Coronavirus Pandemic

Antimicrobial resistance evolution over time during pre-and post-COVID-19 periods at a major tertiary care center in Lebanon

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Abstract

Introduction: The increasing rates of AMR have been tolling the healthcare systems globally. This study aims to explore the evolution of AMR patterns against commonly encountered clinical bacterial pathogens at a major tertiary care center in Lebanon during pre-COVID (2019) and post-COVID (2023) periods.

Methodology: Consecutive non-duplicate isolates of Gram-positive (e.g., *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus* spp.) and Gram-negative pathogens (e.g., *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*) were analyzed using MALDI-TOF identification and CLSI-standardized disk diffusion/Etest methods.

Results: Key findings revealed persistent methicillin-resistant *S. aureus* (MRSA) rates (36%), increased vancomycin-resistant Enterococci (VRE; 7% to 10%), and high penicillin susceptibility among *S. pneumoniae*. Gram-negative isolates exhibited concerning trends: ESBL prevalence rose in *E. coli* (32% to 36%) but remained stable (35% to 34%) in *K. pneumoniae*. Carbapenem-resistant *Enterobacterales* (CRE) rates remained unchanged for *E. coli* (6% to 5%) but declined for *K. pneumoniae* (15% to 6%). *A. baumannii* susceptibility remained critically low (18–55%), while *P. aeruginosa* showed stable susceptibility (76–92%).

Conclusions: An overall increase in the resistance profiles among different bacterial species is noted in comparison with earlier studies from this institution. These findings align with prior multidrug-resistant strains and underscore the need for robust surveillance, antibiotic stewardship, and infection control measures.

Key words: Antimicrobial resistance; Lebanon; gram-negative; gram-positive; surveillance; COVID-19.

Introduction

The ongoing local and global surge of antimicrobial resistance (AMR), despite the ongoing efforts to control it, has been substantially inflicting a heavy burden of morbidity and mortality as well as incurring an unbearable financial toll on the medical and health systems in various aspects [1-3]. Lebanon, like many other countries, has also been suffering from this seriously escalating AMR global health challenge [4,5]. At our medical center, the increasing prevalence rates of critical pathogens have also been observed (Figure 1). To help face such prominent maladies, it is essential to understand the evolution of antimicrobial resistance (AMR) to help limit the emergence of bacterial strains with no drugs to treat [6,7]. To facilitate the control of the AMR challenge, surveillance and antimicrobial profiling should be the fundamental responsibility of the clinical microbiology laboratory [8].

In this regard, our clinical microbiology laboratory has long been actively involved in conducting and publishing several studies as part of these endeavors [4,9-11].

To follow up on the crucial AMR evolution, it was warranted to conduct this study to reveal the AMR patterns and trends during two periods: pre-COVID (2019) and post-COVID (2023), covering the most encountered bacterial pathogens at our clinical microbiology laboratory. For further references on this topic, the study highlights relevant articles published on bacterial antimicrobial resistance from our institution during this period.

Methodology

Bacterial isolates

This study analyzed consecutive non-duplicate Gram-positive and Gram-negative bacterial isolates of commonly recovered pathogens, implicated as possible infectious etiologies, from clinical specimens submitted for culture testing at the Clinical Microbiology Laboratory, Department of Pathology and Laboratory Medicine, American University of Beirut Medical Center (AUBMC), accredited by the College of American Pathologists since 2004. The included isolates covered two periods, at a span of 5 years: the pre-COVID period from July 1, 2018, to June 30, 2019 (thereafter called 2019 isolates), and the post-COVID

period from July 1, 2022, to June 30, 2023 (thereafter called 2023 isolates).

The source of these isolates encompassed different specimens, including blood, respiratory, urine, body screen, wound/pus/abscess, and other fluids.

Identification of the isolates was done by using the matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF) using the MALDI-biotyper software (Bruker Daltonics, Bremen, Germany).

The bacterial species under investigation in 2019 and 2023 included: *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes* (group A strep or GAS); *Streptococcus agalactiae* (group B strep or GBS); coagulase-negative staphylococci (CNS); *Enterococcus* spp; *Haemophilus influenzae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*; *Escherichia coli* and *Klebsiella pneumoniae*.

