Tracking Antibiotic Resistance Trends in Central Iran Amidst the COVID-19 Pandemic From 2021 to 2023: A Comprehensive Epidemiological Study

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Abstract

Background: The emergence of coronavirus disease in 2019 (COVID-19) appears to be having an impact on antibiotic resistance patterns. Specific circumstances during the COVID-19 era may have played a role in the spread of antimicrobial resistance (AMR). This study aimed to look at the changes in AMR patterns of *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii* at Al-Zahra Hospital.

Materials and Methods: From March 2021 to January 2023, 3651 clinical samples were collected from patients hospitalized at Isfahan's Al-Zahra Hospital. The Clinical and Laboratory Standards Institute recommended procedures for detecting gram-negative bacteria and assessing antibiotic susceptibility were used. We divided the information into three years.

Results: Highest resistance rates were seen in *A. baumannii* to Ciprofloxacin (98.0%) and Ampicillin-Sulbactam (97.0%). For *P. aeruginosa* the resistance rate for Ceftazidime (36.1), Levofloxacin (37.8), and Meropenem (47.1) dropped seriously in 2022.

Conclusion: During the second year of the pandemic in central Iran, all three species studied showed rising rates of AMR. This can be attributable to two peaks within Iran on May 6, 2021 and August 27, 2021. The results of this study show that *P. aeruginosa*, *K. pneumoniae*, and *A. baumannii* bacteria in central Iran have a higher level of antibiotic resistance than previously studied strains before the pandemic.

Keywords: *Acinetobacter baumannii,* antibiotic resistance, COVID-19 pandemic, *Klebsiella pneumoniae, Pseudomonas aeruginosa*

INTRODUCTION

The World Health Organization (WHO) declared the Coronavirus 2019 (COVID-19) pandemic on March 11, 2020. The SARS-2 virus, known as COVID-19, spread quickly from Wuhan City, China, to the rest of the world. As of early July 2021, about 547,901,157 COVID-19 cases and 6,339,899 fatalities had been formally reported.[1] Healthcare systems have swiftly modified their infection control procedures in response to the pandemic to ensure they have the city to isolate patients infected with the SARS-CoV-2 virus.[2] Society's attention to the threat posed by this emerging infectious disease has led to an increased understanding of the importance of personal hygiene, environmental contamination, and the use of personal protective equipment.[3]

Antibiotics do not treat COVID-19; however, they are frequently used in patients with respiratory illness due to initial diagnostic uncertainty and worry about bacterial co-infection or secondary infection in those who have confirmed COVID-19.

Antimicrobial resistance (AMR) develops when microorganisms—fungi, bacteria, viruses, and parasites—

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undergo heritable changes due to antimicrobial substances like antibiotics, antifungals, or antivirals. Despite receiving less attention than COVID-19, AMR is ranked among the top ten global health threats by the WHO and could have just as serious adverse effects.[4] The rise in nosocomial infections, also known as hospital-acquired infections (HAIs), is another issue connected to AMR. These infections occur hours after being admitted to a hospital or receiving medical care.[5]

Gram-negative bacteria are a major concern among frequently isolated HAIs, as they have a higher rate of associated complications. Additionally, studies have shown that these bacteria are becoming resistant to most available antibiotic drugs, which can create situations similar to the pre-antibiotic era.[6-8] The WHO identified several bacteria in 2017 that warranted special attention and called for the development of antibiotics. *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli* are a few gram-negative bacteria that should be given priority when creating new antimicrobial treatments because they pose the greatest threat to human health.[9,10]

K. pneumoniae poses a significant threat to human health, leading to a range of illnesses such as respiratory and urinary tract infections, bloodstream infections, and liver abscesses. Historically, bacterial infections have been categorized based on the source of infection, either as community-acquired or nosocomial infections. However, due to the increasing impact of healthcare-associated factors in community-onset infections, these have been further classified into community-onset healthcare-associated (HCA) infections for individuals with recent medical care exposure and community-acquired infections for those without.[11]

The predominant cause of nosocomial infections is *A. baumannii*, a gram-negative bacterium. The infections caused by this bacterium are varied and can range from hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) to urinary tract infections, meningitis, bacteremia, and gastrointestinal and skin/wound infections.[12]

Nosocomial infections are often caused by *P. aeruginosa*, which is an opportunistic pathogen that can negatively impact the health of individuals with compromised immune systems, such as those with diabetes, cancer, cystic fibrosis, advanced HIV infections (acquired immunodeficiency syndrome, AIDS), severely burned patients, and those who have undergone major surgeries.

