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Coronavirus Pandemic

Pre- and post-COVID-19 antimicrobial resistance profile of bacterial pathogens, a comparative study in a tertiary hospital

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Abstract

Introduction: Antimicrobial resistance (AMR) is a natural evolutionary process in bacteria that is accelerated by selection pressure from the frequent and irrational use of antimicrobial drugs. This study aimed to determine the variations in AMR patterns of priority bacterial pathogens at a tertiary care hospital in the Gaza Strip during pre- and post-COVID-19 pandemic.

Methodology: This is a retrospective observational study to determine the AMR patterns of bacterial pathogens at a tertiary hospital in the Gaza Strip in the post-COVID-19 pandemic period compared to the pre-COVID-19 period. Positive-bacterial culture data of 2039 samples from pre-COVID-19 period and 1827 samples from post-COVID-19 period were obtained from microbiology laboratory records. These data were analysed and compared by Chi square test using Statistical Package for Social Sciences (SPSS) Program.

Results: Gram-positive and Gram-negative bacterial pathogens were isolated. *Escherichia coli* was the most prevalent in both study periods. The overall AMR rate was high. There was a statistically significant increase in resistance to cloxacillin, erythromycin, cephalexin, co-trimoxazole and amoxicillin/clavulanic acid in the post-COVID-19 period compared to pre-COVID-19 period. There was also a significant decrease in resistance to cefuroxime, cefotaxime, gentamicin, doxycycline, rifampicin, vancomycin and meropenem in the post-COVID-19 period.

Conclusions: During the COVID-19 pandemic, the AMR rates of restricted and noncommunity-used antimicrobials declined. However, there was an increase in AMR to antimicrobials used without medical prescription. Therefore, restriction on the sale of antimicrobial drugs by community pharmacies without a prescription, hospital antimicrobial stewardship and awareness about the dangers of extensive use of antibiotics are recommended.

Key words: antimicrobials; bacteria; COVID-19; pandemic; resistance.

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Introduction

Antimicrobial resistance (AMR) is one of the leading public health concerns, especially in developing countries where a higher incidence of improper use of antimicrobial drugs and AMR exists [1]. Most antimicrobial drugs in developing countries, particularly in Gaza, are available to be given by the community pharmacist without a prescription and are subject to a lack of regulation [2]. An article in 2021 reviewed all studies published over a period of 20 years and reported widespread multi-drug resistance among bacterial pathogens recovered from clinical specimens and the hospital environment in the Gaza Strip, Palestine [3]. That makes infectious diseases more challenging to treat and increases the risk of disease spread, illness severity or length of illness and morbidity rate, particularly among people with compromised immune system [1,4]. Accordingly, the expenses of treating these infections have grown significantly [4]. Thus, AMR is a leading cause of death worldwide, with the highest burdens in low-resource regions [5,6]. Moreover, AMR threatens medical treatments such as cancer therapy and organ transplants because of the increased risk of infections [7]. Further, rising AMR threatens progress toward global objectives such as the sustainable development goals [4].

AMR is a natural evolutionary process in bacteria that is accelerated by selection pressure due to the frequent and irrational use of antimicrobial drugs in humans and animals, in addition to the insufficiency of

accurate diagnostics and appropriate treatment regimens [8,9]. The mechanisms of developing AMR in bacteria include spontaneous changes in the bacterial genome (microbial adaptation) and the acquisition of another genome segment from another bacteria (horizontal gene transfer). Notably, antimicrobial intake destroys both the disease-causing bacteria and the healthy microbiota; thus, drug-resistant bacteria can multiply more and dominate the bulk of the bacterial environment in humans. Furthermore, drug-resistant bacteria can pass the resistance to other bacterial genera or species [7,10]. Bacterial strains are considered multidrug-resistant (MDR) if they are resistant to three or more different classes of antimicrobials. In addition, the bacterial strains are categorised as extensively drug-resistant if they are resistant to all existing antimicrobials except one or two and pan-drug-resistant if they are resistant to all available antimicrobials [11].

According to the World Health Organization (WHO), coronavirus disease 2019 (COVID-19) became a global health emergency on January 30, 2020, and was proclaimed a worldwide pandemic on March 11, 2020 [12]. Most COVID-19 cases presented with fever, dry cough and tiredness, although clinical presentation ranged from asymptomatic to atypical severe pneumonia [13]. During the COVID-19 pandemic, several antimicrobial drugs were promoted in the treatment protocols [14]. Around 72% of COVID-19 patients received broad-spectrum antimicrobial therapy, with azithromycin, amoxicillin-clavulanate and levofloxacin being the most frequently prescribed ones. Only 7% to 8% of hospitalised patients and 14% of intensive care unit (ICU) patients developed secondary infections, including sepsis and hospital pneumonia [15,16]. However, excessive antimicrobial use in COVID-19 patients and hospital overcrowding likely accelerated the emergence and spread of AMR [17].

The effect of COVID-19 on AMR varied significantly according to each country's healthcare system and public health policy. The incidence of MDR bacteria and the variations in antimicrobial usage before and during the COVID-19 pandemic have been the subject of considerable research and/or review articles [18-29]. There are substantial variations due to the differences in study populations, clinical settings and antimicrobial prescribing patterns in these studies [30]. Consequently, to develop strategies to combat AMR, studies of antimicrobial usage and changes in resistance to antimicrobials in various countries throughout the COVID-19 era are essential [31]. To our knowledge, there are no published studies from Palestine or any Arab country directly comparing AMR rates between the pre-COVID-19 and post-COVID-19 eras [14], and it is not clear yet how the COVID-19 pandemic may affect AMR globally [16]. Therefore, this retrospective study's main objective was to determine the difference between AMR patterns of isolated bacterial pathogens causing infections at Al-Shifa hospital in the Gaza Strip in pre-and post-COVID-19 pandemic periods.

Methodology

Study design

This is a retrospective observational study to determine the difference between antimicrobial resistance patterns of isolated bacterial pathogens at Al-Shifa hospital, the largest medical complex and central hospital in the Gaza Strip, in pre-and post-COVID-19 pandemic periods. The selected study periods were from July 1, 2019 to December 31, 2019 (pre-COVID-19 period) and July 1, 2021 to December 31, 2021 (post-COVID-19 period) when there was a global decline in the rate of COVID-19 cases, although coronavirus infections were still present. Ethical approval was obtained from the Faculty of Pharmacy, Al-Azhar University, Gaza. The general directorate for human research in the Ministry of Health also approved the study.

