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Evaluation of inappropriate antibiotic prescribing and management through pharmacist-led antimicrobial stewardship programmes: a meta-analysis of evidence

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ABSTRACT

Purpose This meta-analysis aims to evaluate inappropriate antibiotic prescribing in the Gulf region and determine the effect of pharmacist-led antimicrobial stewardship (AMS) programmes on reducing inappropriateness.

Method Articles were searched, analysed, and quality assessed through the risk of bias (ROB) quality assessment tool to select articles with a low level of bias. In step 1, 515 articles were searched, in step 2, 2360 articles were searched, and ultimately 32 articles were included by critical analysis. Statistical analysis used to determine risk ratio and standard mean differences were calculated using Review manager 5.4; 95% confidence intervals were calculated using the fixed-effect model. The I^2 statistic assessed heterogeneity. In statistical heterogeneity, subgroup and sensitivity analyses, a random effect model was performed. The α threshold was 0.05. The primary outcome was inappropriateness in antibiotic prescribing in the Gulf region and reduction of inappropriateness through AMS.

Result Detailed review and analysis of 18 studies of inappropriate antibiotic prescribing in the Gulf region showed the risk of inappropriateness was 43 669/100 846=43.3% (pooled RR 1.31, 95% CI 1.30 to 1.32). Test with overall effect was 58.87; in the second step 28 AMS programmes led by pharmacists showed reduced inappropriateness in AMS with pharmacist versus pre-AMS without pharmacist (RR 0.36, 95% CI 0.32 to 0.39).

Conclusion Inappropriate antibiotic prescribing in the Gulf region is alarming and needs to be addressed through pharmacist-led AMS programmes.

BACKGROUND

Antimicrobial resistance is increasing globally, affecting cost, mortality and length of hospital stay. A recently published study showed that by 2050 the leading cause of death will be bacterial infection unless resistance is controlled.[1] A survey of antibiotic resistance in the Gulf region found the susceptibility of community-acquired respiratory tract isolates in the region to be alarming. The report 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'.[2] A study conducted in eight hospitals in Saudi Arabia showed that the most resistant antipseudomonal agent was meropenem followed by ticarcillin, imipenem, and piperacillin; almost 13% of the strains were multidrug resistant.[3] Since 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.[4]

Inappropriate antibiotic prescribing is associated with the emergence of multidrug resistance, which ultimately increases the mortality rate. For example, one study found inappropriate antibiotic prescribing was an essential determinant of multidrug resistance associated with a threefold increase in in-hospital mortality.[5] In a survey of European medical final students, 66% agreed that antibiotic resistance was due to prescribed antibiotics being the wrong choice.[6] Another study, this time in Singapore, showed that inappropriate prescribing of antimicrobials was responsible for increased antimicrobial resistance that could only be resolved with appropriate antimicrobial prescribing.[7]

Rational prescribing can help to reduce antimicrobial resistance. Antimicrobial stewardship (AMS) programmes can help to increase the rational prescribing of antibiotics. A study showed that an AMS programme helped to increase appropriate antimicrobial prescribing by up to 89.3%.[8] The pharmacist plays a vital role in the stewardship team. However, the extent of inappropriate antibiotic prescribing and the impact of the pharmacist on the rational prescribing of antibiotics through AMS programmes is unclear.

This study evaluates inappropriate antibiotic prescribing in the Gulf region and determines the effect of pharmacist-led AMS programmes on rational prescribing.

METHODOLOGY

The methodology for searching articles involved a two-step process. In the first step, we determined the level of inappropriate antimicrobial prescribing in the Gulf region, and in the second step we studied the impact of the pharmacist on inappropriate prescribing through a pharmacist-led AMS programme. Our methodology adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (see PRISMA checklist: online supplemental appendix 1)

Data sources

In step 1, antimicrobial prescribing patterns with inappropriate prescribing were identified by searching PubMed, Embase and Elsevier. The search included all English language articles. Key words used were: 'antibiotic', 'prescribing', and 'Gulf', 'Saudi Arabia','UAE', 'Qatar', 'Bahrain', 'Kuwait', 'Oman' and 'Yemen'. Only original articles were included, while reviews, meta-analyses, surveys and questionnaires showing prescribing practices and inappropriateness were excluded.

In step 2, AMSs were identified by 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 the pharmacist', 'impact on cost', 'outcomes of stewardship', 'hospital readmission', and 'antibiotic consumption'. We only included articles with those values representing the inappropriate prescribing of antibiotics before and after AMS programmes led by the pharmacist. We restricted our search to the primary literature; systematic reviews, meta-analyses and all other types of reviews were excluded. We manually searched the reference lists of systematic reviews to check their inclusion in our analysis.

The search strategy is illustrated in online supplemental appendix 1.

