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Hospital Adoption of Antimicrobial Stewardship Programmes in Gulf Cooperation Council Countries: A Review of Existing Evidence

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Highlights

- Despite the established benefits of antimicrobial stewardship programmes in reducing inappropriate antimicrobial use and resistance, their adoption in Gulf Cooperation Council hospitals remains low
- The adoption of antimicrobial stewardship programmes in hospitals in the region can be facilitated or hindered by a range of Institutional and individual factors
- Six outcome measures to evaluate ASPs in GCC countries hospitals have been reported. These include: reduction of inappropriate prescribing, reduction of healthcare-associated infections, reduction of direct antimicrobial cost, reduction of length of stay/ mortality metrics, reduction of antimicrobial resistance and reduction of broad-spectrum antibiotic use.
- Hospital adoption of ASPs results in improvement in at least one outcome measure.

Abstract

Antimicrobial resistance is increasing at an alarming rate in The Gulf Cooperation Council (GCC) due to the over and misuse of antimicrobials. The novel and rare multi-drug resistant strains can spread globally since the region is a host to the largest expat population in the world and a pilgrimage destination to more than 4 million people annually. The adoption of antimicrobial stewardship programmes could improve the use of antimicrobials and reduce antimicrobial resistance in the region. However, despite the established benefits of these interventions, little is known about the level of their adoption in the region, and the impact of these programmes on antimicrobials use and resistance. This study aims to review the existing evidence on the level of adoption of antimicrobial stewardship programmes, the facilitators/ barriers to their adoption and the outcomes of their adoption in GCC hospitals.

Keywords: Antimicrobial stewardship programmes; ASP; antimicrobial resistance; hospital; Gulf Cooperation Council

1. Introduction

Antimicrobial resistance is a global public health concern undermining efforts to treat infectious diseases, resulting in increased morbidity and mortality, and adding avoidable costs to already strained healthcare systems [1]. Drug resistant strains of common bacterial infections, HIV, TB and malaria are causing the death of hundreds of thousands of people every year. It is estimated that mortality due to antimicrobial resistance will be the highest at 10 million people a year, followed by cancer and other causes by 2050 [2,3].

The burden of antimicrobial resistance continues to increase in the GCC region with reports of Extended Spectrum Beta-Lactamase (ESBL) producing bacteria, Carbapenemase producing bacteria, Pan-drug-resistant Gram-negative bacilli and multi-drug-resistant tuberculosis [4–8]. Further, rare and novel resistant strains have also been reported, possessing bla_{OXA-48} type and bla_{NDM-1} carbapenemase associated with hospital outbreaks and increased mortality [9]. Antimicrobial resistance in the region is implicated in around 20% of paediatric haematology/ oncology patients' deaths [10], 40% deaths in a tertiary hospital in the region [11] and 60-90% causes of ventilator-associated pneumonia that is resistant to most tested antimicrobials [6,12].

The high antimicrobial resistance rates in the region are accompanied with heavy international travel due to the large expatriate population in the region, booming tourism particularly in the United Arab Emirates (UAE), and the influx of more than 4 million pilgrims throughout the year to Saudi Arabia [4,13–15]. Population mobility has been suggested as a main factor in the globalisation of antimicrobial resistance through the distribution of antimicrobial drug-resistant organisms [16]. Tackling the issue of antimicrobial resistance in the region could prevent the emergence of novel multi-drug resistant strains and reduce the globalisation of this health threat.

The misuse of antimicrobials is one of the main causes of antimicrobial resistance, and yet, around 20-50% of antimicrobials prescriptions are deemed unnecessary or inappropriate [17,18]. In the GCC region, retail trends of antimicrobials are high, and they continue to rise; retail increased from 27,844 in 2000 to 38,788 standard units per 1000 population in 2015 in Saudi Arabia, UAE and Kuwait alone [19]. Most of this inappropriate antimicrobial usage occurs outside hospitals, where non-prescription access to antimicrobials in community is widely common in the region. However, interventions to improve antimicrobial usage and reduce antimicrobial resistance have widely focused on hospital settings. These interventions typically involve the adoption of antimicrobial stewardship programmes (ASPs).

ASPs are collective strategies to enhance the appropriate use of antimicrobial agents, and minimise adverse effects and costs that may arise from their use. This is usually achieved through the selection of the right antibiotic regimen, correct dose, duration of use, and how a given agent is administered. ASPs core strategies include; prospective audit with intervention and feedback (back-end strategy), and formulary restriction and preauthorisation (front-end strategy). Supplemental strategies include: education, streamlining/timely de-escalation, dose optimization, parenteral to oral conversion, antimicrobial order forms, combination therapy, computer surveillance and decision support, guidelines and clinical pathways, and automatic stop orders [17,20,21].

The published hospitals experience on the adoption of ASPs is vast, especially in large and tertiary hospitals [22–25]. However, little is known about the level of adoption of these programmes in hospitals in the GCC region. The recent review by Nasr et al. [26] is the first attempt to explore existing ASPs in the Middle East, including in member states of the GCC. However, details of these existing ASPs, barriers and facilitators to their adoption, and the impact of their adoption on patient and institutional outcomes are yet to be established. Understanding the current picture of ASPs in GCC hospitals is imperative to draw upon the current experience and design and adopt more

effective ASPs. Therefore, this study seeks to address this gap by exploring the level of adoption of ASPs, the facilitators/ barriers to their adoption and the outcomes of their adoption in GCC hospitals.

2. Methods

2.1 Search Strategy

We searched the electronic databases of PubMed (MEDLINE), Embase, Scopus, CINAHL Plus, Ovid, Google scholar, grey literature, and official health authorities' websites for each GCC country (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates), from 01/1981 to 07/2017. References lists of retrieved articles and relevant review articles were checked manually for further relevant studies. Table 1 shows the search terms that were used. The search terms in the same group were combined using the Boolean term OR, while the three groups of search terms were combined using the Boolean term AND.

2.2 Study Selection

Search results were exported to Mendeley®, a free reference manager and academic social network (Elsevier). Titles, abstracts and articles were reviewed. We included studies that met the following criteria: 1) conducted in any of the GCC countries; 2) reported ASP in a hospital setting; 3) reported a national ASP/AR policy; 4) published between 01/1981 and 07/2017; and 5) published in English and/or Arabic language. We excluded studies for the following reasons: 1) ASPs in primary healthcare centres, dental centres, cancer centres, and community pharmacies; 2) only reported consumption and resistance rates; or 3) conducted in animals. Since this is an exploratory study, there was no restriction on the type or quality of studies included in the review.

