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Review Article

Relationship between Antibiotic Consumption and Resistance: A Systematic Review

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Background. Unreserved use of antibiotics exerted selective pressure on susceptible bacteria, resulting in the survival of resistant strains. Despite this, the relationship between antibiotic resistance (ABR) and antibiotic consumption (ABC) is rarely studied. This systematic review aims to review the relationship between ABC and ABR from 2016 to 2022. *Methods*. Articles published over 7 years (2016–2022) were searched from December 23 to 31, 2022. The search strategy was developed by using keywords for ABC and ABR. From 3367 articles, 58 eligible articles were included in the final review. *Results*. The pooled ABC was 948017.9 DPDs and 4108.6 DIDs where over 70% of antibiotics were from the Watch and Reserve category based on the WHO AWaRe classification. The average pooled prevalence of ABR was 38.4%. *Enterococcus faecium* (59.4%), *A. baumannii* (52.6%), and *P. aeruginosa* (48.6%) were the most common antibiotic-resistant bacteria. Cephalosporins (76.8%), penicillin (58.3%), and aminoglycosides (52%) were commonly involved antibiotics in ABR. The positive correlation between ABR and consumption accounted for 311 (81%). The correlation between ABR *P. aeruginosa* and ABC accounted for 87 (22.7%), followed by 78 (20.3%) and 77 (20.1%) for ABR *E. coli* and *K. pneumoniae* with ABCs, respectively. Consumption of carbapenems and fluoroquinolones was most commonly correlated with resistance rates of *P. aeruginosa*, *K. pneumoniae*, *E. coli*, and *A. baumannii*. *Conclusion*. There is a positive correlation between ABC and the rate of ABR. The review also revealed a cross-resistance between the consumption of different antibiotics and ABR. Optimizing antibiotic therapy and reducing unnecessary ABC will prevent the emergence and spread of ABR. Thus, advocating the implementation of stewardship programs plays a pivotal role in containing ABR.

1. Introduction

The discovery of antibiotics is the most significant achievement in the twentieth century [1]. It changed medical practice and significantly decreased morbidity and mortality associated with bacterial infections. In recent years, the emergence and spread of antibiotic-resistant pathogens on the one hand and decreased invention of new antibiotics on the other hand challenged healthcare [2, 3]. High rates of resistance against frequently used antibiotics to treat infections have been observed worldwide, resulting in running out of effective antibiotics to treat common infections [4]. Due to this, access to antibiotics remains a critical issue globally [3, 5]. According to the Centers for Disease Control and Prevention (CDC), there were 2,868,700 infections due to resistant pathogens and 35,900 deaths from antibiotic-resistant bacterial infections each year [6].

ABR is a natural phenomenon augmented by human actions such as the inappropriate use of antibiotics [7]. Increased utilization of antibiotics results in an increased frequency of inappropriate antibiotic use [8]. Given the association between antibiotic use and the selection of resistant pathogens, inappropriate use of antibiotics is often used as a surrogate marker for the avoidable ABR [9]. Thus, the increase in bacterial resistance is contributed by selection pressure on antibiotics as a result of use, overuse, and misuse

[10–12], and total consumption of antibiotics is the critical factor in selecting resistance [11]. There were individual studies that confirmed the correlation between ABC and ABR patterns [13–17]. Antibiotic stewardship programs (ASPs) are usually aimed at reducing overall ABC, and thus, preventing and reversing resistance [1, 11]. Thus, it is recommended to monitor antibiotic prescribing to improve the quality of antibiotic use and to reduce ABR [18]. Thus, this review aims to determine the relationship between ABC and rates of ABR based on articles published globally from 2016 to 2022.

2. Methodology

2.1. Study and Data Collection. Eligible articles were identified by the search strategy developed by using keywords for antibiotic resistance and ABC. Mainly the PubMed (Medline) database was used to search for eligible articles. Additional articles were identified by searching from Google Scholar. Searches were performed for 7 years, and it was performed from December 23 to 31, 2022. Search terms used included a combination of keywords like "drug resistance," "antimicrobial resistance," "bacterial resistance," "antibiotic resistance," "antibiotic use," "ABC," "antimicrobial use," and "antimicrobial consumption." Articles were initially reviewed based on title and abstracts, and then, the whole document was read to select eligible articles for review. Articles that had determined the correlation between ABR and ABC using correlation coefficients and association at a P value of 0.05 were included in the review. Thus, articles relating to nonhuman infections, previous systematic reviews, commentaries, editorial letters, and available only in the abstracts were excluded from the review (Figure 1).

For the sake of discussion, the correlation coefficients were classified as very strong (0.9–1), strong (0.7–0.89), moderate (0.4–0.69), weak (0.1–0.39), and negligible (<0.1) [19]. Finally, the results were compiled and described. The defined daily dose (DDD)/100(0) patient days (DPDs) and DDD/1000 inhabitant days per year (DIDs) were used to report ABCs.

3. Results

3.1. General Description of Articles Included in the Review. Overall, 58 articles [20–77] published globally from 2016 to 2022 were included in the systematic review. The summary of articles included, including the correlation between bacterial resistance and ABC, is summarized and annexed in Annex 1.

The majority of the articles 13 (22.3%) were published in China [21, 25–28, 42, 60, 62–64, 68, 72, 77], 4 (6.9%) Europe [48, 49, 74, 75], 4 (6.9%) South Korea [31, 54, 61, 65], 4 (6.9%) Serbia [34, 36, 39, 52], 3 (5.2%) Japan [20, 30, 40], 2 (3.4%) Italy [22, 33], 2 (3.4%) Thailand [35, 57], 2 (3.4%) France [46, 56], 2 (3.4%) Spain [43, 59], 2 (3.4%) Slovenia [47, 71], 2 (3.4%) Switzerland [45, 70], and the rest were in different countries [23, 29, 32, 37, 38, 41, 44, 50, 51, 53, 55, 58, 66, 67, 69, 73, 76, 77]. The majority of the articles 11(23.4%) were published in 2017 [22, 33, 36, 44, 47, 48, 52, 56, 59, 64, 67],