The study aimed to identify any changes in the antibiotic resistance pattern of these bacteria (*K. pneumoniae*, *A. baumannii*, and *P. aeruginosa*) during the COVID-19 pandemic from March 2021 to January 2023. The data obtained from this study will provide valuable insights into the impact of the pandemic on AMR and help in developing effective strategies to combat AMR in healthcare settings.

MATERIALS AND METHODS

Patients and samples

Between March 1, 2021 and January 30, 2023, a cross-sectional study was conducted at Isfahan's Al-Zahra Hospital, which had been designated as a corona center following the pandemic. The study involved the collection of 3651 clinical samples, such as urine, blood, respiratory secretions, wounds, and other specimens from patients admitted to various hospital wards. The central laboratory received all the samples for analysis, but the study excluded multi-samples from the same individual or samples from patients with polymicrobial infection due to the cross-resistance phenomenon.

Sample identification

Standard microbiological techniques were used to process the samples in order to identify gram-negative bacteria. The strains of *P. aeruginosa*, *K. pneumoniae*, and *A. baumannii* were recognized and identified by means of conventional biochemical procedures and protocols. The samples underwent a 24-hour incubation period of 37°C while being cultured on blood agar and MacConkey agar medium. Routine biochemical tests were used to identify the strains, including urea urease, oxidase, citrate, triple sugar iron agar, malonate consumption, sugar oxidation and fermentation, Methyl Red motility, Voges-Proskauer, and indole production.

Antimicrobial susceptibility test

The isolates were tested for their susceptibility to a range of antibiotics, including Ampicillin, Ampicillin-Sulbactam, Amikacin, Piperacillin-Tazobactam, Cefazolin, Cefepime, Ceftriaxone, Cefoxitin, Ceftazidime, Levofloxacin, Meropenem, Co-trimoxazole, Ciprofloxacin, Cefotaxime, and Cefixime. The selection of these antibiotics was based on the Clinical and Laboratory Standards Institute (CLSI) 2020 guidelines. To ensure accuracy and specificity for each bacterium tested in the panel isolates, a specific antibiogram was considered based on the type of bacteria. This approach allowed for a comprehensive assessment of the susceptibility patterns of each bacterium to the different antibacterial drugs that were tested.[13]

Statistical analysis

In this study, the data collected was analyzed using SPSS software, version 26. For describing qualitative variables, frequency (percentage) was used. The age variable underwent normality testing using the Kolmogorov–Smirnov test, with the mean ± standard deviation (SD) being reported. The Chi-square or Fisher exact test was applied to compare qualitative variables. A significance level of $P < 0.05$ was deemed statistically significant, accompanied by a 95% confidence interval (CI). These statistical analyses aimed to uncover any notable relationships or disparities among variables in the study, allowing conclusions to be drawn from the findings.

RESULTS

Bacterial isolates

In this study, 3651 isolates were collected from 2008 (54.9%) females, 1550 (42.4%) males, and 98 (2.7%) of unknown gender admitted at Al-Zahra Hospital. Among 3651 bacterial isolates, 1641 (44.94%) were *K. pneumoniae* and 329 (9.01%) isolates were *P. aeruginosa*.

In addition, 1681 (46.04%) isolates were *A. baumannii*. The mean age of patients was 57.4 ± 8. The frequency of isolates based on hospital wards has been shown in Table 1.

Most isolates were taken from the general ICU (1757), internal part (457), and neurology surgery part (340). The samples were taken from blood, urea, feces, etc., using tools, e.g. blood catheters, urine catheters, etc.

