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Review Article

Antibiotic Resistance in Saudi Arabia: A Systematic Review of the Past Five Years

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Abstract

Multidrug-resistant bacteria are a global issue that counts for high morbidity and mortality rate as well as high budget outlay worldwide. The increase in the prevalence of multidrug-resistant bacteria results in limited choices of antibiotics to treat infections. Thus, the aim of the current systematic review is to summarize the available information about the occurrence of antibiotic resistance in Saudi Arabia in the past five years. The PRISMA guidelines were followed. A systematic search was carried out between January 2018, and October 2022, on the databases Psych INFO, PubMed, Wiley Online Library, Medline, Google Scholar, CINAHL, and NATURE. The language restriction was limited to English and applied only to the Saudi Arabian region for the past five years. Nineteen papers were included in the final analysis. Twenty types of bacteria were identified in the current systematic review including A. baumannii, P. aeruginosa, E. coli, K. pneumoniae, S. maltophilia, Citrobacter, Enterobacter, S. pneumoniae, H. influenzae, S. aureus, Proteus, Enterococcus, Mycobacterium tuberculosis, Staphylococcus, Morganella Morganii, Pseudomonas, H. pylori, Colistin-Resistant Organisms, Pantoea agglomerans and Serratia species. In addition, fifty-two types of antibiotics were commonly used in the past five years in Saudi Arabia. Furthermore, the included articles showed that the majority of these bacteria were multidrug-resistant to the most commonly used antibiotics. We conclude that, in the past five years, a high rate of multidrug-resistant was identified in Saudi Arabia. Therefore, to reduce the magnitude of the seriousness of antibiotic resistance, physicians should prescribe antibiotics based on the findings of culture and sensitivity tests.

Keywords: Antibiotic, Bacterial Infection, Resistance, Saudi Arabia, Systematic Review

Introduction

Antimicrobial resistance (AMR) is a global problem that contributes to high hospital morbidity and death rates [1]. Antibiotic resistance is a significant component of AMR that refers to bacteria that develop resistance to antibiotics [2]. Antibiotic resistance is the capacity of bacteria to survive and proliferate despite the presence of antibiotics [3]. Globally, there is an increasing worry about AMR, which is currently assessed to cause over 700,000 fatalities annually [4]. AMR will cost around 10 million lives and about 100 trillion dollars annually by 2050 if no appropriate actions are taken to prevent its spread [5]. It is one of the most serious risks posed by bacteria since it causes fatal infections, prolonged disease, expensive costs, and increased mortality [6].

Antibiotic resistance is a problem that concerns every country, irrespective of its level of income and development, as resistant pathogens do not respect borders [7]. However, there were considerable gaps in surveillance and a lack of methodological standards in many countries around the world. The World Health Organization (WHO) reported very high resistance rates both for healthcare-associated and community-acquired infections [8]. Furthermore, the WHO recognizes that the development of AMR is an

urgent issue that necessitates a global, coordinated action plan to address [9].

Antibiotic use is the key factor in the emergence and development of resistance [10]. In addition, contamination of the environment with antibiotics may result in the establishment of antibiotic resistance and provide a reservoir for antibiotic-resistant genes [11]. Moreover, it has been consistently shown that in those areas where the usage of antibiotics is high, resistance is widespread both in community and hospital settings [12]. Furthermore, poor management, an unhygienic environment, untrained professionals, overuse, and misuse of antibiotics are major factors that lead to the development of these panic situations in the form of adopting or acquiring resistant genes by bacteria [13].

It is anticipated that 70% of antibiotic resistance is ascending in the Asia region, making it a countrywide and worldwide hazard [14]. According to the data, 92 out of 194 member nations and 5 out of 6 WHO global regions have reported cases of Escherichia coli (E. coli) resistant to fluoroquinolones. Similarly, 86 countries and 5 regions reported 3rd generation cephalosporin resistance. Methicillin-resistant Staphylococcus aureus (S. aureus) and third-generation cephalosporin/carbapenem-resistant Klebsiella pneumoniae (K. pneumoniae) showed similar prevalence rates [15].

In Saudi Arabia, numerous individual studies have been conducted on the prevalence of AMR [16-18]. However, no systematic report has been published to present a comprehensive depiction of antibiotic resistance in Saudi Arabia. This absence of high-quality data is problematic since it often results in inappropriate treatment suggestions for the situation. Furthermore, to design suitable local interventions, it is important to understand the current status of antibiotic resistance. Therefore, the purpose of this systematic review is to summarize the available information about the occurrence of antibiotic resistance in Saudi Arabia in the past five years and to identify knowledge gaps.

Methods

Review Protocol Registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement's guiding guidelines were followed when conducting the current systematic review [19]. The protocol of this systematic review was also listed in PROSPERO, the International Prospective Register of Systematic Reviews (Code no. CRD42022365500).

Eligibility Criteria

Papers were included in this systematic review because they met the following eligibility requirements:1) Participants: inpatients, outpatients, and the general population of any age with bacterial infections; 2) Exposure: microbial infection; and 3) Outcome: AMR.

Nevertheless, the following exclusion criteria were taken into account: (1) papers recruited non-human subjects; (2) studies carried out outside of Saudi Arabia; (3) reviews and meta-analyses papers; (4) non-English language papers; (5) case reports; (6) papers are not reporting bacterial infection and AMR; (7) articles without full text; and (8) papers lacking critical information.

Search Strategy

A systematic search was carried out between January 1, 2018, and October 1, 2022, on the databases PsychINFO, PubMed, Wiley Online Library, Medline, Google Scholar, CINAHL, and NATURE. The language restriction was limited to English and applied only to the Saudi Arabian region for the years 2018–2022. Using truncations, Medical Subject Headings (MESH), and Boolean operators, a set of search phrases was generated (Table 1).

