NATIONAL “ONE HEALTH” ANTIMICROBIAL RESISTANCE STRATEGY

(2019–2024)

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1. INTRODUCTION

Antibiotics, which have been in use for more than 75 years, are antimicrobial medicines that are frequently used for treatment in human and veterinary medicine. The use of antibiotics has significantly reduced mortality and complications related to numerous infectious diseases and has had a significant impact on the development of medicine.

Bacterial resistance to antibiotics is growing rapidly worldwide and has become a serious public health problem, with the consequences of infections with resistant microbes apparent in greater patient mortality, increased treatment complications, longer hospital stays and greater treatment costs. Increased resistance means that antibiotics are no longer effective against the bacteria that caused the infection. Those, particularly at risk include patients who, owing to the type of treatment they are receiving (chemotherapy for malignant diseases, transplants, treatment in intensive care units), are frequently in urgent need of effective antibiotic treatment. Antimicrobial resistance is furthermore associated with additional treatment costs, with ineffective antibiotics frequently leading to more complex and lengthier treatment, which causes a significant additional financial burden for the healthcare system and society as a whole.

The development of bacterial resistance to antibiotics is a natural process that occurs as a result of gene mutations in bacteria. Bacteria develop resistance themselves or acquire it from other bacteria. Bacteria can develop or acquire various resistance mechanisms as a result of which they become resistant to various types of antibiotics. In this way, the range of antibiotics available for treating infections is significantly reduced.

Links exist between antibiotic use and bacterial resistance, although the connection is complex and greatly accelerated by the inappropriate and excessive use of antibiotics. Antibiotics destroy susceptible bacteria, while resistant bacteria continue to multiply when exposed to antibiotics. These resistant bacteria can also spread and cause infections in individuals who have not taken antibiotics.

The use of antibiotics in veterinary medicine began very soon after the introduction of antibiotic treatment in human beings. To begin with, antibiotics were only used to treat specific animal diseases. Later, however, they began to be used to prevent infections in populations with a greater risk of bacterial diseases. The addition of antibiotics to animal feed in order to promote growth (so-called growth promoters) was a problematic issue in the past but has been prohibited in the EU since 2006 (Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition). Given that the development of new antimicrobials is failing to keep pace with the increase in microbial resistance to existing antimicrobials, the additional restrictions on the use of antibiotics in animals set out in the new Regulation (EU) 2019/6 of the European Parliament and of the Council on veterinary medicinal products, published in 2019, will enter into force and the monitoring of their use and reporting on it will be regulated in a uniform manner.

The majority of antibiotics used for the treatment of animals fall into the same or similar pharmacological categories as those that are used for humans. Accordingly, bacteria in animals frequently develop a similar form of secondary resistance, which can lead to problems in the treatment of humans and animals, regardless of the populations in which the resistance was acquired. The phenomenon of multidrug-resistant strains of bacteria in animals is important from the point of view of animal health and, at the same time, the protection of human health.

Action to maintain the effectiveness of antibiotics is essential for the successful treatment of humans and animals and for ensuring food safety. The cooperation of both sectors and all stakeholders is very important in this process.

Particularly important from the point of view of the impact on the development of antimicrobial resistance in the environment are the discharge and release of antimicrobial medicines and resistant bacteria into the environment, along with the discharge of certain other chemicals and hazardous substances that can cause resistance, such as biocides and heavy metals. The main sources and channels via which chemicals that

cause antimicrobial resistance find their way into the environment are: mismanagement of waste medicines, excrement of humans and animals previously treated with antimicrobials, industrial waste water, fertilisation of agricultural land with livestock manure, the use of sewage sludge and the use of compost or digestate obtained from waste in agriculture.

Resistant bacteria can be transmitted between humans, transmitted from humans to animals and vice versa, or acquired from the environment. Resistant microbes can spread throughout the world, something which threatens our ability to treat infectious diseases and also threatens numerous other advances in healthcare and medicine. Important roles in the prevalence of resistance are also played by the public health system (vaccinations, healthcare systems), migration and travel, hygiene conditions and population density.

The spread of antimicrobial resistance is becoming an increasingly serious problem because of the lag in the development of new antimicrobials. This represents a further risk, in that infections that are today considered minor will once again become serious.

Antimicrobial resistance already represents a serious social and economic burden at the global level. According to some estimates, it is responsible for 25,000 deaths every year in the European Union alone (ECDC and EMA, 2009) and a worldwide total of 700,000 deaths. Unless trends change, the number of deaths could grow to 10 million by 2050. This means that by 2050 the number of deaths as a result of antimicrobial resistance would exceed the total annual number of deaths from cancer (8,200,000) and road accidents (1,200,000) (https://amr-review.org/Publications.html, 2016). It is also estimated that the annual costs to the European Union from healthcare needs and lost productivity as a result of antimicrobial resistance are €1.5 billion (ECDC and EMA, 2009). According to an OECD estimate, if countries fail to take effective action, the consequences of antimicrobial resistance will amount to an average of US$3.5 billion a year in the 33 countries included in the analysis. Simple, inexpensive and cost-effective measures at the national level such as hand hygiene and the prudent prescribing of antibiotics could prevent three out of four deaths at a cost of just two US dollars per person per year (OECD Policy Brief, 2018).

The World Health Organisation (WHO) was already warning in 2012 that antimicrobial resistance was one of the biggest health threats facing the world. In 2015 it adopted the Global Action Plan for Antimicrobial Resistance. It also drafted a Global Framework for Development and Stewardship to Combat Antimicrobial Resistance, which was presented at a meeting of the UN General Assembly in October 2018.

In June 2019 the Council of the European Union adopted the ”Council conclusions on the next steps towards making the EU a best practice region in combatting antimicrobial resistance”, in which it emphasises that antimicrobial resistance represents a serious cross-border health threat and calls on Member States to ensure that they have multi-sectoral national action plans and the relevant monitoring mechanisms in place and that sufficient human and financial resources are allocated for their implementation (Official Journal of the European Union 2019/C 214/01).

Among the actions in the field of integrated management and continuous improvement of quality and safety set out by the Resolution on the National Healthcare Plan 2016–2025 “Together for a society of health” (Official Gazette of RS 25/2016), adopted by the National Assembly, is the adoption of a national strategy for the prudent use of antimicrobials and the management of antimicrobial resistance in human and veterinary medicine.

Three-year action plans will be drawn up for the implementation of the strategy. These will define in greater detail the activities relating to the implementation of actions and the bodies responsible for them and provide an estimate of the financial resources required.

1.1 ANTIMICROBIAL RESISTANCE: THE SITUATION IN SLOVENIA

1.1.1 Data

Antimicrobials are among the most commonly prescribed medicines in Slovenia, both in the community (at the primary care level) and in hospitals. Studies for EU Member States show that antibiotics are taken every day by between 1% and more than 3% of the general population and between 20% and 50% of hospital patients. Antibiotics are also frequently prescribed in social care institutions that provide healthcare (nursing homes). Approximately 90% of all antibiotics are prescribed in the community and the remainder in the hospital sector (https://ecdc.europa.eu/en/publications-data/antimicrobial-consumption-annual-epidemiological-report-2016). In Slovenia, antibiotics for the treatment of humans and animals can only be obtained with a prescription from a doctor or vet.

Figures from 2016 show that Slovenia is one of the six countries in the European Union/European Economic Area with the lowest consumption of antibiotics in the community (expressed as DDD per 1,000 inhabitants per day). This figure appears less favourable if expressed as the number of prescriptions per 1,000 inhabitants per year since Sweden had 36% fewer prescriptions than Slovenia. There are clear differences between healthcare regions in Slovenia, with doctors in Slovenia's north-eastern region prescribing more antibiotics than doctors in other regions. In terms of hospital use of antibiotics, Slovenia is one of the eight countries with the lowest consumption, although Slovenia's consumption of antibiotics is 75% higher than that of the Netherlands, the country with the lowest consumption in the European Union. Compared to the European average, the high consumption of carbapenems and the increasing consumption of colistin are a cause for concern.

Hospitals and other healthcare institutions are places where resistant microbes frequently emerge and spread. The results of national cross-sectional studies of hospital-acquired infections show that Slovenia is managing hospital-acquired infections but has not succeeded in reducing them. In order to improve the situation, conditions must be put in place to allow monitoring of the incidence of hospital-acquired infections in intensive care units and monitoring of infections in surgical wounds and infections caused by *Clostridium difficile*. Appropriate measures must also be taken to ensure suitable prevention and control of the most frequent hospital-acquired infections such as pneumonia, septicaemia, urinary tract infections and surgical wound infections. Expert oversight of the implementation of infection prevention and control programmes in the majority of Slovenia's hospitals has shown that the number of doctors and nurses available for hospital-acquired infection control is inadequate for the number of hospital beds and that there are too few single rooms for isolation. Slovenia is, in fact, at the bottom of EU rankings as regards facilities for patient isolation.

Data from a 2016 study by the European Antimicrobial Resistance Surveillance Network (EARS-Net) show that the resistance of the commonest bacteria in Slovenia is at the European average, while the resistance of some bacteria is above it. As in other countries, the bacteria that are the biggest cause for concern in Slovenia are bacteria with carbapenemases, which are resistant to the antibiotics used to treat the most serious illnesses.

It is estimated that up to 50% of antibiotics are prescribed unnecessarily and/or incorrectly. An important role in increasing the resistance of bacteria to antibiotics can therefore be attributed to their excessive and incorrect use. Poor hygiene and poor supervision of hospital hygiene are important factors in the spread of resistance. Hospitals and other healthcare institutions are places where resistant microbes frequently emerge and spread. Successful control of healthcare-associated infections is an important indicator of the quality of work at all levels of healthcare and in social care institutions that also provide healthcare and makes a significant contribution to the safety of patients/users and to reducing treatment costs.

National data on resistant bacteria are scarce. A recent study using EARS-Net data from 2015 estimated that there are 96 deaths in Slovenia each year as a consequence of infection with resistant bacteria and that 2,280 patients become infected with resistant bacteria each year. The majority of infections take place

in hospitals or other healthcare institutions. Each year, patients lose between 100 and 120 years of healthy life as a result of infection with resistant bacteria (Cassini, A. et al., 2019). The economic burden resulting from infections with resistant bacteria is not known. A rough estimate is that the annual costs in Slovenia as a result of additional hospitalisations caused by hospital-acquired infections (infections of surgical wounds, pneumonia, infections linked to vascular catheters, urinary tract infections and infections with MRSA and *C. difficile*) amount to between €55 million and €118 million. These figures take into account the number of hospitalisations in acute hospitals, amounting to approximately 340,000 a year, and the estimated number of additional hospitalisations, totalling approximately 110,000.

