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# **ANTIMICROBIAL RESISTANCE IN MACEDONIA AND MEASURES TO REDUCE/CONTROL ITS DEVELOPMENT**

## **Introduction**

**A**ntibiotics are among the most important discoveries of modern medicine. They have largely contributed to the reduced morbidity and mortality from many bacterial infections. Modern medical procedures and practices such as intensive care, organ transplants and surgeries are impossible without the available effective antibiotics. As a result of inadequately long and increased use of antibiotics, such as the use of broad-spectrum antibiotics when it is not necessary or the use of antibiotics in viral infections contributes to natural selection of bacteria resistant to antibiotics, particularly bacteria resistant to many antibiotics (multidrug-resistant bacteria) such as: Methicillin-resistant *Staphylococcus aureus* (MRSA); Vancomycin-resistant enterococci (VRE); Extended-spectrum beta-lactamase (ESBL) - producing Enterobacteriaceae (examples of Enterobacteriaceae is *Escherichia coli* and *Klebsiella pneumoniae*); Carbapenemase- producing Enterobacteriaceae (eg. *Klebsiella pneumoniae*); multiresistant *Pseudomonas aeruginosa*; *Clostridium difficile*.

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## Context and importance of the problem

Antimicrobial resistance (AMR) is rapidly expanding since the 1970s in Europe and the world, and in the Republic of Macedonia. AMR and the slow development of new antibiotics, are the reason for increased morbidity and mortality from common bacterial infections, increased financial costs for treatment of patients with infections caused by bacteria resistant to available antibiotics, and puts at risk the overall functioning of the health system. With the Decision No 1082/2013/EU of the European Parliament from November 6, 2013, AMR ranks as a threat that recognizes no borders. The movement of people and food globally enables spreading of resistant bacteria. Therefore they are considered as a threat to global stability and national security. Thus, the importance of pan-European approach, i.e. the countries to take joint action in tackling this problem and the need to establish international standards and data exchange. In this regard, the World Health Organization (WHO) in 2011 published its AMR action plan which is based on the WHO Global Strategy for containment of antimicrobial resistance and Community Strategy against antimicrobial resistance of European Commission that affects the health of humans, animals and plants since 2001. Multisectorial commission for surveillance of antimicrobial resistance (MCAMR) which functions under the Ministry of Health of the Republic of Macedonia has prepared its first National Strategy and Action Plan for control of antimicrobial resistance in the Republic of Macedonia 2012-2016, in April 2011. The main goal of the strategy is to protect the health of all residents in Republic of Macedonia, while specific objectives are:

1. Informing and educating patients and the general population about the importance of rational use of antibiotics;
2. Strengthening the systems for surveillance and control of AMR and consumption / use of antibiotics;
3. Application of control and preventive measures to support the rational use of antimicrobial agents and contribute to reducing the spread of infectious diseases;
4. Promoting education and training of health professionals about the AMR problem.

With the aim to contribute to the health literacy through informing and educating patients, the general population and the health professionals, since 2008 Macedonia is implementing awareness raising campaigns on November 18<sup>th</sup>, marking the European Antibiotic Awareness Day.

The final goal of these campaigns is to raise awareness about the necessity of rational use of antibiotics and the risks associated with their over-use and misuse. Each year the activities are focused not only towards the general population but on other target groups such as the 2009 doctors in primary health care; in 2010, doctors from hospitals (secondary and tertiary health care); pharmacists in 2011; in 2012 veterinarians; microbiologists in 2013 and in 2014 all health workers.

In order to provide reliable, standardized and comparable information about the AMR situation, in January 2013, with the support of the Ministry of Health and WHO office in Skopje, R. Macedonia joined CAESAR network (Central Asian and eastern European Surveillance of Antimicrobial Resistance) for surveillance of bacterial susceptibility to antibiotics in non-EU member countries. The network is an initiative of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Dutch Institute for Public Health (RIVM), European Centre for Disease Control ECDC and WHO. It includes all microbiological laboratories, where the assumption that 90% of the strains isolated in Republic Macedonia are registered in the network. Although it must be aware that the number of tested blood cultures in Republic Macedonia is very small, in terms of blood cultures tested in European countries, and that is the reason for the low total number of isolates, and thus the small number of reported isolates.

CAESAR network is using methodology compatible to EARS-Net, which is used by the EU member states. Pathogens that are monitored are isolated from blood and CSF (*S. aureus*, *Str. Pneumoniae*, *E. coli*, *K. pneumoniae*, *E. faecium* and *faecalis*, *Ps. Aeruginosa* and *Acinetobacter* spp.). According to the first available Macedonian data from 2013, 41.8% of isolated *S. aureus* were MRSA versus 18% in the EU, while 59.2% of isolated *E. coli* were ESBL positive and 82.9% of isolated *K. pneumoniae* were resistant to aminoglycosides which is more than all EU countries. According to these data, it is clear that Republic of Macedonia has a serious problem with antimicrobial resistance and rapid interventions are required at several levels.

In that direction is the activity of educating the general population and health professionals about proper hand hygiene conducted on May 5, 2014 when the first time in Republic Macedonia is marked the World Hand Hygiene Day: clean hands save lives. Having in mind that hand hygiene is highly effective and cheapest way for prevention community and hospital acquired infections, correct implementation of hygiene reduces the inappropriate use of antibiotics.