Table 1: Search terms and linkage used in Medline.

Participants	exp Saudi /OR Saudi Arabia* OR inpatients* OR outpatients* OR admitted* OR hospitalized* OR infected
	AND
Exposure	exp bacteria/OR exp infection/OR bacterial isolate* OR gram-negative bacteria* OR gram-positive bacteria
	AND
Outcomes	exp AMR/OR exp antibiotic resistance/OR drug resistance* OR antibiotic susceptibility* OR Antibiotic Resistance Profile* OR antibiotic susceptibility patterns

Data Extraction

The papers from the electronic database searches were compiled using the Mendeley reference management tool. After removing duplicates, a screening was performed to make sure the research complied with the eligibility standards. Title, abstract, and full-text criteria were used in three stages of article screening. The most important data pertaining to the study subject was meticulously obtained and compiled to enable comparison and synthesis of the investigations.

Table 2 lists the first author's name and the year of publication; the study city; the study design; the number of isolates; the patient's types and genders; the sources of the samples; the isolated bacteria; the AMR test; the name of the antibiotic; the rates of antibiotic resistance; and the study's major findings.

Evaluation of the Included Papers Quality

The quality of the qualifying papers was assessed using the National Institutes of Health Quality Assessment method for Observational Cohort and Cross-Sectional Studies [20], which tackles the design, selection bias, data collection, confounders, blinding, and attrition. For each item, a final grade of "good," "fair," or "poor" was given.

Data Analysis

A narrative synthesis was conducted in order to account for confounding, mediating, and moderating variables which are typ-

ically overlooked in meta-analyses. Each study was presented, then compared, examined, and finally synthesized. Because the outcome metrics used in the articles varied, we were unable to do a meta-analysis [21].

Table 2: Summary of the Included Papers.

Author(s) and Year of Publication	City	Study design	No. of Isolates	Patients	Male (%) /Female (%)	Source of Samples	Bacterial Isolates	Antimicrobial susceptibility test	Antibiotic name	Antibiotic resistance low, high rates (%)
Khaled et al. (2021) (*Khaled et al.*, 2021)	Riyadh	Cross-sectional	342	Outpatients	62.28/37.72	Whole body tissues	A. baumannii	Broth dilution	Colistin	48.54
									Azidothymidine	85.96
Al-Tawfiq et al. (2020) (*Al-Tawfiq et al.*, 2020)	Dhahran	In vitro surveillance study	32,890	Hospitalized patients	NM	Whole body tissues	P. aeruginosa	Broth dilution	Imipenem	76
									Amikacin	95
							Non-ESBL E. coli		Nitrofurantoin	20
									Imipenem	100
							K. pneumoniae		Trimethoprim-sulfamethoxazole	86
									Nitrofurantoin	92
							S. maltophilia		Trimethoprim-sulfamethoxazole	65
							Citrobacter		Ceftazidime, Ciprofloxacin, and Piperacillin	71
									Cefepime, Amikacin, Imipenem, and Trimethoprim-sulfamethoxazole	100
							Enterobacter		Cefepime, Amikacin, Imipenem, Gentamicin, and Trimethoprim-sulfamethoxazole	100
							Citrobacter		Cefepime, Ciprofloxacin, Piperacillin, Amikacin, and Imipenem	100
							A. baumanii		Meropenem	56
									Trimethoprim-sulfamethoxazole	73
Torumkuney et al. (2022) (*Torumkuney et al.*, 2022)	Country-level	Country-based surveillance study	55	General public	NM	Respiratory	S. pneumoniae	NM	Penicillin	6.05
									Levofloxacin and Moxifloxacin	100
			36				H. influenzae		Trimethoprim-sulfamethoxazole	52.7
									Ceftriaxone, Clavulanic acid, and Cefpodoxime	100
Kabrah et al. (2021) (*Kabrah et al.*, 2021)	Riyadh	Retrospective study	96	Hospitalized patients	68.8/31.2	Blood, respiratory, urine	K. pneumonia, Staphylococcus, E. coli, A. baumannii, and S. aureus	Disk diffusion	Meropenem	7
									Penicillin	100

Aldrazi et al. (2020) (*Aldrazi et al.,* 2020)	Dammam	Retrospective study	352	Hospitalized patients	65.3/34.7	Pus, urine, blood, respiratory and cerebrospinal fluid	K. pneumoniae, E. coli, Proteus mirabilis, Morganella morganii, Enterobacter and Citrobacter	Disk diffusion	Aztreonam	4.6
									Meropenem	98.7
Farman et al. (2019) (*Farman et al.,* 2019)	Jeddah	Retrospective study	155	Hospitalized patients	NM	NM	Enterococcus faecalis	Broth dilution	Erythromycin	2
									Tigecycline	100
Alyamani et al. (2019) (Alyamani et al., 2019)	Riyadh	Retrospective study	95	Hospitalized patients	95/56	Septum	Mycobacterium tuberculosis	NM	Isoniazid	1.6
									Streptomycin	6.5
Bamshmous et al. (2021) (*Bamshmous et al.,* 2021)	Jeddah	Retrospective	560	Hospitalized patients	57.9/ 42.1	Blood	E. coli	NM	Lincosamides	0
									Glycopeptide	28
							Staphylococcus		Beta-lactams	2
									Penicillin	22
							Acinetobacter		Tetracycline and Lincosamides	0
									Glycopeptide	38.5
							Enterobacter		Lincosamides	0
									Glycopeptide	35.3
							H. influenzae		Tetracycline, Macrolide, Beta-lactams, and Lincosamides	0
									Cephalosporin	35.7
							K. pneumonia		Lincosamides	0
									Glycopeptide	29.2
							M. morgan		Penicillin, Tetracycline, Aminoglycoside, Lincosamides, Quinolones , and Fluoroquinolones	0
									Cephalosporin, Glycopeptide, and Beta-lactams	33.3
							Pseudomonas		Tetracycline	2.1
									Cephalosporin	26
Lagha et al. (2021) (*Lagha et al.,* 2021)	Taif	Cross-sectional	30	Hospitalized patients	53.3/46.7	Blood, sputum, urine, and wound swabs	K. pneumoniae	Broth dilution	Nitrofurantoin and Cefoxitin	12.5
									Piperacillin, Ampicillin, Cefuroxime, and Cefazolin	100
Eed et al. (2019) (*Eed et al.,* 2019)	Taif	Cross-sectional	182	Patients undergoing gastroscopy	41.5/58.5	Gastric biopsies	H. pylori	NM	Tetracycline	7
									Metronidazole	71.3
Taha et al. (2018) (*Taha et al.,* 2018)	Jazan	Cross-sectional	95	Hospitalized patients	NM	Urine, wound, stool, and blood	E. coli	Disc diffusion	Imipenem	16.8
									Ampicillin	84.2

