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SUPPLEMENT ARTICLE

Trends in Inpatient Antibiotic Use Among Adults Hospitalized During the Coronavirus Disease 2019 Pandemic in Argentina, Brazil, and Chile, 2018–2021

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Background. High rates of antibiotic use (AU) among inpatients with coronavirus disease 2019 (COVID-19) despite low rates of bacterial coinfection and secondary infection have been reported. We evaluated the impact of the COVID-19 pandemic on AU in healthcare facilities (HCFs) in South America.

Methods. We conducted an ecologic evaluation of AU in inpatient adult acute care wards in 2 HCFs each in Argentina, Brazil, and Chile. The AU rates for intravenous antibiotics were calculated as the defined daily dose per 1000 patient-days, using pharmacy dispensing records and hospitalization data from March 2018–February 2020 (prepandemic) and March 2020–February 2021 (pandemic). Differences in median AU were compared between the prepandemic and pandemic periods, using the Wilcoxon rank sum test to determine significance. Interrupted time series analysis was used to analyze changes in AU during the COVID-19 pandemic.

Results. Compared with the prepandemic period, the median difference in AU rates for all antibiotics combined increased in 4 of 6 HCFs (percentage change, 6.7%–35.1%; $P < .05$). In the interrupted time series models, 5 of 6 HCFs had significant increases in use of all antibiotics combined immediately at the onset of the pandemic (immediate effect estimate range, 15.4–268), but only 1 of these 5 HCFs experienced a sustained increase over time (change in slope, +8.13; $P < .01$). The effect of the pandemic onset varied by antibiotic group and HCF.

Conclusions. Substantial increases in AU were observed at the beginning of the COVID-19 pandemic, suggesting the need to maintain or strengthen antibiotic stewardship activities as part of pandemic or emergency HCF responses.

Keywords. COVID-19; antibiotic use; South America; antibiotic stewardship.

The coronavirus disease 2019 (COVID-19) pandemic has led to devastation across the globe, with millions of cases and deaths reported worldwide [1]. COVID-19 caused not only substantial patient morbidity and mortality rates but also unveiled significant vulnerabilities in healthcare systems, given overwhelming patient volumes and strained supply chains. Numerous countries have observed increased antibiotic use (AU) among inpatients since the start of the pandemic, despite relatively low rates of bacterial coinfection and secondary infection [2–10]. In a meta-analysis of 154 studies, 74.6% of patients with COVID-19 were prescribed an antibiotic, whereas the estimated bacterial coinfection rate was only 8.6% [3]. Although symptoms of COVID-19 can resemble bacterial pneumonia or sepsis, the etiology is viral and antibiotics are thus ineffective, making the notable discrepancy between high rates of antibiotic prescribing and low rates of bacterial coinfection even more concerning.

Overuse of antibiotics is a leading cause of antibiotic resistance [11]. Antibiotic resistance is recognized as a major public health threat worldwide. In a landmark study evaluating the global burden of bacterial antibiotic resistance in 2019, it was estimated that 4.95 million deaths were associated with bacterial antibiotic resistance, with 1.27 million deaths directly attributed to antibiotic resistance [12]. A recent report produced by the US Centers for Disease Control and Prevention (CDC) outlined substantial increases in antibiotic-resistant infections during the COVID-19 pandemic, driven mainly by

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hospital-onset infections [13]. Furthermore, the Pan American Health Organization issued an alert describing increasing carbapenem-resistant Enterobacterales in Latin America during the pandemic [14]. The overuse of antibiotics seen across healthcare facilities (HCFs) around the world, along with other disruptions in infection prevention and control practices that occurred during the pandemic, poses a serious threat to global rates of antibiotic resistance.

Latin America is among the regions across the globe most affected by the COVID-19 pandemic, given marked increases in COVID-19 cases and related deaths [1]. Few reports describing the aftermath of the pandemic on AU have been published from the region. In a retrospective observational study conducted in intensive care units (ICUs) in a Brazilian hospital, consumption of broad-spectrum antibiotics increased early in the pandemic, including those classified as “reserve” by the World Health Organization [10]. Furthermore, analyses of antibiotic sales data obtained from the Brazilian government identified monthly increase of 5.83% in outpatient consumption of azithromycin during COVID-19 [15]. Data describing HCF-wide AU in South America are limited. Therefore, we evaluated the impact of the COVID-19 pandemic on AU in HCFs in Argentina, Brazil, and Chile.

