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Promoting Cross-Regional Collaboration in Antimicrobial Stewardship: Findings of an Infectious Diseases Working Group Survey in Arab countries of the Middle East

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Abstract

Background

Antimicrobial resistance is a significant global issue that presents an increasing threat to patients' wellbeing. Although a global concern, the emergence of multi-drug resistant organisms is of particular significance in the Middle East. In recent years, this region has seen an alarming increase in antimicrobial resistance presenting a major challenge to physicians managing various infectious diseases.

Methods

A Working Group comprising experts in infectious diseases from Arab countries of Middle East assembled to review similarities and differences in antimicrobial practices and management of multi-drug resistant organisms across the region and assess the barriers to achieving cross-regional collaboration. The Working Group conducted an anonymous online survey to evaluate current practice and understanding of management of multi-drug resistant organisms across the region.

Results

A total of 122 physicians from Arab countries of the Middle East responded to the survey. Their responses demonstrated heterogeneity between countries in awareness of local epidemiology, management of multi-drug resistant organisms and antimicrobial stewardship practices. The Working Group recognized similarities and differences in the management of multi-drug resistant organisms across the region, and these were validated by the data collected in the survey. Overall, the similarities across the region reflect several key issues that can have an impact on the management of multi-drug resistant organisms and the prevention of antimicrobial resistance.

Conclusions

This paper highlights the urgency of addressing antimicrobial resistance in Arab countries of the Middle East. The Working Group identified key barriers to effective management which may guide the development of future coherent strategies to promote effective antimicrobial stewardship in the region. Here, we outline a call to action for the region, with a need to focus on training and education, capacity building, infrastructure, regional research, and regional surveillance.

Keywords: Multi-drug resistant organisms, antimicrobial stewardship, Middle East

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Introduction

Antimicrobial resistance (AMR) is a prevalent and increasing threat to patients' wellbeing on a global scale. (1,2) AMR has increased in clinically relevant bacteria, reducing the efficacy of many antibiotics that are used widely in practice. (3) The development of novel antimicrobials cannot match the speed with which resistance is developing in many organisms, leading to a situation where existing agents are no longer effective and alternative treatment options are limited. (4) As alternative antimicrobials are used in practice, bacteria develop new mechanisms of resistance leading to the generation of multi-drug resistant organisms (MDRO), causing further challenges to the selection of effective treatment regimens. (5)

Although a global issue, the emergence of MDROs is of particular significance in the Middle East. Within this region, it has been noted that overuse or misuse of antimicrobials in humans and animals coupled with a lack of proper infection control measures in many healthcare facilities has led to the alarming increase in AMR among many commonly isolated pathogens. (6) Expansion of the population of the Middle East, population mobilization due to socio-economic and political conflicts, and resulting pressures placed on healthcare systems have all contributed to the challenges facing treating physicians in the region. (7)

Antimicrobial stewardship programs (ASP) are considered vital in addressing the growing threat of AMR. (8,9) Effective ASPs require collaborative, coordinated strategies and interventions targeting antimicrobial prescribing practices and optimization of clinical outcomes associated with antimicrobial use. (8) The Arab nations of the Middle East face specific challenges regarding the implementation of ASPs, the prevention of AMR, and the management of infections caused by MDROs. These challenges relate to multiple factors, including those due to population dynamics and the available infrastructure for surveillance and disease management. A systematic review highlighted key challenges facing the region when implementing ASPs, including a need for clear prescribing policies and interdisciplinary collaboration. (10) Similar findings have been noted in the Gulf Cooperation Council (GCC) States (9,11) and Saudi Arabia, (12) with the need for training, resources and support required to ensure ASP implementation in the region. This study evaluated current practice in the management of MDROs in Arab countries of the Middle East with the aim of identifying initiatives to improve antimicrobial stewardship (AMS) and addressing barriers to achieve cross-regional collaboration.