Al Mayahi et al. (2019) (*Al Mayahi et al.,* 2019)	Riyadh	Cross-sectional	131	ICU admitted patients	90.9/9.1	Nasal, wound, respiratory, and urine	colistin-resistant organisms	NM	Clavulanic acid and Ampicillin	14.3
									Cefotaxime	100
Bandy and Almaeen (2020) (*Bandy and Almaeen* 2020)	Aljouf	Cross-sectional	138	Hospitalized patients	60.4/ 39.6	Blood samples	A. baumannii	NM	Colistin	0
									Cefepime, Ceftazidime, Ciprofloxacin, Imipenem, Meropenem, Levofloxacin, Gentamicin, Ampicillin, Ceftriaxone, Nitrofurantoin, Cefuroxime, Amoxicillin, Cefotaxime, Ertapenem, Tigecycline, Cephalosporin, and Piptazobactam	100
							E. coli		Tigecycline, Meropenem, and Colistin	0
									Cephalosporin	91.3
							K. pneumoniae		Colistin	17.6
									Ampicillin	100
AlDiba et al. (2021) (*AlDiba et al.,* 2021)	Jazan	Retrospective cross-sectional study	513	Inpatients and outpatients with bacterial infections	66.5/33.5	Blood, Ear Swab, Sputum, Urine, Wound Swab, Eye Swab	E. coli, P. aeruginosa, S. aureus and K. pneumoniae	E-Test	Mupirocin	1.4
									Pencillin-g	95.8
Smiley et al. (2021) (*Somily et al.,* 2021)	Jeddah, Riyadh, Dammam	Retrospective multicenter study	461,274	Hospitalized patients	NM	Blood, urine, wound swabs, sputum, and other body sites and fluids	P. aeruginosa	Disk diffusion	Cefepime	2.8
									Aztreonam	17.3
							A. baumannii		Ceftriaxone	7.5
									Amoxicillin	60
							S. maltophilia		Cefepime	10
									Trimethoprim-sulfamethoxazole	89.6
Balkhy et al. (2020) (*Balkhy et al.,* 2020)	Riyadh, Jeddah, Alhassa, and Dammam	Retrospective multicenter study	2012	Inpatients and outpatients	47.2/52.8	Blood, respiratory, and urine	Acinetobacter	NM	Aminoglycoside	50
									Cephalosporin	77.9
							Pseudomonas		Aminoglycoside	12.9
									Carbapenem	36.8
							K. pneumoniae		Fluoroquinolones	6.1
									Cephalosporin	43.1
							E. coli		Cephalosporin	50
									Carbapenem	4.4
									Cephalosporin	52.4

Al Wutayd et al. (2018) (*Al Wutayd et al.,* 2018)	Qassim	Cross-sectional	418	Patients visited Qassim University clinics	17.5/82.5	Urine	E. coli K. pneumonia	Automated VITEK 2 Compact System	Cefpodoxime	27.4
									Meropenem, Amikacin	100
									Cefoxitin	17
									Cefepime	95.8
							K. oxytoca		Ampicillin	0
									Cefalotin	77.7
							Proteus mirabilis		Meropenem	10
									Nitrofurantoin	82.9
							Proteus vulgaris		Cefoxitin, Meropenem, Amikacin, Gentamicin, and Trimethoprim/ sulfamethoxazole	33.3
									Nitrofurantoin	83.3
							P. aeruginosa		Meropenem	17.6
									Ampicillin and Piperacillin	100
							Pseudomonas		Norfloxacin, Trimethoprim/ Sulfamethoxazole, and Ciprofloxacin	20
									Ampicillin, Piperacillin, Cefuroxime, Cefpodoxime, Amoxicillin, Meropenem, Amikacin, Gentamicin, Tobramycin, and Nitrofurantoin	100
							Enterobacter		Amikacin	20.8

									Ampicillin, Ceftazidime, and Trimethoprim/ sulfamethoxazole	100
							Enterobacter		Piperacillin and Cefuroxime	14.3
									Cefalotin, Cefpodoxime, Cefotaxime, Ceftazidime, and Cefepime	100
							Morganellamorganii		Amikacin, Gentamicin, and Tobramycin	18.2
									Meropenem, Cefuroxime, Cefpodoxime, and Cefalotin	100
							Pantoea agglomerans		Meropenem	0
									Cefalotin	85.7
							Citrobacter		Meropenem	0
									Cefpodoxime, Ceftazidime, and Nitrofurantoin	100
							A. baumannii		Meropenem and Amikacin	0
									Ampicillin	82.4
							Acinetobacter lwoffii		Meropenem	0
									Cefalotin	81.8
							Serratia marcescens		Piperacillin and Meropenem	0
									Cefalotin, Cefoxitin, and Nitrofurantoin	64.7
							Serratia fonticola		Meropenem	0
									Piperacillin and Ampicillin	100
							Enterococcus faecalis		Inducible clindamycin resistance	0

