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ORIGINAL ARTICLE

Scenario of Antibiotic Resistance in Pakistan: A Systematic Review

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ABSTRACT

Background: A rise in antimicrobial resistance and a decrease in the discovery of novel antibiotics have occurred in recent years. Pakistan is a South Asian developing nation with a high level of antibiotic resistance, which poses a serious regional and global threat.

Objective: To determine the situation of antimicrobial resistance in Pakistan

Methodology: In the current study the literature was reviewed systematically according to the guidelines of PRISMA. Numerous databases like PUBMED, Embase, Medline and Google scholar were reviewed to determine the prevalence of antimicrobial resistance in Pakistan in the last 10 years from 2012 to 2022. For collection of duplicate data, a standardized extractive datasheet was used. All the data was entered in Microsoft Excel 2019.

Results: In the current study, a total of 82 articles were included for final analysis. Multiple drug resistant bacteria were observed in 8 (9.76%) studies while extensive drug resistant bacteria were observed in 2 (2.44%) studies. High median resistance (95% CI) was shown by E. coli to first line antibiotics. Salmonella spp showed high median resistance to ciprofloxacin (90.5%). High median resistance was observed to majority of available antibiotics by Acinetobacter spp. Pseudomonas spp were highly susceptible (86.5%) to cefoperazone-sulbactam. MRSA S. aureus was reported in 13 studies and they were highly resistant to penicillin (98%), cefoxitin (83%) and levofloxacin (80%).

Conclusion: Our study concludes that antimicrobial resistance pattern of common pathogens was high against commonly prescribed antibiotics. Regularization of monitoring practices, regular local and national monitoring, molecular investigations, and particular efforts to address the risk associated with the rise in antibiotic resistance are required to combat this issue.

Keywords: Antibiotic resistance; Multiple drug resistance, Extensive drug resistance

INTRODUCTION

Antibiotics resistance is defined as the bacterial ability to resist the effect of antibiotic used for treatment or prevention [1]. A rise in antimicrobial resistance and a decrease in the discovery of novel antibiotics have occurred in recent years [2-4]. Antimicrobial resistance is a major cause of death and financial burden across the globe. The extensive usage of antibiotics, usage of antibiotics in animals, poor standard of drugs, insufficient monitoring, and other problems linked with national and individual poverty, such as low healthcare services, malnutrition, recurrent and chronic illnesses, and an inability to buy more expensive and effective medications, have a disproportionately negative impact on developing nations [5, 6]. In addition, the lack of newer medications necessitates the containment of drug resistance before we fail to find out the ways to combat it. Based on the reported published by WHO in 2014 on the global monitoring of antimicrobial resistance, there are still substantial gaps in surveillance, as well as a shortage of standards for technique, information sharing and collaboration. On the other hand, it has been determined that the areas of Africa, Southeast Asia and the Eastern Mediterranean all have significant gaps [3].

Antibiotic resistance is expected to rise by 70% in Asia, posing a county-wide and global threat [7]. Pakistan is a South Asian developing nation with a high level of antibiotic resistance, which poses a serious regional and global threat [8]. In recent years, multidrug-resistant and extensively drug-resistant microorganisms have been reported in Pakistan. Enterobacteriaceae resistance to quinolones has risen in Pakistan during the previous decade [9]. One of the outbreaks of XDR Salmonella in 2016 was one of the first to exhibit complete resistance to fluoroquinolones [10]. A previous study reported that 93.7% bacteria from blood stream were resistant to third-generation cephalosporin [11]. In light of these observations, we are on the edge of treatment with antibiotics. Irrational prescription, temptations for over-prescription, self-medication, unskilled personnel, dearth of proper training, no trend of culture and sensitivity testing, and the incomplete dose taken by patients are all reasons for this, according to numerous research [12]. The frequency of antimicrobial resistance in Pakistan has been the subject of several individual researches. But, no such systematic study has been published in Pakistan to provide a complete picture of antibiotic resistance. The goal of this research was to analyze the prevalence of antimicrobial resistance in clinically significant microorganisms from Pakistan.