METHODS

Study Design and Population

We conducted a retrospective, ecological evaluation of facility-level AU in 6 HCFs in Argentina, Brazil, and Chile (2 HCFs per country), over a 36-month period (March 2018–February 2021). The 36-month study period was stratified into 2 periods: a 24-month prepandemic period (March 2018 to February 2020) and a 12-month pandemic period (March 2020 to February 2021). We included adult (defined as ≥15 years of age) inpatient acute care wards (eg, medical floors, surgical floors, and ICUs). Non–acute care wards, including labor and delivery, psychiatry, and rehabilitation, were excluded. Emergency departments were excluded unless they had observation units in which patients were staying >24 hours and considered inpatients (only these units in the emergency department were included). The investigators in each hospital conducted a comprehensive facility survey to evaluate any changes in facility characteristics, medication dispensing practices, human resources, microbiology practices, and antibiotic stewardship practices during the study period that may have affected AU for our period of interest.

Data Collection

Trained staff collected AU data for intravenously administered antibiotics used to treat respiratory and multidrug-resistant infections from pharmacy dispensing records using standardized data collection tools. Across the 6 HCFs included, treatment guidelines for the management of community-acquired pneumonia, hospital-acquired pneumonia, and sepsis were available for review in 3, 4, and 2 HCFs, respectively. Preferred and alternative antibiotic regimens for each condition were included. We evaluated the following antibiotics: imipenem, meropenem, ertapenem, levofloxacin, moxifloxacin, ciprofloxacin, ceftriaxone, ceftazidime, cefepime, cefotaxime, ceftaroline, azithromycin, piperacillin-tazobactam, ampicillin-sulbactam, vancomycin, linezolid, polymyxin B, colistin, ceftazidime-avibactam, and ceftolozane-tazobactam.

Data collectors abstracted patient-days for included wards from hospital administrative records. AU was aggregated as monthly defined daily dose per 1000 patient-days. For data analyses, antibiotics were categorized as all included antibiotics, ceftriaxone (as a measure of treatment for community-acquired pneumonia), broad-spectrum β-lactam antibiotics with activity against *Pseudomonas aeruginosa* (imipenem, meropenem, ceftazidime, cefepime, piperacillin-tazobactam, ceftazidime-avibactam, and ceftolozane-tazobactam), and broad-spectrum antibiotics with activity against methicillin-resistant *Staphylococcus aureus* (vancomycin and linezolid).

Statistical Analysis

We measured the impact of COVID-19 on HCF-wide AU by first analyzing relative changes in median AU between prepandemic and pandemic periods. The differences in median AU were compared, and statistical significance was determined by means of the Wilcoxon rank sum test, using a 2-tailed *P* value cutoff of <.05. In addition, the significant differences were confirmed using the Hodges-Lehmann method (data not shown). A similar analysis of AU in ICUs at each HCF was conducted.

In addition, we used interrupted-time series analyses with autoregressive models to evaluate the immediate change and changes over time in AU associated with the COVID-19 pandemic [16]. The onset of the COVID-19 pandemic was March 2020 in these countries; thus, this time point marks the start of the pandemic. The equation was defined as follows:

$$Y_t = B_0 + B_1T + B_2X_t + B_3(T - T_i)X_t + E_t,$$

where Y_t is the AU rate measured at time point t; T, the number of months from the start of the study period, ranging from 1 to 36; X, a dichotomous variable indicating the pandemic period (prepandemic, 0; pandemic, 1; and T_i, the number of months that have transpired since the onset of the pandemic. The model parameter B_0 represents the baseline intercept, B_1, the prepandemic slope; B_2, the change in step at the onset of the pandemic (immediate effect); B_3, the change in slope from prepandemic to pandemic; and E, the model’s error term [16].

A series of techniques were used to adjust for autocorrelation, seasonality, and secular trends [16, 17]. The Durbin-Watson test was used to detect autocorrelation, and when detected, the stepwise autoregressive process using the Yule-Walker method was performed for correction [18]. When residual variance volatility was observed, a generalized autoregressive conditional heteroskedasticity (GARCH) approach was added, and the model with the lowest Akaike information criterion was selected [19]. Model fit diagnostics were performed to ensure the mean residual is close to zero, residuals are not distinguishable from white noise, and the autocorrelation function and partial correlation function were within bounds. All statistical analyses were conducted using SAS (version 9.4), and an α value of <0.05 was considered statistically significant.