									Oxacillin, Benzylpenicillin, Gentamicin, Tobramycin, Rifampicin, Nitrofurantoin, and Fosfomycin	100
							Enterococcus faecium		Inducible clindamycin resistance, Linezolid, Teicoplanin, Trimethoprim/sulfamethoxazole, and Mupirocin	0
									Benzylpenicillin, Oxacillin, Tobramycin, Rifampicin, Nitrofurantoin, and Fosfomycin	100
							S. aureus		Cefalotin screen, Moxifloxacin, Linezolid, Tigecycline, Fusidic acid, and Vancomycin	0
									Benzylpenicillin	100
							Staphylococcus saprophyticus		Cefalotin screen, Gentamicin, Tobramycin, Levofloxacin, Moxifloxacin, Linezolid, Mupirocin, Rifampicin, Fusidic acid, Tigecycline, and Vancomycin	0
									Benzylpenicillin	100
Altamimi et al. (2022) (*Altamimi et al.*, 2022)	Riyadh	Retrospective cohort study	99	Hospitalized patients	54.5/45.5	Body fluids, sputum, endotracheal secretions, blood, wound swabs, and urine	P. aeruginosa	E-test	Amikacin	12.1
									Imipenem	39.4
Alhomayani et al. (2022) (*Faisal K. Alhomayani* 2022)	Taif	A single-centered, observational retrospective study	111	Patients with positive urine cultures	44.2/55.8	Urine	E. coli	NM	Tetracycline	4.4
									Ciprofloxacin	82.6
							K. pneumoniae		Tetracycline	0
									Ciprofloxacin	92.3
							Proteus Spp		Piperacillin	4.2
									Ciprofloxacin	91.7
							Enterococcus Spp		Piperacillin	0
									Ciprofloxacin	100

Results

Nine thousand six hundred eighty-four papers were found in the seven databases that were used for the literature search. Four thousand six hundred eighty-five papers were disqualified from the screening based on the title after 2702 duplicates were removed. The remaining 204 papers were left after 1895 of the 2099 abstract-screened papers were taken out. After analyzing the full material, 902 papers were determined to be ineligible, with not meeting the participant's criteria being the most frequent reason. Finally, 19 papers satisfied the requirements for this systematic review. In the PRISMA flowchart (Figure 1), additional details on the exclusion criteria are presented [19].