STUDY SELECTION

In step 1, we included primary literature on all antimicrobial prescribing patterns in the Gulf region. The Gulf region includes seven countries (UAE, Saudi Arabia, Kuwait, Qatar, Oman, Yemen and Bahrain). Articles with inappropriate antibiotic prescribing practices were included. Topical antibiotic prescribing studies were excluded, and studies conducted in countries other than those in the Gulf region were also excluded. In step 2, we included primary literature on all types of AMS programmes (antibiotics, antifungal, antiviral) led by pharmacists, whether retrospective, prospective or quasi-experimental studies. Dichotomous results were extracted from the AMS programme with pharmacists compared with the pre-AMS programme without pharmacists. Only studies with inappropriate antibiotic prescribing as a clinical outcome were included in our analysis. Reviews and abstracts without complete data, studies in languages other than English, and stewardship programmes with antimicrobial outcomes other than inappropriate prescribing practices were excluded.

Two investigators (RKM, MJA) independently assessed eligibility. In case of any discrepancy, a third observer (SWG) adjudicated the eligibility. The extraction forms and risk of bias assessments are available in the online supplemental appendix 1.

Quality assessment

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

OUTCOMES

The primary outcome was inappropriate antibiotic prescribing practices in the Gulf region and the impact of AMS programmes

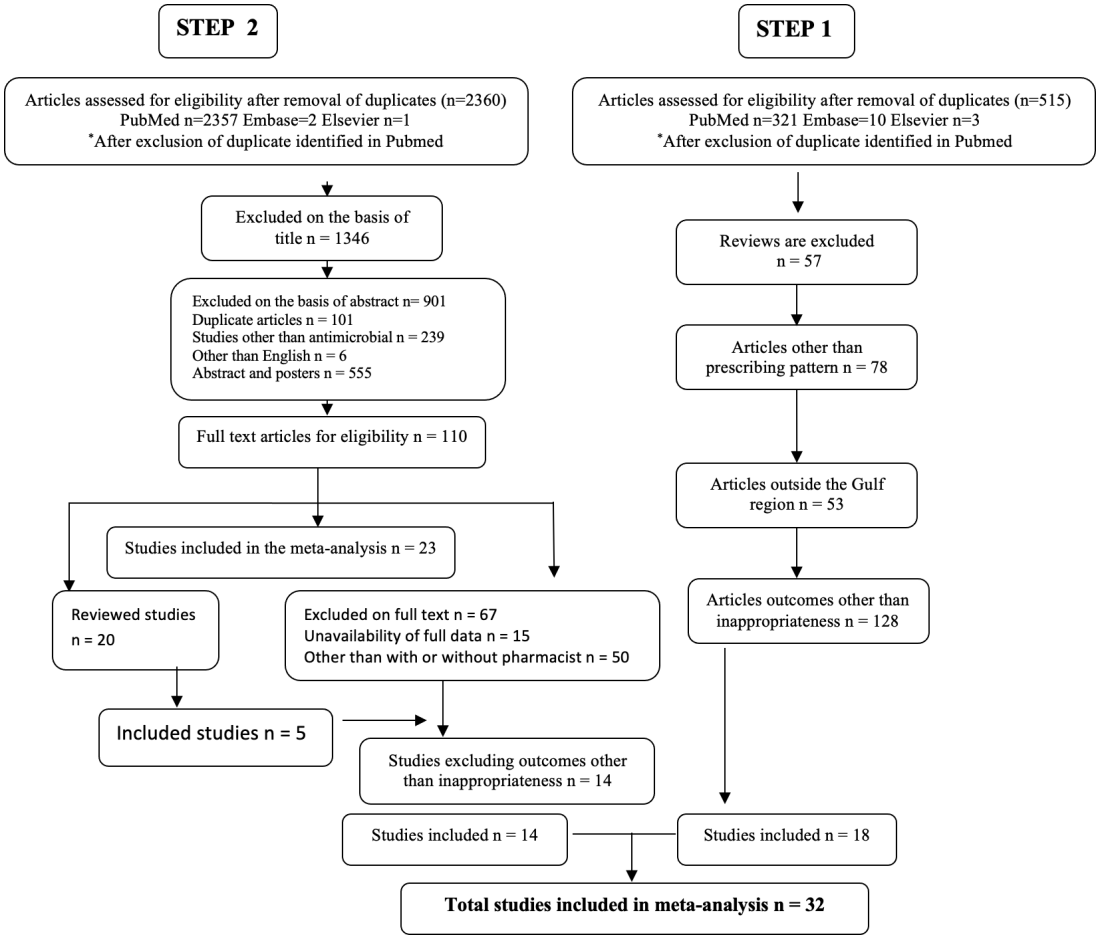

Figure 1 General characteristics of studies included in the meta-analysis.

