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Original Article

Geographical variation in antimicrobial use and multiresistant pathogens in Brazilian intensive care units: a nationwide study

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Abstract

Introduction: Geographical analyses of antibiotic use identify regions with the highest consumption and help design policies for strategic patient groups.

Methodology: We conducted a cross-sectional study based on official data available in July 2022 from Brazilian Health Surveillance Agency (Anvisa). Antibiotics are reported as a defined daily dose (DDD) per 1,000 patient-days, and central line-associated bloodstream infection (CLABSI) is defined according to Anvisa criteria. We also considered multi-drug resistant (MDR) as the critical pathogens the World Health Organization listed. We measured antimicrobial use and CLABSI trends per ICU bed using the compound annual growth rate (CAGR). Results: we evaluated the regional variation in CLABSI by multidrug-resistant pathogens and the antimicrobial use in 1,836 hospital intensive care units (ICUs). In 2020, the leader in use in intensive care units (ICUs) in the North was piperacillin/tazobactam (DDD = 929.7) in the Northeast. Midwest and South were meropenem (DDD = 809.4 and DDD = 688.1, respectively), and Southeast was ceftriaxone (DDD = 751.1). The North has reduced polymyxin use (91.1%), and ciprofloxacin increased (439%) in the South. There was an increase in CLABSI by carbapenem-resistant *Pseudomonas aeruginosa* in the North region (CAGR = 120.5%). Otherwise, CLABSI by vancomycin-resistant *Enterococcus faecium* (VRE) increased in all regions except the North (CAGR = -62.2%), while that carbapenem-resistant *Acinetobacter baumannii* increased in the Midwest (CAGR = 27.3%).

Conclusions: we found heterogeneity in antimicrobial use patterns and CLABSI etiology among Brazilian ICUs. Although Gram-negative bacilli were the primary responsible agent, we observed a notable increase trend of CLABSI by VRE.

Key words: Anti-infective agents; intensive care units; Brazil.

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Introduction

The World Health Organization (WHO) recommends establishing healthcare-associated infection (HAIs) surveillance programs at national and institutional levels [1]. Approximately 70% of all patients admitted to intensive care units (ICU) are treated with antibiotics [2,3], which makes them more prone to infections by multidrug-resistant microorganisms [4]. Several factors influence the rapid spread of multidrug-resistant pathogens in the ICU [4], including antibiotic exposure [5]. The Global Antimicrobial Resistance Surveillance System (GLASS) Report presented an alarming scenario for AMR rates in Brazil [6]. However, the data in this report encompasses the entire hospital, including community and nosocomial infections.

Antibiotic consumption surveillance contributes to the underuse, misuse, or overuse identification [7], and it is crucial to compare antibiotic use patterns in different contexts [8]. Many studies reported substantial geographic variation in antibiotics consumption in the community, especially for broad-spectrum antibiotics [9–13]. Thus, geographical comparison studies may identify regions with the highest consumption [14]. For example, Latin America consumes more reserve antibiotics in adult inpatients compared to other continents, followed by West and Central Asia [15].

European countries showed significant differences in antibiotic consumption in hospitals [16]. Brazilian area is equivalent to about 81% of the European continent [17], and we hypothesized that heterogeneity in antimicrobial use trends and the HAIs epidemiology between Brazilian regions might exist. In 2011, the Brazilian Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária* - Anvisa) implemented a national HAI surveillance system for

reporting these nosocomial infections and antibiotic use in Brazilian ICUs [18]. Therefore, our objective was to investigate the geographic variation in HAIs related to central line-associated bloodstream infection (CLABSI) by MDR pathogens and antimicrobial profile use in Brazilian ICUs, analyzing the notifications from this database.

Methodology

Study design

We performed a cross-sectional study with secondary data from the CLABSI and antimicrobial use in ICUs Brazilian database following the RECORD-PE guidelines. The RECORD-PE statement was derived from rigorous methodology and endorsed by the International Society for Pharmacoepidemiology [19].

Setting and Participants

Brazil is constituted of 27 states grouped into five regions: North, Northeast, Midwest, Southeast, and South (Supplementary Table 1).

We included all hospitals that adhered to the national epidemiological surveillance system for HAIs. Anvisa establishes that hospitals with more than ten ICU beds must report monthly the main HAIs and antimicrobials used [20, 21]. We also evaluated the state reporting compliance by considering how many services registered in the National Registry of Health Establishments (*Cadastro Nacional de Estabelecimento de Saúde* – CNES) were eligible for CLABSI notification and how many services reported CLABSI per year. Anvisa considers as adherent those hospitals that have reported at least ten months each year.

Variables and outcomes

Antibiotics are reported as a defined daily dose (DDD) per 1,000 patient-days. We classified antimicrobials by the Anatomical Therapeutic Chemical (ATC) at the 4th level granularity [22] and the AWaRe classification [23]. Three groups compose the AWaRe classification: Access antibiotics include antibiotics with a lower potential for resistance than the other groups. Then, these antimicrobials are first or second-choice empirical treatments for infectious syndromes. Watch antibiotics should be monitored closely, and Reserve antibiotics should be considered the last therapeutic option. Both groups should be the focus of antimicrobial stewardship programs [23,24]. We listed the antimicrobials monitored by Anvisa in Supplementary Table 2.

