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Increment Antimicrobial Resistance During the COVID-19 Pandemic: Results from the Invifar Network

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Aim: This study aims to assess the changes in antimicrobial resistance among some critical and high-priority microorganisms collected previously and during the coronavirus disease 2019 (COVID-19) pandemic in Mexico.

Methods: We collected antimicrobial susceptibility data for critical and high-priority microorganisms from blood, urine, respiratory samples, and from all specimens, in which the pathogen may be considered a causative agent. Data were stratified and compared for two periods: 2019 versus 2020 and second semester 2019 (prepandemic) versus the second semester 2020 (pandemic).

Results: In the analysis of second semester 2019 versus the second semester 2020, in blood samples, increased resistance to oxacillin (15.2% vs. 36.9%), erythromycin (25.7% vs. 42.8%), and clindamycin (24.8% vs. 43.3%) ($p \leq 0.01$) was detected for *Staphylococcus aureus*, to imipenem (13% vs. 23.4%) and meropenem (11.2% vs. 21.4) ($p \leq 0.01$), for *Klebsiella pneumoniae*.

In all specimens, increased ampicillin and tetracycline resistance was detected for *Enterococcus faecium* ($p \leq 0.01$). In cefepime, meropenem, levofloxacin, and gentamicin ($p \leq 0.01$), resistance was detected for *Escherichia coli*; and in piperacillin-tazobactam, cefepime, imipenem, meropenem, ciprofloxacin, levofloxacin, and gentamicin ($p \leq 0.01$), resistance was detected for *Pseudomonas aeruginosa*.

Conclusion: Antimicrobial resistance increased in Mexico during the COVID-19 pandemic. The increase in oxacillin resistance for *S. aureus* and carbapenem resistance for *K. pneumoniae* recovered from blood specimens deserves special attention. In addition, an increase in erythromycin resistance in *S. aureus* was detected, which may be associated with high azithromycin use. In general, for *Acinetobacter baumannii* and *P. aeruginosa*, increasing resistance rates were detected.

Keywords: antimicrobial resistance, COVID-19 pandemic, INVIFAR, *Staphylococcus aureus*, *Enterococcus faecium*, *Acinetobacter baumannii* complex, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Escherichia coli*

Introduction

In 2016, the World Health Organization (WHO) published a list of microorganisms with high resistance rates to guide efforts in antimicrobial development.[1] Critical priority microorganisms include *Acinetobacter baumannii, Pseudomonas aeruginosa*, and some *Enterobacterales* (formerly *Enterobacteriaceae*). High-priority bacterial species are *Enterococcus faecium* and *Staphylococcus aureus*, among others.[2]

At the end of 2019, acute pneumonia cases associated with the novel coronavirus (SARS-CoV-2) in Wuhan, China, were reported. Soon after that, the COVID-19 (coronavirus disease 2019) outbreak disseminated worldwide, and on March 11, 2020, it was declared a pandemic by the WHO.[3] The first positive SARS-CoV-2 case in Mexico was confirmed at the end of February 2020.[4] The disease spread rapidly throughout the country, with 233,414 cases by July 1, 2020, and 1,413,935 cases by December 31, 2020.[5]

The COVID-19 pandemic may have had an impact on antimicrobial resistance. For example, the disruption of antimicrobial stewardship and infection prevention programs, as well as the high number of patients and limitations of personal protective equipment, likely increase drug

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resistance, and factors such as strict lockdown, social distancing, and the extensive implementation of hand hygiene and face masks may decrease resistance.[6–9]

A recent review highlights that during the COVID-19 pandemic, 75% of adults with comorbidities received an antimicrobial prescription even without pathogen isolation and that the antibiotic was inappropriate in more than one-third of the COVID-19 cases.[10]

In COVID-19 patients, critical and high-priority microorganisms have been reported with high frequency. In Wuhan, China, *A. baumannii* was the most common pathogen reported (35.8%, 91.2% carbapenem-resistant), followed by *Klebsiella pneumoniae* (30.8%, 75.5% carbapenem-resistant).[11] Furthermore, an increase in multidrug-resistant organisms has been reported, with colonization by carbapenem-resistant *Enterobacterales* up to 50%.[11–16]

There is a need for data to define how the COVID-19 pandemic has affected antimicrobial resistance. Thus, this study aims to assess the changes in antimicrobial resistance among some critical and high-priority microorganisms collected previously and during the COVID-19 pandemic in Mexico.