MATERIALS AND METHODS

In this study the literature was reviewed systematically according to the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Numerous databases like PUBMED, Embase, Medline and Google scholar were reviewed to determine the prevalence of antimicrobial resistance in Pakistan in the last 10 years from 2012 to 2022. Various terms like “antibiotic resistance”, “susceptibility pattern”, “antibiogram assay”, “resistant”, “susceptible” and “Pakistan” were combined for identification of studies. The inclusion criteria for our study were previous published studies from January 2012 to January 2022 who isolated at least 30 WHO enlisted priority bacterial pathogen in Pakistan from human samples and then determine their antibiogram assay, studies of only English language, studies in which CLSI guidelines were followed and studies who mentioned properly the total samples size and resistance or susceptibility profile of isolated bacterial pathogens while the exclusion criteria were studies who isolated bacteria from other origin than human, studies published before January 2012, studies in which CLSI guidelines were not followed, isolates number less than 30, studies other than English language and studies in which antibiotic resistance profile was not mentioned properly. The different phases for final selection of studies in our systematic review include Identification, Screening, Eligibility and Included.

These include identification, screening, eligibility and included. Two independent and blind researchers examined the titles and abstracts of the various studies to determine the prevalence of antimicrobial resistance in Pakistan. This examination by two blind researchers will help to remove any possibility of bias in the current study. For collection of duplicate data, a standardized extractive datasheet was used. The data collection was validated by the reviewers two times for completeness and correctness. The research question of the current study was “what is the scenario of antimicrobial resistance

in Pakistan". All the data was entered in Microsoft Excel 2019. The antibiotic resistance was determined for each bacterium in the form of median resistance (CI 95%) by using Agresti-Coull method calculator.

RESULTS

In the current study, a total of 380 articles were explored from various databases like MEDLINE, EMBASE, PubMed and Web of Science. Furthermore, 50 articles were searched in Google scholar. The searching from databases was completed on March 2022. The flow diagram for studies of systematic review is given in Figure 1. Finally a total of 82 articles were included for final analysis.

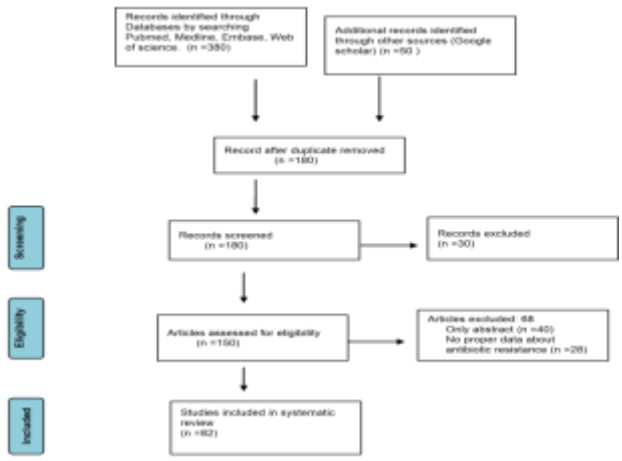

Figure 1: Systematic review flow diagram for article selection

Majorities of the studies (39.02%, n=32) were from Sindh province, 20 (24.39%) studies were from Punjab and 17 (20.73%) studies were from Khyber Pakhtunkhwa, 13 (15.85%) were from Islamabad while there was no data from Baluchistan province. (Figure 2)

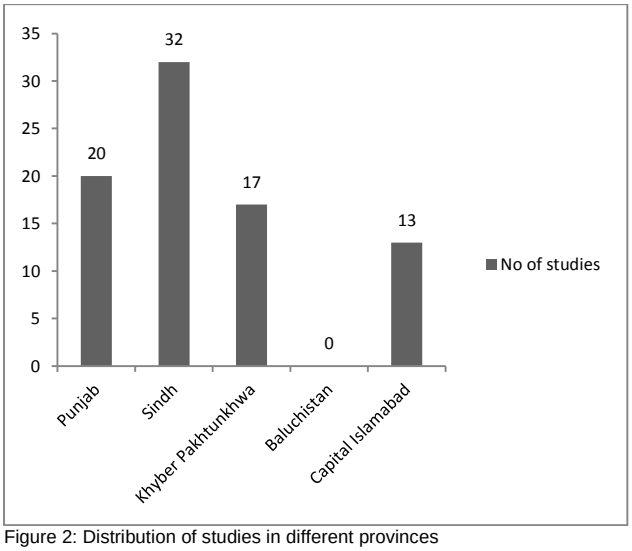

Figure 2: Distribution of studies in different provinces

In the current study multiple drug resistant bacteria were observed in 8 (9.76%) studies while extensive drug resistant bacteria were observed in 2 (2.44%) studies. (Table 1)

