Sys Rev Pharm 2021; 12(5): 278-288
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

Review Article

Inappropriate Antibiotic Prescribing in Different Departments of Gulf Region and Management Through Pharmacist-Led Antimicrobial Stewardship: A Systematic Review and Meta-Analysis

Rana Kamran Mahmood[1, 2], Syed Wasif Gillani[1*], Maryam Jaber Mohamed Abdulla Alzaabi[1], Shabaz Mohiuddin Gulam[1]

[1]Department of Pharmacy, College of Pharmacy, Gulf Medical University, Ajman, United Arab Emirates
[2]Department of Pharmacy, Response Plus Medical, Abu Dhabi, United Arab Emirates

Article History: *Submitted: 17.05.2021* *Accepted: 31.06.2021* *Published: 07.06.2021*

ABSTRACT

Purpose: The aim of this meta-analysis is to evaluate the inappropriate antibiotic prescribing in Gulf region and determine the effect of pharmacist-led antimicrobial stewardship programs to reduction in the inappropriateness.

Method: Articles were searched, analyzed and quality assessed through JSM quality assessment tool to select the articles with low level of bias. In step 1 515 and in step 2 2357 articles searched and 32 articles included by critical analysis. Statistical analysis used to Risk ratio and standard mean differences were calculated using Review manager 5.4. 95% confidence intervals were calculated, using the fixed effect model. The I2 statistic assessed heterogeneity. In case of statistical heterogeneity, subgroup and sensitivity analyses then a random effect model was performed. The alpha threshold was 0.05. Primary outcome is inappropriateness in Gulf region and reduction of inappropriateness through AMS.

Results: Detailed review and analysis of 18 studies with inappropriateness in Gulf region shows risk of inappropriateness is 43669/100846 about 43.3%. Pooled RR=1.31 with 95% CI= (1.30, 1.32). Test with Overall effect is 58.87 in second step 28 antimicrobial stewardships led by pharmacist shows reduction in inappropriateness in AMS with pharmacist vs pre-AMS without pharmacist RR=0.36 with 95% CI= (0.32, 0.39).

Conclusion: Inappropriateness in Gulf region is alarming and need to be addressed through pharmacist-led antimicrobial stewardship programs.

Keywords: Pharmacist, Antimicrobial stewardship, Appropriateness, Gulf region, Antibioticsv

***Correspondence:**
Syed Wasif Gillani, Department of Pharmacy, College of Pharmacy, Gulf Medical University, Ajman, United Arab Emirates, E-mail: wasifgillani@gmail.com

INTRODUCTION

Antimicrobial resistance is increasing globally and affecting cost, mortality and length of stay. Recently published study showed that by 2050 leading cause of death will be bacterial infection unless resistance is controlled (O'Neill J, 2016). Survey of antibiotic resistance in Gulf State published in journal of antimicrobial chemotherapy find out the susceptibility of community acquired respiratory tract isolates in Gulf region shows that "there are large country-specific differences in antibiotic susceptibility even within the same region, with overall antibiotic resistance being the highest in S. pneumoniae and isolates from the UAE" (Jamsheer A, *et al.*, 2016). Study in Saudi Arabia 8 hospitals shows that most resistant antimicrobial is meropenem followed by ticar-cillin, imipenem, and piperacillin; almost 13% of the strains were multidrug resistance (Khan MA and Faiz A, 2016). As of 1998, higher rates of resistant bacteria have been seen in Saudi Arabia. Most of these cases could be attributed to greater and irrational use of antibiotic drugs (Rotimi VO, *et al.*, 1998).

Inappropriate antibiotic prescribing is associated with the resistance leading to multidrug resistance ultimately increases mortality rate. Study published in Critical care journal inappropriate antibiotic prescribing is an important determinant of multidrug resistance which is associated with the 3 fold increase in hospital mortality (Zilberberg MD, *et al.*, 2014). A survey of European medical final students, 66% agrees that antibiotic resistance is due to prescribed antibiotics as an inappropriate choice is responsible (Dyar OJ, *et al.*, 2014). A study in Singapore shows that inappropriate prescribing of antimicrobials are responsible for the increased antimicrobial resistance that can only be cured with appropriate antimicrobial prescribing (Hsu LY, *et al.*, 2008).

Rational prescribing can help to reduce the antimicrobial resistance. Antimicrobial stewardship programs can help to increase the rational prescribing of antibiotics. A study shows that antimicrobial stewardship program can help to increase the appropriate antimicrobial prescribing up to 89.3% (Yanai M, *et al.*, 2018). Pharmacist plays an important role in the stewardship team; how much inappropriate antibiotic prescribing and impact of pharmacist on the rational prescribing of the antibiotics through antimicrobial stewardship programs is unclear.

The aim of this study is to evaluate the inappropriate antibiotic prescribing in Gulf region and determine the effect of pharmacist-led antimicrobial stewardship programs to rational prescribing.

METHODOLOGY

Methodology of searching articles is of two-step process. First step we find out the inappropriate antimicrobial prescribing in the gulf region and second step impact of pharmacist on the inappropriate prescribing through pharmacist led antimicrobial stewardship program. Our methodology adheres to the PRISMA guidelines (see PRISMA checklist: Appendix1)

Data sources

In step 1: Antimicrobial prescribing pattern with inappropriate prescribing were identified searching: Pubmed, Embase and Elsevier. Include all articles with Language English. Keywords used were: "antibiotic", "prescribing", and "Gulf", "Saudi Arabia", "UAE", "Qatar", "Bahrain", "Kuwait", "Oman" and "Yemen". Orignial articles are only

included while reviews and meta-analysis were excluded. Surveys and questionnaire showing the prescribing practice and inappropriateness are excluded.