Anvisa defines CLABSI with the following criteria: (i) central catheter use for a period longer than two days (D1 being the day the device was installed) and that on the date of infection, the patient was using the device, or it was removed previous day; (ii) pathogen identified in one or more blood cultures; and (iii) the microorganism identified is not related to another infectious focus [25].

We evaluated CLABSI caused by pathogens considered critical by the WHO, namely: (i) carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), (ii) carbapenem-resistant *Acinetobacter baumannii* (CRAB); (iii) carbapenem-resistant *Enterobacteriaceae* (CRE); (iv) third- and fourth-generation cephalosporin-resistant *Enterobacteriaceae*; (v) Methicillin-resistant *Staphylococcus aureus* (MRSA); and (vi). Vancomycin-resistant *Enterococcus* spp (VRE) [26]. Additionally, we collected data about CLABSI caused by polymyxin-resistant Gram-negative bacillus and Vancomycin-resistant *Staphylococcus aureus.* Our study considered all pathogens investigated as multidrug-resistant (MDR).

Data sources

Between July and August 2022, we extracted data on CLABSI and antimicrobial use in intensive care units from Brazilian hospitals through the Anvisa website from 2012 to 2020 [27] and the ICU beds for this period from the CNES database [28]. However, due to data availability, we could only evaluate the antimicrobial use in the ICU from 2018 onwards and at a regional level from 2019 onwards.

Data analysis

We calculated the ratio between CLABSI prevalence and ICU beds for each state and region in the respective year. We also evaluated antimicrobial use and CLABSI trends per ICU bed using the compound annual growth rate (CAGR). CAGR reflects the average annual change as a proportion (%) of use in the initial year [16]. We calculated the relative frequencies using the total pathogen isolated regardless of the sensitivity profile as the denominator. All the analyses were conducted at the state, regional, and national levels. We use the R program and Epitools package for data analysis. Since we used public, no ethical appraisal was required.

Results

Data on CLABSI prevalence and antimicrobial use from 1,836 hospitals were included in the analysis. The main pathogen responsible for CLABSI during the

study period was 3rd/4th generation Cephalosporin-resistant *Klebsiella pneumoniae*, followed by carbapenem-resistant *K. pneumoniae*, carbapenem-resistant *Acinetobacter baumannii,* and MRSA. All carbapenem-resistant Gram-negative bacilli showed a negative trend, except *Klebsiella pneumoniae*. However, CLABSI by VRE increased by 19.3% (Table 1).

Table 2 presents the absolute and relative CLABSI frequencies among Brazilian regions. The prevalence of pathogens showed a heterogeneous pattern, with the North presenting the highest CRPA and the South presenting the lowest.

A heterogeneous CLABSI was found among the different Brazilian regions (Table 3). Only the North region presented an increase in CLABSI per CRPA (CAGR = 120.5%); CLABSI per VRE increased in all regions except in the North (CAGR = -62.2%); PSBI and MRSA showed a negative trend in all regions, and CLABSI per CRAB increased only in the Midwest (CAGR = 27.3%).

Table 1. Critical pathogens responsible for central line-associated bloodstream infection in a Brazilian ICU weighted per 1000 bed.

Pathogens CLABSI	Total	2018	2019	2020	CAGR (%)
3rd and/or 4th generation Cephalosporin resistant					
Enterobacter spp	44.5	12.0	19.9	12.6	2.6
Escherichia coli	44.1	13.3	19.3	11.5	-6.8
Klebsiella pneumoniae	316.3	60.6	138.6	117.1	39.0
Carbapenem-resistant					
Acinetobacter baumannii	270.3	95.9	92.7	81.7	-7.7
Enterobacter spp.	29.3	10.3	11.3	7.4	-15.0
Escherichia coli	10.8	3.7	3.8	3.3	-5.9
Klebsiella pneumoniae	312.6	100.9	106.3	105.4	2.2
Pseudomonas aeruginosa	108.2	40.4	38.8	29.0	-15.2
Oxacillin-resistant					
Staphylococcus aureus	240.5	85.6	94.6	60.3	-16.0
Polymyxin-resistant					
Acinetobacter baumannii	13.0	5.4	3.4	4.2	-12.2
Pseudomonas aeruginosa	5.2	1.9	1.3	2.0	1.9
Klebsiella pneumoniae	39.5	8.0	15.5	16.0	41.5
Vancomycin-resistant					
Enterococcus faecium	24.0	7.3	6.3	10.4	19.3
Staphylococcus aureus	16.2	6.7	5.8	3.7	-25.1

CAGR: compound annual growth rate.

Table 2. Clinically relevant pathogens distribution responsible for central line-associated bloodstream infection among Brazilian regions in 2020.

