Republic of Macedonia
Ministry of Health

National Strategy
For Containment of Antimicrobial Resistance
2012-2016

March, 2011

Glossary:

Antimicrobial resistance (AMR) is ability of microorganisms (bacteria, viruses, parasites) to demonstrate resistance to the effects of the antimicrobial agents (medicinal products).

Microorganisms (microbes) are bacteria, viruses, yeast and parasites.

Aantimicrobial agents or antibiotics are medicinal products with ability to kill or to inhibit the growth of microorganisms in the human or animal body and can be used for treatment or prevention of infections in human or animal. It represents all natural, semi synthetic and synthetic products, including antiviral, fungicides and medicines against protozoa and helminthes which have clinical effectiveness.

Microbial resistance is condition when antimicrobial agent used in regular dosage shows no effect on the microorganism. Even the use in maximal dosage will have no effect. .

Microbial susceptibility to antimicrobial agent is a condition when the antibiotic used in therapeutic dosage will have effect on the microorganism.

Moderate microbial susceptibility to antimicrobial agent is a condition where it is anticipated that the increasing of the therapeutic dosage of the antibiotic will have effect on the microorganism (if it is possible according the patient health condition, type of the medicine etc)

MRSA is acronyme for *Staphylococcus aureus* resistant to methicilin. MRSA is resistant to large number of antibiotics including penicillin's and cephalosporins.

Natural resistance is resistance demonstrated after the first introduction of antimicrobial agent.

Acquired resistance is resistance demonstrated after many years of the antimicrobial agent consumption. It is characteristically for chronically diseases, such as tuberculostatics and antiretroviral agents.

Irational use /misuse/ of antibiotics is use of multiple antibiotics in the treatment of one patient (in cases where only one is sufficient), determination of unnecessary long period of usage, proscription of antibiotics when the illnes is self curing (viral infections) when the antibiotics are not neded, usage of antibiotics as profilaksis before and after surgical intervention more frequently and for prolonged duration than usually.

1. Introduction

This first national strategy for containment of the antimicrobial resistance define the goal, plain of activities and the responsibility for containment of the antimicrobial resistance (AMR) in Republic of Macedonia (RM) for the period from 2012 to 2016.

In response to antimicrobial resistance RM is following the WHO Global Strategy for Containment of Antimicrobial Resistance (2001)[1], as well as the EU Council Recommendation for prudent use of antimicrobial agents in human medicine (2002). [2] Thus, RM accomplishes harmonization with global and European efforts to respond to the AMR problem.

The intersectorial nature of AMR problem gives specific meaning to this Strategy, trough integration of all relevant sectors, under the leadership of the Ministry of Health, in realization of the Srategy and it's ultimate goal, which is containment of AMR for public health protection (of the population).

2. AMR as public health problem

Antimicrobial resistance is public health problem: it compromises therapy, leads to inappropriate treatment result, prolonged treatment, high treatment costs and prolonged hospitalization, and has negative social- economical consequences for the whole society.

Three main reasons influence frequent appearance of bacterial strains resistant to antibiotics: irrational/ incorrect (inappropriate) use of antibiotics, dispensing the antibiotics without doctor's prescription and overuse of antibiotics in animal food.

The most frequent reason for antibiotic resistance of microorganisms isolated from humans is the use of antimicrobial agents in human medicine. The level of usage of antibiotics is in correlation with level of antibiotic resistance, respectively, antimicrobial resistance is higher in countries with high usage of antibiotics, according to data from European Antimicrobial Resistance Surveillance System (EARSS), and data gained from Europian Surveillance of Antimicrobial Consumption (ESAC).

3. Intersectorial aspects of AMP

Social and human aspect of AMR and antibiotic usage. Antibiotics have great social effect. Antibiotic prescription has influence not only to one concrete patient. The appearance and spread of resistant strains of microorganisms could have big epidemiological consequences for other persons, as well as for the whole society.

[1] http://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf
[2] 2002/77/EC, OJ 195,13.07.1999

Ecological aspect of antibiotic usage. Antibiotics have effect not only on pathogen bacteria. They had effect to normal micro flora and can lead to ecological misbalance and development of opportunistic infections. Because of the frequent selective pressure, bacteria from normal flora can develop resistance rapidly, which can be transferred to pathogen strains of microorganisms.