Ethical Approval

The CDC Human Subject Research Protection Office reviewed the protocol and determined the activities to be public health evaluation, nonresearch activities under 45 CFR 46.102(1); thus, review by the CDC's institutional review board was not required. The protocol was evaluated and approved by the institutional review board at each participating HCF: Hospital Alemão Oswaldo Cruz (no. 4.511.081), Hospital das Clínicas FMUSP (no. 4.689.274), Clínica Alemana-Universidad del Desarrollo (no. 2021-24), Comité Etico-científico Servicio de Salud Metropolitano Sur Oriente, Hospital Privado Universitario de Córdoba (no. 4-334), and Hospital Español.

RESULTS

HCF Characteristics

Of the 6 HCFs included in the study, 4 were private and 2 were public. The number of ICU beds increased in all 6 HCFs, by 22%–633%. Similarly, the number of ventilators increased in 5 of 6 HCFs, with increases ranging from 15% to 317%. All 6 HCFs reported having an antibiotic stewardship program (ASP) before the pandemic, with no change in stewardship practices occurring in 4 of 6 HCFs. Notably, antibiotic shortages occurred in 3 of 6 HCFs, and healthcare personnel shortages occurred in all 6. Finally, 2 of 6 HCFs reported increased delays in antibiotic susceptibility testing by the clinical microbiology laboratory during the pandemic (Table 1).

Changes in AU

Compared with the prepandemic period, the median rates of use for all included antibiotics combined significantly increased ($P < .05$) in 4 of 6 HCFs during the pandemic period (percentage change [Δ], 6.7%–35.1%; Table 2). Among these 4 HCFs (AR02, BR02, CH01, and CH02), the use of all included antibiotics combined was high during months when COVID-19 patient surges occurred (Figure 1). In BR02, CH01, and CH02, the AU rates for all included antibiotics remained high despite decreases in COVID-19 discharges. AU in ICUs significantly increased in 1 HCF (BR01; Δ, 43.5%; $P < .05$) and decreased in 2 (AR01 and CH02; Δ, −36.6% and −43.5%) during the pandemic period (Supplementary Table 1). Ceftriaxone use was higher

Table 1. Characteristics and Reported Changes During the Coronavirus Disease 2019 Pandemic Among 6 Healthcare Facilities in Argentina, Brazil, and Chile, March 2020 to February 2021

Characteristic or Change	Healthcare Facility					
	AR01	AR02	BR01	BR02	CH01	CH02
Country	Argentina	Argentina	Brazil	Brazil	Chile	Chile
Private/public status	Private	Private	Private	Public	Private	Public
No. of adult inpatient beds	263	126	357	886	371	220
Increase in ICU beds, %[a]	57	22	98	108	116	633
Increase in ventilator use, %[a]	35	0	15	106	15	317
Antibiotic shortages	None	None	None	Linezolid, L-amphotericin, sulfamethoxazole-trimethoprim, piperacillin-tazobactam	Vancomycin	Vancomycin
Personnel shortages by specialty	Respiratory physiotherapists	Nurses	Nurse, nursing assistants, physicians, respiratory therapists	Microbiology technicians	Microbiology and medical technicians	Physicians, nurses, microbiology and medical technicians
Changes in antimicrobial stewardship practices	None	None	AU review interruption	None	Started AU review	None
Changes in microbiology laboratory practices	None	None	None	None	Delayed AST	Delayed identification and AST

Abbreviations: AR, Argentina; AST, antibiotic susceptibility testing; AU, antibiotic use; BR, Brazil; CH, Chile; ICU, intensive care unit.

[a] Percentage change from prepandemic to pandemic time periods.

Table 2. Median Inpatient Antibiotic Use Among 6 Healthcare Facilities in Argentina, Brazil, and Chile, March 2018 to February 2021

