Leading Article

Antimicrobial resistance in Saudi Arabia

An urgent call for an immediate action

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ABSTRACT

تَزايد تسليط الضوء على الميكروبات المقاومة للمضادات كقضية مُلحة لصحة الحيوان ولصحة البشر في جميع أنحاء العالم. يتجلى هذا الموضوع بشكل واضح في البكتيريا التي تقاوم المضادات الحيوية عند استخدامها كخيار أخير. مما ينبيء بعدوى غير قابلة للعلاج في المستقبل. أقترحت الوكالات الدولية استراتيجيات لمكافحة الميكروبات المقاومة للمضادات. هناك العديد من التحديات في المملكة العربية السعودية التي يمكن أن تحفز ظهور وانتشار البكتيريا المقاومة للأدوية المتعددة. لمواجهة هذه التحديات لابد من بذل مجهود من قطاعات متعددة للسيطرة بنجاح على انتشار وظهور الميكروبات المقاومة للمضادات. لابد أن تتضمن الإجراءات المراقبة الفعّالة لتتبع ظهور هذه الميكروبات وانتشارها. ولابد أيضاً من إعطاء الأولوية في تحسين احتياطات الوقاية من العدوى ومكافحتها للحد من انتشارها. من الضروري رفع مستوى الوعي للحد من استخدام المضادات الحيوية غير المناسبة، وينبغي على برامج إدارة المضادات الحيوية في المستشفيات، والعيادات الخارجية، والصيدليات تنظيم الاستخدام المستمر للمضادات الحيوية.

Antimicrobial resistance (AMR) is increasingly being highlighted as an urgent public and animal health issue worldwide. This issue is well demonstrated in bacteria that are resistant to last-line antibiotics, suggesting a future with untreatable infections. International agencies have suggested combating strategies against AMR. Saudi Arabia has several challenges that can stimulate the emergence and spread of multidrug-resistant bacteria. Tackling these challenges need efforts from multiple sectors to successfully control the spread and emergence of AMR in the country. Actions should include active surveillance to monitor the emergence and spread of AMR. Infection prevention and control precautions should also be optimized to limit further spread. Raising awareness is essential to limit inappropriate antibiotics use, and the antibiotic stewardship programs in hospital settings, outpatients, and community pharmacies, should regulate the ongoing use of antimicrobials.

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Antimicrobial resistance (AMR) in bacteria is emerging and spreading rapidly worldwide. This phenomenon is nowadays affecting public and animal health dramatically on a global level. The discovery of penicillin in the last century provided significant advancements in modern medicine, as well as our ability to treat commonly encountered infectious diseases, one of the biggest killers during the pre-antibiotics era. Many of life-saving interventions, such as cancer chemotherapy and major surgeries depend on effective antimicrobials to succeed.[1] Unfortunately however, the current dependence on antibiotics - whether to treat, prevent, or stimulate food animal growths - have exponentially increased this resistance. When antibiotics are used, selective pressure is created, and possibly forcing the exposed bacteria to mutate or acquire pieces of DNA to become antibiotic resistant.[2] The selection pressure resulting from the overwhelming use and misuse of antibiotics is exponentially supporting the AMR phenomenon.[3] Despite this known fact, approximately 10 million tons of antibiotics are globally used every 10 minutes, which mostly are not related to

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justified medical use.[4] As a result to the global march of AMR, common infections, such as urinary-tract infections are becoming difficult to treat. This is mainly due to bacteria that are resistant to last-line antibiotics,[2] or even pan-drug resistant that are not responding to any commercially available antibiotics.[5] The multidrug-resistant (MDR) pathogens are spreading rapidly in many parts of the world causing severe medical and economic consequences. It is estimated that at least every 10 minutes a patient dies in the USA or Europe because of fatal infections caused by antibiotic resistant bacteria.[6] This article gives a brief overview on the current situation of AMR in Saudi Arabia and the immediate actions needed to tackle this issue.