Table 1: Frequency distribution of 3651 isolates based on hospital wards

Ward	Frequency	Percent	Cumulative Frequency
CCU	50	1.4	1.4
General ICU	1757	48.1	49.5
Internal ICU	84	2.3	51.8
NICU	52	1.4	53.2
Orthopedics	58	1.6	54.8
Pediatrics	20	0.5	55.4
Neurology	337	9.2	64.6
Urology	4	0.1	64.7
Transplant	14	0.4	65.1
Surgery	252	6.9	72.0
Neurology surgery	340	9.3	81.3
Cardiac surgery	56	1.5	82.8
General	134	3.7	86.5
Internal	457	12.5	99.0
Obstetrics and gynecology	36	1.0	100.0
Total	3651	100	

The results of the antibiogram using the agar disc diffusion method

The antibiotic resistance patterns of all isolates are presented in Table 2. For *A. baumannii*, the highest resistance was to Ciprofloxacin (98.0%) and Ampicillin-Sulbactam (97.0%). For *K. pneumoniae*, the highest resistance was to Ampicillin-Sulbactam (89.3%) and Ciprofloxacin (83.6%). For *P. aeruginosa*, the highest resistance was seen in Sulfamethoxazole/Trimethoprim (90.3%) and Levofloxacin (67.5%). The least antibiotic resistance in *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa* was seen in Sulfamethoxazole/Trimethoprim (85.4%), Amikacin (67.8%), and Amikacin (40.1%), respectively.

Results by years

The number of samples sent to the laboratory according to three years from 2021 to 2023 is shown in Table 3. In 2022, we had the highest isolations of *A. baumannii* (699), *K. pneumoniae* (626), and *P. aeruginosa* (119) ($P < 0.001$).

Antibiotic resistance patterns of these bacteria between 2021 and 2023 have been shown. Antibiotics selected for each bacterium were based on CLSI 2020.

There was no significant difference in Ciprofloxacin, Trimethoprim-Sulfamethoxazole, and Piperacillin-Tazobactam for *P. aeruginosa* ($P > 0.05$). For *P. aeruginosa*, the resistance rate to Amikacin (60.0%) and Ceftriaxone (68.6%) was higher in 2021 compared to the following two years ($P < 0.001$). On the other hand, the resistance rate for Ceftazidime (36.1), Levofloxacin (37.8), and Meropenem (47.1) dropped seriously in 2022 ($P \leq 0.001$) [Figure 1].

There was no meaningful difference between Trimethoprim-Sulfamethoxazole and Piperacillin-Tazobactam for *K. pneumoniae* ($P > 0.05$). For *K. pneumoniae*, the resistance rate to Ciprofloxacin (88.4%), Ceftazidime (84.7%), and Ampicillin-Sulbactam (93.6%) were remarkably higher in 2021 compared to the subsequent two years ($P \leq 0.001$). The

Table 2: Antibiotic resistance patterns of *K. pneumoniae, P. aeruginosa*, and *A. baumannii*

Species Percentage (number of isolates)	Antibiotic resistance patterns	AK	CAZ	CPM	CIP	LEV	MEM	SAM	SXT	TZP
A.baumannii	Resistant	89.5 (1504)	95.2 (1600)	95.7 (1609)	98.0 (1647)	95.4 (1604)	94.6 (1590)	97.0 (1630)	85.4 (1436)	95.1 (1599)
	Susceptible	10.5 (177)	4.8 (81)	4.3 (72)	2.0 (34)	4.6 (77)	5.4 (91)	3.0 (51)	14.6 (245)	4.9 (82)
K.pneumoniae	Resistant	67.8 (1113)	80.0 (1313)	79.7 (1308)	83.6 (1372)	77.5 (1271)	68.7 (1128)	89.3 (1466)	74.0 (1214)	75.9 (1246)
	Susceptible	32.2 (528)	20.0 (328)	20.3 (333)	16.4 (269)	22.5 (370)	31.3 (513)	10.7 (175)	26.0 (427)	24.1 (395)
P. aeruginosa	Resistant	40.1 (132)	49.5 (163)	54.1 (178)	47.7 (157)	67.5 (222)	61.4 (202)	-	90.3 (297)	57.8 (190)
	Susceptible	59.9 (197)	50.5 (166)	45.9 (151)	52.3 (172)	32.5 (107)	38.6 (127)	-	9.7 (32)	42.2 (139)

