

THE IMPORTANCE OF DATABASES TO MANAGE THE PHENOMENON OF RESISTANCE TO ANTIMICROBIALS FOR VETERINARY USE

IMPORTANȚA BAZELOR DE DATE ÎN GESTIONAREA FENOMENULUI REZISTENȚEI LA ANTIMICROBIENELE DE UZ VETERINAR

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ABSTRACT | REZUMAT

This article aims to present the most significant organisms which are responsible for monitoring antimicrobial resistance (AMR) and principal references for AMR and antibiotic consumption in humans and animals. Databases and surveillance systems, from both the human health and veterinary sector, are becoming increasingly ample in data, and more complex as a result of recently made extensive studies on AMR.

For this purpose, a database was developed in the form of a table, including such sources, but also articles and books. In this report, important data are presented on the extent and implications of the AMR, but also about the importance of databases and monitoring of AMR, as well as the relations between monitoring organisms which are involved in the global fight against AMR.

Keywords: database, monitoring, resistance, antimicrobials

Prezentul articol urmărește prezentarea celor mai importante organisme responsabile cu monitorizarea rezistenței la antimicrobiene (RAM) și principalele surse bibliografice cu privire la consumul și RAM la om și animale. Bazele de date și sistemele de supraveghere, atât din sectorul sănătății umane, cât și din sectorul veterinar devin din ce în ce mai bogate și complexe, ca urmare a studiilor masive pe tema RAM efectuate în ultimul timp. În acest sens a fost concepută o bază de date, sub formă tabelară, care cuprinde aceste surse, dar și articole sau cărți. În acest material sunt prezentate date importante despre amploarea și implicațiile fenomenului, importanța bazelor de date și monitorizarea rezistenței la antimicrobiene, precum și relațiile organismelor de monitorizare în lupta globală împotriva RAM.

Cuvinte cheie: bază de date, monitorizare, rezistență, antimicrobiene

Antimicrobial resistance (AMR) is the ability of microorganisms to adapt to antimicrobial treatments, particularly with antibiotics. Excessive and improper use of antimicrobial drugs and inadequate infection control practices have turned AMR into a severe global public health threat (7, 37). Between 2010 and 2030, global antimicrobial consumption in the livestock sector is expected to increase by approximately 67%. However, only 25% of countries have implemented a national policy to combat RAM (7). EU was the first to recognize the importance of combating AMR, as shown by the Community Strategy of 2001.

This policy was reinforced with the EC's action plan of 2011, which introduced the concept of "One Health"

and where the AMR approach includes both humans and animals (9, 10). A new and comprehensive EU action strategy on AMR was adopted on June 29, 2017, that develops the previous plan and is based on its evaluation, feedback received on AMR, and an open public consultation (9, 10).

A comprehensive and coordinated collection and analysis of antimicrobial resistance (AMR) data are necessary to understand the extent of the problem, identify directions for evolution, determine the link between antimicrobials and AMR, and evaluate the policies and setting priorities for the future.

The information stored in the databases is important for future research that focuses either on finding at least similarly effective remedies like antibiotics, or on alternatives to antibiotics, but also on improving AMR surveillance systems. In terms of monitoring, over the years, this has been improved based on the experience gained in drafting reports. Also, storing information related to antimicrobial consumption and making annual reports at the European level allow to

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track the temporal and spatial trends regarding their use. With the concept of "One Health", and desire a harmonized surveillance system for collecting and reporting data on the use of antimicrobials in animals and humans, the EU adopted an integrated approach, a collaboration between the main monitoring groups.

ABOUT THE EXTENT AND IMPLICATIONS OF THE PHENOMENON OF AMR

Since the discovery of penicillin in 1928, antimicrobial drugs and especially antibiotics have become essential in the treatment of microbial infections in both humans and animals. Antimicrobials have revolutionized medical practice, so diseases that were once deadly have become commonplace and can be treated soon. This advantage, it is now particularly at risk due to excessive or inappropriate use of antimicrobials, which has increased the cases of occurrence and spread of multidrug-resistant bacteria (9, 10, 53).

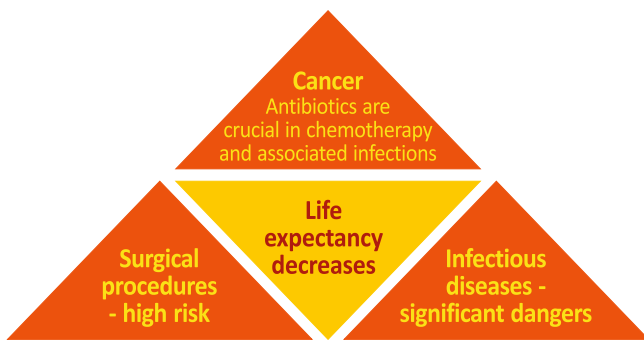


Fig. 1. Risks regarding AMR (11, 53)

These risks (Fig. 1) are because simple infections or wounds, as well as different conventional medical procedures, are based on antibiotic treatment (9, 11, 53).

The consumption of anti-infective drugs in veterinary medicine is significantly higher, compared to human medicine, and it is known that veterinary medicine is a significant contributor to the appearance and spread of antimicrobial resistance (AMR) in the human population (Fig. 2) (11, 40). According to literature, there are countries where the amount of antibiotics used in food-producing animals is almost double that of human medicine (1, 4). The world population is expected to reach 9.7 billion inhabitants by 2050, thus humanity is facing enormous challenges in providing protein foods and at the same time maintaining the health of the animals and the ecosystem (33, 53). With the "One World"- "One Health" concept, priorities for veterinary therapy are dictated by public health, considered principal, and then by animal health issues (40). "One Health" is a term used to describe a principle that recognizes that human health and animal health are interconnected, that the spread and trans-

mission of resistance genes is cross-linked and has been shown to be possible between humans, animals, animals, and humans as well as between animals and the environment (Fig. 2) (9, 11, 33).