In step 2: Antimicrobial stewardships were identified searching: Pubmed, Embase and Elsevier. We included all stewardships, with English language restriction, published from 2012 to 2020. Keywords used were: "antimicrobial stewardship", "antibacterial stewardship"; "mortality"; "appropriateness"; "led by pharmacist", "pharmacist"; "rational prescribing"; "antifungal stewardship"; "impact of pharmacist"; "impact on cost"; "outcomes of stewardship"; "hospital readmission"; "antibiotic consumption". We only include the articles with the values representing the inappropriate prescribing of antibiotics before and after antimicrobial stewardship programs led by pharmacist. We restricted our search to primary literature, systematic reviews and meta-analyses and all other type of reviews are excluded. We manually searched the reference lists of systematic reviews to check they had all already been identified in our study.

Search strategy is illustrated in the Appendix 2.

Study selection

In first step we included primary literature of all antimicrobial prescribing patterns in gulf region. Gulf region includes 7 countries (UAE, Saudi Arabia, Kuwait, Qatar, Oman, Yemen and Bahrain). Articles that is included with the inappropriate prescribing practice of antibiotics. Topical antibiotics prescribing studies were excluded or studies other than Gulf region are excluded. In second step we included primary literature all types of antimicrobial stewardship programs (antibiotics, anti-fungal, anti-viral) led by pharmacist, whether retrospective, prospective or quasi-experimental studies are included. Dichotomous results are extracted, antimicrobial stewardship (AMS) program with pharmacist compared to the pre-antimicrobial stewardship (pre-AMS) program without pharmacist. Inappropriate as a clinical outcome is only included in this study. By excluding reviews and abstract without complete data, studies in other language other than English and stewardship other than antimicrobial outcomes other than inappropriate prescribing practices are excluded.

Two investigators independently assessed eligibility (RKH and MJMAA). In case of discrepancy, a third observer adjudicated the eligibility (SWG). The extraction forms and the risk of bias assessments are attached as Appendix 2.

Quality assessment

Two authors (RKM and SMG) independently assessed trial quality. Internal validity was analyzed with the JSM quality assessment tool. These articles were then rated according to methodological quality: High, moderate, or low.

Outcomes

Primary outcome is inappropriate antibiotic prescribing practice in gulf region and impact of antimicrobial stewardship led by pharmacist in reducing the inappropriate antimicrobial prescribing. Two reviewers (MJMAA and SMG) independently extracted the data for all the outcomes of interest.

Principal summary measures and statistical analysis

Analyses were done using RevMan software version 5.4® (www.cc-ims.net/revman). For all studies we calculated Risk Ratios (RR) with 95% confidence intervals, (95% CI), using the fixed effect model in first approach. Heterogeneity was investigated with the I2 statistic. It measures the proportion of overall variation attributable to between study heterogeneity. I2 values of 25%, >50% and >75% refers respectively to a low, substantial and considerable degree of heterogeneity. In case of statistical heterogeneity, we tried to explain this with subgroup and sensitivity analyses then with funnel plot. Statistical significance was defined with an alpha threshold at 0.05.

RESULTS AND FINDINGS

General characteristics

In first step 515 articles searched after removing duplication 330 from pubmed, 10 from Embase and 3 from Elsevier. 57 reviews are excluded, 78 articles without prescribing pattern were excluded, 53 outside of Gulf region were excluded and 128 articles without inappropriateness were excluded and remaining 18 articles were included (Alhameed AF, *et al.*, 2019; Youssif E, *et al.*, 2018; Aly NY, *et al.*, 2012; Alzahrani AA, *et al.*, 2020; Alanazi MQ, 2018; Alanazi MQ, *et al.*, 2015; Alahdal AM and Elberry AA, 2012; Al-Maliky GR, *et al.*, 2018; Al-Yamani A, *et al.*, 2016; Al-Hadithi D, *et al.*, 2020; Najdi AN, *et al.*, 1988; Khan FY, *et al.*, 2012; Naeem D, *et al.*, 2018; Tolba YY, *et al.*, 2018; Dib JG, *et al.*, 2009; Hammuda A, *et al.*, 2013; Aseeri MA, 2013; Butt AA, *et al.*, 2017). In second step a total of 2357 articles searched after removing duplication 2453 from Pubmed, 2 from Embase and 1 from Elsevier. 901 are excluded based on abstract and 1346 on the basis of title. 110 are included and studied completely. Out of 110, 23 included in meta-analysis, 67 are excluded due to unavailability of complete data or outcome requirement and stewardship other than pharmacist with physician. 23 studies further reviewed and 5 only included in the meta-analysis at the end 14 studies with inappropriateness are included (Brizzi MB, *et al.*, 2020; Burns KW, *et al.*, 2020; Giruzzi ME, *et al.*, 2020; Fay LN, *et al.*, 2019; Bessesen MT, *et al.*, 2015; Sadyrbaeva-Dolgova S, *et al.*, 2020; Cappelletty D and Jacobs D, 2013; Baker SN, *et al.*, 2012; Arensman K, *et al.*, 2020; Apisarnthanarak A, *et al.*, 2015; Ohashi K, *et al.*, 2018; Samura M, *et al.*, 2020; Haque A, *et al.*, 2018; MacMillan KM, *et al.*, 2019). Total 32 studies are included. The details of study characteristics are provided in *Table 1 (Figure 1)*.