Materials and Methods

Study design and data collection

Antimicrobial susceptibility profiles from critical and high-priority microorganisms were collected. *S. aureus*, *E. faecium*, *A. baumannii* complex, *P. aeruginosa*, *K. pneumoniae*, *Enterobacter cloacae*, and *Escherichia coli* isolated from blood, urine, respiratory samples (bronchial lavage and tracheal aspirate), and from all specimens, in which they may be considered causative agent (all specimens), were included. Data from January 1, 2019 to December 31, 2020, were provided by 46 centers: 40 hospital-based laboratories (5 national institutes, 11 specialty hospitals, 17 general hospitals, and 7 mother and child or pediatric hospitals) and 6 external laboratories from the network Red Temática de Investigación y Vigilancia de la Farmacorresistencia (INVIFAR, in its Spanish acronym). Only the first isolate per patient was included. Among centers, 35 attended COVID-19 patients (the whole center or with defined wards) and processed specimens from COVID-19 patients, 6 processed specimens from COVID-19 patients, and 5 did not process specimens from COVID-19 patients.

Data were stratified and compared with 2 approaches: First, comparing data from all centers from January 1 to December 31, 2019 (prepandemic) versus January 1 to December 31, 2020 (pandemic); and second, comparing data from COVID-19 centers (either treated patients or processed specimens) from July 1 to December 31, 2019 (prepandemic, none of the centers had COVID-19 patients) versus July 1 to December 31, 2020 (pandemic, all centers had COVID-19 patients). This analysis allowed us to analyze the impact of COVID-19 on drug resistance.

Identification of strains and antimicrobial susceptibility

Clinical strains were identified by the methodology available in each center: Vitek 2 (bioMérieux, France), Phoenix System (Becton Dickinson, USA), MicroScan WalkAway (Siemens Healthineers, USA), and Sensititre System (TREK Diagnostic Systems, Inc., Thermo Fisher Scientific, USA). In some cases, identification was performed or confirmed with traditional manual methods. Antimicrobial susceptibility profiles were determined with the systems mentioned above, in-house broth microdilution, and/or the disk diffusion method. Breakpoints were assessed for each microorganism according to the Clinical and Laboratory Standards Institute CLSI M-100.[17,18] Participating centers use CARBA-NP and carbapenem inactivation to detect carbapenemase production and the double disk method to detect extended-spectrum beta-lactamase production.

Statistical analysis

Data for each center were introduced to WHONET 5.6 software. All databases were converted with the BacLink 2 tool to obtain the WHONET file format. Absolute and relative frequencies of resistant strains were reported.

Frequencies of antibiotic resistance were compared among periods using the chi-square test or the exact Fisher test as appropriate. Bonferroni correction was used for multiple comparisons. A two-tailed p-value <0.05 was considered statistically significant. Statistical analysis was conducted in Stata version 14.0, and graphs were generated with GraphPad Prism 7. The ethics committee from Antiguo Hospital Civil de Guadalajara ''Fray Antonio Alcalde,'' Jalisco, Mexico approved this study (ref. 129/17).

Results

Stratification of data

Data were stratified, and percentages of resistance were obtained. Raw data, relative frequencies, and p-values can be found in Supplementary File 1. Similar increases were observed between January to December 2019 versus January to December 2020 (comparing all centers) and July to December 2019 versus July to December 2020 (comparing only COVID-19 centers), with some exceptions.

Gram-positive antibiotic resistance

For *S. aureus*, an increase in oxacillin, levofloxacin, erythromycin, and clindamycin resistance were detected in all specimens ($p \leq 0.001$) and oxacillin, erythromycin, and clindamycin in blood ($p \leq 0.01$) and respiratory ($p \leq 0.001$) isolates (Fig. 1).

For *E. faecium*, an increase in resistance to ampicillin and tetracycline was detected in all specimens ($p \leq 0.01$) and urine samples ($p \leq 0.016$) (Fig. 1). In contrast, vancomycin-resistant strains diminished in all samples ($p \leq 0.016$) and blood ($p \leq 0.01$; Fig. 1).