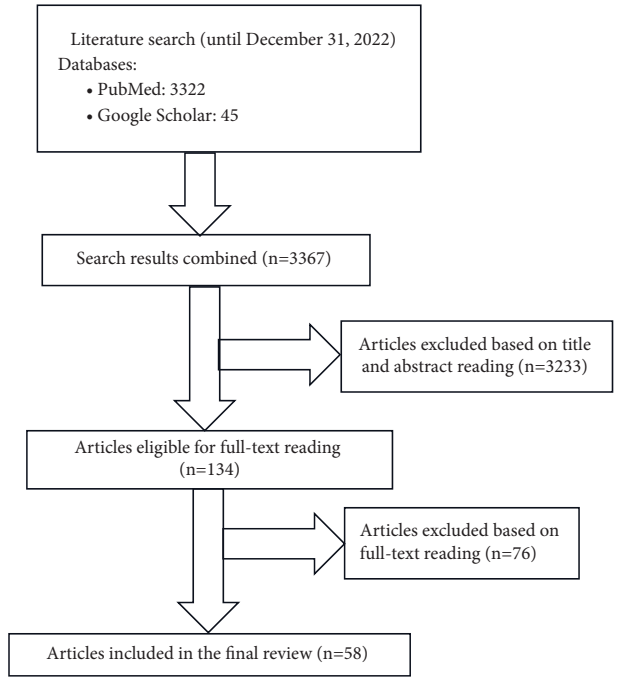

Figure 1: Flowchart for selection of articles for systematic review.

2018 [20, 23, 26, 35, 45, 46, 53, 54, 61, 63, 65], 2019 [21, 25, 30, 31, 40, 42, 43, 50, 51, 55, 62], 2021 [24, 29, 32, 38, 43, 60, 69–71, 75, 76], and each 5 (8.6%) in 2016 [34, 37, 41, 57, 58] and 2022 [68, 72–74, 77], but only 4 were published in 2020 [27, 38, 39, 49]. Almost all 53 (91.4%) of the articles were based on retrospective data, and the rest (8.6%) were prospective observational studies.

3.2. Antibiotic consumption. ABC was measured by different metrics. The unit of measure for ABC was not uniform for all articles. The units of ABC were standardized to 1000 patient days (DPDs) [21–23, 25, 30, 31, 35, 37, 40, 41, 44, 46, 49–52, 55–61, 64–68, 77] and 100 patient days (DPDs) [20, 26–29, 32–34, 36, 38, 39, 42, 43, 45, 53, 69, 70, 73, 76], but in addition, DIDs [30, 40, 47, 48, 56, 59, 65, 66, 68, 71, 72, 74, 75], grams [24], and average/percentage trend [54, 62] were used to measure ABC. Accordingly, about 948017.9 DPDs (904622.9 standardized per 1000 patient days and 4339.5 per 100 patient days) and 4108.6 DIDs were reported, but about 173616.9 and 99800 were reported in average consumption and in grams, respectively. More than 70% of antibiotics were consumed in the Watch and Reserve categories based on the WHO AWaRe classification. Due to a lack of uniform measurement and recording of antibiotics among the articles, overall ABC was not summarized (Table 1).

3.3. Prevalence of Antibiotic Resistance. ABR was reported as a percentage (rate, trend, or prevalence) in all articles except three, which reported the incidence density of ABR [22, 52, 63, 68]. The average pooled prevalence of antibiotic-resistant bacteria was 38.4%, with *Enterococcus* faecium (59.4%), *A*. baumannii (52.6%), *P. aeruginosa* (48.5%), coagulase-negative *Staphylococcus* (43.7%), *Enterobacter*

Table 1: Pooled antibiotic consumption by different metrics of measurement, 2016–2022 ($N = 58$).

Antibiotics	Metrics				
	Average	DDD/100 patient days	DDD/1000 patient days	DDD/1000 inhabitant days	Grams
Amikacin		6.0	22094.2	20.9	3300
Aminoglycosides	155.2	12.4	797.6		
Aminopenicillins				944.0	
Aminopenicillins and enzyme inhibitors				682.3	
Amoxicillin		1.5	110.9		
Amoxicillin/ampicillin		2.7			
Amoxicillin/clavulanate		104.4	258.0		
Amphenicols			5.2		
Ampicillin			21.4		
Ampicillin/sulbactam		3.0	61.3		
Aminoglycosides		3.8			
Antipseudomonal			68.9		
Benzylpenicillin			2.2		
Biapenem		154.6	7.1		
Carbapenems	548.2	190.9	888.0	2.2	
Cefazolin		2			
Cefepime		8.6	8382.6	6.1	
Cefixime			72.0		
Cefotaxime			2156.2	0.1	
Cefoxitin				0.0	
Cefpodoxime			38.0		
Ceftazidime		3.5	70434.2	2.9	
Ceftazidime/cefepime		3.2			
Ceftriaxone		136.3	128296.9		2500
Cefuroxime		5.0	42.1		
Cephalosporins	53411.4	256.1	14660.7	658.8	
Cephamycin			2200.0	0.1	
Ciprofloxacin		136.6	275875.2	26.7	3000
Clarithromycin			10.7		
Clindamycin		6.3	53.4		1000
Cloxacillin/cefazolin			85.2		
Colistin		7.1	883.3		
Daptomycin			6.24		
Doripenem			2.53		
Doripenem		72.5			
Ertapenem		4.1	79.8		
Erythromycin			0.8		
Flucloxacillin		5			
Fluoroquinolones	28630.6	58.7	7554.0	632.1	
Fosfomycin			5.4	0.0	
Gentamicin		81.4	81311.8	42.7	
Glycopeptides	298.3	11.1	118.6		
Imipenem		225.7	57558.2		
Imipenem/cilastatin			99.2	2.6	
Levofloxacin		100.1	573.4	7.1	
Lincosamides			44.5		
Linezolid	21504.6	365.9	5.3		
Macrolides		2.2	9552.3	102.55	
Meropenem		607.3	50276.5	6.3	4800
Metronidazole		102.5	85.8		
Monobactams			4.4		
Moxifloxacin		1.91	153.3		
Nitrofurantoin			0.0	1.32	6000
Norfloxacin		0.8	66.5		
Ofloxacin			141.5		
Oxacephems			30.0		
Oxacillin		2	13.4		6000
Oxazolidinone			7.5		
Panipenem		30.5			
Penicillin		54.9	308.5	12.5	

Table 1: Continued.