Study setting and data eligibility

The study included all the positive microbiological cultures data that Al-Shifa hospital laboratory staff recorded electronically (in Microsoft Excel) in the selected periods. The data included ward name, patient gender, specimen type, isolate identity, susceptibility profiles to tested antimicrobials and date of the test. Inclusion criteria included all patient records with positive bacterial cultures at Al-Shifa hospital within the study periods. Exclusion criteria included polymicrobial cultures, any incomplete data and positive fungal cultures data. Antimicrobial susceptibility testing (AST) was performed according to the Clinical and Laboratory Standard Institute (CLSI) using the disk diffusion method [32]. The susceptibility of each isolated pathogen to the tested antimicrobial agents was classified as S (susceptible), I (intermediate susceptible) and R (resistant). Resistance rates of the bacterial species were considered only if the results of AST revealed resistance to a particular antimicrobial drug in more than 10 cases (or records) [33].

Data collection, processing and analysis

The authors obtained the microbiological data generated during the selected periods by the laboratory staff of the Al-Shifa Hospital diagnostic laboratory.

Data were analysed using Statistical Package for Social Sciences (SPSS) (v. 23) software. Descriptive statistics were calculated for all variables. Categorial data were summarised as frequencies and percentages. The Chi-square test was used to examine the differences between antimicrobial resistance values in pre- and post-COVID-19 periods. Results were considered statistically significant when p values were ≤ 0.05.

Results

Positive culture data

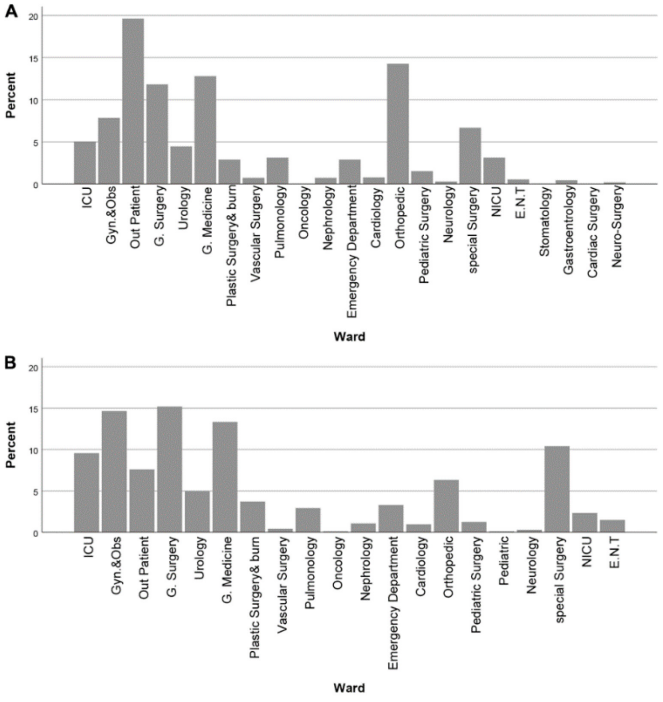
This study included 3866 positive culture data of 3866 clinical samples collected from patients of both genders; 2039 samples were collected during the selected pre-COVID-19 period and 1827 were collected during the post-COVID-19 period. The proportion of males in both pre-COVID-19 and post-COVID-19 periods was 52.38% and 55.88%, respectively. The percentages of females in the pre-COVID-19 and post-COVID-19 periods were 47.62% and 44.12%, respectively. The most frequent source of samples in the pre-COVID-19 period was the outpatient ward, with a percentage of 19.62%; and the general surgery ward in the post-COVID-19 period, with a proportion of 15.81% (Figure 1).

Concerning specimen types distribution, the most frequent specimen type in both designated periods was pus specimens, followed by urine specimens. In the pre-COVID-19 period, specimen types were blood (3.38%), urine (33.35%), pus (54.59%), sputum (3.73%), vaginal swab (2.50%), tissue (0.69%), bone (1.62%) and cerebrospinal fluid (0.15%). In the post-COVID-19 period, specimen types were blood (3.89%), urine (31.09%), pus (53.48%), sputum (5.69%), vaginal swab (5.69%), and ear, nose and eye swabs (0.16%).

Isolated bacterial pathogens in pre-COVID-19 and post-COVID-19 periods

The predominant Gram-negative bacterial pathogens recorded in the positive culture data were *E. coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*, *Acinetobacter* spp. and *Proteus* spp. The prevalent Gram-positive bacterial pathogens included *Staphylococcus aureus*, coagulase-negative *Staphylococci* (CoNS) and *Streptococcus* spp. Other species including *Citrobacter* spp., *Serratia* spp.,

Figure 1. Wards distribution of the samples in the **A**: pre- and **B**: post-COVID-19 periods.



ICU: intensive Care Unit; Gyn & Obs: obstetrics and gynecology; G. Surgery: general surgery; NICU: neonates intensive care unit; E.N.T: ear; nose and throat.

Table 1. Prevalence of bacterial pathogens in pre-COVID-19 and post-COVID-19 periods.

Bacterial pathogen	N, (%)[1] Pre-COVID-19	N, (%) Post-COVID-19
Gram-negative bacteria		
Escherichia coli	603 (29.6%)	496 (27.1%)
Klebsiella spp.	406 (19.9%)	446 (24.4%)
Pseudomonas aeruginosa	252 (12.4%)	152 (8.3%)
Acinetobacter spp.	13 (0.6%)	46 (2.5%)
Proteus spp.	40 (2%)	46 (2.5%)
Gram-positive bacteria		
Staphylococcus aureus	282 (13.8%)	225 (12.3%)
CoNS	245 (12.0%)	194 (10.6%)
Streptococcus spp.	187 (9.2%)	192 (10.5%)
Other species	11 (0.5%)	30 (1.6%)
Total	2039 (100%)	1827 (100%)

[1]Number and percentage of bacterial pathogens in pre-COVID-19 and post-COVID-19 positive culture data. CoNS: Coagulase-negative *Staphylococci*.

Stenotrophomonas maltophilia and *Morganella morganii* were detected with low frequencies. The most prevalent bacterial pathogens in both the pre-COVID-19 and post-COVID-19 periods were *E. coli* and *Klebsiella* spp. (Table 1).