Two authors screened all titles and abstracts independently to determine whether the article met the inclusion criteria and should be retrieved. A third author screened a random 10% sample to check the reliability of the screening. Any discrepancies were resolved through discussion between the authors. Two authors then read and extracted data from the articles included in this review.

We also explored grey literature to broaden the scope of evidence and provide a more complete picture on the level of ASPs adoption in GCC countries hospitals, barriers and facilitators to ASPs adoption and the outcomes of their adoption.

2.3 Data Abstraction & Synthesis

We extracted data on study type, reported ASP, components of the reported ASP, and ASP team members to establish the nature of the evidence, the level of ASP adoption in GCC hospitals, the commonly adopted ASP strategies and the healthcare professionals involved in ASP adoption and implementation. Further, we extracted data on barriers and facilitators to ASP adoption if reported, and ASP outcome measures to highlight the impact of ASP adoption on antimicrobial use and resistance in GCC hospitals. Discrepancies were resolved by consensus.

We presented the evidence in tables showing the country, year of publication, study type, existing ASP, components of ASP, ASP team members, and facilitators and barriers to ASP adoption if reported. We also presented ASP outcomes showing: reduction of inappropriate prescribing, reduction of healthcare-associated infections, reduction of direct antimicrobial costs, reduction of length of stay/ mortality metrics, reduction of

antimicrobial resistance and reduction of broad-spectrum antibiotic use. We summarised our findings and drew conclusions based on a qualitative synthesis of the data.

3. Results

We reviewed 2,801 titles and abstracts from the literature search. Nine hundred and sixty-two duplicates were removed. We excluded 1740 after title review, 48 after abstract review and 27 after full text review, leaving twenty-four articles eligible for inclusion. Grey literature searching identified seven conference publications, and two national ASP/AR policies, totaling 33 included papers. Figure 1 illustrates the literature review process.

The retrieved studies reported evidence of ASPs in all GCC countries, including 13 reports from Saudi Arabia, 5 reports from Qatar, 4 from Bahrain, 4 from Oman, 3 reports from Kuwait and 2 reports from UAE. We also identified two national strategies/guidelines relating to antimicrobial resistance and stewardship at GCC level, and in Saudi Arabia.

3.1 Existing hospital ASPs in GCC countries

We identified evidence of existing ASPs in hospitals in all GCC member states. Saudi hospitals reported the highest level of adoption of ASPs in GCC, followed by Qatar, Oman, Bahrain, Kuwait and UEA respectively. Very little evidence was retrieved from UAE including one study and data from a conference presentation highlighting the lowest level of adoption reported in the region. Further, although Saudi Arabia reports the highest level of adoption of ASPs compared to other hospitals in the region, ASPs are currently mainly adopted in tertiary hospitals and big medical cities. In Qatar, there is evidence of existing ASPs in tertiary hospitals and community hospitals. Most studies from Oman report existing ASPs in tertiary hospitals, particularly, Sultan Qaboos Hospital. All ASPs reported in Bahrain have been adopted only in military hospitals. In Kuwait, only one study involving nine government hospitals has been retrieved. The remaining evidence relate to efforts of the directorate of infection control in the Kuwait Ministry of Health (MOH) to raise awareness of antimicrobial resistance amongst healthcare professionals, patients and the public.

We also identified a strategic plan for combatting antimicrobial resistance in GCC States, which was introduced in 2015 in response to the rising rates of antimicrobial resistance [27]. This is an overall framework to address the problem of resistance in the region, and each member state is expected to formulate their action plan according to their local resistance data and public health resources.

We highlight that Saudi Arabia is so far, the only member state to draft a national ASP plan as part of a reformed overall MOH strategic plan [28,29]. Other member states still lag behind lacking national plans for detecting and reporting antimicrobial resistance, and national plans for antimicrobial stewardship.

Our findings indicate that most ASPs in the region are adopted in tertiary hospitals (Oman, Saudi Arabia and United Arab Emirates) and military hospitals in Bahrain and Saudi Arabia. We found that the main antimicrobial stewardship strategies reported in GCC countries hospitals are antimicrobial guidelines implementation, audit and feedback, and formulary restriction and pre-authorisation. Other antimicrobial stewardship initiatives include: clinical practice guidelines, IV to oral step-down guidelines, education activities for healthcare professionals and patients, de-escalation protocols, monitoring adherence to protocols and guidelines.

Little evidence related to antimicrobial resistance surveillance and reporting, as well as their integration within antimicrobial stewardship initiatives at hospital level was found. The only evidence relates to a national campaign by Kuwait's directorate of infection control in 2012 to raise awareness of antimicrobial resistance among healthcare

professionals, patients and the public [30]. Moreover, this initiative has not been duplicated in Kuwait or other GCC member states.

We explored the involvement of healthcare professionals as part of ASP teams, and we found that most ASP teams only include ID consultants and physicians, physicians, and to a lesser extent infection control specialist nurses. Occasionally, pharmacists were involved in monitoring antimicrobial consumption, and reporting and providing feedback on antimicrobial prescribing practices. Microbiologists appear to only be occasionally involved in somewhat advanced antimicrobial stewardship practices tailoring stewardship interventions around local antimicrobial resistance data (studies from Saudi Arabia). Further, only Saudi Arabia appear to embrace the role of clinical pharmacists in stewardship initiatives; those are pharmacists with a post-graduate clinical diploma and advanced competence in infection control and antimicrobial stewardship.

Several studies did not provide details on the involvement of ASP teams, and occasionally, only referred to antimicrobial subcommittees that are usually a subcommittee of drug and therapeutic committees.

Our findings in relation to the evidence of existing ASPs, components of ASPs and ASP team members are presented in table 2.