	North, N (%)	Northeast, N (%)	Midwest, N (%)	Southeast, N (%)	South, N (%)	*p* value*
3rd and/or 4th generation Cephalosporin resistant						
Enterobacter spp.	21 (13.7)	67 (58.8)	14 (40.0)	177 (41.3)	37 (31.6)	**< 0.001**
Escherichia coli	18 (66.7)	73 (67.6)	20 (46.5)	137 (44.7)	42 (37.5)	**< 0.001**
Klebsiella pneumoniae	84 (77.1)	529 (76.2)	287 (79.3)	1757 (72.1)	283 (49.9)	**< 0.001**
Carbapenem-resistant						
Acinetobacter baumannii	44 (89.8)	371 (84.7)	162 (81.4)	1215 (60.4)	260 (89.0)	**< 0.001**
Enterobacter spp.	26 (17.0)	38 (33.3)	9 (25.7)	96 (22.4)	16 (13.7)	**0.003**
Escherichia coli	4 (14.8)	29 (26.9)	8 (18.6)	38 (12.4)	3 (2.7)	**< 0.001**
Klebsiella pneumoniae	65 (59.6)	507 (73.1)	177 (48.9)	1604 (65.8)	283 (49.9)	**< 0.001**
Pseudomonas aeruginosa	35 (59.3)	207 (50.0)	77 (56.6)	339 (36.6)	71 (19.9)	**< 0.001**
Oxacillin-resistant						
Staphylococcus aureus	51 (56.7)	260 (65.0)	46 (35.7)	946 (61.2)	212 (52.2)	**< 0.001**
Polymyxin-resistant						
Acinetobacter baumannii	1 (2.0)	27 (6.2)	13 (6.5)	54 (2.7)	10 (3.4)	0.070
Klebsiella pneumoniae	13 (11.9)	80 (22.1)	7 (1.9)	268 (11.0)	34 (6.0)	**< 0.001**
Pseudomonas aeruginosa	5 (8.5)	17 (2.4)	4 (2.9)	21 (2.3)	2 (0.6)	**0.006**
Vancomycin-resistant						
Enterococcus faecium	6 (42.9)	46 (63.9)	22 (36.1)	149 (57.3)	38 (60.3)	**0.010**
Staphylococcus aureus	4 (4.4)	23 (5.8)	10 (7.8)	44 (2.8)	13 (3.2)	**0.007**

* *p* values were obtained using the chi-square test or Fisher's exact test.

Table 4 shows the prevalence of CLABSI produced by the pathogens under analysis from 2013 to 2020. All pathogens showed growth except oxacillin- and vancomycin-resistant *Staphylococcus aureus.*

In 2018, the most antimicrobial used was meropenem (total DDD = 4,968.6), followed by polymyxin B (DDD = 3,618.1) and ceftriaxone (DDD = 2,944.3). In 2019, the most consumed antibiotic was vancomycin (DDD = 2,961.7), followed by teicoplanin (DDD = 1,193.6) and meropenem (DDD = 4,973.2). In 2020, meropenem was once again the most antimicrobial used in Brazilian ICUs (DDD = 5,860.2), followed by ceftriaxone (DDD = 4,662.8) and piperacillin/tazobactam (DDD = 3,578.8). In summary,

Table 3. Central Line-associated Bloodstream Infection density caused by clinically relevant pathogens in Brazilian regions per thousand ICU beds between 2019 – 2020.

	North			Northeast			Midwest			Southeast			South		
	2019	**2020**	**CAGR**	**2019**	**2020**	**CAGR**	**2019**	**2020**	**CAGR**	**2019**	**2020**	**CAGR**	**2019**	**2020**	**CAGR**
3rd and/or 4th generation Cephalosporin resistant															
Enterobacter spp.	9.0	6.5	**-28.0%**	68.0	5.9	**-91.4%**	17.0	3.1	**-81.7%**	175.0	53.5	**-69.4%**	29.0	14.2	**-51.0%**
Escherichia coli	12.2	5.6	**-54.6%**	9.9	6.4	**-35.8%**	7.7	4.4	**-42.1%**	74.1	41.4	**-44.2%**	26.2	16.1	**-38.4%**
Klebsiella pneumoniae	50.8	25.9	**-49.0%**	59.8	46.2	**-22.7%**	70.3	63.6	**-9.5%**	599.4	530.8	**-11.4%**	163.3	108.7	**-33.4%**
Carbapenem-resistant															
Acinetobacter baumannii	26.9	13.6	**-49.6%**	43.2	32.4	**-24.9%**	28.2	35.9	**27.3%**	431.8	367.1	**-15.0%**	104.2	99.9	**-4.1%**
Enterobacter spp.	2.4	8.0	**227.6%**	6.2	3.3	**-46.9%**	3.8	2.0	**-47.9%**	51.0	29.0	**-43.2%**	8.1	6.1	**-23.8%**
Escherichia coli	2.4	1.2	**-49.6%**	1.8	2.5	**37.3%**	1.0	1.8	**69.8%**	15.0	11.5	**-23.7%**	5.4	1.2	**-78.6%**
Klebsiella pneumoniae	25.1	20.0	**-20.1%**	35.8	44.3	**23.8%**	68.9	39.2	**-43.1%**	471.0	484.6	**2.9%**	144.5	112.9	**-21.8%**
Pseudomonas aeruginosa	4.9	10.8	**120.5%**	27.1	18.1	**-33.3%**	20.9	17.1	**-18.3%**	136.9	102.4	**-25.2%**	43.0	27.3	**-36.6%**
Oxacillin-resistant															
Staphylococcus aureus	28.2	15.7	**-44.1%**	38.5	22.7	**-41.0%**	13.6	10.2	**-24.9%**	445.2	285.8	**-35.8%**	139.1	81.4	**-41.5%**
Polymyxin-resistant															
Acinetobacter baumannii	0.6	0.3	**-49.6%**	1.1	2.4	**107.7%**	1.7	2.9	**65.5%**	17.2	16.3	**-5.1%**	3.4	3.8	**14.3%**
Klebsiella pneumoniae	2.4	4.0	**63.8%**	3.7	7.0	**89.3%**	7.7	1.6	**-79.7%**	78.9	81.0	**2.6%**	21.5	13.1	**-39.3%**
Pseudomonas aeruginosa	0.6	1.5	**152.0%**	1.0	1.5	**49.4%**	0.0	0.9	NA	5.4	6.3	**18.1%**	1.3	0.8	**-42.8%**
Vancomycin-resistant															
Enterococcus faecium	4.9	1.9	**-62.2%**	1.0	4.0	**304.4%**	1.7	4.9	**180.1%**	32.2	45.0	**39.7%**	9.4	14.6	**55.2%**
Staphylococcus aureus	3.7	1.2	**-66.4%**	2.7	2.0	**-25.5%**	2.1	2.2	**6.1%**	25.2	13.3	**-47.3%**	5.4	5.0	**-7.1%**