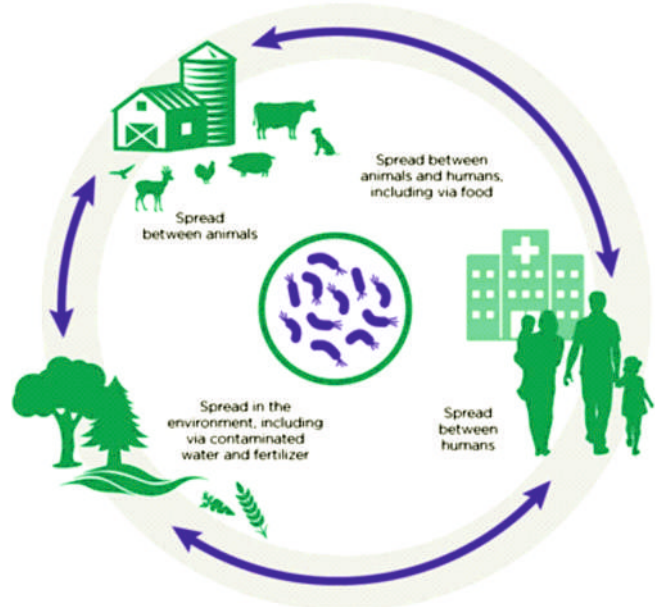


Fig. 2. Correlations and interdependence in the emergence of antimicrobial resistance (AMR) (55).

Antimicrobial resistance is one of the main threats to public health worldwide, it is a basic point in One Health's concerns, considering that the phenomenon can affect any person, regardless of age, gender, or country (12).

According to the European Commission (EC), the impact of the imprudent use of anti-infectives is considerable, so over 70% of the bacteria responsible for intra-hospital infections are resistant to at least one antibiotic. Also, AMR is responsible for approximately 25,000 human deaths / year in the EU and 700,000 worldwide and could cause more deaths than cancer by 2050 (10, 36).

Citing European Centre for Disease Prevention and Control (ECDC) and European Medicines Agency (EMA) due to RAM in the European Union (EU) approximately 2,500,000 days of hospitalization / year are in addition; 900 million euros / year are extra hospitalization costs; 600 million euros / year are losses of productivity, and annually about 4 million patients acquire an infection associated with the medical act (11, 36).

Along with antibiotics used in human medicine, their use for the treatment, prophylaxis, and breeding of animals led to selective pressure, which favoured the emergence and rapid spread of resistant bacterial strains (4, 6, 14, 41, 42). Animals can serve as mediators, reservoirs, and disseminators of resistant bacterial strains and/or resistance genes (26, 34, 42).

In Romania, the main indicator for antimicrobial con-

sumption in the veterinary sector, namely mg / PCU, which indicates the amount of active substance consumed equivalent by the population correction unit (PCU), was 100.5 mg/PCU (Table 1), being almost identical to the EU average (100.6 mg/PCU) in 2015 (27).

For the period 2013-2015, the average total antimicrobial consumption in mg active substance/kg was 124 mg/kg in humans = the average 118 mg/kg (with variations between 50-182 mg/kg) and 152 mg/kg in livestock animals = average 67 mg/kg (with variations between 3 -419 mg/kg). In a report about antibiotic consumption in 30 EU countries, this was lower in livestock than humans in 18 of the 28 EU countries surveyed, in 2 countries it was similar, and in 8 countries the consumption was much higher for animals than humans (11, 17).

The amounts of antimicrobial products for veterinary use sold in different countries are related, among other things, to the demographics of animals in each country, the population correction unit (PCU) was established as the denominator for sales data. One PCU equals one kilogram of animal biomass (27, 29).

Table 1

Consumption in tonnes of active substance of antimicrobial agents for veterinary use in livestock animals, population correction unit (PCU) and sales in mg/PCU in Romania (27, 29)

Consumption (tonnes) for livestock	PCU (1.000 tons)	mg/PCU
257.2	2.559	100.5



$$\text{xx mg} \text{ divided by } \text{xx kg} = \text{xx mg/PCU}$$

In Romania, as in Europe, irresponsible use of antibiotics in food-producing animals has led to the development of resistance to animals or to people who consume meat and meat by-products.

Antibiotic resistance appeared mainly through the use of antibiotics as growth promoters, in the preservation of animal foods or most often by the administration of irrational antibiotics, without prescription and antibiogram (11). The main causes that favour the emergence of resistance to drugs are under-dosing or inadequate dosing, treatment of viral diseases in animals with antibiotics, administration broad-spectrum antibiotics when narrow-spectrum is enough (11).

The link between antibiotic and antimicrobial resistance (Fig. 3) has already been statistically demonstrated ($p < 0.05$) for several antibiotics, as follows: *Escherichia coli* resistant to fluoroquinolones in humans and animals, *Escherichia coli* resistant to cepha-

losporins from generation 3 & 4 in humans, *Escherichia coli* resistant to tetracyclines and polymyxins in animals, *Klebsiella pneumoniae* resistant to carbapenems and polymyxins in humans, *Campylobacter spp* resistant to macrolides from animals associated with cross-resistance in animals and humans (11, 40).

Also, has been reported multiple resistance of *Salmonella typhimurium* to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline (11). An excessive prescribing of antibiotics is not the only source that pollutes the environment. Therefore as early as the 1970s, antibiotics could be found in the meat of cattle, pigs, and birds, and the same antibiotics were later identified in municipal and groundwater systems or soil, with its dramatic consequences. The emergence of resistance to fluoroquinolones following the common infections with *Campylobacter spp.* and *E.coli* in humans, as a result of their use in animal feed, with the transmission of human resistant bacteria, through meat and animal products (11).

Most reports refer to the increasing tendency of the use of antimicrobial substances used in sub-therapeutic doses in cattle and birds. Evidence has shown that the prevalence of antibiotic resistance among humans was triggered by the introduction of enrofloxacin in poultry feed, which prompted the FDA in 2011 to prohibit the use of this antibiotic in birds (11).

Antibiotics given to animals are not completely absorbed, so, depending on the antibiotic, between 30 and 90% of the antibiotic can be excreted in the urine or faeces in the bioactive state, even intact or in the form of metabolites, which can maintain their antimicrobial activity. Antibiotics given to animals can reach soil and water through improperly disposed of medical waste, or through dust from industrial growth units (Fig. 3) (11).