Methods

A diverse Working Group comprising experts in microbiology, infectious diseases, and intensive care medicine from Arab countries of the Middle East was formed and first convened in November 2018. A European expert was also selected to join the Working Group and provide international perspective. The Working Group members were not assigned by health authorities but were instead selected by the chairpersons and founders of the Working Group based on their expertise in the management of MDR infections, with each expert representing their country as either a leading infectious disease researcher, an eminent clinical microbiologist or AMS lead.

To evaluate awareness of local epidemiology, MDRO management and AMS practices in the region, the Working Group developed an anonymous online survey. The survey was composed of 39 multiple choice questions on the understanding of epidemiology, preferred treatment options for mild-to-moderate and severe infections, selection of agents for combination therapy, duration of therapy, empiric treatment selection, factors contributing to antibiotic resistance, and availability of AMS structures. The survey was critically appraised and a pilot test was conducted by the Working Group members to ensure the questions were clear, concise and easy to complete. The survey was programmed into an online platform and a link to the survey was circulated by email through the Working Group members to infectious diseases, internal medicine, microbiology and intensive care departments in their institutions and also through regional society mailing lists. Following the initial invitation to participate in the survey, two reminders were sent by email. Anonymity of respondents was ensured through the survey platform, respondents were not asked to complete any identifying details e.g., name or email address. Survey respondents' Internet Protocol (IP) address was solely used to ensure that respondents only completed the survey once and was not used for identification. Through this survey, the Working Group aimed to reach physicians whose focus is the treatment of patients with MDRO infections in the Arab countries of the Middle East.

In November 2019, the Working Group members reviewed similarities and differences in antimicrobial practices and management of MDROs across the region and assessed the barriers to achieving cross-regional collaboration. These observations/viewpoints were reviewed and analyzed in comparison to data from the survey.

Results

Survey respondents

A total of 122 physicians from Bahrain (3%), Kuwait (25%), Lebanon (14%), Oman (25%) Qatar (13%), Saudi Arabia (9%) and UAE (11%) completed the survey. Respondents

practiced in the following specialties: internal medicine (4%), intensive care (10%), microbiology (37%) and infectious diseases (49%).

Regional similarities and differences

A summary of the Working Group's discussions on the similarities and differences in the management of MDRO between their institutions and countries is presented in Table 1. Barriers to effective MDRO management varied between countries but followed three key themes: lack of resources (including budget, skilled manpower, hospital and laboratory supplies, electronic health system, and access to new drugs), lack of regional guidelines and leadership commitment and lack of national susceptibility testing.

Based on the reported barriers, the Working Group identified five key areas where actions are needed to promote cross-regional collaboration: training and education; building capacity; infrastructure strengthening and support; enhancing regional research; and improving regional surveillance (Table 2).

Epidemiology and antimicrobial resistance

In their discussions, the Working Group noted the increasing AMR across the region affecting a diverse number of micro-organisms and antimicrobial agents. (6) Unanimously they agreed the top pathogens of concern were the WHO critical priority pathogens *Acinetobacter baumannii*, carbapenem-resistant; *Pseudomonas aeruginosa*, carbapenem-resistant; and Enterobacteriaceae, carbapenem-resistant, extended-spectrum beta-lactamase (ESBL)-producing. (13) However, the Working Group acknowledged that there are limited data on resistance at a national level and large variations in estimates, reflecting poor data sources and low data availability on antimicrobial use and resistance rates in key pathogens. This was reinforced by the survey data where respondents were asked about the proportion of ESBL-producing and carbapenem-resistant Enterobacteriaceae (OXA-48 and NDM), carbapenem-resistant *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in their institutions. The responses to these questions were highly variable within each country, highlighting the heterogeneity between institutions and the variable knowledge of bacterial epidemiology or lack of available epidemiology data as demonstrated by the example in Figure 1.