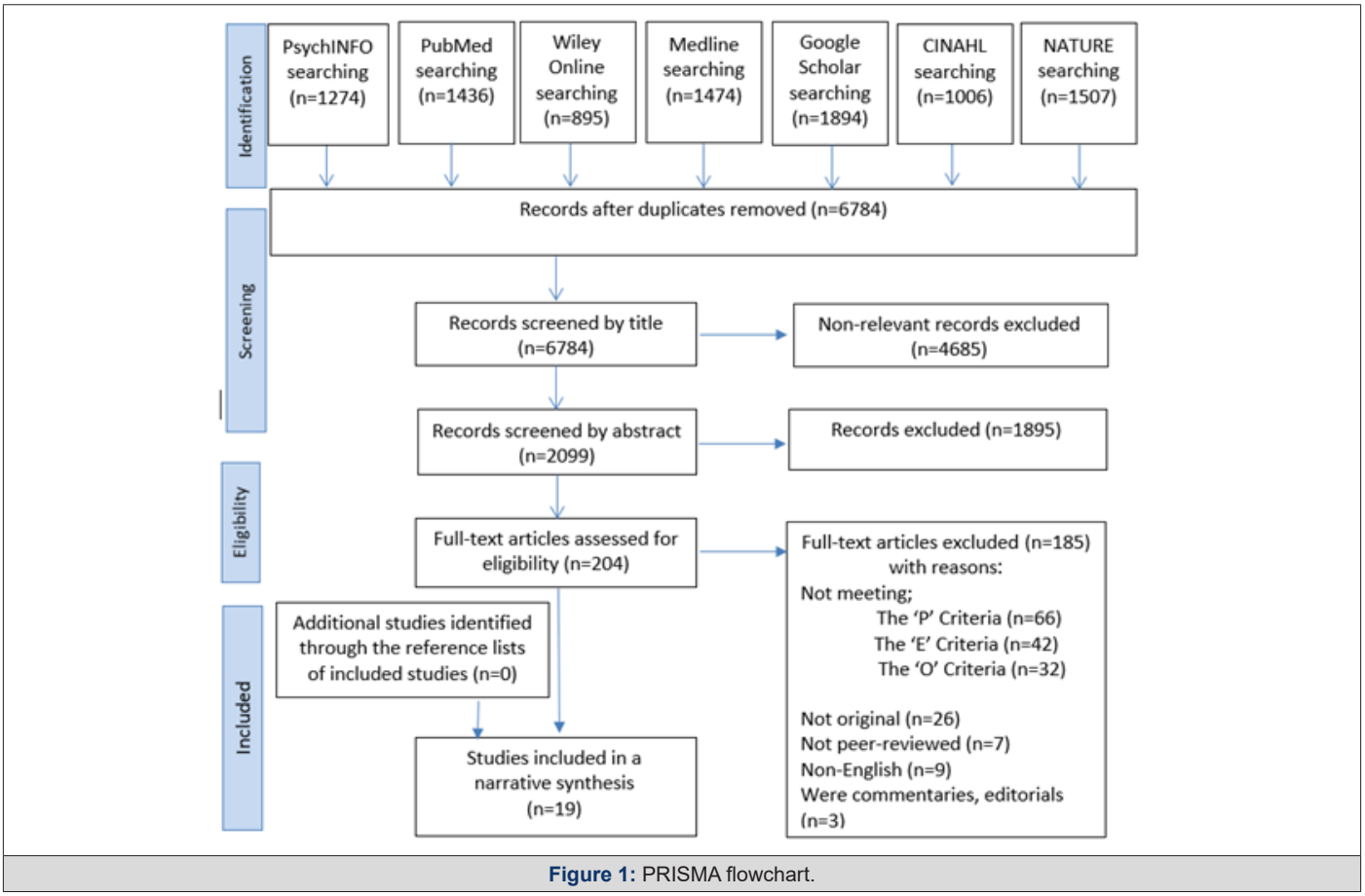

Figure 1: PRISMA flowchart.

Description of the Included Papers

The present systematic review included nineteen studies according to the selection criteria with a total number of isolates of 465448, 15 reported data from hospital settings, one from the general population, and three from mixed settings. While according to the city, four studies were from Riyadh, two were from western Jeddah, two were from Taif, two were from Jazan, one was from Qassim, one was from Dhahran, one was from Aljouf, one was from Dammam, one was country-level study, and two were multi-city studies. Six papers were published in 2021, four in 2019, four in 2021, three in 2022, and two in 2018. Different specimens were collected from body organs and tissues. A wide range of bacterial isolates and antibiotics were reported (Table 2).

Resistance of the Isolated Bacterial to the Antibiotics

Table 3 shows the highest and lowest resistance of each isolated bacteria to the most commonly used antibiotics. In this systematic review, twenty types of bacteria were identified, including A. baumannii, P. aeruginosa, E. coli, K. pneumoniae, S. maltophilia, Citrobacter, Enterobacter, S. pneumoniae, H. influenzae, S. aureus, Proteus Spp, Enterococcus, Mycobacterium tuberculosis, Staphylococcus, Morganella morganii, Pseudomonas, H. pylori, colistin-resistant organisms, Pantoea agglomerans, and Serratia Spp and fifty-two types of antibiotics were commonly used in the included studies.

The main results of the current systematic review indicated that a high prevalence of multidrug-resistant was identified. The results demonstrated that A. baumannii was resistant to azidothymidine, ceftazidime, cefepime, ciprofloxacin, imipenem, meropenem, levofloxacin, gentamicin, ampicillin, ceftriaxone, nitrofurantoin, cefuroxime, amoxicillin, cefotaxime, ertapenem, tigecycline, cephalosporin, trimethoprim-sulfamethoxazole, and piptazobactam. P. aeruginosa was resistant to amikacin, aztreonam, piperacillin, and ampicillin. E. coli was resistant to ciprofloxacin, imipenem, glycopeptide, am-

picillin, cephalosporin, meropenem, and amikacin. K. pneumoniae was resistant to nitrofurantoin, piperacillin, ampicillin, cefuroxime, cefazolin, glycopeptide, cephalosporin, ciprofloxacin, and cefepime. S. maltophilia was resistant to trimethoprim-sulfamethoxazole, and Citrobacter was resistant to cefepime, trimethoprim-sulfamethoxazole, cefpodoxime, ceftazidime, nitrofurantoin, ciprofloxacin, piperacillin, amikacin, ampicillin, glycopeptide, cephalosporin, and cefalotin and imipenem. In addition, Enterobacter was resistant to glycopeptide, cefepime, amikacin, imipenem, gentamicin, trimethoprim-sulfamethoxazole, cefalotin, cefpodoxime, cefotaxime, ceftazidime, meropenem, and cephalosporin. S. pneumoniae was resistant to levofloxacin and moxifloxacin, and H. influenzae was resistant to cephalosporin, ceftriaxone, clavulanic acid, and cefpodoxime. Furthermore, S. aureus was resistant to penicillin-G and penicillin; and Proteus Spp. was resistant to meropenem, nitrofurantoin, and ciprofloxacin. Moreover, Enterococcus was resistant to ciprofloxacin, tigecycline, benzylpenicillin, gentamicin, tobramycin, rifampicin, nitrofurantoin, oxacillin, and fosfomycin. Concerning Mycobacterium tuberculosis was resistant to streptomycin; Staphylococcus was resistant to penicillin and benzylpenicillin, and Morganella morganii was resistant to cephalosporin, glycopeptide, beta-lactams, meropenem, cefuroxime, cefpodoxime, and cefalotin. Additionally, Pseudomonas was resistant to cephalosporin, carbapenem, piperacillin, nitrofurantoin, amikacin, gentamicin, tobramycin, meropenem, ampicillin, cefuroxime, cefpodoxime, and amoxicillin; and H. pylori was resistant to metronidazole. Regarding, Colistin-Resistant Organisms was resistant to cefotaxime; Pantoea Agglomerans was resistant to cefalotin; and Serratia Spp. was resistant to cefalotin, cefoxitin, piperacillin, and ampicillin.

Table 3: Resistance of Isolated Bacteria to Antibiotics.

