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Antimicrobial resistance in the Eastern Mediterranean Region

Executive summary

1. Antimicrobial resistance has emerged as a major public health problem that threatens the advances of modern medicine. Misuse and overuse of antimicrobial medicines, lack of awareness of the magnitude of antimicrobial resistance, absence of robust antimicrobial resistance surveillance systems, and inadequate infection prevention and control programmes are among the main factors contributing to the growth of antimicrobial resistance globally.

2. WHO has led the development of the Global Action Plan on Antimicrobial Resistance, which serves as a blueprint for the response to the threat, and has urged Member States to develop and implement national action plans for antimicrobial resistance based on their local context. At the Sixty-eighth World Health Assembly in May 2015, Member States endorsed resolution WHA 68.7 on a global action plan on antimicrobial resistance, and in 2016, all Heads of State endorsed the political declaration of the high-level meeting of the General Assembly on antimicrobial resistance. However, despite these commitments, significant work is still needed at the country level to respond to antimicrobial resistance.

3. This technical paper describes the current status of the response to antimicrobial resistance in the WHO Eastern Mediterranean Region and outlines the high-impact interventions needed for a comprehensive response at the national level. The highest levels of political support are needed for antimicrobial resistance prevention and control at the country level.

Introduction

4. Antimicrobial resistance, the development of resistance to antimicrobials in microorganisms (bacteria, viruses, fungi and parasites), has emerged as a major public health problem that threatens the advances of modern medicine. The factors responsible for the emergence of antimicrobial resistance include the misuse and overuse of antimicrobials in the human health sector, as well as in the food production and animal sectors, and a lack of adequate infection prevention and control programmes to reduce the incidence of infections and the transmission of resistant pathogens. Low levels of awareness and understanding of antimicrobial resistance, and a lack of robust antimicrobial resistance surveillance systems to accurately measure the burden of resistance, hamper the capacity of countries to control the spread of antimicrobial resistance.

5. Antimicrobial resistance has a serious health and economic impact on populations and countries. A continued rise in resistance by 2050, as suggested by estimates, would lead to 10 million people dying every year and a reduction of 2% to 3.5% in gross domestic product. It is estimated that the cost of antimicrobial resistance could reach up to US$ 100 trillion globally if the growth of antimicrobial resistance is not slowed down today *(1,2)*.

6. Antimicrobial drugs are commonly used to increase food production. An analysis by the Organisation for Economic Co-operation and Development (OECD) has projected that between 2010 and 2030 antimicrobial consumption in food animal production will climb by 67%, two thirds of this increase coming from an increase in food animals and one third resulting from the switch to more intensive animal production systems *(3)*.

7. Antimicrobial resistance has been on WHO's watch list since the 1990s. Multiple World Health Assembly resolutions, World Antibiotic Awareness Week campaigns, high-level ministerial meetings and conferences have created the momentum for addressing antimicrobial resistance, providing an opportunity for a comprehensive global response to the problem.

8. The earliest resolution on antimicrobial resistance (resolution WHA51.17 in 1998) requested Member States to "encourage the development of sustainable systems to detect antimicrobial-resistant pathogens, thereby increasing the awareness of antimicrobial resistance, and to monitor volumes and patterns of use of antimicrobial agents and the impact of control measures". Since then, WHO has adopted resolutions on different areas of antimicrobial resistance. The six-policy package published during World Health Day 2011 re-energized a focused approach to antimicrobial resistance, and the growing global consensus on the importance of the growing antimicrobial resistance threat resulted in the development of the Global Action Plan on Antimicrobial Resistance, through broad multisectoral and Member State consultation, which was endorsed in May 2015 (in resolution WHA 68.7).

9. In light of the grave global challenges that antimicrobial resistance poses to health, food security, and development, in September 2016, for the first time, at the United Nations General Assembly, Heads of States committed to taking a broad, coordinated approach to address the root causes of antimicrobial resistance across multiple sectors, especially human health, animal health and agriculture, and curbing the spread of infections resistant to antimicrobial medicines *(4)*.

