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The strategic plan for combating antimicrobial resistance in Gulf Cooperation Council States

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KEYWORDS

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Summary The Gulf Cooperation Council Center for Infection Control (GCC-IC) has placed the emergence of antimicrobial resistance (AMR) on the top of its agenda for the past four years. The board members have developed the initial draft for the GCC strategic plan for combating AMR in 2014. The strategic plan stems from the WHO mandate to combat AMR at all levels. The need for engaging a large number of stakeholders has prompted the GCC-IC to engage a wider core of professionals in finalizing the plan. A multi-disciplinary group of more than 40 experts were then identified. And a workshop was conducted in Riyadh January 2015 and included, for the first time, representation of relevant ministries and agencies as well as international experts in the field. Participants worked over a period of two and a

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half days in different groups. International experts shared the global experiences and challenges in addressing human, food, animal, and environmental aspects of controlling AMR. Participants were then divided into 4 groups each to address the human, animal, microbiological and diagnostic, or the environmental aspect of AMR. At the end of the workshop, the strategic plan was revised and endorsed by all participants. The GCC-IC board members then approved it as the strategic plan for AMR. The document produced here is the first GCC strategic plan addressing AMR, which shall be adopted by GCC countries to develop country-based plans and related key performance indicators (KPIs). It is now the role of each country to identify the body that will be accountable for implementing the plan at the country level.

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Introduction

The ongoing emergence and spread of antimicrobial resistance (AMR) in bacteria is leading medicine to a post-antibiotic era [1,2]. Urinary-tract infections (UTI), for example, are increasingly caused by bacteria that are resistant to last-line antibiotics [3,4]. Gram-negative bacilli colistin resistance [5] and Pan-drug resistance are being reported more frequently [6,7]. In essence, antimicrobial resistance is not a new phenomenon [8]. Identification of penicillin-resistant bacterial strains has been documented as early as 1940 [9]. While the reliance on antimicrobial agents has led to the advancement of medicine that we see today, such as implantable devices through complex surgical procedures, organ and stem cell transplant, and cures for many advanced cancers that have led to the survival of significantly immunocompromised patients. These interventions would not have been possible without the existence of antimicrobial agents [10]. On the other hand, the misuse of these agents through the lack of hospital and community-based stewardship programs, poor compliance with infection control policies, limited incentives for developing new agents, lack of global surveillance, and limited availability of affordable rapid diagnostics for AMR, have all played a significant role in enhancing the emergence and widespread distribution of AMR [11]. This is a true threat to modern medicine as we know it today.

To mitigate this threat, the WHO launched the Global Action Plan on Antimicrobial Resistance with the "One Health" approach [12]. Despite this not being the first attempt for a global action plan, the "One Health" approach is in desperate need of recognition and global acknowledgment. The plan consists of five pillars: to improve awareness of AMR, to increase knowledge through surveillance, to reduce the incidence of infection, to optimize

the use of antimicrobial agents, and to develop the economic case for sustainable investment in all countries with regards to new and affordable medicines, diagnostic tools, vaccines, and other interventions [12]. As a response to this action plan different countries, including the United Kingdom [13], Australia [14], Canada [15], and the United States [16], initiated their own national AMR action plans. The most notable similarity between them is the willingness of the countries to tackle AMR in human and animal health as well as in food, agriculture, and the environment sectors. Here, we describe the GCC initiative to join the global community in addressing AMR.

The increasing threat of AMR in the GCC States

Countries of the Gulf Cooperation Council (GCC) are a political and economic union. Constituent countries include: The Kingdom of Saudi Arabia, Sultanate Oman, United Arab Emirates (UAE), Kuwait, Qatar, and the Kingdom of Bahrain. Several factors have been linked to the emergence and spread of AMR in this region [17,18]. Heavy international travel due to the large population of expatriate workers, booming tourism in several of the countries, and the hosting of over 4 million pilgrims throughout the year to the holy cities of Mecca and Madinah in the Kingdom of Saudi Arabia [19–22]; where travel is a known risk factor for acquiring and transmitting antibiotic resistant bacteria [22,23]. And similar to other countries worldwide, the GCC countries face challenges with adherence of healthcare providers to infection control practices. The lack of primary healthcare systems and legislation on the prudent and responsible use of antimicrobials is a shared concern. Most hospitals have no established