3.2 Barriers and facilitators to ASPs adoption in GCC hospitals

Nine of the 35 retrieved reports addressed barriers and/or facilitators to ASPs adoption (evidence summarised in table 3). These factors can be either individual or institutional. At an individual level, physicians are naturally the main prescribers in the hospital setting. They reported the following barriers to ASP adoption in their practice setting: lack of up-to-date knowledge regarding appropriate antimicrobial use and resistance, lack of confidence in the currency of the hospital antimicrobial policies and guidelines and their unavailability/ inaccessibility, prescribing norms and reluctance to prescribe antibiotics other than their "usual", lack of knowledge/ experience regarding ASPs, lack of time to perform the required investigations, fear of patient's complications and their hesitance to de-escalate antimicrobial therapy in very sick patients or patients at risk of sepsis. At hospital level, the following were reported as barriers to adopting ASPs: lack of expertise such as infectious diseases specialists, unavailability/ interrupted supply of antibacterial, lack of education and training events regarding appropriate antimicrobial use and resistance, lack of microbiology resources and if found, lack of their integration into antimicrobial policies and stewardship programmes, and lack of administrative/ management support. One hospital in Makkah, Saudi Arabia, specifically referred to the annual Hajj event and the challenges it brings to maintaining adequate control over antimicrobial use and resistance due to increased hospital admission rates and subsequent increase in antimicrobials use [50]. Another tertiary hospital in Saudi Arabia conferred increased resistance rates in the hospital to the high prevalence of antimicrobial resistance in other hospitals in the country and the subsequent transfer of resistance to the specialist hospitals upon admission for last resort interventions [58]. Noteworthy, lack of funding for ASPs and initiatives, which is often determined by ministry of health at government level, was also reported as a barrier to adopting antimicrobial stewardship in hospitals.

Evidence on the facilitators of hospital adoption of ASPs is little. The Kuwaiti infection control directorate advocates that prescribers' experience (in relation to age) and knowledge of antimicrobials can lead to good antimicrobial stewardship [30]. It was found that Omani hospitals that had a consistent, written and accessible antimicrobial policy had better outcomes in relation to post-operative infections [37]. A Saudi study suggests that discussing evidence of antimicrobial stewardship interventions with prescribers and supporting them could reduce prescribers concerns regarding adoption and implantation of ASPs interventions. Further, the authors suggest that engaging

directly with targeted (main) prescribers and influential practitioners (such as consultants) could encourage physicians to support ASP initiatives [51]. The barriers and facilitators to ASPs adoption in GCC countries hospitals are presented in table 3.

3.3 Outcomes of hospital adoption of ASPs in GCC countries

We identified six outcome measures to evaluate ASPs in GCC countries hospitals. These include: reduction of inappropriate prescribing, reduction of healthcare-associated infections, reduction of direct antimicrobial cost, reduction of length of stay/ mortality metrics, reduction of antimicrobial resistance and reduction of broad-spectrum antibiotic use.

Most studies in all GCC states reported improvement in at least one outcome measure as a result of adoption of ASP. Studies in Saudi hospitals mostly used more than one outcome measure to assess effectiveness of ASPs interventions. Studies in the remaining GCC states mainly assessed the impact of ASPs on the reduction of inappropriate prescribing. Noteworthy, only two of the 31 retrieved studies (in Saudi Arabia) measured the impact of ASPs on antimicrobial resistance rates.

The adoption of ASPs and initiatives in GCC states hospitals has reportedly resulted in reduction of inappropriate prescribing especially when adherence to antimicrobial policies and clinical guidelines was enforced and monitored. A Qatari study reported that only 40% of surgical patients received the correct antibiotic due to lack of adherence to antimicrobial policies and guidelines [42]. A study in UAE reported a low 32% adherence to guidelines resulting in appropriate antimicrobial prescribing [60]. A Saudi study reported that education and feedback to prescribers improved adherence to antimicrobial guidelines from 35% to 68% [47].

Reduction in healthcare associated infections was not frequently measured in the reported studies. We retried six studies (4 from Saudi Arabia, 1 from Oman, and 1 from UAE) reporting reduced post-operative infections, and reduced peri-operative infective complications from 32% to 11% in one study [46]. Two out of three studies reported reduction in *C.diff* infection rates [51,59] whereas one Saudi study found no impact on this measure [48].

Direct antimicrobial costs are rarely measured in the included studies. Saudi Arabia appear to be the most advanced in the adoption of ASPs and four studies from hospitals report cost reduction of up to half as a result of ASPs adoption and implementation [48–50,57]. The only other study comes from UEA and reports 40% in antimicrobials consumption and associated costs [59].

Only three studies reported on the impact of ASPs on length of stay and/ or mortality metrics [31,32,48]. Bahrain studies on adoption of ASPs in the outpatient department of a military hospital reported that the outpatient service prevented admissions to hospital (2 out of 101 in 2013 and 6 out of 97 in 2015) as a result of their antimicrobial stewardship practices [31,32]. Another study in a Saudi hospital reported reduction of hospital stay to 376 defined daily doses (DDD) compared to 2404 DDD pre-ASP adoption [48]. The study further reported a decrease in mortality rate from 33% to 17%.

Given the modest engagement of microbiologists in the ASPs and initiatives reported, it is not surprising that most studies neglect to measure/ report the impact of ASPs on antimicrobial resistance rates. One Saudi study reported reduction of antimicrobial resistance from some organism-antibiotic combinations, but an increase in resistance to other antibiotics that were heavily used as an alternative including piperacillin/ tazobactam [51]. Another Saudi study reported that their hospital ASP had no impact on resistance rates [58]. The only other report is a reduction

in multi-drug resistance rates in a UAE hospital, and was obtained from an oral presentation at the international conference on antimicrobial stewardship in Saudi Arabia [59].

The use of broad-spectrum antibiotics remains a challenging practice in GCC hospitals. Studies from all states measured the impact of ASPs adoption on use of broad spectrum antibiotics and only one Qatari study reported a reduction in the use of cefuroxime [45]. It was further reported in another study that the decline in using cephalosporins was accompanied with a rise in using other antibiotics such as penicillins and IV macrolides [44]. Two studies from Bahrain reported increased use of broad spectrum antibiotics like ceftriaxone due to resistance to first and second line options [31,32]. One Omani study reported that 90% of antibiotic prescriptions were for broad spectrum antibiotics due to lack of adherence with antimicrobial guidelines and policies [40]. An oral presentation in 2013 also reports a decline in using broad-spectrum antibiotics in an UAE hospital as a result of antimicrobial stewardship interventions in that setting [59]. The reported outcomes of ASPs adoption in GCC countries hospitals are presented in table 4.