Antibiotics	Metrics				
	Average	DDD/100 patient days	DDD/1000 patient days	DDD/1000 inhabitant days	Grams
Piperacillin/tazobactam	69068.6	77.2	8614.4	22.3	65000
Polymyxin			2.9		
Rifampicin			84.2		
Sodium fusidate			0.3		
Sulfonamides			30.0		
Teicoplanin		1.6	38.9		
Tetracyclines			53.5	890.2	
Tigecycline		8.5	27.0		
Tobramycin			4.7		
Trimethoprim/sulfamethoxazole		1.7	156049.4	0.2	2200
Vancomycin		214.4	97.0		6000
Others		1265.7	4109.8	44.8	0
Total	173616.9	4339.5	904622.9	4108.6	99800

(46.1%), and *P.* mirabilis (48.5%) being the most common resistant bacteria. Cephalosporins (76.8%), penicillin (58.3%), aminoglycosides (52%), fluoroquinolones (48.3%), tetracyclines (48.6%), and carbapenems (30%) were resistant in a different way for each bacterium (Table 2).

3.4. Distribution of Antibiotic Consumption and Resistant Bacteria. The overall systematic review of 58 articles revealed a positive association between bacterial resistance and ABC, both in community and hospital settings. Except for some antibiotics, either increased consumption was associated with increased resistance, or decreased consumption was associated with decreased resistance. The analysis revealed that about 311 (81%) of the correlations between ABC and the ABR rate were directly related to ABC, but 73 (19%) were negatively correlated, indicating the protective nature of ABC for the development of resistance. *P. aeruginosa*, *K. pneumoniae*, *E. coli*, and *A. baumannii* were the bacteria for which a relationship between ABC and the resistance rate or pattern was commonly studied. About 73 (83.9%), 63 (81.8%), 68 (87.2%), and 53 (85.5%) antibiotics were positively correlated with the resistance rates of *P*. aeruginosa, *K*. pneumonia, *E. coli*, and *A*. baumannii, respectively (Table 3).

3.5. Relationship between ABC and ABR. Here, the relationship between ABC and ABR is described for each bacterium based on the correlation coefficient reported by articles [20–78]. However, it has to be noted that all studies did not provide detailed information and similar reports.

There was a very strong correlation between the consumption of meropenem and the incidence of carbapenem-resistant *P. aeruginosa* [44] and meropenem-resistant *P. aeruginosa* [69], penicillin with the incidence of combined-resistant *P. aeruginosa* [44], imipenem [57], and ertapenem [69] with imipenem resistance *P. aeruginosa* [57, 69]. There was also a very strong correlation between amikacin consumption and the resistance rate of *P. aeruginosa* to amikacin [24] and between piperacillin/tazobactam and piperacillin/tazobactam-resistant *P. aeruginosa* [69]. Similarly, there was a strong correlation between imipenem and meropenem and the rate of carbapenem-resistant *P. aeruginosa* [34], carbapenems with the rate of imipenem-resistant [44], meropenem-resistant [44], carbapenem-resistant [44], and ceftazidime-resistant [77] *P. aeruginosa*. There was also a very strong correlation between ciprofloxacin consumption and the resistance rate of *P. aeruginosa* [42].

A strong correlation was observed between the consumption of aminoglycosides and the rate of *P. aeruginosa* resistance to amikacin and gentamicin, gentamicin with the rate of aminoglycoside-resistant *P. aeruginosa* [34], and levofloxacin with the resistance rate of *P. aeruginosa* to levofloxacin [42]. A moderate correlation was found between the consumption of extended-spectrum antibiotics and cephalosporin with resistant P. aeruginosa [37], piperacillin/tazobactam with the incidence of combined-resistant *P. aeruginosa*, and amikacin with aminoglycoside-resistant *P. aeruginosa* [34]. Moderate correlations were found between the consumption of carbapenem and the rate of carbapenem-resistant *P. aeruginosa* [37, 57], carbapenem with imipenem and meropenem-resistant *P. aeruginosa* [30], and amikacin, gentamicin, and levofloxacin with resistant *P. aeruginosa* to respective antibiotics [72].

Some studies reported a decreased resistance rate of *P. aeruginosa* from the consumption of carbapenems. There was a very strong negative correlation between consumption of carbapenem and resistance rates in *P. aeruginosa* [20, 57], a strong negative correlation between carbapenem and the rate of imipenem resistance in *P. aeruginosa* [25], and a moderate negative correlation between carbapenem and the rate of carbapenem-resistant P. aeruginosa [37], and amikacin was very strongly correlated with decreased rates of multidrug-resistant (MDR) *P. aeruginosa* [57].

There was also cross-resistance between ABC and resistance to another antibiotic, which was also common. There was a very strong correlation between consumption of ceftazidime and meropenem-resistant *P. aeruginosa* [69]. There is a very strong correlation between the consumption of carbapenems and the incidence density of *P. aeruginosa* resistance to third-generation cephalosporins and aminoglycosides [22] and aminoglycosides with the rate of imipenem resistance in *P. aeruginosa* [25]. There was a very

Table 2: Average pooled prevalence of antibiotic resistance, 2016–2022 ($N = 58$).