Discussions amongst the Working Group members highlighted the variance in the degree to which resistance occurs and variations in data-collecting approaches. There were additional

discrepancies in susceptibility testing methods, interpretation and definition of MDROs, and diagnostic processes which collectively pose a challenge to comparing data across the region. Although there are hospitals in the region that produce biannual antibiograms, these are not often widely communicated to treating physicians. There is a need for better awareness of resistance trends to prevent further escalation of resistance. Resistance data should be regularly and routinely communicated to end users in order to guide treatment optimization and formulate updated regional and national antimicrobial guidelines.

Treatment options

The survey respondents were asked about preferred treatment options for severe and mild-to-moderate infections, preferred therapy dosage and de-escalation strategies. The physicians were aligned on their selection of treatment options for severe and critically ill patients as highlighted in the example in Figure 2A. However, when physicians were asked about their treatment selection for patients with mild-to-moderate infections they were less aligned (Figure 2B). There was a particular diversity of answers when physicians were questioned on their preferred combination agents for MDRO, highlighting the heterogeneity of available therapy across the region. The Working Group considered that this may reflect a number of contributing factors: regional variation in antimicrobial supplies, interruption of supplies (secondary to financial or social factors, including wars and political conflicts), and local antimicrobial guideline preferences.

Antimicrobial stewardship

The Working Group considered the uptake of formal AMS strategies and variations in the implementation of AMS strategies to be highly variable across the region. In the survey, an awareness of AMS across the region was indicated by 99% of respondents highlighting that they 'always' or 'sometimes' de-escalated from carbapenem (meropenem or imipenem) when antibiotic susceptibility testing showed susceptibility of causative pathogens to narrow-spectrum antibiotics. Evidence of AMS was also suggested by 87% of respondents reporting that they used high-dose colistin with a loading dose for the treatment of patients with infections due to multidrug resistant Gram-negative bacteria (GNB) or extensively drug resistant GNB (12% of physicians would only use a high dose in patients without kidney injury).

Across the region, 79% of respondents either did not have access to, or did not use, therapeutic drug monitoring (TDM) for patients treated with polymyxins. During their

discussions, the Working Group members were aware that there was disparity in the capacity, quality and comprehensiveness of laboratory services across the region. Specifically, the value of a central data collection site or reference laboratory was considered problematic in some nations. The lack of appropriate polymyxin testing methods and TDM resources across the region, as highlighted by the survey, may form a potential barrier to appropriate treatment.

When questioned on whether a risk stratification was usually performed for resistant bacteria, 70% of physicians answered 'Yes, always' or 'Yes, often' compared with 30% of physicians who either 'rarely', 'never' or didn't know if it was performed routinely.

The availability of AMS structures in the survey respondents' institution was assessed and physicians from Kuwait, Oman and UAE were split on the implementation, whereas physicians from Bahrain, Lebanon, Qatar and Saudi Arabia were more aligned (Table 3). This may reflect a range of influential factors, including differences in the availability of a single centralized body to coordinate the ASP across the country, resources, funding and adherence to strategies. Across all nations, it was appreciated that inter-hospital variations could serve as a key driver for implementing a coherent set of strategies to promote responsible antimicrobial use as part of an ASP.

The Working Group considered that implementing ASP core elements throughout the region will ensure effective practices including: clinical leadership, engagement to monitor outcomes, pharmacy leadership, tracking and reporting of antimicrobial use, reporting of AMR, educating providers on optimal use and effects on resistance patterns, and prospective antimicrobial audits to measure appropriate use and specific improvement interventions. (14) At present, many of these elements are deficient in many medical centers in the Arab countries of the Middle East, including a lack of collected data and poor coordination of care and services, which may hinder proper implementation of ASP. Establishing internationally recognized and accredited training programs for AMS is of great importance to improve the skill and competency of ASP committee members.

Discussion

A diverse range of factors contribute towards MDRO management in Arab countries of the Middle East. The Working Group has identified similarities and differences in MDRO management across the region and highlighted the key barriers to effective management. Challenges in the management of MDRO in Arab countries of the Middle East reflect those related to collaborative approaches between different sectors and within the health sector

alone. Furthermore, specific regional challenges may also be noted which highlight the importance of developing guidance for the region, based on adaptation of international practices and standards.