CAGR: compound annual growth rate.

Table 4. Distribution of clinically relevant pathogens responsible for primary bloodstream infections during 2013 - 2020 in Brazilian ICUs.

	2013	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	***p* value**	**CAGR**
3rd and/or 4th generation Cephalosporin resistant										
Enterobacter spp.	262 (27.2)	370 (31.1)	302 (27.7)	189 (28.1)	-[4]	172 (24.3)	297 (43.6)	316 (38.2)	**< 0.001**	2.4%
Escherichia coli	272 (27.4)	496 (29.1)	452 (27.7)	235 (33.3)	-[4]	191 (33.3)	288 (43.2)	290 (48.7)	**< 0.001**	0.8%
Klebsiella pneumoniae	795 (31.7)	1042 (31.9)	1125 (29.6)	858 (27.8)	-[4]	871 (26.6)	2065 (66.1)	2940 (70.5)	**< 0.001**	17.8%
Carbapenem-resistant										
Acinetobacter baumannii	1742 (80.7)	2346 (79.3)	2117 (77.4)	1810 (85.0)	-[4]	1379 (79.0)	1381 (79.6)	2052 (84.8)	**< 0.001**	2.1%
Enterobacter spp.	170 (17.7)	250 (21.0)	235 (24.9)	122 (18.2)	-[4]	148 (20.9)	169 (24.8)	185 (22.3)	**< 0.001**	1.1%
Escherichia coli	69 (6.9)	203 (11.9)	158 (9.7)	70 (9.9)	-[4]	53 (9.3)	57 (8.6)	82 (13.8)	**< 0.001**	2.2%
Klebsiella pneumoniae	828 (33.0)	1266 (38.8)	1125 (29.6)	1444 (46.8)	-[4]	1450 (44.3)	1583 (50.7)	2647 (63.5)	**< 0.001**	15.6%
Pseudomonas aeruginosa	692 (7.4)	1032 (41.6)	877 (39.1)	621 (42.9)	-[4]	581 (41.4)	578 (40.3)	729 (38.5)	**0.012**	0.7%
Oxacillin-resistant										
Staphylococcus aureus	1606 (60.9)	2916 (74.6)	1699 (57.4)	1508 (63.1)	-[4]	1230 (52.3)	1410 (57.6)	1515 (58.9)	**< 0.001**	-0.7%
Polymyxin-resistant										
Acinetobacter baumannii	-[3]	-[3]	-[3]	-[3]	-[4]	78 (3.3)	50 (2.6)	105 (4.3)	**0.008**	10.4%
Klebsiella pneumoniae	-[3]	-[3]	-[3]	-[3]	-[4]	115 (6.6)	231 (7.4)	402 (9.6)	**< 0.001**	51.8%
Pseudomonas aeruginosa	-[3]	-[3]	-[3]	-[3]	-[4]	27 (1.9)	20 (1.4)	49 (2.6)	**0.048**	22.0%
Vancomycin-resistant										
Enterococcus faecium	-[1]	-[1]	-[1]	-[1]	-[4]	105 (53.3)	94 (50.0)	261 (62.1)	**0.009**	35.5%
Staphylococcus aureus	-[2]	-[2]	-[2]	-[2]	-[4]	96 (4.1)	86 (12.6)	94 (3.7)	**< 0.001**	-0.7%

**p* values were obtained using the chi-square test or Fisher's exact test; [1] Anvisa data grouped in *Enterococcus* spp., it is not possible to measure rates for *Enterococcus faecium;* [2] Anvisa did not monitor vancomycin-resistant *Staphylococcus aureus* in the period; [3]Anvisa did not monitor polymyxin resistance during this period. ;[4]Anvisa only released the relative frequencies. CAGR: compound annual growth rate.

from 2018 to 2020, meropenem was the most used agent in Brazilian ICUs, followed by ceftriaxone, piperacillin/tazobactam, polymyxin, and vancomycin. The antimicrobials that increased use were intravenous linezolid, ceftriaxone, piperacillin and tazobactam, teicoplanin, meropenem, and vancomycin. Intravenous linezolid was the antimicrobial with the highest tendency to increase (36.10%). Complete data on antimicrobial use at the national level are available in Supplementary Table 3.