Bacterial Isolates	Antibiotic Name	Antibiotic Resistance
A. baumannii	Azidothymidine, Ceftazidime, Cefepime, Ciprofloxacin, Imipenem, Meropenem, Levofloxacin, Gentamicin, Ampicillin, Ceftriaxone, Nitrofurantoin, Cefuroxime, Amoxicillin, Cefotaxime, Ertapenem, Tigecycline, Cephalosporin, Trimethoprim-sulfamethoxazole, and Piptazobactam	Highest
	Colistin and Meropenem	Lowest
P. aeruginosa	Amikacin, Aztreonam, Piperacillin, and Ampicillin	Highest
	Imipenem, Cefepime, and Meropenem	Lowest
E. coli	Ciprofloxacin, Imipenem, Glycopeptide, Ampicillinm, Cephalosporin, Meropenem, and Amikacin	Highest
	Nitrofurantoin, Lincosamides, Tigecycline, Carbapenem, Tetracycline, Cefpodoxime, and Colistin	Lowest
K. pneumoniae	Nitrofurantoin, Piperacillin, Ampicillin, Cefuroxime, Cefazolin, Glycopeptide, Cephalosporin, Ciprofloxacin, and Cefepime	Highest
	Trimethoprim-sulfamethoxazole, Cefoxitin, Colistin, Lincosamides, Carbapenem, Tetracycline, Penicillin, Meropenem and Cefalotin	Lowest
S. maltophilia	Trimethoprim-sulfamethoxazole	Highest
	Cefepime	Lowest
Citrobacter	Cefepime, Trimethoprim-sulfamethoxazole, Cefpodoxime, Ceftazidime, Nitrofurantoin, Ciprofloxacin, Piperacillin, Amikacin, Ampicillin, Glycopeptide, Cephalosporin, and Cefalotin and Imipenem	Highest
	Meropenem, Aminoglycoside, Lincosamides, Tetracycline, Meropenem, and Amikacin and Aztreonam	Lowest
Enterobacter	Glycopeptide, Cefepime, Amikacin, Imipenem, Gentamicin, Trimethoprim-sulfamethoxazole, Cefalotin, Cefpodoxime, Cefotaxime, Ceftazidime, Meropenem, and Cephalosporin	Highest
	Carbapenem, Lincosamides, Piperacillin, Cefuroxime, Aztreonam, and Ampicillin	Lowest
S. pneumoniae	Levofloxacin, and Moxifloxacin	Highest
	Penicillin	Lowest

H. influenzae	Cephalosporin, Ceftriaxone, Clavulanic acid, and Cefpodoxime	Highest
	Trimethoprim-sulfamethoxazole, Lincosamides, Beta-lactams, and Macrolide	Lowest
S. aureus	Pencillin-g and Penicillin	Highest
	Meropenem	Lowest
Proteus Spp	Meropenem, Nitrofurantoin, and Ciprofloxacin	Highest
	Aztreonam, Piperacillin, Trimethoprim/sulfamethoxazole, Cefoxitin, Meropenem, Amikacin, and Gentamicin	Lowest
Enterococcus	Ciprofloxacin, Tigecycline, Benzylpenicillin, Gentamicin, Tobramycin, Rifampicin, Nitrofurantoin, Oxacillin, and Fosfomycin	Highest
	Piperacillin, Clindamycin, Linezolid, Teicoplanin, Trimethoprim/sulfamethoxazole, and Mupirocin	Lowest
Mycobacterium tuberculosis	Streptomycin	Highest
	Isoniazid	Lowest
Staphylococcus	Penicillin, and Benzylpenicillin	Highest
	Cefalotin, Macrolide, Beta-lactams, Gentamicin, Tobramycin, Levofloxacin, Moxifloxacin, Tigecycline, Meropenem, Vancomycin, Linezolid, Mupirocin, Rifampicin, and Fusidic acid	Lowest
Morganella morganii	Cephalosporin, Glycopeptide, Beta-lactams, Meropenem, Cefuroxime, Cefpodoxime, and Cefalotin	Highest
	Aminoglycoside, Penicillin, Tetracycline, Quinolones, Lincosamides, Fluoroquinolones, Tobramycin, Aztreonam, Amikacin, and Gentamicin	Lowest
Pseudomonas	Cephalosporin, Carbapenem, Piperacillin, Nitrofurantoin, Amikacin, Gentamicin, Tobramycin, Meropenem, Ampicillin, Cefuroxime, Cefpodoxime, and Amoxicillin	Highest
	Lincosamides, Aminoglycoside, Trimethoprim/sulfamethoxazole, Ciprofloxacin, and Norfloxacin	Lowest
H. pylori	Metronidazole	Highest
	Tetracycline	Lowest
Colistin-Resistant Organisms	Cefotaxime	Highest
	Vancomycin	Lowest
Pantoea agglomerans	Cefalotin	Highest
	Meropenem	Lowest
Serratia Spp.	Cefalotin, Cefoxitin, Piperacillin, and Ampicillin	Highest
	Meropenem	Lowest

On the other hand, this systematic review revealed that for A. baumannii, the most suitable antibiotics were colistin and meropenem; for P. aeruginosa, the most suitable antibiotics were imipenem, cefepime, and meropenem; and for E. coli the most suitable antibiotics were nitrofurantoin, lincosamides, tigecycline, carbapenem, tetracycline, cefpodoxime, and colistin. In addition, for K. pneumoniae, the most suitable antibiotics were trimethoprim/sulfamethoxazole, cefoxitin, colistin, lincosamides, carbapenem, tetracycline, penicillin, meropenem, and cefalotin. For S. maltophilia, the most suitable antibiotic was cefepime. Regarding Citrobacter bacteria, meropenem, aminoglycoside, lincosamides, tetracycline, meropenem, amikacin, and aztreonam were the most suitable antibiotics; while for Enterobacter, carbapenem, lincosamides, piperacillin, cefuroxime, aztreonam, and ampicillin were the most suitable antibiotics. Furthermore, penicillin was the most suitable antibiotic for S. pneumoniae; trimethoprim/sulfamethoxazole, lincosamides, beta-lactams, and macrolide were the most suitable antibiotics for H. influenzae; and meropenem was the most suitable antibiotic for S. aureus. Concerning Proteus Spp., aztreonam, piperacillin, trimethoprim/sulfamethoxazole, cefoxitin, meropenem, amikacin, and gentamicin were the most suitable antibiotics; and for Enterococcus bacteria, piperacillin, clindamycin, linezolid, teicoplanin, trimethoprim/sulfamethoxazole, and mupirocin were the most suitable antibiotics. Moreover, the results demonstrated