Additionally, continuous education of doctors in the primary, secondary

and tertiary level, about rational prescribing of antibiotics is performing by national and international experts, through workshops and seminars, and through on-line courses.

Also, activities for determination of the antibiotics consumption in hospitals as well as the protocols that are followed in the process of prescription are started, due to direct effect of the consumption and prescribing practices on antimicrobial resistance. The consumption of antibiotics in primary level is monitored by the Health Insurance Fund.

With aim to be included in the research projects of new medicines R. Macedonia joined the COMBACTE, EU network for clinical and laboratory testing of new agents for treatment of resistant bacteria.

### **International and national actions against the development of antimicrobial resistance**

1. Promotion of rational use of antibiotics or the use of antimicrobial therapy only by indication or based on the results from microbiological investigation;
2. Monitoring the correct application of antimicrobial therapy by the patient/client;
3. Use of national guidelines/ protocols for antimicrobial therapy;
4. Establishment and implementation of measures for infection control in hospitals, herd or flock with special emphasis on hand hygiene;
5. The development of new antibiotics with new mechanisms of action;
6. Use and development of vaccines;
7. Continuous education of health professionals/veterinarians;
8. Education of patients/clients to use antibiotics in a responsible manner and other measures for relief the symptoms.

### **Recommendations for new policy and implementation**

There are several strategic approaches and policies whose implementation needs to be strengthened or established through existing action plan or developing a new action plan in 2016 in order to ensure rational use of antibiotics and preserve their activity.

- 1. Strengthening the inter-sectoral coordination, having in mind** that AMR is not just a health issue but also includes community (patients, families), agriculture, private sector (pharmacy companies, etc.), govern-

ment (regulatory agencies, politicians, etc.) and is a large social and economic issue. That is way, in order to develop, implement and evaluate undertaken activities it is necessary to have multidisciplinary approach.

2. **Strengthening the surveillance of AMR** at the local, national, regional and global levels is useful for: strengthening national capacities and harmonize global standards, rapid detection of resistant strains of public health importance, support rapid reporting and investigation of epidemics, evidence based decisions for clinical treatment, recommending health policies, monitoring the effectiveness of interventions (eg. measures for infections control).

For this purpose, besides efforts to improve the surveillance through CAESAR, Macedonia will join the Global AMR surveillance system 2015-2019 (GLASS = EARSNet + CAESAR + ReLAVRA) WHO.

3. **Promotion of rational use** of antibiotics through developing clinical guidelines / protocols that are based on national resistance data and that will facilitate decision on the appropriate treatment of patients with bacterial infection based on evidence. In addition, should be developed protocols for each level of health care and to be updated at a specified interval. In order to rationalize the use of antibiotics is recommended to use rapid tests for distinguishing bacterial from viral infection, such as in case of sore throat, which is the most common cause of antibiotic use in primary care.
4. **Strengthening the surveillance of antibiotic consumption** with particular focus on the surveillance of antibiotic consumption in hospitals and monitoring the use of protocols for prescription of antibiotics. Of particular importance in this process has continuous availability of essential medications, according to a prepared national list of essential medications. Additionally it is important to conduct supervision on prescribing practices at all levels of health care that will be supportive, educational and person-to-person with antibiotics prescribers.
5. **Strengthening the control and surveillance of intra-hospital infection** which will greatly reduce the use of antibiotics. In this direction, hand hygiene campaign will continue, and the continuous monitoring of the causes for intra-hospital infections and measures for their prevention, screening for carriers of resistant strains, promotion of blood cultures as a method of detection of infections and AMR and isolation of positive patients in all health institutions in Macedonia.
6. **Prevention of the occurrence of resistance in the veterinary sector** and food production by regulating the use of antibiotics in food manufacturing i.e. in the animal growth.

7. **Promotion of immunization** as very effective way to prevent viral and bacterial infections, and therefore promote rational use of antibiotics.
8. **Improving awareness of reasonable use of antibiotics** and population safety through education on the effects of antibiotics, their proper use according to the recommendations of health professionals.
9. **Promotion of innovations and research of new medications** through involvement in national and international research networks for clinical and laboratory testing of new agents for treatment of resistant bacteria.

Considering the fact that **“Nobody is exempt from the problem nor from playing a part in the solution”** (WHO Global Strategy for Containment of Antimicrobial Resistance), the AMR control is compliant with the whole-of-society approach, which is the basis of the National Strategy Health 2020 of the Republic of Macedonia.

## **Executive summary**

Antibiotics are among the most important discoveries of modern medicine. They have largely contributed to the reduced morbidity and mortality from many bacterial infections. Their use is associated with Antimicrobial resistance (AMR), which is rapidly expanding since the 1970s in Europe and the world, and in the Republic of Macedonia. The movement of people and food globally enables spreading of resistant bacteria. Therefore they are considered as a threat to global stability and national security. Thus, the importance of pan-European approach, i.e. the countries to take joint action in tackling this problem and the need to establish international standards and data exchange.

This policy brief on the situation with antimicrobial resistance overviews the problem in the Republic of Macedonia and possible solutions, and is prepared at the occasion of the first World Antibiotic Awareness Week, 16-22 November established upon initiative of the World Health Organization (WHO). It is a contribution to the preparation of the new action plan for the period 2016- 2020 and to the National Strategy Health 2020 of the Republic of Macedonia.

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