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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.

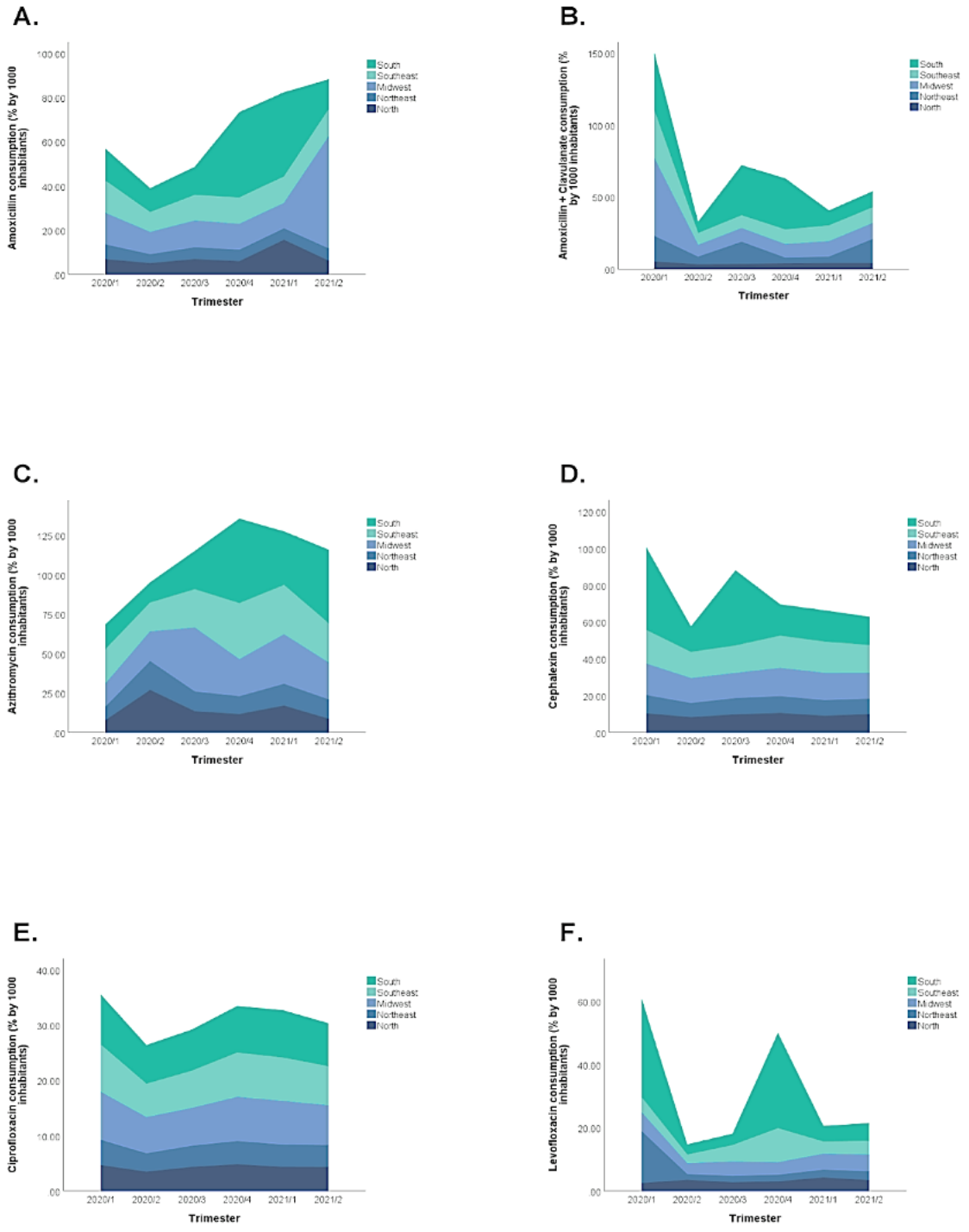

Figure 1. Trimestral consumption of ATMs from January 2020 until June 2021. Data expressed as cumulative frequencies (consumption % per 1,000 inhabitants).