10. Antimicrobial resistance is relevant to many of the Sustainable Development Goals (SDGs), and if not addressed will endanger their achievement. Good health and well-being (SDG 3) is threatened by antimicrobial resistance that impedes control of communicable diseases, efforts to improve maternal and child health, control of sexually transmitted infections, tuberculosis, malaria and HIV, and the safety and effectiveness of life-saving procedures, such as surgical interventions, cancer treatment and organ transplants *(5)*. The high cost of treating infections due to antimicrobial resistance also slows down progress towards eradicating poverty (SDG 1), and by adding an extra burden to states' health expenditure, leading to losses in gross domestic product, undermines efforts for sustainable economic growth (SDG 8). The increased consumption of antimicrobials as growth promoters, in response to the increasing demand for food, has to be addressed if we are to end hunger (SDG 2), while increasing and sustaining access to water, sanitation and hygiene for vulnerable groups is critical for achieving clean water and sanitation (SDG 6), and thereby ensuring good health and well-being (SDG 3) *(6)*. As antibiotics are a scarce and potentially non-renewable global resource, ensuring sustainable consumption and production patterns (SDG 12) for antibiotics requires a multipronged approach that ensures access to effective antibiotics, reduces the need for antibiotics while ensuring their appropriate use, and promote the development of new antimicrobials and diagnostics. In the context of antimicrobial resistance, governments and their international cooperation constitute the primary global partnership for sustainable development (SDG 17).

11. Despite the global high-level political commitments made by all relevant sectors, including One Health partners, antimicrobial resistance has not gained the attention it requires. Several WHO surveys have shown that the infrastructure and human resources for containment of antimicrobial resistance are inadequate in the countries of the Eastern Mediterranean Region *(7)*.

12. At its 49th session in 2002, the Regional Committee for the Eastern Mediterranean adopted resolution EM/RC49/R.10 on antimicrobial resistance and rational use of antimicrobial agents. The resolution urged Member States to "establish a national intersectoral task force, under leadership of the Ministry of Health, for antimicrobial resistance containment". The growing problem of antimicrobial resistance, and the need for a surveillance system and to ensure the rational use of antimicrobials, were also highlighted in resolution EM/RC60/R.1 in 2013. However, no concrete interventions have been documented since then, mainly due to a lack of infrastructure, inadequate local evidence on the magnitude of the problem, and a lack of awareness and understanding at all levels.

13. At its Sixty-eighth session in May 2015, the World Health Assembly endorsed in resolution WHA68.7 a global action plan to tackle antimicrobial resistance, including antibiotic resistance, the most urgent drug resistance trend. The goal of the global action plan is to ensure, for as long as possible, the successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them. Resolution WHA68.7 urged Member States to "have in place, by the Seventieth World Health Assembly, national action plans on antimicrobial resistance that are aligned with the global action plan on antimicrobial resistance and with standards and guidelines established by relevant intergovernmental bodies".

14. Antimicrobial resistance has now reached a very high threat level to health security, both globally and regionally. It is of the utmost importance that countries fully commit to combatting antimicrobial resistance to prevent its spread and damaging impact on human health. This technical paper outlines the immediate actions that require political endorsement at the highest level by Member States, with special attention to the initiation of a multisectoral response to antimicrobial resistance by the countries of the Region.

Situation in the Eastern Mediterranean Region

15. The situation of antimicrobial resistance in the countries of the Eastern Mediterranean Region is very concerning. Surveillance data on antimicrobial resistance at the national level are often lacking, due to the absence of national surveillance systems for antimicrobial resistance in most countries; however, published data indicate the problem is of significant threat to public health in the Region. Multiple publications exist in the peer-reviewed literature, often from large academic centres in the Region, and show high rates of resistance in bacteria that cause common health-care associated and community-acquired infections (such as urinary tract infections and pneumonia), as summarized in the first global report on antimicrobial resistance surveillance *(8)*. The report specifically indicated up to 54% resistance among *Escherichia coli* and *Klebsiella pneumoniae* to third generation cephalosporin antibiotics, and highlighted significant gaps in surveillance and a lack of standard methodology, data sharing and coordination. Table 1 summarizes selected reports that indicate the severity and spread of antimicrobial resistance in the Region.