Economical aspect. According the research done in USA the treatment of a patient infected with MRSA in USA cost 60000 USD.Total cost for treatment of infections caused by resistant strains of bacteria for one year in USA were estimated on 6,7 billions USD. Besides the influence on the increase of the expenses for hospital care, the expenses for post hospital care were also increased because of the frequent visits to the doctors in primary care and need for frequent control examinations in the hospital. According the EARSS data in the European Union every year around 25.000 patients are dying as a result of infections with resistant microorganisms, and extra expenses for health protection and lost of working days/ productivity were estimated to around 1,5 billion euro/ year.

Intersectorial character of AMR problem impose the need for integration and coordination of national efforts for AMR control in context of European approach " Health in all policies" especially having in mind the veterinary medicine, education, environmental protection, social protection and finance.

4. AMR in global and European context

Global context. Today AMR represent a global problem. Resistance of microorganisms to certain antibiotics can lead to his (its) exclusion from therapeutic usage. The appearance of multiresistant microorganisms is increasing and this is the reason of discussion for "post antibiotic era" among scientists. Wide international communications and travelling, trading animal and plant allow rapid spread of microorganisms throughout the world, so the resistance problem from one part of the world, very quickly became global problem. Travelers receiving hospital care when travel in the country with high prevalence of antimicrobial resistance when returned in their country can be colonized or infected with multiresistant bacteria, and they are potential base for infections.
AMR is important factor for death from infectious diseases. According the WHO data infectious diseases are the reason for death of approx. 9, 5 million peoples every year. More than 85% of those infections are respiratory diseases, HIV/AIDS, diarrhea, tuberculosis and malaria. More than 55 % Streptococcus pneumoniae strains are resistant on usually used antibiotics, more than 90% of Shigella strains, cause of disentheria, are resistant to thrimethoprim/sulfametoksazol and nalidixic acid. In the last years there were outbreaks of abdominal typhus with multiresistant *Salmonella typhi*. Almost 22% of bacillus tuberculosis in patients with tuberculosis is multiresistant.

European context. According the EARSS[3] data northern countries such as Scandinavia and Netherlands are with low resistance rate , and south countries in Europe are with

[3] http://www.rivm.nl/earss/

high resistance rate. Countries with low antimicrobial resistance rate had in general low usage of antimicrobial agents and analogous, and in countries with high antimicrobial resistance rate, the usage of antibiotics is high.
In certain European countries the trend of decreasing the usage of antibiotics among patients in community is registered an the same time with decrease of antimicrobial resistance of bacteria (responsible for community acquired infections). Six countries, EU members (France, Belgium, Slovakia, Check Republic, Slovenia and Sweden) show decreasing trend of usage of antibiotics in community, and in France and Belgium, decreasing is supported with national campaign for rational use of antibiotics.

The EARSS report for 2007, and the national data as well, indicate decreasing of the trend of the resistance in *Streptococcus pneumoniae*, bacteria responsible for community acquired infections esspecialy among children, as well as significant decrease in percentage of methicillin resistant *Staphylococcus aureus* responsible for bloodstream infections (condition of sepsis). It is accomplished with increased efforts for infection controle, hand hygiene, and policy for prudent use of antibiotics in the hospitals in these countries (according the national data from Slovenia, France and UK).

Although these data are encouraging, nevertheless antimicrobial resistance is still high or increasing in many countries, especially for most frequent bacteria such as *Staphylococcus aureus* (MRSA), *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Infections caused by multiresistant bacteria or bacteria completely resistant to antibiotics are actuel problem in European Union. Examples for such bacteria are carbapenemase (KPC) producing *Enterobacteriacea* (mostly *Klebsiella pneumoniae*), and hospital multiresistant strains of *Acinetobacter* that show resistance to a number of antimicrobial agents.

This new trend is very disturbing and because of his complexity, there is a need for hard work in the following years. The modern medicine depends on capability of effective antibiotics in case of complications during infections, or in their successful usage in prophylaxis. Intensive care, organ transplantation, chemotherapy in malignant diseases, care for premature born babies, or surgical procedures such as transplantation of knee or haunch, will be impossible without effective antibiotics.