Antimicrobial susceptibility testing

The disk diffusion (DD) antimicrobial susceptibility testing was done using commercial disks (BBL, Becton Dickinson, USA) and interpreted according to the annually updated CLSI published standards [12].

To screen for carbapenemase producers, ertapenem disks (10 µg) were used. The isolates showing < 25 mm zone of inhibition were then assessed by Etest to confirm the MICs of ertapenem, imipenem, and meropenem.

The minimal inhibitory concentrations (MICs) of ertapenem, imipenem, and meropenem were determined using the Etest methodology (AB BIODISK, Solna, Sweden) according to the manufacturer's guidelines, as was reported earlier [13]. The span of MIC levels on these strips ranges between ≤ 0.025 and ≥ 32 µg/mL. Testing and interpretation of results (as susceptible, intermediate, and resistant) were based on standard breakpoints published by CLSI and

Figure 1. Prevalence rates of critical pathogens.
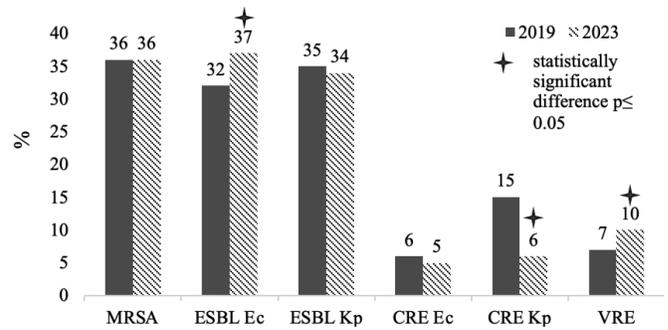
MRSA: Methicillin-resistant *Staphylococcus aureus*; ESBL: Extended-Spectrum Beta-Lactamase; CRE: Carbapenem-resistant Enterobacterales; VRE: Vancomycin Resistant *Enterococci*; Ec: *Escherichia coli*; Kp: *Klebsiella pneumoniae*.

updated annually [12].

Quality control

The American Type Culture Collection (ATCC) quality control strains of *E. coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853) were used to ensure correct performance of the Etest and disk diffusion methods. The quality control reference strains for colistin [CDC *E. coli* reference strains MCR-1 (AR-Bank # 0349, specified colistin MIC of 2-4 µg/mL) and MCR-1 (AR-Bank # 0346, specified colistin MIC of 4 µg/mL)] were also used to ensure the quality of testing.

Statistical analysis

Statistical analysis was carried out using the IBM SPSS Statistics version 29.0 to determine the *p* value, considering a value of ≤ 0.05 as statistically significant.

Results and discussion

The results of the antimicrobial susceptibility findings will be presented in tabulation form showing the relevant different antimicrobials reported during the two study periods (2019 and 2023). In addition to discussing the current findings, a brief highlight of published studies conducted at AUBMC during the same study period, as it relates to our topic, will be

Table 1. Antimicrobial susceptibility of S. aureus and Coagulase Negative Staphylococci (CNS).

Antimicrobial Agents	% susceptible in year			
	S. aureus		(CNS)	
	2019 (n = 646)	2023 (n = 639)	2019 (n = 1279)	2023 (n = 993)
Oxacillin	64	64	38	56*
Erythromycin	76	77	30	38*
Clindamycin	78	83*	57	65*
Levofloxacin	77	80	48	58*
Trimeth/sulfa†	94	98*	62	72*
Nitrofurantoin	100	100	100	100
Vancomycin	100	100	100	100
MRSA^prevalence (%)	**36**	**36**	**62**	**44***

*Indicates statistically significant difference *p* ≤ 0.05, while numbers with no asterisk marking refers to values that show no significant difference. †Trimeth/Sulf: Trimethoprim/ Sulfamethoxazole. ^ MRSA: Methicillin resistant *S. aureus*.

provided. Noting that other studies on the relevant pathogens conducted between 2012 and 2018 will be excluded. In this context, our results' presentation and discussion will start with the Gram-positive pathogens, followed by the Gram-negative ones.