The collection of data on the sale of antimicrobials for use in animals in Slovenia, as reported by drug wholesalers, began before 2010, when total annual sales of antimicrobials (antibiotics) amounted to 10 tonnes or more. Since 2010, data on the sale of antimicrobials are reported in a standardised form (using the Anatomical Therapeutic Chemical classification system for veterinary medicinal products, or ATCvet) to the European Medicines Agency (EMA) as part of the ESVAC project (European Surveillance of Veterinary Antimicrobial Consumption).

Estimated total sales of antimicrobials for use in veterinary medicine in Slovenia, in general, fell from 8.8. tonnes in 2010 to 5.8 tonnes in 2016. According to figures from the ESVAC project, sales of these medicines for animals for food production in mg/PCU (Population Correction Unit) fell from 46.9 mg/PCU in 2010 to 30.3 mg/PCU in 2016 (a reduction of 35%). Of the 30 EU/EEA countries, only Finland, Iceland, Latvia, Norway and Sweden had lower estimated sales (in mg/PCU) for food-producing animals than Slovenia in 2016 (ESVAC Reports). In the case of the group of antibiotics from the list of critically important antimicrobials (CIA) published by the WHO, ESVAC figures indicate slightly higher consumption of fluoroquinolones, so more attention will need to be devoted to their more careful and responsible use, so that this is limited to justified cases in which other possibilities of effective treatment of animals have been exhausted.

Since Slovenia is a relatively small country with predominantly small livestock farms and only a few large farms, a serious problem on one large farm with intensive production can be strongly reflected both in the structure and total sales of antimicrobials and in this way change the situation for Slovenia as a whole.

1.1.2 Legislative regime and basic structures

Human medicine

The area of hospital-acquired infections or infections associated with healthcare in human medicine (healthcare-associated infections) is regulated by the Communicable Diseases Act, which provides that all healthcare providers must have a prevention and control programme for healthcare-associated infections. The professional, organisational and technical conditions for the drafting and implementation of the programme are set out in the Rules on conditions governing the preparation and implementation of a prevention and control programme for hospital-acquired infections (Official Gazette of RS 74/99, 92/06 and 10/11). Procedures for the provision of expert oversight in this field were laid down by the Rules on expert oversight of the implementation of prevention and control programmes for hospital-acquired infections, adopted in 2006 (Official Gazette of RS 92/06). In 2011 both sets of Rules were supplemented by provisions introducing a programme of prudent use and monitoring of consumption of antimicrobials, including a provision on the establishment of an organisational body or individual to be responsible for this field, for which they must be suitably qualified. The Rules also define expert oversight of the implementation of the programme of prudent use and monitoring of consumption of antimicrobials, which has been implemented since 2013.

Implementation of legislative provisions covering the field of communicable diseases and healthcare-associated infections is monitored by the **Health Inspectorate of the Republic of Slovenia (ZIRS)** as part of official controls.

Two committees have been appointed by ministerial resolution of the **Ministry of Health** to control antimicrobial resistance. These are the National Committee for the Prevention and Control of Hospital-Acquired Infections (NAKOBO) and the National Antimicrobial Stewardship Committee.

The **National Committee for the Prevention and Control of Hospital-Acquired Infections (NAKOBO)** was appointed in 2003 for the purpose of determining policy for the prevention and control of hospital-acquired infections (or healthcare-associated infections), planning actions and measuring effectiveness in this area, and international liaison. NAKOBO prepares technical documentation and guidelines for infection prevention and control and other instructions for experts. It also prepares information for patients and their families.

The **National Antimicrobial Stewardship Committee** was appointed in 2005 and brought together experts from the fields of human and veterinary medicine according to the "one health" principle. The committee advises the health minister and the minister responsible for agriculture and veterinary science on the consumption and prudent use of antimicrobials and other aspects of antimicrobial resistance in microorganisms. Its work focuses on supervising and directing the monitoring of the resistance of microorganisms to antibiotics. It also identifies priority tasks and, in the field of human medicine, informs community and hospital doctors about relevant practices. Representatives of the Ministry of the Environment and Spatial Planning joined the committee in 2018.

The National Institute of Public Health (NIJZ) is a public service institution which performs numerous functions pursuant to the Health Services Act (Official Gazette of RS 23/05 [official consolidated version], 15/08 – ZPacP, 23/08, 58/08 – ZZdrS-E, 77/08 – ZDZdr, 40/12 – ZUJF, 14/13 and 88/16 – ZdZPZD, Official Gazette of RS 74/99, 92/06, 10/11, 64/17 and 1/19 [Constitutional Court ruling]). These functions include monitoring communicable diseases, including healthcare-associated infections, and early detection of and response to events that represent a risk to public health. It is the competent institution in Slovenia for cooperation and liaison with the European Centre for Disease Prevention and Control (EDCD) in Stockholm and the national contact point in the Early Warning and Response System (EWRS) of the European Union. Together with the Institute of Microbiology and Immunology at the Faculty of Medicine of the University of Ljubljana, it is the coordinator of EARS-Net Slovenia, part of a Europe-wide network of epidemiological monitoring of the resistance of selected bacterial pathogens using data based on invasive isolates from blood and/or cerebrospinal fluid.

The **National Laboratory for Health, Environment and Food (NLZOH)** is Slovenia's central public health laboratory, where the identification, study and monitoring of antimicrobial resistance are among the important priority areas. Diagnostic microbiological activities are carried out by the National Laboratory's Centre for Medical Microbiology in eight locations, thus providing coverage for the majority of regions in Slovenia. In addition to diagnostic activities, the National Laboratory also performs public health microbiological activities (nationwide monitoring of pathogens causing infections that are prevented through vaccination and their antimicrobial resistance, etc.). Independently or in conjunction with other institutions, it undertakes research and participates in international projects and studies in the field of antimicrobial resistance (molecular research of multidrug-resistant bacteria, determination of microbial resistance in specific infections, cooperation with EARS-Net, ECDC monitoring networks for Salmonella, Campylobacter and Meningococcus, and other European networks) and is actively involved in the response to exceptional events such as the emergence of highly resistant microbes. In the field of the prevention and control of healthcare-associated infections, it cooperates actively with other healthcare institutions, particularly hospitals.

The **Institute for Microbiology and Immunology at the Faculty of Medicine of the University of Ljubljana** is a university microbiological laboratory that performs diagnostic activities for the Central Slovenia region and its university and other healthcare institutions. It conducts specific special procedures at the national level and at the same time carries out research and teaching activities. Among its most important tasks are the determination of antimicrobial resistance, monitoring resistance and trends and, at the reference level, in-depth molecular definition of resistance mechanisms. It uses and introduces new methods for the rapid identification and definition of the resistance mechanisms of bacteria, viruses and

fungi and carries out molecular analysis of outbreaks of infections with multidrug-resistant bacteria. In cooperation with other institutions in Slovenia and abroad, it drafts and adopts guidelines for preventing the spread of multidrug-resistant bacteria. It carries out scientific research on resistance mechanisms in the context of the "Relationships of Parasitic Existence" programme funded by the Slovenian Research Agency and international projects. It cooperates with EARS-Net and ECDC networks for monitoring the resistance of Enterobacter, Gonococcus, etc. It is part of a round-the-clock biosecurity threat response unit and since 2001 has been a member of the WHO's Global Outbreak Alert and Response Network (GOARN), which brings together a global network of laboratories for rapid response to epidemics. For more than 15 years it has been organising a hospital hygiene course for doctors and nurses, where all experts in this field in Slovenia have trained. It is currently setting up programmes to provide rapid electronic notifications and alerts regarding multidrug-resistant microbes.

Hospital clinical microbiology laboratories with an operating licence issued by the Ministry of Health operate at the Respiratory Disease and Allergy Clinic in Golnik, Slovenj Gradec General Hospital and the Dr Franc Derganc General Hospital in Nova Gorica. In addition to microbiological diagnostic activities and participation in national and international monitoring networks for epidemiologically significant microorganisms, hospital laboratories play an important role in the control and prevention of healthcare-associated infections and in limiting the spread of multidrug-resistant bacteria. The Mycobacteriology Laboratory at the Respiratory Disease and Allergy Clinic in Golnik is the national reference laboratory for tuberculosis and one of the foundations of the successful national tuberculosis control programme.

The **Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP)** is the competent authority in the field of medicines for use in human and veterinary medicine, medical devices, blood and blood products, human tissues and cells, and the manufacture and sale of class 2 and 3 controlled substances. The JAZMP exercises public powers under the law regulating medicines, the law regulating medical aids, the law regulating the supply of blood, the law regulating the quality and safety of human tissues and cells intended for therapeutic use, the law regulating the manufacture and sale of controlled substances, the law regulating the pharmacy sector, the law regulating public agencies and the resolution establishing the JAZMP. The tasks performed by the JAZMP are of an administrative, supervisory and technical nature. Through its activities, the JAZMP also participates in the work of international institutions in the above areas of work.

The **Medical Chamber of Slovenia** is an autonomous and independent professional organisation that ensures the upholding of the fundamental values of the medical profession and regulates the medical profession on behalf of the state. It also adopts the code of medical deontology and takes action in connection with infringements of the code; it participates in the drafting of laws and other regulations relating to healthcare; it has a co-decision role in the determination of starting points for the conclusion of contracts and represents the interests of private physicians in the conclusion of contracts with the Health Insurance Institute of Slovenia; it participates in the conclusion of collective agreements on behalf of private physicians as employers.

Veterinary medicine and agriculture

In veterinary medicine, the area of medicinal products for use in Slovenia is regulated in accordance with EU legislation, for the most part by the Medicinal Products Act (Official Gazette of RS 17/14) and also in part by the Veterinary Compliance Criteria Act (Official Gazette of RS 93/05, 90/12 – ZdZPVHVVR, 23/13 – ZZZiv-C, 40/14 – ZIN-B and 22/18) and the Veterinary Practice Act (Official Gazette of RS 33/01, 45/04 – ZdZPKG, 62/04 [Constitutional Court ruling], 93/05 – ZVMS, 90/12 – ZdZPVHVVR and 22/18) and implementing regulations issued pursuant to them. Antimicrobials (antibiotics) are not available over the counter in Slovenia and may only be prescribed for the treatment of animals by the treating veterinary practitioner. They may also be dispensed by pharmacies, but only on the basis of a prescription from a veterinary practitioner who is qualified and authorised to prescribe medicinal products in accordance with regulations.

Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition prohibited the use of antibiotics as feed additives to promote growth in the European Union, and thus also in Slovenia, in 2006.

The functions of the **Food Safety, Veterinary and Plant Protection Administration (UVHVVR)** include monitoring the volume of traffic in antimicrobials for use in veterinary medicine that are used to treat animals and the use-related traceability of medicinal products from drug wholesalers to end users. It is responsible for reporting on their consumption to the European Medicines Agency (EMA) and the World Organisation for Animal Health (OIE). It is also responsible for preparing the programme for monitoring antimicrobial resistance in veterinary medicine and for reporting the results to the European Food Safety Authority (EFSA). The UVHVVR also appoints the official laboratories that conduct investigations under the resistance monitoring programme and the National Reference Laboratory for monitoring antimicrobial resistance.