4. Discussion

We explored the evidence on ASPs' adoption, barriers and facilitators affecting their adoption, and the outcomes of their adoption in hospitals in all six-member states of the GCC. Our findings suggest that hospitals in the region have adopted fragments/ initiatives of ASPs. This is consistent with the recent review findings of the impact of ASPs on antibiotic appropriateness and prescribing behaviours in selected countries in the Middle East [26]. Although the GCC strategic plan to combat antimicrobial resistance is still at its infancy [27], it is nonetheless, the first step towards establishing common ASPs across the region, taking advantage of the common geographic, economic and social characteristics amongst the member states; similar to the example of the European Union adoption of ASPs in hospitals in 2006 [61].

The main antimicrobial stewardship strategies reported in GCC countries hospitals are antimicrobial guidelines implementation, audit and feedback, and formulary restriction and pre-authorisation. These strategies are commonly employed as part of ASPs adoption, and have been identified in previous systematic reviews as common practice [26,62].

We identified that the barriers to adopting ASPs in GCC countries hospitals are mostly physician related, and that the challenges can be further exacerbated by lack of leadership and support by hospital management. Hajj poses a specific threat to antimicrobial stewardship adoption and implementation especially in hospitals in Saudi Arabia. The sheer volume of pilgrims leads to increased hospital admissions, increased antimicrobial consumption, and increased risks of resistance development and transmission to other healthcare facilities in the country [50].

Further, ASPs reported in GCC hospitals are mostly led by Infectious Diseases (ID) physicians and consultants; they are a key determinant/ facilitator to adoption and success of ASPs interventions. Interestingly, one of the main reported barriers to ASPs adoption in GCC hospitals is the lack of ID consultants and microbiologists. Currently, there are 57 ID physicians (Tropical medicine) (25 registrars and 32 consultants) in Saudi MOH hospitals (274 hospital) [63]. Factors contributing to the low numbers may include unattractive working condition and low remuneration in comparison to private sector [64]. This situation is not unique to GCC countries, as reports by [65,66] show that only 50-58% of smaller US hospitals have access to ID physicians.

Microbiologists and ID specialists are leading ASPs team members, but they also require the help of hospital pharmacists to monitor patterns of drug use in the various clinical departments, enabling analysis and feedback to prescribers and providing expert advice about antimicrobials [67]. In this review, we highlight the lack of involvement

of other healthcare professionals such as clinical pharmacists in ASPs teams, ASPs design and implementation. This is a missed opportunity to enhance antimicrobial stewardship especially since evidence point to the importance of multi-disciplinarily to improve timeliness and appropriateness of antimicrobial therapy [68,69].

We also identified individual and institutional factors relating to culture and resources. Physicians referred to their knowledge, prescribing behaviour, workload, and fear of blame if patients deteriorate upon changing antimicrobial therapy. Hospitals lack IT infrastructure, human and financial resources, leadership support and effective communication channels. These factors and others have been extensively reviewed by [70] and highlighted in a qualitative study in 2014 [71]. Further, a recent systematic review suggests that hospitals in the region may not foster an open, blame-free culture where reporting and learning from errors is encouraged [72]. In that, prescribers do not routinely adhere to antimicrobial prophylaxis guidelines, with treatments routinely extending beyond the suggested three days recommendation; in order to reduce the risk of complications and patients' deterioration, and the subsequent blame.

Facilitators to ASPs adoption in GCC countries hospitals include: prescriber's knowledge and experience, clear, accessible and consistent antimicrobial policies and open, face-to-face communication and feedback on prescribing patterns. These findings are consistent with previous findings by [73,74], highlighting the importance of experienced physicians and ID leadership and expertise, and engagement with clinicians to improve antimicrobial use.

The benefits of antimicrobial stewardship adoption in healthcare settings are well-established including improving appropriate antimicrobial use [24], reducing emergence of antimicrobial resistance [25] and reducing associated healthcare costs [23]. Here, we found that the reported ASPs in GCC countries hospitals, although small-scaled and not sophisticatedly-designed, led to improved antimicrobial prescribing practices and better patient outcomes, especially when adherence to ASPs guidelines is enforced and monitored. Lack of adherence (or lack of) to antimicrobial guidelines continues to be a challenge world-wide. Various studies have shown that the adherence to guidelines is suboptimal in many hospitals [75,76]. The role of pharmacists in monitoring guidelines adherence and providing feedback to prescribers has been strongly advocated as a means to improving adherence and subsequently, ensuring appropriate antimicrobial prescribing [77].

Despite the established evidence of reducing antimicrobial resistance [25,78,79], we found very little evidence of this in GCC hospitals. Firstly, we found that reduction of antimicrobial resistance rates was not a frequently measured outcome. This is consistent with findings of an earlier systematic review [62] that they retrieved six studies that reported the impact of antimicrobial stewardship on resistance rates reporting reduction in certain resistant strains and increased rates of others [62]. Secondly, we found that there was either no effect on resistance rates or a reduction in resistance for certain organism-antibiotic combinations and a rise for other organism-antibiotic combinations. This could be because the interventions are poorly designed resulting in reduced prescribing of certain antibiotics but a parallel rise in prescribing alternative antibiotics, and the scarcity/ lack of integration of microbiology services in designing and implementing ASPs in hospitals. Further, microbiologists in the region report a lack of a standardised method for phenotypic and genotypic methods for antimicrobial susceptibility testing, and the sporadic and inconsistent reporting of antibiotic resistance bacteria; when antimicrobial resistance surveillance is conducted, it is typically in laboratories of large hospitals that are not linked within a national network [80].

Limitations and future research

Although the previous review by Nasr et al (2017) explored the antimicrobial stewardship practices in the region, this is the first comprehensive review of evidence on hospital adoption of ASPs in GCC countries. We reviewed published evidence from a variety of study types, programme goals and outcomes. We also collected grey literature to broaden the scope of evidence and provide a more complete picture on the level of ASPs adoption in GCC countries hospitals, barriers and facilitators to ASPs adoption and the outcomes of their adoption. However, most of the studies neglected to define ASPs and their details. Further, methodological limitations were noted in the available evidence, including validity, and unmeasured or unreported changes as a result of ASP adoption. Also, the reviewed studies were small, and with short or no follow-up period. Larger pre-and post-studies with longer follow up periods are required to effectively evaluate antimicrobial stewardship interventions in the region and demonstrate how challenges to their successful adoption could be overcome. We also urge researchers and clinicians in the region to provide more detailed reporting of ASPs adoption and evaluation in relation to adopted ASP strategies and the various outcomes to measure ASPs impact on antimicrobials use and resistance.