Bacterial pathogens prevalent in each specimen type

In the pre-COVID-19 period, the most prevalent pathogens were CoNS (50.7%) in blood specimens, *E. coli* (57.6%) in urine specimens, and *S. aureus* (20.1%), *P. aeruginosa* (17.3%) and *Klebsiella* spp. (17.2%) in pus specimens. The most prevalent pathogen in sputum specimens was *Streptococcus* spp. (34.2%), followed by *Klebsiella* spp. (26.3%). The most predominant pathogens in vaginal swabs were *Klebsiella* spp. (33.3%) and *E. coli* (29.4%). *S. aureus* was the prevalent pathogen (50%) in tissue and bone specimens, while CoNS was the predominant pathogen in cerebrospinal fluid (CSF) specimens (Table 2).

In the post-COVID-19 period, the most prevalent pathogen in blood specimens was *Klebsiella* spp. (26.8%), followed by CoNS (21.1%). The most prevalent pathogen in urine specimens was *E. coli* (51.1%), in pus specimens were *S. aureus* (18.9%) and CoNS (17.9%), in sputum specimens was *Streptococcus* spp. (33.7%), in vaginal swabs were *Klebsiella* spp. (30.8%) and *E. coli* (26.0%), and in ear, nose and eye swabs was *P. aeruginosa* (Table 2).

Antimicrobial resistance rates of isolated bacterial pathogens in both study periods

Based on the available data, 21 antimicrobials were tested in both study periods. In the pre-COVID-19 period, the highest recorded resistance rates were against cefazolin (74.2%), cephalexin (73.5%) and nalidixic acid (70.3%). The lowest resistance rates were for colistin (8.4%), rifampicin (13.2%), vancomycin (14.8%) and piperacillin-tazobactam (17.2%). In the post-COVID-19 period, the highest antimicrobial resistance rates were observed for amoxicillin/clavulanic acid (88.7%), cloxacillin (88%), cephalexin (80.1%) and cefazolin (78.1%). The lowest resistance rates were recorded against rifampicin (7.1%), colistin (8%), vancomycin (8.5%) and meropenem (13.3%) (Table 3).

Statistically significant ($p < 0.05$) increases in resistance rates were observed in the post-COVID-19 period compared to the pre-COVID-19 period, in the cases of amoxicillin/clavulanic acid (65.1% to 88.7%), cephalexin (73.5% to 80.1%), cloxacillin (46.5% to 88.0%), co-trimoxazole (62.0% to 71.5%) and erythromycin (47.9% to 63.4%). In comparison, there was a significant decrease ($p < 0.05$) in resistance rates to cefotaxime (69.5% to 63.8%), cefuroxime (64.8% to 58.9%), doxycycline (56.5% to 47.7%), gentamicin (34.9% to 30.2%), meropenem (21.0% to 13.3%), rifampicin (13.2% to 7.1%) and vancomycin (14.8% to 8.5%) (Table 3).

Antimicrobial resistance rates of Gram-negative bacterial pathogens

The antimicrobial resistance rates of the Gram-negative bacteria *E. coli*, *Klebsiella* spp., *Proteus* spp., *P. aeruginosa* and *Acinetobacter* spp. were recorded. *E. coli* isolates showed variable resistance rates in both study periods against the tested antimicrobials ranging from 2.8% to 88.6%, with the highest resistance rate being against cefuroxime (74.3%) in the pre-COVID-19 period and against cephalexin (88.6%) in the post-COVID-19 period. Low resistance rates, ranging from 2.8% to 18%, were recorded against amikacin, colistin, meropenem and piperacillin-tazobactam.

Table 2. Prevalence of bacterial pathogens in each specimen type in pre-COVID-19 and post-COVID-19 periods.

Bacterial pathogen	Percentage of bacterial pathogens isolated from pre-COVID-19 and post-COVID-19 positive bacterial cultures																			
	Blood		Urine		Pus		Sputum		Vaginal Swab		Tissue		Bone		CSF		Ear & Nose & Eye swab		Total	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Gram-negative bacteria																				
E. coli	2.9	15.5	57.6	51.1	16.9	16.5	6.6	6.7	29.4	26.0	0	0	3.0	0	0	0	0	0	29.6	27.1
Klebsiella spp.	8.7	26.8	24.7	33.5	17.2	18.2	26.3	26.0	33.3	30.8	21.4	0	3.0	0	0	0	0	0	19.9	24.4
P. aeruginosa	0	4.2	6.2	4.6	17.3	11.1	15.8	11.5	0	1.0	7.1	0	12.1	0	0	0	0	66.7	12.4	8.3
Acinetobacter spp.	5.8	4.2	0	0.2	0.6	3.2	2.6	9.6	0	1.0	0	0	0	0	0	0	0	0	0.6	2.5
Proteus spp.	0	1.4	2.1	2.5	2.2	3.2	0	0	2.0	0	0	0	0	0	0	0	0	0	2.0	2.5
Gram-positive bacteria																				
S. aureus	2.9	4.2	3.1	2.1	20.1	18.9	13.2	10.6	7.8	13.5	50.0	0	42.4	0	0	0	0	0	13.8	12.3
CoNS	50.7	21.1	0.1	0.7	17.4	17.9	0	0	0	0	14.3	0	30.3	0	100	0	0	0	12.0	10.6
Streptococcus spp.	27.5	19.7	6.0	5.3	7.5	8.7	34.2	33.7	27.5	26.0	7.1	0	9.1	0	0	0	0	33.3	9.2	10.5
Other species	1.4	2.8	0.1	0.2	0.7	2.4	1.3	1.9	0	1.9	0	0	0	0	0	0	0	0	0.5	1.6

Pre: Pre-COVID-19; Post: Post-COVID-19, CSF: Cerebrospinal fluid.

Table 3. The overall antimicrobial resistance rates in both study periods.

Antimicrobial agent	Pre-COVID-19 R%[1]	Post-COVID-19 R%	*p* value
Amikacin	15.9%	17.2%	0.453
Amoxicillin/Clavulanic acid	65.1%	88.7%	0.000*
Cefazolin	74.2%	78.1%	0.132
Cefotaxime	69.5%	63.8%	0.003*
Ceftazidime	61.8%	62.4%	0.766
Ceftriaxone	67.4%	66.9%	0.797
Cefuroxime	64.8%	58.9%	0.030*
Cephalexin	73.5%	80.1%	0.001*
Ciprofloxacin	49.0%	49.2%	0.960
Clindamycin	51.3%	47.9%	0.245
Cloxacillin	46.5%	88.0%	0.000*
Colistin	8.4%	8.0%	0.778
Co-trimoxazole	62.0%	71.5%	0.000*
Doxycycline	56.5%	47.7%	0.000*
Erythromycin	47.9%	63.4%	0.000*
Gentamicin	34.9%	30.2%	0.045*
Meropenem	21.0%	13.3%	0.017*
Nalidixic acid	70.3%	72.3%	0.480
Nitrofurantoin	29.3%	42.9%	0.446
Piperacillin-Tazobactam	17.2%	22.7%	0.055
Rifampicin	13.2%	7.1%	0.001*
Vancomycin	14.8%	8.5%	0.001*

[1]R%: overall resistance rate for each antimicrobial agent; *statistically significant change.

