Professor Alexandru Rafila is currently the Chief of Microbiology Department of University of Medicine and Pharmacy “Carol Davila” and of the National Institute for Infectious Diseases “Matei Bals” in Bucharest, Romania. He received his medical degree in 1987 and attained a Ph.D degree in Microbiology in 2004. He has been a senior specialist in Laboratory Medicine/Microbiology and Public Health since 2000. He is also Honorary Personal Adviser of the Minister of Health for policies. In addition he is Director of the Aspen Healthcare & Quality of Life Program.

Dr. Rafila is the elected President of the Romanian Society of Microbiology and has served in central administration as Secretary of State for Medical Assistance and Public Health, General Director for Public Health and several times as Personal Adviser of the Minister of Health. He is a previous Director of the Public Health Institute Bucharest.

In addition to his standing in his own country, Professor Rafila’s expertise is fully recognized as expert for WHO, NATO and European Commission. He was (2014-2017) Member of Standing Committee of Regional Office of Europe of WHO and represented Romania in the Management Board of ECDC (2009-2014). He was recently elected by World Health Assembly to represent Romania in the Management Board of the organization. Professor Rafila is an active organizer and participant in many national and international medical conferences and events on public health and microbiology. Dr. Rafila has authored articles, manuals, book chapters and guidelines for public health and microbiology practice. He decisively contributed to the reestablishment in 2016 of Medical Microbiology as a specialty in Romania based on recommendations of UEMS where he represents Romania.

**Reporter (R):** Professor, many thanks for your kindness to accept to discuss with us about a subject of topical interest concerning medical world at both national level, but also at European level: antimicrobial resistance (AMR). As Romania has undertaken the Presidency of the Council of the European Union, it would be pertinent to learn from you the main guiding marks framing and consolidating this mandate in health field.

- Do you consider that, within the current Romanian context, health is regarded and considered as a national priority?

**ALEXANDRU RAFILA (AR):** In my opinion, health will be truly a priority when there is a policy assumed on midterm, with clear objectives, responding to the public health and healthcare needs, and taking into account the experience of other states with recognized results in prioritizing and decision making process; their experience shows that effectiveness and efficiency is acquired when the rising the resources allocated to the health system prevails their economic growth. Health could not be a priority as long as we do not entirely finance the strategic measures necessary to cover the needs, and if we continue to have just punctual approaches of certain problems which must be treated as a matter of priority, even it should be a broader approach, and this strategy should be committed by all the governments.

Solution for punctual problems would be their integrated approach within coherent sustainable policies and strategies, and I would underline health in all policies, at national level. Sectorial policies are important, but they should be correlated, and one of the key elements here is a multi-sectorial approach of health.

- Which are the public health priorities proposed for action by Romania at the EU level, within the current mandate?

**AR:** According to the Romanian Presidency Programme at the Council of the European Union, mandate held between January 1st - June 30th, 2019, there are several objectives to be considered, among which I would remind the following: promoting the universal access of patients to medicines, fighting against antimicrobial resistance, improving the vaccination coverage, reducing the excessive drug consumption, and improving the control of communicable diseases. Patient mobility and patient access to medicines are important issues to be pursued.

Regarding the vaccination, focus will be on determining the way to increase the vaccine coverage in the context of threats at public health, by facilitating the exchange of good practices and expertise. Antimicrobial resistance (AMR), and healthcare-associated infections, are important aspects for the Romanian Presidency of the Council of the European Union. One of the main objectives will target advanced discussions regarding the united approach in the human, veterinary and environmental sectors - One Health approach. In this regard, a set of conclusions of the EU Council, concerning the fight against antimicrobial resistance and healthcare-associated infections, is to be elaborated.

Health Technology Assessment will be among the topics on this mandate agenda, and aiming to continue negotiations within the Council concerning the regulation proposed regarding the coordination of Health Technology Assessment. A special attention will be also paid to health aspects within the regulation proposed for the European Social Fund (ESF+), the successor of the European Union Health Programme. Health digitalization (e-Health) will also be a subject of interest for the Romanian Presidency, and we will organize a Ministerial meeting including the e-Health network.