It is notable that Arab nations of the Middle East have experienced substantial population increases over recent decades, secondary to economic growth and development. Population dynamics within these nations are prone to fluctuation and encompass a broad range of nationalities, expanding the potential for the spread of resistant organisms across national borders. (15) Commensurate with the population growth seen in the region, there has been a rapid growth in the health system to meet population health needs. (16) However, healthcare growth and funding, along with the development of expertise and standards of care, need to accelerate to meet expanding population needs in the region. Therefore, resource and funding challenges may be faced when implementing international standards of ASP. Engaging decision makers is critical to ensure long-term cost effectiveness of implementing ASP. Institutions have found that effective ASP will shorten the hospital stay of patients and reduce unnecessary use of antimicrobial agents.

In addition to the effective implementation of AMS strategies, there is a need to consider how collaborative practice may influence antimicrobial use and resistance monitoring. It is not sufficient to focus on healthcare providers alone, as an integrated system is needed to ensure a holistic and multi-sectorial approach. Firstly, there is a need to engage healthcare providers, patients and the general public in effective strategies that contribute towards AMS. (17) Indeed, the use of antimicrobials by patients, including inappropriate use, medication hoarding, and poor adherence may contribute to AMR. (18) Education and support provided by healthcare professionals can be effective in promoting patient awareness of AMR, as well as improvements in appropriate antimicrobial use. (17) Further collaboration is also needed between healthcare professionals and wider sectors that may contribute to AMR in the environment. (19) It is recommended that national laboratories and public health agencies in each country take the lead in empowering the implementation of ASPs through the development of guidelines, that aim to unify practice and mentor progress on the national level.

There are also specific cultural and social factors that may be linked to AMR and approaches to antimicrobial use in the population. Cultural and social practices regarding disease and medication use may influence help-seeking, drug adherence and wider medication management. (20) Therefore, culturally appropriate strategies to educate the general population are needed, highlighting the importance of regional approaches to implementing international guidance.

Finally, regional conflicts and civil unrest have generated unique challenges to population health, secondary to interruption of health services and the emergence of refugees across the region. (21) These factors pose challenges to the reliability of medication supplies, microbiology test results, (22) health service operations and wider population health. (21) Therefore, MDRO management in the region needs to take into account factors that are specific to the region, as well as the wider global guidance on ASP.

Moreover, only recently has there been relevant data from the region regarding antibiotic consumption in the animal sector (23) and environment, (24) both having been firmly established as significant contributors to AMR in other parts of the world. Strategies for addressing AMR as a “one health approach” have been proposed by many organizations, including the National Institutes of Health, (25) the Food and Agriculture Organization of the United Nations (26) and the World Health Organization. (27) However, most Arab countries of the Middle East are lagging behind in implementing this multidisciplinary approach.

Intra-regional variations can limit the potential to implement guidelines consistently and may pose barriers to cross-regional cooperation. These variations in the challenges to managing MDRO suggest the need for tailored strategies for each nation, targeting the most important risk factors for resistance and poor adherence to ASP guidelines (where available). Although many nations experience similar challenges to managing MDROs in practice, the capacity for individual nations to address these challenges may differ considerably. Indeed, where different types of diagnostic criteria are utilized a difference in the classification of resistant microorganisms are evident between nations, making analysis and comparison of regional data more complex. Solutions and actions need to appreciate intra-regional variation in MDRO management, based on analysis of barriers to treatment.

Some limitations of the online survey should be noted. Firstly, the survey was only circulated among specialists in intensive care medicine, microbiology, infectious diseases and internal medicine. These specialties were selected for their leadership in infection control and AMS in Arab countries of the Middle East. The survey did not include other specialists including hematologists, transplant physicians/surgeons as across the Arab countries of the Middle East, these specialties are infrequently involved in setting antimicrobial stewardship practices. In addition, clinical pharmacists were not included in the survey respondents as they are not consistently available in most countries in the region. Further research will be required to understand these specialties' perspectives on management of MDRO and AMS in the region. Additionally, given the use of regional email databases to circulate the survey we were unable

to calculate the proportion of completed surveys of those that were sent out, which may have hindered our analysis.