5. AMR in RM

AMR data in RM are collected non systematically and they originate from expert and scientific studies and projects mainly performed in the Institute for microbiology and parasitology at the Medical faculty in Skopje. In the last 20 years there were two scientific projects, 4 doctoral theses, and 5 master theses realized from the Institute and they were in correlation with resistance of bacteria isolated from hospitalized patients or outpatients treated at the University Clinic in Skopje. Research are related to *Staphylococcus aureus and MRSA, uropathogenic E.coli, ESBL positive enterobacteria, Streptococcus pneumoniae, Enterococcus, Pseudomonas aeruginosa, Acinetobacter baumanii, Bacteroides fragilis, Campylobacter* and *Helicobacter*. There are expert

reports for the resistance in general and special hospitals in Macedonia and for the bacterial resistance isolated from the patients treated in the outpatients services.

In the last two decades through the Association of Macedonian microbiologist activities for standardization of susceptibility testing were performed. Strains of resistant bacteria are not stored, neither sent to the Institute for microbiology and parasitology or Institute for public health for confirmation. This is a main reason why Republic of Macedonia is not present in the European reports for AMR.

Existing data for AMR in Republic of Macedonia are not different from the data from our neighboring countries: Serbia, Bulgaria and Greece, which means that there are no significant differences among data from South Europe countries and Mediterranean, where the usage of antibiotics and the rate of resistant bacterial strains are usually high

There is a possibility for relevant research, for antimicrobial treatment, consumption of medicines, type, amount and price, diagnosis data, treatment success, cause of the disease and their susceptibility on antibiotics at hospital treated patients. In case of patients treated in primary care there is no possibility for complete surveillance for the antimicrobial agens choice, indications for prescriptions, and patient data. More then 80% of antibiotics are prescribed by the primary care.

Results from the investigations performed in early nineties for the treatment of respiratory infections, conducted in ten ambulants randomly choosen in RM were more than disturbing, it was noted that majority of antibiotics were prescribed incorectly, opposite to the evidence based medicine.

In the last 10 years with the project for continuous medical education around 500 primary care doctors were educated for rational prescribing of antibiotics. In the same time, trainings for rational use of antimicrobial therapy in hospitals were conducted and Guidelines for evidence based medicine (where the treatment of infections were included) were published in 2006.. Still, there is a need for further implementation of measures for prudent use of antimicrobial therapy in the future.

As a response to this condition, we propose the strategy aiming to organize the efforts in RM in respond to AMR as public health problem, in accordance with the evidence based medicine, global and regional strategies for AMR containment in the world and Europe.

6. Objectives of the National strategy for containment of antimicrobial resistance

Main objective of the National strategy for containment of AMR is improvement of the health status of the population in RM and securing the quality health protection at all levels, through the AMR control.

Specific objectives of the National strategy for containment of AMR are:

1. Information and education of patients and community for the importance of prudent use of antibiotics.
2. Strengthening the system for AMR surveillance and controle and consumption/usage of antibiotics.
3. Implementation of controle and preventive measures to support prudent use of antimicrobial agents and to contribute to decreasing the spread of infectious disease.
4. Promotion of education and training of health professionals on AMR problem.

With respect to realisation of these objectives an **Action plan** included in the National strategy for containment of AMR, with determined activities on AMR control, responsible institutions, time frames and financial resources needed and sources for funding.

7. Coordination on implementation of the National strategy for containment of AMR

Intersectorial Commission for control of AMR shall be established by the Government of the Republic of Macedonia with assignment to coordinate the implementation of the strategy and action plan for AMR containment.

Action Plan
for achievement of the results and objectives of the
National strategy for containment of antimicrobial resistance

Area of activities	Objective/result	Activities	Time for realization	Responsible institution	Financial resources	Source of financing
1. PATIENTS AND COMMUNITY	**Information's and educations**	1.1 Information and education of patients and community on: 1.1.1. prudent use of antibiotics. 1.1.2.importance of the measures for inhibition of infections, such as immunization, vectors control etc, as well as simple measures which can decrease the transfer of infections in families and community such as hand hygiene, food hygiene etc. 1.1.3 Appropriate and informed conducting when requesting the health protection and in application of prescribed therapy. 1.1.4 Appropriate alternatives for antibiotics	continuous	Doctors from primary care Institute and Centers for Public Health	In the frame of their routine work In the frame of their routine work	National program for public health