that isoniazid was the most suitable antibiotic for Mycobacterium tuberculosis; and Cefalotin, macrolide, beta-lactams, gentamicin, tobramycin, levofloxacin, moxifloxacin, tigecycline, meropenem, vancomycin, linezolid, mupirocin, rifampicin, and fusidic acid were the most suitable antibiotics for Staphylococcus. Additionally, aminoglycoside, penicillin, tetracycline, quinolones, lincosamides, fluoroquinolones, tobramycin, aztreonam, amikacin, and gentamicin were the most suitable antibiotics for Morganella morganii; and lincosamides, aminoglycoside, trimethoprim/sulfamethoxazole, ciprofloxacin, and norfloxacin were the most suitable antibiotics for Pseudomonas. Finally, tetracycline was the most suitable antibiotic for H. pylori; vancomycin was the most suitable antibiotic for colistin-resistant organisms, and meropenem was the most suitable antibiotic for Pantoea agglomerans and Serratia Spp.

Discussion

All local and international health organizations are sounding the alarm about antibiotic resistance. In addition, continuous monitoring of all pathogenic microbes that resist standard antibiotics used for treating bacterial infections is the first and fundamental step in facing this health problem. Accordingly, the comprehensive information on antimicrobial resistance in Saudi Arabia between 2018 and 2022 has been summarized in this systematic review, which included nineteen studies according to the selection criteria, with a total number of isolates of 465448. Of them, 15 studies reported data from hospital settings, one from the general population, and three from mixed environments.

In addition, the primary sources of bacteria samples in the current systematic review include nasal, septum, respiratory, blood, wound, urine, rectal, cerebrospinal fluid, tissue, pleural fluid, trophic ulcer, sacral, peritoneal fluid, intra-abdominal, bedsores, pus, gastric biopsies, stool, ear swab, eye swab, endotracheal secretions, and whole-body tissues.

The monitoring and investigation of antimicrobial-resistant A. baumannii strains are so significant. It has been reported that these strains are associated with nosocomial microbial infections worldwide, and they have become a significant health problem in several hospital units [22,23]. A. baumannii is a gram-negative, pleomorphic, aerobic, and non-motile bacillus, which is responsible for a high incidence of opportunistic infections among immunocompromised individuals, mainly those who have undergone a long (> 90-day) hospital stay [24]. The individual's immune status is a critical point for all age groups when it comes to infection by bacterial pathogens, including A. baumannii strains [25]. Therefore, looking for alternative antibiotics to face the health problems caused by multidrug-resistant A. baumannii strains is very important. The emergence of A. baumannii strains that resist an extremely wide range of standard antibiotics will be a health imperilment that must be faced by all national and international health organizations. Additionally, polymyxin antibiotics such as colistin have resurfaced as effective last-resort antimicrobials against multidrug-resistant Gram-negative pathogens, including A. baumannii [26]. A. baumannii infections are challenging to treat and have limited treatment options. Moreover, carbapenems, including meropenem, are currently considered the first-line agents for treating infections caused by A. baumannii [27].

Furthermore, infection with multidrug-resistant P. aeruginosa strains has become more common in recent years, posing a threat to public health. These strains cause serious illnesses, especially in hospitalized and immunocompromised patients. Cefepime is one of the few antibiotics reported to have consistent activity against P. aeruginosa infections [28]. Although carbapenems, such as imipenem and meropenem, are still effective in treating severe multidrug-resistant P. aeruginosa infections, the situation is deteriorating [29].

Moreover, E. coli is becoming resistant to antibiotics by producing extended-spectrum beta-lactamase, an enzyme rendering certain antibiotics ineffective and leads to multidrug resistance [30]. We recommend a more extensive multi-center clinical and laboratory study, together with local studies, to confirm ciprofloxacin, imipenem, glycopeptide, ampicillin, cephalosporin, meropenem, and amikacin efficacy against multidrug-resistant E. coli.

Furthermore, multidrug-resistant K. pneumoniae is recognized in healthcare settings as a cause of high morbidity and mortality among patients with severe infections. In addition, the findings of the preceding research demonstrated that multidrug-resistant K. pneumoniae, a significant nosocomial pathogen, produces infections with high morbidity and fatality rates due to restricted treatment choices. [31]. K. pneumoniae has been observed to develop antibiotic resistance more quickly than most bacteria through the production of enzymes such as extended-spectrum β-Lactamase and carbapenemase [32]. Moreover, S. maltophilia strains are intrinsically resistant to multiple antibiotics, and the emergence of trimethoprim/sulfamethoxazole-resistant S. maltophilia is becoming a severe problem and needs more attention [33]. Additionally, Blondeau JM et al. showed that ceftazidime was the most active antibiotic against S. maltophilia [34]. The results of this systematic review support these findings. In addition, clinically isolated Citrobacter spp. are frequently resistant to multiple classes of antibiotics [35]. Citrobacter infections caused by multidrug-resistant strains have been linked to a greater risk of death in hospitalized patients than infections caused by susceptible strains [35].

Furthermore, Enterobacter spp. is often resistant to multiple classes of antibiotics owing to the production of constitutive AmpC beta-lactamase [36]. For S. Pneumoniae, penicillin is the drug of choice for susceptible infections, and other beta-lactams do not provide further benefit or coverage. [37]. On the other hand, H. influenzae is one of the major bacterial pathogens of respiratory tract infections [38]. Trimethoprim/sulfamethoxazole was used as a drug of choice for respiratory tract infections due to H. influenzae [39]. Further studies are recommended to confirm trimethoprim/sulfamethoxazole, lincosamides, beta-lactams, and macrolide efficacy against multidrug-resistant H. influenza.