Table 4. Antimicrobial resistance rates of Gram-negative bacterial pathogens.

Antimicrobial	*Escherichia coli*			*Klebsiella* spp.			*Pseudomonas aeruginosa*			*Proteus* spp.			*Acinetobacter* spp.		
	Pre-COVID R% (N)[1]	Post-COVID R% (N)	*p* value	Pre-COVID R% (N)	Post-COVID R% (N)	*p* value	Pre-COVID R% (N)	Post-COVID R% (N)	*p* value	Pre-COVID R% (N)	Post-COVID R% (N)	*p* value	Pre-COVID R% (N)	Post-COVID R% (N)	*p* value
Amikacin	8.2% (378)	9.4% (394)	0.560	16.6% (301)	18.4% (364)	0.543	23.8% (214)	22.5% (138)	0.767	26.7% (30)	19.5% (41)	0.476	66.7% (12)	51.1% (45)	0.336
Cefazolin	68.1% (207)	69.3% (274)	0.774	82.8% (134)	82.7% (289)	0.972	83.6% (67)	93.2% (88)	0.058	52.6% (19)	59.4% (32)	0.638	-	-	-
Cefotaxime	63.8% (547)	60% (490)	0.208	78.1% (389)	72.5% (436)	0.060	69.0% (229)	56.3% (151)	0.012*	54.3% (35)	41.3% (46)	0.246	-	-	-
Ceftazidime	57.7% (580)	58.7% (312)	0.774	72.4% (388)	65.2% (313)	0.039*	52.6% (234)	42.7% (96)	0.104	57.9% (38)	50.0% (32)	0.509	-	-	-
Ceftriaxone	64.1% (574)	64.4% (494)	0.929	76.1% (393)	76.9% (438)	0.770	61.6% (242)	53.6% (151)	0.121	52.6% (38)	45.7% (46)	0.524	-	-	-
Cefuroxime	74.5% (310)	65.2% (158)	0.035*	79.3% (188)	76.0% (104)	0.515	-	-	-	-	-	-	-	-	-
Cephalexin	80.3% (233)	88.6% (280)	0.009*	84.2% (146)	92.6% (216)	0.012*	90.7% (118)	94.1% (34)	0.527	-	-	-	-	-	-
Ciprofloxacin	53.9% (395)	48.6% (148)	0.273	49.6% (276)	55.6% (90)	0.329	44.4% (178)	29.6% (27)	0.148	65.4% (26)	44.4% (9)	NC	-	-	-
Colistin	2.8% (178)	4.6% (196)	0.359	11.6% (198)	4.5% (244)	0.005*	4.9% (184)	3.4% (118)	0.518	54.5% (22)	74.2% (31)	0.137	0.0% (13)	4.5% (44)	0.434
Co-trimoxazole	69.8% (338)	73.0% (423)	0.327	71.0% (186)	82.9% (403)	0.001*	95.9% (74)	90.1% (141)	0.129	71.4% (14)	80.5% (41)	0.479	-	-	-
Doxycycline	68.6% (236)	56.4% (236)	0.006*	75.2% (165)	49.8% (201)	0.000*	-	-	-	94.1% (17)	65.2% (23)	0.030*	54.5% (11)	40.0% (30)	0.406
Gentamicin	34.6% (298)	26.7% (172)	0.079	36.0% (186)	33.3% (162)	0.599	43.9% (123)	37.3% (51)	0.419	60.0% (20)	26.1% (23)	0.025*	-	-	-
Meropenem	10.8% (491)	9.2% (65)	0.708	20.9% (359)	10.2% (59)	0.053	36.9% (225)	8.0% (25)	0.004*	-	-	-	84.6% (13)	56.3% (16)	0.101
Nalidixic acid	70.0% (333)	69.4% (284)	0.871	68.1% (141)	72.2% (176)	0.430	81.1% (37)	92.6% (27)	0.191	-	-	-	-	-	-
Nitrofurantoin	20.9% (86)	100% (1)	NC	33.3% (36)	40.0% (5)	NC	77.8% (9)	0% (1)	NC	-	-	-	-	-	-
Piperacillin-tazobactam	5.5% (127)	18.0% (161)	0.001*	25.5% (110)	23.2% (168)	0.669	22.4% (76)	20.0% (95)	0.706	12.5% (8)	11.8% (17)	NC	100% (2)	51.7% (29)	NC

[1]N: number of cases tested against this antimicrobial; R%: percentage of antimicrobial resistance; NC: Not considered; *statistically significant change; -: not tested.

E. coli had a statistically significant increase in resistance rates in the post-COVID-19 period compared to the pre-COVID-19 period against cephalexin (80.3% to 88.6%, $p = 0.009$) and piperacillin-tazobactam (5.5% to 18.0%, $p = 0.001$). Significant decreases were recorded against cefuroxime (74.5% to 65.2%, $p = 0.035$) and doxycycline (68.6% to 56.4%, $p = 0.006$) (Table 4).

Antimicrobial resistance in *Klebsiella* spp. isolates varied between 4.5% to 92.6% in both study periods. The highest resistance rates were against cephalexin, cefazolin, cefuroxime, cefotaxime and co-trimoxazole ranging from 71% to 92.6%. Low resistance rates of *Klebsiella* spp. were observed against amikacin, colistin and meropenem, ranging from 4.5% to 18.4%. *Klebsiella* app. showed a statistically significant increase in the resistance rates against cephalexin (84.2% to 92.6%, $p = 0.012$) and co-trimoxazole (71.0% to 82.9%, $p = 0.001$) and statistically significant decrease in resistance against ceftazidime (72.4% to 65.2%, $p = 0.039$), colistin (11.6% to 4.5%, $p = 0.005$) and doxycycline (75.2% to 49.8%, $p = 0.000$) in the post-COVID-19 period compared to the pre-COVID-19 period (Table 4).

