among patients with VREf infections are associated with solid tumors (27%), cardiovascular diseases (31%), cerebrovascular diseases (12%) and joint diseases (23%), increasing the risk of mortality by up to 73% and hospitalization time by up to 124 days.[25] Additionally, non-observance of good hospital biosafety practices by healthcare professionals, such as proper hand hygiene, may represent a risk of contamination for outpatients belonging to these clinics, since healthcare professionals can be vectors for the dissemination of VREf in extra-hospital settings.[23,24] Thus, it is necessary to intensify the prevention and control measures of this microorganism in this health unit, such as contact precautions, decolonization, active surveillance culture and cleaning of settings.

During the study period, a low occurrence of *Enterococcus* species was observed.[8-9] However, all VREf isolates were found to harbor the *vanA* gene associated with vancomycin resistance and exhibited resistance to commonly used antimicrobial agents.

This study highlights the importance of epidemiological surveillance in the healthcare institution to identify, monitor and control the spread of VREf in hospital settings. The high incidence of VREf isolates carrying *vanA* genes represents an important risk factor for the emergence of hospital outbreaks, which may directly reflect the increase in mortality caused by *Enterococci* and other microbial infections, since this genetic element of vancomycin resistance can be easily transferred between the different bacterial species.

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AUTHORS' CONTRIBUTIONS

Igor Vasconcelos Rocha contributed to the conception of the study, data curation, analysis and interpretation of data, methodology, and drafting of the original manuscript. **Carlos Alberto das Neves de Andrade** contributed to the conception of the study, data curation, analysis and interpretation of data, and methodology. **Antônio Marcos Saraiva** contributed to data curation, analysis and interpretation of data, and methodology. **Erika Danielle Gameiro da Fonsêca** contributed to data curation, analysis and interpretation of data, methodology, and drafting of the manuscript. **Danilo Elias Xavier** contributed to project administration and writing. **Danielle Patrícia Cerqueira Macêdo** contributed to the conception of the study, project administration, and writing.

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

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

Revista de Epidemiologia e Controle de Infecção

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ORIGINAL ARTICLE

Association between burnout and quality of life in military police officers from two Brazilian corporations

Associação entre burnout e qualidade de vida em policiais militares de duas corporações brasileiras

Asociación entre burnout y calidad de vida en policías militares de dos corporaciones brasileñas

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ABSTRACT

Background and Objectives: military police officers face stress related to increase in violence and devaluation of their profession, which can lead to burnout and compromised quality of life. This study aimed to analyze the association between burnout and quality of life in military police officers from two Brazilian corporations. **Methods:** this was a cross-sectional study of 773 military police officers, 506 (65.5%) from battalions of the Country Police Command - 5th Region in São Paulo state and 267 (34.5%) from 3rd Military Police Battalion in Paraná state. Data was collected between January and December 2018 using a questionnaire with sociodemographic and professional variables: the Maslach Burnout Inventory (MBI), translated and adapted into Portuguese by Robayo-Tamayo; and the abbreviated version of the World Health Organization Quality of Life (WHOQOL-Bref). **Results:** police officers from São Paulo had significantly better levels of quality of life than police officers from Paraná. There was a predominance of a high level of depersonalization (21.3%) among police officers from Paraná; a medium level of depersonalization (33.9%) among police officers from São Paulo; a medium level of emotional exhaustion and a high level of personal accomplishment in both police forces. **Conclusion:** police officers with low levels of depersonalization and emotional exhaustion had a higher quality of life in the physical health, psychological health, social relationships, environmental health and overall quality of life domains, and police officers with higher levels of personal accomplishment had higher quality of life scores.

Keywords: *Military Health. Burnout, Professional. Quality of Life. Occupational Health.*

RESUMO

Justificativa e Objetivos: os policiais militares enfrentam desgastes relacionados ao aumento da violência e à desvalorização da profissão que podem levar ao esgotamento e comprometimento da qualidade de vida. Este estudo teve como objetivo analisar a associação entre o *burnout* e a qualidade de vida em policiais militares de duas corporações brasileiras. Métodos: estudo transversal, com 773 policiais militares, sendo 506 (65,5%) dos batalhões do Comando de Policiamento do Interior – 5ª Região do estado de São Paulo e 267 (34,5%) do 3º Batalhão de Polícia Militar do Paraná. Os dados foram coletados entre janeiro e dezembro de 2018, utilizando-se um questionário com variáveis sociodemográficas e profissionais: o Inventário de *Burnout* de Maslach (MBI), traduzido e adaptado para o português por Robayo-Tamayo; e a versão abreviada do *World Health Organization Quality of Life* (WHOQOL-Bref). **Resultados:** os policiais paulistas apresentaram níveis de qualidade de vida significativamente melhores dos que os policiais paranaenses. Houve predomínio alto nível de despersonalização (21,3%) entre policiais paranaenses; nível médio de despersonalização (33,9%) entre policiais paulistas; nível médio de exaustão emocional; e nível alto de realização pessoal em ambas as corporações. Quanto maiores os níveis de despersonalização e exaustão emocional dos policiais militares, menor a qualidade de vida. Por outro lado, quanto maior a realização pessoal, maior a qualidade de vida dos profissionais. **Conclusão:** policiais com níveis baixos de despersonalização e de exaustão emocional apresentaram maior qualidade de vida nos domínios físico, psicológico, relações sociais, meio ambiente e na avaliação da qualidade de vida geral, e os policiais com níveis mais elevados de realização pessoal tinham maiores escores de qualidade de vida.

***Descritores*:** *Saúde Militar. Esgotamento Profissional. Qualidade de Vida. Saúde Ocupacional.*

RESUMEN

Justificación y Objetivos: los policías militares enfrentan estrés relacionado con el aumento de la violencia y la devaluación de la profesión, lo que puede provocar agotamiento y comprometer la calidad de vida. Este estudio tuvo como objetivo analizar la asociación entre burnout y calidad de vida en policías militares de dos cuerpos brasileños. **Métodos:** se trató de un estudio transversal de 773 policías militares, 506 (65,5%) de los batallones del Comando de Policía Interior - 5ª Región en estado de São Paulo y 267 (34,5%) del 3º Batallón de Policía Militar en estado de Paraná. Los datos se recogieron entre enero y diciembre de 2018, mediante cuestionario con variables sociodemográficas y profesionales: el Inventario de *Burnout* de Maslach (MBI), traducido y adaptado al portugués por Robayo-Tamayo; y la versión abreviada del *World Health Organization Quality of Life* (WHOQOL-Bref). **Resultados:** los policías de São Paulo tenían niveles de calidad de vida significativamente mejores que los policías de Paraná. Predominó un alto nivel de despersonalización (21,3%) entre los policías de Paraná; nivel medio de despersonalización (33,9%) entre los agentes de policía de São Paulo; nivel medio de agotamiento emocional; y alto nivel de realización personal en ambas corporaciones. **Conclusión:** los policías con bajos niveles de despersonalización y agotamiento emocional presentaron mayor calidad de vida en el ámbito físico, psicológico, relaciones sociales, entorno y en la valoración de la calidad de vida general, y los policías con niveles más altos de realización personal tenían puntuaciones más altas en calidad de vida.