An **interministerial committee tasked with drafting measures to improve access to medicinal products for use in veterinary medicine and monitoring the situation regarding medicinal products for use in veterinary medicine** was appointed in 2017. The committee prepares, for the health minister and the agriculture minister, proposals for measures to improve access to medicinal products for use in veterinary medicine, including vaccines and antimicrobials, since disruptions in the availability of specific drugs can result in the use of an antimicrobial with a broader spectrum than necessary, or even a last-resort or critically important antimicrobial, instead of, for example, a narrow-spectrum antimicrobial targeted to a specific pathogen.

The **National Veterinary Institute (NVI)** is an institution that provides the public veterinary services defined in the Veterinary Practice Act and the Veterinary Compliance Criteria Act. It conducts laboratory investigations of animal material, foodstuffs and raw materials for the purpose of diagnosing epizootic and other animal diseases or in order to establish the wholesomeness of foodstuffs of animal origin, animal feed and water for animals and other products. It also carries out pathomorphological investigations, provides a veterinary hygiene service, prepares background documentation for the planning of animal healthcare measures and ensuring food safety and animal feed safety, monitors animal health and artificial insemination at the national level, monitors the health and treatment of bees, fish and wild animals, and carries out disinfection, disinfestation and rodent control.

The NVI oversees 30 reference laboratories, including the **National Reference Laboratory (NRL)** for the determination of the antimicrobial resistance of bacteria. The latter ensures the reliability of its results through standardised operation conforming to the standard that defines operating criteria for test laboratories (SIST EN ISO/IEC 17025:2005).

Veterinary microbiology laboratories determine the susceptibility of bacteria to antimicrobial agents in veterinary medicine. The most important role is played by the **Institute of Microbiology and Parasitology (IMP) at the Veterinary Faculty of the University of Ljubljana**. Its two fundamental tasks are carrying out investigations of clinical and pathological samples of animals and performing the function of the National Reference Laboratory for the determination of the antimicrobial resistance of bacteria. Within the scope of activities of the NVI, the IMP also monitors the identification of resistant bacteria under the programme prepared by the UVHVVR, for national needs, or under coordinated programmes at the European Union level. In order to determine the susceptibility of clinical isolates, cooperation with veterinary clinicians on the treatment of infections is also necessary, as is cooperation on the prevention and control of veterinary-associated and other infections, microbial resistance tracing and cooperation on other veterinary activities. The IMP laboratory holds accreditation for the use of the microdilution method to determine the minimum inhibitory concentration, in which context it is subject to external quality assurance.

Regional veterinary laboratories are located in Murska Sobota, Maribor, Ptuj, Celje, Novo Mesto, Kranj and Nova Gorica and only carry out testing of the susceptibility of bacteria to antibiotics on a small scale for clinical isolates obtained, for the most part, from samples from small animals or cows suffering from mastitis.

The **Veterinary Chamber of Slovenia** is the autonomous and independent professional organisation of doctors of veterinary medicine in Slovenia. It represents and asserts their professional, economic and social interests.

The **Chamber of Agriculture and Forestry of Slovenia** is a non-governmental organisation that brings together natural persons and legal entities involved in agriculture, forestry and fishing. It protects and represents the interests of its members, advises them and promotes economically and environmentally sound agriculture, forestry and fishing.

Environment

Through its policies, strategies and regulations, the **Ministry of the Environment and Spatial Planning** ensures a healthy living environment for all inhabitants of Slovenia and promotes and coordinates efforts towards sustainable development which, while ensuring social well-being, is based on the prudent and sparing use of natural resources. It endeavours to increase society's awareness of the need to preserve natural balance and biodiversity in the country, in the belief that biodiversity is an important legacy for future generations.

The **Slovenian Environment Agency** performs technical, analytical and administrative functions in the environmental field at the national level. It monitors the state of the environment and provides high-quality public environmental data, safeguards the environment as required by regulations, preserves natural resources and biodiversity and ensures the sustainable development of the country. To these ends, the Agency implements more than 200 different types of administrative procedures required by domestic and European environmental legislation.

The **Slovenian Waters Agency** performs technical, analytical and administrative functions in the water management field in accordance with regulations governing waters at the national level. Its aim is to establish a water management system that facilitates the integrated management of waters: to exploit Slovenia's water potential as a development opportunity, take water capacity into account in spatial planning and reduce threats to life, health and property. An integrated water management system is organised at the national level and by river basins at the regional and local levels. The Agency facilitates the efficient provision of public services, management of investments and cooperation with the water sector and stakeholders.

1.1.3 Why do we need a national strategy?

Slovenia has not hitherto had an integrated interministerial, governmental antimicrobial resistance strategy that combines the areas of prescription, consumption and monitoring of antimicrobials, the control of infections associated with healthcare or veterinary medicine, and microbiological activities in the fields of human medicine, veterinary medicine and the environment.

Despite this, numerous activities have taken place in accordance with the document "Strategy of the fight against antimicrobial resistance", published in 2008 in *ISIS*, the journal of the Medical Chamber of Slovenia (Čižman, M. et al., 2008). This document contains expert guidance and recommendations drawn up by the National Antimicrobial Stewardship Committee. Following this guidance, specialist training has been provided for primary care practitioners in healthcare regions with high consumption of antibiotics and expert oversight has been introduced in hospitals. Activities have taken place every year on European Antibiotic Awareness Day with the aim of educating medical and veterinary professionals and the general public (Čižman, M. 2013, Čižman, M., et al., 2005, Svetlin, A., 2008, 2009, 2010, 2012, 2013, 2014, 2016, 2017, 2018, MKGP_VURS, Svetlin, A., 2011). An important role in the reduction of community consumption of antibiotics has also been played by the Health Insurance Institute of Slovenia (ZZZS), with which the National Antimicrobial Stewardship Committee has planned restrictive measures for the prescription of several classes of antibiotics at the primary care level (Čižman, M. et al., 2005, Furst, J. et al., 2015).

Through such restrictive measures, the training of primary care practitioners and numerous other activities, Slovenia has reduced the community consumption of antibiotics by more than 30% since 2000 (Furst, J. et al., 2015). It has also been successful in reducing the frequency of isolations for Methicillin-resistant *Staphylococcus aureus* (Tomic, V. et al., 2008).

Increasing antimicrobial resistance and its consequences mean that a binding government strategy and action plan are necessary. A strategy prepared in accordance with the "one health" principle, which takes into account human health, animal health and environmental health, will link the health, agriculture and environment ministries and experts and stakeholders in this field. Numerous activities in the field of antimicrobial resistance have taken place in Slovenia, but in a manner that is too fragmented and disconnected, while the part that is not normatively regulated is insufficiently binding. Integrated monitoring and planning have also been absent and there has been no mechanism connecting all the elements necessary for the effective control of antimicrobial resistance and infections with resistant microbes. Only an integrated approach is capable of halting the increase in antimicrobial resistance or attempting to reduce it. As a result of the global problem of growing antimicrobial resistance, international efforts are of key importance even in the context of action at the national level.

With this strategy, Slovenia joins other countries around the world in the common fight against antimicrobial resistance. Through the political declaration of the United Nations at the high-level meeting on antimicrobial resistance in September 2016, these countries supported the Global Action Plan on Antimicrobial Resistance. The Global Action Plan, drawn up by the WHO with the support of food, agriculture and animal health organisations such as the FAO and OIE (https://www.who.int/antimicrobial-resistance/global-action-plan/en/), sets out the following strategic objectives: improve awareness and understanding of antimicrobial resistance; strengthen the knowledge and evidence base through surveillance and research; reduce the incidence of infection; optimise the use of antimicrobial medicines; and develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions. In 2016 the European Union adopted Council conclusions on strengthened cooperation in the health sector in the European Union (https://www.consilium.europa.eu/sl/press/press-releases/2016/06/17/epsco-conclusions-antimicrobial-resistance/), followed in June 2019 by Council conclusions on the next steps towards making the EU a best practice region in combatting antimicrobial resistance (Official Journal of the European Union 2019/C 214/01). The Global Action Plan and the conclusions of the Council of the European Union called on Member States to prepare national action plans on antimicrobial resistance and the consumption of antibiotics, define special national objectives for the control of antimicrobial resistance and the consumption of antibiotics in humans and animals, and allocate sufficient human and financial resources for their implementation.

Adoption of the antimicrobial resistance strategy, which also sets out the actions necessary for ensuring the country's readiness and response in the event of dangers to human health, also derives from the recommendations of the Joint external evaluation of IHR core capacities of the Republic of Slovenia (WHO, Mission Report, 2017).

The strategy is based on the starting points prepared by the experts of the National Antimicrobial Stewardship Committee and the National Committee for the Prevention and Control of Hospital-Acquired Infections.

2. PURPOSE AND OBJECTIVES OF THE STRATEGY

Purpose

The purpose of the strategy is to ensure joint and integrated inter-sectoral and inter-institutional action to halt or reduce antimicrobial resistance in healthcare, veterinary medicine, agriculture and the environment, and in this way contribute to reducing it at the global level. Antimicrobial medicines are a common good and we must preserve their effectiveness for future generations. Effective action against increasing

antimicrobial resistance will contribute to the better health of the population, greater productivity and, last but not least, a more sustainable healthcare budget.

Strategic objectives

1. Reduce overall consumption of antimicrobials.
2. Achieve the more prudent use of antimicrobials.
3. Improve the awareness of the professional and general public and understanding of the reasons for the development and spread of antimicrobial resistance.
4. Reduce the number of infections with resistant bacteria and transmissions of multidrug-resistant microbes.
5. Contribute to the control of antimicrobial resistance at the global level.
6. Encourage and accelerate the development of new technologies and innovations in the monitoring and control of the use of antimicrobials and the control of antimicrobial resistance.

Special objectives by sector

Human medicine

- Reduce total community use of antibiotics (expressed as DDD per 1,000 inhabitants per day) by 20% compared to 2017.
- Reduce community use of broad-spectrum antibiotics such as amoxicillin with clavulanic acid, fluoroquinolones, macrolides with a long half-life (azithromycin) and second- and third-generation cephalosporins.
- Reduce total hospital use of antibiotics by 10% compared to 2017.
- Reduce the use of third-generation cephalosporins, carbapenems and, in particular, fluoroquinolones in hospitals compared to 2017.
- Reduce the prescription of antibiotics from 485 prescriptions per 1,000 inhabitants per year in 2017 to 350 prescriptions per 1,000 inhabitants per year.
- Improve the awareness of healthcare personnel and the population and improve understanding of the reasons for the development and spread of antimicrobial resistance.
- Enhance the current system for monitoring antimicrobial consumption by including monitoring of consumption in social care institutions that provide healthcare, separating consumption by hospitalised patients and consumption by outpatients in hospitals, and monitoring the consumption of antibiotics for parenteral use outside hospitals.
- Improve the quality of prescribing with modern near-patient microbiological diagnostic testing.
- Establish a stable system for monitoring resistance that will provide reliable, timely and comparable data on antimicrobial resistance.
- Establish a system for early detection of and response to emergencies such as the appearance or suspected accumulation of resistant microbes.
- Reduce the incidence of all healthcare-associated infections, particularly the most important ones (pneumonia, septicaemia, urinary tract infections and surgical wound infections) in all departments, including intensive care units.