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

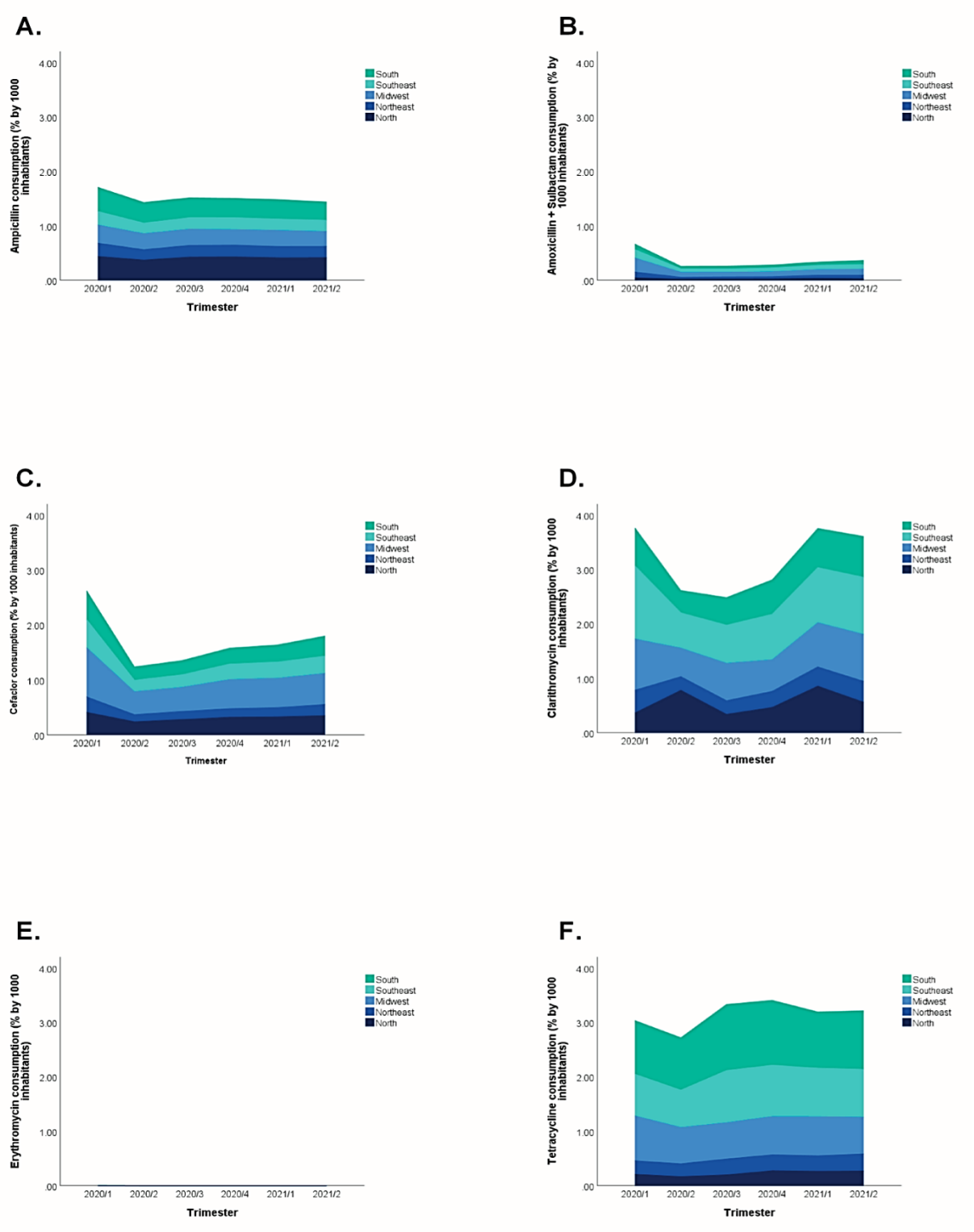

Figure 1S. Trimestral consumption for Ampicillin, Amoxicillin plus Sulbactam, Cefaclor, Clarithromycin, Erythromycin, and Tetracycline. Data expressed as cumulative frequencies (consumption % per 1,000 inhabitants)