Palabras Clave: *Salud Militar. Agotamiento Profesional. Calidad de Vida. Salud Laboral.*

INTRODUCTION

Military police officers perform important functions, ensuring the safety and well-being of all citizens. These professionals are responsible for inhibiting attacks on social order, providing security and freedom so that all citizens live in accordance with the principles of the law.[1]

Despite the important role played by these professionals, in many regions of Brazil, military police officers experience a lack of professional recognition, low pay and precarious working conditions which, associated with high crime rates, insecurity and lack of technical preparation, have a negative impact on the physical and emotional health, causing exhaustion and compromising quality of life.[2,3]

Studies have shown that soldiers and military police officers have worse mental health and a lower quality of life due to experiencing traumatic events. Furthermore, reduced time for rest, smoking and lack of healthy lifestyle habits are associated with lower levels of quality of life among police officers.[2,4,5]

According to the Brazilian Public Security Yearbook 2021, in 2019 and 2020, 418 deaths of military police officers were recorded in Brazil due to intentional lethal violent crimes, 26% of which were due to suicide.[6] However, police officers still avoid seeking professional help due to fear of ostracization and stigmatization by the military organization itself, circumstances that end up making access to treatment difficult.[7]

Police work is one of the most frequent causes of conflicts in the family environment, and police officers are among the professionals with the highest divorce rates, in addition to the highest propensity for developing Burnout Syndrome (BS).[3,4,8] BS is an occupational phenomenon characterized by professional exhaustion,

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resulting from long exposure to stressors in the work environment and is characterized by physical, mental and emotional exhaustion. Considered an occupational disease by the World Health Organization (WHO), this syndrome is identified as an important cause of high rates of sick leave, absence from work and devaluation of military police officers by their superiors.[9]

In this context, military police officers' health is considered by the Brazilian National Health Promotion Policy (*Política Nacional de Promoção da Saúde*) as a priority factor to be worked on.[10] Stress related to police work, accompanied by a culture in which the display of emotions is seen as a sign of weakness, can affect several dimensions of work and life.[11] Thus, there is a need to work on aspects related to these professionals' quality of life, as physical fatigue and compromised mental health can lead them to adopt irrational attitudes during crises and chaotic situations, which can lead to ineffective performance of professional exercise.[8,12]

In this context, we understand that knowing the association between burnout and quality of life in military police officers can contribute to reducing vulnerabilities and risks of illness related to these professionals' environment and work process, in addition to supporting the implementation of interventions that promote police officers' mental health and quality of life.

Considering the above, this study aimed to analyze the association between burnout and quality of life in military police officers from two Brazilian corporations.

METHODS

This is a quantitative, observational, cross-sectional, descriptive and correlational study, carried out with military police officers from two Brazilian Military Police Battalions, such as Country Policing Command – 5th Region of the state of São Paulo (CPI-5/SP) and 3rd Military Police Battalion of the state of Paraná (3rd BPM/PR).

The CPI-5/SP has a staff of 2,200 police officers and covers an area of 96 municipalities, with approximately 1.4 million inhabitants. The 3rd BPM/PR belongs to the 5th Regional Military Police Command of the State and has a staff of 312 police officers, who serve a population of approximately 260 thousand inhabitants. The choice of these battalions occurred due to the existence of a previous connection with the researchers (one of them a former military police officer), who were aware of the labor difficulties that permeate police activity in different regions of Brazil.

All military police officers belonging to the CPI-5/SP and the 3rd BPM/PR were considered eligible for the study and, after being invited, consented to participate in the study. Those who were on vacation or away from professional activities, for any reason, during the data collection period, were excluded. All military police officers were invited to participate in the study. The sample was constituted by convenience and consisted of 506 police officers from the CPI-5/SP and 267 police officers from the 3rd BPM/PR.

Data were collected in 2018, using a questionnaire prepared by the authors, containing sociodemographic (age, sex, age group, marital status, education) and professional (position, length of service and work shift of professionals, practice of physical activity and whether they have already responded to the Disciplinary or Justice Council) variables of military police officers, the Maslach Burnout Inventory (MBI), translated and adapted into Portuguese by Robayo-Tamayo,[13] and the abbreviated version of the World Health Organization Quality of Life (WHOQOL-Bref).[14]

The MBI is a self-administered scale composed of 22 questions, which assess BS, based on feelings and attitudes related to work. The scale has three dimensions: emotional exhaustion (EE); depersonalization (DP); and personal achievement (PA). Answers to the questions are given on a five-point Likert scale, where: 1= never; 2 = rarely; 3 = sometimes; 4 = often; 5 = always. The variation of the scale recommended by Robayo-Tamayo[13] was used, as it was considered easier to understand by respondents.

The WHOQOL-Bref is a reduced version of the WHOQOL-100 questionnaire, which has 26 questions, divided into four domains, such as physical health, psychological health, environmental health and social relationships. The answers to each question are given on a Likert-type scale of four types: intensity; capacity; frequency; and assessment. The result is obtained by calculating the mean of the values for each domain.[14] Quality of life scores are a positive scale, i.e., the higher the score, the better the quality of life.[15]

Data collection occurred after authorization from those responsible for each corporation. The researchers contacted the Battalion commanders, explained the objectives of the study and handed over the instruments to the military police officers. After filling out, the police officers delivered the instruments to the Battalion administration in sealed envelopes to guarantee data confidentiality. Each professional had a period of up to 30 days to respond to the research instruments.

Upon receiving the self-administered instruments, no police officer formally refused to participate in the study. However, only 773 returned the answered instruments, 506 (65.5%) police officers from the CPI-5/SP and 267 (34.5%) police officers from the 3rd BPM/PR.

The data obtained were entered and stored in a Microsoft Excel® spreadsheet, in order to enable analysis according to the proposed objectives. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25.0.

For BS analysis, the mean of the scores obtained in each dimension was calculated.[13] Professionals with high scores in EE (≥ 27 points) and DP (≥ 13 points) dimensions and low values in PA dimension (≥ 39 points) are considered to have BS.[16]

To assess quality of life, WHOQOL-Bref scores were calculated according to the statistical model provided by the WHOQOL Group, which establishes the calculation of scores on a scale of 4 to 20 for each domain of the questionnaire. To facilitate comparison with other studies, the scores obtained on a scale of 4 to 20 are transformed to a

scale of 0 to 100 using the formula [(Average-4)x100/16].[14]

To assess the levels of DP, EE and PA according to battalion, sex and age group of military police officers, Pearson's chi-square test was applied. To compare quality of life levels according to these sociodemographic variables, t-test was used for two means and Analysis of Variance (ANOVA) for three or more means.

The comparison of quality of life scores with the levels of EE, DP and PA was performed using the ANOVA test. Pearson's correlation test was applied to verify the degree of relationship between the WHOQOL-Bref domains and the MBI domains. A confidence level of 5% ($p \leq 0.05$) was considered.

In compliance with current ethical aspects regarding research involving human beings (Resolution 466/2012 of the Brazilian National Health Council), the study was approved by the *Faculdade de Medicina de São José do Rio Preto* (FAMERP) Research Ethics Committee on 4 December 2017, under Certificate of Presentation for Ethical Consideration (CAAE - *Certificado de Apresentação para Apreciação Ética*) 47885715.8.0000.5415 and Opinion 2,412,594. Upon receiving the questionnaires, prior to data collection, the police officers who agreed to participate in the study, after providing the necessary clarifications about the research, signed the Informed Consent Form.

Table 1. Sociodemographic profile of military police officers (n=773).