stewardship programs and community pharmacies frequently dispense antimicrobial agents with no prescription [17]. Furthermore, the use of antibiotics is prevalent and without supervision in the treatment of animals, and in some of the countries there is growing evidence that antibiotics are used as growth promoters [24,25]. As a result, a significant AMR burden has been described in the GCC region [26,27]; including: Extended Spectrum Beta-Lactamase (ESBL) producing bacteria [20,28], Carbapenemase-producing bacteria [29], Pan-drug-resistant Gram-negative bacilli (GNB) [6], as well as multidrug-resistant tuberculosis [27]. Between 60 and 90% of *Klebsiella pneumoniae* isolates are ESBL producers [18], which is associated with up to 40% mortality [30]. Additionally, 60–90% of *Acinetobacter* causing ventilator-associated pneumonia were shown to be resistant to most tested antimicrobials, including carbapenems, with significant negative clinical impact [29,31]. Multidrug resistant organisms were implicated in 20% of mortality caused by bloodstream infections in pediatric hematology/oncology patients [32].

More recent region-wide surveillance studies reported more alarming results. The majority of Carbapenem Resistant Enterobacteriaceae (CRE) from the GCC have been found to possess *bla*_{OXA-48-type}, and *bla*_{NDM-1} carbapenemase [33]. Multi-drug Carbapenem-resistant *K. pneumoniae* infection from the GCC countries were found to produce OXA-48 and were associated with hospital outbreaks and hospitalization mortality [30,34]. Additionally, several reports from GCC countries showed that Carbapenem resistant *Acinetobacter baumannii* (CRAB) is producing OXA-23-type Carbapenemase [35–39]. Large clusters of CRAB have been found to be identical not only to other isolates within hospitals but also to isolates found in hospitals located across borders [36]. This might explain why the majority of CRAB is found to be associated with healthcare exposures [36], and the increasing incidence of CRAB-related outbreaks in the region [20,40]. Another recent study found that the digestive tracts of 6% of ICU patients were colonized with OXA-23-producing CRAB [35].

The identification of novel and rare resistance mechanisms in patients from the GCC countries demonstrates that the region might harbor other antibiotic resistance mechanisms in addition to what is commonly known or what has been published. PME-1 *Pseudomonas aeruginosa*, isolated from Qatar, belongs to the 'high-risk' clone ST654 [41], a clone that is known to cause infections in many different parts of the world [42–44]. Additionally, the identification of the Pan-drug-resistant *K. pneumoniae*, which belongs to the

internationally disseminated ST147 and has a history of causing outbreaks [45–52], is a very significant finding. The recently published literature is an eye opener to the potential catastrophic future of AMR in the region, which requires attention.

The AMR issue in GCC countries is not only restricted to GNB. In a recent study from Riyadh, *Staphylococcus aureus* was found in 40% of the nasal cavities of 200 tested healthcare workers and that 45% were methicillin-resistant *S. aureus* (MRSA), making the total prevalence of MRSA carriage in the study 18% [53]. Another study analyzed the antibiotic susceptibility profiles for a range of *Streptococcus pneumoniae*, and found that the rate of penicillin resistance was 72% [54]. On the other hand, a national survey on Anti-tuberculosis drug resistance found that only 1.6% of all TB strains demonstrated MDR phenotype [55].

The leading role of the GCC-center for infection control to combat AMR in the region

The cooperative nature among the GCC countries has expanded to cover health-related aspects, as demonstrated by the establishment of the Executive Board of Health Ministers' Council for GCC States in 1991 and the GCC center for Infection Control (GCC-IC) in 2005. The GCC-IC was established to assist the member countries in creating and executing a shared vision toward internationally recognized infection prevention and control programs in the region [56–59]. During the early establishment of the GCC-IC, expertise and knowledge to develop the aims and goals for the center were shared. It was clear that building human capacity in the field of infection control and developing a standardized method of practice were two major priorities. The center developed a unified infection control manual as a reference for the countries on best practices in infection control [57]. The manual based its policies on the established international guidelines of the WHO, CDC and major healthcare societies such as the Society for Healthcare Epidemiology of America (SHEA) and the Association for Professionals in Infection Control and Epidemiology (APIC). The GCC infection control manual is now in its second edition [57]. A second publication was produced on surveillance for healthcare associated infection (HAI), also in an effort to unify surveillance methodology with the long term goal of developing a regional bench mark for HAIs [58,59]. The GCC-IC has led and participated in many educational activities in the region

geared toward infection control workshops, surveillance training programs, hand hygiene monitoring education workshops, and many other programs, including a biannual GCC-IC symposium, hosted by a GCC member country.