Our findings highlight the existing initiatives in the region in secondary care, but further research is also required to explore the misuse of antibiotics over the counter and the potential adoption of antimicrobial stewardship in community pharmacy and primary care.

Implications for practice

For policy makers

The adoption of ASPs in hospitals in GCC member states remains low due to a variety of individual and institutional barriers. A national strategy regarding antimicrobial stewardship for local implementation is essential to drive forward the efforts to curb inappropriate antimicrobial use and reduce resistance [27,81]. Further, any national antimicrobial strategy should contribute to the overall regional targets of reducing resistance and improving antimicrobials use, especially since GCC member states collaborate extensively in relation to healthcare services, allow free movement of persons, and share characteristics of geography, culture, and economic resources.

Although GCC has recently developed an antimicrobial resistance strategic plan in 2015 [27] following the example of European Union [61] and the WHO One Health model [81]. The plan is still at its infancy, and so far, only Saudi Arabia has a national ASP policy, with communications from MOH to MOH hospitals to encourage adopting ASPs since 2014 [28,29]. Since private hospitals and primary care centres are yet to engage with this initiative, antimicrobial stewardship strategies should be more inclusive. Further, regulation and inspection could improve enforceability of policies.

For healthcare institutions

The literature on adoption of ASPs provides a detailed map of how hospitals could adopt this practice. Further, facilitating and sharing regional experiences of adoption from Saudi Arabia could improve organisational learning. For successful ASPs adoption, hospital leadership is paramount to ensuring implementation and enforcement of guidelines and recommendations in collaboration with clinicians and other stakeholders. Further, providing education and training on appropriate antimicrobial use and resistance, as part of the medical curriculum and continuing professional development, can improve healthcare professionals' adoption of antimicrobial stewardship practices.

Conclusion

Antimicrobial resistance in the region is developing very rapidly, with alarming reports of novel and rare multi-drug resistant strains. There is a strong body of evidence supporting the benefits of ASPs in reducing resistance and

sustaining appropriate antimicrobials use. Despite the well-established benefits of ASPs adoption in healthcare settings, adoption in hospitals in GCC states remains low and underreported. The lack of national strategies to tackle antimicrobial resistance further hinders its local implementation. Reporting of antimicrobial resistance should be consistent and prompt as part of a national surveillance programme, and this resistance data should be included in the design and implementation of ASPs in hospitals in the region, with a strong multi-disciplinary engagement of healthcare professionals, and continuous collaboration with management at local and strategic levels. Nevertheless, the current state of antimicrobial resistance in the region warrants urgent action from governments and institutions.

Declarations

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Figure 1: Literature review flow chart of data extraction and study selection process