Variable by Antibiotic Group[a]	AR01	AR02	BR01	BR02	CH01	CH02
All antibiotics						
AU, median, DDD/1000 patient-days						
Prepandemic	501.7	601.9	423.3	448.4	201.5	449.8
Pandemic	480.1	642	423.54	605.8	245.12	602.1
Change, %	−4.3	6.7	0.0	35.1	21.6	33.9
P value	.19	<.05[b]	.93	<.05[b]	<.05[b]	<.05[b]
Ceftriaxone						
AU, median, DDD/1000 patient-days						
Prepandemic	75.84	86.57	132.1	116.1	114.1	282.9
Pandemic	96.03	131.2	141.02	147.6	108.6	299.2
Change, %	26.6	51.6	6.8	27.1	−4.8	5.8
P value	<.05[b]	<.05[b]	.17	<.05[b]	.31	.11
Anti-PSA β-lactams						
AU, median, DDD/1000 patient-days						
Prepandemic	207.7	193.9	173.66	156.8	34.04	78.1
Pandemic	168.5	191.9	181.07	205.94	61.45	142.5
Change, %	−18.9	−1.0	4.3	31.3	80.5	82.5
P value	<.05[b]	.96	.18	<.05[b]	<.05[b]	<.05[b]
Anti-MRSA antibiotics						
AU, median, DDD/1000 patient-days						
Prepandemic	52.4	69.1	37.8	63.5	18.6	40.2
Pandemic	46.2	72	41.7	86.9	29.5	71.2
Change, %	−13.4	4.2	10.3	36.9	58.6	77.1
P value	.11	.46	.15	<.05[b]	<.05[b]	<.05[b]

Abbreviations: AR, Argentina; AU, antibiotic use; BR, Brazil; CH, Chile; MRSA, methicillin-resistant *Staphylococcus aureus*; PSA, *Pseudomonas aeruginosa*.

[a] "All antibiotics" include imipenem, meropenem, ertapenem, levofloxacin, moxifloxacin, ciprofloxacin, ceftriaxone, ceftazidime, cefepime, cefotaxime, ceftaroline, azithromycin, piperacillin-tazobactam, ampicillin-sulbactam, vancomycin, linezolid, polymyxin B, colistin, ceftazidime-avibactam, and ceftolozane-tazobactam; anti-PSA β-lactams, imipenem, meropenem, ceftazidime, cefepime, piperacillin-tazobactam, ceftazidime-avibactam, and ceftolozane-tazobactam; and anti-MRSA antibiotics, vancomycin, and linezolid. The prepandemic period was defined as March 2018 to February 2020, and the pandemic period as March 2020 to February 2021.

[b] Significant at $P < .05$.

in 3 of 6 HCFs (AR01, AR02, and BR02) during the pandemic period (Δ, 26.6%–51.6%; $P < .05$). In the ICU analysis, ceftriaxone use increased significantly in 2 HCFs (AR02 and BR01; Δ, 45.9% and 35.6%; $P < .05$) and decreased in 2 (CH01 and CH02; Δ, −15.5% and −62.5%; $P < .05$).

The use of β-lactam antibiotics with activity against *P. aeruginosa* increased in 3 of 6 HCFs (BR02, CH01, and CH02; Δ, 31.3%–82.5%; $P < .05$) and decreased in 1 (AR01; Δ, −18.9%; $P < .05$). In the ICUs in BR01 and CH01, the use of these agents increased significantly ($P < .05$), by 28.5% and 33.5%, respectively. Use decreased significantly in AR01 (Δ, −29%). Vancomycin and linezolid use increased in 3 of 6 HCFs (BR02, CH01, and CH02; Δ, 36.9%–77.1%; $P < .05$). The use of these agents increased in the ICU only in BR01 (Δ, 40.7%; $P < .05$) and decreased in AR01 (Δ, −30.2%; $P < .05$). Of note, when considering data from all acute care wards, the public hospital in Brazil, BR02, experienced increases in all antibiotic groups examined during the pandemic. Finally, when analysis was restricted to ICUs only, AU across all antibiotic groups increased during the pandemic in BR01.

Analysis of the data using an interrupted time series autoregessive model produced complementary results, as seen in Table 3. The immediate change and change over time effects varied by antibiotic grouping and HCF, and the trends of use for each antibiotic grouping over time are depicted in Figure 1.

In 5 of 6 HCFs (AR01, AR02, BR01, BR02, and CH01), an immediate increase in use of all included antibiotics combined was observed after the onset of the COVID-19 pandemic (immediate effect estimate range, 15.4–268). However, the interrupted time series analyses found that only 1 of these 5 HCFs, CH01, experienced a sustained significant increase in AU rate over time during the pandemic period compared with the prepandemic period for all included antibiotics combined (change in slope, +8.53; $P < .01$). Despite initial increases in use of all included antibiotics combined seen at the onset of the pandemic in AR01 and BR01, significant declines in use over time were observed as the pandemic progressed (change in slope, −28.08 and −7.94, respectively; $P < .01$).