Table 1: MDR and XDR bacteria from studies included in our systematic review

Name of bacteria	No of isolates	MDR/XDR	Prevalence (%)	Authors
Escherichia Coli	150	MDR	63.3%	Farooq et al.[13]
Pseudomonas spp	176	MDR	55%	Farooq et al.[14]
Salmonella spp	154	MDR	30.5%	Qaiser et al.[15]
Salmonella spp	80	MDR	58.7%	Afzal et al.[16]
Acinetobacter spp	87	MDR	96.67%	Hasan et al.[17]
Acinetobacter spp	136	MDR	99.27%	Khurshid et al.[18]
Acinetobacter spp	36	MDR	100%	Miyan et al.[19]
Acinetobacter spp	26	XDR	28.88%	Hasan et al.[17]
Acinetobacter spp	129	XDR	94.16%	Khurshid et al [18]
Salmonella spp	33	XDR	100%	Elizabeth J. Klemm, et al. [20]

High median resistance (95% CI) was shown by E. coli to penicillin (100%), cephradine, ampicillin (90.55%) and amoxicillin (85%) while susceptibility shown by E.coli to colistin, cefoperazone-sulbactam, imipenem and meropenem was 100%, 94.5%, 93.5% and 93% respectively. Klebsiella spp shows median high resistance (95% CI) to cefaclor (100%) and cefotaxime (82.5%) whereas they were highly susceptible to colistin (100%), cefoperazone-sulbactam (91.5%) and imipenem (92%). Proteus spp shows high median resistance (95% CI) in only two studies to cefotaxime (66.5%), ceftriaxone (62.5%) and tobramycin (59.5%). Salmonella spp showed high median resistance (95% CI) to ciprofloxacin (90.5%) whereas the range of susceptibility to imipenem, ceftriaxone and meropenem was 99 to 100%. Highest resistance was shown by Shigella spp to co-trimoxazole (80%) and ampicillin (68%). The efficient antibiotics against Shigella spp were ofloxacin and nalidixic acid with median resistance of 2.5% and 3% respectively. High resistance (Median resistance 95% CI) was shown by H. pylori to metronidazole (89%), tetracycline (96%) and ofloxacin (76%). High median resistance was observed to majority of available antibiotics by Acinetobacter spp except certain antibiotics who shows susceptibility like colistin (99.5%), tigecycline (97.15%) and minocycline (67%). High median resistance (95% CI) was shown by Pseudomonas spp to ceftazidime (73.5%) and aztreonam (70%). The pattern of median resistance (95% CI) for carbapenems was 18% and 26.5% in meropenem and imipenem respectively. Pseudomonas spp were highly susceptible (86.5%) to cefoperazone-sulbactam. MRSA S. aureus was reported in 13 studies and they were highly resistant to penicillin (98%), cefoxitin (83%) and levofloxacin (80%) whereas high susceptibility to S. aureus was shown by tigecycline (100%), tetracycline (100%), linezolid (99%), and vancomycin (98%). The antibiogram profile of all the selected pathogen with median resistance (95% CI) is given in table 2.