Genomic screening techniques have not yet been able to fulfil their promise of "revolution" in discovering of new antimicrobial structures, so, no new antibiotics have been introduced for a long time yet (Fig. 4), fact that in time led to the appearance of the "superbugs" (i.e., bacteria resistant to most antibiotics used). Classical examples of "superbugs" are *Methicillin-Resistant Staphylococcus aureus* (MRSA) and *M. tuberculosis* super-resistant to antibiotics (11).

At the global level, resistance is no longer considered a novelty to health as it was in 1950 when it was first observed. Today, there are numerous national and international agencies concerned with taking the necessary measures to alleviate the phenomenon of antibiotic resistance and to maintain the health of human and animal populations. Noting early on the importance of this phenomenon, the EU is at the forefront of actions to address the AMR. However, a single, isolated action cannot offer the appropriate solution (9).

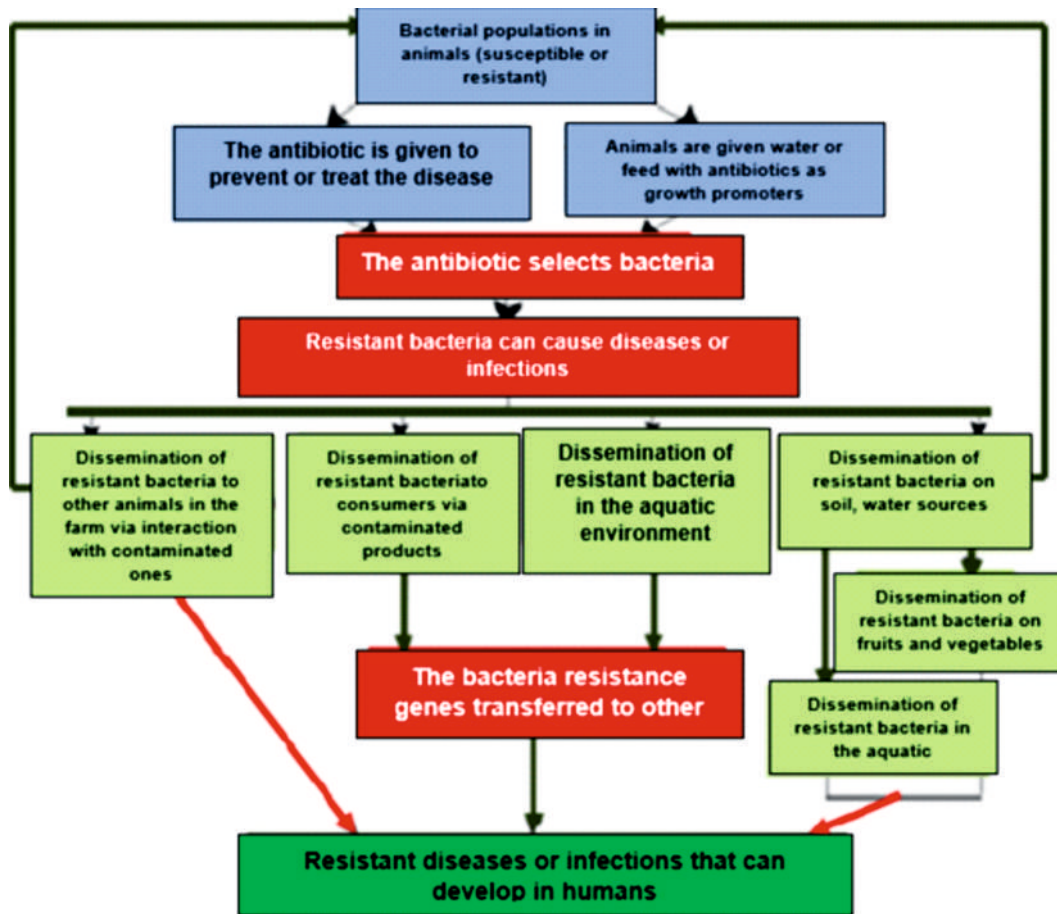


Fig. 3. Mechanisms for transmitting AMR (11)

In November 2011, the Council of Europe, through the EMA, launched the first action plan with direct involvement on the risks posed by AMR (10, 11). The Council of Europe concluded five years later that there is a need for a new and comprehensive action plan, which is based on a holistic approach, in line with the "One Health" initiative. The action plan establishes twelve specific measures to be taken in the sector of human and/or veterinary health. At the European level, the surveillance of the phenomenon of resistance is principally coordinated by the ECDC (9, 10, 11, 20).

Following this plan, EU action focused on assisting the Member States in the initiation, implementation and monitoring of national action plans of "One Health" (9).

In Romania, efforts are still being made to collect primary data on animal resistance to establish the link with the official monitoring systems in the EU. However, the control and recovery of antimicrobial resistance tend to become a priority also for public health in Romania (11, 12).

Among the European countries, an example of good practice is Denmark, which has become an international leader in the fight against AMR. In this country, all sales of antibiotics for human and veterinary use, as well as all reports of resistance to humans, animals,

and animal products are monitored by the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) (11, 39).

INTERNATIONAL DATABASES RESPONSIBLE FOR MONITORING AMR

The database has been organized in the form of a biological list and includes articles, books, website databases, and reports regarding AMR from 1992 to the present. In this paper, the most important sources and organisms that are fighting against AMR have been selected to be described. The most popular databases (3) (Table 2), which include anti-infectious products and their resistance are Antimicrobial Drug Database (AMDD), The Comprehensive Antibiotic Resistance Database (CARD), European Antimicrobial Resistance Surveillance Network (EARS-Net) and the Mycology Antifungal Resistance Database (MARDy).