In the case of *P. aeruginosa*, the resistance rates varied from 4.9% to 95.9% against tested antimicrobials in both study periods. In the pre-COVID-19 period, the highest resistance rates were against co-trimoxazole (95.9%), cephalexin (90.70%) and cefazolin (83.6%) and the lowest resistance rate was against colistin (4.9%). In the post-COVID-19 period, the higher resistance rates of *P. aeruginosa* bacteria were against cephalexin (94.1%), cefazolin (93.2%), nalidixic acid (92.6%) and co-trimoxazole (90.1%), while the lowest resistance rates were against colistin (3.4%) and meropenem (8%). *P. aeruginosa* bacteria resistance rates significantly decreased in the post-COVID-19 period against cefotaxime (69.0% to 56.3%, $p = 0.012$) and meropenem (36.9% to 8.0%, $p = 0.004$) (Table 4).

The highest resistance rates of *Proteus* spp. in the pre- and post-COVID-19 periods were against doxycycline (94.1%) and co-trimoxazole (80.5%), respectively. The lowest resistance rate of *Proteus* spp. in the pre- and post-COVID-19 periods was against piperacillin-tazobactam, with resistance rates of 12.50% and 11.80%, respectively. There was a statistically significant decrease in *Proteus* bacteria resistance rate against both doxycycline (94.1% to 65.2%, $p = 0.030$) and gentamicin (60.0% to 26.1%, $p = 0.025$) (Table 4).

Acinetobacter spp. bacteria did not show a statistically significant increase or decrease in resistance rates between study periods (Table 4).

Antimicrobial resistance rates of Gram-positive bacterial pathogens

Among the Gram-positive bacteria, *Streptococcus* spp., *S. aureus* and CoNS, showed significant changes in their resistance rates in the post-COVID-19 period compared to the pre-COVID-19 period. In the case of *S. aureus*, the highest resistance rate was observed in both periods against amoxicillin/clavulanic acid (67.9% and 93.9%, respectively), in addition to cloxacillin (83.2%) in the post-COVID-19 period. Low resistance rates were detected against cefuroxime, doxycycline, gentamicin, rifampicin and vancomycin, ranging from 2.8% to 20% in both study periods. There were statistically significant increases in antimicrobial resistance during the post-COVID-19 period against amoxicillin/clavulanic acid (67.9% to 93.9%, $p = 0.000$), cloxacillin (34.5% to 83.2%, $p = 0.000$) and erythromycin (39.9% to 49.7%, $p = 0.041$). Significant decreases were recorded against cefuroxime (25.2% to 7.5%, $p = 0.016$), clindamycin (45.9% to 30.5%, $p = 0.001$), doxycycline (32.4% to 20.0%, $p= 0.032$), gentamicin (33.1% to 8.1%, $p = 0.000$), rifampicin (7.0% to 2.8%, $p = 0.048$) and vancomycin (10.9% to 5.0%, $p = 0.018$) (Table 5).

In the case of CoNS, the highest resistance rate in the pre-COVID-19 period was observed against amoxicillin/clavulanic acid (62.6%), while it was observed against amoxicillin/clavulanic acid (92.0%) and cloxacillin (90.3%) in the post-COVID-19 period. In both study periods, low resistance rates were recorded against doxycycline, rifampicin and vancomycin, ranging from 0.5% to 19.1%. CoNS bacteria showed significant increases in resistance rates against amoxicillin/clavulanic acid (62.6% to 92.0%, $p = 0.000$), cephalexin (41.7% to 65.7%, $p = 0.000$), cloxacillin (37.6% to 90.3%, $p = 0.000$) and erythromycin (46.5% to 70.1%, $p = 0.000$) in the post-COVID-19 period; however, a significant decrease in CoNS resistance rate was observed only against vancomycin (7.8% to 0.5%, $p = 0.000$) (Table 5).

Streptococcus spp. showed the highest resistance rates in both study periods against amoxicillin/clavulanic acid, cephalexin, cloxacillin, clindamycin, co-trimoxazole and erythromycin ranging from 64.5% to 91.6%. In contrast, the lowest resistance rate was detected against rifampicin (8.90%). *Streptococcus* spp. resistance rates significantly increased during the post-COVID-19 period against

amoxicillin/clavulanic acid (64.5% to 81.0%, p = 0.002), cloxacillin (76.5% to 91.6%, p = 0.006), co-trimoxazole (72.7% to 82.5%, p = 0.047), erythromycin (61.2% to 73.4%, p = 0.023) and gentamicin (20.8% to 43.5%, p = 0.002) and significantly decreased against rifampicin (21.0% to 8.9%, p = 0.003) (Table 5).

Discussion

AMR is a leading cause of death worldwide, with an estimated 1.27 million deaths directly attributable to bacterial antimicrobial resistance in 2019 based on a predictive statistical model [6]. Globally, there are at least 700,000 deaths per year due to drug-resistant infections, and by the year 2050, it is expected that 10 million people will die every year [17,34]. During the COVID-19 pandemic, antimicrobial medication usage increased in both developed and developing nations, although overuse and abuse have been far more widespread in developing countries. This might negatively impact AMR, especially because several developing countries have already documented the emergence of MDR microbial pathogens before the pandemic [14]. It is unclear whether the consequences of the practices that occurred during the COVID-19 pandemic will have a net positive or negative impact on the rates of AMR [35]. Additionally, to our knowledge, there are no published studies from Palestine or another Arab country comparing AMR rates before and after the COVID-19 pandemic [15]. Thus, this retrospective study aimed to determine the difference between the AMR patterns in isolated bacteria at Al-Shifa tertiary care hospital in the Gaza Strip in selected periods before and following the COVID-19 outbreak.

In the current study, pus and urine samples had the highest percentage of positive cultures in both study periods; and blood and sputum specimens had lower rates. This may be attributed to false-negative culture results for blood samples because of the administration of antibiotics before collecting blood specimens and the inherent lower bacterial count in blood cultures [36,37]. In addition, sputum cultures are problematic as contamination with oral bacterial microbiota often makes it challenging to isolate pathogens. Different priority pathogens were isolated from specimens in this study, including *E. coli*, *Klebsiella* spp., *Streptococcus* spp., *S. aureus*, CoNS, *P. aeruginosa*, *Acinetobacter* spp. and *Proteus* spp., that pose extreme threat to human health and need urgent action [38]. The most predominant pathogen in both study periods was *E. coli*, which is similar to other studies in the EARS-Net report [39] and Romania [18].

Regarding the distribution of isolated bacterial pathogens from different specimens, CoNS was the predominant pathogen in blood specimens in the pre-

Table 5. Antimicrobial resistance rates of Gram-positive bacterial pathogens.