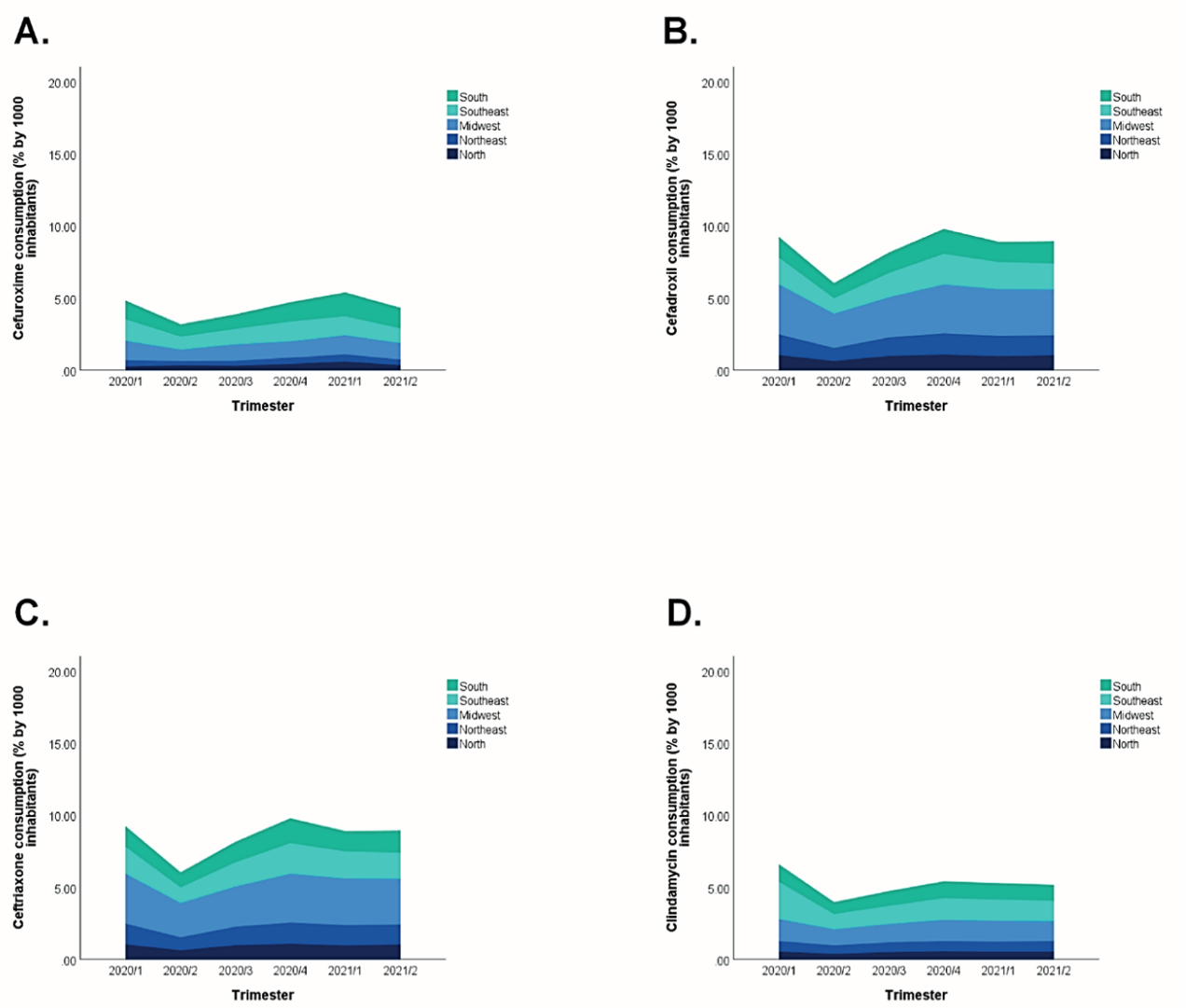

Figure 2S. Trimestral consumption for Cefuroxime, Cefadroxil, Ceftriaxone, and Clindamycin. Data expressed as cumulative frequencies (consumption % per 1,000 inhabitants)