Antimicrobial Drug Database (AMDD)

It is a biological database, which seeks to consolidate information on antibacterial and antifungal drugs from a variety of sources, such as PubChem, PubChem Bioassay, ZINC, ChemDB and DrugBank (Fig. 5), to advance in the field of antimicrobial resistant agents'

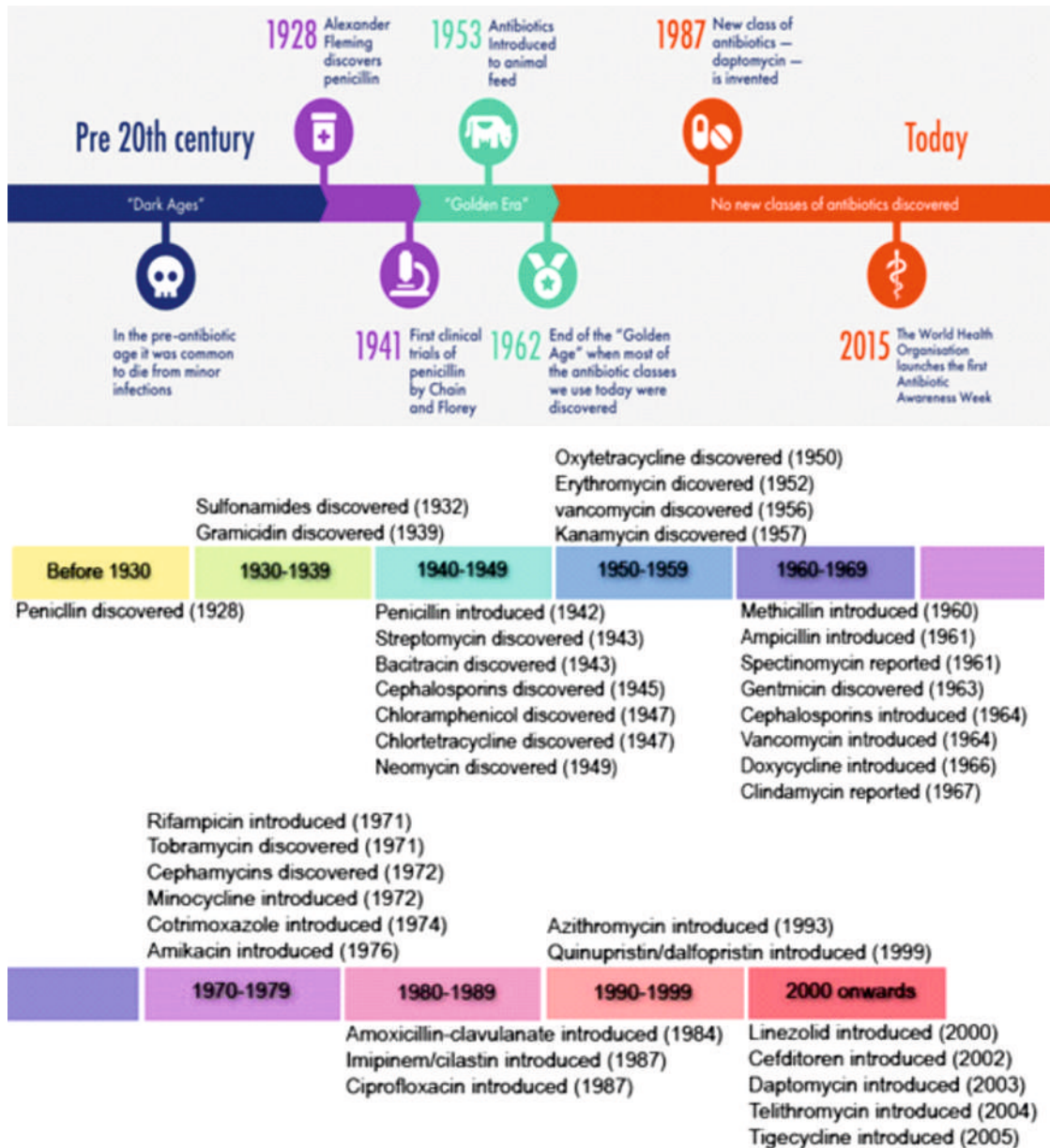


Fig. 4. Antimicrobial evolution up to the "superbug" era (11, 45)

therapy (13). In 2012 AMDD contained approximately 2,900 antibacterial compounds and 1,200 antifungal compounds. These compounds were organized based on their description, action, format, bioanalysis, molecular mass, hydrogen bond donors and hydrogen bond acceptors (13). The function of this database is to provide a complete tool to facilitate the development of new antibacterial and antifungal compounds (13).

Antibiotic Resistance Database (ARDB) and Comprehensive Antibiotic Resistance Database (CARD)

It is a database that tracks antibiotic resistance genes, mechanisms of action, resistance profile and ontology. In the year of the creation of the ARDB (2009),

there was no similar system. ARDB contains resistance information for 13,293 genes, 377, 257 antibiotic types, 632 genomes, 933 species, and 124 genera (38). Recently, all the information from the ARDB was transferred to the Comprehensive Antibiotic Resistance Database (CARD), which is a biological database that collects and organizes information on resistance genes, proteins, and antimicrobial resistance phenotypes. The database includes all types of drug classes and resistance mechanisms, and the information is structured based on the ontology (38).

Mainly CARD is based on molecular determinants of antibiotic resistance, genes, and gene regulators that confer antibiotic resistance and contains molecular sequences from over 1,600 antibiotic resistance genes.