16. A global survey to map progress in implementation of the Global Action Plan on Antimicrobial Resistance (*20)* was conducted in 2016/2017, with 14 countries from the Eastern Mediterranean Region responding to the survey questionnaire. The observations made by WHO during technical missions and the survey results provided by national antimicrobial resistance focal points were used in preparing this technical paper.

Table 1. Summary of selected publications on types and rates of resistance in the Eastern Mediterranean Region

Country	Year	Rate of resistance	Type of resistance
Pakistan *(9)*	2016	63%	*K. pneumoniae* resistance to third generation cephalosporin antibiotics
Iraq *(11)*	2015	(73.2%)	Methicillin-resistant *Staphylococcus aureus* (MRSA) in chronic sinusitis patients
Morocco *(12)*	2015	11.9%	Extended spectrum beta-lactamases (ESBL) *E.coli* in hospitalized patients
Somalia *(13)*	1976	92.9%	*Shigella* strains resistant to sulphonamides
Palestine *(14)*	2011	65%	*E.coli* resistance to ampicillin
Afghanistan *(15)*	2014	(51.9%)	Multidrug resistant (MDR) gram negative bacteria from blood cultures (resistance to ampicillin, gentamicin, third generation cephalosporin antibiotics, fluoroquinolone antibiotics and co-trimoxazole)
Saudi Arabia, Bahrain and United Arab Emirates *(16)*	2012–2015	4 *E.coli*: two from Bahrain, one from Saudi Arabia and one from United Arab Emirates	*E.coli* resistance to colistin
Egypt *(17)*	2016	92.8%	MDR *Acinetobacter spp.*
Jordan/Syrian Arab Republic *(18)*	2017	66%	MDR gram negative bacteria isolated from war-injured refugees from Syrian Arab Republic
Yemen *(19)*	2011	35.4%	ESBL producers

Antimicrobial resistance governance and national action plans on antimicrobial resistance

17. The fight against antimicrobial resistance should be steered by a multisectoral high-level political mechanism with decision-making authority to oversee the development and implementation of a national action plan on antimicrobial resistance and to allocate critical domestic resources to ensure the sustainability of interventions. The human health, food and agriculture, animal health, environment and economic sectors are the primary internal stakeholders. Eleven countries in the Region have reported that a multisectoral working group or coordination committee on antimicrobial resistance is in place that includes representatives of the human health, animal health, environment and other sectors, with government leadership.

18. In 9 countries, a national antimicrobial resistance action plan has been drafted that addresses human and animal health. Information on how many of these are officially endorsed, and how these plans will be implemented, is not available.

19. The awareness and understanding of antibiotics and their proper use is very limited. A number of studies from the Region indicate extensive misuse and overuse of antibiotics *(21,22,23)*. A WHO-commissioned survey, carried out in September/October 2015 among some 10 000 members of the public in 12 countries *(24)*, including Egypt and Sudan from the Eastern Mediterranean Region, highlighted widespread antibiotic use: 54% of respondents in Egypt reported antibiotics use in the past month and more than three quarters of respondents in Egypt and Sudan had taken them in the past six months; 73% of respondents in Egypt and 80% in Sudan believed that viral infections such as colds and influenza can be treated with antibiotics; 34% of respondents in Egypt and 27% in Sudan considered it acceptable to use antibiotics that had been given to a friend or family member, as long as they were used to treat the same illness; 51% of respondents in Egypt and 27% in Sudan considered it acceptable when sick to buy, or request from a physician, the same antibiotics that had helped them get better previously when they had the same symptoms; and while 32% of all respondents thought that they should stop taking antibiotics when they felt better, respondents in Egypt and Sudan were particularly likely to think so. Despite these alarming rates of risk practices, antimicrobial resistance communication efforts remain limited in the Region. In a recent survey, most countries of the Region reported that communication efforts are conducted on ad hoc basis, with only three countries having conducted public awareness efforts at the national level, although activities have been conducted on a limited scale in health care settings and among dispensers (WHO, unpublished data, 2017). No countries reported monitoring and evaluating their efforts or publishing data on antimicrobial resistance communication activities. This highlights the lack of an evidence-base on communication efforts, which is urgently needed in order to increase our understanding of what type of interventions are effective in improving awareness and changing behaviour in the Region.