Variable	n (%)
Battalion	267 (34.5)
Paraná	506 (65.5)
São Paulo	
Age group	14 (1.8)
Up to 20 years	250 (32.3)
21 - 30 years	307 (39.7)
31 - 40 years	200 (25.9)
41 years or older	2 (0.3)
Not reported	
Sex	674 (87.2)
Male	98 (12.7)
Female	1 (0.1)
Not reported	
Marital status	518 (67.0)
Married	202 (26.1)
Single	44 (5.7)
Divorced/separated	7 (0.9)
Widower	2 (0.3)
Not reported	
Education	7 (0.9)
Elementary school	434 (56.2)
High school	324 (41.9)
Higher education	8 (1.0)
Not reported	

RESULTS

A total of 773 military police officers participated in the study, 506 (65.5%) belonging to the CPI-5/SP and 267 (34.5%) to the 3rd BPM/PR. Police officers' mean age was 34.5 years (standard deviation: ±7.8 years), with a predominance of professionals aged between 31 and 40 years (39.7%). There was also a higher frequency of male police officers (87.2%), married (67.0%) and with high school (56.2%) (Table 1).

In relation to BS assessment, it was observed that 44.8% of police officers had high levels of DP (≥ 13 points), 67.3% considered high levels of EE (≥ 27 points) and 5.2% low levels of PA (≥ 39 points). No professional presented BS, however, a high risk for developing the syndrome was identified among professionals, given the high prevalence of DP and EE.

In relation to burnout dimensions, there was a predominance of professionals with a high level of DP (21.3%) among military police officers from the 3rd BPM/PR and a predominance of professionals with a medium level of DP (7 to 12 points) among military police officers from the CPI-5/SP (33.9%), in addition to predominance of police officers with a medium level of EE (17 to 26 points) in both corporations (3rd BPM/PR: 15.5%; CPI-5/SP: 35.2%) and predominance of police officers with a high level of PA (≤ 31 points) in both corporations (3rd BPM/PR: 28.4%; CPI-5/SP: 39.1%). It was also observed a predominance of police officers aged between 31 and 40 years old with medium levels (7 to 12 points) of DP (22.0%) and EE (17 to 26 points) (21.1%) and high level (≤ 31 points) of PA (29.7%), and a predominance of police officers with high school and a medium level of EE (17 to 26 points) (28.2%) (Table 2).

Police officers assessed the general quality of life positively (mean score 69.1). In relation to the WHOQOL-Bref domains, the results showed that police officers have a better level of social relationships (mean score 72.9), showing satisfaction in relationships with friends, family and spouses. On the other hand, the environmental health domain presented the lowest score (61.0), indicating a loss of satisfaction among professionals with aspects involving this domain, such as physical safety and security, financial resources, health and social care, opportunities for acquiring new information and skills, participation in and opportunities for recreation and leisure, in addition to the physical environment.

As shown in Table 3, military police officers from the CPI-5/SP had significantly better quality of life levels than police officers from the 3rd BPM/PR in all WHOQOL-Bref domains ($p<0.001$); there was no statistically significant difference between male and female police officers ($p>0.05$); younger police officers had better quality of life scores in social relationships ($p=0.030$), environmental health ($p=0.008$) and general quality of life ($p=0.023$) domains; and police officers with higher education had a lower quality of life score in the social relationships domain ($p=0.033$) than police officers with less education.

When analyzing the association between the quality of life domains and burnout domains (Table 4), it was found that professionals with low levels of DP (≤ 6 points) and EE (≤ 16 points) presented significantly higher scores quality of life in the physical health, psychological

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Table 2. Assessment of burnout dimensions according to battalion, gender and age group of military police officers.

	Depersonalization			Emotional exhaustion			Personal achievement		
Variables	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**
Battalion		(n=769)			(n=770)			(n=70)	
Paraná	6 (0.8)	34 (12.2)	167 (21.7)	39 (5.1)	135 (17.5)	93 (12.1)	2 (0.3)	46 (6.0)	219 (28.4)
São Paulo	62 (8.1)	261 (33.9)	179 (23.3)	146 (19.0)	271 (35.2)	86 (11.2)	38 (4.9)	164 (21.3)	301 (39.1)
p-value		**<0.001**			**<0.001**			**<0.001**	
Sex		(n=768)			(n=769)			(n=769)	
Male	61 (7.9)	309 (40.2)	300 (39.1)	166 (21.6)	352 (45.8)	153 (19.9)	37 (4.8)	185 (24.1)	449 (58.4)
Female	7 (0.9)	46 (6.0)	45 (5.9)	19 (2.5)	53 (6.9)	26 (3.4)	3 (0.4)	25 (3.3)	70 (9.1)
p-value		0.802			0.456			0.610	
Age group		(n=767)			(n=768)			(n=768)	
Up to 20 years	2 (0.3)	10 (1.3)	2 (0.3)	6 (0.8)	8 (1.0)	-	1 (0.1)	3 (0.4)	10 (1.3)
21 - 30 years	27 (3.5)	118 (15.4)	105 (13.7)	81 (10.5)	119 (15.5)	50 (6.5)	18 (2.3)	64 (8.3)	168 (21.9)
31 - 40 years	12 (1.6)	125 (16.3)	169 (22.0)	50 (6.5)	162 (21.1)	95 (12.4)	7 (0.9)	72 (9.4)	228 (29.7)
41 years or older	26 (3.4)	101 (13.2)	70 (9.1)	47 (6.1)	117 (15.2)	33 (4.3)	14 (1.8)	70 (9.1)	113 (14.7)
p-value		**<0.001**			**<0.001**			**0.001**	
Education		(n=761)			(n=762)			(n=762)	
Elementary school	-	4 (0.5)	3 (0.4)	1 (0.1)	6 (0.8)	-	-	4 (0.5)	3 (0.4)
High school	46 (6.0)	200 (26.3)	185 (24.3)	121 (15.0)	215 (28.2)	96 (12.6)	28 (3.7)	118 (15.5)	286 (37.5)
Higher education	21 (2.8)	149 (19.6)	153 (20.1)	59 (7.7)	184 (24.1)	80 (10.5)	12 (1.6)	85 (11.2)	226 (29.7)
p-value		0.442			**0.011**			0.355	

Table 3. Assessment of quality of life according to battalion, sex and age group of military police officers

Variables	**Physical health domain**	**Psychological health domain**	**Social relationships domain**	**Environmental health domain**	**General quality of life**
Battalion					
Paraná	68.1 ± 14.7	67.5 ± 15.6	68.8 ± 17.4	58.7 ± 13.1	65.8 ± 12.5
São Paulo	71.7 ± 14.0	74.6 ± 14.1	75.1 ± 16.0	62.2 ± 13.5	70.9 ± 12.1
p-value	**0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Sex					
Male	70.7 ± 14.5	72.5 ± 15.2	73.1 ± 16.8	60.9 ± 13.6	69.3 ± 12.6
Female	68.3 ± 13.4	69.9 ± 13.5	71.6 ± 16.2	61.4 ± 12.6	67.8 ± 11.3
p-value	0.099	0.085	0.386	0.760	0.219
Age group					
Up to 20 years	74.0 ± 9.7	77.1 ± 9.9	80.4 ± 20.3	65.0 ± 16.6	74.1 ± 12.5
21 - 30 years	72.1 ± 14.0	72.9 ± 15.5	74.1 ± 16.8	62.1 ± 13.7	70.3 ± 12.6
31 - 40 years	69.5 ± 14.4	70.9 ± 14.8	71.0 ± 16.8	59.0 ± 13.7	67.6 ± 12.4
41 years or older	70.5 ± 14.8	72.8 ± 15.0	73.9 ± 16.0	62.4 ± 12.2	69.7 ± 12.2
p-value	0.119	0.193	**0.030**	**0.008**	**0.023**
Education					
Elementary school	67.9 ± 8.0	69.0 ± 17.7	72.0 ± 7.0	62.1 ± 5.2	67.7 ± 7.4
High school	70.9 ± 14.7	73.2 ± 15.2	74.3 ± 16.4	61.0 ± 13.7	69.9 ± 12.6
Higher education	69.9 ± 14.0	70.7 ± 14.6	71.1 ± 17.2	61.0 ± 13.3	68.2 ± 12.3
p-value	0.539	0.070	**0.033**	0.978	0.171

health, social relationships, environmental health and assessment of general quality of life. On the other hand, significantly higher quality of life was observed among police officers who presented higher levels of PA (≤ 31 points).