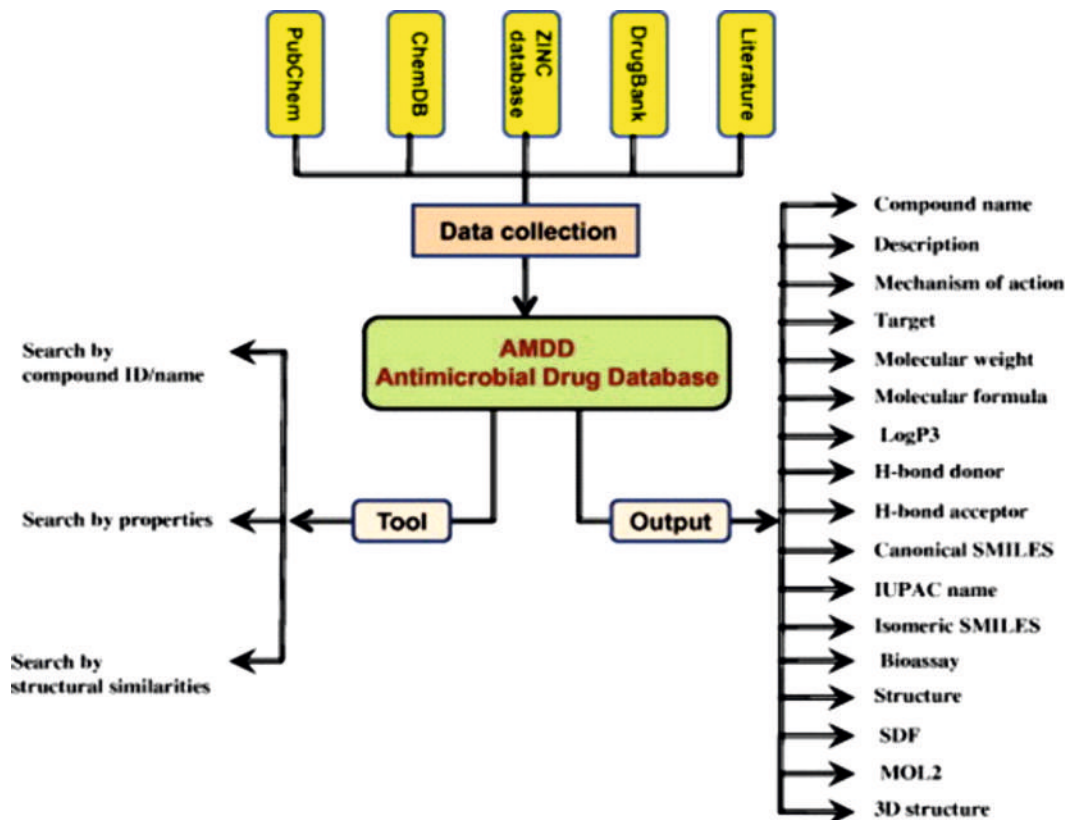


Fig. 5. AMDD structure (13)

The key to CARD development was the establishment of an ontology with antibiotic resistance (ARO) (47). All CARD molecular sequences are classified and organized based on ontology to define their role within the cell (e.g., genome, gene, transcript, and polypeptide).

At the base of the CARD is a new Antibiotic Resistance Ontology (ARO) (47). Within the ARO, the core of this organization of molecular data is the relationship of drugs to antibiotic resistance targets and genes (Fig. 6) (47).

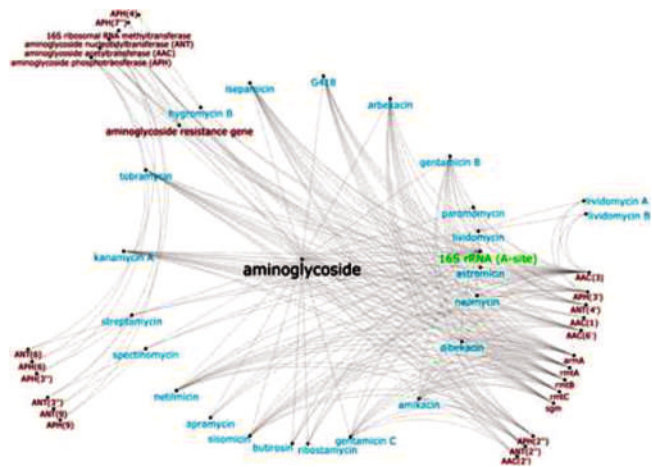


Fig. 6. Organization of antibiotics in the aminoglycoside class (blue), their target (green), and the aminoglycoside resistance genes (red) in the CARD ontology, illustrating the diversity of genes conferring resistance. Nodes represent the ontological terms, while the edges represent the relationships between the ontological terms (47)

CARD contains information about antibiotic resistance genes, antibiotic ontology, and antibiotic resistance mechanisms (Fig. 7). As of May 22, 2019 CARD contained: predictors of resistance: 82 pathogens, 5,524 chromosomes, 7,305 plasmids, 76,710 WGS assemblies, 175,753 alleles. There are currently 85 pathogens, 8,046 chromosomes, 18,337 plasmids, 90,531 WGS assemblies, 182,532 alleles (38).

The European Antimicrobial Resistance Surveillance Network (EARS-Net)

It is a central and comprehensive database for the EU, focusing on seven bacterial agents, namely: *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium* (20).

EARS-Net is the result of the collaborative effort of 29 countries, where the information contained is about antibiotic resistance, and the data is determined according to the EUCAST standard. About 80% of the participating countries use the EUCAST standard for the detection of antibiotic resistance. EARS-Net was esta-

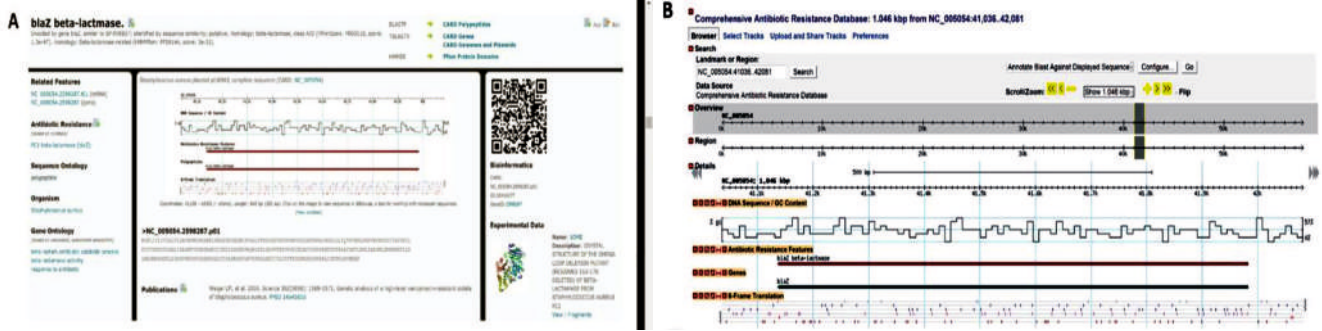


Fig. 7. Presentation of the blaZ gene in beta-lactamase-producing *Staphylococcus aureus* in CARD: (A) The CARD gene web page provides annotation, access, source information, ontological classification, and associated molecular characteristics (mRNA, polypeptides, coding sequences); (B) Dynamic navigation and blaZ gene analysis (47)

published in 1998 as EARSS, funded by the Directorate General of EC for Health and Consumer Affairs in collaboration with the Ministry of Health, Welfare and Sport of the Netherlands. In January 2010, EARSS was transferred to the European Centre for Disease Prevention and Control (ECDC) and was renamed EARS-Net (20).