20. In a recent global survey on the progress of implementation of the Global Action Plan on Antimicrobial Resistance, only three countries reported that antimicrobial resistance is systematically incorporated in pre-service training curricula for all relevant health cadres and that regular continuing professional development on antimicrobial resistance reaches all relevant groups for human health nationwide, in both public and private sectors *(20)*.

Antimicrobial resistance surveillance

21. In order to inform national, regional and global decision-making, with the goal of fostering national antimicrobial resistance surveillance systems and to enable the collection, integrated analysis and sharing of standardized and validated data on antimicrobial resistance, WHO has launched the Global Antimicrobial Resistance Surveillance System (GLASS) as a platform for global data sharing on antimicrobial resistance worldwide.

22. Antimicrobial resistance surveillance combines patient, laboratory and epidemiological data to enhance understanding of the extent and impact of antimicrobial resistance on populations *(25)*. Close collaboration between clinicians, epidemiologists and microbiologists is essential for understanding the type and magnitude of the problem among populations. Only one country in the Region has reported the existence of a functioning national antimicrobial resistance surveillance system covering antibiotics in hospitals and outpatient clinics, with external quality assurance, and a national coordinating centre producing reports on resistance levels. Fifty per cent of countries report that antimicrobial resistance data are collated locally for common bacteria, but may not use a standardized approach and lack national representation, coordination and/or quality management.

23. Laboratories play an essential role at various levels of antimicrobial resistance surveillance. At the individual patient level, laboratory results guide prescription decisions and treatment monitoring. At the institutional level, they inform clinical practice guidelines, infection prevention and control, and antimicrobial stewardship programmes. At the national level, they allow evaluation of the emergence and prevalence of resistant strains and provide evidence for policy decisions. Finally, at the global level, through GLASS, the results of laboratory investigations help track global trends in the evolution and spread of resistant strains and inform global policy decisions and coordination.

24. WHO conducted capacity review missions and laboratory assessments for implementation of antimicrobial resistance surveillance in a number of countries between November 2015 and July 2017. These missions have identified a number of challenges common to all the countries visited. In particular, different, and mostly outdated, editions of Clinical and Laboratory Standards Institute standards are being used for the interpretation of antibacterial susceptibility testing (AST) results, even in different facilities of the same country, which raises questions about their accuracy and comparability. AST results are submitted only to requesting clinicians, and sometimes to infection prevention and control committees, but are never used for antimicrobial resistance surveillance. No formalized networks exist for verification of unusual or new resistance patterns, genotyping, or investigation of atypical samples. There is also little or no interaction between human and animal health laboratories.

25. To establish an effective and sustainable antimicrobial resistance surveillance system, countries need to urgently take a number of actions to: strengthen quality management systems and biosafety; ensure consistent provision and use of quality control strains; adopt evidence-based, workload-sensitive budgeting; enhance reporting, analysis and use of AST data; establish networks for the verification of unusual or new resistance patterns, genotyping, and investigation of atypical samples; address the role of private laboratories; and strengthen cross-sectoral collaboration.

26. WHO encourages countries to enrol in GLASS. To date, only nine countries of the Region (41%) are enrolled in and have initiated early implementation of GLASS.

Infection prevention and control

27. Health care-associated infections (HAIs) are among the most common and most serious adverse events in health care and their prevention is one of the fundamental elements of antimicrobial resistance control programmes. About three in every 20 hospitalized patients get an infection while receiving health care in low- and middle-income countries, compared to 1 in 25 in the United States of America and 1 in 18 in Europe *(26,27,28,29)*. Up to 32% of surgical patients get post-operative infection and up to 51% of those infections are due to antibiotic-resistant germs *(30)*. The Eastern Mediterranean Region has one of the highest frequencies of HAIs in the world *(31)*, with the prevalence of HAIs in several countries reported to vary from 12% to 18%. Transmission of resistant bacteria from patient to patient (and to others) within health care facilities amplifies the problem of antimicrobial resistance. Robust infection prevention and control programmes are crucial to reduce the occurrence and spread of infections, including drug-resistant ones, and consequently to reduce the use of antibiotics.