The emergence and spread of AMR bacteria in Saudi Arabia. ***Current and future challenges.*** A systematic literature review of MDR in Gram-negative bacilli (GNB) showed a substantial increase in the rate of carbapenem-resistant GNB in Saudi Arabia over the last decade in comparison with the rates of the 1990s. It also documented the increasing prevalence of extended spectrum beta-lactamase (ESBL) producing isolates from Saudi Arabia, where some institutes had 29% ESBL rates among *Escherichia coli* (*E. coli*) and 65% ESBL rates among *Klebsiella pneumoniae (K. pneumoniae)*. As a result, these increasing rates have been associated with many reported outbreaks and mortality that ranged between 11-40%.[7]

Recent region-wide surveillance studies reported that most of carbapenem resistant Enterobacteriaceae (CRE) from the Gulf Cooperation Council States (GCC) have been found to harbor the carbapenemase encoding genes $bla_{\text{OXA-48-type}}$, and $bla_{\text{NDM-1}}$.[8] Carbapenem resistant *Acinetobacter baumannii (A. baumannii)* (CRAB) from Saudi Arabia have also increased dramatically over the years. A recent study from Riyadh[9] showed that the susceptibilities of *A. baumannii* to meropenem and imipenem in 2006 ranged between 64-81.2%, while the susceptibility in 2012 ranged between 8.3-11%. Molecular investigation on different CRAB isolates obtained from all of the GCC states revealed that large number of isolates, from different states, have clustered together, suggesting clonality.[10]

The last-line resource antibiotic currently available to tackle many of carbapenem resistant GNB is colistin. However, colistin resistant and even pan-drug resistant GNB have already been reported. Colistin resistance is typically chromosomally mediated and generally not transmissible between bacteria. Nevertheless, the recent description of plasmid-mediated colistin resistance mechanism *mcr-1* has enormous implications on the lifespan of colistin.[11] Plasmid carrying *mcr-1* was found in many parts of the world among Enterobacteriaceae and non-fermentative GNB.[11] A recent report highlighted the presence of the *mcr-1* gene in 4 *E. coli* that were isolated between 2012-2015 from Saudi Arabia, Bahrain, and the United Arab Emirates.[12] It is likely though that *mcr-1* carrying GNB are widely disseminated in more isolates and between other species in the Arabian Peninsula.

Other studies from the GCC region[5,13] affirmed that the region harbours other rare and novel antibiotic resistance mechanisms. For example, PME-1 ESBL producing *Pseudomonas aeruginosa (P. aeruginosa)* from Qatar,[13] and the pandrug-resistant *K. pneumoniae* from neighboring UAE.[5] The latter report provides a very significant finding, as this breakthrough should raise the global attention to avoid the possible catastrophic future of AMR, which can be caused by such an untreatable pathogen.

A Saudi national surveillance on Gram-positive cocci demonstrated that 32% of *Staphylococcus aureus* (*S. aureus*) are methicillin-resistant (MRSA), and 33% of *Streptococcus pneumoniae* are resistant penicillin G and 26% are resistant to erythromycin.[14] A study from Riyadh[15] demonstrated that *S. aureus* was colonizing the nasal cavity of 40% of the 200 tested healthcare workers. Among those *S. aureus*, 45% were methicillin-resistant (MRSA), resulting in total prevalence of 18% health workers carrying MRSA. A national survey[16] on anti-tuberculosis drug resistance found that only 1.6% of total TB demonstrated MDR phenotype. These figures of high prevalence among different bacterial species in Saudi Arabia are unfortunately likely to be sustained, if not increased to due to several factors.

Local risk factors contributing to the emergence and spread of AMR. Several factors are associated to the increasing emergence and spread of MDR bacteria in Saudi Arabia. It is evident that the unoptimized use of antibiotics is a major factor for AMR development. A hospital in Riyadh has well demonstrated the overuse of antimicrobial agents from 4 adult ICUs in 2010, where the highest use was meropenem (33.2 defined daily doses [DDD] per 100 bed-days), followed by piperacillin-tazobactam (16.0 DDD/100 bed-days). On the other hand, the DDD/100 bed-days in 37 ICUs

in the United States was 3.75 for carbapenems and 7.08 for antipseudomonal penicillins.[7] Over-the-counter antibiotics without prescription in Saudi community pharmacies is another issue that is driving the improper use of antibiotics. Only one out of 88 pharmacists in Eastern province refused to sell antibiotics without a prescription, and 77.6% of the pharmacies in Riyadh dispensed antibiotics without a prescription.[7] To my knowledge these are no published evidences from Saudi Arabia demonstrating the use of antibiotics as a growth promoter. However, several reports, in fact, have described the isolation of various MDR GNB from food animal specimens.[7]