As shown in Table 5, a weak, negative and significant correlation was identified between the DP dimension and the physical health, psychological health, social relationships and environmental health domains, and a moderate, negative and significant correlation between DP and general quality of life. EE showed a moderate, negative and significant correlation with all quality of life domains (physical health, psychological health, social relationships and environmental health) and with general quality of life. PA showed a positive and significant correlation with all quality of life domains, with a weak correlation with the physical health, social relationships and environmental health domains and moderate with the psychological health domain and general quality of life.

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Table 4. Association between quality of life and burnout domains in military police officers.

	Quality of life				
Burnout	**Physical health domain**	**Psychological health domain**	**Social relationships domain**	**Environmental health domain**	**General quality of life**
Depersonalization					
Low level	79.54 ± 14.15	81.48 ±15.83	82.72 ± 17.06	70.26 ± 13.06	78.50 ± 12.82
Moderate level	72.95 ± 12.43	75.45 ± 11.82	75.45 ± 14.43	64.02 ± 11.89	71.97 ± 10.23
High level	66.07 ± 14.85	66.82 ± 15.75	68.20 ± 17.46	56 ± 13.20	64.27 ± 12.54
p-value	0.02*	0.01*	0.01*	0.02*	0.02*
Emotional exhaustion					
Low level	80.53 ± 11.88	82.48 ± 11.27	82.97 ± 14.11	69.68 ± 12.03	78.92 ± 10.05
Moderate level	70.38 ± 11.72	72.35 ± 12.09	72.14 ± 14.45	60.06 ± 11.79	68.87 ± 9.84
High level	60.14 ± 14.85	60.94 ± 16.26	64.06 ± 18.58	52.87 ± 13.18	59.50 ± 12.41
p-value	0.01*	0.01*	0.01*	0.02*	0.02*
Personal achievement					
Low level	67.36 ± 13.91	68.53 ± 14.42	69.34 ± 16.46	57.88 ± 12.77	65.78 ± 11.78
Moderate level	75.57 ± 12.58	78.61 ± 12.72	78.67 ± 14.78	66.32 ± 12.02	74.79 ± 10.37
High level	83.57 ± 14.17	84.90 ± 14.46	88.12 ± 13.19	73.36 ± 13.89	82.49 ± 11.74
p-value	0.01*	0.01*	0.01*	0.01*	0.01*

*Note: *One-Way ANOVA test.*

Table 5. Correlation between quality of life and burnout domains in military police officers.

	Quality of life				
Burnout	**Physical health domain**	**Psychological health domain**	**Social relationships domain**	**Environmental health domain**	**General quality of life**
Depersonalization	-0.357	-0.395	-0.333	-0.390	-0.438
p-value	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
Emotional exhaustion	-0.562	-0.566	-0.422	-0.488	-0.605
p-value	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
Personal achievement	0.367	0.425	0.327	0.359	0.440
p-value	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*

*Note: *Significant correlation at the 0.01 level; Pearson's correlation test.*

DISCUSSION

Military police officers assessed their general quality of life positively, despite showing a slight loss of satisfaction related to the environmental health domain, which includes physical safety and security, financial resources, health and social care, opportunities for acquiring new information and skills, participation in and opportunities for recreation and leisure. Although no police officer presented BS, the prevalence of professionals with high DP (44.8%) and/or EE (67.3%) highlights the risk of developing BS. Quality of life correlated inversely with DP and EE and positively with PA.

These results support the literature, which indicates good levels of satisfaction among military police officers with their quality of life, although they present losses in the environmental domain.[8,17] However, it is essential to carry out actions that promote awareness about mental health among public security professionals, aiming to facilitate the implementation of prevention and intervention measures in mental health.[18]

As it is an environment permeated by constant pressure, due to the rigidity of the hierarchical culture, precarious conditions, violence and risk of death, the work of military police officers can alter their way of acting and thinking, causing feelings of fear, escape and despair, in addition to make it difficult to carry out daily activities and harm the establishment of priorities, negatively impacting the quality of life of these professionals.[7,19]

Fear is present daily in the activities of these professionals, who fear for themselves or their families, given the high rate of victimization of police officers, both while on duty and on their days off. Furthermore, high physical, cognitive and psychological demands placed on police officers during work activities may exceed their ability to cope.[20-22] In this context, professionals become susceptible to the development of BS, as we saw in this study.

As burnout is a disease with a significant impact on workers' health and performance, with the potential to influence the activities of daily living and the quality of life of military police officers, it is important to implement public policies that include actions capable of reducing the negative impacts of occupational stress present in police work, since interventions and actions aimed at

promoting the quality of life and well-being of police officers in military institutions are still incipient.[7,18,23]

In the environment of military corporations, it is common for emotional reactions to be perceived as weakness and the expectation that people should not have emotional reactions can generate internal conflicts within police officers. In this context, public stigma (others' perception of individuals) and/or low self-esteem (a person's perception of themselves) can trigger a feeling of not belonging, which negatively affects police officers' mental health.[24]

Some fundamental aspects characterize BS, such as emotional insensitivity, excessive tiredness, a feeling of "emptiness" and loss of self-esteem[25]. In the present study, the number of police officers with high levels of DP or EE draws attention to the need to implement preventive actions and programs to reduce emotional, physical and social damage caused by professionals' work practice.

In this context, the results point to the emerging need for strategies and interventions that seek to address the problems experienced by military police officers and the consequences for these professionals' physical and mental health, in addition to addressing the barriers that impede the development of strategies and interventions in military organizations.

The main limitation of this study is related to the convenience sample, which poses a risk of obtaining responses from professionals who are more encouraged and have better quality of life and mental health conditions. On the other hand, the results provide a diagnosis of police officers' perception of their quality of life, in addition to identifying the high risk for the development of BS in the study population. They thus contribute to identifying the need for management strategies and health care for these workers, which can improve police officers' working conditions and favor the improvement of public safety in local society.

The study showed that police officers with low levels of DP and EE had a higher quality of life in the physical health, psychological health, social relationships, environmental health and assessment of general quality of life. Police officers with higher levels of PA had higher quality of life scores. There was also a negative association between DP and EE with quality of life domains. These results show that military police officers are subject to losses in quality of life as a result of compromised mental health, reinforcing the importance of developing strategies and interventions that promote the quality of life of these workers, identify and prevent the factors that cause exhaustion and that contribute to the development of negative feelings, such as DP and EE.

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AUTHORS' CONTRIBUTIONS

Jacqueline Flores de Oliveira, **Luciano Garcia Lourenção and Fernando Braga dos Santos** contributed to project design and administration; writing the manuscript and approving the final version. **Thiago Roberto Arroyo**, **Evellym Vieira** and **Marcio Andrade Borges** contributed to the critical review of the manuscript and approval of the final version.

All authors are responsible for all aspects of the work, including ensuring its accuracy and integrity.