Enterobacterales antibiotic resistance

For *K. pneumoniae*, increasing resistance was detected in all specimens for some antibiotics, including cefoxitin, cefepime, imipenem, meropenem, and levofloxacin ($p \leq 0.001$). When only COVID-19 centers were compared, an increase in resistance to gentamicin ($p \leq 0.001$) was detected. Respiratory isolates showed increasing resistance percentages

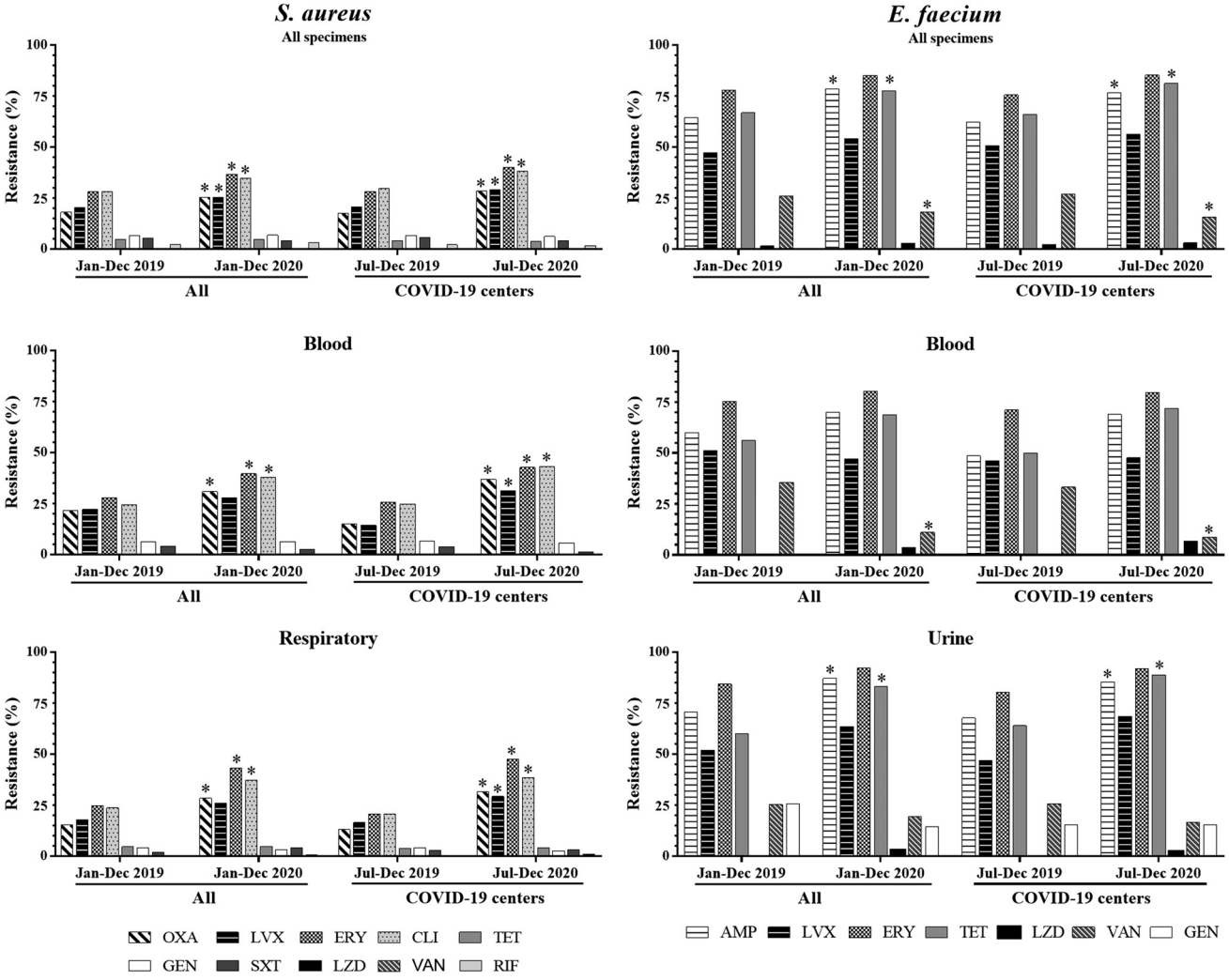

FIG. 1. Comparison of antimicrobial susceptibility profiles of *Staphylococcus aureus* and *Enterococcus faecium* strains isolated between 2019 and 2020. *Statistically significant *p*-value; AMP, ampicillin; CLI, clindamycin; ERY, erythromycin; GEN, gentamicin; LVX, levofloxacin; LZD, linezolid; OXA, oxacillin; PEN, penicillin; RIF, rifampicin; TET, tetracycline; SXT, trimethoprim/sulfamethoxazole; VAN, vancomycin.

for imipenem and meropenem ($p \leq 0.01$), but this trend disappeared for imipenem resistance when only COVID-19 centers were analyzed. Analysis of isolates from blood indicated increased resistance to imipenem and meropenem ($p \leq 0.01$) in both analyses. Likewise, urine samples also showed an increased resistance toward cefoxitin, imipenem, and meropenem ($p \leq 0.01$). The COVID-19 centers analysis showed that this trend continued only for meropenem, and higher resistance was identified for cefepime and gentamicin ($p \leq 0.01$) (Fig. 2 and Supplementary Table S1).