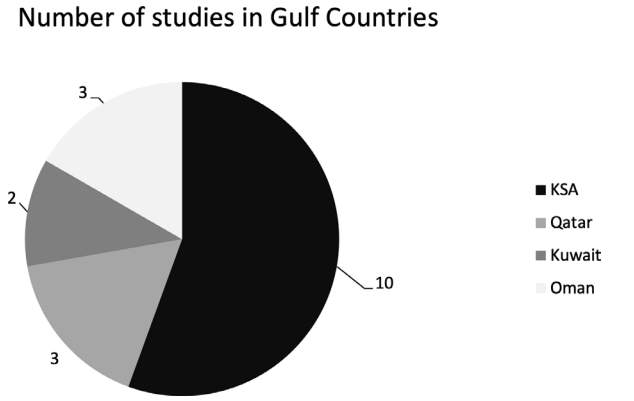

Figure 2 Number of studies in the different countries of the Gulf region.

led by pharmacists in reducing inappropriate antimicrobial prescribing. Two reviewers (MJA, SMG) independently extracted the data for all the outcomes of interest.

Inappropriate prescribing

Antibiotic prescribing is termed ' inappropriate' if the prescribing does not meet prescribing guidelines. If the dose, frequency, dosage form, indication and route of administration were not correct then the prescribing was considered to be inappropriate.

Principal summary measures and statistical analysis

Analyses were done using RevMan software version 5.4 (http://www.cc-ims.net/revman). We calculated risk ratios (RR) with 95% confidence intervals (95 % CI) for all studies, using the fixed-effect model in the first approach. Heterogeneity was investigated with the I^2 statistic. It measures the proportion of overall variation attributable to between-study heterogeneity. I^2 values of 25%, >50%, and >75% refer respectively to low, substantial, and considerable degrees of heterogeneity. In case of statistical heterogeneity, we tried to explain this with subgroup and sensitivity analyses rather than with funnel plots. Statistical significance was defined with an α threshold at 0.05.

RESULTS AND FINDINGS

General characteristics

In the first step, 515 articles were searched and, after removing duplications, 330 were from PubMed, 10 from Embase and three from Elsevier (figure 1). Articles excluded were 57 reviews, 78 articles without prescribing patterns, 53 that came from outside the Gulf region, and 128 articles with outcomes other than inappropriateness; the remaining 18 articles were included.[9–26] In the second step, a total of 2453 articles were searched, and after removing duplications 2357 were from PubMed, two from Embase and one from Elsevier. Nine hundred and one articles were excluded based on the abstract, and 1349 based on the title; 110 articles were included and studied thoroughly. Of these 110 articles, 23 were included and 67 were excluded (unavailability of complete data, outcome requirement and stewardship other than pharmacist but with the physician). These 23 studies were further reviewed, and five only were included in the meta-analysis; in the end, 14 studies with inappropriateness were included.[27–40] Therefore a total 32 studies were eventually included in the study; details of the study characteristics are provided in online supplemental table 1.

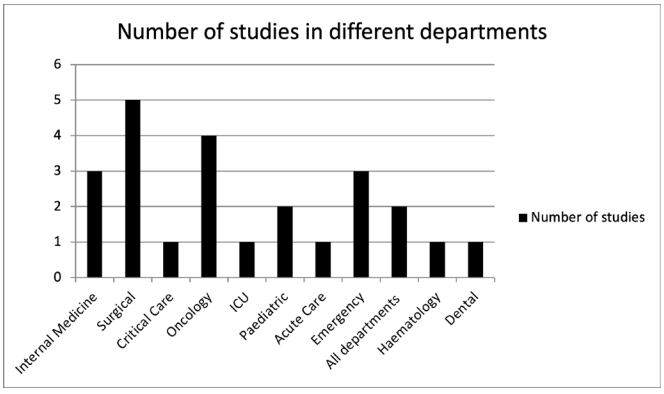

Figure 3 Number of studies in different departments of hospitals in the Gulf region.

Quality assessment

Quality assessment was performed using the JSM tool for all the studies screened and the included studies that reported low or medium levels of bias. Quality assessment details are attached as a supplementary document. Articles were assessed in detail with purpose, methodology, results, and discussions. Online supplemental table 2 shows the quality assessment tool results.

Inappropriate antibiotic prescribing

The inappropriate prescribing of antibiotics in all departments in the tertiary care setting were measured. Among all seven Gulf countries, inappropriate prescribing was reported in four countries: Saudi Arabia with 10 primary articles, three studies in Oman and Qatar, two in Kuwait, while no studies were found in UAE, Bahrain and Yemen (figure 2). Studies on the prescribing patterns of antibiotics with inappropriateness have been available in Saudi Arabia since 1988, and there was a new study in Oman in 2020. Prescribing patterns have been studied in different departments of the hospitals, and it was found that most of the studies took place in the surgical,[5] oncology,[4] emergency, and internal medicine departments,[3 3] as shown in figure 3. Eighteen articles discussed inappropriate antibiotic prescribing patterns. We found that 14 studies showed the positive outcome of reducing inappropriate antimicrobial prescribing, as shown in figure 2. The risk of inappropriate prescribing of antimicrobials is less in AMS with a pharmacist than pre-AMS without a pharmacist.