28. The interim results of the WHO global period prevalence survey on drug-resistant organisms in health care conducted in 2014 indicated a high resistant pattern in the Region. Laboratories from six countries (Bahrain, Egypt, Islamic Republic of Iran, Kuwait, Lebanon, Saudi Arabia) in the Region participated in the survey. Isolates from the Region ranked first compared to other Regions in the proportion of vancomycin-resistant enterococci (VRE), with seven (11.4%) being resistant. The Region ranked second globally, following the South-East Asia Region, in the proportion of resistance in *E. coli* and *K. pneumoniae* organisms, including ESBL producers and carbapenem-resistant Enterobacteriaceae (CRE) *(32)*. Table 2 summarizes the results from the countries of the Region.

29. It is now accepted that a structured hospital infection control programme, together with a well-designed surveillance system, can reduce infection rates by up to 32%. Despite the importance of HAIs in the Region, information concerning interventions and activities aimed at control of HAI is limited. Eight countries have reported some structural organization, such as an infection prevention and control section or department, at the national level. The results of the Global Antimicrobial Resistance Survey in 2016/2017 indicate that only four countries of the Region (18%) have all relevant infection control measures implemented in all targeted health facilities, with compliance and effectiveness regularly evaluated and published. Three countries have a national infection prevention and control policy or operational plan, with standard operating procedures, guidelines and protocols available to all hospitals, while five countries have national infection prevention and control standard operating procedures, guidelines and protocols that are implemented in selected health-care facilities.

Table 2. Total and resistant isolates reported from laboratories in health care facilities in the Eastern Mediterranean Region, WHO global period prevalence survey (2014)

Enterococci spp.		E.coli			Klebsiella spp.		
Total number of isolates	VRE number (%)	Total number of isolates	ESBL number (%)	CRE number (%)	Total number of isolates	ESBL number (%)	CRE number (%)
61	7 (11.4%)	229	91 (39.7%)	4 (1.7%)	105	51 (48.7%)	11 (10.4%)

Optimizing the use of antimicrobial agents

30. Misuse and overuse of antimicrobials in humans is known to be the major driver for development of antimicrobial resistance *(33,34,35)*. Optimizing the use of antimicrobial medicines is an essential approach to the prevention and control of antimicrobial resistance. This requires a stewardship programme informed by antimicrobial resistance surveillance information that monitors and promotes optimal antimicrobial use at national and local levels in accordance with international standards to ensure evidence-based choices of medicines at the correct dose. Access to quality medicines is a challenge in several countries of the Region.

31. The 2016 antimicrobial resistance survey found that only one country in the Region (4.5%) reported a system in place for the surveillance of antimicrobial use that included monitoring national sales or consumption of antibiotics and the rational use of antibiotics in health services. Three countries reported that total sales of antimicrobials were monitored at the national level and/or some monitoring of antibiotic use at the subnational level. One country reported that prescribing practices and antibiotic use are monitored through a national sample of health care settings. No country in the Region collects and reports data on a regular basis (annually) on antimicrobial sales or consumption at the national level for human use. In an unpublished WHO report, oral and injectable forms of antibiotics were reported to be available for over-the-counter sale in 15 out of 22 countries of the Region.

Research and innovation

32. Although there are many papers published from the Region on antimicrobial resistance, most of these report data from single institutions and often do not represent the national situation. Studies to evaluate innovative approaches to the control of antimicrobial resistance in the regional context are limited. As part of WHO's research activities, antimicrobial resistance has been prioritized as a research topic for grant proposals. Last year, as part of the call for proposals for research grants in priority areas of public health, 17 proposals related to antimicrobial resistance were received, of which one was recommended for funding. Owing to the complexity of antimicrobial resistance and the response to it, as well as the underdevelopment of health research systems in the Region, the establishment and prioritization of an antimicrobial resistance research agenda, using scientific methodologies and supporting operational research based on identified priorities, has become crucial.