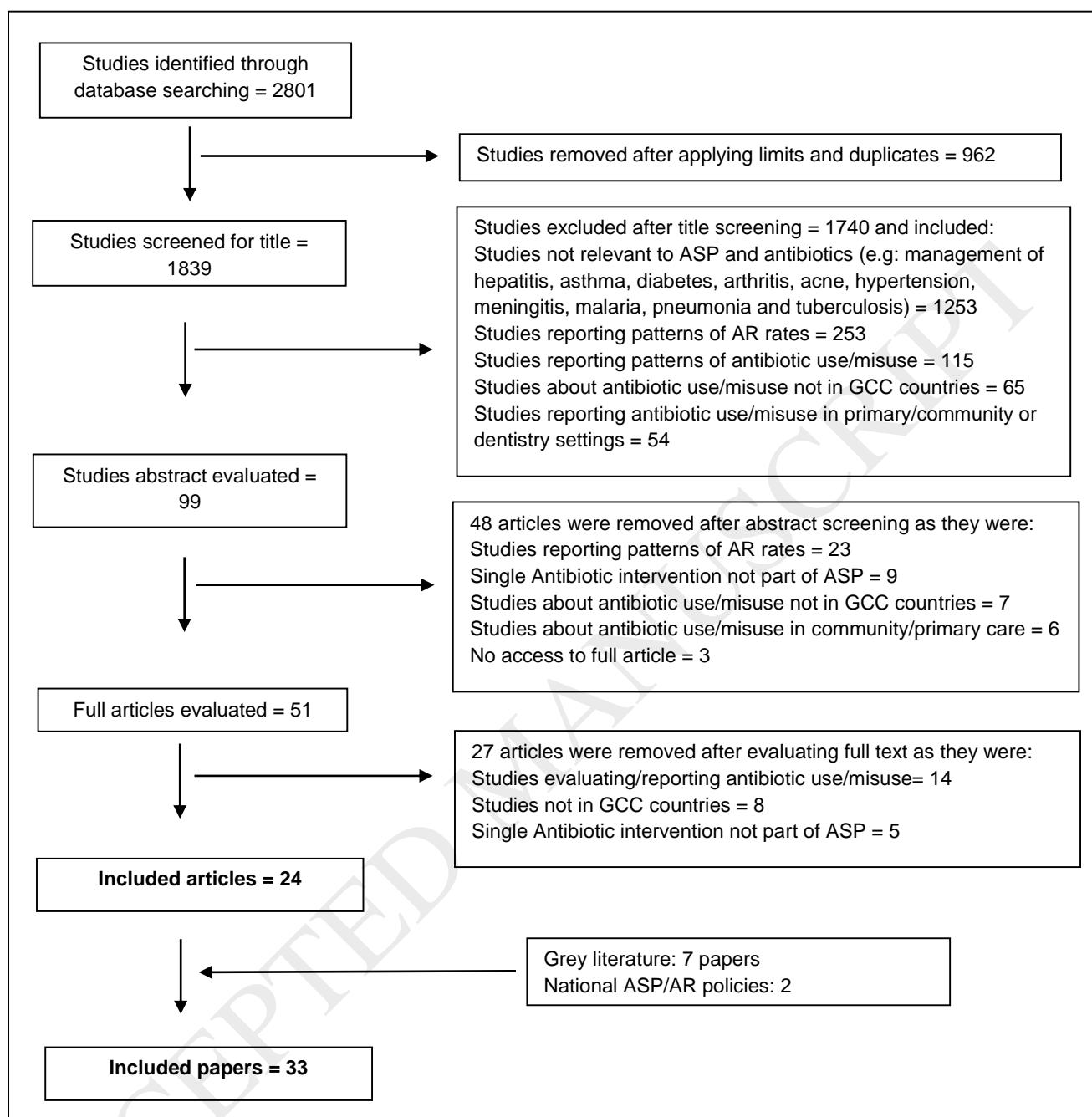


Table 1 Search terms

Antimicrobial stewardship programme terms	Strategies terms	Gulf Cooperation Council terms
Antimicrobial stewardship program(s), Antimicrobial stewardship programme(s), Antimicrobial stewardship, Antimicrobial control program(s), Antimicrobial control programme(s), Antimicrobial management, Antimicrobial stewardship model, Antibiotic stewardship program(s), Antibiotic stewardship programme(s), Antibiotic stewardship, Antibiotic control, Antibiotic management	Strategy (s), measure (s), intervention(s), policy (s), practice (s), protocol (s), surveillance, procedure (s), implementation, adoption, recommendation	Gulf Cooperation Council, Gulf countries, GCC, Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates (UAEs).

Table 2: Evidence of ASPs in GCC hospitals

Country	Authors	Setting	Study Type	Existing ASPs	Components of ASPs	ASP Team
Bahrain	Al Ansari et al., 2013 [31]	Outpatient setting attached to Bahrain Military hospital	Audit of antimicrobials used, patients treated, patient satisfaction and total costs comparison	Strategy to reduce the risk of healthcare associated infections and patients' length of stay	Outpatient parenteral antimicrobial therapy: Treatment policy and protocol	ID physician, Chief resident family physician, specialist nurse, pharmacist
	Al Alawi et al., 2015 [32]	Outpatient setting attached to Bahrain Military hospital	retrospective review of case notes of patients admitted to OAPT clinic	Strategy to reduce the risk of healthcare associated infections and patients' length of stay	Establishing guideline and protocol of ceftriaxone use in OPAT treatment policy and protocol. No involvement of antibiograms	ID consultant, family physician and specialist nurse
	Alqahtani, 2015 [33] (Conference presentation)	400-bed defence force hospital	Before/after study	Strategy to reduce Multi-drug resistance bacteria and antibiotic consumption	Formulary restrictions and preauthorization, local antibiotic susceptibility antibiogram, parenteral to oral conversion, guideline and clinical pathways, antibiotic audit with intervention and feedback, education	AMS teams and committees
	World Health Organisation, 2016 [34] (WHO report)	Country's preparedness and capacities	International mission report	Hospitals have various elements of ASPs since 2012. No national plan for detection and reporting of AMR pathogens or infections. No national plan for ASPs at central or facility level. No centres implementing ASPs. No ASPs exist in private hospitals or primary care centres	AMS teams and committees, antimicrobial use guidelines, and staff training. Strong NHRA control (National Health Regulatory Agency).	AMS teams and committees
Kuwait	Al Mousa & Aly, 2012 [35]	The Directorate of Infection Control in Kuwait organised a national campaign to encourage judicious use of antibiotics in healthcare settings during the period 19–26 March, 2009	Letter to editor and campaign report on ministry of health website	Campaign to raise awareness of doctors, pharmacists, patients and the public regarding appropriate antibiotics use called: 'Wise use or lose' .	Education activities to healthcare professionals, patient and public. Reminder SMS communication to Drs to use antibiotics wisely. Posters displayed on hospital corridors	Organised by National directorate of infection control, Scientific and Awareness committee. No involvement of teams within hospitals in design
	Aly et al., 2012 [36]	9 government hospitals	Audit of medical records in 9 government hospitals assessing adherence to hospital antibiotic policy	National antibiotic policy printed and distributed in booklets to hospitals since 2007. Hospitals use the national policy as basis for their local antibiotic policy. Existing antibiotic policy and guidelines at national and local levels.	Antibiotic policy contains broad evidence-based guidelines for the prescription of antibiotics to ensure appropriate prescribing	Organised by National directorate of infection control, Scientific and Awareness committee. No involvement of teams within hospitals in design
	Kuwaiti Infection Control Directorate, 2014 [30] (Government online report)	Nationwide Campaign including: Audits of adherence to national/ hospital antibiotic policy (first one reported by Aly, 2012. National awareness campaigns (1st one reported by Al-Moussa & Aly, 2012).	Campaign on antimicrobial resistance and judicious use targeting doctors in the private sector	Antibiotic policy, audits of adherence to policy. National awareness campaigns Education workshop 14/11/12 to private sector and campaign activities in government hospitals and primary care centres	Antibiotic policy Audits of prescribing and adherence to policy	Organised by National directorate of infection control, Scientific and Awareness committee. No involvement of teams within hospitals in design
Oman	Gunn et al., 2009 [37]	Four major hospitals	Retrospective examination of medical records of patients admitted for Lower Segment Caesarean Sections (LSCS)	The Ministry of Health Antibiotic Chemotherapy Policy & Guidelines were published in 1998 and cover the use of antibacterials in prophylaxis and treatment	most major hospitals in Oman have established their own "in house" guidelines for almost all antibiotic use	
	Al-Abri et al., 2012 [38]	Tertiary hospital (Royal Hospital) Muscat	Retrospective case study involving a review of case notes of 342 patients	CAP guidelines	Guidelines and antimicrobial use policy	