The process of developing the GCC AMR strategic plan

AMR rose to the top of the GCC-IC board meeting agenda in 2013. During the first months of discussing AMR, the countries shared their experience and conducted a situational analysis that discussed in detail the gaps identified and the efforts needed to combat AMR. The involvement of multiple stakeholders and the fact that they report to ministries or agencies other than the Ministry of Health was a clear initial challenge that needed to be addressed. The members conducted a detailed literature review on AMR and developed the initial draft for the GCC AMR strategic plan in 2014. The next step was to engage, through a workshop, all necessary stakeholders for input and to finalize the strategic plan for the countries to adopt. In January 2015, the GCC-IC arranged for the workshop and finalized the AMR strategic plan described here. Participants of the workshop included representatives from Ministry of Health, Ministry of Agriculture, Infectious Disease Societies, Academic and Research Centers, and Food and Drug Authority and were from all GCC countries. In April 2015, the center managed to finalize the GCC AMR strategic plan representing the collective expert views of the stakeholders; which complements the global action plan issued by the WHO in 2001 and again in 2015 [12]. It is very important to emphasize that this GCC strategic plan for combating AMR does not replace the need for developing tailored national strategic plans.

This endeavor is following the lead of the European Union (EU), whose AMR initiative is a remarkable example [60]. By sharing statistics, unifying surveillance methods, and transparency in revealing the strength and limitations of their data; the EU plays a leading role in policy development and experience sharing for the sake of reducing the impact of AMR in their countries, as well as others. A second example of addressing AMR in a challenging environment was by India in announcing the Chennai declaration [61]. The declaration resulted after the first meeting of most medical societies in India and representatives from local and international medical and health authorities. The meeting discussed the need to tackle AMR and set a plan to draw a road map addressing the AMR challenge from the Indian perspective [61]. The following section

is summarizing the recommendations addressed in the GCC strategic plan for combating AMR.

The GCC strategic plan for combating AMR

Five strategic aims are identified as the pillars of the GCC AMR strategic plan: first, countries must develop an understanding of the magnitude of AMR in the GCC countries among humans and animals, as well as in agriculture and the environment. Second, countries must restrict the use of the available and limited effective agents to preserve their efficiency. Third, countries should develop early identification capacity for emerging MDR microorganisms. Fourth, countries should limit the spread of resistant pathogens through patients, animals, and agriculture. Finally, countries must encourage collaborative research activities regarding AMR in humans, animals, and the environment.

There are clear and significant challenges in addressing this plan in different countries. The initial challenge is soliciting support from leadership. Heads of state need to be able to empower and hold responsible ministries/agencies accountable for adopting the plan. Another challenge is, agreeing on the appropriate key performance indicators (KPIs). Further, is to provide the logistical support for the execution and maintenance of any initiative in any and all involved sectors.

In summary, the GCC AMR strategic plan addressed herein aims to draw a road map for the implementation of a tailored national action plan in every GCC country. The action plan is particularly important for improving adherence to stringent infection control measures, applying regulations controlling antibiotic use in both human and animal sectors, implementing proactive surveillance of resistance, and enhance awareness and education about AMR among healthcare workers, public, veterinarians, and the food sectors.

Elements of the strategic plan

- I. Develop an understanding of the magnitude of AMR in the GCC countries among humans and animals as well as in agriculture and the environment
 - Laboratory (human):
 - Measurable elements:*
 - a. Ensure access to microbiology laboratory services that match the level of those provided by hospitals (e.g., secondary, tertiary).