- Establish a stable system of epidemiological monitoring of healthcare-associated infections, in accordance with the epidemiological monitoring of healthcare-associated infections coordinated by the European Centre for Disease Prevention and Control.
- Establish programmes for the prevention and control of healthcare-associated infections in all institutions where healthcare is provided and long-term care institutions in accordance with international expert guidelines.
- Accelerate the development of new drugs, antimicrobial agents (e.g. microbiota) and technological innovations for improved diagnostics, more effective (targeted) monitoring of drug consumption and substitution of antibiotic use with new alternative approaches and active substances.

Veterinary medicine and agriculture

- Maintain the low level of prescription/consumption of antimicrobials for the treatment of animals so that Slovenia remains in the bottom third of EU Member States in terms of consumption, or, through good care of animals, prudent prescribing and the prevention of infections in animals, reduce it, in particular on holdings with high (above-average) consumption.
- Reduce the prescription/consumption of broad-spectrum antimicrobials, in particular, those from the CIA group, in particular fluoroquinolones.
- Modernise monitoring of the sale of antimicrobials for animals.
- Introduce monitoring of antimicrobial consumption by animal species on agricultural holdings, which will enable the detection of above-average or excessive consumers in a comparable manner in order to eliminate the causes.
- Establish an integrated system for monitoring the resistance of microorganisms in veterinary medicine which will enable the acquisition of comparable and reliable data on antimicrobial resistance.
- Establish monitoring of isolates with special forms of resistance (multidrug-resistant isolates and isolates with special resistance patterns).
- The agricultural sector uses plant protection products (PPPs) classified as pesticides to protect plants and crops against pathogens and weeds. The use of antibiotics is banned in the EU or Slovenia. Article 14 of Directive 128/2009/EC calls on Member States to adopt National Action Plans (NAPs) designed to reduce the use of PPPs. The Slovenian government adopted the NAP in November 2012 and submitted it to the European Commission (link to contents of NAP: http://www.uvhvvr.gov.si/si/delovna_podrocja/fitofarmacevtska_sredstva/nacionalni_akcijski_program/).

3. PRIORITY AREAS

1. Optimising the prescription of antimicrobials
2. Monitoring the consumption of antimicrobials
3. Monitoring microbial resistance
4. Monitoring, preventing and managing infections, connected with healthcare and veterinary medicine
5. Educating professionals and the general public
6. Research and development
7. International cooperation

1.2 OPTIMISING THE PRESCRIPTION OF ANTIMICROBIALS

1.2.1 Optimising the prescription of antimicrobials in human medicine

Slovenia is successful when it comes to antibiotic consumption, expressed as DDD/1,000 inhabitants/day, as in 2016 only five EU member states – the Netherlands, Estonia, Sweden, Latvia, and Austria recorded a lower rate of consumption. If we express consumption in terms of the number of prescriptions per 1,000 inhabitants per year, then the situation is not so favourable. In comparison with Sweden, in 2016 Slovenia had 36% more medical prescriptions (318 v 494 Rp/1,000 inhabitants/year), which indicates that there is still much potential for reducing consumption in Slovenia (Fig. 1). For many years in Slovenia we have noticed differences in the writing of prescriptions between different healthcare regions – doctors in north-eastern Slovenia prescribe more antibiotics than doctors in other regions. From an analysis of antibiotics prescriptions according to age groups, it is also clear that most antibiotics are prescribed to children aged between one and four years.

Hospital consumption in 2016 was 1.69 DDD/1,000 inhabitants/day, which is less than the average of 23 EU and EEA member states (2.06). Seven countries consumed less than Slovenia – Sweden, Portugal (only public hospitals), Bulgaria, Poland, Norway, Hungary and the Netherlands (Fig. 2). Slovenia consumes 75% more than the Netherlands (1.7 v 0.97 DDD/1,000 inhabitants/day).

Doctors often prescribe antibiotics to nursing home residents. Despite the fact that the number of antibiotics prescribed in nursing homes in Slovenia is among the lowest in Europe, residents often receive prescriptions for broad-spectrum antibiotics. In addition, microbiological diagnosis is rarely performed in these cases (WHO Evidence brief for policy, 2018).

Considering the above and the continued large consumption of antimicrobials in Slovenia we may conclude that the writing of prescriptions is not optimal. The aim of optimal or meaningful use of antibiotics is not only to reduce consumption but also for prescriptions to be appropriate, which means that antibiotics are taken only by those who benefit from them.

Line ministry: Ministry of Health (MZ); participating ministry: Ministry Of Labour, Family And Social Affairs (MDDSZ)

Measures:

1. Prepare, implement and regularly update recommendations/guidelines for prescribing antimicrobials (in primary healthcare, hospitals and social institutions, which provide healthcare – nursing homes).
2. Enhance regular training sessions for doctors and other healthcare workers at the primary level, in hospitals and social institutions that perform healthcare activities, especially in healthcare regions with above-average prescriptions of antimicrobials.
3. The establishment of a national consultation point with an infectious disease specialist for healthcare providers that do not employ an infectious disease specialist.
4. Improve the implementation of the programme for monitoring the consumption of antimicrobials in hospitals in compliance with the valid Rules on the conditions for preparing and implementing

programmes for the prevention and control of healthcare-associated infections and ensuring appropriate conditions for establishing a programme with all healthcare providers.

5. Ensure quality and safety in the field of antimicrobial prescriptions.

1.2.2 Optimising prescriptions in veterinary medicine

Slovenia's goal is to reduce the consumption of antimicrobials for the treatment of animals, especially in holdings where consumption is high, and generally reduce the consumption of antimicrobials from the CIA list (fluoroquinolones). According to statistics from ESVAC (European Surveillance of Veterinary Antimicrobial Consumption), the estimated total sales of antimicrobials for use in veterinary medicine in Slovenia fell between 2010 and 2016 from 8.8 to 5.8 tonnes (ESVAC Reports). The sale of these medicines for animals for food production in mg/PCU (Population Correction Unit) was calculated by the ESVAC project to have been reduced by 35% from 46.9 mg/PCU in 2010 to 30.3 mg/PCU in 2016.

Line ministry: MINISTRY OF AGRICULTURE, FORESTRY AND FOOD (MKGP)

Measures:

1. Improve the understanding and management of microbe resistance through training and raising the awareness of veterinarians and animal owners about the importance of limiting the use of antimicrobials for animals (the use of antimicrobials must be under veterinary supervision), and the connections between health, farming and the environment.
2. Prepare, apply and regularly update national recommendations, guidelines and protocols for treating animals with antimicrobials, ensuring the prudent and responsible use of these medicines.
3. Improve the market supply of vaccines and antimicrobials of first and second choice.
4. Limit the use of decisively important antimicrobials (from the CIA list) in justified cases.

1.3 MONITORING THE CONSUMPTION OF ANTIMICROBIALS

1.3.1 Monitoring the consumption of antimicrobials in human medicine

Reasons for monitoring the consumption of antimicrobials on a national level include determining consumption trends, enabling comparisons of the use of antimicrobials between similar types of hospitals, wards and regions in the country, measuring the effectiveness of measures, providing feedback to those who prescribe medicines, analysing the connections between the consumption of antimicrobials and resistance, reducing expenses through the use of equally effective but cheaper antibiotics, and international comparisons.

For all the above reasons it is necessary to monitor the national consumption of antimicrobials prescribed to outpatients, in hospitals and social institutions that provide healthcare.

The source of information on national outpatient consumption is the National Institute of Public Health (NIJZ), which tells the Clinic for Infectious Diseases and Febrile Illnesses the number of prescriptions written according to age, gender, specialisation of the prescriber and region.

Slovenia has a well-established network for monitoring the consumption of antimicrobials in hospitals as it monitors consumption in all 29 hospitals, in five wards of general hospitals (surgical, internal medicine, gynaecology, paediatrics, intensive care) and in both university medical centres. The drawback with

monitoring consumption in hospitals is that hospitals do not differentiate between consumption by inpatients and in day clinics. The monitoring results are used by the Committee for the appropriate use of antimicrobials for planning professional monitoring in hospitals and it informs hospital committees for medicines and antibiotics about the results. Hospitals receive results that have been processed using the same methodology and can compare them with hospitals and wards of the same kind. In 2013 members of the National antimicrobial stewardship committee in Slovenia began implementing professional monitoring in hospitals concerning the appropriate use of antimicrobials in compliance with the Rules on expert supervision of the implementation of the programme on prevention and control of hospital infections (Official Gazette of RS, No. 10/11). Professional monitoring was first introduced in hospitals with the highest consumption of antimicrobials (Indicators of quality in healthcare, report for 2012 and 2013).

Hospital pharmacies are the source of information on antimicrobials in hospitals as they provide clinical wards and outpatient clinics with the numbers of prescribed antimicrobials. The system for monitoring consumption could be thoroughly improved if the consumption of medicines received by the patient was monitored and not the consumption of medicines in a particular ward. We must strive to obtain information about the actual consumption of antimicrobials by introducing an electronic prescription system and recording each patient's medicine consumption.

According to the Rules on conditions for preparing and implementing the programme for preventing and managing hospital infections (Official Gazette of RS, Nos. 74/99, 92/06 and 10/11) the data gathered from hospitals is collected by the Department of Infectious Diseases and Febrile Illnesses, University Medical Centre Ljubljana, which then sends them into the ESAC-net network.

In 2008 the Anbico web IT solution was set up for monitoring the consumption of antimicrobials. It enables the calculation of the consumption of antimicrobials per inhabitant, filtered by outpatient consumption, hospital consumption, days of treatment, number of patients treated and if necessary also by other parameters. Consumption is monitored also through the prescriptions issued for antimicrobial medicines and the costs incurred.

The data is stored in on-line transaction processing (OLTP) database or in an internet application at https://anbico.si-map.org, where due to the number of records gathered there are problems with the speed of data processing and the responsiveness of the IT solution.

The data warehouse includes several databases: outpatient consumption of medicines or prescriptions issued, where the sources of data are the Health Insurance Institute of Slovenia (ZZZS) and the National Institute of Public Health (NIJZ), medicines consumed in hospitals, where the data source is the hospital pharmacy and the data on Slovenia's inhabitants where the data source is the Statistical Office of the Republic of Slovenia (SURS). The purpose of the data warehouse is to store large quantities of gathered and sorted information to be used for various analyses and reports or business intelligence. The data in the data warehouse is sorted hierarchically and suitably prepared and may be rapidly accessed using different tools.