In this systematic review, S. aureus was found to be resistant to penicillin. S. aureus's resistance to penicillin is mediated by blaZ gene. This gene encodes the β-lactamase enzyme, which is an extracellular enzyme that is synthesized in response to exposure to

β-lactam antibiotics and hydrolyzes the β-lactam ring, rendering the β-lactam antibiotics inactive [40]. In contrast, meropenem is active against S. aureus and most strains of methicillin-susceptible coagulase-negative staphylococci [41]. The results of the current systematic review support these findings. Additionally, multidrug-resistant strains of P. mirabilis generally produce extended-spectrum β-lactamases or AmpC-type cephalosporins and rarely carbapenemases, and their prevalence in some settings is relatively high [42]. Furthermore, the mechanisms underlying antibiotic resistance in Enterococci may be intrinsic to the species or acquired through mutation of intrinsic genes or horizontal exchange of genetic material encoding resistance determinants [43].

In addition, streptomycin resistance in Mycobacterium tuberculosis is associated with either base substitutions at position 904 in the 16S rRNA or missense mutations in the rpsL gene, which encodes ribosomal protein S12 [44]. On the other hand, Staphylococcus resistance mechanisms include enzymatic inactivation of the antibiotic and alteration of the target with decreased affinity for the antibiotic. In addition, staphylococcal resistance to penicillin is mediated by blaZ, the gene that encodes β-lactamase [45]. Furthermore, Staphylococcus resistance to benzylpenicillin is the result of a supplemental penicillin-binding protein (PBP 2a) encoded by the chromosomal mecA gene [46]. Additionally, Morganella morganii resistance is mediated by various enzyme combinations; the most frequent of these combinations is the modifying enzyme ANT(2)-I [47]. Also, the mechanisms of antibiotic resistance possessed by Pseudomonas include restricted outer-membrane permeability, efflux systems that pump antibiotics out of the cells, and the production of antibiotic-inactivating enzymes [48]. Moreover, H. pylori's resistance to metronidazole is mediated by a null mutation in the rdxA gene, which encodes for the NADPH nitroreductase enzyme [49]. The results of the current systematic review showed resistance to cefotaxime; the resistance mechanism is mediated by the expression of the arnBCADTEF operon and the eptB gene [50]. Finally, many previous studies showed that meropenem is the preferred therapy for Pantoea agglomerans and Serratia spp. [51,52]. The results of this systematic review support these findings.

The main strengths of the current systematic review are that it is the first systematic review that summarizes the available information about the occurrence of antibiotic resistance in Saudi Arabia in the past five years. However, our study has several limitations. The current systematic review excludes non-English language reports, as articles from Arabic speakers might be missed, biasing this review. There is also a possibility of bias from the lack of data regarding the antimicrobial susceptibility test in many of the included studies. Additionally, resistance data obtained with different laboratory methodologies were combined for this review.

Conclusion

To the best of our knowledge, this study is the first to comprehensively evaluate the frequency of antibiotic resistance in Saudi Arabia using a systematic approach. Our study concluded that in Saudi Arabia, twenty types of bacteria were identified, and fifty-two types of antibiotics were commonly used in the past five years. In addition, a high percentage of the included bacteria were multidrug-resistant. Concerning the most suitable antibiotics, for A. Baumannii were Colistin and Meropenem; for P. Aeruginosa were Imipenem, Cefepime and Meropenem; for E. Coli were Nitrofurantoin, Lincosamides, Tigecycline, Carbapenem, Tetracycline, Cefpodoxime and Colistin; for K. Pneumoniae were Trimethoprim/sulfamethoxazole, Cefoxitin, Colistin, Lincosamides, Carbapenem, Tetracycline, Penicillin, Meropenem and Cefalotin; for S. Maltophilia was Cefepime; for Citrobacter were Meropenem, Aminoglycoside, Lincosamides, Tetracycline, Meropenem, Amikacin and Aztreonam; for Enterobacter were Carbapenem, Lincosamides, Piperacillin, Cefuroxime, Aztreonam and Ampicillin; for S. Pneumoniae was Penicillin; for H. Influenzae were Trimethoprim/sulfamethoxazole, Lincosamides, Beta-lactams and Macrolide; for S. Aureus was Meropenem; for Proteus were Aztreonam, Piperacillin, Trimethoprim/sulfamethoxazole, Cefoxitin, Meropenem, Amikacin and Gentamicin; for Enterococcus were Piperacillin, Clindamycin, Linezolid, Teicoplanin, Trimethoprim/sulfamethoxazole and Mupirocin; for Mycobacterium Tuberculosis was Isoniazid; for Staphylococcus were Cefalotin, Macrolide, Beta-lactams, Gentamicin, Tobramycin, Levofloxacin, Moxifloxacin, Tigecycline, Meropenem, Vancomycin, Linezolid, Mupirocin, Rifampicin and Fusidic acid; for Morganella Morganii were Aminoglycoside, Penicillin, Tetracycline, Quinolones, Lincosamides, Fluoroquinolones, Tobramycin, Aztreonam, Amikacin and Gentamicin; for Pseudomonas were Lincosamides, Aminoglycoside, Trimethoprim/sulfamethoxazole, Ciprofloxacin and Norfloxacin; for H. Pylori was Tetracycline; and for Colistin-Resistant Organisms was Vancomycin. Furthermore, Meropenem was the most suitable antibiotic for Pantoea agglomerans and Serratia species. Finally, to reduce the magnitude of the seriousness of antibiotic resistance, physicians should prescribe antibiotics based on the results of culture and sensitivity tests.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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