Antibiotics	*A. baumannii*	CON *staphylococci*	*E. coli*	*Enterobacter*	*Enterobacter cloacae*	*Enterobacteriaceae*	*Enterococcus faecalis*	*Enterococcus faecium*	*H. influenza*	*H. pylori*	*K. pneumoniae*	*N. meningitidis*	*P. aeruginosa*	*P. mirabilis*	*S. aureus*	*S. pneumonia*	Total
3GC			24.4					60			37.5						40.6
Amikacin	43.3		1.8		17.8	5.3					9.4		17.7				16.6
Aminoglycosides	60.8		34.3				64.0				63.0		45.1				52.0
Aminopenicillins							24.5										24.5
Amoxicillin			62.0							0.2						46.0	36.1
Amoxicillin/clavulanic acid			39.0						20.0		19.8						24.6
Ampicillin			83.4				20.8	97.7	84.0		26.4				92.1		67.4
Ampicillin/sulbactam	26.6		57.5								52.1						40.7
Aztreonam			22.1		20.4						36.0						26.2
Benzylpenicillin															1.0		1.0
Carbapenems	55.5		8.6	74.1	6.9						23.4		33.3	53.8			33.6
Cefaclor									55.5								55.5
Cefazolin			62.3								69.7						66.0
Cefepime	56.7		8.8		18.2						16.4		22.0				27.7
Cefoperazone/sulbactam	59.0																59.0
Cefotaxime	100.0		27.3									11.0	100.0			35.1	46.8
Cefotetan			0.6								20.0						10.3
Cefoxitin			17.0										100.0		25.7		47.6
Ceftazidime	66.4		25.3		24.8						29.5		25.3				32.3
Ceftazidime/cefepime	95.2												22.9				59.1
Ceftriaxone	62.8		41.3		20.8	25.4					37.6		91.4			38.2	45.6
Cefuroxime			7.0						32.5		19.5						19.7
Cephalosporins			87.4								68	0	0	48.5	0	0	76.8
Chloramphenicol									3.9							6.0	5.0
Ciprofloxacin	56.2	57.8	36.3		1.0	5.1		86.0			20.1	17.0	25.4	54.7	21.3		32.4
Clarithromycin										21.4							21.4
Clindamycin															25.8		25.8
Clindamycin		72.3													37.2		54.8
Colistin	3.8										30.1		7.0				14.1
Doripenem	24.4										33.4		8.1				24.8
Ertapenem				18	10						27.5		43.5			0.3	22.7
Erythromycin								88							27.8	55.8	51.1
ESBLs			18.2			26.7					34.3			25.0			26.8
Fluoroquinolones	71.7		39.5			16.0					42.7		38.8		81.5		48.3
Fosfomycin			1								27.9						14.5
Fosfomycin			14								80						47
Gentamicin	40.4	50.7	22.5		4.5		59.1				19.1		21.6	29.2	28.3		27.6
Glycopeptides								33.0									33.0
Imipenem	51.4		0.6		8.3						19.9		27.7				27.2
Imipenem/cilastatin													13				13
Levofloxacin	21.2		46.2		1.2			70.0		15.8	13.5		30.3		17.9	0.3	26.9
Linezolid	11.9	1															6.5
Meropenem	57.8		1.4			7.9					11.6		24.3			36.6	28.7
Methicillin															44.9		44.9
Metronidazole										38.9							38.9
Moxifloxacin															1.7		1.7
Multidrug	44.3		24.0								49.1		28.8				39.5
Nalidixic acid			52														52
Nitrofurantoin			4.6			3		5.9			10.4						5.4
Ofloxacin									0.3								0.3
Oxacillin		89.7													36.6		45.4
Penicillin			67					98.1							93	16.7	58.3
Piperacillin													9				9
Piperacillin/tazobactam	63.0		14.9		13.9	12.2					30.4		27.2	8.8			29.4
Rifampicin		13.6								0.9					17.85		13.61
Teicoplanin							28.0										28.0
Tetracycline								75.0	5.8						34.0	94.0	48.6
Tigecycline	6.1					0.8					6.9						5.6
Tobramycin	14.2		15.4								15.0		33.7				19.5
TXS	54	58.1	45.2		13.5	18.7					42.0				5.2	75.5	37.6
Vancomycin		6.5					23.3	33.2							10.4		21.3
Beta-lactam/beta-lactamase inhibitor			64.3				14.0										39.1
Total average (%)	52.6	43.7	27.4	46.1	12.8	17.7	33.4	59.4	28.9	15.4	28.8	14.0	29.0	48.6	29.7	36.7	38.4

ESBLs: extended-spectrum beta-lactam/beta lactamase-inhibitor; TXS: trimethoprim sulfamethoxazole; 3GC: third-generation cephalosporins.

Table 3: Distribution of correlation between ABC and antibiotic-resistant bacteria, 2016–2022 ($N = 58$).

ABC	Resistant antibiotic	Bacterial resistance to antibiotic in question (±)							
		P. aeruginosa	*K. pneumonia*	*E. coli*	*N. gonorrhoeae*	*A. baumannii*	*E. cloacae*	MRSA	Others (11)
Positive and negative correlation between ABC and rate of resistance		73/14	63/14	68/10	8	53/9	12(5)	15(11)	29
Overall correlation between ABC and rate of resistance		87	77	78	8	62	17	26	29
Carbapenem	Carbapenem	6(2)	8(1)	3		11	3	1	1
	Levofloxacin			0/1					0
	Imipenem	4(1)				2			0
	Ceftazidime	1	0/1						0
	Amikacin						1		0
	Fluoroquinolone	1	1						0
	3GC		1	1					0
	Meropenem	2							0
	Ciprofloxacin			0/1					0
Monobactam	Monobactam								
	Carbapenems					1	2		
Meropenem	Meropenem	3				1		1	0
	Piperacillin/tazobactam								1
	Carbapenems	2							0
Cefepime/Cefotaxime	Cefepime/Cefotaxime	1		2(1)		2			1
Imipenem	Imipenem	1(1)	1			1			0
	Meropenem		1						
	Piperacillin/tazobactam	1							
	Carbapenems	1							0
Imipenem/cilastatin	Imipenem/cilastatin	1	1	1				0/1	0
Piperacillin/tazobactam	Piperacillin/tazobactam	4		2		2	0/1	0/1	3
	Imipenem		1						
	Meropenem		1						
	Aminoglycoside		1						0
Linezolid	Linezolid								1
Fluroquinolone	Fluroquinolone	3	3(1)	5	1	1			3
	Trimethoprim/sulfamethoxazole		1						0
	Levofloxacin			3		2			1
	Imipenem	1				0/1			0
	Ceftazidime		2						0
	Amikacin						1		0
	Carbapenem		0/1	1(1)					1
	Ciprofloxacin	2(2)	3(1)	3(1)	1	3	0/1	1(2)	3
	3GC		1	2					0
Levofloxacin	Levofloxacin	2		1		1		1	0
	Fluoroquinolone	1	1	1					0
	Carbapenem		1						0

Table 3: Continued.

ABC	Resistant antibiotic	Bacterial resistance to antibiotic in question (±)							
		P. aeruginosa	*K. pneumonia*	*E. coli*	*N. gonorrhoeae*	*A. baumannii*	*E. cloacae*	MRSA	Others (11)
Ciprofloxacin	Ciprofloxacin	2(1)	2	3		1 (1)			1
	Carbapenem		0/1						0
	Meropenem					1			
	Imipenem					1			
	Piperacillin/tazobactam								
	Fluoroquinolone			1					0
Norfloxacin	Norfloxacin								0
	Carbapenem		0/1	1					0
Ofloxacin	Ofloxacin								0
	Carbapenem		0/1	0/1					0
Beta-lactam/beta-lactamase inhibitor	Beta-lactam/beta-lactamase inhibitor		1	2					0
	Carbapenem			1		4	2(1)		0
	Levofloxacin		2						0
	Imipenem	2				1			0
	Piperacillin/tazobactam	0/1							0
	Ceftazidime	4							0
Amoxicillin/clavulanate	Amoxicillin/clavulanate	1	1(1)	2				1(2)	2
	3GC		1						0
Cephalosporin	Cephalosporin	1	7(1)	7	1	1		2	0
	Amoxicillin/clavulanate			1					0
	Trimethoprim/sulfamethoxazole			1					0
	Levofloxacin		1			1			0
	3GC		1	2					0
	Ciprofloxacin				1				0
	Carbapenem		1			3			0
	Piperacillin/tazobactam	2	0/1						0
	Cefotaxime			2					
	Cefepime	0/1	2	2(1)					
	Ceftazidime		0/1						0
Aminoglycosides	Aminoglycosides	1				2(2)		0/1	0
	3GC		1(1)	1(1)					0
	Ciprofloxacin			1(1)	1				0
	Imipenem	1				1			0
	Ceftazidime		1						0
	Amikacin	2					1		0
	Gentamicin	2							0
	Carbapenems	1							0
Macrolides	Macrolides				1				2
	Cefixime				1				0
	Ciprofloxacin				1				0
	Clarithromycin								2