Line ministry: MZ

Measures:

1. Establish an information system for monitoring antimicrobial consumption in hospitals, or connect it with other information systems to ensure faster, automatic and better quality transfer of data in hospitals.

2. Prepare an appropriate selection of indicators for monitoring the consumption of antimicrobials and setting up a system for collecting data.

1.3.2 Monitoring the consumption of antimicrobials in veterinary medicine

The current legislation, which governs the field of veterinary medicines, demands the management and recording of all prescription records to ensure the traceability of medicines from wholesalers to the consumption of medicines in compliance with regulations. In veterinary medicine, it is necessary to continue the already introduced activities and to strengthen them in certain areas (in particular to set up the monitoring of antimicrobial consumption according to animal species in holdings, and reduce or limit the consumption of the most important antimicrobials from the CIA list to justified cases).

In order to achieve the goals it will be necessary to provide extra human and financial resources.

Line ministry: MINISTRY OF AGRICULTURE, FORESTRY AND FOOD (MKGP)

Measures:

1. Connect the existing monitoring of data on the wholesale of antimicrobials for use in animals, which is continuously updated with other information systems to ensure high quality and faster data transfer (e.g. the collection of medicines at the Agency for Medicinal Products and Medical Devices of the Republic of Slovenia etc.).
2. In addition to the already introduced monitoring of data on the wholesale of antimicrobials, it is also necessary to introduce the monitoring of consumption according to separate groups of antimicrobials for the major animal species and categories of animals in holdings in order to:
   - compare consumption in general and for individual groups of antimicrobials for major species and animal groups in different holdings,
   - monitoring and action in the event of above-average or excessive consumption in holdings,
   - reporting on the animal consumption of antimicrobials to local and international institutions, which gather, process and publish data.
3. Arrange administration of the information system for monitoring the sale and consumption of antimicrobials in veterinary medicine and determine data managers who will be responsible for the content and quality of the data and reporting.

1.4 MONITORING ANTIMICROBIAL RESISTANCE

1.4.1 Monitoring resistance in human medicine

Due to globalisation and patient mobility, the potential for the development and transfer of antimicrobial resistance is greater not only within the country but also internationally. That is why it is important to have a stable system for monitoring resistance, which ensures reliable, prompt and comparable data on microbial resistance to antimicrobials. International cooperation is also very important.

The WHO recognised that managing antimicrobial resistance should be an important priority in medicine already at the turn of the millennium. In 2017 it published a priority list of 12 bacteria that have an important impact on human morbidity and mortality, for which we urgently need intensive research and the development of new antimicrobials, Table 1. For these bacteria, it is also important to monitor resistance.

Table 1: List of bacteria determined by the WHO as priorities for research and development of new antibiotics (WHO, 2017).

Priority:	**Bacteria**	**Resistance to antimicrobials**
1. **CRITICAL***	*Acinetobacter baumannii*	carbapenems
	Pseudomonas aeruginosa	carbapenems
	Enterobacteriaceae (*Klebsiella pneumoniae, Escherichia coli, Enterobacter* spp., *Serratia* spp*., Proteus* spp., *Providentia* spp., *Morganella* spp*.)*	3rd generation cephalosporins, carbapenems
2. **HIGH**	*Enterococcus faecium*	vancomycin
	Staphylococcus aureus	MRSA, vancomycin
	Helicobacter pylori	clarithromycin
	Campylobacter spp.	fluoroquinolones
	Salmonella spp.	fluoroquinolones
	Neisseria gonorrhoeae	3rd generation cephalosporins, fluoroquinolones
3. **MEDIUM**	*Streptococcus pneumoniae*	penicillin
	Haemophilus influenzae	ampicillin
	Shigella spp.	fluoroquinolones

Note * under critical bacteria we also include mycobacteria (including *Mycobacterium tuberculosis*, which causes tuberculosis in humans), but which is already featured on the WHO's priority list.

Slovenia already has a system for monitoring bacterial resistance on a national level within the Slovenian National Antimicrobial Susceptibility Testing Committee (SKUOPZ). All the microbiological laboratories in the country participate in the committee. Data from 2011 onwards can be found at: http://www.imi.si/skuopz/. By providing data on resistance and other epidemiological data Slovenia is also cooperating with international networks coordinated by the ECDC. The data enables comparison between different countries. A comparison of data in the EARS-Net (European Antimicrobial Resistance Surveillance Network, it includes 28 countries of the European Union and 2 countries of the European Economic Area) for 2016 shows that the resistance of Slovenian isolates is close to the European average. The share of bacteria *Escherichia coli* with ESBL enzymes (Extended-spectrum beta-lactamases) is a little greater than

the European average. The *E. coli* bacteria is the most common cause of infections both in and outside hospitals, and the presence of ESBL enzymes means that the bacteria is resistant to many antibiotics. Antibiotics from the group of carbapenems are most frequently used for infections with ESBL producing bacteria. They are the right medicine for the most serious infections and are often the last effective medicine for infections with resistant bacteria.

Similarly to other European countries, there is also a worrying incidence of Enterobacteriaceae with carbapenemase enzymes in Slovenia, due to which bacteria are also resistant to carbapenems and at the same time to the vast majority of other antibiotics. These bacteria often cause serious infections in the most vulnerable patients. As they can spread successfully from one person to another they represent a major health risk. Enterobacteriaceae with carbapenemase enzymes sometimes crop up in Slovenian hospitals borne by travellers and above all patients from other countries. There was a small outbreak in 2014, which was successfully contained.

When bacteria with carbapenemase enzymes appeared, an analysis of the state of these and other resistant bacteria discovered that in Slovenia we require a legal basis for registering cases, reporting and taking measures. It is necessary to harmonise the activity of various institutions and coordinate the activities of medical microbiological laboratories with reference laboratories, to ensure additional research to explain the incidence or outbreak of resistant bacteria. Existing monitoring of resistance provides insight into the situation concerning certain bacteria only once annually. In certain cases, interdepartmental cooperation with experts from the fields of veterinary medicine, farming and the environment is also necessary.

The prompt detection of resistance, accumulation of cases and other changes in resistant bacteria requires in-depth and above all molecular microbiological diagnostics, which is the task of ordinary and reference laboratories. Microbiological reference laboratories in Slovenia in the field of human medicine are not officially named. The tasks of reference laboratories are defined in the ECDC document (reference ECDC *Core functions of microbiology reference laboratories for communicable diseases, 2010).* For effective measures to be taken when resistant microbes appear and accumulate it is necessary to establish a system for early detection and coordinated action. The cooperation of all stakeholders is of crucial importance: clinical microbiologists, public health specialists, infectious diseases specialists, doctors with other specialisations, hygienists and other professionals. Most measures are only effective if they are implemented on time.

Due to the importance of discovering, preventing and managing the resistance of microbes and the infections they cause, the network of laboratories, including the reference laboratories, is in the public interest. This is also defined in the Resolution on the National Healthcare Plan 2016–2025 (ReNPZV16–25).

Line ministry: Ministry of Health (MZ); participating ministries: Ministry Of Labour, Family And Social Affairs (MDDSZ), Ministry of the Environment and Spatial Planning (MOP)

Measures:

1. Determine the whole system for monitoring the resistance of microorganisms in human medicine, including the legal basis, by defining a network of microbiological laboratories, reference microbiological laboratories and establishment/naming of a national coordination centre (NKC) for monitoring resistance in compliance with ECDC and WHO documents.
2. Define the rules for managing databases and the results of analyses of antimicrobial resistance.
3. Update and upgrade the information system for recording and analysing data, which will in the above laboratories enable a single output of data, appropriate warnings and the rapid transfer of data between stakeholders.

4. Determine or supplement content for permanent (regular) and periodic microbiological monitoring of resistance depending on the epidemiological situation, including detecting resistant microbes in the environment. It is necessary to establish systematic monitoring of the resistance of fungi and viruses and ensure it can be implemented.
5. Set up warning (alarm) monitoring of extremely resistant bacteria and suspected accumulation of resistant microbes (extremely resistant and others), and together with stakeholders involved in managing infections, public healthcare and other experts, determine mutual notification, action, cooperation and reporting on these incidences with the aim of a timely and effective response.
6. Define procedures and sources for referential and other research not included in the regular work of laboratories but which is necessary for knowing and understanding the incidence, frequency and spreading of important mechanisms of resistance (molecular epidemiology of resistance, e.g. molecular typing and determining the mechanisms of resistance of selected populations of epidemiologically and clinically important isolates, such as Enterobacteriaceae with carbapenemases) and other related microbe characteristics.
7. Establish collaboration between the system for monitoring the resistance of microbes in human medicine with other strategic fields, including veterinary medicine (consumption of antibiotics, preventing infections, including healthcare-associated infections, programmes for educating and raising awareness, research), at regional, national and international levels.

1.4.2 Monitoring resistance in veterinary medicine

For monitoring bacterial resistance in veterinary medicine it is necessary to establish an integrated system, which will enable the acquisition of comparable and reliable data on the occurrence of microbial resistance against antimicrobials.

In Slovenia, we are implementing a programme for monitoring resistance against antimicrobials in veterinary medicine, which is part of the Programme for Monitoring Zoonoses and Zoonotic Agents (hereinafter: Programme for Monitoring Zoonoses) and includes the monitoring of the resistance of certain bacteria found in some animal species intended for the production of food, and in some foods. The programme for monitoring resistance will gradually have to be expanded to include additional microorganisms or animal species, recommended by international institutions or which are deemed to be of national significance, and with molecular diagnostics.

The system must enable the formation of a permanent database to evaluate trends and sources in connection with resistance, monitoring the occurrence of multi-resistant bacteria and detecting bacteria with special patterns of resistance. The gathered data must also provide the information necessary for evaluating the way medicines are prescribed in practice, for evaluating the following recommendations for appropriate consumption of antimicrobials and for evaluating and determining the effect of measures for fighting against microorganism resistance. In addition, the system must provide reliable data on microbe resistance for direct treatment of animals.

Line ministry: MINISTRY OF AGRICULTURE, FORESTRY AND FOOD (MKGP)

Measures:

1. Determine the framework for regular monitoring of the resistance of isolates.
2. Determine the system for monitoring resistance to clinical isolates.

3. Include molecular methods in the resistance monitoring system.

1.5 MONITORING, PREVENTION AND CONTROL HEALTHCARE-ASSOCIATED INFECTIONS AND VETERINARY MEDICINE

1.5.1 Monitoring, prevention and control of healthcare-associated infections

An important and indispensable part of the effective struggle against resistant microbes, especially multi-resistant microbes, is the field of epidemiological monitoring and prevention, and managing healthcare-associated infections. This takes place in accordance with the provisions of the Communicable Diseases Act (Official Gazette of RS, No. 33/06) and the EU Council recommendations of 9 June 2009 on patient safety, including the prevention and control of healthcare-associated infections (2009/C 151/01), which are in the second chapter of the recommendations. In accordance with these recommendations, an independent, expert national strategy for the prevention and control of healthcare-associated infections will be prepared and adopted.