	Za'abi et al., 2013 [39]	Tertiary hospital (Sultan Qaboos university hospital)	A review of patients' medical records of 365 patients	Antibiotic handbook (antibiotic policy) produced by the hospital in 2006 is the primary antibiotic protocol Restricted Antibiotic-Vancomycin	Antibiotic policy/ guidelines and restricted antibiotics	
	Al-Maliky et al., 2017 [40]	Tertiary hospital (Sultan Qaboos University hospital)	Observational study involving 366 patients	Local infections guidelines and Restricted antibiotic policy	Antimicrobial guidelines restricted antibiotic policy	
Qatar	Khan et al., 2010 [41]	Tertiary hospital (Hamad General Hospital)	Retrospective audit of medical records of 69 patients	Local infection guideline: Guidelines for management of CAP	local infection guideline	
	Abdel-Aziz et al., 2013 [42]	Tertiary hospital (Hamad General Hospital)	Retrospective analysis of patient data from different surgical units in hospital	Surgical antimicrobial prophylaxis guidelines	Antimicrobial guidelines	
	Pawluk et al., 2015 [43]	primary/ community and secondary care	Cross-sectional survey targeting all pharmacists practicing in Qatar	Various ASP strategies reported by pharmacist in secondary care in Qatar	Formulary restriction of antibiotics, clinical practice guidelines for infectious diseases, audit and feedback, IV to oral step-down guidelines, patient education, prescriber education, protocols that transfer authority from prescribers to pharmacists, antimicrobial cycling	Pharmacists review medication and feedback to prescribers
	Garcell et al., 2016 [44]	Community hospital (75-bed facility)	Observational study monitoring antibiotic consumption and compliance with policies (2012-2015)	Hospital has an established ASP programme Current strategies for ASP in hospital	Antimicrobial prescribing policy for therapeutic use and surgical prophylaxis including antibiotic stop orders, switching from IV to oral antibiotics and antibiotic restriction. Prescribing audits, antimicrobial consumption monitoring, feedback to medical staff and management, data dissemination, staff training and development.	pharmacists monitor consumption and disseminate rates to medical and management staff. Infection prevention and control committee working closely with Quality and Patient Safety committees.
	Garcell et al., 2016 [45]	Community hospital (2013-15)	Interventional study to determine the impact of ASP on antimicrobial related activities in hospital	Existing, fully functional ASP focusing on appendectomies with quality indicators (compliance with timing, selection and dose, discontinuation of antibiotic prophylaxis as per protocol).	Staff education, monitoring antimicrobial consumption and providing feedback to prescribers	Compliance with antibiotic prophylaxis was monitored by an infection control practitioner. Monitoring of antimicrobial consumption was monitored by pharmacists.
Saudi Arabia	Jacobs et al. 2003 [46]	Riyadh Armed forces hospital	Interventional study involving 228 patients admitted to Intensive Care Unit for Percutaneous Dilatational Tracheostomy	Antibiotic protocol and procedure guidelines	Microbiology/ antibiotic protocol	
	Dib et al., 2009 [47]	Tertiary hospital Dhahran Health Centre	Interventional study with reviews of medical records pre- and post-intervention	Hospital infection control practices advisory committee producing antimicrobial use guidelines, education and feedback	antimicrobial use guidelines, education and feedback	Clinical pharmacist review and feedback to prescriber regarding adherence to guidelines. Infectious disease consultants used in persistent use cases

Amer et al., 2013 [48]	Tertiary hospital (KFSHRC)	Comparative historically-controlled study. 24 patients enrolled on the active ASP arm and 49 patients on the historical control arm	ASP implementation in 2011 including ASP team, prospective audit and feedback, and education interventions. Appropriateness of prescribing assessed against formulary restrictions, adapted international infection guidelines. Verbal and written reports to ICU prescribers.	Proactive core strategies: formulary restriction and pre-approval strategies, prospective audit and feedback. Supplementary strategies: education interventions, guidelines, antimicrobial order forms, pharmacodynamics dose optimisation, antimicrobial cycling.	ASP team (ID/ Intensivist physician and ASP pharmacists)
Malhani et al., 2014 [49] (conference poster)	Medical City (King Fahad)	Retrospective audit of medical records 172 patients before ASP implementation and 205 patients' post-implementation	Report on one ASP strategy implementation in hospital	Audit and feedback to prescriber regarding IV to oral switch and duration of therapy	ASP team not identified possibly including pharmacists
Al-Somai et al., 2014 [50]	Tertiary hospital (King Abdullah Medical City) Makkah.	Pre- and post-study to explore the impact of implementation of antimicrobial policy	Antimicrobial policy	Antimicrobial policy adapted from international infectious disease guidelines	clinical pharmacist, ID consultant
Al-Tawfiq et al., 2015 [51]	Dhahran Health Centre 380-bed general hospital	Interventional study	Selective reporting of Gram-negative bacillus susceptibility by clinical laboratory services and pharmacy, considering local resistance rates and international guidelines. Education activities	Cascade and restrictive reporting. Formulary restriction, guidelines and education activities	Microbiologists- microbiology lab
Al-Harhi et al., 2015 [52]	University hospitals, private hospitals and public hospitals	A cross-sectional self-administered questionnaire		To investigate the perceptions, attitude, and prescribing practice among clinicians about AR	
AlAwdah et al., 2015 [53] (Conference poster)	Tertiary hospital (Riyadh)	Pilot prospective quality-improvement interventional study in paediatric ICU a	Reported existence of ASP Formulary restriction	Formulary restriction	ASP team mentioned but not identified. Most likely including clinical pharmacist reviewing medication and recommending antimicrobial optimisation according to restricted formulary recommendations.
Haseeb et al., 2015 [54] (conference paper)	Survey of ASPs in Makkah hospitals	Survey targeting hospitals in Makkah region	Existing elements of ASP	Audit of antimicrobial use, education and training, and infection control and surveillance. Most common types of strategies were formulary restrictions for broad-spectrum antimicrobials and use of automatic stop orders to limit empirical therapy of antimicrobials in Makkah hospitals	
Alawi and Darwesh 2016 [55]	1002-bed tertiary care university hospital	Prospective before/after	Audit, review and restriction	Audit and review Number of prescriptions and dispensations, incidence of Multi drug resistance (MDR) and cost	
Salahuddin et al., 2016 [56]	Specialist hospital in Riyadh (King Faisal specialist hospital)	prospective cohort study	antibiotic protocol and sepsis guidelines	De-escalation strategy and Sepsis guideline adapted from an international guideline (2012)	
Enani, 2016 [57]	Mainly in tertiary hospitals	Regional survey targeting healthcare professionals in hospitals involving several GCC countries.	Evidence of existing ASPs in tertiary care settings in Saudi Arabia.	Although the definition of ASPs was not provided, restricted list of antimicrobial agents and antimicrobial audits were the main strategies reported	
Alshukairi et al., 2016 [58]	Specialist hospital (King Faisal specialist hospital,) Jeddah	pre-post intervention study	De-escalation protocol	De-escalation protocol, education and training of nurses and physicians re	

					protocol, and auditing adherence to protocol	
United Arab Emirates	Hashmey, 2013 [59] (oral presentation)	Tawam tertiary hospital, National Oncology referral centre	Report	Existing functional ASP	pre-approval antibiotics (restricted antimicrobials), guidelines and pathways, IT setting of infection control antibiotic stewardship worklist, prospective audit with feedback	Microbiologists, ID physicians, ID pharmacists, Infection Control Practitioners liaising with IT and Quality office.
	El Hassan et al., 2014 [60]	Mafraq hospital, Abu Dhabi	Retrospective review of data of 250 patients	Surgical antimicrobial prophylaxis guidelines	Hospital guidelines on surgical antimicrobial prophylaxis and use of bacterial antibiograms	Surgeons, clinical pharmacists and surgical nursing staff. Med review by pharmacists