SAM (Ampicillin-Sulbactam), CPM (Cefepime), MEM (Meropenem), AK (Amikacin), CIP (Ciprofloxacin), LEV (Levofloxacin), SXT (Sulfamethoxazole/Trimethoprim), TZP (Piperacillin-tazobactam), and CAZ (Ceftazidime). *Samples that have not undergone antibiotic resistance testing are labeled with."–"
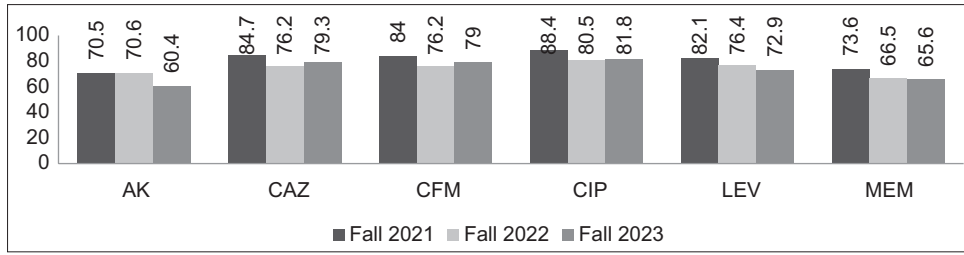
Figure 1: Antibiotic resistance patterns of *A. baumannii* between 2021 and 2023
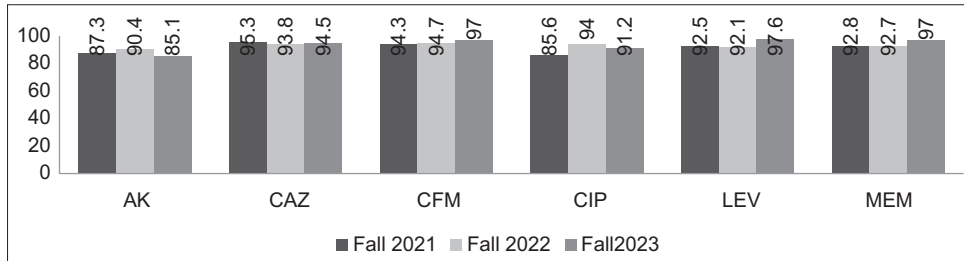

Figure 2: Antibiotic resistance patterns of *K. pneumoniae* between 2021 and 2023
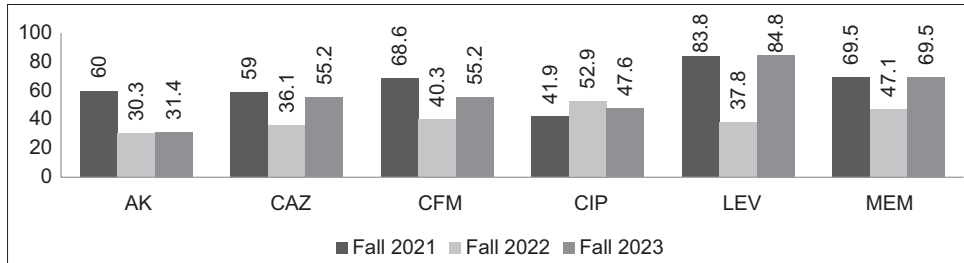

Figure 3: Antibiotic resistance patterns of *P. aeruginosa* between 2021 and 2023

resistance rate for Amikacin (60.4%) was relatively higher in 2023 ($P < 0.001$) [Figures 2 and 3].

Table 4 indicates the medication results of these bacteria between 2021 and 2023. Out of these three bacteria, *A. baumannii* not only had the highest number of isolates in this period of time (1681) but also had the highest number of deaths 505 (30.0%) compared to the other bacteria.

DISCUSSION

AMR is a global public health issue and has created a crisis where common antimicrobial medicines are less effective than before.[14] With the advent of the COVID-19 pandemic, AMR has been exacerbated and even neglected in some countries.[15,16] The increased use of antibiotics may explain concerns about bacterial co-infections and difficulty in distinguishing between COVID-19 and bacterial infections early in the pandemic, which led to an overall increase in AMR in some cases,[16] which explains why in most of these cases this increase was seen in the second year of the pandemic (2022), but there was a decrease in the third year of the pandemic. For example, in *A. baumannii*, there was a highly significant increase in Trimethoprim-Sulfamethoxazole (87.1%) and Ciprofloxacin (94.0%) resistance in 2022 compared to the other two years ($P < 0.001$).