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ORIGINAL ARTICLE

Development and validation of a questionnaire on the use of antimicrobials in primary health care

Desenvolvimento e validação de questionário sobre o uso de antimicrobianos na atenção primária à saúde

Desarrollo y validación de un cuestionario sobre el uso de antimicrobianos en la atención primaria de salud

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ABSTRACT

Background and Objectives: Antimicrobial resistance is a global threat to public health and is related to excessive and inappropriate use of antimicrobials. In Brazil, there are few studies on infection prevention and control strategies and antimicrobial management in primary healthcare. In this study, we developed and validated a questionnaire to assess these strategies. The aim of this study was to develop and validate an evaluation tool designed to investigate the strategies adopted by primary healthcare services to prevent and control infections and manage the use of antimicrobials. **Methods:** Between February and April 2022, the study involved five Steps: literature review, question development, expert validation, questionnaire finalization, and dissemination. The Content Validity Index was calculated to assess the expert agreement. **Results:** The final questionnaire with 102 questions was refined based on feedback from experts. The overall average CVI was 0.74, indicating good agreement between experts regarding the representativeness of the items. These suggestions resulted in improvements in the vocabulary and structure of the questionnaire. **Conclusion**: The questionnaire developed and validated is an accurate and reliable tool for evaluating infection prevention and control strategies and antimicrobial stewardship in primary healthcare. Its use can provide important data for improving health practices, with a view to reducing antimicrobial resistance and improving the quality of services. This study highlights the importance of research in this area to promote the rational use of antimicrobials and strengthen the health system in primary health care.

Keywords: *Primary Health Care. Antimicrobial Stewardship. Infection Control. Surveys and Questionnaires. Validation Study.*

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RESUMO

Justificativa e Objetivos: A resistência antimicrobiana é uma ameaça global à saúde pública, relacionada ao uso excessivo e inadequado de antimicrobianos. No Brasil, há poucos estudos sobre estratégias de prevenção e controle de infecções e gerenciamento de antimicrobianos na atenção primária à saúde. O objetivo deste estudo foi desenvolver e validar uma ferramenta de avaliação destinada a investigar as estratégias adotadas pelos serviços de atenção primária à saúde para a prevenção e controle de infecções e o gerenciamento do uso de antimicrobianos. **Métodos:** Realizado entre fevereiro e abril de 2022, o estudo envolveu cinco etapas: revisão da literatura, desenvolvimento das questões, validação por especialistas, finalização do questionário e disseminação. O Índice de Validade de Conteúdo foi calculado para avaliar a concordância dos especialistas. **Resultados:** O questionário final, com 102 questões, foi refinado com base no feedback dos especialistas. O IVC médio geral foi de 0,74, indicando boa concordância entre os especialistas quanto à representatividade dos itens. As sugestões resultaram em melhorias no vocabulário e estrutura do questionário. **Conclusão:** O questionário desenvolvido e validado é uma ferramenta precisa e confiável para avaliar estratégias de prevenção e controle de infecções e gerenciamento de antimicrobianos na Atenção Primária à Saúde. Sua utilização pode fornecer dados importantes para melhorar as práticas de saúde, visando à redução da resistência antimicrobiana e à melhoria da qualidade dos serviços. Este estudo destaca a importância de pesquisas nesta área para promover o uso racional de antimicrobianos e fortalecer o sistema de saúde.

Descritores: *Atenção Primária à Saúde. Gestão de Antimicrobianos. Controle de Infecções. Inquéritos e Questionários. Estudo de Validação.*

RESUMEN

Justificación y Objetivos: La resistencia antimicrobiana representa una amenaza global para la salud pública, asociada al uso excesivo e inadecuado de antimicrobianos. En Brasil, hay pocos estudios sobre estrategias de prevención y control de infecciones y gestión de antimicrobianos en la atención primaria de salud. Este estudio desarrolló y validó un cuestionario para evaluar dichas estrategias. El objetivo de este estudio fue desarrollar y validar una herramienta de evaluación destinada a investigar las estrategias adoptadas por los servicios de atención primaria de salud para la prevención y control de infecciones, así como para el manejo del uso de antimicrobianos. **Métodos:** Realizado entre febrero y abril de 2022, el estudio comprendió cinco etapas: revisión de literatura, desarrollo de preguntas, validación por expertos, finalización del cuestionario y difusión. Se calculó el Índice de Validez de Contenido para evaluar la concordancia de los expertos. **Resultados:** El cuestionario final, con 102 preguntas, se refinó según la retroalimentación de los expertos. El IVC medio general fue de 0,74, indicando una buena concordancia entre los especialistas en cuanto a la representatividad de los elementos. Las sugerencias resultaron en mejoras en el vocabulario y estructura del cuestionario. **Conclusión:** El cuestionario desarrollado y validado es una herramienta precisa y confiable para evaluar estrategias de prevención y control de infecciones y gestión de antimicrobianos en la Atención Primaria de Salud. Su uso puede proporcionar datos importantes para mejorar las prácticas de salud, con el objetivo de reducir la resistencia antimicrobiana y mejorar la calidad de los servicios. Este estudio destaca la importancia de la investigación en esta área para promover el uso racional de antimicrobianos y fortalecer el sistema de salud.

Palabras Clave: *Atención Primaria de Salud. Programas de Optimización del Uso de los Antimicrobianos. Control de Infecciones. Encuestas y Cuestionarios. Estudio de Validación.*

INTRODUCTION

Antimicrobial resistance (AMR) is a global public health threat that is intrinsically linked to the use of antimicrobial agents (AMAs). Estimates from 2019 indicate that there were approximately 4.95 million deaths worldwide associated with bacterial AMR, with 1.27 million of these deaths directly attributable to this resistance.[1] A recent study reveals that approximately three-quarters of AMA consumption occurs in the community, where Primary Health Care (PHC) professionals play a key role in prescribing.[2]

Although Primary Health Care (PHC) is fundamental to reducing the use of AMA, allowing direct interaction with users and their families, there is still a gap in knowledge about the impact of Infection Prevention and Control (IPC) strategies and AMA Management Measures in the Brazilian context. This study seeks to fill this gap by proposing the construction of a tool capable of measuring AMA management actions and strategies in PHC. The aim of this study was to develop and validate a precise tool that evaluates the interactional triad between IPC, AMA and PHC.

METHODS

During the months of February to April 2022, this study was dedicated to designing and validating a questionnaire for PHC professionals. The questionnaire addressed IPC strategies and AMA management measu-

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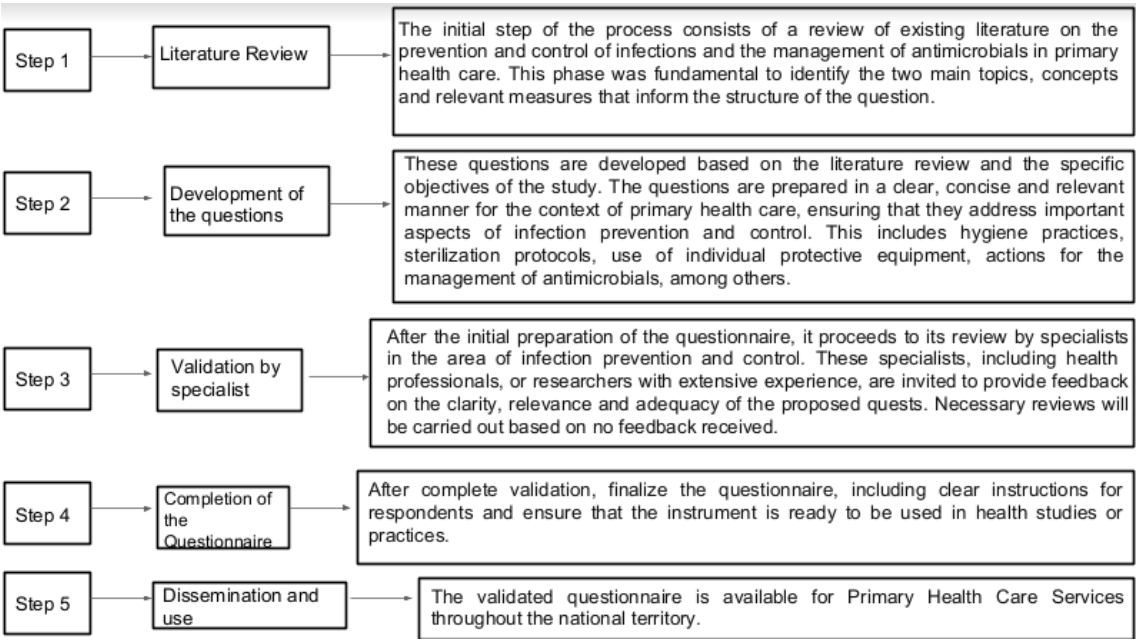

Source: elaborated by the authors, 2024.