		to relief the symptoms as well as to discourage self treatment of patients, except in specific circumstances, after consultation with doctor.				
2. HEALTH WORKERS	**1. Continuous education**	2.1.1 Continuous education of health workers on: 2.1.1.1 importance of prudent use of antibiotics and containment of the antimicrobial susceptibility/resistance 2.1.1.2 disease prevention (including immunization) and control of infections. 2.1.1.3 factors which can seriosly affect their prescribing habits (negative influence of economical stimulations, influence of promotions and influence of the pharmaceutical industry in prescribing and dispensing the medicines)	continuous	Institute and Centers for Public Health Chambers of health workers	In the frame of their routine work In the frame of their routine work	National program for public health Chambers income

		2.1.2 Promotion of target oriented undergraduate and postgraduate educational programs for AMR control intended for health professionals and veterinary	continuous	Intersectoral Committee on AMR control	In the framework of their routine work	
		2.1.3 Encouraging the health professionals to educate patients on proper use of antibiotics and on importance for keeping to the proscribed treatment.	continuous	Institute for public health Centers for public health	In the framework of their routine work	Annual national program for public health
	2. Clinical instruction and expert surveillance on their implementation	2.2.1 Preparation of the standardized methods for microbiological diagnostic and their regular update	2012-2016	Microbiology association Institute for microbiology – Medical faculty Skopje, Institute for public health	In the framework of their routine work	
		2.2.2. Preparation of the guidelines for diagnostic and treatment of infectious diseases	2012-2016	Association of microbiologists of RM	In the framework of their routine work	

		2.2.3.Improvement of the AMR control in the clinical practice, trough control of the implementation of the written guidelines for diagnostic and treatment	2012-2016	Commission on health care quality control in the hospital Hospital Expert committee for HAI	In the framework of their routine work	
		2.2.4 Expert control on the prescribing and dispensing the medicinal products with respect to the control of irrational use of antibiotics	2012-2016	Expert control committee, established by MoH Bureau for medicines	In the framework of their routine work In the framework of their routine work	
3. **HOSPITALS**	**1. Management**	3.1.1 Establishing of programs for AMR control in the hospitals :all hospitals to prepare written policy and program for AMR control.	2012-2013	Hospital management	Regular work of the hospital management	

		3.1.2 Expert control commission in hospitals to include regular control of AMR in their work program	2012-2016	Commission for control of health care quality in the hospitals	In the framework of their routine work	
		3.1.3 Expert control commission in the hospitals to develop and use hospital formats for AMR control	2012-2013	Commission for control of health care quality in the hospitals	In the framework of their routine work	
		3.1.4 To enable organized system for monitoring of the antibiotic use, including diagnose, quantity and the patterns of use, as well as reflexive results	2012-2014	Commission for control of health care quality in the hospitals	In the framework of their routine work	
	2. Diagnostic laboratories	3.2.1 To provide access to the microbiological laboratory services. To prepare guideline for cooperation between laboratories with respect to access provision	2012-2016	Hospital management	In the framework of their routine work	
		3.2.2 Top provide performing and provision of adequate diagnostic tests, microbiological	2012-2016	Hospital management	In the framework of their routine work	

		identification, tests for AMR susceptibility for key pathogens, as well as timely and relevant information for the results.				
		3.2.3 To provide arranging and keeping of the laboratory data and results (preferably in the data base) that will allow timely clinical end epidemiological monitoring of the susceptibility of the pathogen agents, with referral information for the antibiotic prescribers. 3.2.4. Selection of strains of multirezistant microorganisms that shall be sent for confirmation in the referent laboratories- Institute for microbiology- Medical Faculty Skopje and referent labs of the Institutes for public health	2012-2016	Hospital management Head of the laboratory	In the framework of their routine work In the framework of their routine work	
	3. Interaction with the pharmaceutical industry	3.3.1 Inspection control on the advertising of the pharmaceutical industry in the hospitals, in	2012-2016	State sanitary and health inspectorate	In the framework of their routine work т	