While a statistically significant immediate increase in ceftriaxone use was detected in 4 of 6 HCFs (AR01, AR02, BR01, and BR02) at the pandemic onset, its use over time either remained stable (BR02) or decreased (AR01, AR02, and BR01). In CH02, although there was no statistically significant trend in the immediate use of ceftriaxone after the pandemic onset, its use decreased over time (change in slope, −10.7; $P = .03$). Finally, an immediate decrease was identified in 1 HCF (CH01), but the

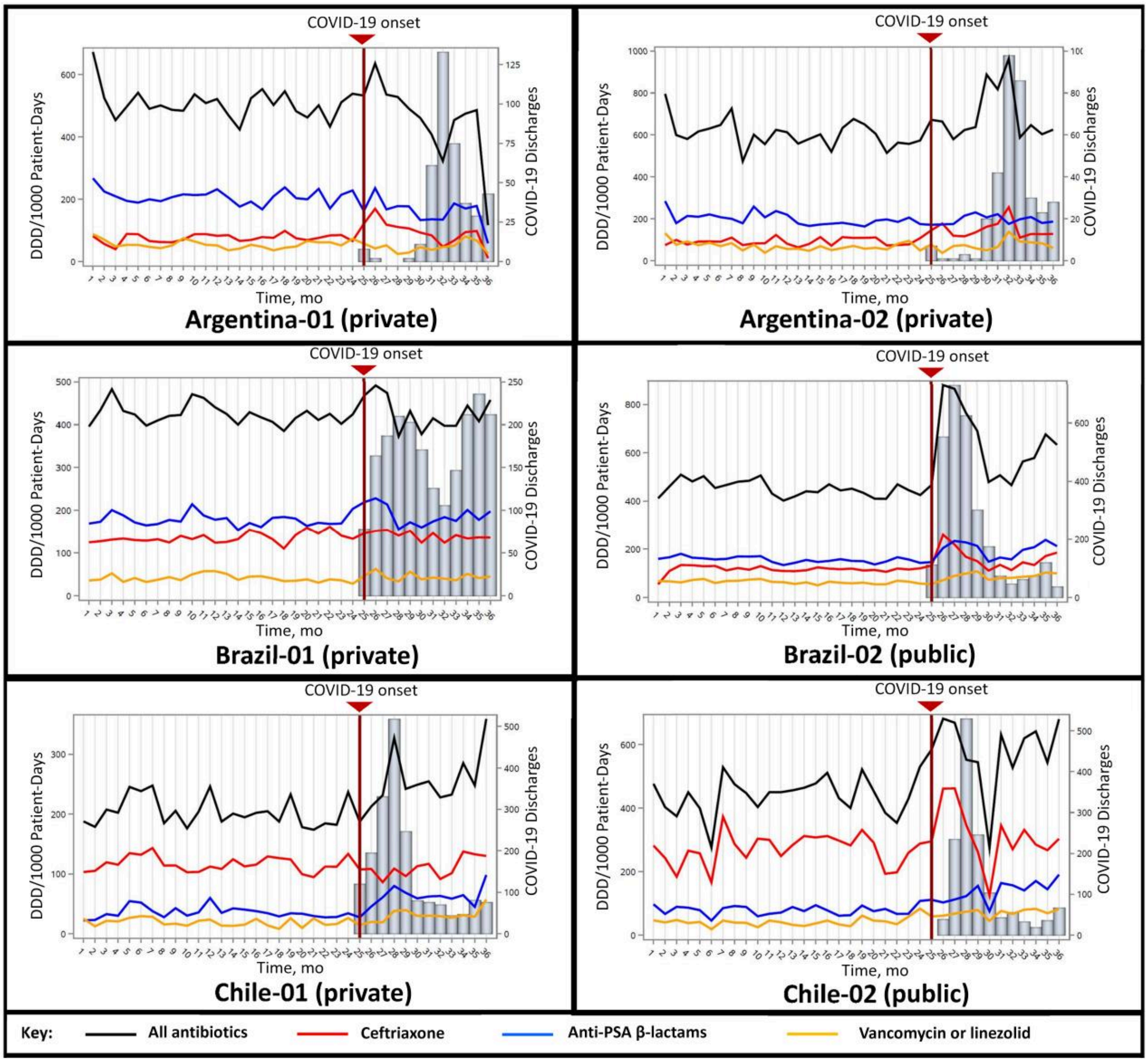

Figure 1. Monthly antibiotic use and coronavirus disease 2019 (COVID-19) discharges from March 2018 through February 2021 (36 months) in healthcare facilities in Argentina, Brazil, and Chile (2 facilities from each country). "All antibiotics" include intravenous administered azithromycin, ampicillin-sulbactam, levofloxacin, moxifloxacin, ciprofloxacin, ceftriaxone, ceftazidime, cefepime, piperacillin-tazobactam, ertapenem, meropenem, imipenem, vancomycin, linezolid, colistin, polymyxin B, ceftazidime-avibactam, and ceftolozane-tazobactam. Anti–*Pseudomonas aeruginosa* (PSA) β–lactams include ceftazidime, cefepime, piperacillin-tazobactam, meropenem, imipenem, ceftazidime-avibactam, and ceftolozane-tazobactam. Abbreviation: DDD, defined daily dose.