Conclusion

This paper highlights the importance of AMR in Arab countries of the Middle East, which presents a range of challenges to health services. AMR is associated with reduced antimicrobial efficacy and the potential for poor patient outcomes. Inappropriate use or misuse of antimicrobials across health, animal and marine sectors can all contribute to the development of MDRO. The Working Group highlighted key barriers to effective MDRO management and provided recommendations to guide the future development of coherent strategies to promote effective ASP in the region. This document outlines a call to action for the region, with a need to focus on training and education, capacity building, infrastructure, regional research, and regional surveillance.

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Ethical Approval

Not required

Competing interests

None declared

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Similarities	Differences
<ul style="list-style-type: none"> • Same problematic pathogens: <ul style="list-style-type: none"> – Enterobacteriaceae <ul style="list-style-type: none"> ▪ <i>E.coli</i> (ESBL and CRE) ▪ <i>Klebsiella</i> (ESBL) – <i>Acinetobacter baumannii</i> – <i>Pseudomonas aeruginosa</i> • Rates of resistance • Types and sites of infection • Lack of IT systems to extract data on prevalence or incidence • Lack of unified MDR guidelines • Lack of unanimous multidisciplinary approach • Lack of trained manpower • Lack of unified matrix and key performance indicators • Use of “poor” generic drugs (no regulation of generic agents entering the market) • Unavailability of new drugs in all countries • Lack of national data on antibiotic consumption for humans, animals, and agriculture • Lack of laboratory standards to perform susceptibility testing of colistin and tigecycline • Variable hospital infrastructure 	<ul style="list-style-type: none"> • Incidence of infections and pathogens (e.g. SSTI infections more common in countries receiving war injuries) • Different molecular strains of CRE, e.g. KPC, OXA, etc. • Methodology of collection and reporting, e.g. different cut-offs (EUCAST, etc.) • Availability of rapid molecular diagnostics • Availability of country-specific published guidelines • Implementation of antimicrobial policy • Implementation of antimicrobial stewardship • Reported availability of hospital antibiograms • Compliance with infection control practices • Accessibility of over-the-counter antibiotics • Intermittent antibiotic supply • Clinical governance • Geographic • Allocated budget/resources for ASP

Table 1. Similarities and differences identified in countries across the region regarding ASP

ASP, antimicrobial stewardship programs; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum beta-lactamase; EUCAST, European Committee on Antimicrobial Susceptibility Testing; IT, information technology; KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multi-drug resistant; SSTI, skin and soft tissue infections

Key area	Key actions
Training and education	<ul style="list-style-type: none"> • Training and education should be focused specifically on AMR and ASP, as these are key areas relating to the use and misuse of antimicrobials in practice • Training should be available for IT and support staff, as the use of technology is vital in monitoring resistance trends and use of antimicrobials • Laboratory staff should be trained to ensure they have the required skills to perform antimicrobial susceptibility testing • Media engagement is vital to promote education of lay people, which may contribute to promoting more responsible use of antimicrobials and thereby reducing the development of resistance
Building capacity	<ul style="list-style-type: none"> • Continuing medical education and continuing professional development to ensure healthcare professionals have up-to-date skills and knowledge regarding AMR and ASP • Undergraduate training in AMR and ASP is needed to build skills and knowledge from an early stage • Online courses and ASP should be implemented to overcome resource barriers and cost of travel for healthcare professionals or students to attend training • Collaboration with WHO and EMRO to promote AMR activities and coordination of service development
Infrastructure strengthening and support	<ul style="list-style-type: none"> • Infrastructure development is needed in the form of electronic patient records across the region • Tracking capabilities and standards of monitoring to ensure consistency in data collection and analysis • Efficient use of budgets should be encouraged to ensure effective and sustainable services • Adaptability in governance to develop infrastructures for ASP implementation at the department level and consistent with available resources • Acquisition and rapid registration of new drugs in the region should be promoted and encouraged to ensure effective