		accordance with the legislation, , in order to control the irrational use of antibiotics				
4 Diagnostic laboratories out of the Hospitals		4.1. same as 3.2.2 , 3.2.3 and 3.2.4.	2012-2016	Diagnostic laboratories out of the hospitals	In the framework of their routine work	
		4.2. Enforcement of the control on the implementation of the Law on protection of the population against communicable diseases in relation to the sending data on detected AMR to the Institute for public health	2012-2016	State sanitary and health inspectorate	In the framework of their routine work	
		4.3. Preparation and adoption of the guideline for selection of the strains of multiresistant microorganisms that are sent by microbiological labs for confirmation and additional laboratory tests in the Institute for microbiology-Medical Faculty Skopje and referent laboratories of the Institute for public health	2012-2014	Association of microbiologists in coordination with Intersectorial committee for AMR control,	Regular obligation	
5 USE OF		5.1 Strengthening of the	2012-2016	Inspectorate of the	Regular obligation	

ANTIBIOTICS AT FOOD PRODUCING ANIMALS		control of supply and use of antibiotics on prescription, for control of the diseases at animals		Agency for food and veterinary	of the inspectorate	
		5.2 Updating of the system for monitoring of the use of antibiotics at animals	2012-2016	Agency for Food and Veterinary	regular obligations	
		5.3 Monitoring of the antibiotics for animal use susceptibility in order to identify new health problems and take adequate corrective measures for human health protection.	2012-2016	Agency for Food and Veterinary Veterinary faculty	regular obligations Regular obligations	
		5.4 development of the guidelines in the veterinary medicine with respect to decreasing the overuse and misuse of antibiotics at animals.	2012-2016	Agency for food and veterinary	Regular obligations	
6 INTERSECTORIAL POLICY AND COOPERATION	**6.1.Intersectorial policy and cooperation**	6.1.1 AM control is the priority of the Government: intersectorial commission, for AMR control is established	2012-2016	Government of RM	Not needed	
	6.2. Policies and guidelines	6.2.1 Improvement of the immunization scope and	2012-2016	Ministry of Health, Preventive heath	Regular obligations	

		other measures for diseases p[prevention, thus providing for decresing of the use of antibiotics in medicine and veterinary		care teams within the health centers, Agency for Food and veterinary		
	6.3. Researches on resistance, use of antibiotics and disease burden	6.3.1 Assignment of the Institute for Public Health as a referent center for the AMR data base and communication with the international institutions.	2012-2016	Ministry of Health	Funds needed shall be provided every year trough the National annual program for public health	
		6.3.2 Adaptation and implementation of the WHO model for AMR research and provision of the data flow 6.3.3.Assignment of the Institute for microbiology –Medical faculty and Laboratories of the Institutes for public health as a referent laboratories for laboratory monitoring of AMR	2012-2016	Association of microbiologists of RM in coordination with Intersectorial Commission on AMR control Ministry of Health	Funds are not needed Funds needed for performing confirmation tests shall be provided every year trough the National Annual program on public health	
7 PHARMACEUTICAL PROMOTION		7.1 Strenghtening of the inspection control on the antibiotics advertisement, in accordance with the legislation	2012-2016	State sanitary and Health inspectorate Bureau for medicines	Regular obligations	
8 INTERNATIONAL		8.1 Encouraging	2012-2016	Minsitry of health,	Regular obligation	

ACTIVITIES ORIENTED TO AMR CONTROL		cooperatiin between governmental and non-governmental organizations, professional associations and international agencies for AMR control, in context to the monitoring and implementation of the WHO, and EU recommendation and EU legislation		Agency for Food and Veterinary		
		8.2 Support pof the activities for control of the counterfeit antibiotics, in accordance to the WHO and EU recommendations	2012-2016	Bureau for medicines	Regular obligation	
		8.3.Project cooperation with WHO and ECDC for support of the data base in order to monitor AMR in human and veterinary medicine and possibilities for data exchange	2012-2016	Ministry of Health	regular obligation	
9.INTRODUCIBNG IT TECHNOLOGY IN COMMUNICATIONS		9.1 Introducing IT technology in the health care institutions with respect to the fast data exchange on AMR spread	2012-2016	Health institutions, Institute for public health	Funds are allocated trough the MoH-IT project	
10.SCIENTIFIC		10.1. Continuous	2012-2016	Medical faculty,		

RESEARCHES		cooperation with the Ministry of education and science on the scientific projects related to AMR		Pharmaceutical Faculty, Faculty of Dentistry, Institute for public Health, Ministry of Health, Ministry of Education		