Table 3: Frequency of samples sent to the laboratory based on years

Years	*A. baumannii*	*K. pneumoniae*	*P. aeruginosa*
2021	38.9 (654)	35.1 (576)	31.9 (105)
2022	41.6 (699)	38.1 (626)	36.2 (119)
2023	19.5 (328)	26.8 (439)	31.9 (105)

Table 4: Death and discharged percentage based on bacteria

Bacteria	Discharged	Death	Total
K. pneumoniae	1336 (81.4%)	292 (17.8%)	1641
A. baumannii	1157 (68.8%)	505 (30.0%)	1681
P. aeruginosa	274 (83.3%)	48 (14.6%)	329

With that in mind, there were instances where a reduced antibiotic resistance rate was observed, potentially limiting the capacity to gather more comprehensive data on the actual AMR shifts and increasing the likelihood of an undetected AMR pandemic.[17] For instance, in *K. pneumoniae* the highest resistance rate was reported in 2021 for Ceftazidime (84.7%), Ciprofloxacin (88.4%), and Ampicillin-Sulbactam (93.6%), which was highly significantly more than the next two years ($P < 0.001$).

In this study, it was found that *A. baumannii* not only had the highest number of isolates in the COVID-19 pandemic era but also had the highest number of deaths [505 (30.0%)] compared to the other bacteria. In a study performed by Boral J *et al.* in 2022, the rate of isolation of this bacterium in hospitals was assessed during the pre-COVID-19 and COVID-19 pandemic era. Based on this study, compared to the pre-pandemic period, the rate of *A. baumannii* infection during the pandemic was 1.90 times higher (odds ratio [OR]: 1.90, 95% CI: [1.197, 3.033]), although the case fatality rate of the pre-pandemic and pandemic era was not different statistically (83.33% vs. 81.48%, *P* = 0.835). This study found that the lack of high turnover of the janitorial staff and work overload might be the reason for this increase in these isolates.[18] Rangel K *et al.* (2021) assessed a study about the prevalence of *A. baumannii* in the hospitals of various countries during the pandemic. In this study, it was assessed that the pandemic could be the cause of immunocompromised patients. These patients are hospitalized, and since this bacterium is a nosocomial infection, there is a high chance that these people will more likely get secondary infections with *A. baumannii*. This can explain the high prevalence of these bacteria during the pandemic.[19] Li J *et al.* reported that among 159 strains of bacteria isolated from 102 hospitalized COVID-19 patients with acquired secondary bacterial infections in China, A. baumannii was the most common pathogen (35.8%; n = 57), followed by *K. pneumoniae* (30.8%; n = 49).[20]

During the initial days of SARS-CoV-2 infection, severely ill COVID-19 patients may experience pulmonary dysbiosis or disruption of the respiratory tract, which can progress into a secondary bacterial or fungal infection after several weeks.[21-23]

In a retrospective cohort study conducted in a UK secondary care setting, a significant proportion of COVID-19 patients (9 out of 14) in the ICUs were found to have secondary VAP.[24] Hughes S *et al.* pinpointed *A. baumannii* as the causative agent in a COVID-19 patient with VAP. This could account for the majority of the isolates in this study being obtained from the general ICU (48.1%).

In an observational study conducted at a University Hospital in Spain involving COVID-19 patients, 16% were found to have fungal or bacterial co-infections/superinfections. Multi-drug-resistant *A. baumannii* was the primary cause of respiratory infections and bacteremia, with an outbreak contributing to this outcome.[25] Chen N *et al.* (2020) also noted that bacterial and fungal co-infections in COVID-19 patients, including one case with a highly antibiotic-resistant *A. baumannii* infection, led to challenges in anti-infective treatment and an increased likelihood of septic shock.[26] In another study, researchers examined data from 212 critically ill COVID-19 patients at a public tertiary hospital dedicated to treating COVID-19 patients during the pandemic. They analyzed the relationship between fungal/bacterial co-infections and patient mortality. *A. baumannii* was the second most frequently isolated bacteria in patients with positive bacterial cultures and accounted for the third-highest mortality rate among COVID-19 patients.[27] AMR might be responsible for causing more COVID-19 deaths, as secondary bacterial infections can worsen the outcome of critical COVID-19 illness.[19] This might explain why most deaths in this study were related to *A. baumannii* 505 (30.0%) [Table 4].