Table 2: Antibiogram profile of all the selected pathogen with median resistance (95% CI)

Bacteria	Antibiotic	No of isolates	Median resistance	Lower limit (95% CI)	Upper limit (95% CI)
Escherichia Coli [19, 21-36]	Tobramycin	1876	59%	00%	88%

	Sulfomethoxozle-trimethoprim	2075	78%	65%	82%
	Piperacillin-tazobactem	2695	10%	6%	27%
	Penicillin	445	100%	82%	100%
	Ofloxicin	1704	50%	22%	82%
	Norfloxacin	1740	52%	11%	81%
	Nalidixic acid	2051	77%	60%	92%
	Moxifloxacin	1488	59%	30%	82%
	Meropenem	2265	8%	3%	14%
	Levofloxacin	987	65%	50%	82%
	Imipenam	2811	6.5%	3%	37%
	Gentamycin	4045	53%	40%	67%
	Fosfomycin	573	8.5%	0%	55%
	Enoxacine	1308	70.5%	70%	100%
	Doxycyclin	2394	70%	54%	88%
	Colistin	185	00%	00%	00%
	Ciprofloxacin	4592	67%	58%	74%
	Chloramphinicole	829	42%	26%	49%
	Cephradine	639	92%	74%	95%
	Cefuroxime	2439	80%	55%	98%
	Cefoperazone-sulbactum	1119	5.5%	3%	6%
	Cefoperazone	1757	70.5%	10%	74%
	Ceftazidime	3640	71%	57%	90%
	Ceftriaxone	2594	71%	43%	80%
	Cefotaxime	3581	76%	72%	98%
	Cefixime	1211	76%	54%	100%
	Cefepime	834	60%	7%	80%
	Cefactor	2020	80%	50%	100%
	Aztreonam	2901	64%	45%	82%
	Ampicillin	2174	90.5%	83%	96%
	Amoxiclav	1993	63%	40%	92%
	Amoxicillin	1394	85%	33%	100%
	Amikacin	3756	13%	5%	42%
Klebsiella spp.[19, 29, 32-35, 37-40]	Tobramycin	594	61%	00%	80%
	Sulfomethoxozle	239	67%	58%	69%
	Tetracyclin	171	70%	27%	76%
	Piperacillin-tazobactem	17228	21.5%	4%	87%
	Moxifloxacin	1033	65%	19%	82%
	Meropenem	1076	21%	09%	80%
	Levofloxacin	1120	70%	17%	82%
	Imipenam	1149	8%	0%	30%
	Fosfomycin	136	29%	20%	38%
	Doxycyclin	440	75%	70%	80%
	Colistin	223	00%	00%	10%
	Ciprofloxacin	17443	67%	24%	86%
	Chloramphinicole	203	32%	30%	40%
	Cefoperazone-sulbactum	678	9.5%	5%	14%
	Ceftazidime	1517	73%	44%	96%
	Ceftriaxone	1024	65%	22%	100%
	Cefotaxime	1416	82.5%	22%	100%
	Aztreonam	643	90%	00%	97%
	Amikacin	17467	24%	6%	59%
Proteus spp[19, 26, 41, 42]	Tobramycin	129	59.5%	36%	83%
	Imipenam	129	9%	15%	13%
	Gentamycin	129	57.5%	32%	83%
	Ciprofloxacin	129	36.5%	20%	53%
	Ceftriaxone	129	62.5%	49%	76%
	Cefpriome	129	58%	45%	71%
	Cefotaxime	129	66.5%	59%	74%
	Amikacin	129	28%	10%	46%
Salmonella spp[10, 16, 20, 43-46]	Sulfomethoxozle-trimethoprim	7483	56%	30%	100%
	Meropenem	968	00%	00%	55%
	Ciprofloxacin	7329	90.5%	2%	100%
	Chloramphinicole	7144	50.5%	32%	100%
	Ceftriaxone	7420	0.2%	0%	100%
	Cefixime	4418	0.54%	00%	12%
	Azithromycin	915	1.5%	0%	67%
	Ampicillin	7483	66%	31%	100%
Shigella spp[47, 48]	Ofloxicin	395	2%	00%	7%
	Nalidixic acid	395	3%	2%	13%
	Co-trimoxazole	440	80%	56%	85%
	Ciprofloxacin	140	19%	13%	25%
	Chloramphinicole	2108	41%	3%	73%
	Ceftriaxone	1713	8%	2%	20%
	Cefixime	140	18%	8%	28%
	Ampicillin	2108	68%	4%	97%