In Slovenia, the prevention and control of healthcare-associated infections is regulated in legislation through regulations in the field of control of infectious diseases, as is set out in more detail in the document's introduction. The regulations determine that any natural or legal person performing healthcare activities implements programmes for the prevention and control of hospital infections that are prepared by the person responsible for the healthcare activity. The implementation of the programme in hospitals is provided by the commissions for the control of hospital-acquired infections (KOBO), whose compulsory members include general hospital managers, head nurses, doctors responsible for the control of infections (ZOBO), nurses responsible for the control of hospital infections (SOBO), doctors specialised in microbiology, epidemiology, infectious diseases, pharmacy, surgeons or doctors having some other specialisation. The National Commission for the Control and Prevention of Hospital-Acquired Infections (NAKOBO) prepares professional guidelines for preventing healthcare-associated infections for monitoring the implementation of the prevention and control of hospital-acquired infections programme and planning and proposing measures for improvements in the field of prevention and control of healthcare-associated infections.

Planning the prevention and control of healthcare-associated infections is evidence-based so is possible only with the results of epidemiological monitoring. The European Centre for Disease Control and Prevention (ECDC) coordinates the standardised epidemiological monitoring of healthcare-associated infections, in acute-care hospitals in EU and EEA countries. In two Slovenian cross-sectional studies of hospital infections coordinated by the National Institute of Public Health in the years 2011 and 2017, the estimated prevalence of hospital infections was almost the same (6.4% and 6.5% in 2011 and 2017) and the prevalence of hospital infections in intensive care units was also not significantly lower (35.7% and 32.6% in 2011 and 2017).

The results of both studies show that we are managing hospital infections but that we have not succeeded in reducing them. In order to improve the identified situation we must provide the conditions necessary for monitoring the incidence of hospital infections in intensive care units, monitoring infections in surgical wounds and infections caused by *Clostridium difficile*. Through appropriate measures, we must also ensure suitable prevention and control of the most frequent hospital infections such as pneumonia, and infections of the blood, the urinary tract and surgical wounds.

Monitoring, prevention and control of infections are also important in social institutions, which provide healthcare activities (nursing homes) and other institutions for long-term care. The results of the European HALT-2 study (Healthcare-Associated Infections and Antimicrobial Use in European Long-Term Care Facilities Project) from 2013, which covered 19 European countries including Slovenia, showed that long-term care facilities annually recorded 4.2 million healthcare-associated infections, while European acute-care hospitals recorded 3.5 million such infections. The study encompassed 77,264 residents in 1,181 long-term care facilities. On any one day of the study 2,626 (3.4%) residents had at least one healthcare-related

infection and on each day more than 150,650 residents received at least one antimicrobial. As only two long-term care facilities from Slovenia participated in the study, the data is insufficient for reaching conclusions about the situation in Slovenian long-term care facilities. An in-depth study of the situation in Slovenia is required. Residents of nursing homes or other long-term care facilities are often colonised by multi-resistant bacteria against which broad-spectrum antibiotics are ineffective. Nursing homes and other long-term care facilities are places where resistant microbes can spread easily as residents live in a relatively closed environment with limited mobility, have repeated contact with other residents, staff and visitors and are often in contact with the hospital environment. For successful control of microbe resistance in nursing homes and other long-term care facilities, it will be necessary to also introduce measures such as preparing guidelines for diagnostics and treatment of common infections, staff training, and informing residents and their families in these environments (WHO Evidence brief for policy, 2018).

Successful control of healthcare-associated infections is an important indicator of the quality of work in hospitals and makes a significant contribution to the safety of patients and reducing treatment costs.

In Slovenia, we have introduced two important indicators of quality in the field of preventing healthcare-associated infections, for MRSA (2005) and hand hygiene (2015). Both indicators make a significant contribution to improving the prevention and control of healthcare-associated infections and will continue to be the foundations for planning improvements. While preventing healthcare-associated infections, we reduce the transfer of microbes and thereby significantly limit the spreading of multi-resistant microbes. Although a minor but important share of healthcare-associated infections are caused by multi-resistant microbes for which only a limited number of antimicrobials are on offer or do not even exist, the quality and successful prevention of healthcare-associated infections is one of the most important foundations of the strategy for control of microbe resistance. By successfully preventing healthcare-associated infections we also contribute to reducing the consumption of antimicrobials, which at the same time decreases the probability of microbes developing resistance.

Line ministry: Ministry of Health (MZ); participating ministry: Ministry Of Labour, Family And Social Affairs (MDDSZ)

Measures:

1. Prepare and update guidelines, standards and recommendations for the prevention and control of healthcare-associated infections, with an emphasis on multi-resistant microbes for all types of healthcare service providers and different healthcare and caring environments.
2. Continue developing the national system for epidemiological monitoring of healthcare-associated infections, which is coordinated by the National Institute of Public Health, in accordance with ECDC expert guidelines, and which will also provide data about healthcare-associated infections caused by multi-resistant microbes.
3. Ensure an environment for the treatment of patients where there is a smaller probability for the incidence of healthcare-associated infections and the spreading of multi-resistant microbes for the successful prevention and control of healthcare-associated infections and multi-resistant microbes.
4. Upgrade the existing system of regular monitoring and professional control of the implementation of the programme for prevention and control of healthcare-associated infections and expand to include all healthcare service providers, including social institutions.
5. Train a sufficient number of experts to implement programmes for the prevention and control of healthcare-related infections, including control of multi-resistant microbes (doctors, nurses, sanitary engineers, and other healthcare workers).
6. Ensure quality and safety in the field of managing healthcare-associated infections.

7. Together with other stakeholders ensure a rapid and effective response to the incidence of new and extremely resistant bacteria and take measures in the event of outbreaks caused by multi-resistant microbes.

1.5.1.1 Vaccination

Vaccination is one of the most effective measures for curbing infectious diseases and is an important factor in managing microbe resistance to antimicrobials. Thanks to vaccination the incidence of bacterial infections is smaller so the need for treatment with antimicrobials and the occurrence of resistant strains are reduced. By reducing the incidence of viral infections the possibility of inappropriate treatment with antibiotics and the need for antibiotics due to the occurrence of secondary bacterial infections are also reduced. The greater the number of vaccinated people, the smaller the need for hospital treatment and therefore also the smaller the exposure of patients to resistant microbes in the hospital environment. In order to limit infectious diseases it is therefore important that existing vaccines are used as widely as possible and that new vaccines are developed.

In Slovenia, vaccination takes place in compliance with the annual vaccination and medical protection programme, which includes vaccination programmes for preschool and school-age children, the working population and other groups. As a rule, vaccination is carried out at the primary level of healthcare.

From the point of view of managing the resistance of microbes to antimicrobials, the most important vaccines are the ones against pneumococcal infections, flu, whooping cough, meningococcal infections and infections with *Haemophilus influenzae type* B. Vaccines in the process of being developed, which will play an important role in preventing infection with multi-resistant microorganisms, are vaccines against infection with *S. aureus, C. difficile* and *E.coli*.

Measures:

1. Renew legislation in the field of vaccines.
2. Increase the accessibility of vaccines with the possibility of receiving most vaccines from your chosen doctor.
3. Expand the selection of vaccines covered by compulsory health insurance.
4. Raise awareness amongst the general public about the benefits of vaccines through media campaigns and promotional material with an emphasis on the importance of vaccination in all age groups.
5. Educate the professional public about vaccination.

1.5.2 Monitoring, prevention and control of infections connected with veterinary medicine

The Veterinary Compliance Criteria Act (Official Gazette of RS, Nos. 93/05, 90/12 – ZdZPVHVVR, 23/13 – ZZZiv-C, 40/14 – ZIN-B and 22/18) defines the conditions for classifying animal illnesses, taking action and reporting cases of suspected or actual animal illnesses. The Rules on Animal Diseases (Official Gazette of RS, Nos. 81/07 and 24/10) define in more detail some provisions of the act, including preventive and other measures implemented by animal owners, classification of illnesses, obligations regarding registering and reporting animal illnesses depending on the classification, preventive vaccination, national veterinary laboratories. Examinations of official samples must in compliance with the Rules on the information system for monitoring, control and reporting of certain animal diseases (Official Gazette of RS, No. 50/10) be entered in the information system for monitoring, control and reporting of certain animal diseases (EPI). The data in the system is the basis for reporting on animal illnesses.

The Veterinary Practice Act (Official Gazette of RS, Nos. 33/01, 45/04 – ZdZPKG, 62/04 – Constitutional Court decision, 93/05 – ZVMS, 90/12 – ZdZPVHVVR and 22/18) is the legal basis for the minimal scope of animal healthcare and expenses of animal healthcare, veterinary activities and their implementation, public authorisations for the veterinary board and concessions. On the basis of this act, an order is adopted every year about the implementation of systematic animal health monitoring, programmes to eradicate animal illnesses and animal vaccination, which determines examinations for certain illnesses in certain animal species and preventive vaccination.

Preventing, treating and managing infections is a permanent task involving animal owners, veterinarians, various associations, professional and educational institutions and competent authorities. It is necessary to respect the protocols for preventing the spread of illnesses, managing infections and hygiene of animals intended for food production as well as pets and other animals not intended for food production. There must also be an emphasis on introducing and implementing best practices.

A very important and responsible role in ensuring the health of animals belongs primarily to:

- animal owners/breeders: by implementing appropriate hygiene and other biosafety measures, looking after animals well and ensuring a good state of health, with measures for appropriate animal food/fodder and water hygiene, and other necessary preventive measures as instructed by the veterinarian;
- veterinarians: by actively monitoring the health of animals, annual veterinary check-ups and regular periodic visits of holdings and providing appropriate advice and instructions to animal owners concerning preventive measures, and protective vaccination wherever possible.

Preventing infections connected with veterinary medicine should be directed towards:

- preventing the transfer of (resistant) bacteria in livestock holdings (poultry, pigs, cattle etc.);
- preventing the transfer of (resistant) bacteria between different holdings;
- preventing hospital infections in clinics and hospitals for pets.

Line ministry: MINISTRY OF AGRICULTURE, FORESTRY AND FOOD (MKGP)

Measures:

1. Promote activities to prevent the entry and spreading of animal infections/illnesses and resistant bacteria into and inside livestock production facilities, between facilities and from these facilities into the environment, and promote good communication between stakeholders.
2. Use alternatives to antimicrobials.
3. Promote the introduction of programmes to eradicate illnesses or to acquire the status of free-determined illnesses for the preservation or improvement of animal health in the population.
4. Promote research to improve systems for breeding and keeping animals in order to achieve a better state of health, and study optimal ways of protecting animals against infections with the aim of rationally using antimicrobials in the rearing of animals intended for food production.