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Table 3: Identified barriers and facilitators to ASPs adoption in GCC hospitals

Country	Authors	Facilitators	Barriers
Kuwait	Kuwaiti Infection Control Directorate, 2014 [30] (Government online report)	Experience (in relation to age) and antibiotics knowledge can lead to good antimicrobial stewardship	Excessive antibiotics prescribing as reported by Drs include: lack of time to perform the required investigation, fear of complication and antibiotic resistance concerns. Barriers to adherence to policy as reported by Drs include: non-availability or poor distribution of the policy, neglect of reading the policy, being incomplete or not updated and interrupted supply of some antibiotics. Knowledge of types of resistant organisms & isolation precautions
Oman	Gunn et al., 2009 [37]	Those hospitals that had a consistent policy and especially a written policy, made known to all staff, had better outcomes as far as post-operative infections	Many health workers considered the guidelines to be out-dated
Qatar	Pawluk et al., 2015 [43]		Non-availability of an infectious diseases specialist is the most prominent perceived barrier to implementation and expansion of ASP Training of pharmacists and pharmacy staff on elements of ASP are also perceived barriers.
Saudi Arabia	Al-Tawfiq et al., 2015 [51]	Alleviate prescribers concerns through discussing evidence of intervention and providing support. Held small group meetings with targeted (main) prescribers and key/ influential prescribers to encourage physicians to support ASP initiative	Many physicians were comfortable only with prescribing familiar antibiotics, difficulty persuading physicians to prescribe specific agents/ combinations, relevant microbiology not always available, no incentive for prescribers to choose more appropriate antibiotics
	Al-Somai et al., 2014 [50]		Maintaining antimicrobial control during time of Hajj in Makkah is a challenge because of increased number of admitted patients and increased antimicrobial use.
	Haseeb et al., 2015 [54] (conference paper)		Majority of the hospitals lacked local antimicrobial guidelines based on hospital-wide antibiograms
	Salahuddin et al., 2016 [56]		reluctance of physicians to de-escalate antimicrobial therapy in complicated, sicker patients with drug resistance or fungal sepsis
	Enani, 2016 [57]		Lack of programme funding and personnel as main barriers. Other barriers include obstruction from prescribers, and administration, lack of awareness of ASPs
	Alshukairi et al., 2016 [58]		High resistance rates in other centres and transfer of resistance to specialist centres upon admission for last resort intervention

Table 4: Outcomes of hospital adoption of ASPs adoption in GCC countries

Country	Authors	Reduction of inappropriate prescribing	Reduction of healthcare associated infections	Reduction of direct antimicrobial cost	Reduction of length of stay/ mortality metrics	Reduction of antimicrobial resistance	Reduction of Broad spectrum antibiotic use
Bahrain	Al Ansari et al., 2013 [31]				Only 2 out of 101 patients were admitted to hospital		High usage of Ceftriaxone
	Al Alawi et al., 2015 [32]				Only 6 out of 97 patients admitted to hospital		increased use of broad-spectrum antibiotics due to resistance to first and second line.
	World Health Organisation, 2016 [34] (WHO report)					Detection and identification of AMR	
Oman	Gunn et al., 2009 [37]		Hospitals that had a consistent policy and especially a written policy, made known to all staff, had better outcomes as far as post-operative infections				
	Al-Abri et al., 2012 [38]	80% adherence to antimicrobial treatment guidelines of CAP but excessive IV use of macrolides					
	Al-Maliky et al., 2017 [40]						High use of broad spectrum antibiotics (90% of antibiotic prescriptions) due to lack of adherence/ compliance with guidelines and policy
Qatar	Khan et al., 2010 [41]	Adherence to guideline in 75% of cases					
	Abdel-Aziz et al., 2013 [42]	Only 40% of surgical patients received the right antibiotic due to lack of adherence to hospital policy.					
	Garcell et al., 2016 [44]						Reduction in use of cephalosporins but rise in use of other antibiotics such as oral penicillin's and IV macrolides.
	Garcell et al., 2016 [45]	Appropriate prescribing and administration of antibiotics improved					reduction in antimicrobial use especially cefuroxime
Saudi Arabia	Jacobs et al. 2003 [46]	eliminated inappropriate prescribing	Reduced perioperative infective complications from 32% to 11%				
	Dib et al., 2009 [47]	Education and feedback to prescriber enhanced adherence to guidelines from 35% to 68%.					
	Amer et al., 2013 [48]	appropriate empirical antibiotics improved from 31% to 100%	No impact on C diff rates	half the total cost of antibacterial agents	Reduction of hospital stay 376 DDD compared to 2404 DDD pre-ASP. Deaths decreased from 33% to 17%.		
	Malhani et al., 2014 [49] (conference poster)			Cost savings reported as a result of ASP team interventions			
	Al-Somai et al., 2014 [50]	ASP interventions resulted in 37% reduction in antimicrobial consumptions		Reduction of direct antimicrobial cost			

	Al-Tawfiq et al., 2015 [51]		Reduced C.diff rates			Reduction of antimicrobial resistance for some organism-antibiotic combinations and increase in resistance of the heavily used antibacterial (piperacillin-tazobactam)	
	AlAwdah et al., 2015 [53] (Conference poster)	Improved antimicrobial prescribing in relation to reduced DOT for major antibiotics used.					
	Enani, 2016 [57]	Two thirds report the outcome	Two thirds report the outcome	Two thirds report the outcome	60% report the outcome	55% report the outcome	Two thirds report the outcome
	Alshukairi et al., 2016 [58]					no significant effect on antimicrobial resistance	
United Arab Emirates	Hashmey, 2013 [59] (oral presentation)		reduction in c diff	40% reduction in consumption and associated costs		reduction in MDR	reduction in use of broad spectrum antibiotics
	El Hassan et al., 2014 [60]	Low adherence to hospital guidelines (32%) resulted in inappropriate SAP prescribing					