Table 5 presents the antimicrobials used in ICUs across Brazilian regions. The leader in use in ICUs in the North was piperacillin/tazobactam and vancomycin in the Northeast. Midwest and South were meropenem, and Southeast was ceftriaxone. The North has significantly reduced polymyxin (-91.1%). However, we observed a considerable increase in ceftazidime and teicoplanin use (264.7% and 112.0%, respectively). The fluoroquinolones use declined in general. Otherwise, parenteral levofloxacin use in ICUs increased by 91.9% in the Midwest, and oral ciprofloxacin increased by 439% in the South.

We also observed a heterogeneous usage pattern across Brazilian regions regarding the AWaRe classification. In the North, the Reserve antimicrobials use represented 11.2% (DDD = 913), In the Northeast 9.7% (DDD = 761), Midwest 22.2% (DDD = 778), Southeast 13.4% (DDD = 393) and in the South 10.6% (DDD = 211).

In 2020, of the 1856 hospitals that should report CLABSI to Anvisa's HAIs surveillance system, 1,720 did (93% adherence). Complete data on adherence from 2013 to 2020 by the Brazilian state is available in Supplementary Table 4.

Discussion

To our knowledge, our study is the first to investigate antimicrobial use and the prevalence of CLABSI by MDR in ICUs throughout Brazil. We used official data collected by Anvisa. The results demonstrated significant geographic variation in both parameters analyzed in Brazilian ICUs. Unlike Brazil, Switzerland showed a consistent decline in MRSA across the country's ICUs [29], and Swedish researchers noted a consistent increase in 3rd and 4th-generation cephalosporin-resistant *K. pneumoniae* and *E. Coli* [30].

Table 5. Anti-infective agents use (DDD) notified to Anvisa between 2019 and 2020.

4th Level of ATC	Anti-infective agentes	North			Northeast			Midwest			Southeast			South		
		DDD 2019	DDD 2020	CAGR	DDD 2019	DDD 2020	CAGR	DDD 2019	DDD 2020	CAGR	DDD 2019	DDD 2020	CAGR	DDD 2019	DDD 2020	CAGR
Reserve																
J01XB Polymyxins	Colistin	16.9	1.5	**-91.1%**	0	0.0	-	0	0.0	-	0	0.0	-	0	0.0	-
	Polymyxin B	744.9	658.6	**-11.6%**	787.8	678.2	**-13.9%**	490.7	645.0	**31.4%**	259.4	358.9	**38.4%**	197.4	358.9	**81.8%**
J01XX Other antibacterials	Daptomycin	0	0.0	-	0	0.0	-	43.1	35.7	**-17.2%**	2.8	0.0	**-100.0%**	0	0.0	-
	Linezolida (P)	151.7	197.1	**29.9%**	83.5	81.6	**-2.3%**	54.8	53.5	**-2.4%**	24.8	23.8	**-4.0%**	8.3	23.8	**186.7%**
J01AA Tetracyclines	Tigecycline	120.4	55.8	**-53.7%**	30	0.9	**-97.0%**	33.1	44.2	**33.5%**	7.4	10.2	**37.8%**	0	10.2	-
Watch																
J01DE Fourth generation cephalosporins	Cefepime	799.3	409.6	**-48.8%**	281.6	133.4	**-52.6%**	67.9	48.3	**-28.9%**	131.8	100.9	**-23.4%**	164.4	100.7	**-38.7%**
J01DD Third generation cephalosporins	Cefotaxime	12.2	1.8	**-85.2%**	0	0.0	-	0	0.0	-	0	0.0	-	0	0.0	-
	Ceftazidime	45	164.1	**264.7%**	39.5	16.2	**-59.0%**	0.5	0.1	**-80.0%**	5.5	4.8	**-12.7%**	21.7	9.6	**-55.8%**
	Ceftriaxone	1047.9	1.134.0	**8.2%**	1099.8	1.656.3	**50.6%**	655.8	693.8	**5.8%**	498	751.1	**50.8%**	327.9	427.6	**30.4%**
J01MA Fluoroquinolones	Ciprofloxacin (O)	11	4.4	**-60.0%**	9.5	2.6	**-72.6%**	2.3	0.7	**-69.6%**	2.6	2.9	**11.5%**	2.3	12.4	**439.1%**
	Ciprofloxacin (P)	596.2	323.0	**-45.8%**	201.8	159.0	**-21.2%**	71	45.2	**-36.3%**	63.3	48.7	**-23.1%**	36.2	29.1	**-19.6%**
	Levofloxacin (O)	9.2	1.30	**-85.9%**	3.3	3.8	**15.2%**	0.4	0.3	**-25.0%**	1.6	0.8	**-50.0%**	2.1	0.4	**-81.0%**
	Levofloxacin (P)	309.2	219.0	**-29.2%**	217.8	174.6	**-19.8%**	38.5	73.9	**91.9%**	39.3	41.2	**4.8%**	33.1	27.0	**-18.4%**
	Moxifloxacin(O)	0	0.0	-	0	0.0	-	0	0.0	-	0	0.0	-	0	0.0	-
	Moxifloxacin (P)	0	0.0	-	1.2	0.8	**-33.3%**	1.6	1.6	0.0%	0	0.0	-	0	0.0	-
J01DH Carbapenems	Ertapenem	27.5	29.6	**7.6%**	0.3	0.0	**-100.0%**	10.9	12.5	**14.7%**	0.1	0.0	**-100.0%**	0	0.0	-
	Imipenem	369	413.8	**12.1%**	56.7	13.5	**-76.2%**	13.5	10.8	**-20.0%**	0.1	0.0	**-100.0%**	1.4	0.0	**-100.0%**
	Meropenem	1347.2	1.656.5	**23.0%**	1805	2.193.9	**21.5%**	767.6	809.4	**5.4%**	625	688.1	**10.1%**	428.4	688.1	**60.6%**
J01CR Combinations of penicillins.	Piperacillin/ Tazobactam	682.2	929.7	**36.3%**	1090.2	1.169.8	**7.3%**	389.2	591.4	**52.0%**	425.4	499.4	**17.4%**	351	499.4	**42.3%**
J01XA Glycopeptide	Teicoplanin	369.9	784.1	**112.0%**	595	630.5	**6.0%**	182.8	163.6	-10.5%	34.1	66.3	**94.4%**	11.8	66.3	**461.9%**
	Vancomycin	1276	1.134.5	**-11.1%**	856	887.7	**3.7%**	266.9	277.4	**3.9%**	353.4	388.4	**9.9%**	209.4	388.4	**85.5%**
Access																
J01CR Combinations of penicillins.	Ampicillin and sulbactam	59.1	102.7	**73.8%**	42.0	23.0	**-45.2%**	19.1	20.8	**8.9%**	0.9	2.2	**144.4%**	45.2	52.0	**15.0%**
Antifungals																
J02AA Antibiotics	Amphotericin B	162.2	51.2	**-68.4%**	6.1	2.4	**-60.7%**	2.5	3.4	**36.0%**	5.1	1.6	**-68.6%**	7.2	2.3	**-68.1%**
	Amphotericin B liposomal	0	0.0	-	0.5	0.0	**-100.0%**	2.6	0.7	**-73.1%**	0	0.0	-	0	0.0	-
J02AX Other antimycotics	Anidulafungin	0	0.0	-	10.2	14.2	**39.2%**	33.8	2.4	**-92.9%**	0	0.0	-	0	0.0	-
	Micafungin	48.2	32.8	**-32.0%**	7.4	84.5	**1041.9%**	11.7	17.0	45.3%	0	0.0	-	0	0.0	-
	Caspofungin	27.2	3.4	**-87.5%**	0	0.0	-	0	0.0	-	0	0.0	-	0	0.0	-
J02AC - Triazole and tetrazole derivatives	Fluconazole (P)	778.4	874.5	**12.3%**	777.5	657.7	**-15.4%**	198.8	231.0	**16.2%**	206	139.1	**-32.5%**	140.7	127.7	**-9.2%**
	Voriconazole	6.2	0.0	**-100.0%**	0	0.0	NA	0.2	0.0	**-100.0%**	0	0.0	-	0	0.0	-