Table 3: Continued.

ABC	Resistant antibiotic	Bacterial resistance to antibiotic in question (±)							
		P. aeruginosa	*K. pneumonia*	*E. coli*	*N. gonorrhoeae*	*A. baumannii*	*E. cloacae*	MRSA	Others (11)
Tigecycline	Tigecycline					1			0
	Piperacillin/tazobactam	0/1							0
Amikacin	Amikacin	3(2)				0/1			0
	Aminoglycosides	1							0
	Imipenem	1 (1)				0/1			0
	Meropenem					0/1			0
Gentamicin	Gentamicin	1	1(1)	1		1			1
	Aminoglycosides	1							0
Fosfomycin	Fosfomycin			1		1			0
Oxacephems	Oxacephems					1			0
	Levofloxacin			1					0
	Imipenem	2				0/1			0
	Ceftazidime		1						0
Sulfonamides	Sulfonamides		2	2				1	0
	Imipenem	1							0
	Ceftazidime		1						0
All antibiotics	All antibiotics		1	1			1		2
	Fluoroquinolone		1	1		1			0
	Levofloxacin			1					0
	3GC		1	1					0
	Carbapenem		1	1					0
	Cloxacillin							1	0
	Macrolides								1
β-Lactam antibiotics	β-Lactam antibiotics		1						0
	3GC		2	1					0
	Carbapenem	1	1						0
Cloxacillin	Cloxacillin							1	0
Tetracycline	Tetracycline								0
	Fluoroquinolone			1					0
	Nalidixic acid			1					0
	Carbapenem					1			0

Table 3: Continued.

ABC	Resistant antibiotic	Bacterial resistance to antibiotic in question (±)							
		P. aeruginosa	*K. pneumonia*	*E. coli*	*N. gonorrhoeae*	*A. baumannii*	*E. cloacae*	MRSA	Others (11)
Ceftazidime	Ceftazidime	1							
	Imipenem					1			
	Meropenem	1				1			
Glycopeptides	Glycopeptides	1					1	0/2	1
	Amikacin			0/1		0/1	0/1		0
	Gentamicin						0/1	1(1)	3
	Carbapenem		1			1			
	Piperacillin/tazobactam	1						1	0
	Extended-spectrum cephalosporin			1					
	Amikacin	1		1		1			1
	Oxacillin							1	0
Others				1				2 (1)	0

3GC: third-generation cephalosporins.

strong cross-correlation between consumption of amikacin and rates of imipenem resistance strains of *P. aeruginosa* and MDR strains of *P. aeruginosa* [57] and aminoglycosides with rates of *P. aeruginosa* resistance to tazobactam-piperacillin [39].

A strong cross-correlation was recorded between consumption of all beta-lactam antibiotics and the rate of carbapenem-resistant P. aeruginosa [34], penicillin with the resistance density of carbapenem-resistant *P. aeruginosa* [53], beta-lactam/beta-lactamase inhibitor combinations, oxacephems, sulfonamides, and quinolones with the rate of imipenem resistance in *P. aeruginosa* [25], and carbapenems with the rate of ceftazidime-resistant *P. aeruginosa* [77]. But moderate cross-resistance was observed between quinolone consumption and resistance density of carbapenem-resistant *P. aeruginosa* [53] and all beta-lactam antibiotics with rate carbapenem-resistant *P. aeruginosa* [34], carbapenems and glycoproteins with aminoglycosides-resistant *P. aeruginosa* [68], cephalosporin/beta-lactamase inhibitor and penicillin/beta-lactamase inhibitor combinations with ceftazidime-resistant P. aeruginosa [77], and penicillin/beta-lactamase inhibitor combinations, fluoroquinolones, imidazole, colistin, and tigecycline consumption with piperacillin-tazobactam-resistant *P. aeruginosa* [39].

Similar to *P. aeruginosa*, there were records on the relationship between the rate of antibiotic-resistant *A. baumannii* and ABC. Consumption of carbapenems was very strongly correlated with imipenem resistance in *A. baumannii* [25] and with carbapenem resistance in *A. baumannii* [60, 68]. Consumption of carbapenems was strongly correlated with the rate of carbapenem-resistant *A. baumannii* [33, 37, 52, 77] and carbapenems and imipenem with imipenem-resistant A. *baumannii* [55, 61], but meropenem was moderately correlated with the rate of meropenem-resistant A. *baumannii* [32].

Likewise, consumption of cefepime was very strongly correlated with cefepime-resistant *A. baumannii* [33] and tigecycline with the incidence density of *Acinetobacter* [52]. The consumption of piperacillin/tazobactam and extended-spectrum cephalosporins was strongly correlated with piperacillin/tazobactam-resistant and extended-spectrum cephalosporin-resistant *A. baumannii* retrospectively [37]. There was also a strong correlation between the consumption of fluoroquinolones and ciprofloxacin-resistant *A. baumannii* [62]. A moderate correlation was found between the consumption of cefepime and ciprofloxacin with cefepime and ciprofloxacin-resistant *A. baumannii*, respectively [32], gentamicin with gentamicin-resistant *A. baumannii* [58], and fosfomycin with the rate of fosfomycin resistance in *A. baumannii* [55]. However, there were strong negative correlations between the consumption of aminoglycosides and an incidence density of aminoglycoside-resistant *Acinetobacter* spp. [52] and a moderate negative correlation between ciprofloxacin and ciprofloxacin-resistant *A. baumannii* [37].