Heavy international travel activities are occurring due to the large population of expatriates and to pilgrimage the holy cities. Travel is a known risk factor for acquiring and transmitting infectious diseases, including those caused by antibiotic resistant bacteria. A recent study[17] showed that returned travellers from Hajj have acquired MDR *A. baumannii* and NDM producing *E. coli* during the Hajj event. Previous data from 2 major hospitals in Makkah showed that ceftazidime resistance is evident in 24.6% of *E. coli*, 34.4% of *K. pneumoniae*, and 52.7% of *P. aeruginosa*. Another report showed that septicemia episodes in Makkah are increased by 16.5% during Hajj time due to the influx of international patients.[7]

Another issue that can contribute to the spread of AMR is the challenges related to the adherence of infection control practices. The hand hygiene compliance rate in a hospital in Makkah in 2011 was 50.3%. The effectiveness of hand hygiene compliance was well demonstrated in controlling a nosocomial outbreak caused by carbapenem-resistant *K. pneumoniae* in Riyadh.[7] **Figure 1** illustrates the several factors that may contribute to the emergence and spread of AMR.

Immediate actions needed. To limit this alarming threat on human health, the World Health Organization launched the Global Action Plan on Antimicrobial Resistance.[18] This plan was signed off by most of member states, including Saudi Arabia during the

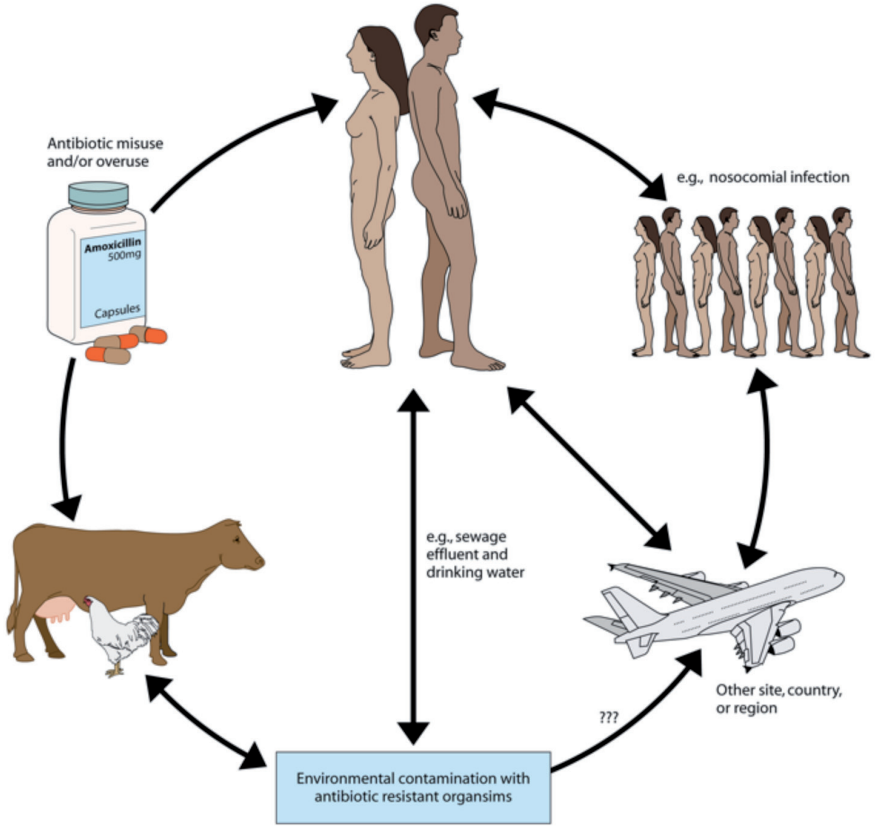

Figure 1 - Different factors can stimulate the emergence and spread of multidrug-resistant bacteria.

World Health Assembly in 2015. The plan consists of 5 pillars; to improve awareness, stringing knowledge through surveillance, reduce the incidence of infection, optimize the use of antimicrobial agents, and develop the economic case for sustainable investment to support the need in all countries in regards to new medicines, diagnostic tools, vaccines, and other interventions. To have tailored strategies, different countries initiated their own national AMR action plans, and the most notable similarity between all action plans is the willingness to tackle the antimicrobial misuse in both human and animal/agricultural sectors.