Mycology Antifungal Resistance Database (MARDy)

It is a database that contains resistance mechanisms and associated antifungal drugs. This database has the potential to become a significant tool for clinicians and researchers in their fight against antifungal drug resistance.

MARDy includes resistance mechanisms identified to humans, animals, and plants for the main drugs used in antifungal therapy. The complete database can be downloaded, and has been arranged in several files as follows: based on the organism, based on the number of chromosomes and genes, as well as on the type of antifungal (Fig. 8) (35).

While CARD and ARD are databases that include mechanisms of bacterial resistance to antibiotics and FunResDB is limited to the mutation of Cyp51A gene, MARDy become the first database for the fungal kingdom to contain broad resistance mechanisms of the fungal genome (35).

ORGANISATIONS INVOLVED IN ANTIMICROBIAL RESISTANCE MONITORING

EU is not the only one who recognizes the threat of AMR, and in approaching this subject at the highest political level, many countries outside the EU, as well as international organizations participate. International cooperation is a fundamental element of the AMR action plan (7).

World Health Organization (WHO)

It is pursuing a comprehensive strategy and clear directions to help countries introduce effective antibiotic resistance monitoring systems and implement intervention actions, such as antibiotics being bought only on a prescription basis (51).

European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA) and European Medicines Agency (EMA)

There are three broad categories of entities between which this cooperation takes place, namely: EU-level decision-makers (European Commission, European Council, and European Parliament), scientific consultants (EMA, EFSA, and ECDC) and international organizations (WHO, FAO, OIE) (Fig. 9) (7).

The first significant collaborations in this direction between organizations led to a report published in the EFSA Journal, on January 30, 2015, and is a collaboration between ECDC, EFSA, and EMA (16, 17).



Fig. 8. MARDy - files in the database (<http://www.mardy.net/>)



Fig. 9. Decision-makers in the EU, scientific consultants and international organizations (7)

For the first time, they have jointly explored the associations between antimicrobial consumption and antimicrobial resistance of bacteria from humans and animals, using data from 2011 and 2012, data available from five monitoring networks in the EU (16).

Data on antimicrobial use and resistance in animals / people to countries that reported were analysed using logical regression models. This cooperation, which eventually resulted in a report, was briefly called Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA). On June 28, 2017, a second report was also published by JIACRA on the integrated analysis of antimicrobial and AMR consumption in bacteria from humans and animals, as a result of data obtained by EU surveillance agencies for 2013-2015 (16, 17). In addition to these joint reports, other agencies, such as ECDC, publish annual reports on antimicrobial use, such as the one published in Stockholm in 2018 (51), others such as guidelines for prudent antimicrobial use in 2017 (54) or a 2019 report that provides us with information on deficiencies in health care regarding antibiotic use (15).

ECDC also provides several useful tools for antibiotic use and resistance, such as Antimicrobial resistance in Europe - Data visualization tool, Atlas of Infectious Diseases and Antimicrobial Resistance or different surveillance systems such as EARS-Net (European Antimicrobial Resistance Surveillance System) or TESSy (Table 2) (18, 19, 20, 21, 22).

Data visualization tool is an interactive infographic which shows us the percentage resistance to *Salmonella* spp., and *E. coli* in food, animal and human / countries for different types of antibiotics (Fig. 10).

Another useful tool proposed by ECDC is the Surveillance Atlas of Infectious Diseases and Antimicrobial Resistance (Fig. 11), that provides us data related to surveillance but also microbial agents regarding antimicrobial resistance. It also publishes annual reports on antimicrobial resistance surveillance in Europe.

EFSA is an organization of EU, responsible for assessing health risks, directly related to food and feed, nutrition, animal health and welfare, and also plant health and protection. EFSA issues scientific opinions and communicates on existing risks (46). EFSA is another agency actively involved, which has published alone or in collaboration with ECDC some reports on antimicrobial resistance of bacteria in humans, animals, and food in 2010, 2016, and 2017 (25, 26, 27).

In Romania, within the National Sanitary Veterinary and Food Safety Authority (ANSVSA) is an EFSA Focal Point, considering its areas of interest, ANSVSA acts in partnership with it (46). ANSVSA and EFSA organized at Bucharest a National Conference with title Focal Point EFSA, on 25.10.2018 where they presented different issues related to health risk assessment of food in the EU, including the evolution and implications of AMR in the light of "One-Health" in Romania (11, 49).

EMA published in 2017 a comprehensive report about sales and consumption of antimicrobials in 30 European countries in 2015. EMA also established the Antimicrobial Advice ad-hoc Expert Group Recommendations (AMEG) to guide the impact on public health and animal health, the use of antibiotics in animals, as



Fig. 10. Tetracycline resistance in pigs in Romania, according to Data visualization tool (18)