O: oral route; P: parenteral route; Anvisa: *Agência Nacional de Vigilância Sanitária*; CAGR: compound annual growth rate, **p* values were obtained using the chi-square test or Fisher's exact test.

Geographical variations in antimicrobial consumption are well described in the literature [16,31–33]. However, regional epidemiological differences do not always explain these variability [34]. We observed heterogeneous trends in the growth of antimicrobials use across Brazilian regions that did not follow the CLABSI pathogen trends. For example, CLABSI by MRSA declined in all regions, but the use of glycopeptides increased in all locations, with a considerable increase in the South region. However, the Midwest, which had the lowest MRSA reduction rate, was the only region that reduced teicoplanin use and also had the lowest vancomycin growth rate. According to the European Center for Disease Prevention and Control (ECDC), glycopeptide consumption has increased in France, Croatia, Estonia, and Hungary [35]. All these countries showed an increase in MRSA isolates, which may explain the higher glycopeptide consumption [36]. ECDC data covered the entire hospital sector, while our study was ICU-specific.

Sjövall *et al.* conducted a study in Swedish ICUs where they described antimicrobial consumption. The authors report that the most consumed antibiotics were isoxazolyl penicillins (ATC group J01CF); penicillins with beta-lactamase inhibitors, mainly piperacillin/tazobactam (J01CR); 3rd or/and 4th generation cephalosporins (J01DD or DE); and carbapenems (J01DH) [30]. Previous studies reported discrepant prevalence points in Brazilian ICUs t [37,38]. Porto and colleagues described ceftriaxone, meropenem, and vancomycin as the most used antimicrobials [38]. On the other hand, Nunes Castro et al. identified piperacillin/tazobactam, amoxicillin/clavulanate, azithromycin, and teicoplanin [37].

Our result showed that the most used antibiotics in Brazilian ICUs were meropenem (J01DH), followed by ceftriaxone (J01DD), piperacillin/tazobactam (J01CR), and polymyxin (J01XB). Additionally, meropenem utilization increased between 2018 and 2020 in Brazilian ICUs, which the high prevalence of cephalosporin-resistant pathogens may explain. Furthermore, we noticed that the incidence of ICU-acquired infection, as well as the prevalence of MDR pathogen infections, are higher in LMICs than in developed countries [39] and, consequently, the Reserve antimicrobials consumption is also higher in LMICs [15,40]. As expected, Brazilian ICU patients are more exposed to Reserve antibiotics than others: We found 40% of Reserve antibiotics in Brazilian ICUs, compared to 16% in Sweden in 2018.