effect of the pandemic over time actually indicated an increasing rate of ceftriaxone use (+2.94; $P < .01$) (Table 3).

Among β-lactam antibiotics with activity against *P. aeruginosa*, 4 of 6 HCFs (BR01, BR02, CH01, and CH02) had an immediate increase in use (estimate range, 21.3–31.4), but the increases remained over time during the pandemic in 2 only of these HCFs (CH01 and CH02). In AR01, an opposite trend was observed, with no significant increase in these antibiotics at the onset of the pandemic and a significant decrease over time (change in slope, −6.8; $P < .01$). Finally, broad-spectrum antibiotics with activity against methicillin-resistant *S. aureus* increased at the onset of the pandemic in 1 HCF (BR02; immediate effect estimate, 22.5; $P = .01$), and in 2 HCFs (BR02 and CH01) increases were observed over time (changes in slope, +2.48 and +2.1; $P < .01$) (Table 3).

DISCUSSION

The increases we observed in inpatient intravenous AU during the COVID-19 pandemic in South America align with previously published reports from other regions [2–9]. In some of the HCFs, we observed a striking trend wherein intravenous AU peaked during months when COVID-19 patient volumes were high. Similarly, another study evaluating hospital wide

Table 3. Parameter Estimates From Interrupted Time Series Analysis of Antibiotic Use Among 6 Healthcare Facilities in Argentina, Brazil, and Chile, March 2018 to February 2021

		Immediate Effect of COVID-19 Pandemic		Impact of COVID-19 Pandemic Over Time[b]			
HCF	Antibiotic Group[a]	Estimate (SE)	*P* Value	Prepandemic Estimate	Pandemic Estimate	Change in Slope (SE)	*P* Value
AR01	All antibiotics	155.57 (58.39)	<.01[c]	−1.37	−29.45	−28.08 (8.3)	<.01[c]
	Ceftriaxone	63.51 (8.59)	<.01[c]	0.58	−8.17	−8.75 (4.01)	<.01[c]
	Anti-PSA β-lactams	0.737 (16.18)	.96	−0.28	−7.08	−6.8 (1.9)	<.01[c]
	Anti-MRSA	−11.41 (10.56)	.28	−0.24	0.89	+1.13 (1.27)	.38
AR02	All antibiotics	134.5 (61)	.04[c]	−4.09	1.81	+5.9 (7.6)	.42
	Ceftriaxone	61.76 (11.27)	<.01[c]	0.39	−3.02	−3.63 (1.59)	.02[c]
	Anti-PSA β-lactams	−3.8 (18.68)	.8	−1.48	1.32	+3.06 (1.98)	.12
	Anti-MRSA	3.42 (15.2)	.82	−1.18	2.42	+3.6 (1.8)	.06
BR01	All antibiotics	62.31 (5.77)	<.01[c]	−.67	−8.61	−7.94 (0.56)	<.01[c]
	Ceftriaxone	13.16 (5.75)	.02[c]	0.62	−1.51	−2.5 (0.63)	<.01[c]
	Anti-PSA β-lactams	25.6 (8.8)	<.01[c]	−0.13	−1.96	−1.83 (1.09)	.1
	Anti-MRSA	10.67 (6)	.08	−0.26	−0.6	−0.31 (0.73)	.66
BR02	All antibiotics	268 (54)	<.01[c]	−1.44	−13.03	−11.59 (6.3)	.07
	Ceftriaxone	83.89 (11.82)	<.01[c]	−1.02	−4.12	−3.1 (1.98)	.11
	Anti-PSA β-lactams	31.35 (12.76)	.01[c]	−0.82	2.05	+2.87 (1.82)	.11
	Anti-MRSA	22.45 (1.02)	<.01[c]	−0.69	1.79	+2.48 (0.19)	<.01[c]
CH01	All antibiotics	15.377 (1.543)	<.01[c]	−0.74	7.79	+8.53 (0.13)	<.01[c]
	Ceftriaxone	−23.14 (8.2)	<.01[c]	−0.16	2.78	+2.94 (0.96)	<.01[c]
	Anti-PSA β-lactams	21.49 (5.45)	<.001[c]	−0.19	1.64	+1.83 (0.75)	.01[c]
	Anti-MRSA	0.814 (5.4)	.88	−0.2	1.9	+2.1 (0.65)	<.01[c]
CH02	All antibiotics	116.94 (59.84)	.06	1.46	0.91	−0.55 (7.25)	.93
	Ceftriaxone	44.26 (48.9)	.36	2.8	−7.92	−10.72 (5.02)	.03[c]
	Anti-PSA β-lactams	21.3 (7.6)	<.01[c]	−0.02	5.7	+5.9 (.9)	<.01[c]
	Anti-MRSA	19.08 (12.59)	.129	0.62	0.465	−0.155 (1.84)	.93