	<p>treatment options are available to patients with MDRO infections</p> <ul style="list-style-type: none"> • Implementation of a rapid molecular test to detect antimicrobial resistance
Enhancing regional and international collaborative research	<ul style="list-style-type: none"> • Research to provide insights into AMR rates across the region • Point prevalence data of resistance and antibiotic use using cross-sectional and longitudinal methods to monitor trends • Collaboration between professionals and governments or national bodies to facilitate regional and international research
Improving regional surveillance	<ul style="list-style-type: none"> • National surveillance data across the region to monitor AMR rates and antimicrobial use • Consistency in the categorization of resistance and surveillance techniques to provide data that may be compared across the region • A central database to ensure regional data analysis and strategic development • Enhanced Global Antimicrobial Resistance Surveillance System (GLASS) enrollment should be encouraged, in addition to improvement in reporting and adherence to GLASS principles

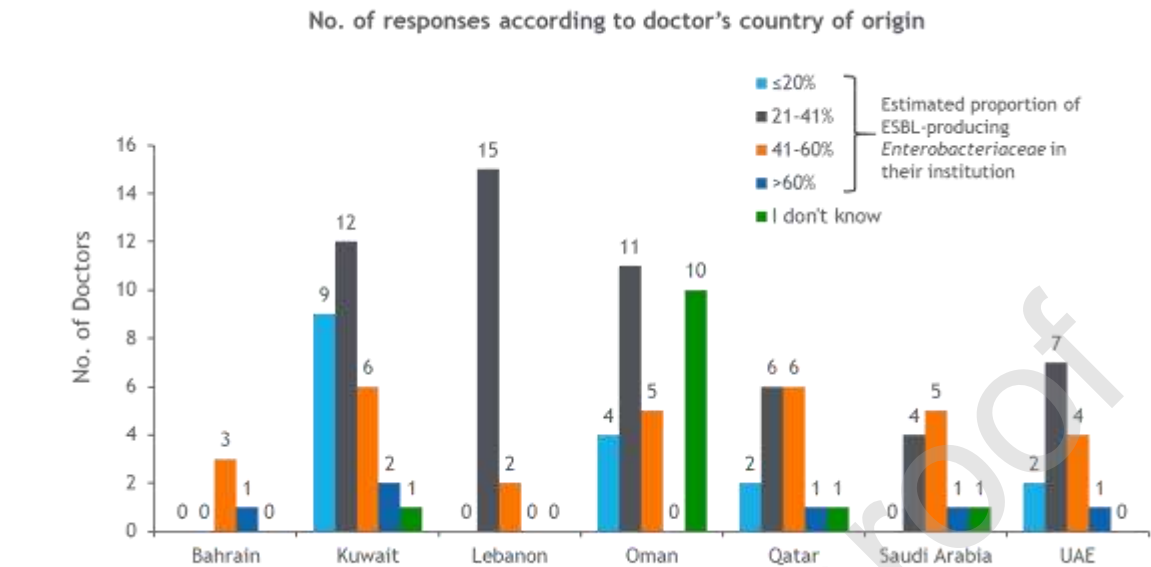
Table 2. Five key areas providing solutions for the challenges of antimicrobial stewardship in Arab countries of the Middle East and recommendations for future initiatives

AMR, antimicrobial resistance; ASP, antimicrobial stewardship program; EMRO, World Health Organization Regional Office for the Eastern Mediterranean; IT, information technology; GLASS, Global Antimicrobial Resistance Surveillance System; WHO, World Health Organization. MDRO: multi drug resistant organisms.