POOLED ANALYSIS

Total inappropriateness in prescribing pattern in the Gulf region in 18 studies was 43 669/100 846=43.3% (pooled RR 1.31, 95% CI 1.30 to 1.32). The test with the overall effect was 58.87 ($p<0.00001$). Heterogeneity was calculated at about $I^2=99\%$. A funnel plot used to reduce the bias is shown in online supplemental figure 4. Inappropriateness was reduced to $I^2=64\%$. (figure 4)

SUB-GROUP ANALYSIS

Calculation of inappropriateness differed from one study to another. Al-Hameed calculated the inappropriate prescribing with the dose and monitoring of antibiotics like vancomycin, and compared with standard guidelines such as the American Society of Health-System Pharmacists/Infectious Diseases Society of America (ASHP/IDSA) guidelines,[9] showed 40% of inappropriate dosing and monitoring. Youssif calculated the inappropriate antibiotic prescribing in the surgical ward for broad-spectrum antibiotics by requesting culture within 24 hours and the number of days to de-escalate once the results of culture were received,[10] and showed 66% of inappropriate prescribing in the surgical

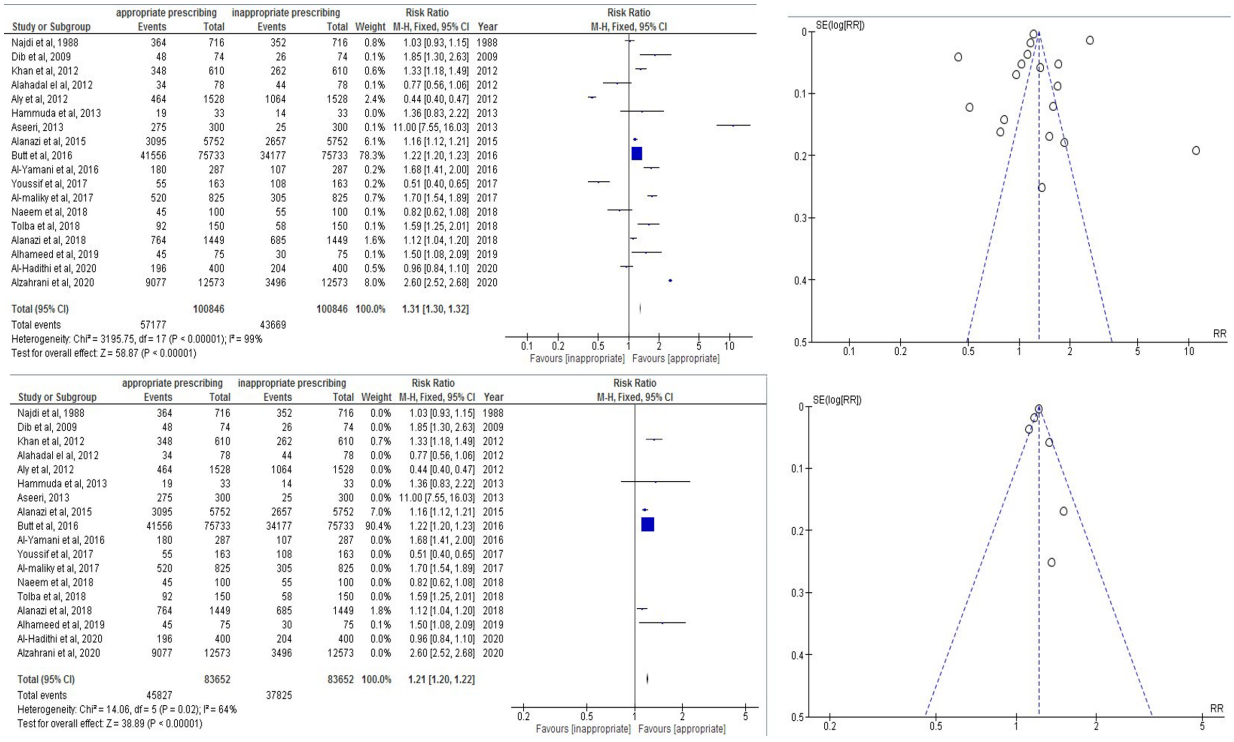

Figure 4 The 18 studies with inappropriateness and reduction of bias through funnel plots.

ward. Aly checked the antibiotic prescribing concordance with hospital guidelines and found that 69.6% of prescribed antibiotic prescriptions were not concordant.[11] Alzahrani audited the antibiotic prescribing pattern in the dental department and found that antibiotics were prescribed in 27.8% of consultations in which antibiotics were not recommended.[12] Alanazi reviewed the antibiotic prescribing pattern in the emergency department and found inappropriate prescribing with major errors in dose (37%), then duration, frequency and selection of antimicrobials, and found overall inappropriateness of 41.4%[13]; and in another study in 2015 found inappropriateness on the same basis in the emergency department of 46.12%.[14] A study in King Abdulaziz university hospital found that in 56.4% of patients with renal failure, antibiotic doses were not adjusted.[15] Antibiotic prescribing compliance with the local guidelines and the overall restricted antibiotic policy adherence at Sultan Qaboos University Hospital found that 36.96% of antibiotic prescribing were not up to the mark.[16] Another study in Oman checked the rational prescribing of antibiotics depending on local standard guidelines, and the experience of the infectious diseases consultant found irrational antibiotic prescribing in 37.28% of cases.[17] Meropenem inappropriate prescribing in Oman—with