Table 1: Included studies characteristics

S.No	Authors	Year and Place	Title	Design	Variable	Conclusion
1	Dib JG, *et al.*	KSA	Improvement in vancomycin utilization in adults in a Saudi Arabian Medical Center using the Hospital Infection Control Practices Advisory Committee guidelines and simple educational activity	Quasi-experimental	Inappropriate, IM, CC, Oncology and Surgery	Effective methods to decrease inappropriate vancomycin usage are educational efforts with chart review and feedback to physician.
2	Youssif E, *et al.*	KSA	Retrospective evaluation of piperacillin–tazobactam, imipenem–cilastatin and meropenem used on surgical floors at a tertiary care hospital in Saudi Arabia	Retrospective	Inappropriate, Surgery	Broad spectrum antibiotics use is unjustified and need interventions like culture and sensitivity test requests within 24 h of starting the broad spectrum antibiotics and de-escalation.

3	Hammuda A, *et al.*	Qatar	Point prevalence survey of antimicrobial utilization in oncology patients	Retrospective	Inappropriate, Oncology,	Broad spectrum antibiotics are frequently used and need antimicrobial stewardship programs.
4	Al-Maliky GR, *et al.*	Oman	Evaluation of antibiotic prescribing for adult inpatients at Sultan Qaboos University Hospital, Sultanate of Oman	Observational	ICU, Inappropriate	Diagnosis was documented in 89% and compliance with SQUH antibiotic prescribing guidelines was suboptimal. Studies are required to cope with reasons behind the non-compliance with guidelines.
5	Aseeri M	KSA	The Impact of a Pediatric Antibiotic Standard Dosing Table on Dosing Errors	Retrospective	Pediatric	Implementation of dosing standard in pediatric department reduces the dosing errors.
6	Khan FY, *et al.*	Qatar	Evaluation of the use of piperacillin/tazobactam (Tazocin®) at Hamad General Hospital, Qatar: are there unjustified prescriptions?	Retrospective	Surgical,	Study shows that use of piperacillin/ tazobactam at our hospital was unjustified, evidenced inappropriate empiric prescriptions and inappropriate drug modifications, depends upon the microbial cultures.
7	Alahdal AM, Elberry AA	KSA	Evaluation of applying drug dose adjustment by physicians in patients with renal impairment	Retrospective	Medical ward, Renal dose Adj	Physicians are not taking care of dose adjustment in renal failure patients need clinical pharmacist interventions and education to prescribers.
8	Al-Yamani A, *et al.*	Oman	Patterns of Antimicrobial Prescribing in a Tertiary Care Hospital in Oman	Retrospective	Acute care, AB Selection	Misuse and overuse of antibiotics proves that need National guidelines. Antibiotics prescribing in different hospitals need to be evaluated.
9	Naeem D, *et al.*	KSA	Prescribing Empiric Antibiotics for Febrile Neutropenia: Compliance with Institutional Febrile Neutropenia Guidelines	Cross sectional	Oncology, Compliance	FN management guidelines are not followed in our institute. Appropriate empiric antibiotic indications and doses as per institutional guidelines are recommended.
10	Alhameed AF, *et al.*	KSA	Bridging the Gap between Theory and Practice; the Active Role of Inpatient Pharmacists in Therapeutic Drug Monitoring	Quasi-experimental	Emergency, Medical, surgical, optimal initial dosing	Study highlights the importance of Therapeutic drug monitoring led by pharmacist to optimize the initial dose of antibiotics.
11	Butt AA, *et al.*	Qatar	Antibiotic prescription patterns for upper respiratory tract infections in the outpatient Qatari population in the private sector	Retrospective	All specialties	Inappropriate antibiotic prescription for acute URTIs is very high in the private health sector in Qatar. To reduce this inappropriateness interventions are needed.
12	Al-Hadithi D, *et al.*	Oman	Evaluation of the appropriateness of meropenem prescribing at a tertiary care hospital: A retrospective study in Oman	Retrospective	Oncology, Haematology, indication of meropenem	Meropenem orders are highly inappropriate and unjustified by culture results that need proper guidelines and education to stop, de-esclate and judicious use of meropenem.

13	Alzahrani AA, *et al.*	KSA	Inappropriate Dental Antibiotic Prescriptions: Potential Driver of the Antimicrobial Resistance in Albaha Region, Saudi Arabia	Retrospective	Dental	Some of dental prescriptions are unnecessary and need interventions to reduce the inappropriateness.
14	Alanazi MQ	KSA	An evaluation of community-acquired urinary tract infection and appropriateness of treatment in an emergency department in Saudi Arabia	Cross- sectional	Emergency department, inappropriateness	In emergency department of Saudi Arabia revealed highly inappropriate use of antibiotics for UTI.
15	Najdi AN, *et al.*	Kuwait	Antibiotic misuse in a pediatric teaching department in Kuwait	Retrospective	Inappropriate, pediatric	High rate of antibiotic use and misuse due to lack of policies and procedures worldwide.
16	Alanazi MQ, *et al.*	KSA	Prevalence and predictors of antibiotic prescription errors in an emergency department, Central Saudi Arabia	Cross-sectional	Inappropriate, all emergency department	Emergency department shows high number errors in prescribing of antibiotics and errors were common with narrow spectrum and UTI infections.
17	Aly NY, *et al.*	Kuwait	Audit of Physicians' Adherence to the Antibiotic Policy Guidelines in Kuwait	Retrospective	Adherence, hospital department	Adherence to the antibiotic policy guidelines is very low. Antibiotics prescribing practice of Physician need to be overlooked. It is recommended that policy should be followed.
18	Tolba YY, *et al.*	KSA	An observational study of perioperative antibiotic-prophylaxis use at a major quaternary care and referral hospital in Saudi Arabia	Retrospective	Surgical, inappropriate	In surgical antibiotic prophylaxis it is observed the difference of practice and guidelines dose exist and need to follow up the guidelines.
19	Apisarnthanarak A, *et al.*	2015 Thailand	Design and analysis of a pharmacist-enhanced antimicrobial stewardship program in Thailand	Prospective	Inappropriateness,	Study suggest a better outcomes with IDCP training and incorporation of pharmacist in the stewardship.
20	Arensman K, *et al.*	2020 USA	Impact of Mandatory Infectious Diseases Consultation and Real-time Antimicrobial Stewardship Pharmacist Intervention on Staphylococcus aureus Bacteremia Bundle Adherence	Retrospective	Inappropriateness,	The addition of AMS pharmacist review to mandatory Infectious disease consultation impact on the outcome measures of stewardship.
21	Baker SN, *et al.*	2012 USA	Pharmacist-managed antimicrobial stewardship program for patients discharged from the emergency department	Retrospective	Inappropriateness	An EPh-managed antimicrobial stewardship program significantly reduced time to culture that effect the appropriate prescribing.