Figure 1. Steps for developing and validating the questionnaire.

res and was evaluated by experts who analyzed the representativeness of the content areas and the relevance of the objectives.

In this study, questionnaires with consolidated scales were used to collect data from health research, providing valuable insights into clinical and prescriptive AMA practice. This has contributed to improving strategies for managing and controlling the use of these drugs. The process of developing and validating the questionnaire consisted of five distinct Steps: Step 1 - Literature Review; Step 2 - Question Development; Step 3 - Expert Validation; Step 4 - Questionnaire Finalization; Step 5 - Questionnaire Dissemination. The steps for developing and validating the questionnaire are detailed in the flowchart below.

Content validation is fundamental in the validation of psychometric instruments, guaranteeing the accuracy of the items in measuring the proposed construct, as well as their relevance and representativeness for the target population and specific context; thus, Pasquali highlights methods and criteria for this validation, emphasizing the participation of experts in assessing the clarity, relevance and comprehensiveness of the items.[3]

Under this theoretical methodology, a convenience method was adopted to select the experts, taking into account criteria such as professional experience and involvement with the State Coordination Offices and the Ministry of Health. Initial communication took place via an e-mail invitation letter, detailing the aspects of the study. A total of 31 experts were contacted, and those who did not respond within 7 days were excluded from the evaluation process. The experts who responded were directed to take part in the validation via a virtual form. In this way, 15 experts actively contributed to the validation of the tool.

In order to make it easier for the experts to evaluate the questions, spaces were included adjacent to each item so that they could record their evaluations, as well as specific areas for comments and suggestions, guaranteeing comprehensive feedback. The experts analyzed the instruments in isolation and context, considering criteria such as vocabulary and the instructional sequence of the domains. They were responsible for determining whether each domain was adequate, inadequate or required changes.

The Content Validity Index (CVI) was calculated to assess the experts' agreement as to the representativeness of the items in relation to the content studied. According to Coluci et al,4 this index is calculated using the following formula:

$$CVI = \frac{\text{N of experts who rated the item as adequate with changes or adequate}}{\text{Total number of specialists}}$$

In this study, only the items considered adequate by the experts were used to calculate the Content Validity Index (CVI). To determine the overall average CVI of the instrument, all the CVIs calculated individually were added together and divided by the total number of items. A minimum index of 0.75 was established as acceptable for both the evaluation of each item and the overall evaluation of the instrument.[5]

In accordance with the rules contained in Resolution No. 466/2012, this research project was submitted to and approved by the Research Ethics Committee on March 17, 2022, under Certificate of Presentation and Ethical Appreciation No. 5.413.514. The favorable opinion of the Research Ethics Committee was obtained under CAAE: 57866222.3.1001.5343.

RESULTS

This study was conducted in five main methodological Steps, each playing a crucial role in the construction and validation of the tool for assessing the interaction between IPC, AMA and PHC.[6-7]

Step 1 - Literature Review: The review was conducted by accessing the LILACS (Latin American and Caribbean Health Sciences Literature) and SciELO (Scientific Electronic Library Online) databases. The health science descriptors in Portuguese or the corresponding terms in Spanish or English used in the search were: questionnaire; infection control; antimicrobial stewardship; primary health care. It was found that there were no previous studies that simultaneously addressed the topics of IPC and AMA management in Brazilian PHC. The questionnaire was segmented and organized into "domains" (D), i.e. sets of questions that addressed the same aspect. The multiple-choice variables were structured as dichotomous variables.

Step 2 - Developing the questions: given the difficulty in finding literature on the topics, we decided to use the texts of the National Program for the Prevention and Control of Healthcare-Related Infections (PNPCIRAS 2021-2025) of the National Health Surveillance Agency (ANVISA) and the National Action Plan for the Control of Antimicrobial Resistance in the Single Health Sector 2018 (PAN-BR) as guidelines.

Thus, the first two domains of the "D" questionnaire were designed to cover the following domains, respectively: D1) Health service profile and D2) Clinical and epidemiological profile of the health service.

For the preparation of the questions related to precautionary measures contained in domain D3): Actions related to the prevention and control of infections, we used as a reference the study "The role of Primary Care in the prevention of Healthcare-Related Infections" carried out by Maria Clara Padoveze and Rosely Moralez de Figueiredo.[8] In the same domain, but in the subdomain entitled biosafety and waste management, the questions were based on RDC No. 222 of February 28, 2018, which provides for Technical Regulations for the management of health service waste.

With regard to domain D4) Actions for managing the use of AMA; D5) Health education on IPC measures; D6) Health education focusing on managing the use of AMA, the following were used as a basis, respectively: the National Guideline for Preparing a Program for Managing the Use of Antimicrobials in Health Services, published by Anvisa (2017)[9], o (PAN-BR)[6] and the Centers for Disease Control and Prevention's Checklist of Basic Elements for Antibiotic Use in Outpatient Settings (CDC, 2016).[10] (Table 1)

Step 3 - Validation of Experts: there was a predominance of females (86.6%), and the majority lived in the Midwest region (60%), followed by the Southeast region (20%). Around 53.3% had a degree in nursing, while 26.6% were pharmacists. All the experts were linked to public bodies related to Primary Health Care and Health Surveillance at state level. Representatives from the General Coordination for Guaranteeing Primary Care Attri-

Table 1. Description of the domains and the main questions included in the questionnaire.

Domain / Questions
D1) Health service profile
- Average number of visits per month; main visits; and number of health professionals involved.
- Existence of computers; computerized system; and network access.
D2) Clinical and epidemiological profile of the health service
- Main age groups of patients seen.
- Main pathologies.
D3) Actions related to IPC measures
- General PCI measures; hand hygiene; precautionary measures; biosafety and waste management; cleaning, disinfection and sterilization of articles (instruments).
D4) Actions to manage AMA use
- Existence of dispensing of AMA without prescription.
- There is pressure from patients to prescribe AMA.
- Existence of control and dispensing of AMA by the responsible professional.
- Existence of a formal document/protocol for the diagnosis and treatment of the main infections.
- Existence of a policy/protocol obliging prescribers to record: dose, duration and indication of treatment.
- Existence of training to adopt the measures provided for in these protocols.
- Existence of a standardized list of these medicines in accordance with the National List of Medicines (RENAME), State (REM) or Municipal (REMUME).
- Existence of AMA prescriptions guided by laboratory tests, including antibiograms, with an interface with a clinical/microbiological analysis laboratory.
D5) Health education on infection prevention and control measures
- The health service provides ongoing education on IPC measures. For what reasons does the health service have no ongoing education on IPC measures?
- Permanent education actions include periodic training on IPC measures for all professionals.
- What topics are covered in the training so that professionals are able to implement IPC measures.
- The health service promotes actions aimed at patients, which include the distribution of printed material, such as pamphlets and booklets, containing guidance on the importance of IPC measures.
D6) Health education with a focus on ATM use management
- Carrying out continuing education actions for its professionals to improve awareness of the use of AMA: frequency and topics covered in training.
- Training topics that healthcare professionals need to know and master in order to implement antimicrobial stewardship measures.
- Patient guidance on AMA use: the way in which AMA guidance is passed on to patients, including strategies to improve patient understanding.
- Distribution of printed material (pamphlets, booklets, etc.) containing guidance on the correct and rational use of AMA.