Staphylococcus aureus and coagulase-negative staphylococci (CNS)

The prevalence of MRSA remained unchanged from 2019 to 2023 at 36%, which was greater than the rates reported in 2006 and 2009 (20% and 29%, respectively). In this period, no VISA or VRSA were recovered. A minor increase in the percentage of susceptibility to erythromycin has been observed, whereby it was 76% in 2019 compared to 77% in 2023. As for clindamycin, levofloxacin, and trimethoprim/sulfamethoxazole, an increase in the percent of susceptibility was noticed from 2019 to 2023: 78% to 83%, 77% to 80%, and 94% to 98%, respectively. However, for nitrofurantoin and vancomycin, the percentage of susceptibility remained uniform at 100% (Table 1).

Streptococcus pneumoniae

Generally, the antimicrobial susceptibility of the tested drugs for this pathogen showed fluctuating patterns during the two studied periods. *S. pneumoniae* showed high susceptibility to penicillin by MIC testing (Table 2). Vancomycin and levofloxacin were the most susceptible ($\geq$ 95%). As for erythromycin, clindamycin, and SXT, their susceptibility rates at the two tested periods were generally low (58% to 75%). A previously published study conducted on this pathogen at our center during this study period confirmed this resistance phenotype [4]. Lately, two studies were conducted.

The first study addressed the emergence of invasive *S. pneumoniae* serotype 24F in Lebanon. This serotype showed high virulence and AMR due to changes in penicillin-binding protein, and the presence of macrolide and tetracycline resistance genes [14].

The second study was a nationwide surveillance assessing the impact of vaccination on the burden of invasive pneumococcal disease in Lebanon. It highlighted the importance of vaccines in minimizing

Table 2. Antimicrobial susceptibility of *S. pneumonaie*.

Antimicrobials / Test method	% Susceptible in year	
	2019 (n = 83)	2023 (n = 91)
Disk diffusion Penicillin$^\infty$	46	35*
Oxacillin	46	35*
Erythromycin	58	62*
Clindamycin	70	75*
Ciprofloxacin/ Levofloxacin	100	95*
Trimeth/Sulfa†	67	65
Vancomycin	100	100
$^\infty$MIC $_{90}$ (μg/mL)	2019	2023
Penicillin	1 (0.012-1)	1.5 (0.016-1.5)
Ceftriaxone	0.38 (0.008-0.75)	0.38 (0.006-0.5)

*Indicates statistically significant difference $p \leq 0.05$, while numbers with no asterisk marking refer to values that show no significant difference. †Trimeth/Sulf: Trimethoprim/ Sulfamethoxazole.

Table 3. Antimicrobial susceptibility of *Enterococcus* spp.

Antimicrobials	% Susceptible in year	
	2019 (n = 960)	2023 (n = 835)
Nitrofurantoin	97	92*
Teicoplanin	95	90*
Vancomycin	93	90
Ciprofloacin	55	51
Tetracyclin	14	16
Ampicillin	78	78
Erythromycin	15	17
VRE$^\pm$ prevalence (%)	7*	10*

*Indicates statistically significant difference $p \leq 0.05$, while numbers with no asterisk marking refers to values that show no significant difference. $^\pm$VRE: Vancomycin Resistant Enterococci.

AMR resistance to penicillin, erythromycin, and clindamycin [15].

Enterococcus spp.

Generally, the *Enterococcus* species showed no significant or minor change in susceptibilities for the tested antimicrobial agents from 2019 to 2023. Regarding VRE, an increase in prevalence from 7% in 2019 to 10% in 2023 was observed (Table 3).

Streptococcus pyogenes (group A strep or GAS)

S. pyogenes showed stable high susceptibility for penicillin (100%) and erythromycin (86%), and close susceptibility for clindamycin (84% vs 87%) in 2019 and 2023, respectively (Table 4).