Challenges

33. There are several major challenges that need to be addressed through the national adaptation of the Global Action Plan on Antimicrobial Resistance in the form of an inclusive national action plan on antimicrobial resistance. These include:

- a shortage of human resources educated on antimicrobial resistance;
- the lack of awareness of the magnitude and severity of antimicrobial resistance due to an absence of reliable national data on antimicrobial resistance and the consumption of antibiotics in all sectors, a lack of robust antimicrobial resistance surveillance, and weak microbiological laboratory systems;
- a lack of effective policies or enforcement systems to ensure compliance with policies, strategies and national guidelines/good practices;
- insufficient domestic funding, despite the political commitments made;
- the unregulated incentivizing practices of companies regarding antimicrobial use; and
- a lack of operational plans for the implementation of national action plans on antimicrobial resistance.

Priority interventions by countries

34. The development and implementation of a national action plan on antimicrobial resistance is an inclusive effort that requires careful planning and coordination to design and implement interventions and actions by all stakeholders, national and international, under the leadership of the Ministry of Health. National action plans should be adapted to and aligned with each country's specific context, political and socioeconomic environment, available resources and capacities, and overarching health and development strategies, laws and regulations. A national action plan on antimicrobial resistance is the key starting point for the response to antimicrobial resistance.

35. It is crucial that countries establish a multisectoral high-level political mechanism (or include antimicrobial resistance in the agenda of existing mechanisms if feasible), with decision-making authority, to oversee the development and implementation of a national action plan on antimicrobial resistance and to allocate appropriate resources.

36. Other critical actions by countries include the following.

- Development and implementation of a national communication strategy for antimicrobial resistance behavior change, jointly with Food and Agriculture Organization of the United Nations (FAO) and World Organisation for Animal Health (OIE), informed by the results of an assessment of the knowledge and behaviour of the general public, policy-makers, health care providers, veterinarians, other animal health service providers, and farmers.
- Establishment of national integrated antimicrobial resistance surveillance, with initial early implementation of GLASS, and its integration with antimicrobial resistance surveillance in the animal health, food and agriculture sectors, and antimicrobial consumption surveillance in the human and agriculture sectors.
- Development and implementation of national infection prevention and control programmes that foster infection control at the national level, through appropriate policies, strategies, training and education of heath care providers at all levels.
- Promotion of research in academic and public health institutions to identify the health and economic burden of antimicrobial resistance, and innovative interventions to combat antimicrobial resistance, adapted to national and regional contexts.
- Development of a national action plan on antimicrobial resistance with a timeline and the required resources, through an inclusive consultative process and consensus-building with relevant stakeholders, and an action plan endorsed by the highest-level authorities possible.
- Mobilization of the necessary human, technical and financial resources from domestic sources (to ensure sustainability) and partners.
- Beginning implementation of the national action plan on antimicrobial resistance as soon as possible, based on available capacities and resources in the country, with priority given to early implementation of GLASS, infection prevention and control, and awareness-raising and behaviour change activities.

Conclusions and recommendations

37. Antimicrobial resistance is a looming pandemic that affects everyone and everywhere; it is growing at a fast pace, exceeding the development of new classes of medicines. However, it is largely avoidable. Antimicrobial resistance, at its current scale, is a multisectoral problem that demands a multisectoral response. WHO and its partners have developed a number of tools and guidelines that assist the countries in their fight against antimicrobial resistance *(36)*. The following recommendations are proposed for Member States.

- Establish a multisectoral national coordination group composed of high-level policy-makers in the health, food and agriculture, livestock, environment and economic sectors to oversee, coordinate and guide the response to the antimicrobial resistance threat at the national level and accelerate the development and implementation of a multisectoral national action plan on antimicrobial resistance, based on national capacities.
- Develop and implement multisectoral national communication strategies for antimicrobial resistance awareness-raising and behaviour change adapted to the local cultural context and values.

- Expedite integrated antimicrobial resistance surveillance at the national level that informs national antimicrobial resistance policies, strategies and plans, through early implementation of and enrolment in GLASS.
- Establish national infection prevention and control programmes that include support mechanisms for promoting national educational programmes for infection prevention and control and periodic HAI point prevalence surveys to inform national programmes.
- Establish antimicrobial stewardship programmes that monitor and promote the responsible use of antimicrobials.
- Ensure high priority is given to antimicrobial resistance research within the national health research agenda and foster antimicrobial resistance knowledge and practices through research and innovation, according to the country context.

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