- At European level, what would the AMR improvement consist in, given the Plan that has to be implemented?

**AR:** There is a large variety in regard of solving capacity and the stage of implementing measures at the EU level. Some countries are more advanced, while others try to maintain the rhythm and to create premises for an effective implementation. In the current mandate, Romania plays an important role in continuing the steps for limiting the phenomenon induced by the AMR. Few years ago, in 2016, during the Dutch Presidency, a Ministerial meeting on a similar topic took place, resulting in specific recommendations. The recommendations after this meeting emphasized the necessity to implement three key elements in the Member States:
inter-sectorial committee, strategy, and action plan. After these premises are covered, the EU structures are to monitor, to plan periodical meetings for monitoring progresses, and efforts to be done including for developing a joint database for multi-resistant bacteria surveillance in human and veterinary sectors, as well as integration of data.

R: Concerns for antimicrobial resistance were on the public health agenda at both national and European level, and the current stage claims the implementation of strategic measures aimed to strengthen the progresses already accomplished?

AR: Healthcare-associated infections and vaccination are two aspects found also in other countries, even some among the developed ones. Particularity of the Romanian context is given by the magnitude of these problems, determining major challenges in their solving.

Vaccination not only prevents the occurrence of disease, but certain vaccines also prevent the extension of antibiotic resistance, as vaccination prevents the occurrence of an infectious disease that will determine consumption of antibiotics. The most usual example would be the pneumococcal vaccine. Moreover, new vaccines are in progress in order to be used against certain bacteria which generate healthcare-associated infections, and I would give the example of the vaccine against Clostridium difficile infection, as being in advanced stage of research.

Healthcare-associated infections (HCAI) are not unusual; up to a certain point, they are normal for the medical activity. Surveillance of the Centers for Disease Control and Prevention (CDC) aims the invasive infections, as they are produced by multidrug-resistant bacteria, those infections endangering the patient life, and most of these invasive infections are correlated, many times, with the occurrence of healthcare-associated infections.

But reporting the healthcare-associated infections in Romania, is still a problem; they are clearly underreported, because their level in all the EU countries exceeds 5% of total patients discharged from hospitals, while here, the reported level is around 0.5%.

What is the reason for underreporting HCAI in Romania?

AR: There are multiple reasons. Some of them are historical motives, while others are related to comprehension, education, as well as to the public perception on these infections.

For a better understanding, I think we should talk about an aspect seldom debated, namely, the patient safety. Patient safety is a concept more recently developed, which should involve education measures, especially for the health personnel, regarding the respect and application of several procedures aimed to avoid the occurrence of consequences, because patient safety does not relate only to healthcare-associated infections, but also to many other adverse events which may cause the patient harm. From this perspective, general recommendations are to not apply punitive measures, but instead to educate the personnel, so that to develop a safe behavior and safe practice for the patient, as understood and accountable.

As for HCAI, the problem in Romania is related to underreporting the infections.

Many times, this is generated by the sensitivity and reaction of public opinion when these infections are declared. General opinion of population is often that the hospitals reporting this kind of infections are much unsafe than the hospitals without reporting these infections. There was a hospital performance indicator in the hospital management contract, and the hospital manager was disadvantaged or underscored if reporting such infections in their hospital. Therefore, there is a pseudo-competition between hospitals, inclining to report unrealistic levels of the infection phenomenon.

It is hard to believe that there is no healthcare-associated infection in one hospital, on a few-years period. I think the mentality and comprehension are wrong, including at the hospital management level. The healthcare-associated infection should not necessarily be correlated with a severe infection

- And what aspects do you consider to be the first in order to decrease the gap toward the countries more advanced in this subject matter?

AR: Most of the HCAI are common infections, such as surgical site infections, or urinary infections, occurring during the treatment, especially in high-risk hospital departments, such as surgical departments and intensive care units. It is important to identify, to report and to control these infections, especially the invasive bacterial infections with multi-resistant germs endangering the patient life. In order to be able to do it, we need supporting tools. Many times, the hospital laboratory is missing, and the current situation must be changed quickly. In my opinion, the hospital needs its own microbiology laboratory, or a microbiology compartment within the hospital laboratory.