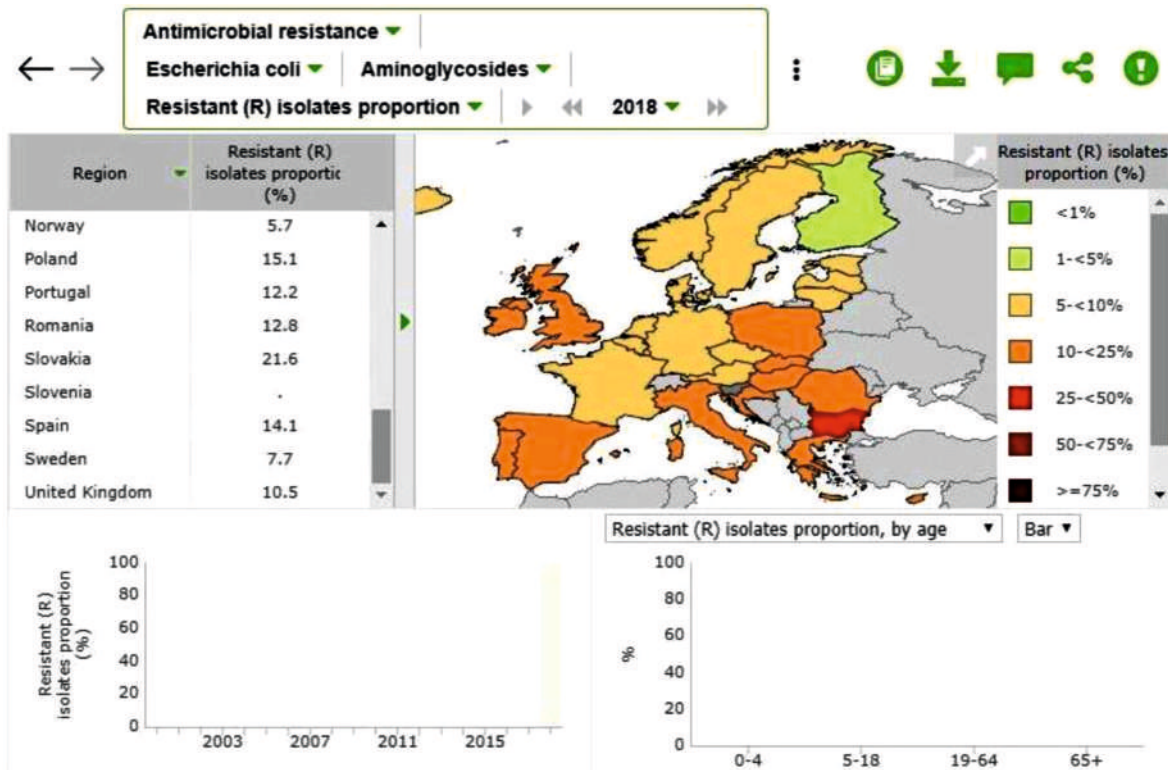


Fig. 11. *E.coli* resistance to aminoglycosides in Europe (21)

well as the measures needed to control human risk. AMEG is a group established by mutual agreement between the Committee for Veterinary Medicinal Products (CVMP) and the Committee for Medicinal Products for Human Use (CHMP) (12, 29, 30).

CVMP is part of the European Medicines Agency (EMA), responsible for veterinary medicinal products. CVMP plays a vital role in the authorization of veterinary medicinal products in EU. In 2016, CVMP adopted the strategy on antimicrobials for veterinary use for the period 2016-2020, which contains six main goals (28). The latest action in Europe held in Brussels on 15 October 2019, on EU action on AMR, as part of the European action plan "One Health" against antimicrobial resistance (8, 9).

Food and Drug Administration of the United States Department of Health and Human Services

Another important report on the sale and distribution of antimicrobials for use in livestock was published by the FDA (Food and Drug Administration) in 2018. The FDA is active in the US, and a similar organism in the EU is EMA (the European Medicines Agency) (32).

NETWORKS INVOLVED IN ANTIMICROBIAL RESISTANCE MONITORING

The European antimicrobial consumption and antimicrobial resistance surveillance networks are: the European Surveillance of Antimicrobial Consumption

Network (ESAC-Net), European Antimicrobial Resistance Surveillance Network (EARS-Net) and European Surveillance of Veterinary Antimicrobial Consumption (ESVAC-Net). In addition to these at the national level, each country has its surveillance network.

European Surveillance of Antimicrobial Consumption Network (ESAC-Net)

It is a surveillance network at the European level, providing baseline data on antimicrobial consumption. ESAC-Net collects and analyses data on antimicrobial consumption in EU and / EEA countries, both in the community and in the human hospital sector, with help of the European Surveillance System (TESSy). This surveillance network is based on the system of classification of antibiotics by type ATC (Anatomical, Therapeutic, Chemical) proposed by the WHO and controlled by ECDC, thus the national surveillance networks upload the information in a central database (19). ESAC-Net coordination was transferred from the University of Antwerp, Belgium, to the European Center for Disease Prevention and Control, in July 2011 (19).

European Antimicrobial Resistance Surveillance System (EARS-Net)

EARS-Net is the largest public network that surveillance antimicrobial resistance in Europe, and is also coordinated by ECDC (20). In the EARS-Net project are included 30 countries, and it is one of the frequently used databases under ECDC coordination, according to the 2014 ECDC statistics (Fig. 12) (20, 54).

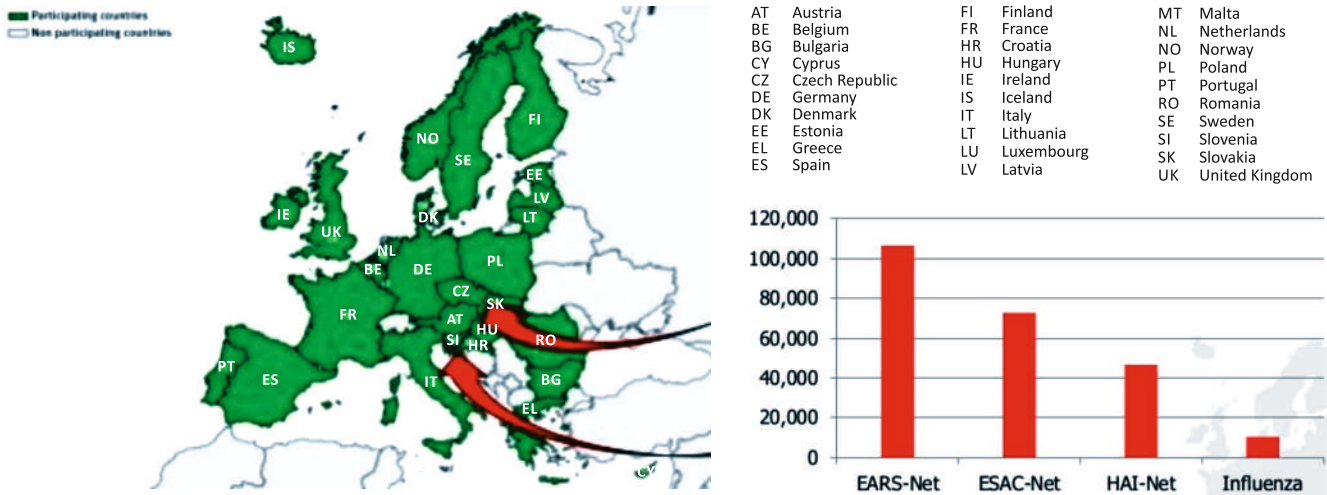


Fig. 12. The 30 countries participating EARS-Net and the use of the ECDC database during the January-October period of 2014 (54)

The EARS-Net objectives: (1) collecting comparable, representative and accurate data about AMR; (2) analysis of temporal and spatial trends of AMR in Europe; (3) providing timely data on AMR; and (4) encourage the implementation, maintenance, and improvement of national programs for monitoring AMR (20).