Antimicrobial	*Staphylococcus aureus*			CoNS			*Streptococcus* spp.		
	Pre-COVID R% (N)	Post-COVID R% (N)	*p* value	Pre-COVID R% (N)	Post-COVID R% (N)	*p* value	Pre-COVID R% (N)[1]	Post-COVID R% (N)	*p* value
Amoxicillin/Clavulanic acid	67.9% (262)	93.9% (131)	0.000*	62.6% (235)	92.0% (100)	0.000*	64.5% (169)	81.0% (121)	0.002*
Cefuroxime	25.2% (127)	7.5% (40)	0.016*	34.5% (110)	37.8% (378)	0.717	48.2% (83)	39.0% (59)	0.276
Cephalexin	46.9% (98)	55.1% (198)	0.189	41.7% (96)	65.7% (166)	0.000*	79.7% (59)	78.4% (167)	0.844
Clindamycin	45.9% (222)	30.5% (213)	0.001*	40.3% (191)	47.4% (175)	0.170	74.1% (143)	69.5% (174)	0.368
Cloxacillin	34.5% (84)	83.2% (143)	0.000*	37.6% (85)	90.3% (113)	0.000*	76.5% (51)	91.6% (131)	0.006*
Co-Trimoxazole	21.2% (203)	25.4% (185)	0.325	59.0% (173)	66.1% (168)	0.175	72.7% (143)	82.5% (143)	0.047*
Doxycycline	32.4% (182)	20.0% (90)	0.032*	19.1% (141)	19.0% (84)	0.985	43.3% (91)	38.5% (96)	0.506
Erythromycin	39.9% (268)	49.7% (179)	0.041*	46.5% (228)	70.1% (157)	0.000*	61.2% (178)	73.4% (139)	0.023*
Gentamicin	33.1% (121)	8.1% (74)	0.000*	32.7% (113)	26.8% (71)	0.391	20.8% (101)	43.5% (69)	0.002*
Rifampicin	7.0% (214)	2.8% (214)	0.048*	14.9% (161)	10.6% (179)	0.227	21.0% (124)	8.9% (169)	0.003*
Vancomycin	10.9% (275)	5.0% (220)	0.018*	7.8% (231)	0.5% (20)	0.000*	29.8% (181)	21.1% (181)	0.057

[1]N: number of cases tested against this antimicrobial; R%: percentage of antimicrobial resistance; NC: not considered; *statistically significant change; CoNS: coagulase-negative *Staphylococci.*

COVID-19 period (50.7%). Similar results have been reported from India [40]. In comparison, *Klebsiella* spp. and CoNS were the most frequently isolated pathogens in blood specimens in the post-COVID-19 period (26.8% and 21.1%, respectively). This finding is consistent with the cohort research that was carried out over two years in Kuwait, Saudi Arabia and the United Arab Emirates [41]. However, it is challenging to determine whether CoNS have a pathogenic role because CoNS bacteria have become the predominant bloodstream pathogen, especially in immunocompromised patients. The leading causes of the rise in CoNS bloodstream infections are the increased use of intravascular devices such as indwelling catheters and underlying immune system dysregulation, in addition to failure to prevent device-associated infections [27]. *E. coli* was the predominant pathogen in urine specimens during both pre-COVID-19 and post-COVID-19 periods (57.6% and 51.1%, respectively), which was consistent with studies from Gaza [42], Bangladesh [43] and Romania [18]. In pus specimens, the predominant pathogen was *S. aureus* in both periods (20.1% and 18.9%), and similar results were reported in India [40]. *Streptococcus* spp. was the most frequently isolated pathogen in sputum specimens (34.2% and 33.7%), consistent with Helou *et al*. [44] findings. The most frequently isolated pathogens in vaginal swabs were *Klebsiella* spp. (33.3% and 30.8%) and *E. coli* (29.4% and 26%), comparable to a hospital-based prospective study conducted in a tertiary care hospital for two years in India, where *E. coli* was the predominant pathogen (18.2%), followed by *Klebsiella* spp. (16.3%) [45].

Overall, AMR rates in both study periods were high. About half of the 21 tested antimicrobials in the current study exhibited resistance rates greater than 50%. AMR rates in the pre-COVID-19 period and post-COVID-19 period varied; there was an increase in the resistance rates of some antibiotics and a decrease in the resistance rates of others. The two antimicrobial agents with the highest resistance rates during the post-COVID-19 period were amoxicillin/clavulanic acid and cloxacillin, whose resistance rates dramatically increased in the post-COVID-19 period. This may be due to increased methicillin-resistant staphylococcal infections stated in the CDC 2022 report [46] or the regular use of amoxicillin/clavulanic acid by the community pharmacies and healthcare clinics in the Gaza Strip during the COVID-19 pandemic [28].

In our study, amoxicillin/clavulanic acid, cephalexin, cloxacillin, co-trimoxazole and erythromycin demonstrated statistically significant ($p < 0.05$) increases in resistance rates by the isolated bacterial pathogens in the post-COVID-19 period. In contrast, the resistance rates were significantly decreased for cefuroxime, cefotaxime, gentamicin, doxycycline, rifampicin, vancomycin and meropenem. The increase in erythromycin resistance rate in the post-COVID-19 period, even though it is not commonly used in Gaza hospitals or by community pharmacies, was due to its cross-resistance with azithromycin, which was used extensively during the COVID-19 pandemic as a part of the treatment protocol [32]. Besides, cloxacillin has cross-resistance with amoxicillin/clavulanic acid [47], and erythromycin has cross-resistance with azithromycin. During the COVID-19 pandemic, amoxicillin/clavulanic acid and azithromycin antimicrobials were frequently used in Gaza hospitals and sold with or without prescriptions by Gaza community pharmacies. These findings support that self-medication (the taking of drugs on one's own initiative, or the advice of another person, without consulting a doctor) and the prescription of antimicrobial drugs by community pharmacies may be significant drivers of AMR in the Gaza Strip during the COVID-19 pandemic. These findings agreed with many other previous studies [3,14,15,24,48,49].