22	Bessesen MT, *et al.*	2015 USA	Antimicrobial Stewardship Programs: Comparison of a Program with Infectious Diseases Pharmacist Support to a Program with a Geographic Pharmacist Staffing Model	Retrospective	Inappropriateness,	Pharmacist through stewardship responsible for better antibiotic prescribing measures and conversion from parenteral to oral therapy
23	Brizzi MB, *et al.*	2020 USA	Impact of Pharmacist-Driven Antiretroviral Stewardship and Transitions of Care Interventions on Persons With Human Immunodeficiency Virus	Retrospective	Inappropriateness	A pharmacist-led ARV stewardship and TOC program impact on prescribing practice and readmissions.
24	Burns KW, *et al.*	2020 USA	Implementing outpatient antimicrobial stewardship in a primary care office through ambulatory care pharmacist-led audit and feedback	Retrospective	Inappropriate	An ACP-led ASP intervention within a primary care office incorporating audit and feedback improved antibiotic prescribing practice for URIs and UTIs including duration of therapy.
25	Cappelletty D, Jacobs D	2013 USA	Evaluating the impact of a pharmacist's absence from an antimicrobial stewardship team	Retrospective	Inappropriateness	Inappropriate prescribing increase with the absence of pharmacist.
26	Sadyrbaeva-Dolgova S, *et al.*	2019 Spain	Pharmacist recommendations for Carbapenem de-escalation in urinary tract infection within an antimicrobial stewardship program	Prospective	Inappropriateness	Carbapenem de-escalation in accordance with pharmacist recommendation proves a positive intervention that can help to reduce the mortality, inappropriateness and readmission.
27	Fay LN, *et al.*	2019 USA	Pharmacist-led antimicrobial stewardship program in an urgent care setting	Retrospective	Inappropriateness	A pharmacist-led urgent care ASP was associated with reduction in inappropriate prescribing and readmission.
28	Giruzzi ME, *et al.*	2019 USA	Evaluation of Antibiotic Utilization in an Emergency Department After Implementation of an Antimicrobial Stewardship Pharmacist Culture Review Service	Retrospective	Inappropriateness	ASP pharmacist evaluation of positive cultures in the ED has positive impact in reduction in the time to appropriate therapy.
29	Haque A, *et al.*	2017 Pakistan	Impact of pharmacist-led antibiotic stewardship program in a PICU of low/middle-income country	Prospective	Inappropriateness	Study shows the impact of pharmacist on cost, consumption, mortality and inappropriate antimicrobial prescribing.
30	MacMillan KM, *et al.*	2019 Canada	Evaluation of a pharmacist led antimicrobial stewardship service in a pediatric emergency department	Retrospective	Inappropriateness	Although this pharmacist-led AMS program did not affect the readmission, it may have led to much better result on inappropriate prescribing.
31	Ohashi K, *et al.*	2018 Japan	Evaluation of treatment outcomes of patients with MRSA bacteremia following antimicrobial stewardship programs with pharmacist intervention.	Prospective	Inappropriateness	Use of an appropriate bundle, established by an AST with pharmacist intervention, can effect significantly to the treatment of MRSA-B and impact on other outcomes.

32	Samura M, *et al.*	2020 Japan	Support for fungal infection treatment mediated by pharmacist-led antifungal stewardship activities	Retrospective	Inappropriateness	These results suggest that pharmacist-led antifungal stewardship has positive impact on outcome measures like cost, consumption and mortality.