Streptococcus agalactiae (group B strep or GBS)

S. agalactiae maintained stable high susceptibility to penicillin (100%) while decreasing trends were observed for the susceptibility to erythromycin (68% to

Table 4. Antimicrobial susceptibility of *S. pyogenes* and *S. agalactiae*.

Antimicrobials	% Susceptible in year			
	S. pyogenes		*S. agalactiae*	
	2019 (n = 104)	2023 (n = 174)	2019 (n = 343)	2023 (n = 351)
Penicillin	100	100	100	100
Erythromycin	86	86	68	54*
Clindamycin	84	87	68	55*

*Indicates statistically significant difference $p \leq 0.05$, while numbers with no asterisk marking refers to values that show no significant difference. $^\infty$NT; not tested by disc diffusion as it requires MIC testing.

54%) and clindamycin (68% to 55%) from 2019 and 2023 (Table 4).

H. influenzae

During the years 2019 and 2023, *H. influenzae* showed stable high susceptibility to amoxicillin/clavulanate (97%). As for the other antimicrobials, an unchanging/ persistent stable susceptibility profile was noticed: ampicillin (82% vs 80%), cefuroxime (90% vs 86%), levofloxacin (92% vs 97%). As for SXT, the percent susceptibility significantly increased in 2023 compared to 2019 (76% vs 56%). No BLNAR strains were detected during these study periods (Table 5).

Acinetobacter spp.

These bacteria are major nosocomial pathogens worldwide and are intrinsically resistant to numerous drugs. They constitute a serious threat to hospitals due to the increasing prevalence of infections caused by multidrug-resistant (MDR) isolates worldwide [16].

In our study, and along with the global resistance trend, *Acinetobacter baumanni* showed a very low percent susceptibility to antimicrobials over the years, as shown in 2019 (ranging between 18% and 25%) and 2023 (ranging between 44% to 55%) (Table 6).

The decreasing resistance among the *Acenietobacter baumanii* in the post-COVID era is a surprisingly interesting finding, as one would have anticipated an increase in its AMR along with the international reports. Though the exact explanation for this decrease in AMR results remains to be revealed, it is suggested that the admissions to intensive care units (ICUs) due to COVID-19 may have used more targeted antibiotics to non-*Acinetobacter* pathogens, better infection control measures, more vigilant antimicrobial stewardship, and the potential decrease in overall infection rates due to quarantine measures and reduced social contact.

Pseudomonas aeruginosa

Generally, comparable susceptibilities against the eight tested antimicrobials were observed during the two study periods. These susceptibilities ranged between 77% and 92% for the year 2019, and 76% and 92% for the year 2023 (Table 7).

During our study periods, a newly introduced antibiotic was used: ceftolozane/ tazobactam (C/T), which warranted our investigation of it in two studies against Gram-negative bacteria.

The first study addressed the activity of C/T against Gram-negative bacteria in Lebanon. For *P. aeruginosa*

isolates, C/T demonstrated significantly greater activity against non-MDR strains (with a low MIC_{90} of 3 μg/mL and 96% susceptibility), compared to MDR strains, which exhibited a high MIC_{90} (≥ 256 μg/mL) and only 42% susceptibility [17].

The second study addressed the genomic characterization of C/T MDR *P. aeruginosa* clinical isolates using whole-genome sequencing to reveal antimicrobial resistance determinants and their genetic context [11].

Another study on this pathogen addressed molecular characterization and differential effects of levofloxacin and ciprofloxacin on the potential for developing quinolone resistance among clinical *P. aeruginosa* isolates. It showed that levofloxacin required fewer passages to reach its breakpoints in 10 isolates and the same number of passages in 9 isolates as compared to ciprofloxacin [18]

Table 5. Antimicrobial susceptibility of *H. influenzae.*

Antimicrobials	% Susceptible in year	
	2019 (n = 119)	2023 (n = 153)
Trimeth/Sulfa[†]	56	76*
Ampicillin	82	80
Amoxicillin/clavulanate	97	97
Cefuroxime	90	86
Levofloxacin	92	97

*Indicates statistically significant difference $p \leq 0.05$, while numbers with no asterisk marking refer to values that show no significant difference. [†]Trimeth/Sulf: Trimethoprim/ Sulfamethoxazole.