For *E. coli* from all specimens, an increasing resistance to almost all the antimicrobials evaluated was observed, including ampicillin-sulbactam, ampicillin, cefoxitin, ceftazidime, cefepime, imipenem, meropenem, ciprofloxacin, levofloxacin, gentamicin, and trimethoprim-sulfamethoxazole ($p \leq 0.01$; Fig. 2). This trend disappeared for ceftazidime, imipenem, and trimethoprim-sulfamethoxazole when only COVID-19 centers were considered. When the comparison was made in blood isolates, the increasing trend was detected for amoxicillin-clavulanic acid and ampicillin-sulbactam ($p \leq 0.01$). Furthermore, the analysis with COVID-19 centers showed an increase in levofloxacin resistance ($p \leq 0.016$). Urine isolates showed similar trends for the comparison of all specimens.

Nonfermenters antibiotic resistance

A. baumannii isolates from all specimens exhibited increased resistance to piperacillin-tazobactam, imipenem, meropenem, ciprofloxacin, levofloxacin, and gentamicin ($p \leq 0.016$; Fig. 3). This trend was observed in the COVID-19 centers analysis only for piperacillin-tazobactam. In addition, resistance rates for *A. baumannii* isolated from respiratory samples increased for piperacillin-tazobactam and imipenem ($p \leq 0.01$), but disappeared when the COVID-19 centers were considered for analysis. In blood samples, increases were significant for meropenem ($p \leq 0.016$), but disappeared too in the second analysis. No significant tendencies were observed in urine samples.