Cross-resistance was also reported for different antibiotics and resistant *A. baumannii*. There was a very strong correlation between consumption of ceftazidime and both imipenem and meropenem-resistant *A. baumannii* [69], cephalosporin/beta-lactamase inhibitor combinations [60, 77], and tetracyclines [60] with carbapenem-resistant *A. baumannii*. There was a strong correlation between consumption of cephalosporins, cephalosporin/beta-lactamase inhibitor combinations, and other beta-lactam/beta-lactamase inhibitor combinations with carbapenem-resistant *A. baumannii* [77], but a moderate correlation was evident between cephalosporin carbapenem-resistant *A. baumannii* [77] and glycoprotein with carbapenem-resistant A. *baumannii* [68], and monobactams were moderately correlated with rates of carbapenem-resistant *A. baumannii* [77], but amikacin was very strongly and negatively correlated with rates of MDR strain *A. baumannii*, rates of imipenem-resistant strain *A. baumannii*, and rates of resistant meropenem strain *A. baumannii* [57]. A negative strong cross-correlation was also reported between the consumption of glycopeptides and amikacin-resistant *A. baumannii* [62] and aminoglycosides, quinolones, and oxacephems with imipenem-resistant *A. baumannii* [25], whereas ciprofloxacin was strongly and negatively correlated with both imipenem and meropenem-resistant *A. baumannii* [69].

Similarly, there was a very strong correlation between the consumption of imipenem/cilastatin and the resistance rate of *K. pneumoniae* to imipenem/cilastatin and fluoroquinolones with the prevalence of ciprofloxacin-resistant *K. pneumoniae* [43], but there were very strong negative correlations between imipenem and imipenem- and meropenem-resistant *K. pneumoniae* [69]. There was a strong correlation between the consumption of carbapenems and carbapenem-resistant *K. pneumoniae* [77] and extended-spectrum cephalosporins with extended-spectrum cephalosporin-resistant *K. pneumoniae* [69]. Colistin resistance was strongly correlated with the consumption of colistin [39]. Consumption of carbapenems was moderately correlated with doripenem-resistant, ertapenem-resistant, and meropenem-resistant *K. pneumoniae* [39] and carbapenem-resistant *K. pneumoniae* [44]. Consumption of cephalosporins was also moderately correlated with the rate of cephalosporin-resistant *K. pneumoniae* [44] and fluoroquinolones with ciprofloxacin-resistant *K. pneumoniae* [61].

A very strong cross-correlation was observed between the consumption of piperacillin/tazobactam and aminoglycoside-resistant *K. pneumoniae* [22], meropenem-resistant and imipenem-resistant *K. pneumoniae* [69], fluoroquinolones with trimethoprim/sulfamethoxazole-resistant *K. pneumoniae* [22], and the beta-lactam/beta-lactamase inhibitor combinations with carbapenem-resistant *K. pneumoniae* [22]. Consumption of sulfonamides was also very strongly correlated with the rate of ceftazidime-resistant *K. pneumoniae* and ceftazidime with quinolone-resistant *K. pneumoniae* [25]. There was a strong correlation between colistin-resistant *K. pneumoniae* and imidazoles, carbapenems, and colistin [39], doripenem-resistant *K. pneumoniae* with the consumption of imidazoles, ertapenem-resistant *K. pneumoniae* with glycopeptides, and meropenem-resistant *K. pneumoniae* with glycopeptides [39], and ceftriaxone was moderately correlated with the rate of carbapenem-resistant *K. pneumoniae* [35] and carbapenems with *K. pneumoniae* resistant to third-generation cephalosporin [63]. A moderate cross-correlation was observed

between the consumption of glycopeptides and carbapenem-resistant *K. pneumoniae* [68].

A very strong negative cross-resistance was found between consumption of beta-lactam/beta-lactamase inhibitor combinations with fluoroquinolone-resistant *K. pneumoniae* [22], between doripenem-resistant *K. pneumoniae* and first- and second-generation cephalosporins, and aminoglycosides [39]. There was a strong negative correlation between the consumption of ciprofloxacin, ofloxacin, and norfloxacin with carbapenem-resistant *K. pneumoniae* [35]; colistin-resistant *K. pneumoniae* with first- and second-generation cephalosporins and penicillin/beta-lactamase inhibitor; between doripenem-resistant *K. pneumoniae* and third- and fourth-generation cephalosporin and glycopeptides; between ertapenem-resistant *K. pneumoniae* and first- and second-generation cephalosporins; and between meropenem-resistant *K. pneumoniae* and penicillin/beta-lactamase inhibitor combinations, fluoroquinolone, and tigecycline [39]. A strong correlation was also found between carbapenem and rates of ceftazidime resistance in *K. pneumoniae* [25], fourth-generation cephalosporins, and fluoroquinolone within cefepime-resistant and ciprofloxacin-resistant *K. pneumoniae* [62].

Antibiotic-resistant *E. coli* was also correlated with the consumption of several antibiotics. There was a very strong correlation between ciprofloxacin consumption with fluoroquinolone-resistant *E. coli* [65], and a strong correlation was found between fluoroquinolone and fluoroquinolone-resistant *E. coli* [48, 65], fluoroquinolones with the resistance rate of *E. coli* to levofloxacin and resistance rate of *E. coli* to ciprofloxacin [42], and ciprofloxacin with ciprofloxacin-resistant *E. coli* [37], but there was a strong negative correlation between fluoroquinolone and ciprofloxacin-resistant *E. coli* [62]. There was also a very strong correlation between cefotaxime and cefotaxime-resistant *E. coli* and a strong correlation between cefoxitin and cefoxitin-resistant *E. coli* [65], gentamicin with resistant *E. coli* [33], extended-spectrum cephalosporin with resistant *E. coli* [37], and imipenem/cilastatin with imipenem/cilastatin-resistant *E. coli* [62].

There was a very strong cross-correlation between third- and fourth-generation cephalosporin use and *E. coli* resistance rates to cefotaxime and cephamycin use with *E. coli* resistance rates to cefoxitin [65]. A strong cross-correlation was found between carbapenems and third-generation cephalosporin-resistant *E. coli* [61] and beta-lactam/beta-lactamase inhibitor combinations with resistance density of third-generation cephalosporin-resistant *E. coli* [62], but fourth-generation cephalosporins were negatively correlated with cefepime-resistant *E.*coli, glycopeptides with amikacin-resistant *E. coli* [62], aminoglycosides [35, 61], and ofloxacin with carbapenem-resistant *E. coli* [35].