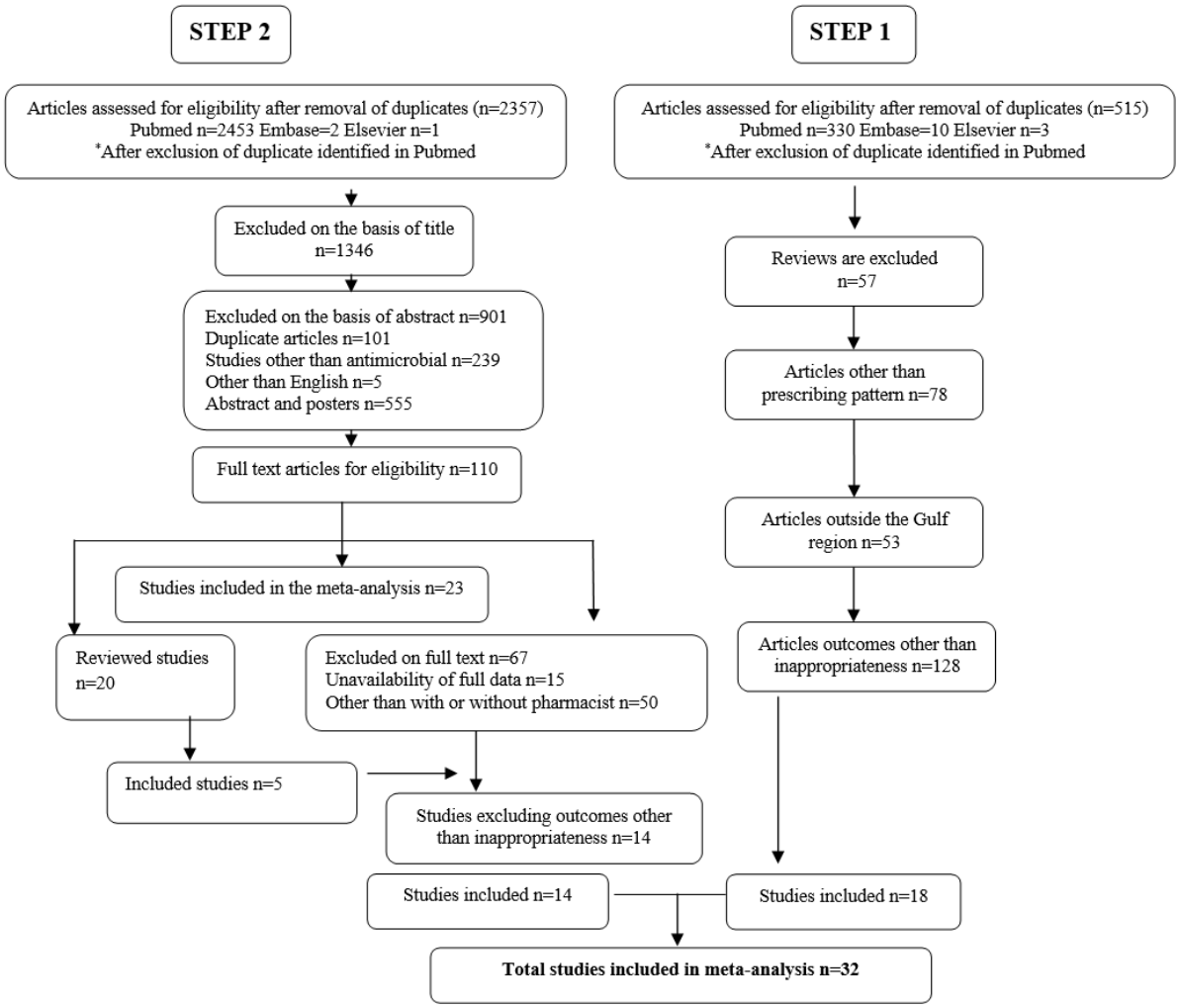

Figure 1: The general characteristics of studies included in meta-analysis

Quality assessment

Quality assessment performed using JSM as quality assessment tool for all of the studies run and included studies have low or medium level of bias. Quality assessment details are attached as supplementary documents with all details. Articles are assessed in detail with purpose, methodology, results, and discussions. *Table 2* shows the quality assessment tool.

Inappropriate antibiotic prescribing

Antibiotics inappropriate prescribing in the Gulf region in all departments are calculated and measure of inappropriateness is different from different articles. Out of seven gulf countries inappropriateness is reported in four countries leading Saudi Arabia with 10 primary articles, 3 studies in Oman and Qatar and only 2 in Kuwait while there is no study found in UAE, Bahrain and Yemen with mentioned inappropriateness in number as shown in *Figure 2*. Prescribing pattern of antibiotics with inappropriateness is available from 1988 in Saudi Arabia till new study in 2020 in Oman. Prescribing patterns are studied in different departments of the hospital and it is found that most of the studies took place in surgical department (5), Oncology (4), Emergency and Internal Medicine (3, 3) and others as shown in *Figure 3*. 18 articles discussed about the inappropriate antibiotic prescribing pattern with inappropriateness. We have found all 14 studies shows positive outcome of reduction in inappropriate antimicrobial prescribing as shown in *Figure 2*. Risk of inappropriate prescribing of antimicrobials is less in AMS with pharmacist than pre-AMS without pharmacist.

Pooled analysis

Total inappropriateness in prescribing pattern in Gulf region in 18 studies is 43669/100846 about 43.3%. Pooled RR=1.31 with 95% CI=(1.30, 1.32). Test with Overall effect is 58.87 (P<0.00001). Heterogeneity is calculated about I2=99%. Funnel plot used to reduce the bias as shown in *Figure 4*. Inappropriateness reduced to I2=64%.