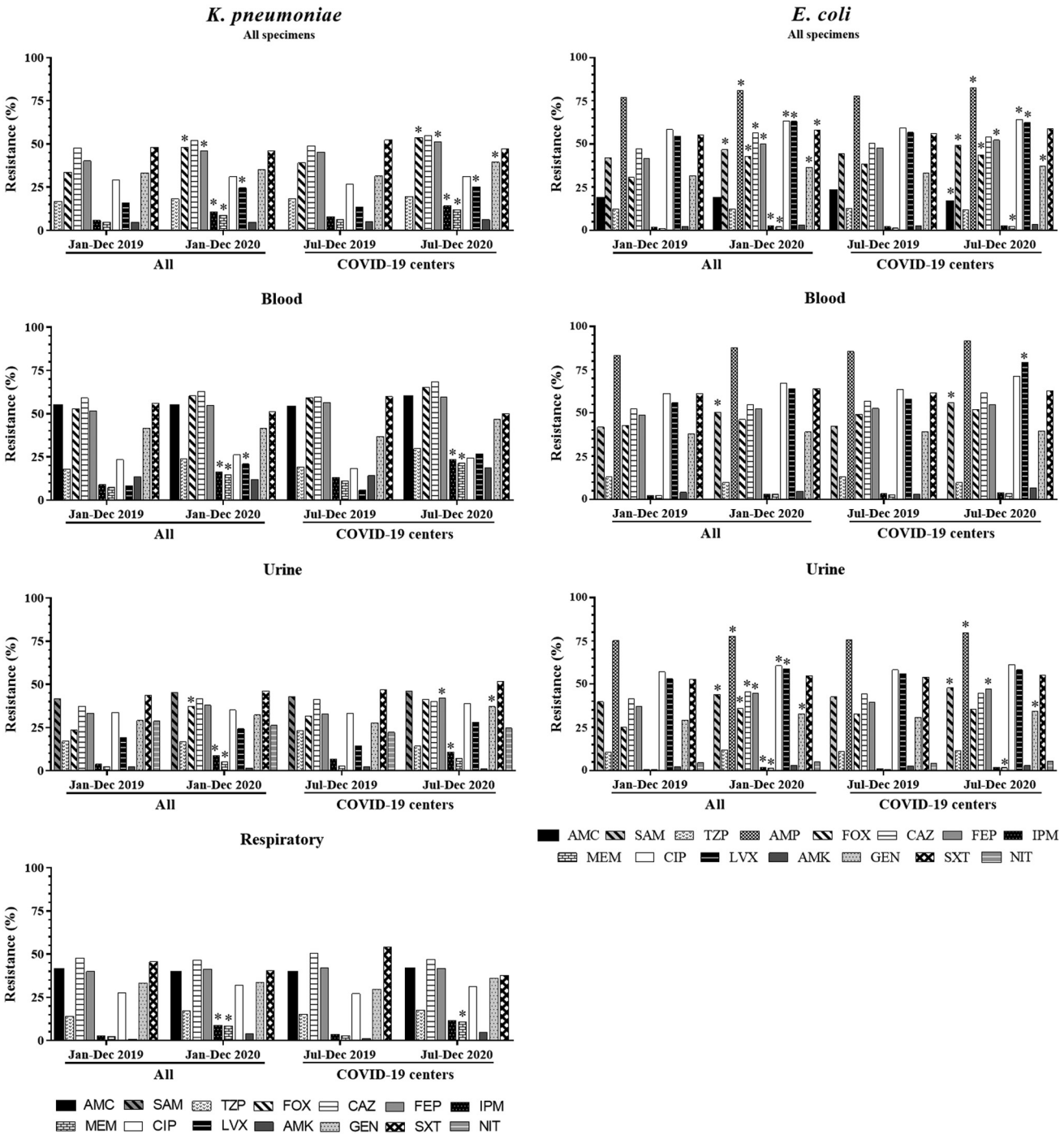

FIG. 2. *Klebsiella pneumoniae* and *Escherichia coli* strains isolated between 2019 and 2020. *Statistically significant *p*-value; AMK, amikacin; AMC, amoxicillin/clavulanic acid; SAM, ampicillin/sulbactam; FEP, cefepime; FOX, cefoxitin; CAZ, ceftazidime; CIP, ciprofloxacin; GEN, gentamicin; IMP, imipenem; LVX, levofloxacin; MEM, meropenem; NIT, nitrofurantoin; TZP, piperacillin/tazobactam; TOB, tobramycin; SXT, trimethoprim/sulfamethoxazole.

Furthermore, *P. aeruginosa* from all specimens increasing resistance rates were detected for piperacillin-tazobactam, cefepime, imipenem, meropenem, ciprofloxacin, and levofloxacin ($p \leq 0.01$). These trends continued with the COVID-19 centers analysis, and, additionally, a higher resistance rate was found for gentamicin ($p \leq 0.01$).

Isolates from respiratory samples showed increasing resistance of *P. aeruginosa* to piperacillin-tazobactam, cefepime, meropenem, and ciprofloxacin ($p \leq 0.016$). The second analysis additionally showed an increase in resistance to gentamicin ($p \leq 0.01$).

No significant trend was observed in isolates from blood samples. Urine isolates exhibited higher antibiotic resistance for piperacillin-tazobactam, cefepime, imipenem, meropenem, ciprofloxacin, and levofloxacin ($p \leq 0.016$); however, this trend was lost for levofloxacin and added for gentamicin when only COVID-19 centers were analyzed.