European Antimicrobial Consumption Surveillance System in Veterinary Medicine (ESVAC-Net)

It collects information on the administration of antimicrobial drugs in animals throughout the EU (Fig. 13)

(31). This type of information is essential to identify potential risk factors that could lead to the development and spread of antimicrobial resistance in animals. The European Medicines Agency (EMA) started this project in 2009, following a request from EC to establish a harmonized system for data collection and reporting on the use of antimicrobials in animals in the EU and European Economic Area (EEA) (31). To ensure an integrated approach, EMA requested to consult ECDC, EFSA, and the reference laboratory of the EU for antimicrobial resistance (EURL-AMR) (5, 27).

Since 2009, ESVAC-Net has been producing annual reports on antimicrobial / country sales, taking into account an approximation of the total number of “potentially exposed to treatment” animals in each country (population correction unit - PCU) (5, 29). ESVAC-Net collects data on the marketing of veterinary medi-

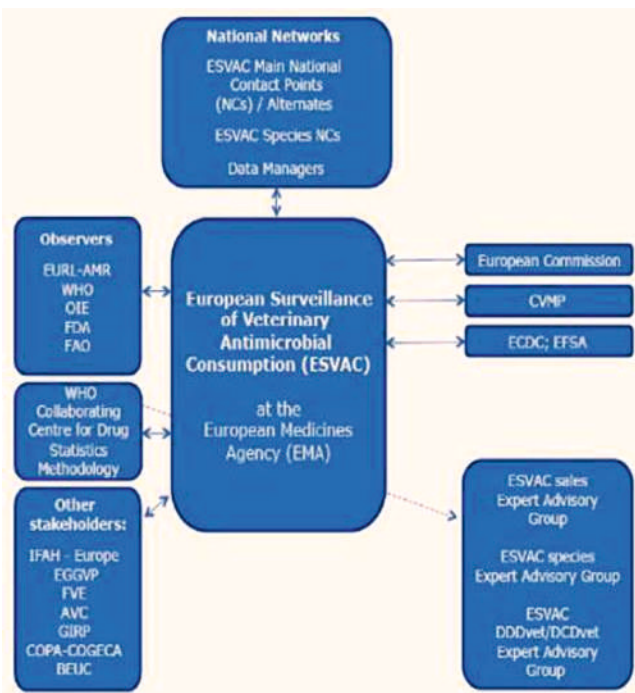


Fig. 13. The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) Network about AMR (11)



Fig. 14. The five components of an efficient, coordinated and complementary surveillance system (43)

cial products in the EU Member States, EEA countries and Switzerland. In the 2016 report, ESVAC established the average daily dose of active substance used / kg body by species (defined daily doses for animals - DDDvet) and the average dose of a treatment, correlated with the weight of the animal and the species to which it belongs (defined course doses for animals DCDvet) (5, 29).

Surveillance and monitoring are known as critical components in antimicrobial resistance by the World Health Organization and are part of the strategic priorities of the global AMR action plan (43, 44).

An efficient surveillance system should be coordinated and complementary (Fig. 14) between sectors and levels, but many small countries with average incomes, are unable to establish and maintain these surveillance systems to collect and use data about antimicrobial resistance (44).

All EU Member States are required to monitor consumption but also antimicrobial resistance and to report national data to ESAC-Net, EARS-Net and ESVAC-Net (7).

THE ROMANIAN STRATEGY FOR THE PRUDENT USE OF ANTIMICROBIAL SUBSTANCES

In Romania, the Ministry of Health elaborated in 2016 the "National Plan for the surveillance and control of nosocomial infections and for monitoring the use of antibiotics and antibiotic resistance".

Also in 2016, the National Veterinary Sanitary and Food Safety Authority (ANSVSA) issued a guide entitled "Guidelines for the prudent use of antimicrobial substances in veterinary medicine (2015 / C 299/04)" (2, 50). The livestock sector, which is a large consumer of antibiotics, is under the control of ANSVSA, the only authority that can control and limit the administration of antimicrobials in animals. Also, ANSVSA through the Institute for the Control of Biological Products and Veterinary Medicines (ICPBMV) made reports in 2014, 2015, and 2016 on the consumption of antimicrobial veterinary medicinal products (5).

Reporting of the consumption of veterinary antimicrobial medicinal products is carried out according to the requirements of the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project, an initiative of EC coordinated by EMA (5).

In Romania, it was established by Government Decision no. 879/2018, the National Committee for the Limitation of Antimicrobial Resistance (CNLRA). CNLRA is coordinated by the Ministry of Health and the expert group will have a total of 15 members and whose membership will be determined every three years by decision of the president of CNLRA (52).

DATABASE OF THE SURVEILLANCE OF ANTIMICROBIAL CONSUMPTION AND AMR

Currently, one of the most important topics in the biomedical field is antimicrobial resistance, so the preparation of databases with the most important sources and monitoring organisms in this topic is absolutely necessary. A database of AMR monitoring organisms, which is, in fact, a way of storing as much information in one place, with the rapid possibility of updating and retrieving them, in a period when studies in this field are accelerated, it is a useful tool for future research. After consulting the current literature existing in the field of AMR, with the help of online search engines, it was made a list in the form of a table of the principal references (Table 2).

CONCLUSIONS

In addition to simple monitoring of consumption and antimicrobial resistance, all monitoring systems have a data storage base, either their own or they transmit the data to a central database.

Databases and surveillance systems from both the human health sector and the veterinary sector are becoming increasingly ample and complex as a result of extensive studies of AMR made lately in an attempt to solve the problem. Research, data, and high-quality analysis are essential as a basis for new actions against AMR and to help decision-makers from the EU level to improve existing measures.

Although the EU has a wide range of programs and monitoring activities across different sectors, nevertheless remain some gaps in the surveillance, especially if there is no effective collaboration, and some states involved do not apply the recommendations.

A well-made database remains a starting point for effective management of antimicrobial resistance, and a global fight with international cooperation is an essential element of the action plan against AMR.

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Table 2

A database proposal on surveillance of antimicrobial consumption and AMR

Nr. crt.	Name of organism / article / book / report / internet link
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