Source: Elaborated by the authors, 2024.

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butes (CGGAP), the Family Health Department (DESF), the Primary Health Care Secretariat (SAPS) and the Ministry of Health (MS), as well as members of ANVISA's Health Services Surveillance and Monitoring Management (GVIMS), participated as experts at the federal level. We present the particularities recommended by experts for each domain addressed in the questionnaire (Table 2).

The experts proposed changes to the questionnaire's vocabulary, totaling a significant 91 suggestions. These suggestions reflect the importance of using precise and appropriate language to ensure the clarity and effectiveness of the questionnaire. By making changes to the vocabulary, the experts may have sought to make the questions more comprehensible to the target audience by eliminating

Table 2. Special features suggested by the experts according to each domain of the questionnaire.

Domain	Special features suggested for amendment		
D1) Health service profile	- No suggested changes.		
D2) Clinical and Epidemiological profile	- Ask questions about the main services provided at the healthcare facility.		
D3) Actions related to PCI measures	**Improved question formulation** - Exclude subjective questions. - Objectivity / Simplification. - Remove personal opinions. - Add to the alternatives if there are records. - Change the terms of the questions. - Change the order of the questions.	**Inclusion of specific information and questions** - Specify whether sanitizing products are related to the sterilization process. - Add information on disinfection, including types and products used. - Include details on chemical and physical sterilization methods. - Insert questions about tests used as sterilization indicators. - Insert utensils used in the cleaning and disinfection process. - Cover more details about the sterilization process, including equipment and packaging. - Include other sanitizing products in the cleaning and disinfection process. - Include other cleaning and sanitizing products. - Include details on the process of hand hygiene by workers.	**Organizing and refining questions** - Insert question about the availability of alcohol gel for teams. - Insert question about protocols related to infection prevention and control measures. - Insert question about the frequency of hand hygiene training. - Insert question about the frequency of hand hygiene training. - Insert question about written records of periodic procedures.
D4) Actions to manage AMA use	**Adjustments and clarifications** - Adjust RDC No. 222/2018, which provides for good practices in the management of healthcare waste - Clarify whether the questions are aimed at HAIs or infections found in establishments. - Change the term AMA dispensation to supply or delivery of medicines.	**Adding Information** - Include the State Medicines List. - Add other professions that prescribe antimicrobials in PHC. - Add questions about the regularity of AMA supplies.	**Other changes** - Exclusion of Subjective Questions. - Insert a third option that considers clarifying and guiding the patient and then prescribing because we think it may reflect the reality of some services, in the question about health professionals in the health service being pressured by patients to prescribe AMA.
D5) Health education on IPC measures	- Changing the wording of questions.		
D6) Health education with a focus on AMA use management	- No suggested changes.		

Source: Elaborated by the authors, 2024.

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excessively complex or ambiguous technical terms.

All the items in domains 1, 2, 5 and 6 had a CVI of over 0.75. However, in domains 3 and 4, the CVI was lower than the reference value (0.75), and the main changes made, based on the suggestions of the expert-evaluators, were terminological adjustments, spelling corrections and text detailing. The overall average CVI was 0.74 with standard deviation (SD ± 0.29) (Table 3).

Step 4 - Finalizing the Questionnaire: a comparison was made between the initial and final versions of the document. They observed a significant reduction in the number of questions, from a total of 135 in the first version to 102 in the final version. (Table 4)

The average time taken to complete a questionnaire is a crucial aspect to consider in its design and application. This metric not only affects the respondent's experience, but also influences the quality and integrity of the answers. Authors state that the questionnaire is a valuable tool for collecting data in research, due to its time savings, practicality, accuracy in obtaining answers, standardization, uniformity and greater openness on the part of the participants.[11] In this context, it is essential to understand the estimated time needed to complete the questionnaire, thus guaranteeing the active participation of the respondents and the accuracy of the data collected. In the current survey, the average time taken to complete the questionnaire was approximately 20 minutes.

Step 5 - Dissemination of the questionnaire: this took place by sending a link and a letter containing instructions on how to fill it out to the emails of the State Health Secretariats, State Health Surveillance Centers and Health Coordinating Offices. The questionnaire is now called: "National evaluation of strategies for infection control and management of antimicrobial use in Primary Health Care", which can be accessed in full through supplementary data.

Table 3. Experts' assessment of the questionnaire's related items in different regions of Primary Care in Brazil.

Domain	Assessment		CVI	CVI mean
	Suitable items with changes n (%)	Suitable items n (%)		
D1) Health service profile	0 (0.0)	15 (100)	1	
D2) Clinical and epidemiological profile	1 (6.7)	14 (93.3)	0.93	
D3) Actions related to infection prevention and control measures	11 (73.3)	4 (27.0)	0.27	0.74
D4) Actions to manage AMA use	9 (60)	6 (40)	0.40	
D5) Health education on infection prevention and control measures	1 (6.7)	14 (93.3)	0.93	
D6) Health education focusing on the management of AMA use	1 (6.7)	14 (93.3)	0.93	

Source: Elaborated by the authors, 2024.

Table 4. Comparison of the questionnaire between the pre and post expert validation Step.

Domain	Pre-Validation Step No. of Questions	Post-Validation Step No. of Questions	Overall opinion
D1) Health service profile	8	5	Exclusion of 3 questions
D2) Clinical and epidemiological profile	5	3	Exclusion of 2 questions
D3) Actions related to infection prevention and control measures	77	57	
D4) Actions to manage AMA use	28	20	Exclusion of 20 questions
D5) Health education on infection prevention and control measures	8	8	Exclusion of 8 questions
D6) Health education focusing on the management of AMA use	9	9	Maintained

Source: Elaborated by the authors, 2024.

DISCUSSION

According to experts, improving the wording of questions is essential for the quality and effectiveness of questionnaires. Removing subjective questions and ensuring objectivity eliminates personal opinions, making the questionnaire more reliable and impartial. In addition, simplifying questions makes them easier to understand and increases the accuracy of responses. Changing terms avoids ambiguities and improves interpretation, while rearranging the order of questions positively influences participants' perception and response, organizing the questionnaire in a logical and fluid manner.

This emphasis on adjustments is essential, as well-designed questionnaires are an effective research technique, consisting of a specific set of questions presented in writing to a group of individuals, with the aim of obtaining information about their opinions. This

approach offers several advantages, including the ability to reach a large number of participants, even in geographically distant areas, the flexibility to answer questions at their convenience, and minimizing the influence of the interviewer on the respondents' responses.