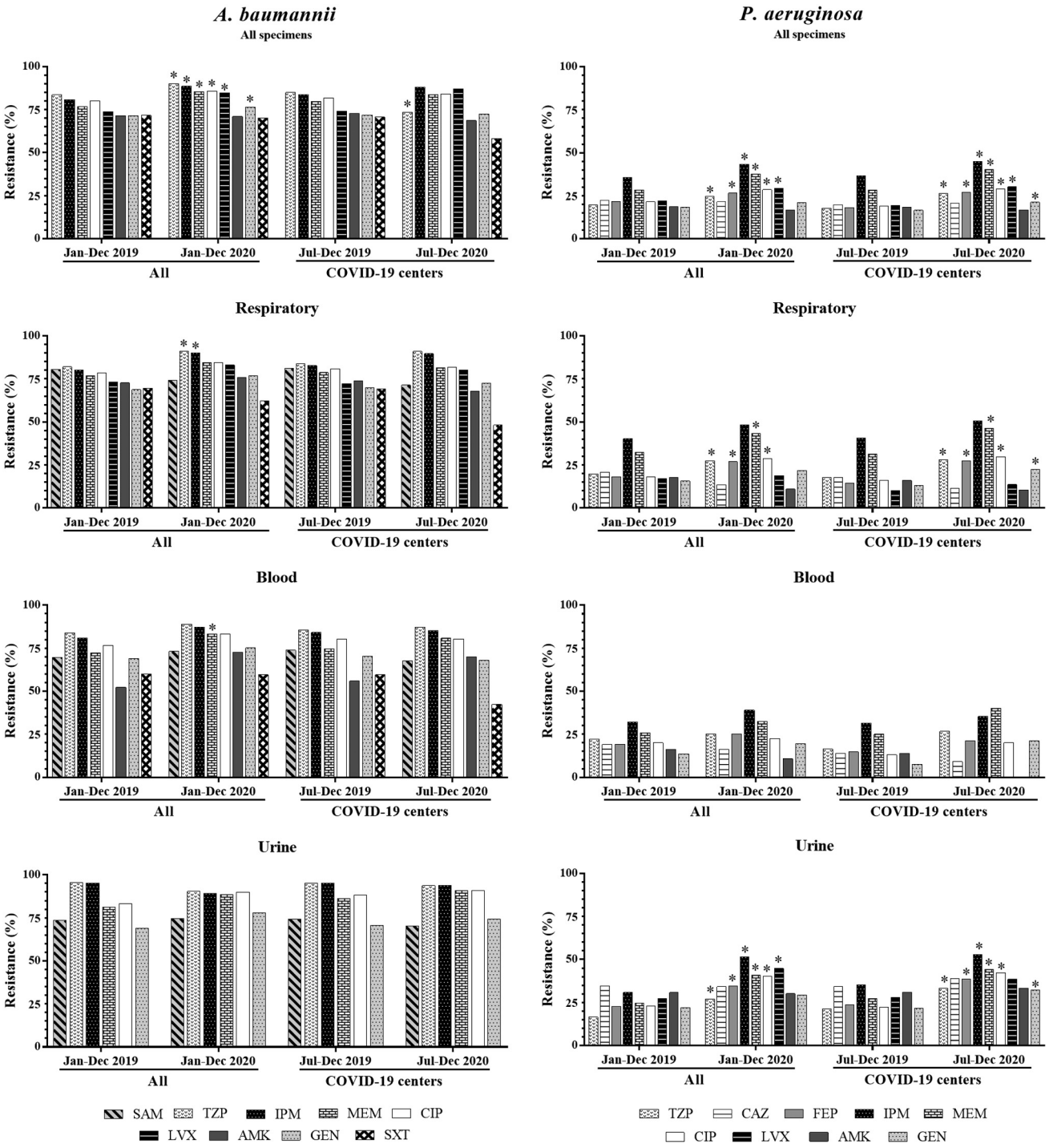

FIG. 3. Comparison of antimicrobial susceptibility profiles *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, isolated between 2019 and 2020.*Statistically significant *p*-value; AMK, amikacin; AMC, amoxicillin/clavulanic acid; SAM, ampicillin/sulbactam; FEP, cefepime; CAZ, ceftazidime; CIP, ciprofloxacin; GEN, gentamicin; IMP, imipenem; LVX, levofloxacin; MEM, meropenem; TZP, piperacillin/tazobactam; TOB, rifampicin; tobramycin; SXT, trimethoprim/sulfamethoxazole.