Gram-negative MDR bacilli are the main pathogens responsible for HAIs in low and middle-income countries (LMIC) like Brazil [39,41]. However, we identified that CLABSI by VRE increased in all regions except in the North. The South region presented the most significant increase in CLABSI by VRE but the lowest growth in overall CLABSI by MDR. Although VRE is not primarily responsible for CLABSI in Brazilian ICUs, excessive glycopeptide utilization could be among the causes of the growth of CLABSI by VRE.

The South region presented the most favorable scenario for overall CLABSI by MDR, probably because one of its three states (i.e., Paraná) reported having fully implemented a GLASS antimicrobial surveillance program [42]. In contrast, the South was the region with the most significant increase in linezolid and polymyxin B use, which is not following CLABSI by MDR trends, especially when we identified a considerable increase in CLABSI by polymyxin-resistant *Klebsiella pneumoni*ae. Although the susceptibility *in vitro* assays for polymyxins has several limitations and does not always provide reliable results [43], this potentially inappropriate antimicrobial selection discordance should be considered.

Brazil is still lagging in epidemiological HAIs surveillance compared to countries such as the United States [44] or Sweden [33]. Our study used data from the national HAI surveillance system where not all regions had 100% reporting adherence. In addition, Brazil monitors HAIs through passive surveillance, which usually has low sensitivity and can lead to misclassification and underreporting [45]. Anvisa has recently implemented policies to reduce the MDR prevalence in hospitals [46].

Conclusions

This paper summarizes the antimicrobials use and the CLABSI by MDR prevalence with the respective growth trends from 2018 to 2020 in Brazilian ICUs. In summary, we identified and visualized an important heterogeneity in the antimicrobial utilization in Brazilian ICUs and a discrepant CLABSI microbiological profile across Brazilian regions. Some inappropriate antibiotic use trends include regions where MRSA prevalence decreased while glycopeptide use increased. Despite the increasing overall VRE prevalence, Gram-negative bacilli remain the main responsible for CLABSI in Brazilian ICUs. Aiming to reduce the prevalence of HAI by MDR in all regions, Anvisa has recently implemented new policies.

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Annex – Supplementary Items

Supplementary Table 1. Geographic composition of Brazilian regions.

Region	State name	State name abbreviation
Northeast	Bahia	BA
	Ceará	CE
	Maranhão	MA
	Paraíba	PB
	Pernambuco	PE
	Piauí	PI
	Rio Grande do Norte	RN
	Sergipe	SE
	Alagoas	AL
North	Acre	AC
	Amapá	AP
	Amazonas	AM
	Pará	PA
	Rondônia	RO
	Roraima	RR
	Tocantins	TO
Midwest	Goiás	GO
	Distrito Federal	DF
	Mato Grosso	MT
	Mato Grosso do Sul	MS
Southeast	Espirito Santo	ES
	Minas Gerais	MG
	Rio de Janeiro	RJ
	São Paulo	SP
South	Paraná	PR
	Rio Grande do Sul	RS
	Santa Catarina	SC

Supplementary Table 2. Antimicrobials with compulsory notification to the National Health Surveillance Agency (Brazil). ATC and AWARE classification of antimicrobials monitored by Anvisa.

AWaRe Classification	4th Level of ATC	ATC Code	Antimicrobials
Access	J01CR Combinations of penicillins, incl. beta-lactamase inhibitors	J01CR01	Ampicillin and Sulbactam
Watch		J01CR05	Piperacillin/tazobactam
Reserve	J01XX Other antibacterials	J01XX09	Daptomycin
		J01XX08	Linezolid
	J01XB Polymyxins	J01XB02	Polymyxin B
		J01XB01	Colistin
	J01AA Tetracyclines	J01AA12	Tigecycline
Watch	J01DE Fourth generation cephalosporins	J01DE01	Cefepime
	J01DD Third generation cephalosporins	J01DD01	Cefotaxime
		J01DD02	Ceftazidime
		J01DD04	Ceftriaxone
	J01DH Carbapenems	J01DH03	Ertapenem
		J01DH51	Imipenem
		J01DH02	Meropenem
	J01MA Fluoroquinolones	J01MA12	Levofloxacin
		J01MA02	Ciprofloxacin
		J01MA14	Moxifloxacin
	J01XA Glycopeptide antibacterials	J01XA02	Teicoplanin
		J01XA01	Vancomycin
not classified	J02AA Antibiotics	J02AA01	Amphotericin B
	J02AX Other antimycotics for systemic use	J02AX06	Anidulafungin
		J02AX04	Caspofungin
		J02AX05	Micafungin
	J02AC - Triazole and tetrazole derivatives	J02AC01	Fluconazole
		J02AC03	Voriconazole

Supplementary Table 3. Anti-infective agents use (DDD) notified to Anvisa between 2018 and 2020.