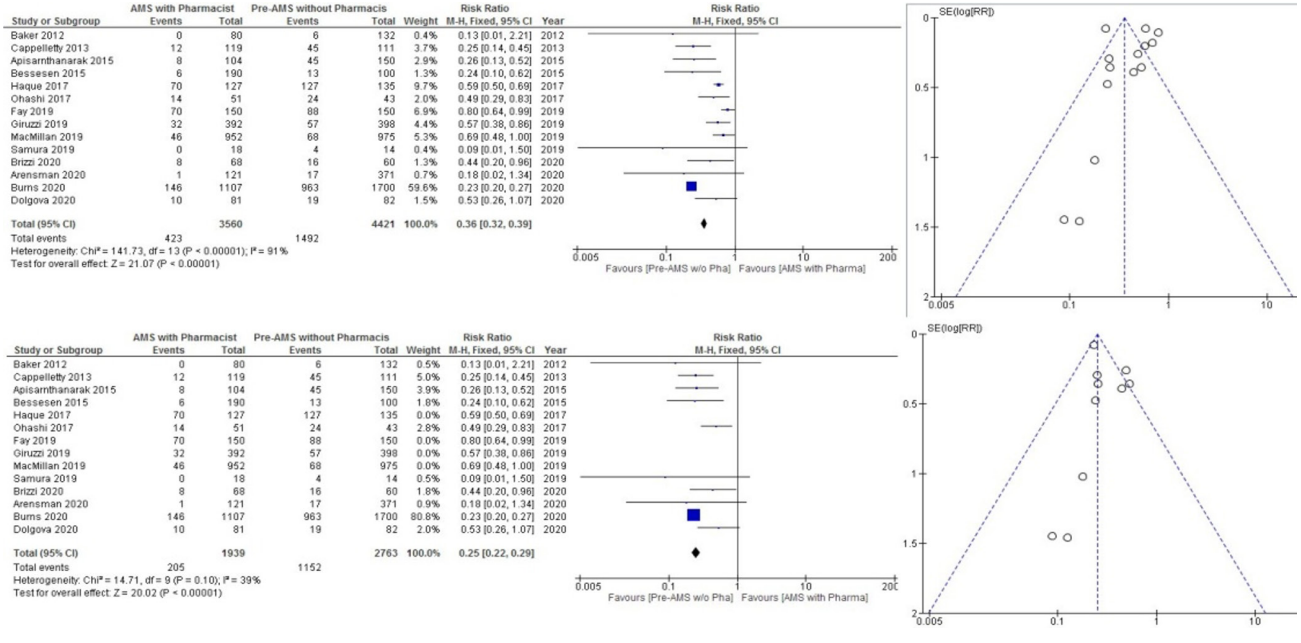

Figure 5 Fourteen antimicrobial stewardship (AMS) results for inappropriate antimicrobial prescribing.

inappropriateness assessed by specific meropenem-use criteria developed from pre-specified, literature-based criteria and then modified by an expert panel of infectious diseases specialists—found inappropriateness in 51% of cases.[18] Antibiotic misuse in the paediatric department of Kuwait was assessed using local guidelines and found mistakes such as inappropriate use, duration, route, unnecessary use, and a combination of the factors, in 49.16% of cases.[19] Unjustified piperacillin-tazobactam prescription in Qatar, identified by setting specific criteria, found 42.95% of unjustified use cases.[20] Empirical treatment for febrile neutropenia using King Abdulaziz Medical City-Western Region (KAMC-WR) empirical therapy guidelines found that 55% of guidelines were non-compliant with treatment.[21] Antibiotic prophylaxis assessed against guidelines published by the Scottish Intercollegiate Guidelines Network (SIGN), ASHP and the Saudi Ministry of Health (MOH) found that 38.6% of cases of antibiotic prophylaxis were not recommended.[22] Vancomycin use in a Saudi Arabian medical centre assessed by a clinical pharmacist along with an infectious disease consultant found that 35% of cases were inappropriate.[23] Antimicrobial use in oncology in Qatar assessed by local prescribing restriction guidelines found 42% of prescriptions did not comply with the guidelines.[24] Paediatric antibiotic dosing standard assessed with the standard if >110% or <90% were considered an inappropriate dose found a dosing error rate of 30%[25] before implementing stewardship. Antibiotics for upper respiratory tract infection in the outpatient setting assessed by the expert opinion of infectious diseases specialists found a 45% level of inappropriateness.[26]

REDUCTION IN INAPPROPRIATENESS

There have been reports of a total of 14 AMS programmes led by pharmacists in the last 8 years, discussing appropriate antibiotic therapy. Eight AMS programmes led by pharmacist were from the USA, two were from Japan, and one each from Spain, Thailand, and Pakistan. Nine studies were retrospective, and five were prospective in nature. Different strategies were used in every AMS programme. We found that all 14 studies showed a positive outcome in reducing inappropriate antimicrobial prescribing, as shown in figure 5. The risk of inappropriate prescribing of antimicrobials was less in AMS with pharmacist than pre-AMS without pharmacist.