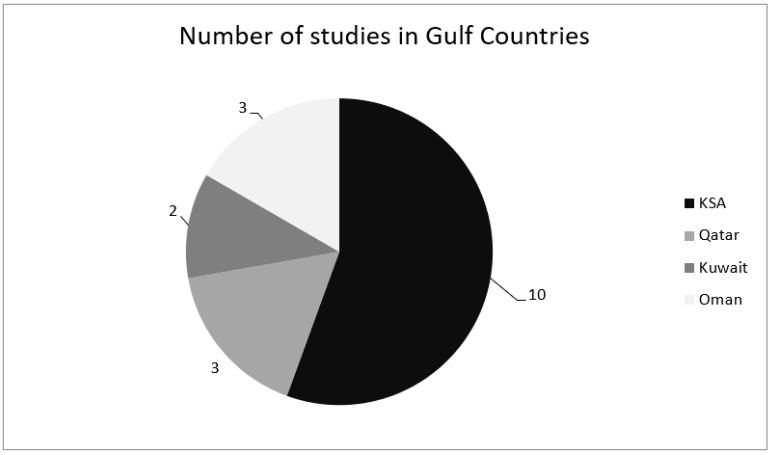

Figure 2: The number of studies in different countries of Gulf region

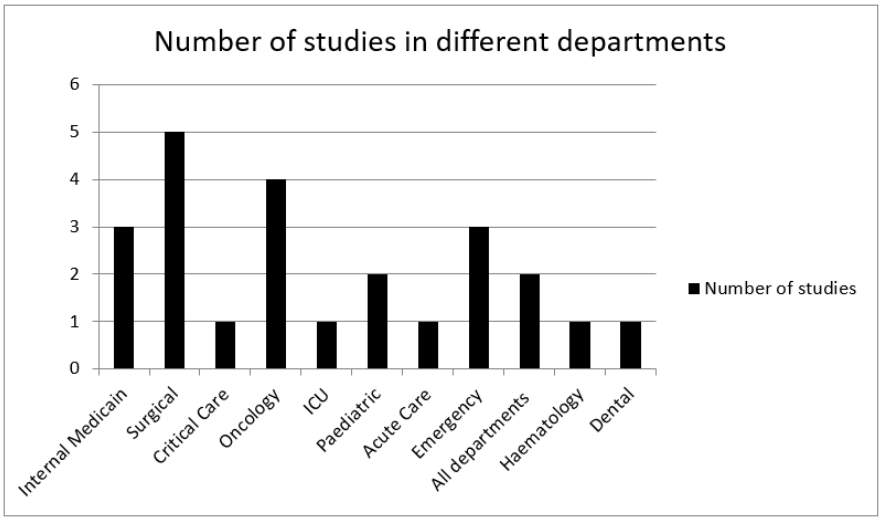

Figure 3: The number of studies in different departments of Hospitals in Gulf region

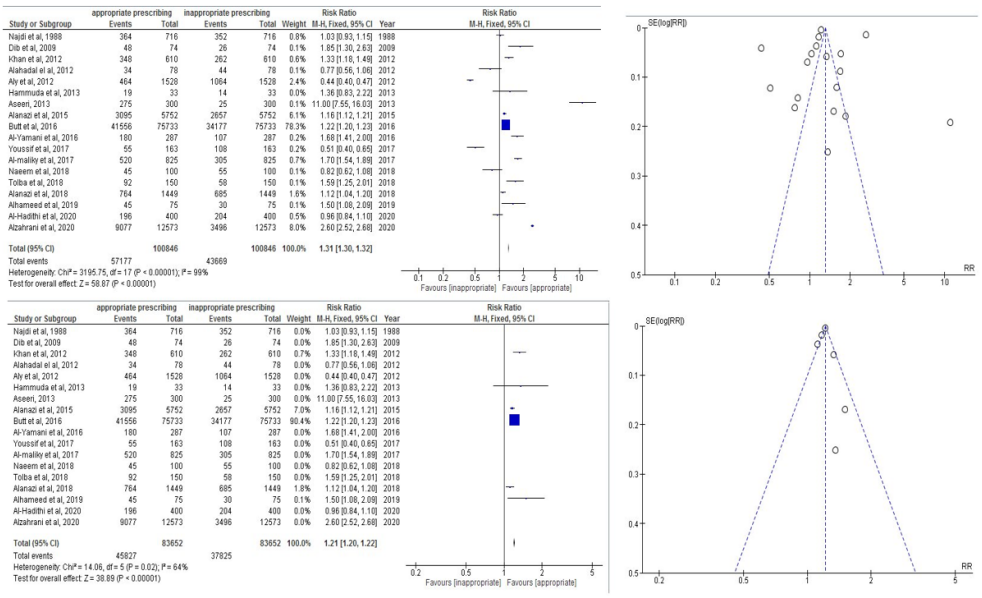

Figure 4: The 18 studies with inappropriateness and reduction of bias through funnel plot

Table 2: Shows the studies quality assessment through JSM tool

		Scale Items												
S.No	**Study Name**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Score**
1	Dib JG, *et al.*	Y	Y	Y	Y	CD	Y	Y	N	NR	Y	Y	Y	L
2	Youssif E, *et al.*	Y	Y	Y	Y	Y	Y	Y	NR	NR	Y	Y	N	L
3	Hammuda A, *et al.*	Y	Y	Y	Y	N	Y	Y	NR	NR	Y	Y	CD	M
4	Al-Maliky GR, *et al.*	Y	Y	Y	Y	NR	Y	Y	NR	CD	Y	Y	NR	M
5	Aseeri M	Y	Y	Y	Y	CD	Y	Y	CD	Y	Y	Y	NR	L
6	Khan FY, *et al.*	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	NR	CD	L
7	Alahdal AM, Elberry AA	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	CD	NR	L
8	Al-Yamani A, *et al.*	Y	Y	Y	Y	CD	Y	Y	Y	CD	Y	CD	N	M
9	Naeem D, *et al.*	Y	Y	Y	Y	Y	Y	Y	NR	Y	Y	Y	Y	L
10	Alhameed AF, *et al.*	Y	Y	Y	Y	Y	Y	Y	NR	CD	Y	Y	N	M
11	Butt AA, *et al.*	Y	Y	Y	Y	NR	Y	Y	N	NR	Y	Y	N	M
12	Al-Hadithi D, *et al.*	Y	Y	Y	Y	CD	Y	Y	CD	NR	Y	Y	Y	L
13	Alzahrani AA, *et al.*	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	Y	Y	L
14	Alanazi MQ	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	NR	NR	L
15	Najdi AN, *et al.*	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	NR	NR	L
16	Alanazi MQ, *et al.*	Y	CD	Y	Y	Y	Y	Y	CD	Y	Y	Y	Y	L
17	Aly NY, *et al.*	Y	Y	Y	Y	N	Y	Y	CD	NR	Y	NR	Y	M
18	Tolba YY, *et al.*	Y	Y	Y	Y	N	Y	Y	NR	CD	Y	NR	Y	M
19	Apisarnthanarak A, *et al.*	Y	Y	Y	Y	CD	Y	Y	N	CD	Y	Y	N	L
20	Arensman K, *et al.*	Y	Y	Y	Y	Y	Y	Y	NR	CD	Y	Y	N	L
21	Baker SN, *et al.*	Y	Y	Y	Y	CD	Y	Y	N	Y	Y	Y	N	L
22	Bessesen MT, *et al.*	Y	Y	Y	Y	N	Y	Y	NR	Y	Y	N	CD	M
23	Brizzi MB, *et al.*	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	CD	L
24	Burns KW, *et al.*	Y	Y	Y	Y	Y	Y	Y	NR	CD	Y	Y	N	L
25	Cappelletty D, Jacobs D	Y	CD	Y	Y	CD	Y	Y	NR	CD	Y	Y	N	M
26	Sadyrbaeva-Dolgova S, *et al.*	Y	Y	Y	Y	Y	Y	Y	NR	CD	Y	Y	Y	L
27	Fay LN, *et al.*	Y	Y	Y	Y	Y	Y	Y	NR	NR	Y	Y	CD	L
28	Giruzzi ME, *et al.*	Y	Y	Y	Y	Y	Y	Y	NR	NR	Y	CD	Y	L
29	Haque A, *et al.*	Y	Y	Y	Y	CD	Y	Y	N	NR	Y	N	Y	M
30	MacMillan KM, *et al.*	Y	Y	Y	Y	Y	Y	Y	CD	NR	Y	Y	Y	L
31	Ohashi K, *et al.*	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	NR	Y	L
32	Samura M, *et al.*	Y	Y	Y	Y	Y	Y	Y	N	NR	Y	NR	Y	L