Abbreviations: AR, Argentina; BR, Brazil; CH, Chile; COVID-19, coronavirus disease 2019; HCF, healthcare facility; MRSA, methicillin-resistant *Staphylococcus aureus*; PSA, *Pseudomonas aeruginosa*; SE, standard error.

[a] "All antibiotics" include imipenem, meropenem, ertapenem, levofloxacin, moxifloxacin, ciprofloxacin, ceftriaxone, ceftazidime, cefepime, cefotaxime, ceftaroline, azithromycin, piperacillin-tazobactam, ampicillin-sulbactam, vancomycin, linezolid, polymyxin B, colistin, ceftazidime-avibactam, and ceftolozane-tazobactam; anti-PSA β-lactams, imipenem, meropenem, ceftazidime, cefepime, piperacillin-tazobactam, ceftazidime-avibactam, and ceftolozane-tazobactam; and anti-MRSA antibiotics, vancomycin, and linezolid.

[b] The prepandemic period was defined as March 2018 to February 2020, and the pandemic period as March 2020 to February 2021.

[c] Significant at $P < .05$.

trends of AU in a large cohort of US hospitals observed the largest increases in use of ceftriaxone, cefepime, azithromycin, and doxycycline were in hospitals with higher COVID-19 burdens [20].

An increase in use for ≥ 1 antibiotic group analyzed was observed in the interrupted time series analysis for all 6 South American HCFs immediately after the onset of the pandemic. We observed an increase in overall AU ranging from 6.7% to 35.1% in 4 HCFs during the pandemic. However, the increases were sustained during the 12 months after the pandemic onset in only 1 of these HCFs, and the reasons for the sustained high AU need to be further explored. The high AU rates observed early during the pandemic are not surprising, as there was more uncertainty in the appropriate management of patients with COVID-19 at the onset of the pandemic. In addition, there was concern for bacterial coinfection and/or secondary infection, given clinical presentation [5].

All HCFs included in the current analysis reported an increase in ICU beds during the pandemic, suggesting a substantial rise in patient acuity. Furthermore, distinguishing bacterial pathogens from viral causes can be especially challenging in low- and middle-income countries, as biomarkers are not readily available and capacity in microbiology laboratories can be limited [21]. Finally, all 6 HCFs experienced shortages in healthcare workers, and 2 HCFs also reported increased delays in microbiology results during the pandemic. Thus, surges of patients with high acuity, lack of ideal laboratory diagnostics, and an overwhelmed healthcare system can create the perfect storm for overuse of antibiotics, even in the setting of a viral pandemic.

Antibiotic use is generally higher in patients admitted to ICUs [22]. This is evident in our data when comparing the magnitude of median AU rate in ICUs with that in all wards within each HCF (prepandemic, 309.4–6611.1 vs 201.5–601.9 defined daily dose per 1000 patient-days, respectively). Interestingly, when comparing the median AU in the prepandemic period with that in the pandemic period in ICUs, we did not consistently find the same significant increases that we found in analyses of all acute care wards. Thus, the AU in ICUs was not the main driver of the overall increases seen in AU during the pandemic in the included HCFs. This is likely a reflection of how the burden of COVID-19 affected the entire HCF, not just the ICUs. Furthermore, although all 6 HCFs experienced increases in the number of ICU beds, changes in AU were not proportional to that increase. For example, even though CH02 saw a 633% increase in the number of ICU beds, the median AU actually decreased significantly. However, in an analysis of data collected from all wards at this HCF, AU increased significantly. During the pandemic, many healthcare-related resources were diverted to the ICU, leading to potentially more oversight of therapeutics administered to these patients. The opposite may have been true in other wards.