- b. Ensure performance and quality assurance of appropriate diagnostic tests, microbial identification, antimicrobial susceptibility tests of key pathogens, and the timely and relevant reporting of results.
 - c. Ensure that laboratory data are recorded, preferably in an electronic database, and are used to produce clinically and epidemiologically useful surveillance reports of resistance patterns among common pathogens and infections in a timely manner with feedback to prescribers and to the infection control program.
 - d. Adopt an international system of antimicrobial breakpoints interpretation (in microbiology laboratories in the GCC).
 - Infection prevention and control (human)
 - Measurable elements:*
 - a. Characterize the rates of MRSA, vancomycin resistant *Enterococci* (VRE), *Clostridium difficile*, and CRE using data from GCC hospitals.
 - b. Characterize and quantify MDR related hospital-acquired infections (HAIs) using available data on healthcare associated infections routinely collected from GCC hospitals.
 - Laboratory (animals)
 - Measurable elements:*
 - a. Generate baseline and periodic point prevalence studies on antimicrobial use in animals based on the World Organization for Animal Health (OIE) standards and using data from the Ministry of Agriculture (MoA) [62]. In addition to the generation of data, this will ensure compliance with the WHO list of Critically Important Antimicrobials (CIA) for Human Health as described by the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) [63].
 - b. Generate baseline and periodic point prevalence data on the presence of antimicrobial residue in food of animal origin with necessary collaboration between the Ministry of Health (MOH), and Drug Authorities.
- II. Preserve the available and limited effective agents for human use
- Legislation
 - Measurable elements:*
 - a. Link the dispensing of all antimicrobial agents to a prescription and unique prescriber/pharmacist identifiers.
 - b. Identify a restricted list of antibiotics that will not be available in community pharmacies.
 - c. Monitor the trend of the amount of antimicrobial use through a defined daily does/days of therapy (DDD/DOT) [64].
 - d. Develop standards for selecting and using generic antimicrobial agents that meet international standards of quality, safety, and efficacy when granting marketing authorization.
 - e. Restrict the use of the CIA in animals [62,63].
 - f. Require obligatory prescriptions by licensed veterinarians for all antimicrobials used for disease control in food animals.
 - g. Terminate or rapidly phase out the use of antimicrobials for growth promotions.
 - h. Create national systems to monitor antimicrobial usage in food animals according to the World Organization for Animal Health (OIE) standards [65].
 - i. Introduce legal requirements for manufacturers to collect and report data on antimicrobial distribution (including import/export).
 - j. Create economic incentives for the appropriate use of antimicrobials.
 - k. Introduce requirements for pharmaceutical companies to comply with national or international codes of practice on promotional activities.
 - l. Ensure that national or international codes of practice cover direct-to-consumer advertising, including advertising on the Internet.
 - m. Develop and legislate adult and pediatric vaccine programs including, but not limited to, influenza, pneumococcal, and conjugate meningococcal vaccines.
- Prescriber
 - Measurable elements:*
 - a. Educate all groups of antimicrobial prescribers and dispensers on:
 - The importance of appropriate antimicrobial use and containment of antimicrobial resistance.
 - Disease prevention, specifically, immunization programs and infection control.
 - Factors that may strongly influence their prescribing habits, such as economic incentives, promotional activities and inducements by the pharmaceutical industry.
 - Educating patients on antimicrobial use and the importance of adherence to prescribed treatments.