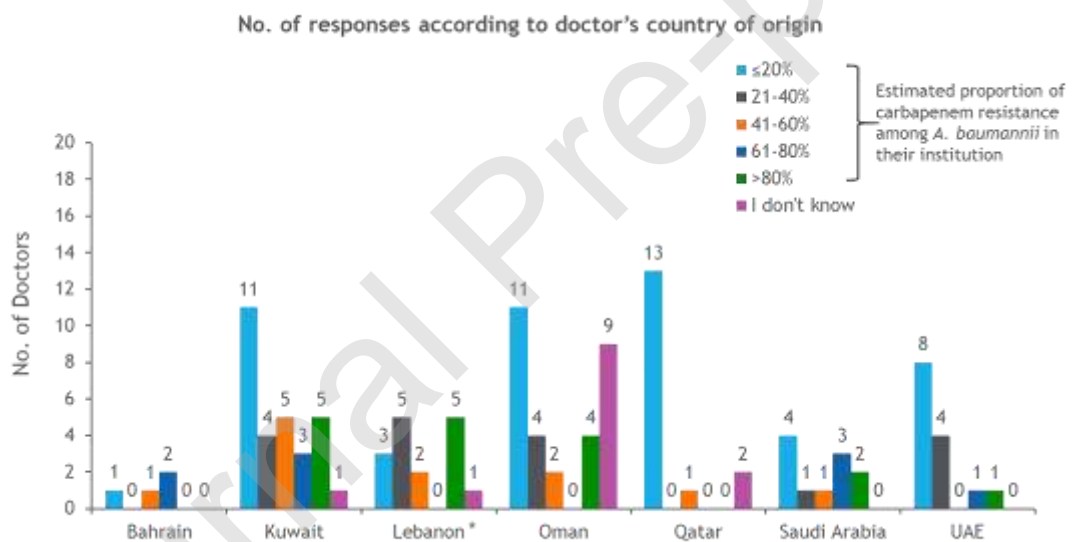
AMS structure	Bahrain	Kuwait	Lebanon	Oman	Qatar	Saudi Arabia	United Arab Emirates	Average across the region
Surveillance of antimicrobial consumption	100%	21%	87%	62%	100%	80%	64%	73%
Surveillance of antimicrobial resistance	100%	85%	93%	90%	100%	91%	100%	94%
AMS formal body	50%	41%	67%	78%	100%	91%	85%	73%
AMS team	100%	50%	87%	81%	100%	82%	93%	85%
AMS program	100%	28%	80%	85%	100%	89%	93%	82%
Local guidelines	75%	85%	53%	76%	100%	70%	86%	78%
Measurement of compliance with local guidelines	50%	32%	40%	31%	73%	40%	67%	48%
Pre-authorization for antibiotics	100%	52%	80%	55%	100%	82%	62%	76%
Indication for antibiotics in the notes	100%	52%	87%	48%	79%	64%	69%	71%
Auditing of antibiotic surgical prophylaxis	50%	55%	80%	67%	87%	80%	79%	71%
Education in AMS	100%	55%	87%	68%	100%	90%	79%	83%
Pre-prescription review of antibiotics	50%	35%	47%	41%	67%	55%	50%	49%
Post-prescription review of antibiotics	50%	46%	87%	66%	93%	73%	85%	71%
AMS incorporated in electronic health system	100%	22%	40%	42%	53%	50%	54%	52%
Overall average per country	80%	47%	72%	64%	89%	74%	76%	

Table 3. Positive responses to the question “Which of the AMS structures are implemented in your institution?”

AMS, antimicrobial stewardship



A.



B.

Figure 1. (A) Responses to the question “What proportion of Enterobacteriaceae in your institution are ESBL producing?” (B) Responses to the question “What proportion of *Acinetobacter baumannii* in your institution are carbapenem-resistant?”