Why should laboratory belong to the hospital? Because patients carrying multi-resistant bacteria have to be screened and cared of differently than other patients, especially in surgical and IC units, in order to prevent the spread of these bacteria. Carrying status can be identified if we have the possibility to diagnose microbiologically. There are carrying patients and we need to know this reality. But we know it only if we have a prompt microbiologic diagnostic. We may diagnose bacterial infections if we have a microbiology laboratory where the samples can be received and worked immediately, at any moment of the day. Externalizing these laboratories makes impossible the testing of a carrying patient or a potentially infected patient. There is no need for a specialist physician on each shift, but somebody from the lab needs to be available to take the sample as quickly as possible. The time is essential for a right diagnostic. The shorter time, the better, more valuable processing, insemination or preparation for an indicative microscopic result are, and consequently microbiologic diagnostic is improved.

The awareness for this microbiologic laboratory within the hospital needs to be increased. I have to mention that, in most of the EU countries, microbiologist plays an essential role, sometimes even being responsible for the infections control, in certain hospitals. Clinical microbiology is correlated with infectious diseases. For example, in the UK there is only one medical specialty - Infectious diseases and clinical microbiology. We also accomplished this, three years ago, when we succeeded to reintroduce the Clinical Microbiology specialty, which existed in Romania before. Although the Clinical Microbiology specialty in our country had worldwide recognition, inexplicably it was dissolved in 1994 and included in the specialty of laboratory medicine.
There is no such a situation anywhere. Clinical Microbiology is a different specialty, important by its essential contribution to: diagnosing the infectious diseases, identifying multi-resistant bacteria, giving therapeutic solutions by testing bacteria sensitivity or resistance to antibiotic. It has nothing to do with other specialties such as hematology, biochemistry - which test, if you want, only the variations of some biological parameters of a patient. Those are totally different things. It wasn’t a favorable issue, as far as it caused the weakening of microbiologic diagnosing capacity in hospitals, and generally in Romanian institutions. Fortunately, the specialty was reintroduced three years ago, but this fact is not going to change things unless we double it by a revision of legislation about the organization of a microbiology laboratory or lab compartment within clinical hospitals, standardize the diagnostic and interpretation of antibiotic resistance, so that the epidemiologist and clinical physicians in charge with prescription of antibiotics to benefit from good quality data, consistent at national level. These measures seem urgently needed within the adequate decision making process for surveillance and control of antimicrobial resistance, as well of healthcare-associated infections, and implicitly, for improving the patient safety. Although there are structures with clear responsibilities of HCAI surveillance and control at the hospital level, these structures do not possess action tools. Measures for strengthening the capacity should be considered the first.

- Regarding the vaccination, what factors determine the vaccination refusal?

**AR**: I do not believe that vaccination refusal rate would be significantly higher in Romania than in other countries, and in order to know exactly how we stand, we plan to develop research studies in collaboration with the Faculty of Sociology. There are multiple causes. The lack of information first of all would be, followed by other factors, such as: disappearance of many communicable diseases from the infectious pathology range, media and social-media channels intoxicated the population with false information or with information unsupported by scientific evidences, population inclination to not comply with general rules, reticence in accepting synthetic products, conspiracy theory, and other factors making population sensitive and reacting as of a mass effect. And, of course, sometimes we observe a poor organization, planning and coordination of the health authorities, we should not forget their fault, because it is a factor which may be objectively corrected, for example lack of timely and sufficient provision with vaccines, even if sometimes there are objective motives explaining this deficiency.