Sub-group analysis

Calculation of inappropriateness is different from one another. Al-hameed calculated the inappropriate prescribing with the dose and monitoring of antibiotics like vancomycin and compare with standard guidelines such as ASHP/IDSA guidelines (Alhameed AF, *et al.*, 2019) shows 40% of inappropriate dosing and monitoring. Youssif calculated the inappropriate antibiotics prescribing in surgical ward for broad spectrum antibiotics with help of requesting culture in 24 hr and number of days to deescalate once culture receive (Youssif E, *et al.*, 2018) shows 66% of inappropriate prescribing in surgical ward. Aly checked the antibiotic prescribing concordance with hospital guidelines and found 69.6% of prescribed antibiotic prescribing were not concordant to the guidelines (Aly NY, *et al.*, 2012). Alzahrani has audited the antibiotic prescribing pattern in dental department and found that antibiotics are prescribed in 27.8% of consultation in which antibiotics were not recommended (Alzahrani AA, *et al.*, 2020). Alanazi reviewed the antibiotics prescribing pattern in emergency department and found inappropriate prescribing with major errors in dose (37%) then duration, frequency and selection of antimicrobials found overall inappropriateness of 41.4% (Alanazi MQ, 2018) and in another study in 2015 found inappropriateness on same basis in emergency department is 46.12% (Alanazi MQ, *et al.*, 2015). A study in King Abdulaziz university hospital found that 56.4% patient with renal failure antibiotics dose was not adjusted (Alahdal AM and Elberry AA, 2012). Antibiotic prescribing compliance with the local guidelines as well as the overall restricted antibiotic policy adherence at Sultan Qaboos University Hospital (SQUH) found that 36.96% of antibiotics prescribing was not up to the mark (Al-Maliky GR, *et al.*, 2018). Another study in Oman checked the rational prescribing of antibiotics depending on local standard guidelines and the experience of the ID consultant found that 37.28% of irrational antibiotic prescribing (Al-Yamani A, *et al.*, 2016). Meropenem inappropriate prescribing in Oman, inappropriateness accessed by specific meropenem-use criteria, that were developed from pre-specified, literature-based criteria and then modified by an expert panel of Infectious Diseases specialists found that indication is inappropriate in 51% of cases (Al-Hadithi D, *et al.*, 2020). Antibiotic misuse in pediatric department of Kuwait accessed using Local guidelines and found overall mistakes 49.16% as of inappropriate use, duration, route, unnecessary use and combination (Najdi AN, *et al.*, 1988). Unjustified tazocin prescription in Qatar identified through setting specific criteria

and found that 42.95% of unjustified use (Khan FY, *et al.*, 2012). Empirical treatment for febrile neutropenia using KAMC-WR empirical therapy guidelines found that 55% of guidelines non-complaint treatment (Naeem D, *et al.*, 2018). Antibiotic prophylaxis was accessed by Scottish Intercollegiate Guidelines Network (SIGN), American Society of Health-System Pharmacists (ASHP) and Saudi Ministry of Health (MOH) and found 38.6% antibiotic prophylaxis is not recommended (Tolba YY, *et al.*, 2018). Vancomycin use in Saudi Arabian medical center accessed by a clinical pharmacist along with an Infectious Disease consultant collected and reviewed and found that 35% inappropriate (Dib JG, *et al.*, 2009). Antimicrobial use in Oncology in Qatar accessed by local prescribing restriction guidelines found 42% of prescriptions not complied with guidelines (Hammuda A, *et al.*, 2013). Pediatric antibiotic dosing standard accessed with standard if more than 110% or less than 90% considered inappropriate dose and found 30% of dosing error (Hammuda A, *et al.*, 2013) before implementing stewardship. Antibiotic for upper respiratory tract infection in outpatient inappropriate prescribing accessed by expert opinion of infectious diseases specialists was used and found 45% of inappropriateness (Butt AA, *et al.*, 2017).