Table 6. Antimicrobial susceptibility of *Acinetobacter baumannii.*

Antimicrobials	% Susceptible in year	
	2019 (n = 463)	2023 (n = 446)
Cefepime	18	48*
Ceftazidime	20	45*
Piperacillin/Tazobactam	22	44*
Imipenem	24	48*
Ciprofloxacin	22	46*
Amikacin	25	51*
Gentamicin	24	49*
Trimeth/Sulfa[†]	25	55*

*Indicates statistically significant difference $p \leq 0.05$, while numbers with no asterisk marking refer to values that show no significant difference. [†]Trimeth/Sulf: Trimethoprim/ Sulfamethoxazole. Aztreonam was not listed as it is not tested by disc diffusion.

Table 7. Antimicrobial susceptibility of *P. aeruginosa.*

Antimicrobials	% Susceptible in year	
	2019 (n = 1077)	2023 (n = 1256)
Piperacillin/Tazobactam	80	85*
Gentamicin	85	92*
Aztreonam	80	80
Cefepime	92	88
Ceftazidime	85	86
Imipenem	77	76
Ciprofloxacin	78	78
Amikacin	90	90

*Indicates statistically significant difference $p \leq 0.05$, while numbers with no asterisk marking refer to values that show no significant difference.

E. coli and Klebsiella pneumoniae

E. coli and *K. pneumoniae* are the two most recovered Gram-negative species from clinical specimens. Regarding *E. coli* and *K. pneumoniae*, no consistent antimicrobial susceptibility trends could be delineated among the different tested antimicrobial agents (AMA) between 2019 and 2023, as shown in Tables 8 and 9. For example, a significant increase in susceptibility was noted against the penicillin group, amoxicillin clavulanic acid, cefixime, cefotaxime, gentamicin, and SXT for both *E. coli* and *K. pneumoniae* in 2023 compared to 2019. A significant decrease in antimicrobial susceptibility (AMS) was observed among both species for ciprofloxacin. However, regarding the other AMA, different changes of either increase, decrease, or no change were observed.

Concerning the prevalence of ESBLs and CRE, the percentages for ESBL were increased for *E. coli* but remained the same for *K. pneumoniae*, while the percentages for CRE remained almost the same for *E. coli* but showed a significant decrease for *K. pneumoniae* between the two study periods.

In view of the preponderance of these pathogens, their evolving challenges of antimicrobial resistance, and their significant morbidity and mortality, most of our studies addressed these pathogens over time. Before the current study period and since 2008, 10 publications have been conducted at our medical center to tackle the antimicrobial resistance in Enterobacterales with a focus on molecular characterization. These studies were cited in the article entitled "antimicrobial agents active against carbapenem-resistant *Escherichia coli* and *Klebsiella pneumoniae* isolates in Lebanon" [9].

Due to the fluctuating increase in AMR among the Gram-negative pathogens (particularly *E. coli* and *K. pneumoniae*) at our medical center, the focus of research, between 2018 and 2024, was directed toward the molecular characterization of these pathogens. Several aspects of the molecular features of these pathogens were addressed, including the characterization of OXA genes, exploring resistance mechanisms, and treatment efficacy in CR bacteria with emphasis on plasmid-mediated resistance and emerging drug resistance. In addition, the genomic characterization of MDR *Enterobacter* spp. and *K. aerogenes*, as well as the mechanisms of metallo-beta-lactamases, were addressed, highlighting the importance of infection control and antimicrobial stewardship programs [19-28].

For relevance, our current study is compared to what was reported globally during the same study period in a systematic review and meta-analysis by Langford *et al.* [29]. Their search was conducted in December 2021 in the WHO COVID-19 Research Database, looking for studies evaluating the impact of COVID-19 on AMR. Of 6036 studies screened, 28 were included, and 23 provided sufficient data for meta-analysis. A non-statistically significant increase was noted for resistant Gram-negative organisms (i.e., extended-spectrum beta-lactamase, carbapenem-resistant Enterobacterales, carbapenem or multi-drug resistant, or carbapenem-resistant *Pseudomonas aeruginosa* or *Acinetobacter baumannii*. They reported a considerable heterogeneity in both the AMR metrics

Table 8. Antimicrobial susceptibility of *E. coli*.