There is a Vaccination Law Project in stand-by for two years in the Romanian Parliament, initially approved by the Senate, but occluded in the Deputy Chamber instead of being finalized. This law could solve the problems, starting with vaccines procurement, and continuing with education and information for the health personnel and especially for population, offering to Romanian children a framework and optimal conditions to be vaccinated, and thus to be much more protected from diseases. As the vaccination rate is not satisfactory in our country, with vaccination coverage under 85% in most vaccines, we consider it to be far under the threshold recommended by the WHO, of 95%, as the one stopping the spread of infection. For certain vaccines, such as anti-measles, -mumps and -rubella vaccine (ROR - Romania), the second dose administration is necessary, and the vaccination coverage for the second stage is even lower. The whole vaccines delivery system should also be reviewed and reconsidered, the cold chain at the level of family doctor practice, and a higher involvement of the Ministry of Education is necessary in health education, including the vaccination among the training topics. Currently, health education is optional in Romanian schools, and consequently only 5% of students benefit from health information. We need to find the way for health education to become part of health promotion campaigns, because we cannot progress economically and socially without health, and the health system costs are not sustainable if we do not develop preventive behaviors starting during the childhood. Vaccination, food, physical exercise, tobacco and alcohol consumption, periodical medical exam for healthy individuals – all have to be as systematically approached and organized, so that to allow skills and premises for healthy behaviors in early ages.

**R**: The new AMR Strategic Plan is proposed as a working frame for continuous action for reducing AMR spread and for increasing development of effective new antimicrobials.

-Please clarify what is the meaning of the concept “One Health” within the AMR policies.

**AR**: *One Health* notion refers to the attempt to control the broadening of antimicrobial resistance in general, and especially of antibiotic resistance. Antibiotics are the medicines to treat bacterial infections. Antibiotic resistance is due to excessive or inappropriate use in two sectors – the human, and especially the veterinary sector. At global level, it is about over half of antibiotic volume used in veterinary sector.

An important aspect is the existence of microorganisms producing sickness in humans and in animals, so that the possibility of cross-communication of microorganisms appears; in this context, microorganism resistance appearing in veterinary sector could produce consequences on humans. Another important aspect, discussed at the WHO level, is to define one list of antibiotics to be used exclusively in the human sector and never in veterinary sector. We have to mention that, in the veterinary sector, the antibiotics are not used only for treating animal diseases, but also in other two purposes: first, the preventive administration – in order to prevent occurrence of disease, and the second one is the use through the animal food, in fact a pseudo-use determining a rapid animal breeding by avoiding sickness. Current European regulations forbid antibiotic use for other purposes than treating infectious diseases in animals. But there are many other countries having an enormous use of antibiotics in veterinary sector. There are many examples: China, India, also countries of North-American or South-American continents. Phenomenon is harder to be controlled in these areas, with a more permissive legislation.

The third element, besides human medicine and veterinary medicine, is the environment. Presence of antibiotics in varying environments (for example, waste water) indicates their extended use and they are an indicator of the risk of emergent antibiotic resistance. Therefore, the need for monitoring the environment in terms of antibiotic presence, is clear. For example, the waste water which may get in the clean and drinking water, after passing through the sewage treatment.

We are in a paradoxical situation. The greatest progresses of medicine, such as vaccines, antibiotics, disinfectants and antiseptics, allowing important gains related to
decreasing morbidity and mortality due to diseases infectious, on the one hand, and increasing the life expectancy by drastic reducing of infant mortality, on the other hand, are currently challenged. We are witnessing an increasingly lower acception of vaccination, including in many developed countries (attention!), and, on the other hand, there is an emergence of infections induced by multi-drug resistant bacteria, in most cases the infection following the medical care. In this context, important advances of medicine are endangered, such as: transplantation, treatment of cancer patients using radio- and chemo-therapy, treating patients in intensive care units, and all of these will have a major impact. We may assume we are heading toward a post-antibiotic era, characterized by changing the morbidity and mortality models, with a formidable financial impact at the global GDP level, estimated by the World Bank at approximately 100 trillions of USD, up to 2050. There is also a risk of world economy decline, as global GDP, caused by the infections produced by multi-drug resistant bacteria. In conclusion, I would say that this “One Health” concept should integrate all the aspects mentioned before, starting from the human medicine issue, and extending to the veterinary sector, and then taking into account the environmental aspects.