Reduction in inappropriateness

A total of 14 antimicrobial stewardships led by pharmacist in last 8 years and discuss about appropriate antibiotic therapy. 8 antimicrobial stewardship programs led by pharmacist run in USA while 2 in Japan and 1 in Spain, Thailand, and Pakistan. 9 studies are retrospective and 5 are prospective studies. There are different strategies used in every antimicrobial stewardship programs. We have found all 14 studies shows positive outcome of reduction in inappropriate antimicrobial prescribing as shown in *Figure 5*. Risk of inappropriate prescribing of antimicrobials is less in AMS with pharmacist than pre-AMS without pharmacist.

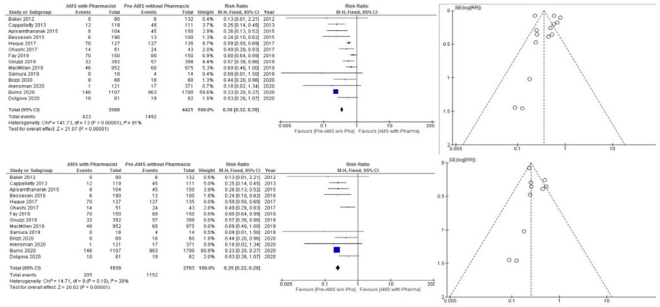

Figure 5: The 14 AMS results for inappropriate antimicrobial prescribing

Pooled analysis

Total inappropriateness in AMS with pharmacist is 423/3560 (11.88%) whereas in pre-AMS without pharmacist is 1492/4421 (33.74%). Pooled RR=0.36 with 95% CI=(0.32, 0.39). Test with Overall effect is 21.27 (P<0.00001). Heterogeneity is calculated about I2=91%. Funnel plot used to reduce the bias as shown in *Figure 5*. Inappropriateness reduced to I2=39%.

DISCUSSION

Antibiotic prescribing pattern are studied all over the world and in the Gulf region as well. Antibiotics prescribed with the use and indication and overall trends are studied with the rational prescribing. Antibiotics prescribing pattern in the Gulf region shows a variation in all departments with respect to the inappropriate prescribing. Standards of inappropriate prescribing differ from study to study some with guidelines local or international, dosing, frequency, monitoring, indication and prophylaxis. It has been observed most of the inappropriate antibiotics prescribing studied in the Saudi Arabia and three other countries while UAE, Bahrain and Yemen have no study that shows the inappropriate antibiotic prescribing in the region. Surgical ward inappropriate antibiotics prescribing is most studied in the Gulf region as this department is responsible for both prophylaxis and treatment and is related to the emergency department so high chances of lack of concordance with the guidelines and policies. Oncology, Emergency and Internal Medicine for long term patient or patient with multiple disorders need attention as high chances of inappropriate antibiotic use. Study in 2012 Kuwait shows a very high inappropriate antibiotics prescribing as physicians are not adhere to guidelines in almost 70% of the cases that is incredibly very high (Aly NY, *et al.*, 2012). Another study shows least inappropriate antibiotic prescribing practice as low as 27% (Alzahrani AA, *et al.*, 2020) shows low inappropriateness in dental department in Saudi Arabia and shows 27% of cases shows overuse of antibiotics. This shows that average inappropriate antibiotic prescribing in Gulf region is very high that need to be attended with education, stewardships, seminars, awareness, concordance with guidelines and implementation of clinical pharmacist in hospital and infectious disease specialists. A study in Colombia shows that inappropriate antibiotics prescribing for acute bronchiolitis shows 65% of inappropriateness (Buendía JA and Feliciano-Alfonso JE, 2021). Study in US Prevalence of Inappropriate Antibiotic Prescribing by Antibiotic Among Privately and Publicly Insured Non-Elderly enroll 18 million using antibiotics shows 18% are inappropriate prescribing (Chua KP and Linder JA, 2020) a very high number of patients in private and public sector and shows the average inappropriate prescribing in US that is 22% less than the least reported in the Gulf region. 9-year study of antibiotic inappropriateness in US emergency department shows that 70% of the cases with bronchiolitis had prescribed antibiotics without documented bacterial co-infection.

Antimicrobial stewardship programs can help to reduce the inappropriate prescribing pattern. Pharmacist is an integral part of healthcare system and involve from drug dispensing, monitoring and compounding and working as a clinical pharmacist can help to develop the stewardship programs and can involve in at as responsible for all departments of the hospital. Antimicrobial stewardship programs led by pharmacist searched that shows a positive impact all of 14 studies shows the positive impact on the reduction of inappropriate antibiotic prescribing. Average inappropriateness was 37% reduced to 11.88% after the implementation of pharmacist led AMS. Antimicrobial stewardship programs in Gulf region stating the appropriateness and corrected from 30% to 100% in medical intensive care unit of tertiary care hospital in Saudi Arabia (Amer MR, *et al.*, 2013). Another stewardship in tertiary care hospital in Qatar have stated that appropriateness improves to 95.7% with the help of antimicrobial stewardships (Nasr Z, *et al.*, 2019). Lack of pharmacist led stewardship is noted in the Gulf region and need improvements. Gulf Cooperation Council surveys for AMS in all Gulf region and responded from 47 countries out of which 38 from Saudi Arabia responded and UAE, Bahrain and Oman only 2 responded while there is no response from rest of states (Enani MA, 2016). As per the survey 5 respondents were pharmacist whereas 23 were infection control consultant. That shows a less response from the pharmacist. As per the survey reduction of inappropriate prescribing is 68%, still not up to the mark. There are lot of other factors need to be studied else than stewardship as infection control measures and self-medications that have an impact on resistance and stewardship programs.

CONCLUSION

Antibiotic inappropriate prescribing in Gulf region is widely spread that need to be addressed with antimicrobial stewardships. Number of stewardships in Gulf region is very low and pharmacist led antimicrobial stewardship is still not in practice in Gulf region that may help to

improve appropriate antibiotic use.

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