	Amoxiclav	395	11%	5%	75%
H. pylori[49-51]	Tetracyclin	316	4%	4%	12%
	Ofloxacin	217	34.5%	19%	30%
	Metronidazole	316	89%	74%	98%
	Clarithomycin	316	36%	5%	48%
	Amoxicillin	316	37%	2%	54%
Acinetobacter spp[17, 18, 29, 32, 40, 52-59]	Tobramycin	966	83%	37%	100%
	Tigecyclin	1119	2.85%	0%	36%
	Tetracycline	133	66%	62%	70%
	Sulfomethoxozle-trimethoprim	1736	91%	78%	100%
	Piperacillin-tazobactem	1861	89.5%	84%	98%
	Piperacillin	293	94%	99%	100%
	Minocyclin	364	33%	2%	93%
	Meropenem	1359	91.5%	93%	100%
	Levofloxacin	963%	90%	54%	100%
	Imipenam	1687%	88.5%	62%	100%
	Gentamycin	1438	91%	36%	98%
	Doxycyclin	1272	64%	8%	100%
	Colistin	1450	00%	00%	36%
	Ciprofloxacin	1816	96.5%	89%	100%
	Ceftazidime	1444	100%	98%	100%
	Ceftriaxone	1355	100%	99%	100%
	Cefotaxime	1278	100%	77%	100%
	Cefepime	1496	99.5%	89%	100%
	Amikacin	2006	89.5%	80%	97%
Pseudomonas Spp[9, 14, 35, 36, 60-63]	Tobramycin	524%	42.5%	38%	60%
	Piperacillin-tazobactem	1066%	18.5%	2%	79%
	Meropenem	785%	18%	5%	100%
	Levofloxacin	193	59%	49%	100%
	Imipenam	1301	26.5%	6%	82%
	Gentamycin	1276	48%	34%	74%
	Colistin	390	20%	0%	41%
	Ciprofloxacin	1397	45%	35%	85%
	Ceftazidime	1117	73.5%	42%	100%
	Cefepime	527	46%	34%	64%
	Aztreonam	606	70%	21%	80%
	Amikacin	1499	41%	20%	63%
S. aureus[19, 34, 36, 40, 63-72]	Vancomycin	5582	2%	0%	12%
	Tetracyclin	1131	67%	48%	82%
	Sulfomethoxozle-trimethoprim	5631	43%	12%	69%
	Rifampin	786	10%	6%	50%
	Penicillin	675	98%	95%	100%
	Ofloxicin	2419	56%	30%	90%
	linezolid	1542	1%	00%	29%
	Levofloxacin	392	80%	56%	85%
	Gentamycin	2381	56%	15%	79%
	Fusidic acid	5949	15%	4%	61%
	Erythromycin	5188	52%	22%	82%
	Doxycyclin	1955	41.5%	1%	80%
	Clindamycin	6727	40.5%	16%	66%
	Clarithomycin	550	65%	54%	70%
	Chloramphinicole	1370	16%	7%	95%
	Ciprofloxacin	4822	55%	38%	80%
	Cefoxitin	3647	83%	48%	100%
	Azithromycin	932	61.5%	55%	68%

DISCUSSION

Both in undeveloped and developed countries, antimicrobial resistance (AMR) have arisen as a serious public health problem. The World Health Organization has suggested continuous monitoring of AMR as a vital step in managing the development of resistance as well as diseases caused by resistant organisms [73]. In spite of the pressing need to examine AMR trends, only a few studies have identified pathogen resistance patterns in Pakistan to far. The present research aims to overcome this information gap about AMR trends on a nationwide level. In our study, amongst bacterial pathogens, E. coli was resistant to first-line antibiotics in maximum number of studies. High median resistance (95% CI) was shown by E. coli to penicillin (100%), cephradine, ampicillin (90.55%) and amoxicillin (85%) while susceptibility shown by E.coli to colistin, cefoperazone-sulbactam, imipenem and meropenem was 100%, 94.5%, 93.5% and 93% respectively. These findings were almost similar to previous studies from Bangladesh and Africa because in almost all developing countries, antibiotics are used inappropriately. In our study, the median resistance was high to tetracycline and levofloxacin as compare to the studies from Bangladesh and Africa which might be due to testing methods of antimicrobial resistance [74, 75]. If necessary, physicians may use alternate medications like tigecycline, fosfomycin, carbapenems, nitrofurantoin and other antibiotics in this situation [76, 77]. The increasing pattern of resistance to fluoroquinolone by Salmonella spp was supported by our study in the Asian countries. The median resistance (95% CI) of Salmonella spp to ciprofloxacin was 90.5% amongst 7392 isolates [78]. Carbapenem, cefixime and ceftriaxone have all been documented to have substantial sensitivity; therefore doctors may choose to use these drugs. In our study, highest resistance was shown by Shigella spp to co-trimoxazole (80%) and ampicillin (68%). The efficient antibiotics against Shigella spp were ofloxacin and nalidixic acid with median resistance of 2.5% and 3% respectively. Shigella spp. is the