E. coli is a Gram-negative bacterium and a common cause of infectious diseases, including diarrhoea, urinary tract infections and bloodstream infections [4]. In the current study, *E. coli* isolates showed high resistance rates in the selected pre- and post-COVID-19 periods against cephalexin, cefuroxime, co-trimoxazole, nalidixic acid and cefazolin. The lowest *E. coli* resistance rate was against colistin in both study periods (2.8% and 4.6%), similar to the finding of a study in Kuwait [50], followed by meropenem and piperacillin-tazobactam. High resistance rates of *E. coli* were reported against nalidixic acid at 88.2% and co-trimoxazole at 76.5% in a previous study in Gaza [51], while a low resistance rate against carbapenems was also reported in Gaza [52]. During the post-COVID-19 period, significant increases in *E. coli* resistance rates were observed against cephalexin (80.3% to 88.6%) and piperacillin-tazobactam (5.5% to 18.0%). Similarly, an increase in *E. coli* resistance rate against piperacillin-tazobactam during the COVID-19 pandemic was reported in Saudi Arabia [53]. The significant increase in *E. coli* resistance against cephalexin in the current study may be due to its extensive use during the COVID-19 pandemic in Gaza. In addition, a considerable increase in *E. coli* resistance against piperacillin-tazobactam may be due to poor adherence to hospital restriction policies related to

piperacillin-tazobactam prescription during the COVID-19 pandemic, especially in treating urinary tract infections. However, the decline in *E. coli* resistance rates in the post-COVID-19 period against cefuroxime (74.5% to 65.2%) and doxycycline (68.6% to 56.4%) may be due to the reduced use of these antimicrobials during COVID-19 pandemic.

Klebsiella spp. is a common disease-causing pathogen found in the human gut. *K. pneumoniae* can cause infections ranging from urinary and upper respiratory tract infections to sepsis and meningitis. It is also a significant cause of hospital-acquired infections [4]. High *Klebsiella* spp. resistance rates were observed in both study periods against cephalexin, cefazolin, cefuroxime, cefotaxime and co-cotrimoxazole, ranging from 71% to 92.6%. In comparison, low resistance rates were detected against amikacin, colistin and meropenem. These results were comparable to resistance rates of *Klebsiella* spp. reported in the Arab region (63% – 86%) [54]. *Klebsiella* spp. resistance rates against amikacin (16.6%, 18.4%), colistin (11.6%, 4.5%), gentamicin (36%, 33.3%) in the current study were lower than those reported as 26%, 31.6%, 55%, respectively, in a previous study in Gaza [51]. Significant increase in *Klebsiella* spp. resistance rates was recorded against cephalexin (84.2% to 92.6%) and co-trimoxazole (71.0% to 82.9%) in the post-COVID-19 period. This may be due to their irrational use during the pandemic, including self-medication and prescribing by community pharmacies for treating respiratory and urinary tract infections owing to the closure of outpatient clinics and patients' fear of going to hospitals during the COVID-19 pandemic. However, the significant decreases in *Klebsiella* spp. resistance rates against ceftazidime and doxycycline may be due to the reduced use of these antimicrobial drugs during the COVID-19 pandemic in hospitals and the community. There is a restriction on using colistin as it is a hospital antibiotic. Doxycycline is not commonly prescribed by community pharmacies and is usually prescribed by dermatologists. Moreover, strict infection control measures and awareness, hand sanitation, mask-wearing and social distancing might decrease community-acquired infections and thus reduce the consumption of these antibiotics. However, an increase in *Klebsiella* spp. resistance rate against colistin in the post-COVID-19 period compared to the pre-COVID-19 period (5% to 50%) was reported in Brazil [23].

P. aeruginosa can be found in natural environments such as human skin or environments including hospitals or hospital equipment. This pathogen is a major cause of nosocomial infections and infections among people with reduced immunity. Infections may include respiratory tract, urinary tract or bloodstream infections [4]. Antipseudomonal drugs include piperacillin, ticarcillin, ceftazidime, cefepime, aztreonam, imipenem, meropenem and doripenem from beta-lactam antibiotics, gentamycin, tobramycin and amikacin from aminoglycosides, ciprofloxacin, levofloxacin and ofloxacin from fluoroquinolones and colistin [55]. In the current study, *P. aeruginosa* bacteria showed high resistance rates in both study periods, while the highest resistance rates were against cefuroxime, cefazolin, nalidixic acid and co-trimoxazole, with resistance rates above 90%. These findings are consistent with the fact that all these antibiotics are not antipseudomonal antibiotics and thus are not used in treating *P. aeruginosa* infections. Conversely, the lowest resistance rate was against colistin, which may be due to the fact that colistin is the last resort option and not frequently used. A similar finding was observed in a systematic review conducted in Malaysia to identify global studies relevant to AMR during COVID-19 [56]. *P. aeruginosa* resistance significantly decreased against cefotaxime (69.0% to 56.3%) and meropenem (36.9% to 8.0%) in the post-COVID-19 period. This decrease may be related to the control of using these antimicrobials during the COVID-19 pandemic and to the decline in hospital-acquired infections (HAIs) incidences during COVID-19 due to patients' fear of going to hospitals and the infection prevention and control measures.

Proteus spp., part of the *Enterobacteriaceae* family of Gram-negative bacilli, are most commonly found in the human intestinal tract as part of normal human intestinal flora. *Proteus* spp. are also found in several environmental habitats, including long-term care facilities and hospitals [57]. In this study, the highest resistance rates in *Proteus* spp. were against co-trimoxazole, colistin and doxycycline. Correspondingly, *Proteus* spp. are naturally resistant to polymyxins (colistin), nitrofurans, tigecycline and tetracyclines [58]. In addition, a systematic review and meta-analysis in Iran revealed that co-trimoxazole is unsuitable for treating urinary tract infections caused by *Proteus* spp. [59]. Conversely, the lowest resistance rates were against piperacillin-tazobactam and amikacin. Similar results have been documented in Saudi Arabia [60] and Pakistan [29]. Significant decreases in *Proteus* spp. resistance rates against doxycycline and gentamicin were detected in the post-COVID-19 period. This may be due to the reduced use of these antibiotics during the COVID-19 pandemic,

both in hospitals and community pharmacies. Even so, the sample size of *Proteus* spp. for most tested antibiotics was small and may not be representative.

Acinetobacter is a complex genus, and historically, there has been confusion about the existence of multiple species. *Acinetobacter* species commonly cause nosocomial infections, predominantly aspiration pneumonia and catheter-associated bacteremia, but can also cause soft tissue and urinary tract infections. The usual therapy approach is to combine colistin and carbapenem to treat *Acinetobacter* infections. Rifampin may be helpful in diseases of the central nervous system, bone, or prosthetic materials [61]. In general, high resistance rates of *Acinetobacter* spp. against most tested antimicrobials except for colistin were observed, which corresponded with the results of a systematic review on AMR in *Acinetobacter* spp. [54]. However, in post-COVID-19, there was a decline in *Acinetobacter* spp. resistance against tested antimicrobials except for colistin (0.0% to 4.5%). This decrease may be due to reduced incidences of HAIs during COVID-19 due to patients' concern about going to hospitals and strict infection prevention and control measures. However, all of these differences are not statistically significant. Besides, the low sample size of *Acinetobacter* spp. for most tested antibiotics may not be representative.