1.6 EDUCATING PROFESSIONALS AND THE GENERAL PUBLIC

In order to achieve targets and positive changes in the field of antibiotic use and managing microbe resistance, appropriate knowledge and information transfer are crucially important. Not only the professional public is important but also the general public as patients, parents, consumers, animal owners

or farmers can have an important influence on the use of antibiotics and thereby on the development of resistance. The population gains information and knowledge about this from different sources. This is why it is necessary to empower individuals with appropriate information at all stages of life.

Education in the early years is very important for the development of good habits. For a person's healthy adult life, it is important that they become acquainted with this information as a child and that content is upgraded during the adolescent years and in all later periods of life. In addition to the content for developing healthy habits the education systems (in the fields of pharmacy, chemistry, biotechnology and other life sciences) must also include the solving of current problems and the search for innovative solutions as an important contribution to achieving the goals of this strategy.

It is necessary to establish communication between the community that monitors and hinders resistance and the innovative environment in the field of medicine and health, which can find new solutions and follow global trends for controlling microbe resistance and the use of antibiotics. The innovative environment is developing new medicines, diagnostics and other products and services with which it is making an important contribution to the goals of this strategy.

The professional public becomes acquainted with the content in programmes of regular and optional education.

Line ministries: Ministry of Health, Ministry of Education, Science and Sport, Ministry of Agriculture, Forestry and Food, Ministry of Labour, Family, Social Affairs and Equal Opportunities, Ministry of the Environment and Spatial Planning

Measures:

1. Constantly inform the general public about the meaningful and prudent use of antibiotics and the importance of preventing infections.
2. Introduce content on the rational use of antibiotics, preventing and managing infectious diseases and microbe resistance in all levels of the education system (preschool, primary schools, secondary schools, universities).
3. Introduce content on the rational use of antibiotics, preventing and managing infectious diseases, microbe resistance and preventing healthcare-associated infections in the education system for the professional public at different levels of formal education (undergraduate, postgraduate, traineeships, specialisations, continuous vocational education) and ensure training is implemented.

1.7 RESEARCH AND DEVELOPMENT

One of the priority areas of this strategy is research, which enables an understanding of the incidence, mechanisms and epidemiology of the resistance of microbes in different populations (including in connection with the resistance of veterinary isolates and isolates from the environment) and different clinical syndromes. Research makes an important contribution to reducing and controlling resistance to antimicrobials. It is necessary to upgrade research in human and veterinary medicine from basic research, clinical research and research in the field of public health. Slovenia can cooperate in international studies or plan and carry out important research for the state within the framework of national projects. For successful work in this field, it is necessary to ensure adequate inter-sectoral, harmonised research.

Above all, it will be important in research to link data from the field of monitoring resistance with data on the use of antibiotics and data on the results of measures to prevent the spreading of resistant isolates and the effects of preventive public health and educational measures.

The other important field of development is research in the field of microbiological methods for determining and studying microbe resistance mechanisms and other microbe properties connected with resistance and epidemiology, detecting resistant bacteria and molecular microbiological research for defining outbreaks of resistance. It will be necessary to study the possible connection between resistance in human medicine and the field of veterinary science and the environment.

The field of bacterial resistance is also one of the priority areas of the Strategic Development-Innovation Partnership in Medicine and Health. In addition to encouraging research into resistance, it is also necessary to promote applied research and the development of technological and other solutions, which would not be useful only in Slovenia but also internationally.

Resistance is a global problem so cooperation in international research programmes, projects and studies will continue to be essential.

Line ministries: MINISTRY OF EDUCATION, SCIENCE AND SPORT, MINISTRY OF HEALTH, MINISTRY OF AGRICULTURE, FORESTRY AND FOOD, MINISTRY OF LABOUR, FAMILY, SOCIAL AFFAIRS AND EQUAL OPPORTUNITIES, MINISTRY OF THE ENVIRONMENT AND SPATIAL PLANNING, MINISTRY OF ECONOMIC DEVELOPMENT AND TECHNOLOGY

Measures:

1. Cooperation of experts in international research projects.
2. Carrying out research (especially on a national level) in the field of determining microorganism resistance in the environment**,** identifying, studying, epidemiology and controlling microbe resistance (including methods for molecular epidemiology of resistance), connections between the use of antimicrobials and resistance and research into managing the spread of resistance (managing healthcare or veterinary care-associated infections, and others). A priority area is multi drug-resistant bacteria, the connection between resistance and the use of antimicrobials, the connection between resistance and measures for managing healthcare-associated infections and connections with veterinary medicine.
3. The development of information-supported prescription of antimicrobials.
4. Development of new antimicrobial active ingredients and vaccines.

1.8 INTERNATIONAL COOPERATION

Microbe resistance against antimicrobial ingredients is a global problem so measures must be taken on a global level. It is necessary to increase international awareness and harmonise strategic approaches. Joint initiatives by Europe and the USA, such as TATFAR (Transatlantic Task Force on Antimicrobial Resistance) (Summary the modified Delphi process for common structure and process indicators for hospital antimicrobial stewardship programs, 2015), are necessary for exchanging data, technologies and accelerating research. International research is also increasing in the EU, where measures are being harmonised between different countries and sectors for the prevention of infections and laboratory monitoring is making the transition to the molecular level so everything is becoming more demanding. The EU is monitoring the realisation of proposed measures in different states with precise analyses. There is a need for close cooperation with the European Commission, ECDC, WHO, ESCMID and other organisations and professional institutions in the fields of medicine, pharmacy, veterinary medicine and other related fields. Increased cooperation is necessary for the introduction of novelties in developing new antimicrobials and diagnostic methods. Cooperation between researchers working in the field of microbe resistance in medicine, veterinary medicine and the environment must be furthered.

There are numerous international initiatives in the field of research and development of antibiotics (Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), The Innovative Medicines Initiative (IMI) etc.), and Slovenia is already participating in some of them. In March 2017 the UN announced the foundation of an international coordinating group for antibiotics, which is preparing guidelines for development in this field, and which was reported on at the UN General Assembly in September 2018.

Line ministries: MINISTRY OF HEALTH, MINISTRY OF AGRICULTURE, FORESTRY AND FOOD

Measures:

1. Study the connections with international institutions, the connection between national structures for managing resistance and international organisations.
2. Further and strengthen cooperation of national institutions in international organisations and connections.
3. Establish a flow of information on Slovenia's international cooperation in the country amongst relevant stakeholders.

4. MANAGING THE IMPLEMENTATION OF THE STRATEGY AND RESPONSIBILITY FOR IT

Implementing the strategy is based on connecting sectors within the fields of health, farming and the environment, and on the cooperation of all stakeholders.

To ensure coordination and cooperation of all stakeholders in implementing the strategy, the Slovenian government will appoint a national coordinating body, which will prepare periodic harmonised implementation plans for the implementation of the strategy and reports on the successfulness of implementation, reporting to the Slovenian government and the professional and general public. The reports will be the basis for drawing up future implementation plans. It is important that following the example of other countries, in Slovenia too we regularly publish data on the consumption of antimicrobials and microbe resistance to antimicrobials in human and veterinary medicine in a joint national publication. The national coordinating body will contain representatives of all three sectors (health, veterinary medicine/farming and the environment) and professional institutions and experts working on priority areas of the strategy.

5. DETAILED ASSESSMENT OF THE SITUATION IN SLOVENIA

5.1 SITUATION IN THE FIELD OF HUMAN MEDICINE

5.1.1 Antimicrobial consumption

The data on outpatient use of antimicrobials is collected by the Health Insurance Institute of Slovenia (ZZZS) which communicates the data to the National Institute of Public Health (NIJZ) and the NIJZ, in turn, to a team that processes the data and sends the final data to the European Surveillance of Antimicrobial

Consumption Network (ESAC-Net) at the ECDC. The ZZZS processes independently all prescriptions issued to persons insured by the ZZZS (green prescriptions), and the NIJZ additional prescriptions (white prescriptions) of persons who do not have compulsory health insurance.

The data on outpatient use in Slovenia compared to countries of the European Union is described in section 3.1.1 and indicated in Figure 1.

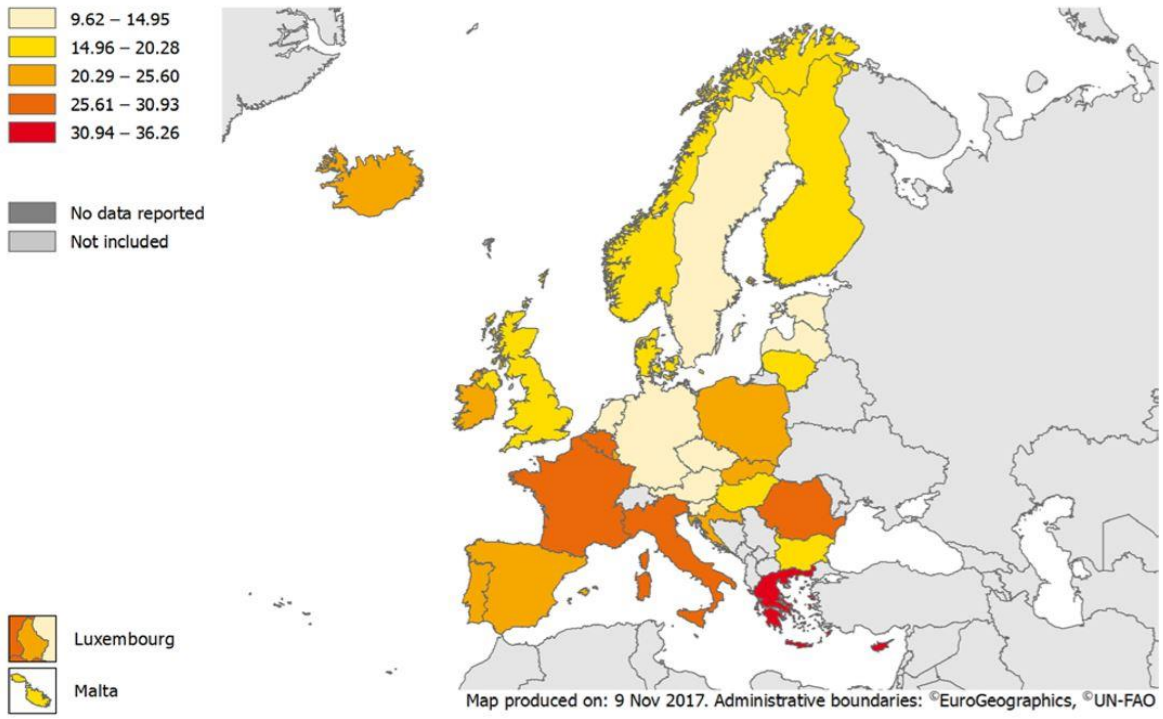

Figure 1: Antibiotic consumption (J01) in EU/EEA countries in 2016 (Source: ECDC 2018 Antibiotic consumption, Annual epidemiological report for 2016)

In Slovenia, differences have been perceived for several years in prescribing between different health regions – doctors in north-eastern Slovenia prescribe more antibiotics than doctors in other regions (Figure 2).