- b. Encourage the development and use of Antimicrobial guidelines and treatment algorithms to foster the appropriate use of antimicrobials.
 - c. Improve antimicrobial use by the supervision and support of clinical practices, especially diagnostic and treatment strategies.
 - d. Audit prescribing and dispensing practices and utilize peer group or external standard comparisons to provide feedback and endorsements of appropriate antimicrobial prescribing.
 - e. Promote targeted undergraduate and post-graduate educational programs on the accurate diagnosis and management of common infections for all health care providers and veterinarians.
 - f. Establish an Essential Drugs List (EDL) consistent with national and WHO STGs and ensure the accessibility and quality of these drugs [66].
- Patient
- Measurable elements:*
- a. Educate patients and the general community on the appropriate use of antimicrobials.
 - b. Educate patients on the importance of measures to prevent infection, such as immunization, hygiene, and cough etiquette.
 - c. Educate patients on suitable alternatives to antimicrobials for the relief of symptoms, and discourage patient self-initiation of treatment, except in specific circumstances.
 - d. Educate patients on simple measures that may reduce transmission of infection in the household and community, such as hand washing, food hygiene, and so on.
 - e. Encourage appropriate and informed health care seeking behavior.
 - f. Educate students in primary, elementary, and high schools about personal hygiene and how to prevent the spread of infections.
- III. Develop the ability for the early identification of emerging MDR microorganisms
- Improve access to and the use of surveillance data in human, animal, food, and environment sectors through new arrangements that facilitate greater consistency and standardization of the data collected across the system and encourage improved data linkage
- Measurable elements:*
- a. Adopt a unified method to conduct systematic surveillance on MDR organisms from the clinical laboratories through available WHO tools and make the data publicly available for the policy makers and the public
 - b. Adopt a unified method to identify the burden of MDR organisms on HAIs starting by major HAIs such as central line-associated bloodstream infection (CLABSI), ventilator-associated pneumonia (VAP), and surgical site infections (SSIs); and make the data publicly available to policy makers and the public [58].
 - c. Designate or develop reference microbiology laboratory facilities to coordinate effective epidemiologically sound surveillance of antimicrobial resistance among common pathogens in the community, hospitals, and other health care facilities.
 - d. Adopt World Organization for Animal Health (OIE) standards for surveillance in the animal sector [65].
- Make the responsible body accountable to the prompt action on these data
- Measurable elements:*
- a. Identify infection prevention and control (IPC) programs in the hospital as separate departments reporting to the highest authority.
 - b. Make IPC accountable for leading such activities outlined in (a) and (b) of the previous point.
- IV. Limit the spread of resistant pathogens through patients, animals, and agriculture
- Humans
- Measurable elements:*
- a. Monitor and improve infection prevention and control practices in healthcare facilities.
 - b. Establish an inter hospital transfer system that ensures the identification of patients with MDR organisms between hospitals in one country and the transfer of patients between hospitals to and from different GCC countries to encourage proper isolation precautions.
 - c. Improve the healthcare systems within the GCC countries to ensure minimum infection control requirements while contracting new facilities or renovating old ones.
- Animals:
- Measurable elements:*
- a. Monitor and improve infection prevention and control practices in animal health, both through the enhanced dissemination and implementation of best practices and the better use of data, diagnostics, and vaccines.
 - b. Enhance the availability of veterinarians to prioritize the diagnosis of disease in

livestock, poultry, and companion animals and to encourage the early use of appropriate diagnostic testing, in particular, bacterial culture and sensitivity testing.

- c. Make available the use of vaccines in husbandry.
 - d. Encourage livestock farmers to adhere to government guidance regarding bio-security, animal husbandry and for farm health planning for each of the major farming sectors and to take proactive measures to reduce the risk of disease occurring in their animals under experienced veterinarian supervision.
 - e. Consider the use of 'farm assurance schemes' as a mechanism to increase adherence to best husbandry including the isolation of sick animals, testing new stock, and the responsible use of antibiotic by veterinarians only while ensuring animal health and welfare.
 - f. Encouraging retailers to review their standards for meat and animal products and to set clear specifications concerning bio-security, antimicrobial stewardship and good husbandry throughout the supply chain for overseas as well as national meat and animal products, working with suppliers and veterinarians to ensure compliance, all in accordance with the World Trade Organization (WTO) guidelines that are set by World Organization for Animal Health (OIE), the Food and Agriculture Organization (FAO), the Codex, and the Intergovernmental Panel on Climate Change (IPPC) [67–70].
 - g. Implement standard screening protocols for animal trading.
- V. Encourage collaborative research activities regarding AMR in humans, animals and the environment
- Measurable elements:*
- a. Identify and provide financial support for research projects in the AMR field as a national priority.
 - b. Make academic centers and funding agencies within the GCC countries aware of this priority.
 - c. Include all relevant sectors, such as health-care, food and drug regulatory agencies, veterinarian care, and agriculture and environmental agencies.
 - d. Conduct research that measures the effectiveness of interventions such as drug restriction, guidelines, campaigns, and other strategies.

Moving forward

Significant progress on this issue has been accomplished through the past few years. Networking has taken place to identify key players. They have acknowledged the importance of AMR and the immediate need for a national/regional strategic action plan. The plan is now at the stage of full adaptation at the highest national level and for countries to identify an accountable body to oversee its implementation. This will take time to establish, allocate resources, and identify KPIs as well as to train the involved personal. In order to sustain this momentum, the GCC-IC will conduct an annual AMR workshop to address the success and share experiences on the progress and challenges of implementation. Further, countries will be given a platform to announce and raise awareness on this issue through the *Journal of Infection and Public Health (JIPH)*. In the upcoming issues of this journal country specific achievements will be published.

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