4th Level of ATC	Anti-infective agents	Total	2018	2019	2020	CAGR (%)
Reserve						
J01XB Polymyxins	Colistin	18.4	0	16.9	1.5	-
	Polymyxin B	8642.9	3618.1	2480.2	2544.6	-16.1
J01XX Other antibacterials	Daptomycin	138.9	57.3	45.9	35.7	-21.1
	Linezolid (oral)	0	0	0	0	-
	Linezolid (parenteral)	883.1	196.4	323.1	363.6	36.1
J01AA Tetracyclines	Tigecycline	479.5	177.5	190.9	111.1	-20.9
Watch						
J01DE Fourth generation cephalosporins	Cefepime	3496.5	1258.6	1445	792.9	-20.6
J01DD Third generation cephalosporins	Cefotaxime	14	0	12.2	1.8	-
	Ceftazidime	561.1	254.1	112.2	194.8	-12.4
	Ceftriaxone	11236.5	2944.3	3629.4	4662.8	25.8
J01MA Fluoroquinolones	Ciprofloxacin (oral)	76.3	25.6	27.7	23	-5.2
	Ciprofloxacin (parenteral)	2439.4	865.9	968.5	605	-16.4
	Levofloxacin (oral)	113.6	90.45	16.6	6.6	-73
	Levofloxacin (parenteral)	2182.8	1009.2	637.9	535.7	-27.1
	Moxifloxacin (oral)	0	0	0	0	-
	Moxifloxacin (parenteral)		23.3	2.8	2.4	-67.9
J01DH Carbapenems	Ertapenem	28.5	43	38.8	42.1	-1.1
	Imipenem	1281.4	402.6	440.7	438.1	4.3
	Meropenem	15802	4968.6	4973.2	5860.2	8.6
J01CR Combinations of penicillins	Piperacillin/tazobactam	9057.5	2540.7	2938	3578.8	18.7
J01XA Glycopeptide antibacterials	Teicoplanin	4144.5	1306.4	1.193.60	1644.5	12.2
	Vancomycin	8632.5	2711.9	2.961.70	2958.9	4.5
Access						
J01CR Combinations of penicillins	Ampicillin/sulbactam	723.7	356.7	166.3	200.7	-25
Antifungals						
J02AA Antibiotics	Amphotericin B	284	40	183.1	60.9	23.4
	Amphotericin B liposomal	7.6	3.8	3.1	0.7	-57.1
J02AX Other antimycotics for systemic use	Anidulafungin	101.6	41	44	16.6	-36.4
	Micafungin	201.6	0	67.3	134.3	
	Caspofungin	77.8	47.2	27.2	3.4	-73.2
J02AC - Triazole and tetrazole derivatives	Fluconazole (parenteral)	6623.4	2492	2.101.4	2030	-9.7
	Voriconazole	6.7	0.3	6.4	0	-100

Supplementary Table 4. Adherence to Anvisa's HAI surveillance system among Brazilian states between 2016 and 2020.

State	Abbreviation	2020	2019	2018	2017	2016
Brazil	BR	92.67%	95.01%	77.00%	78.00%	53.00%
Acre	AC	100.00%	100.00%	75.00%	75.00%	29.00%
Alagoas	AL	80.00%	68.18%	33.00%	25.00%	14.00%
Amazonas	AM	100.00%	95.45%	86.00%	86.00%	78.00%
Amapá	AP	66.67%	66.67%	33.00%	50.00%	40.00%
Bahia	BA	81.82%	83.95%	44.00%	69.00%	49.00%
Ceará	CE	88.68%	86.67%	73.00%	84.00%	56.00%
Distrito Federal	DF	100.00%	100.00%	94.00%	91.00%	81.00%
Espírito Santo	ES	95.35%	100.00%	92.00%	92.00%	62.00%
Goiás	GO	95.24%	89.04%	75.00%	78.00%	53.00%
Maranhão	MA	89.19%	83.33%	53.00%	52.00%	44.00%
Minas Gerais	MG	93.48%	92.90%	81.25%	69.00%	48.00%
Mato Grosso do Sul	MS	95.83%	91.30%	50.00%	64.00%	33.00%
Mato Grosso	MT	94.87%	93.94%	70.00%	65.00%	32.00%
Pará	PA	88.68%	110.26%	63.83%	49.00%	23.00%
Paraíba	PB	87.50%	91.18%	27.27%	32.00%	5.00%
Pernambuco	PE	95.83%	92.19%	83.76%	78.00%	69.00%
Piauí	PI	90.00%	100.00%	79.71%	68.00%	23.00%
Paraná	PR	91.74%	101.96%	52.63%	75.00%	33.00%
Rio de Janeiro	RJ	92.66%	94.64%	78.67%	77.00%	44.00%
Rio Grande do Norte	RN	92.59%	100.00%	60.00%	67.00%	31.00%
Rondônia	RO	94.12%	88.24%	50.00%	60.00%	38.00%
Roraima	RR	100.00%	100.00%	33.33%	33.00%	50.00%
Rio Grande do Sul	RS	90.10%	87.50%	75.82%	80.00%	47.00%
Santa Catarina	SC	100.00%	105.66%	96.15%	92.00%	84.00%
Sergipe	SE	100.00%	100.00%	92.86%	93.00%	77.00%
São Paulo	SP	94.07%	97.91%	93.56%	96.00%	74.00%
Tocantins	TO	100.00%	333.33%	44.44%	100.00%	18.00%