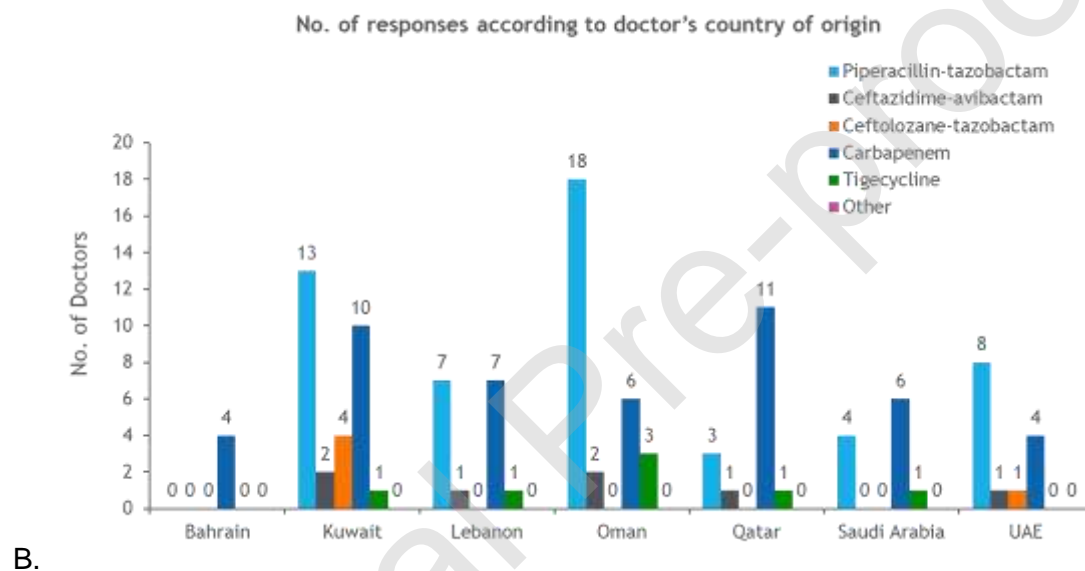
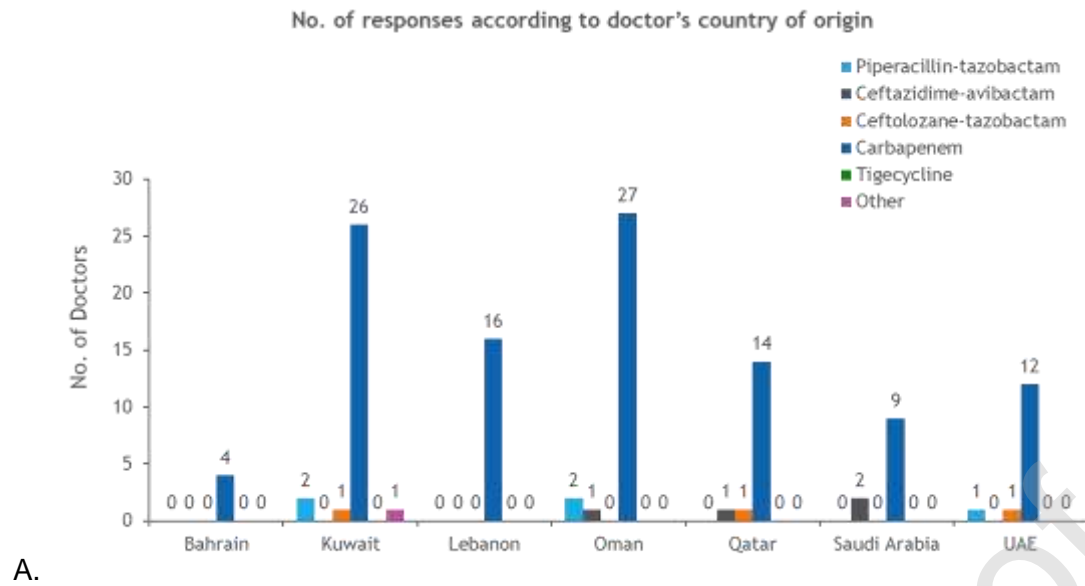


Figure 2. (A) Responses to the question “Which would be your preferred option for treatment of severe infections (sepsis, septic shock or immunocompromised) due to ESBL producers?” (B) Responses to the question “Which would be your preferred option for treatment of mild-to-moderate infections due to ESBL producers?”