The economic impact of implementing the strategic measures able to control the expansion of antibiotic resistance, is important in elaborating policies, and concerns several bearings: need to develop new products; banning the antibiotic use for other purposes than treating animals; and circulation of goods or products of animal origin containing antibiotic traces. I think this synthetic definition is the essence of the “One Health” concept.

-What measures do you consider necessary for solving the AMR phenomenon?

AR: The “One Health” concept integrates, in fact, three key institutions of the United Nations system: WHO (World Health Organization), FAO (Food and Agriculture Organization), and OIE (World Health Organization for Animal Health), and the environmental agencies. The industry should also be associated here, as the domain that could find solutions to the current situation, through advanced scientific research, of course. Unfortunately, pharmaceutical companies are not interested in producing new antibiotics, because the process is expensive and very time-consuming until these products are marketed.

In addition, two phenomena occur and should be mentioned. First, the antibiotic treatment is a discontinued treatment provided to the patients on limited periods of time, thus we do not discuss about a chronic disease with permanent treatment. The second element is the relative rapid occurrence, in a few years, of the resistant bacterial strains, conducting to an inefficient investment in time for the companies, without investment return - in most situations. Consequently, because of these phenomena conducting to a low interest in producing new antibiotics, building-up partnerships between governments of developed countries and pharmaceutical industry are to be done in order to develop new products, because this time we do not discuss about the treatment of a certain disease, but about a public health problem registered at national, regional and global level. There is one more thing to do, very important: to limit the use of antibiotics. This solution derives from the evidences confirming that there are very clear correlations between the uncontrolled use of antibiotics, and the occurrence of multi-resistant bacteria.

Therefore, in those countries with an extremely well controlled consumption, presence of multi-drug resistant bacteria is much more limited than in the countries with a high consumption at both human and veterinary sector. One bacteria does not become resistant to a certain antibiotic, unless it comes in contact with the antibiotic, especially with small quantities of antibiotic which do not destroy the bacteria, but allow the generation of a resistance mechanism. For example, consumption of food containing small quantities of antibiotic (especially food of animal origin), is such a trigger for resistance.

I would add the fact that, at the EU level, there is currently a concern and there are discussions about testing the imported products of animal origin for antibiotic contents. This could have a significant impact on the international food trade.

-What premises should exists so that the EU Strategy “a European One Health Action Plan against Antimicrobial Resistance (AMR)” to be efficiently applied in Romania?

AR: In order to implement the AMR recommendations, Romania, like the other EU member states, should get through few essential stages. First of all, each EU country has to have an Inter-sectorial Committee with representatives of all stakeholders involved in the limitation of antimicrobial resistance. This Committee should approve a national specific strategy including / covering all the sectors, with an action plan with clear responsibilities, implementation issues for each of the three major sectors involved: the human sector, the veterinary sector / agriculture, and the environment. And a possibility to develop research for discovering new antimicrobial substances, should be added and complete these three elements mentioned.

I would like to underline the crucial role of the Inter-sectorial Committee for the decision-making process: representatives of the Ministries have to be included, and for Romania, the secretaries of state from the Ministries should be included. The Technical Committee of Experts is also important and it should elaborate strategic documents and, subsequently, implementation proceeding of the Plan of action.

Reporter: Professor, you have a prolific experience in managing representative organizations, with excellent impact and results for the health system, population and patients, and you have faced various challenges and also get many professional satisfactions during your carrier. An important position you currently held is the one as a member in the WHO Executive Committee, with implicit responsibilities and benefits for Romania.

- What challenges health systems do face? Do they represent issues of global interest at the WHO level?

AR: There are many current problems at global level, sometimes overlapping with the national ones, and if we briefly analyze the topics on the agenda of the WHO Committee Conference, of January 2019, we see that current concerns of global interest refer to aspects such as: universal coverage of population with health services; access to medicines and vaccines (with a special focus on the access to the oncologic medicines); preparation for responding to public health emergencies, building / develop the capacity for rapid response to the public health problems in the member states, so that to enable the utilization of resources at global level; poliomyelitis eradication etc.

Many thanks for answering to our questions. Interview translated by Cipriana Mihăiescu Pinția