High rates of ceftriaxone use early in the pandemic were anticipated, as this is the preferred antibiotic for empiric treatment of community-acquired pneumonia in all 6 HCFs. However, the early and sustained increases in use of broad-spectrum β-lactam antibiotics with activity against *P. aeruginosa* are particularly concerning. Of the agents included in this antibiotic grouping, the most common antibiotics used were piperacillin-tazobactam, followed by cefepime, imipenem, and meropenem (data not shown). Although 1 HCF reported a shortage of piperacillin-tazobactam, use significantly increased immediately following the onset of the pandemic. Similarly, although the 2 HCFs in Chile reported a shortage of vancomycin, the median use of vancomycin and linezolid increased in these HCFs during the pandemic compared to the prepandemic period. Although vancomycin and linezolid use accounted for the lowest proportion of "all included antibiotics," important increases were seen in overall use of these antibiotics during the pandemic, causing concern for emergence of antibiotic resistance. In a retrospective analysis of 196 linezolid- and vancomycin-resistant *Enterococcus faecium* cases, 71.4% of the patients had prior linezolid exposure, demonstrating an association between increased linezolid consumption and rising rates of linezolid resistance [23].

Although the impact of the COVID-19 pandemic on global rates of antibiotic resistance is unknown, the overuse of broad-spectrum antibiotics can worsen this evolving public health threat. Notably, reports of the rising incidence of antibiotic-resistant pathogens during the COVID-19 pandemic have emerged [13, 14]. During the pandemic, national reference laboratories in Latin America began issuing alerts on the emergence of new carbapenemases found in Enterobacterales, significant increases in the number of isolates positive for previously reported carbapenemases, and emergence of isolates coexpressing ≥2 carbapenemases. For example, a report of 77 isolates of *Klebsiella pneumoniae* collected from 27 hospitals between May 2020 and June 2021 that showed concern for coexpression of enzymes revealed that most isolates carried $bla_{\mathrm{KPC}} + bla_{\mathrm{NDM}}$ [14, 24]. Emergence of these multidrug-resistant bacteria have detrimental effects on patient outcomes because the availability of active therapeutics without toxic adverse effects is limited [25]. Given the accelerated rate of antibiotic resistance during the pandemic, previous reports outlining deaths due to antibiotic resistance likely underestimate the current situation [12].

ASPs can effectively control the use of antibiotics as a strategy to mitigate emergence of antibiotic resistance [26, 27]. Our study highlights an important target for ASPs as the COVID-19 pandemic continues. A critical review of antibiotic prescribing patterns among patients with COVID-19 is warranted, and guidance on which patients should receive empiric antibiotics should be developed [28–30]. Common ASP practices, such as antibiotic restriction by preauthorization or prospective audit with prompt feedback, should be used to control AU even in the setting of a pandemic. Importantly, ASPs with different models and daily workflow have shown to be successful in regulating AU during the pandemic [31]. Integrated workflows may be necessary, especially in settings with limited resources. Furthermore, ASPs can also be used to appropriately deploy COVID-19 therapeutics that may be limited in supply to ensure optimal patient outcomes [30].

Our study has important limitations to consider. Because this was not a patient-level analysis, we are unable to stratify our analyses by COVID-19 diagnosis, bacterial infection diagnosis, or disease severity. Therefore, the reported rates of AU reflect changes that occurred in the HCF, and we cannot determine whether the changes in AU were driven by patients hospitalized with COVID-19 or by the overall patient population. Understanding how the increase in AU compares with rates of bacterial infections during this time period is critical, especially given reports of increasing antibiotic-resistant pathogens found in the region. Our study represents only the burden of AU among inpatients, as we did not analyze data from outpatients in these countries. Finally, trends in AU among pediatric patients in these HCFs remains unknown as only AU data among adult patients were collected.

In conclusion, we demonstrated significant increases in intravenous AU during the COVID-19 pandemic in inpatient acute care settings in Argentina, Brazil, and Chile. Although most increases were observed immediately after the onset of the pandemic, continued monitoring of AU in inpatient settings and understanding trends in antibiotic resistance in South America is important to inform preventive actions. The COVID-19 pandemic demonstrated the need for HCFs to have pandemic preparedness plans that include implementing or strengthening both diagnostics and ASPs to mitigate overuse of antibiotics.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention or the Agency for Toxic Substances and Disease Registry.

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