POOLED ANALYSIS

Total inappropriateness in AMS with a pharmacist was 423/3560 (11.88%), whereas in pre-AMS without a pharmacist it was 1492/4421 (33.74%) (pooled RR 0.36, 95% CI 0.32 to 0.39). The test with the overall effect was 21.27 ($p<0.00001$). Heterogeneity was calculated at about $I^2=91\%$. A funnel plot was used to reduce the bias. Inappropriateness was reduced to $I^2=39\%$.

DISCUSSION

Antibiotic prescribing patterns are studied all over the world, including in the Gulf region. Antibiotic prescription with use and indication, and overall trends are studied with the rational prescribing. Antibiotic prescribing patterns in the Gulf region show a variation in all departments concerning inappropriate prescribing. Standards of inappropriate prescribing differ from study to study, some using local or international guidelines, dosing, frequency, monitoring, indication and prophylaxis. It has been observed that most of the inappropriate antibiotic prescribing studies in the Gulf are from Saudi Arabia and three other countries, while UAE, Bahrain and Yemen have no studies that show the levels of inappropriate antibiotic prescribing in the region. Surgical ward inappropriate antibiotic prescribing is most studied in the Gulf region. This department is responsible for both prophylaxis and treatment and is related to the emergency department, so the chances of a lack of concordance with the guidelines and policies are high. Oncology, emergency, and internal medicine departments for long-term patients or patients with multiple disorders need attention as the chances of inappropriate antibiotic use are high. A study in Kuwait in 2012 showed very high inappropriate antibiotic prescribing as physicians did not adhere to guidelines in almost 70% of the incredibly high cases.[11] Another study showed least inappropriate antibiotic prescribing practice as low as 27%,[12] showed low inappropriateness in the dental department in Saudi Arabia, and showed 27% of cases of overuse of antibiotics. It showed that the average level of inappropriate antibiotic prescribing in the Gulf region is very high, and recommends education, stewardships, seminars, awareness, concordance with guidelines and implementation of clinical pharmacists in hospitals and infectious disease specialists. A study in Colombia showed a level of inappropriate antibiotic prescribing for acute bronchiolitis at 65%.[41] A study in the USA reported 18% of inappropriate prescribing of antibiotics in 18 million non-elderly population.[42] Even with this number of patients, the level of inappropriate antibiotic prescribing in the USA is less than the least reported in the Gulf region. A 9 year study of antibiotic inappropriateness in a US emergency department showed that 70% of the cases with bronchiolitis had been prescribed antibiotics without documented bacterial co-infection.

AMS programmes can help to reduce inappropriate prescribing patterns. The pharmacist is an integral part of the healthcare system and involves drug dispensing, monitoring and compounding, and working as a clinical pharmacist to help develop the stewardship programmes. The search for studies on AMS programmes led by pharmacists shows a positive impact on inappropriate antibiotic prescribing in all 14 studies included in the analysis. Average inappropriateness was 37% which was reduced to 11.88% after the implementation of a pharmacist-led AMS. An AMS programme conducted in the Gulf region has stated that the level of appropriateness was corrected from 30% to 100% in a medical intensive care unit of a tertiary care hospital in Saudi Arabia.[43] Another stewardship in a tertiary care hospital in Qatar stated that appropriateness improved to 95.7% with the help of AMS.[44] A lack of pharmacist-led stewardship is noted in the Gulf region and need improvements. A survey of 47 participants from the Gulf Cooperation Council (GCC) reports the reduction of inappropriate prescribing at 68%, which is still not up to the mark.[45] Other factors need to be studied beyond stewardship, as infection control measures and self-medication have an impact on resistance and stewardship programmes.

CONCLUSION

Inappropriate prescribing of antibiotics in the Gulf region is widespread and needs to be addressed with AMS programmes. There have been few reports on the stewardship programmes in the Gulf region, and pharmacist-led AMS programmes that may help to improve appropriate antibiotic use are still not in operation in the region.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