Antibiotic-resistant *N. gonorrhoeae* was reported in two studies [23, 49]. Consumption of ceftriaxone was strongly correlated with resistant *N. gonorrhoeae*, but consumption of ciprofloxacin was moderately correlated [23]. Macrolide consumption and cefixime resistance in *N. gonorrhoeae* and consumption of cephalosporin, macrolide, and quinolone were strongly correlated with ciprofloxacin resistance in *N. gonorrhoeae* [49]. Consumption of quinolones and cefotaxime was positively associated with ciprofloxacin-resistant and cefotaxime-resistant *N. gonorrhoeae*, respectively [74].

Consumption of aminoglycosides, quinolones, and carbapenem was strongly correlated with amikacin-resistant *E. cloacae* [25]. But carbapenem-resistant *E. cloacae* showed significant, very strong negative correlations with the usage of penicillin/beta-lactamase inhibitor I combinations, beta-lactam/beta-lactamase inhibitor combinations, meropenem, and carbapenems, but a very strong positive correlation was shown with total cephalosporin use [60]. Consumption of piperacillin/tazobactam was very strongly correlated with resistant *C. difficile*, but it was very strongly but negatively correlated with vancomycin [31] and ESBL-positive *Enterobacteriaceae* rates [33]. A positive association was also reported from the consumption of macrolides and clarithromycin-resistant *H. pylori* [50, 75] and consumption of quinolones with levofloxacin-resistant *H. pylori* [75].

Consumption of meropenem was very strongly correlated with piperacillin/tazobactam-resistant *Enterobacter* spp. [69] and meropenem and ciprofloxacin with piperacillin/tazobactam-resistant *Enterobacter* spp. [69], and piperacillin/tazobactam and resistant *C. difficile* [31] and strong correlation between carbapenems with carbapenem-resistant *E. cloacae* [77], aminoglycoside and quinolone with amikacin-resistant *E. cloacae* [25], and fluoroquinolone and MDR *H. influenzae* and *Shigella* spp. [41], but the moderate correlation was shown between macrolide and macrolide-resistant *T. pallidum* [51], carbapenem and carbapenem-resistant *Enterobacteriales* [70], and carbapenems, monobactams, cephalosporin/beta-lactamase inhibitor, and penicillin/beta-lactamase inhibitor with carbapenem-resistant *E. cloacae* [77]. A very strong negative correlation was reported between the consumption of vancomycin and resistant *C. difficile* [31] and piperacillin/tazobactam and third- and fourth-generation cephalosporin-resistant *P. mirabilis* [22]; a strong negative relationship was observed between piperacillin/tazobactam and piperacillin/tazobactam-resistant *Proteus* spp. and ESBL-positive *Enterobacteriaceae* [33].

A very strong correlation was observed between the consumption of beta-lactams or beta-lactam/beta-lactamase inhibitors and methicillin-resistant *S. aureus* [22] and clindamycin with oxacillin-resistant *S. aureus* [69]. There was a strong correlation between the consumption of extended-spectrum cephalosporin [70] and cloxacillin [48] and methicillin-resistant *S. aureus* [48, 70], and third-generation cephalosporins, carbapenems, glycopeptides, and monobactams were also moderately correlated with MRSA [63]; monobactams and sulphonamides were also were moderately correlated with MRSA [64]. A very strong correlation was between the consumption of linezolid [38] and vancomycin [69] with vancomycin-resistant *E. faecium* [38, 69]. A moderate correlation was shown between glycopeptides and glycopeptide-resistant *E. faecalis/faecium* [70], penicillin with penicillin resistance in *S. pneumoniae* [71], and extended-spectrum penicillin and penicillin/beta-lactamase inhibitor combinations with the resistance of *S. pneumoniae* to respective antibiotics [71].

There was a very strong negative correlation between the consumption of fluoroquinolone with ciprofloxacin-resistant *E. faecalis* [62] and third-generation cephalosporins and Hlr-gentamicin-resistant *E. faecalis* [22] and strong negative correlation between the consumption of fluoroquinolone and ciprofloxacin-resistant *S. aureus*, glycopeptides, and gentamicin-resistant *S. aureus*, glycopeptides, and gentamicin-resistant CoN *Staphylococcus*; glycopeptides with amikacin-resistant *E. faecium* and gentamicin-resistant *E. faecalis* [62] and piperacillin/tazobactam and vancomycin with oxacillin-resistant *S. aureus* [33]. A moderate correlation was shown between the consumption of gentamicin and gentamicin-resistant *E. faecalis* [48] and fluoroquinolone with ciprofloxacin-resistant *CoN Staphylococcus* [62]. The consumption of amoxicillin/clavulanate and oxacillin resistance in *S. aureus* [33] and imipenem/cilastatin and imipenem/cilastatin-resistant MRSA were very strongly and negatively correlated [42]. Consumption of glycopeptides and aminoglycosides was negatively correlated with MRSA [64].

4. Discussion

ABR is identified as one of the top threats to public health and challenges progress in health care, food production, and life expectancy [6, 78]. Due to overuse and misuse of antibiotics, bacteria have become increasingly resistant to various antibiotics [1]. A recent point prevalence survey at the global level reported about 136 million per year hospital-associated infections resistant to antibiotics caused by high-priority pathogens (*E. coli, Acinetobacter* spp., *Klebsiella* spp., *S. aureus, Enterobacter* spp., *and Pseudomonas* spp.) [79]. The current review revealed 38.4% of the average pooled prevalence of antibiotic resistance to bacteria, with *E.* faecium (59.4%), *A. baumannii* (52.6%), *P. aeruginosa* (48.5%), coagulase-negative *Staphylococcus* (43.7%), *Enterobacter* (46.1%), and *P. mirabilis* (48.5%). This complements the global concerns on the ABR [1, 6, 78, 79]. The burden of the *ESKAPE* and antibiotic resistance pattern calls for surveillance of antibiotic resistance targeting these pathogens by incorporating them into the infection control policy [80, 81]. It requires preventing infections as priority, slowing the development of ABR through better antibiotic use, and stopping the spread of ABR when it develops [78].