Antimicrobials	% Susceptible in year	
	2019 (n = 4938)	2023 (n = 2912)
Ampicillin	23	31*
Amoxicillin/Clavulanate	60	66*
Aztreonam	65	58*
Cefixime	52	60*
Cefuroxime	50	39*
Cefotaxime	53	58*
Ceftazidime	65	58*
Ciprofloxacin	52	48*
Gentamicin	80	85*
Trimet/Sulfa[†]	50	56*
Amikacin	99	98
Cefepime	65	63
Cefoxitin	80	82
Piperacillin/Tazobactam	85	85
Imipenem	95	95
Nitrofurantoin	97	96
ESBL prevalence[δ] (%)	32	37*
CRE prevalence[ӿ] (%)	6	5

*Indicates statistically significant difference $p \leq 0.05$, while numbers with no asterisk marking refers to values that show no significant difference. [†]Trimet/Sulf: Trimethoprim/ Sulfamethoxazole. [δ]ESBL: extended spectrum beta-lactamase. [ӿ]CRE: Carbapenem-Resistant *Enterobacterales*

Table 9. Antimicrobial susceptibility of *K. pneumoniae*.

Antimicrobials	% Susceptible in year	
	2019 (n = 1681)	2023 (n = 1365)
Amoxicillin/Clavulanate	55	67*
Cefepime	60	68*
Cefixime	58	62*
Cefotaxime	50	60*
Ceftazidime	55	60*
Imipenem	86	94*
Ciprofloxacin	70	58*
Amikacin	90	97*
Gentamicin	75	86*
Trimeth/Sulfa[†]	50	62*
Nitrofurantoin	55	65*
Aztreonam	60	60
Cefoxitin	79	82
Cefuroxime	48	46
Piperacillin/Tazobactam	75	78
ESBL prevalence[δ] (%)	35	34
CRE prevalence[ӿ] (%)	15	6*

* Indicates statistically significant difference $p \leq 0.05$, while numbers with no asterisk marking refer to values that show no significant difference. [†]Trimeth/Sulf: Trimethoprim/ Sulfamethoxazole. [δ]ESBL: extended spectrum beta-lactamase. [ӿ]CRE: Carbapenem-Resistant *Enterobacterales*.

used and the rate of resistance reported across studies.

Their findings reinforce the need for strengthened infection prevention, antimicrobial stewardship, and AMR surveillance and antimicrobial test standardization in the context of the COVID-19 pandemic.

In our current study, bacterial isolates at AUBMC showed high rates of AMR in some and fluctuating rates in others. The overall resistance trends highlighted in this study turned out to be higher than what was reported earlier from the same Clinical Microbiology Laboratory at this institution [9].

Conclusions

Antimicrobial-resistant organisms are almost always associated with increased attributable mortality, prolonged hospital stay, and excess costs. Bacterial isolates from Lebanon, herein represented by data from AUBMC, showed high rates of AMR in some and fluctuating rates in others. The resistance trends highlighted in this study turned out to be higher than what was reported earlier by this institution. Knowledge about the local antimicrobial susceptibility patterns is needed to guide empirical therapy for the various infections encountered in the community as well as in hospital settings, especially the life-threatening ones. To help control infection, guide empirical antibiotic therapy, and prevent any continuation of misuse of AMA, causing the alarming rising rates in antimicrobial resistance, several interventional measures should be disseminated, promoted, implemented, and maintained. These include providing a guide to empirical antibiotic therapy, implementation of antibiotic usage policy, monitoring and surveillance of antibiotic resistance, hand hygiene with other infection control measures, and antibiotic stewardship that ensures appropriate use of antimicrobial agents.

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Conflict of interest
No conflict of interest is declared.

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