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Supplementary

Table 1: Included studies characteristics

#	Author and year	Place	Title	Design	Variable	Conclusion
1	Dib et al, 2009	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 the Physician.
2	Youssif et al, 2017	KSA	Retrospective evaluation of piperacillin–tazobactam,imipenem–cilastatin and meropenem used on surgical floors at atertiary care hospital in Saudi Arabia	Retrospective	Inappropriate, Surgery	Broad-spectrum antibiotics use is unjustified and needs interventions like culture and sensitivity test requests within 24 h of starting the broad-spectrum antibiotics and de-escalation.
3	Hammuda et al, 2013	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 et al, 2017	Oman	Evaluation of antibiotic prescribing for adult inpatients at Sultan Qaboos University Hospital,Sultanate of Oman	Observational	ICU, Inappropriate	The diagnosis documented in 89%, and compliance with SQUH antibiotic prescribing guidelines was suboptimal. Studies are required to cope with the reasons behind the non-compliance with guidelines.
5	Aseeri, 2013	KSA	The Impact of a Pediatric Antibiotic Standard Dosing Tableon Dosing Errors	Retrospective	Pediatric	Implementation of dosing standard in the pediatric department reduces the dosing errors.
6	Khan et al, 2012	Qatar	Evaluation of the use of piperacillin/tazobactam (Tazocin®) at Hamad General Hospital, Qatar: are there unjustified prescriptions?	Retrospective	Surgical,	The study shows that the use of piperacillin/tazobactam at our hospital was unjustified, evidenced inappropriate empiric prescriptions and inappropriate drug modifications, depends upon the microbial cultures.

7	Alahdal et al, 2012	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 et al, 2016	Oman	Patterns of Antimicrobial Prescribing in a Tertiary Care Hospital in Oman	Retrospective	Acute care, AB Selection	Misuse and overuse of antibiotics prove that need National guidelines. Antibiotics prescribing in different hospitals need to evaluate.
9	Naeem et al, 2018	KSA	Prescribing Empiric Antibiotics for Febrile Neutropenia: Compliance with Institutional Febrile Neutropenia Guidelines	Cross sectional	Oncology, Compliance	FN management guidelines not following in our institute. Appropriate empiric antibiotic indications and doses as per institutional guidelines recommended.
10	Alhameed et al, 2019	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	The study highlights the importance of Therapeutic drug monitoring led by the pharmacist to optimize the initial dose of antibiotics.
11	Butt et al, 2016	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. Interventions required to reduce inappropriateness.
12	Al-Hadithi et al, 2020	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, deescalate and judicious use of meropenem.
13	Alzahrani et al, 2020	KSA	Inappropriate Dental Antibiotic Prescriptions:Potential Driver of the Antimicrobial Resistance in Albaha Region, Saudi Arabia	Retrospective	dental	Some dental prescriptions are unnecessary and need interventions to reduce the inappropriateness.
14	Alanazi et al, 2018	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	The emergency department of Saudi Arabia revealed highly inappropriate use of antibiotics for UTI.

15	Najdi et al, 1988	Kuwait	Antibiotic misuse in a pediatric teachingdepartment in Kuwait	Retrospective	Inappropriate, pediatric	High rate of antibiotic use and misuse reported due to lack of policies and procedures worldwide.
16	Alanazi et al, 2015	KSA	Prevalence and predictors of antibiotic prescription errors in an emergency department, Central Saudi Arabia	Cross-sectional	Inappropriate, all emergency department	The emergency department shows many errors in prescribing antibiotics, and errors were common with the narrow spectrum and UTI infections.
17	Aly et al, 2012	Kuwait	Audit of Physicians' Adherence to theAntibiotic Policy Guidelines in Kuwait	Retrospective	Adherence, hospital department	Adherence to the antibiotic policy guidelines is very low. Antibiotics were prescribing practice of Physician need to overlook. The recommendation is to follow the policy.
18	Tolba et al, 2018	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, the difference of practice and guidelines does exist and need to follow up the guidelines.
19	Apisarnthanarak et al, 2015	2015 Thailand	Design and analysis of a pharmacist-enhanced antimicrobial stewardship program in Thailand	Prospective	Inappropriateness,	The study suggests better outcomes with IDCP training and incorporation of pharmacist in the stewardship.
20	Arensman et al, 2020	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 impacts the outcome measures of stewardship.
21	Baker et al, 2012	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 the culture that affects the appropriate prescribing.
22	*Bessesen et al, 2015*	2015 USA	Antimicrobial Stewardship Programs: Comparison of aProgram 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 et al, 2020	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 impacts prescribing practice and readmissions.
24	Burns et al, 2020	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 et al, 2013	2013 USA	Evaluating the impact of a pharmacist's absence from an antimicrobial stewardship team	Retrospective	inappropriateness	Inappropriate prescribing increase with the absence of a pharmacist.
26	Dolgova et al, 2019	2019 Spain	Pharmacist recommendations for Carbapenem de-escalation in urinary tract infection within an antimicrobial stewardship program	Prospective	Inappropriateness	Carbapenem de-escalation under pharmacist recommendation proves a positive intervention that can help to reduce mortality, inappropriateness and readmission.
27	Fay et al, 2019	2019 USA	Pharmacist-led antimicrobial stewardship program in an urgent care setting	Retrospective	Inappropriateness	A pharmacist-led urgent care ASP was associated with a reduction in inappropriate prescribing and readmission.
28	Giruzzi et al, 2019	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 a positive impact on reducing the time to appropriate therapy.
29	Haque et al, 2017	2017 Pakistan	Impact of pharmacist-led antibiotic stewardship program in a PICU of low/middle-income country	prospective	inappropriateness	The study shows the Impact of pharmacist on cost, consumption, mortality and inappropriate antimicrobial prescribing.
30	MacMillan et al, 2019	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 et al, 2018	2018 Japan	Evaluation of treatment outcomes of patients with MRSA bacteremia following antimicrobial stewardship programs with pharmacist intervention.	Prospective	inappropriateness	The use of an appropriate bundle, established by an AST with pharmacist intervention, can affect the treatment of MRSA-B and Impact other outcomes significantly.
32	Samura et al, 2019	2020 Japan	Support for fungal infection treatment mediated by pharmacist-led antifungal stewardship activities	Retrospective	inappropriateness	These results suggest that pharmacist-led antifungal stewardship positively impacts outcome measures like cost, consumption, and mortality.