According to a recent report from a global point prevalence survey, high use of antibiotics (62.0%) and prolonged surgical antibiotic prophylaxis (60.9%) were the most common problems [82]. Thus, overuse and inappropriate use of antibiotics are recognized as a significant driver of the emergence of resistant strains of bacteria as the increased exposure to antibiotics encourages the development of ABR [83–85]. Increased ABC of broad-spectrum and last-resort antibiotics is a serious concern for public health [84–86]. Inappropriate consumption of antibiotics has also been shown to contribute to the occurrence of MDR organisms [86]. The current review [20–78] has clearly shown the relationship between ABC and ABR. It revealed more than 70% consumption of antibiotics from the Watch and Reserve categories based on the WHO AWaRe classification, among which consumption of carbapenems and fluoroquinolones were the most frequently involved in ABR including cross-resistance with consumption of other antibiotics. This was in line with a recent report from the global level which concluded, "*a large proportion of prescriptions for key Watch antibiotics were issued for indications other than those for which they were included in the Essential Medicine List*" [82]. Thus, a direct epidemiological relationship between ABC and the emergence and dissemination of resistant bacterial strains needs to be worked on for further understanding.

Biofilm-forming pathogens such as *P. aeruginosa, A. baumannii, C. jejuni, C. difficile, C. perfringens, E. faecalis, K. pneumonia, P. mirabilis, B. cepacia, P. pseudomallei, H. influenza, E. coli, S. aureus, S. epidermidis, S. pneumonia, S. pyogenes, Salmonella* spp., *L. monocytogenes, S. agalactiae, and V. cholerae* are very difficult to treat with conventional antibiotics due to their greater resistance profile [87, 88]. The CDC and WHO classified most of these microorganisms as threats to healthcare [6, 78] and call for close monitoring of resistance patterns for highly susceptible antibiotics [6, 78]. WHO classified carbapenem- and third-generation cephalosporin-resistant *P. aeruginosa*, *A. baumannii*, *Enterobacteriaceae*, *K. pneumoniae*, *E. coli*, *Enterobacter* spp., *Serratia* spp., *Proteus* spp., *Providencia* spp., and *Morganella* spp. as critical threats (top priority) to health care and vancomycin-resistant *E. faecium*, methicillin-resistant and vancomycin-intermediate and resistant *S. aureus*, clarithromycin-resistant *H. pylori*, fluoroquinolone-resistant *Campylobacter* spp., fluoroquinolone-resistant *Salmonella* spp., and third-generation cephalosporin-resistant fluoroquinolone-resistant *N. gonorrhoeae* as a high priority [78]. The direct relationship between ABCs as evidenced from the current review [20–78] indicates a need for developing new therapeutic strategies that can be effective against common infections in addition to optimizing the use of available antibiotics.

Similarly, the CDC classified carbapenem-resistant *Acinetobacter*, *C. difficile*, carbapenem-resistant *Enterobacteriaceae*, and drug-resistant *N. gonorrhoeae* as urgent threats and drug-resistant *Campylobacter*, extended-spectrum beta-lactamase-producing *Enterobacteriaceae*, vancomycin-resistant *Enterococci*, MDR *P. aeruginosa*, drug-resistant nontyphoidal *Salmonella*, drug-resistant *Salmonella serotype Typhi*, drug-resistant *Shigella*, methicillin-resistant *S. aureus*, drug-resistant *S. pneumoniae*, and drug-resistant *Tuberculosis* as serious threats to health care [6]. As can be noted, the current review strengthens the need to approach pathogens as a major issue problem related to resistance against antimicrobial agents.

Antibiotics with "high resistance potential," even with limited use, have been associated with the emergence of MDR Gram-negative bacteria, e.g., imipenem, ceftazidime, gentamicin/tobramycin, and ciprofloxacin [89]. ASP is known to result in decreased ABC and ABR [90]. Due to a strong association between ABC and the development of antibiotic resistance [83], reducing the need for and inappropriate consumption of antibiotics through the implementation of appropriate ASPs can help delay the emergence and spread of ABR [90, 91]. Prudent use of

antibiotics has to be a pillar in the fight against ABR [82]. This requires aligning practice with evidence which requires changes in prescribing behavior based on the implementation of effective strategies to modify prescribing practices by aligning them with evidence-based recommendations for diagnosis and management [92]. Thus, the initial step in fight against ABR in healthcare institutions has to be to measure the situation of antimicrobial use and resistance in their setting to raise awareness on areas of improvement of local prescribing behaviors [82]. The current review will help to understand the relationship between ABC and resistance and justify the need for universal funding and urgency for implementation of ASPs taking into account the local context for sustainable behavioral change in physicians' antibiotic prescribing practices.

The review will serve as an important basis to better understand the issue and will inform policies, regulations, and interventions to optimize antibiotic use while reducing ABR. However, it has to be noted that the review does have limitations. The review includes literature in the English language and was not evaluated by independent evaluators. Because of the multiple numbers of antibiotics and microorganisms tested, risk assessment for bias and quality was not considered. Since most of the studies were done retrospectively, they may not necessarily show the true relationship between ABC and the rate of resistance. There are no data on the relationship between the consumption of antibiotics and the respective resistance rates in all parts of the world.

In conclusion, there was a strong relationship between antibiotic consumption and antibiotic resistance. The review also revealed a significant cross-resistance among different antibiotics. Most correlations were positively related, but a minority was negatively correlated, indicating the protective nature of antibiotic consumption for the development of resistance. There was a very strong correlation between fluoroquinolones, carbapenems, aminoglycosides, and penicillin consumption and respective resistance rates, but colistin, imipenem/cilastatin, and fluoroquinolones consumption was strongly correlated with the resistance rate of *K. pneumoniae*. Carbapenems were the most commonly used and strongly correlated with the rate of resistance for *A. baumannii*. Strict use of antibiotics is thus crucial to minimize the risk of emerging resistant organisms. ASP will help to optimize antibiotic therapy while reducing the amount of ABC to prevent the development and rate of ABR. Systems to assess institutional antibiotic utilization and the relationship between the trend of antibiotic use and rates of antibiotic resistance are strongly needed in health facilities to reduce resistance. Furthermore, special emphasis should be paid to antibiotics in the Watch and Reserve category of the WHO AWaRe classifications such as carbapenems, fluoroquinolones, macrolides, glycopeptides, and second-fourth generation cephalosporins.

Data Availability

Since all data are included in the review, no additional data is required to support the findings of this study.

Ethical Approval

Ethical clearance is not required for the review article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

AAA was involved in the conception, study design, execution, and acquisition of data, analysis and interpretation, and writing and review of manuscript. TGF was involved in the conception, study design, manuscript writing, and review. GY was involved in the writing and review of the manuscript.

Supplementary Materials

Annex 1: summary of relationship between antibiotic consumption and antibiotic resistance, 2016-2022, (N=58). (*Supplementary Materials*)

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