Our research highlights the "dominance of *K. pneumoniae*" compared to *P. aeruginosa* in COVID-19 patients. The high frequency of *K. pneumoniae* isolation and its decreased susceptibility drugs such as Amikacin and Ciprofloxacin are concerning and require immediate action through effective infection control and antimicrobial stewardship interventions.[28] Following the Coronavirus pandemic, a notable surge in *K. pneumoniae*'s antibiotic resistance has been documented in a recent report written by Hamidi Hesari M *et al.*[29] The findings of the study indicate that while there were no unforeseen changes in the prevalence or category of infectious agents causing urinary tract infections, there was a marked increase in *Klebsiella* sp. isolates' resistance to three antibiotics, namely Ceftriaxone, Imipenem, and Gentamicin. This phenomenon may have arisen as a result of the administration of antibiotics for preventative and therapeutic purposes among SARS-CoV-2 patients during this brief period. In line with our results, Karimi K *et al.* performed a research on antibiotic resistance and biofilm formation in clinical isolates of *K. pneumoniae* in 2021. It showed that the prevalence of resistance to SAM, AK, LEV, SXT, and CAZ was 87, 67, 85, 73, 78%, respectively, in *K. pneumoniae* clinical isolates.[30] We have figured out the same resistance rate.

In this study, it was found that, in general, the number of *A.baumannii* isolates that were resistant to different antibiotics was more than other bacteria. Various studies have shown that these bacteria, in general, are highly resistant to antibiotics in Iran, even pre-covid pandemic. For example, a study performed by Fazeli *et al.* in 2014 in a teaching hospital in Isfahan showed multi-drug resistance in all of the *A. baumannii* isolates and a high amount of drug resistance in these bacteria. In this study which was a pre-pandemic era, the resistance toward Ceftriaxone (100%), Ciprofloxacin (100%), Meropenem (100%), and Trimethoprim-Sulfamethoxazole (99.2%) was higher compared to this study according to Table 2. This might indicate an AMR silent pandemic. That being said, the resistance toward Amikacin (87.6%) and Ampicillin-Sulbactam (33.9%) was lower than this study in the pandemic era (89.5% and 97.0% for Amikacin and Ampicillin-Sulbactam, respectively).[28] In a similar study performed by Azizi M *et al.* in the west of Iran in 2017 (pre-pandemic era), the resistance rate toward Ampicillin-Sulbactam was 52.5% which was still lower than this study.[31]

In a study performed by Azimi T *et al.* in a children's hospital in Iran, the resistance profile toward gram-negative bacteria, including *P. aeruginosa* was evaluated from 2013 to 2018. The resistance rate toward Amikacin (23.7%),

Piperacillin-tazobactam (60.5%), Levofloxacin (8.0%), Ciprofloxacin (17.8%), Ceftriaxone (89.7%), Meropenem (78.9%), and Ceftazidime (55.8%) was reported and based on Table 2 in this study, the resistance rate toward all of the antibiotics have decrease except since then except for Amikacin, Levofloxacin, and Ciprofloxacin. In the study performed by Azimi T *et al.*, it is reported that Levofloxacin has the highest effect against *P. aeruginosa* whereas, in this study, the resistance rate toward this antibiotic has increased significantly and among the antibiotics that were tested on this bacterium, Amikacin showed the lowest resistance.[32]

In this study, it was found that the highest resistance rate in *P. aeruginosa* is toward Trimethoprim-Sulfamethoxazole (90.0%). A recent study reported that *P. aeruginosa* isolated from COVID-19 patients showed 100% resistance to Trimethoprim-Sulfamethoxazole.[33] Even before the COVID era, this bacterium had high resistance to Trimethoprim-Sulfamethoxazole. In a study performed by Silva A *et al.* in 2022, the resistance rate to trimethoprim-sulfamethoxazole was 97.0%. *P. aeruginosa* is highly resistant to Trimethoprim Sulfamethoxazole since the proteins in these bacteria are too small to let this antibiotic enter the cell.[34]

CONCLUSION

This study highlights the alarming increase in antibiotic resistance among strains of *P. aeruginosa*, *K. pneumoniae*, and *A. baumannii* during the second year of the pandemic (2021). Notably, two distinct peaks were observed on May 6, 2021 and August 27, 2021. These findings underscore the urgent need for proactive measures to address the growing threat of antibiotic resistance, such as implementing antimicrobial stewardship programs, promoting infection prevention and control practices, and fostering research and development of novel antimicrobial agents. By taking decisive action now, we can mitigate the impact of antibiotic resistance and ensure the continued effectiveness of antibiotics in treating infectious diseases, both during the pandemic and beyond. It is imperative that healthcare providers, researchers, policymakers, and the public work collaboratively to combat this global health challenge and safeguard the future of healthcare.

Conflicts of interest

The authors declare that they have no conflict of interest.

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