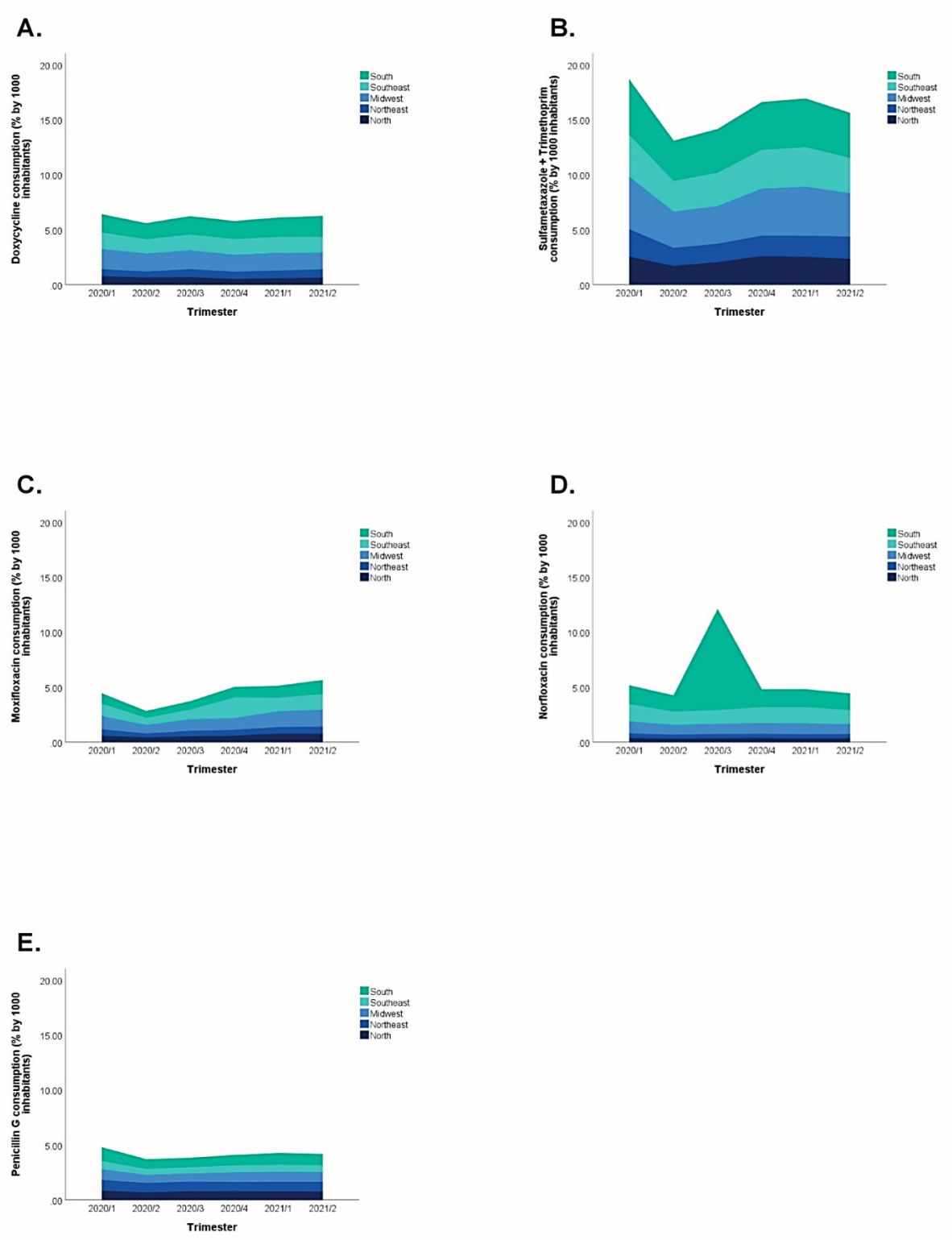

Figure 3S. Trimestral consumption for Doxycycline, Sulfamethoxazole plus Trimethoprim, Moxifloxacin, Norfloxacin, and Penicillin G. Data expressed as cumulative frequencies (consumption % per 1,000 inhabitants)

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