S. aureus is commonly found on the skin or carried asymptomatically in the nares and is a frequent cause of skin, respiratory, and bloodstream infections. *S. aureus* is also a severe problem in hospitals, particularly methicillin-resistant *S. aureus*, and is responsible for many nosocomial infections. Depending on the local resistance outline, several treatment recommendations include penicillins, cephalosporins, clindamycin, or vancomycin [4]. The highest resistance rate was observed in both pre- and post-COVID periods against amoxicillin/clavulanic acid, while it was also observed against cloxacillin in the post-COVID-19 period. Low resistance rates were detected against rifampicin, vancomycin, cefuroxime, gentamicin, co-trimoxazole and doxycycline. Significant increases in *S. aureus* resistance rates were observed against amoxicillin/clavulanic acid, cloxacillin, and erythromycin in the post-COVID-19 period. This is explained by the regular use of amoxicillin/clavulanic acid and erythromycin to treat *S. aureus* infections [4]. The decrease in *S. aureus* resistance rate was observed against each gentamicin, cefuroxime, clindamycin, doxycycline, rifampicin and vancomycin. Correspondingly, a decrease in *S. aureus* resistance rates against gentamicin and vancomycin was reported in Iraq [28] and Pakistan [29]. As for CoNS, the highest resistance rate was observed in the pre-COVID-19 period only against amoxicillin/clavulanic acid, while resistance was observed against amoxicillin/clavulanic acid, cloxacillin, erythromycin and co-trimoxazole in the post-COVID-19 period. Low resistance rates were detected against vancomycin, rifampicin, doxycycline, gentamicin and cefuroxime in both periods. Significant increases in CoNS resistance rates were observed against amoxicillin/clavulanic acid, cloxacillin, cephalexin, erythromycin and gentamicin in the post-COVID-19 period. In contrast, a considerable decrease in CoNS resistance rate was observed only against vancomycin, which may be due to a decline in use in the post-COVID-19 period in hospitals due to patients' fear of going to hospitals during the COVID-19 pandemic.

Streptococcus bacteria are often carried asymptomatically in the human respiratory tract or sinuses and are a leading cause of pneumonia and meningitis. Individuals with weakened immune systems, including the elderly or young, are particularly vulnerable to infection with *S. pneumoniae* which can also cause a range of localised and invasive diseases. Treatment guidelines for streptococcal conditions may vary with the infection site, but beta-lactam antibiotics such as amoxicillin or cephalosporins are often recommended for treatment [4]. In the current study, *Streptococcus* spp. showed high resistance rates in both study periods against amoxicillin/clavulanic acid, cephalexin, cloxacillin, clindamycin, co-trimoxazole and erythromycin while low resistance rates were detected against rifampicin. Significant increase in *Streptococcus* spp. resistance rates were observed against amoxicillin/clavulanic acid, cloxacillin, erythromycin, gentamicin, co-trimoxazole and in the post-COVID-19 period. An increase in *Streptococcus* spp. resistance rates may be due to the everyday use of disinfectants [28] and the frequent use of antimicrobial therapy for respiratory infections in hospitals and the community. These antimicrobials commonly sold in community pharmacies without medical prescriptions include amoxicillin/clavulanic acid and co-trimoxazole. Erythromycin resistance is mainly a result of the frequent use of azithromycin during the COVID-19 pandemic. Gentamicin resistance may be due to the routine use of gentamicin in combination with beta-lactams for respiratory tract infections which highly increased during the COVID-19 pandemic, and cloxacillin resistance may be due to cross-resistance with amoxicillin/clavulanic acid or a result of the everyday use of disinfectants during the pandemic. An

increase in resistance to gentamicin (33.3% to 55.5%) and amoxicillin/clavulanic acid (75% to 100%) during the pandemic were observed in Iraq [28]. However, the significant decrease in *Streptococcus* spp. resistance rate to rifampicin (21.0% to 8.9%) may be due to its infrequent use and unavailability in community pharmacies.

The current study has some limitations due to its retrospective design. These limitations include a lack of data such as the patient's age and positive COVID-19 patient cultures among isolated cultures data and low sample size in some pathogen-antibiotic combination results. Moreover, there are limited reports identifying antibiotic use in the Gaza Strip before and during the COVID-19 pandemic.

Conclusions

The current study investigated the status of AMR profiles of priority bacterial pathogens isolated in pre- and post-COVID-19 selected periods at a tertiary care hospital in Gaza. Overall, the AMR rates were high among bacterial isolates in both study periods as they showed above 50% resistance rates against most of the 21 antimicrobials tested in the current study. Compared to the pre-COVID-19 period data, the resistance rates of the antimicrobials amoxicillin/clavulanic acid, cephalexin, cloxacillin, co-trimoxazole and erythromycin significantly increased during the pandemic. In contrast, the resistance rates of cefuroxime, cefotaxime, doxycycline, gentamicin, meropenem, rifampicin and vancomycin decreased. In comparison, the antimicrobials colistin, rifampicin and vancomycin showed the lowest resistance rates in both periods, in addition to piperacillin-tazobactam in the pre-COVID-19 period and meropenem in the post-COVID-19 period.

Based on the results of the current study, it was noticeable that most antimicrobial drugs that had a significant increase in their resistance rates were frequently used in hospitals, health clinics and community by community pharmacies. Thus, extensive use, self-medication and irrational sale of antibiotics without medical prescriptions were essential drivers for AMR in the Gaza Strip during the COVID-19 pandemic. The antimicrobials that had a decrease in resistance rate, like colistin, were hospital antibiotics with restriction policies. The reduction in their AMR was also due to the decline in infection rates owing to the implementation of facemasks, social distancing, increased hand hygiene, mandatory lockdowns, stay-at-home orders, closure of outpatient clinics and patients' fear of going to hospitals. Thus, effective preventive measures should be followed even after the pandemic in both healthcare settings and the community. In addition, the actual implementation of antimicrobial stewardship programs in hospitals, including Gaza Strip hospitals, and setting a policy that regulates antibiotic use in the community and increases awareness among people about antibiotic resistance and appropriate antibiotic use are warranted. Regular surveys of antimicrobial resistance in Gaza Strip hospitals and hospitals in developing countries should be carried out, and data dissemination to stakeholders should occur. Empirical treatment protocols should be reviewed periodically based on local updated AMR data in each country and international guidelines.

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