However, questionnaires can produce unexpected results due to the different interpretations that respondents may have of the items. Furthermore, excessive questionnaire length may result in a low response rate.[12] Given the vast territory of Brazil, the use of online questionnaires makes it possible to reach a wide variety of health professionals in different locations throughout the country. This ensures a more comprehensive and representative sample, while eliminating the need for printing, physical distribution and manual collection of questionnaires, resulting in a significant reduction in the costs associated with the survey.[13]

An online questionnaire offers the convenience of being accessed and answered at any time and place, providing greater flexibility and facilitating participation. For this reason, the development and validation of this online questionnaire was carefully planned and executed based on the latest evidence and demands on aspects related to infection prevention and control, with a view to meeting the need for actions aimed at the rational use of AMAs and the reduction of antimicrobial resistance in PHC. Health professionals working in Primary Health Care often deal with intense workloads. In this sense, it is essential that the tools available are resolutive, of high quality and capable of giving healthcare providers greater autonomy. This would make it easier for these professionals to access innovations.[14]

The items in a questionnaire should be designed to assess the desired results, and their psychometric properties should be evaluated for construct validity, internal consistency, reliability and other relevant aspects. The internal consistency of the instrument's items indicates how well they relate to each other and similarly represent the construct that the instrument aims to measure. On the other hand, reliability is measured by the squared correlation between the true score and the observed score, reflecting the stability and precision of the measures obtained.[15]

The antibiotic stewardship program assessment tool consists of the Core Elements of Hospital Antibiotic Stewardship Programs. It offers examples of the implementation of these elements, aimed at optimizing antibiotic prescribing, and can be applied according to the need or feasibility of each healthcare institution. Periodic use of the assessment tool provides data that is collected instantly and can be compiled and analyzed quickly and efficiently, making it possible to document the infrastructure and activities of the ongoing program and helping to identify areas for improvement. It is suggested to include specific details, such as points of contact or particular guidelines with dates, in the "comments" column, in order to provide useful references for the team responsible for antibiotic stewardship.[16]

Content validity is essential to ensure that the elements of the measuring instrument adequately represent the concept to be assessed. Therefore, when constructing a questionnaire, it is essential to address all relevant aspects of the phenomenon in question. The authors suggest guidelines for content validation, such as defining the scope of the questionnaire, involving experts in generating, evaluating and correcting the content, and using additional analyses to improve the instrument.[17]

It is commonly stated that ensuring the quality of health services on a global level requires a uniformly high approach, maintaining consistent standards. The first step to achieving this uniformity is to understand the contextual and cultural determinants specific to different countries and, from there, develop strategies to deal with these nuances. Decision-making in health is an intricate process, deeply influenced by context, which encompasses multiple participants and actions. This complexity is especially visible in decision-making related to antibiotic use, where different priorities and contextual factors influence clinical behavior.[18]

Content validity is the extent to which the content of an assessment instrument adequately reflects the construct being measured. As there is no specific statistical test to assess content validity, a qualitative approach is generally used, involving evaluation by a committee of experts. Subsequently, a quantitative approach can be carried out using the CVI.[19] In this study, validation with a group of experts was essential, generating valuable comments that guided the revision of the questionnaires, this Step served to improve the questions, ensuring greater understanding.

In relation to the CVI, the score found ranged from 0.23 to 1.00, while the overall average was 0.74 (SD ± 0.29), in another study[20] the score given by the experts ranged from 0.777 to 1.00, with a mean of 0.902 (SD ± 0.076).

Thus, this study resulted in the creation of an accurate tool for assessing the interaction between IPC, AMA and PHC, with the aim of continuously improving the quality of health services, suggesting that the instruments assessed in this study showed a more consistent and stronger correspondence with the construct being measured, compared to the overall average found.

The changes implemented were a result of the feedback received, especially in relation to questions that proved difficult to interpret. Improving the wording of questions is essential for the quality and effectiveness of questionnaires. Excluding subjective questions and ensuring objectivity eliminates personal opinions, making the questionnaire more reliable and impartial. Simplifying questions makes them easier to understand, increasing the accuracy of responses. Changing terms avoids ambiguity and improves interpretation, while rearranging the order of questions positively influences the participants' perception and response, organizing the questionnaire in a logical and fluid manner.

These improvements suggested by the evaluators demonstrate a deep understanding of the importance of precise and objective questions. Ensuring clarity in the language used and a logical sequence in the questions

promotes a better experience for respondents and increases the validity of the results obtained. In short, these strategies reflect a commitment to excellence in questionnaire design, aiming to maximize efficiency and validity in data collection.

The comparison between the questionnaire in the pre- and post-validation Steps of the experts shows that the reduction in questions can be attributed to factors such as the elimination of redundant or irrelevant questions for the research objectives. This analysis simplifies the questionnaire, making it easier to answer and reducing the time required to complete it. In addition, the experts may have identified questions that are not aligned with the research focus or that do not contribute significantly to the desired data collection.

Therefore, these questions were removed to ensure that the questionnaire remained concise and targeted. In summary, the reduction from 135 to 102 questions in the final version of the questionnaire indicates a process of refinement and optimization, aimed at improving the effectiveness and usability of the research instrument. Adapting the vocabulary was essential to ensure that the questionnaire was suitable for different demographic groups, taking into account linguistic and contextual variations. Overall, the revision of the questionnaire vocabulary reflects the experts' commitment to improving the quality of the research, which allowed for greater understanding by the participants.

Although the results of this study are promising, it is important to consider some limitations, such as: variable interpretation of the questions by participants may result in inconsistent responses, affecting the reliability of the data collected. The lack of direct comparison between the questionnaires used in these two key areas of public health may undermine the external validity and generalizability of the results. Without a reference point to compare the effectiveness and accuracy of the domain-specific questionnaires, it is difficult to determine whether the instruments are adequately capturing the nuances and complexities of infection prevention and control practices, as well as AMA management. Due to time constraints, it was not feasible to conduct a second round of evaluation with the experts, and it is suggested that future studies consider two-Step validation to ensure a more complete and robust evaluation. Conducting research on AMA management and infection prevention in primary health care in Brazil is crucial to promote the rational use of AMA, prevent adverse events, and improve the quality of health care provided to patients. These studies also contribute to optimizing health resources, strengthening epidemiological surveillance, and reducing the burden of infectious diseases, in addition to strengthening the Brazilian health system and contributing to global public health.[21]

A limitation of this study is the possible variability in the responses of PHC professionals due to regional and contextual differences in clinical practice and health policies. In addition, self-assessment may introduce biases, such as social desirability, where respondents may provide answers that they consider more acceptable than true.

This study contributes significantly to clinical practice by offering a validated tool that can be used to assess and improve IPC strategies and AMA management in PHC. The tool will allow more accurate monitoring of antimicrobial use, facilitating targeted interventions to reduce AMR. Furthermore, the application of the tool can promote greater awareness among health professionals about best practices in AMA use, encouraging a more rational and evidence-based approach.

The validation presented in this work showed that the developed questionnaires can be used as accurate and reliable tools to measure the implementation of AMA management programs at the national level, and can be replicated safely and reliably. The main objective was to build a robust and reliable instrument capable of providing relevant data to improve practices in this specific context, aiming at the continuous improvement of the quality of health services.

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Rochele Mosmann Menezes contributed to the literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Paula Trevisan** contributed to the project administration, literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics. **Mara Rubia Santos Gonçalves and Magda Machado de Miranda Costa** contributed to the writing of the abstract, methodology, interpretation of results, conclusions, review and statistics**. Mariana Portela de Assis and Adália Pinheiro Loureiro** contributed to the writing of the abstract, review and statistics. **Henrique Ziembowicz and Eliane Carlosso Krumennauer** contributed to the project administration, literature search, review and statistics. **Jane Renner Pollo Renner and Marcelo Carneiro** contributed to the project administration, literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics.

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