Table 2: shows the studies quality assessment through JSM tool.

		Scale Items[a]												
SN	**Study Name**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Score**
1	**Dib et al, 2009**	Y	Y	Y	Y	CD	Y	Y	N	NR	Y	Y	Y	**L**
2	**Youssif et al, 2017**	Y	Y	Y	Y	Y	Y	Y	NR	NR	Y	Y	N	**L**
3	**Hammuda et al, 2013**	Y	Y	Y	Y	N	Y	Y	NR	NR	Y	Y	CD	**M**
4	**Al-Maliky et al, 2017**	Y	Y	Y	Y	NR	Y	Y	NR	CD	Y	Y	NR	**M**
5	**Aseeri, 2013**	Y	Y	Y	Y	CD	Y	Y	CD	Y	Y	Y	NR	**L**
6	**Khan et al, 2012**	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	NR	CD	**L**
7	**Alahdal et al, 2012**	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	CD	NR	**L**
8	**Al-Yamani et al, 2016**	Y	Y	Y	Y	CD	Y	Y	Y	CD	Y	CD	N	**M**
9	**Naeem et al, 2018**	Y	Y	Y	Y	Y	Y	Y	NR	Y	Y	Y	Y	**L**
10	**Alhameed et al, 2019**	Y	Y	Y	Y	Y	Y	Y	NR	CD	Y	Y	N	**M**
11	**Butt et al, 2016**	Y	Y	Y	Y	NR	Y	Y	N	NR	Y	Y	N	**M**
12	**Al-Hadithi et al, 2020**	Y	Y	Y	Y	CD	Y	Y	CD	NR	Y	Y	Y	**L**
13	**Alzahrani et al, 2020**	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	Y	Y	**L**
14	**Alanazi et al, 2018**	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	NR	NR	**L**
15	**Najdi et al, 1988**	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	NR	NR	**L**
16	**Alanazi et al, 2015**	Y	CD	Y	Y	Y	Y	Y	CD	Y	Y	Y	Y	**L**
17	**Aly et al, 2012**	Y	Y	Y	Y	N	Y	Y	CD	NR	Y	NR	Y	**M**
18	**Tolba et al, 2018**	Y	Y	Y	Y	N	Y	Y	NR	CD	Y	NR	Y	**M**
19	**Apisarnthanarak et al, 2015**	Y	Y	Y	Y	CD	Y	Y	N	CD	Y	Y	N	**L**

20	**Arensman et al, 2020**	Y	Y	Y	Y	Y	Y	Y	NR	CD	Y	Y	N	**L**
21	**Baker et al, 2012**	Y	Y	Y	Y	CD	Y	Y	N	Y	Y	Y	N	**L**
22	**Bessesen et al, 2015**	Y	Y	Y	Y	N	Y	Y	NR	Y	Y	N	CD	**M**
23	**Brizzi et al, 2020**	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	CD	**L**
24	**Burns et al, 2020**	Y	Y	Y	Y	Y	Y	Y	NR	CD	Y	Y	N	**L**
25	**Cappelletty et al, 2013**	Y	CD	Y	Y	CD	Y	Y	NR	CD	Y	Y	N	**M**
26	**Dolgova et al, 2020**	Y	Y	Y	Y	Y	Y	Y	NR	CD	Y	Y	Y	**L**
27	**Fay et al, 2019**	Y	Y	Y	Y	Y	Y	Y	NR	NR	Y	Y	CD	**L**
28	**Giruzzi et al, 2019**	Y	Y	Y	Y	Y	Y	Y	NR	NR	Y	CD	Y	**L**
29	**Haque et al, 2017**	Y	Y	Y	Y	CD	Y	Y	N	NR	Y	N	Y	**M**
30	**MacMillan et al, 2019**	Y	Y	Y	Y	Y	Y	Y	CD	NR	Y	Y	Y	**L**
31	**Ohashi et al, 2017**	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	NR	Y	**L**
32	**Samura et al, 2020**	Y	Y	Y	Y	Y	Y	Y	N	NR	Y	NR	Y	**L**

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	no
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3 Appendix
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3-5

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Table 2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3-5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3-5

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Figure 4 & 5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	No additional analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1 and 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 4&5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	No additional analysis
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	No funding

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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