Raising public, medical, and veterinary awareness of AMR is an important element that is urgently needed to tackle AMR in Saudi Arabia. Previous research[7] has shown that antibiotics are widely used in the community, without prescription, to treat unrelated scenarios. Multilevel and nationwide awareness campaigns in Saudi Arabia are needed to align with the World Antibiotic Awareness Week. The success of these campaigns can be dependent on the tailored and relevant content and key messages that are designed after formative research. The increasing use of social media platforms in the country can also help to disseminate awareness messages. It is very essential however, to consider all segments and socioeconomic groups in the Saudi society, as some members might not speak the local language, or actively use social media platform.[19]

Infection prevention and control plays a very important role to limit the spread of AMR. Conducting educational programs for healthcare workers regarding the importance of hand hygiene compliance can limit the spread of outbreak stains within hospitals, and potentially to the community.[7] Hospitals might apply screening scheme for high-risk patients prior to admission to identify carriers of MDR pathogens and to apply isolation or contact precautions in order to limit spread.

Active ongoing surveillance on AMR is essential to aid the development of tailored treatment guidelines for empirical antibiotic therapy, particularly for community-acquired infections. Developing local surveillance of AMR bacteria that are related to nosocomial infections can also helps to track emerging resistance to antibiotics and to identify outbreaks.[7] Hence, microbiology laboratories should be well equipped to provide valid and reliable identification for pathogen, as well as antibiotic susceptibility tastings. As part of their routine services, microbiology laboratories should also be able to provide up-to-date antibiograms at a hospital level and contribute to local surveillance programs. With the widely accessible molecular-based techniques and

Table 1 - Recommendations for actions to stakeholders in the Saudi Arabia to combat antimicrobial resistance.

Recommendations
Antimicrobial stewardship programs
Active guidelines should be implemented to restrict unnecessary use of antibiotics in Saudi hospitals.
Abolition of over-the-counter sales of antimicrobials without prescriptions.
Regulations and strategies should be used to enforce the ban of antibiotics as growth-promoters in Saudi animal farms and restrict the use of important antimicrobials as listed by the World Health Organization - Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGSIR).
Initiating mass educational campaign about antibiotic use
To raise awareness about antibiotic resistance and limit the improper use of antibiotics.
Cultural differences should be considered when implementing educational campaigns to be delivered to the population of Saudi Arabia.
The highly utilized social media platforms should be used to disseminate messages, but not solely.
Basic infection control precautions (for example, hand hygiene)
Should be emphasized among healthcare workers.
Patients who have been hospitalized internationally need to be screened by the receiving institute for multidrug-resistant organisms.
Infection prevention policy defining at-risk patients and management strategies (for example, empirical treatment, and isolation) should be developed.
Microbiology laboratories
Microbiologists should be updated with local, national, regional and international surveillance to prepare screening and confirmatory testing for emerging resistance mechanisms.
Molecular and protein-based identification tools should also be considered to improve diagnosis and to reduce turn-around time.
Active surveillance
Developing local surveillance of antimicrobial resistant organisms in hospitals, regional and national levels to help suggesting empirical treatments and in outbreak tracking.
Molecular-based techniques and whole genome sequencing should be utilized to give greater insight about the antibiotic resistance mechanisms and clone disseminations.

whole genome sequencing, the use of these technologies on AMR can provide a richer insight on the clonal disseminations of certain species, and the genotypic characterization of antibiotic resistance mechanisms.[7] Surveillance in Saudi Arabia can help contribute to the global understanding of the burden of the AMR, which is still poorly quantified.[2] It was suggested that countries should introduce death register records "deaths caused by antimicrobial-resistant infection".[6]

Last but not least, active antibiotic stewardship guidelines should be implemented to restrict the irrational use of antibiotics in Saudi Arabia. These guidelines should aim to reduce over prescription and misprescription of antibiotics in outpatient settings, community pharmacies, hospital, and agricultural sectors. The WHO and Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGSIR) have published an updated list of antimicrobials according to their importance in human medicine.[20] This list can immediately be used to control the use of medically important antimicrobials from food animal and agricultural settings in Saudi Arabia. **Table 1** summarizes actions needed to tackle AMR in Saudi Arabia.

In conclusion, AMR is a global issue that requires tremendous attention. International agencies have suggested recommendations and plans to combat AMR. It is now up to countries to take the lead and implement local actions plans to limit AMR. Saudi Arabia faces several challenges that can stimulate the emergence and spread of MDR bacteria. These challenges require cultivated efforts from different sectors to successfully achieve a significant control of AMR in the country. Actions should include active surveillance of AMR on hospital-based, regional, and nationwide levels. Infection prevention and control precautions should also be optimized to limit the spread. Raising awareness of AMR is an essential mandate to limit inappropriate use of antibiotics, and the use of antimicrobial should be maintained by antibiotic stewardship programs not only in hospital settings, but also in outpatients and community pharmacies.

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