Discussion

The COVID-19 pandemic and the threat of bacterial co-infections have led to increased use of antibiotics and the potential increase in drug resistance. This study analyzed changes in antimicrobial resistance among some microorganisms during the COVID-19 pandemic. In *S. aureus* recovered from blood, we detected a significant increase in resistance to erythromycin (from 25.7% to 42.8%) and oxacillin (from 15.2% to 36.9%) when only COVID-19 centers were analyzed.

An increase in resistance to erythromycin was expected because azithromycin (another macrolide) has been widely prescribed for COVID-19. This antibiotic has shown weak

evidence of antiviral and immunomodulating effects[19] and has been reported that adding azithromycin to standard of care in patients with severe COVID-19 did not improve clinical outcomes.[20] Even with this low evidence, azithromycin was widely used in COVID-19 patients and our results suggest that this use may be associated with increased resistance to erythromycin in *S. aureus*. A steady decrease in erythromycin and oxacillin drug resistance was reported for *S. aureus* during the previous ten years (from 2009 to 2018).[21] Thus, our results reinforce the need to strengthen infection control measures to preserve advances that have been made in the control of antibiotic resistance.

Recently, a review of carbapenem-resistant *K. pneumoniae* infection in patients hospitalized for COVID-19 (11 studies, 6 countries: Italy, China, Egypt, United States, Spain, and Peru) showed that the prevalence of *K. pneumoniae* carbapenem resistance ranged from 0.35% to 53% and the predominantly associated genes were KPC, OXA-48, and NDM.[22] In our study, carbapenem resistance for *K. pneumoniae* blood isolates increased from 7.3% in 2019 to 14.6% in 2020; these figures worsen when we only considered COVID-19 centers, showing an increase from 11.2% to 21.4%. We have no data on the genes associated with this carbapenem resistance in the COVID-19 pandemic. However, according to a previous report from the INVIFAR network that included clinical isolates from January to March 2020, the $bla_{\text{NDM-type}}$ genes is the most frequent carbapenemase encoding gene in Mexico.[23]

Unrestricted use of broad-spectrum antibiotics in treating severe cases of COVID-19 has been reported, with an increase in carbapenem use during the first wave of the COVID-19 pandemic.[24,25] Unfortunately, we did not collect data from the COVID-19 period regarding carbapenem consumption; but a recent study that included 15 Mexican hospitals showed high consumption of cephalosporins, carbapenems, and vancomycin.[26] Thus, the increase in carbapenem resistance may be associated with the increased consumption of these antibiotics.

This study has some strengths: it represents 46 centers from Mexico, provides 2 different approaches (whole-year analysis and exclusive COVID-19 centers analysis) of a 2-year comparison of prepandemic and pandemic periods, including critical and high-priority microorganisms.

This study also has some limitations. For example, we have no information about the number of antimicrobials prescribed during the COVID-19 pandemic, the patient populations among participating centers are different, some antimicrobials were not evaluated in all cases, antimicrobial susceptibility profiles were not performed with the same methodology, and results with molecular techniques were not included.

The real impact of the COVID-19 pandemic on antimicrobial resistance is unknown. However, our results indicate that antimicrobial resistance has increased in Mexico during the period of the pandemic included in the study. This increase may be associated with inappropriate and excessive prescription of antibiotics and weakness in antimicrobial stewardship programs.

In conclusion, antimicrobial resistance increased in Mexico during the COVID-19 pandemic. The increase in oxacillin resistance for *S. aureus* and carbapenem resistance for *K. pneumoniae* recovered from blood specimens deserves special attention. In addition, an increase in erythromycin resistance in *S. aureus* was detected, which may be associated with high azithromycin use. In general, for *A. baumannii* and *P. aeruginosa*, increasing resistance rates were detected.

Disclosure Statement

No competing financial interests exist.

Funding Information

This research received no funding.

Supplementary Material

Supplementary Table S1
Supplementary File 1

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