predominant bacterium that causes community-acquired illness, according to the WHO [79], hence additional study is needed to have a deeper understanding. In the current systematic review, high resistance (Median resistance 95% CI) was shown by H. pylori to metronidazole (89%). This resistance is higher than reported resistance of H. pylori to metronidazole in China (77%) and Malaysia (82%) [80]. Metronidazole resistance is likely owing to increasing prescription and easy accessibility in Pakistan [81]. Due to the lack of data from Pakistan, we recommend further study on the development of antibiotic resistance against Proteus spp, Neisseria gonorrhoeae, Streptococcus pneumoniae, Haemophilus influenzae, Campylobacter spp and Serratia spp. In our study, high median resistance was observed to majority of available antibiotics by Acinetobacter spp except certain antibiotics who shows susceptibility like colistin (99.5%), tigecycline (97.15%) and minocycline (67%). High median resistance (95% CI) was shown by Pseudomonas spp to ceftazidime (73.5%) and aztreonam (70%). The pattern of median resistance (95% CI) for carbapenems was 18% and 26.5% in meropenem and imipenem respectively. Pseudomonas spp was highly susceptible (86.5%) to cefoperazone-sulbactam. This new pattern of antibiotic resistance is the result of acquired resistance [82]. Our results back with a 2017 WHO study that designated Pseudomonas spp and Acinetobacter spp as critically important bacteria [83]. MRSA S. aureus was reported in 13 studies and they were highly resistant to penicillin (98%), cefoxitin (83%) and levofloxacin (80%) whereas high susceptibility to S. aureus was shown by tigecycline (100%), tetracycline (100%), linezolid (99%), and vancomycin (98%). Similar trend of antibiotic resistance was also reported from Bangladesh [74]. We advise doctors to prescribe adequate doses of colistin and carbapenem, since bacteria have evolved plasmid-mediated resistance to these due to their horizontal transferability [84]. There were a few gaps in the surveillance, such as; no studies from the region of Baluchistan were found. Baluchistan province, as well as Pakistan's small towns and cities, deserve further investigation. To address this pan-drug resistance phenomenon, molecular investigations needed a unique approach. The current research concentrates on antibiotic resistance in Pakistan; but, their implications are global. The geographical position of Pakistan is strategically very important because of sharing borders with India, China, Afghanistan and Iran. Resistant species from the reservoir have been documented to spread to other parts of the globe through humans, animals and water [85]. For Pakistan, its impacts appear to be the greatest threat. Antimicrobial resistance is highly prevalent in Pakistan, and both the health care and community care institutions must pay particular emphasis to this problem. The community must be made aware of the need of careful medication administration and completion. Self-medication in the community must be outlawed. To reduce the risk of rising antibiotic resistance, guidelines for antibiotic use in agriculture and human health should be realistic and based on Pakistan's antimicrobial resistance network Antibiotic-resistant bacteria may be prevented in health care facilities by following suggested preventive practices like contacting precautions, individual hand hygiene, and proper training and education of healthcare staff.

CONCLUSION

Our study concludes that antimicrobial resistance pattern of common pathogens was high against commonly prescribed antibiotics. In the surveillance, substantial gap was observed as no study about microbial resistance was reported from Baluchistan province. There are just a few molecular studies available that are essential for successful and appropriate therapeutic drug usage. As a result, regularization of monitoring practices, regular local and national monitoring, molecular investigations, and particular efforts to address the risk associated with the rise in antibiotic resistance are required.

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