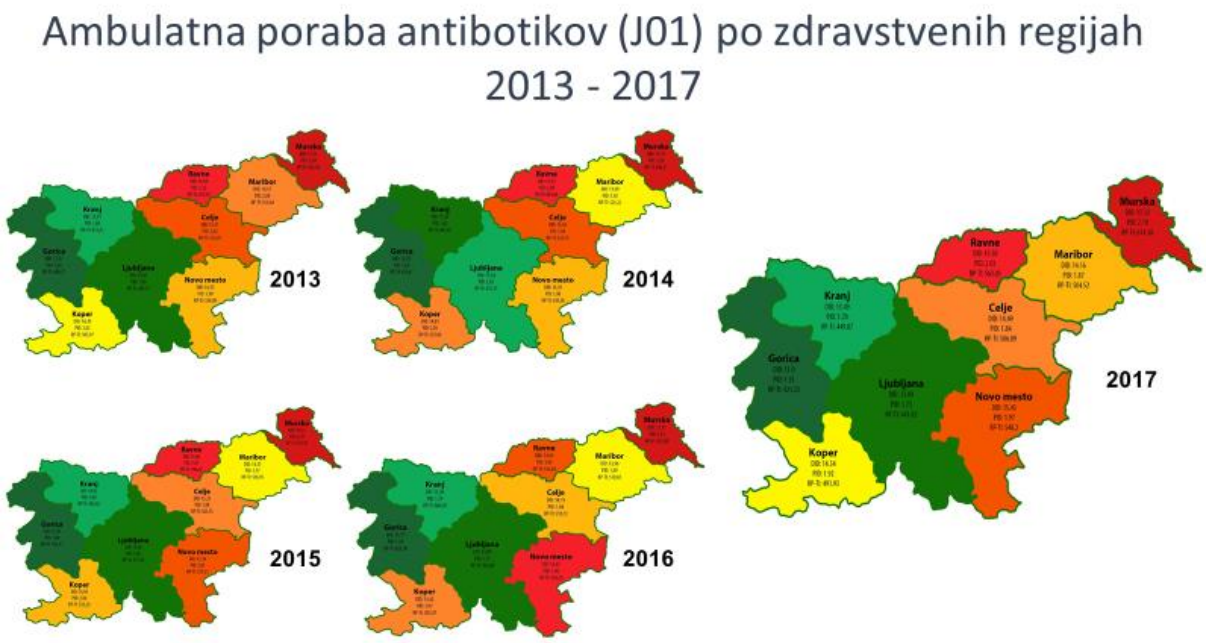

Figure 2: Outpatient antibiotic use (J01) by health region in Slovenia, 2013-2017

Ambulantna poraba antibiotikov (J01) po zdravstvenih regijah 2013–2017	Outpatient antibiotic use (J01) by health region, 2013-2017

Most antibiotics are prescribed to children aged 1-4 years (Figure 3).

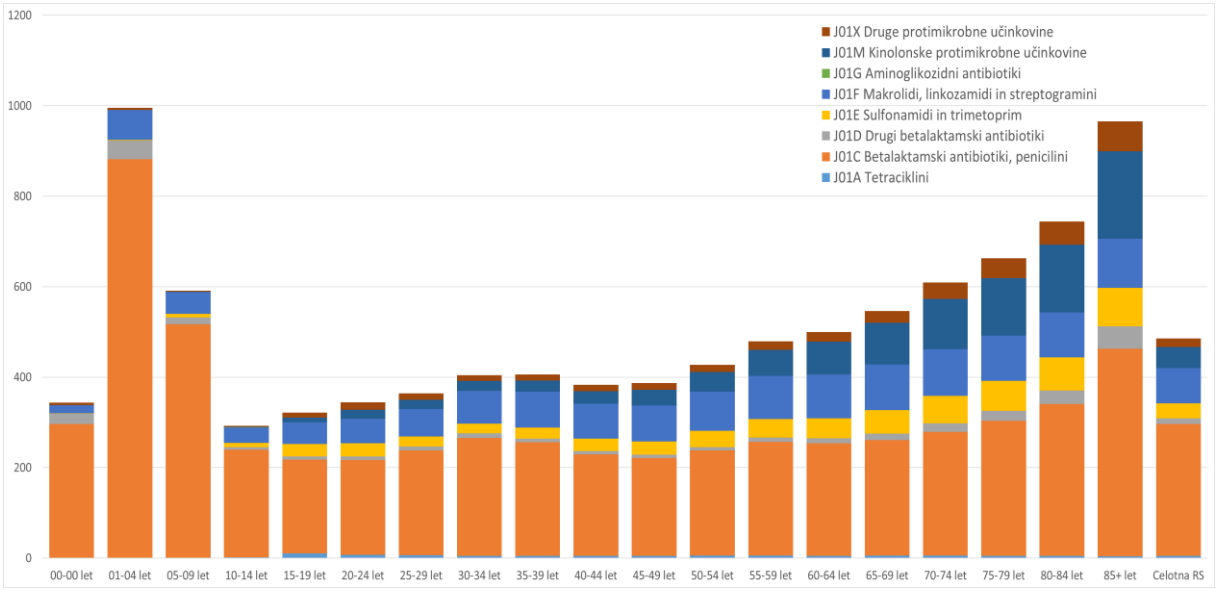

Figure 3: Use (number of prescriptions per 1 000 inhabitants/year) of antibiotics by age group in Slovenia in 2017

	J01X Other antibacterials
	J01M Quinolone antibacterials
	J01G Aminoglycoside antibacterials
	J01F Macrolides, lincosamides and streptogramins
	J01E Sulfonamides and trimethoprim
	J01D Other beta-lactam antibacterials
	J01C Beta-lactam antibacterials, penicillins
	J01A Tetracyclines
	00-00 years
	01-04 years
	05-09 years
	10-14 years
	15-19 years
	20-24 years
	25-29 years
	30-34 years
	35-39 years
	40-44 years
	45-49 years
	50-54 years
	55-59 years
	60-64 years
	65-69 years
	70-74 years
	75-79 years
	80-84 years
	85+ years
	Entire Republic of Slovenia

Consumption in hospitals is reported by hospital pharmacists. The data source is the medicines dispensed from the pharmacy, per ward. To analyse antimicrobial consumption more accurately the actual therapy of each patient should be recorded. According to the Rules on conditions for the preparation and implementation of hospital-acquired infection prevention and control programme (Official Gazette of the Republic of Slovenia, Nos. 74/99, 92/06 and 10/11) the data is collected by the Clinic for infectious diseases and fever conditions, University Medical Centre Ljubljana, which also sends such data to the ESAC-Net. Hospital consumption in Slovenia compared to the countries of the European Union in 2016 is indicated in section 3.1.1 and shown in Figure 4.

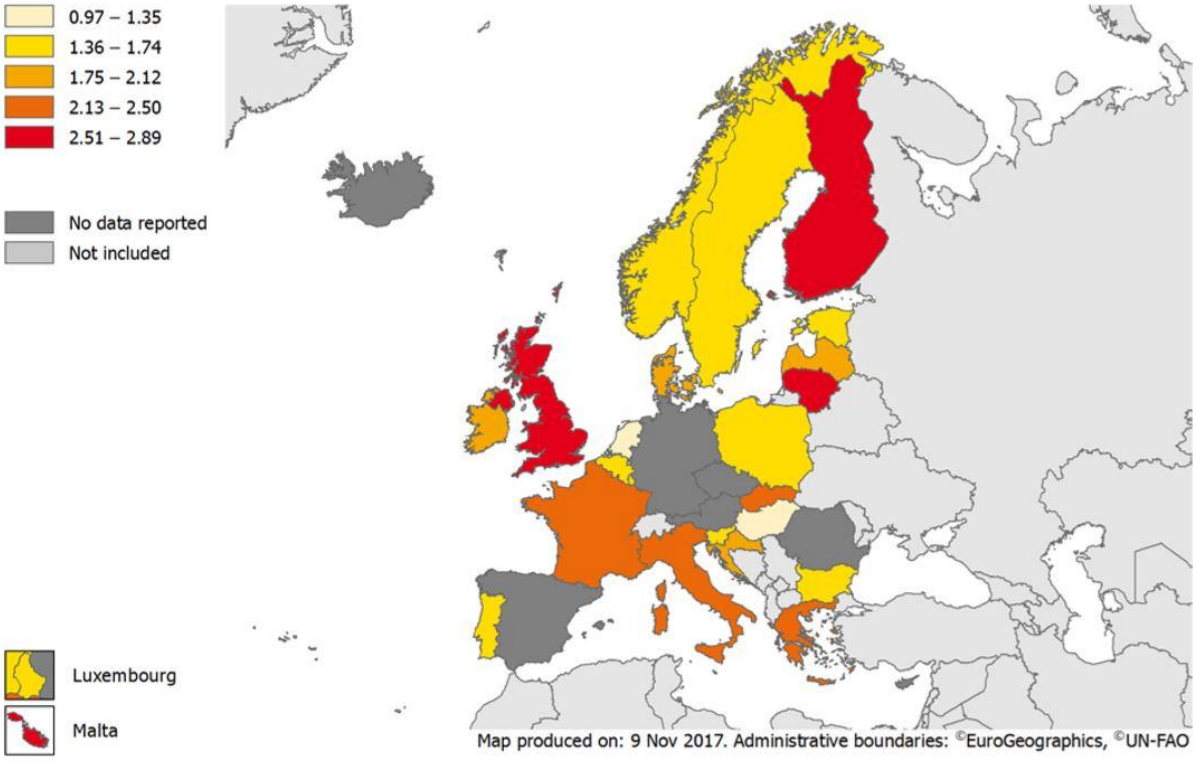

Figure 4: Hospital antibiotic consumption (J01) in EU/EEA countries in 2016 (Source: ECDC 2018 Antibiotic consumption, Annual epidemiological report for 2016)

In Slovenia, the high consumption of carbapenems (0.07 DDD/1 000 inhabitants per day in 2016), which is higher than the EU/EEA average (0.05 DDD/1 000 inhabitants per day), and the increasing consumption of colistin are of concern.

5.1.2 Resistance of microbes isolated from humans

Medical microbiology laboratories

Fourteen medical microbiology laboratories approved by the Ministry of Health carry out antimicrobial susceptibility testing in Slovenia. The laboratories belong to five institutions: National Laboratory for Health, Environment and Food (NLZOH), Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, University Clinic of Pulmonary and Allergic Diseases Golnik, Slovenj Gradec General Hospital and Dr Franc Derganc General Hospital, Nova Gorica. Antibiotic susceptibility testing is performed on bacterial isolates from clinical specimens and surveillance cultures, selected isolates from the hospital and other settings, food samples from sanitary microbiology laboratories, and isolates of selected bacteria from European-Slovenian epidemiological programmes (e.g. national and European surveillance of Salmonella, Campylobacter and other medically important bacteria). Susceptibility testing for antifungal and antiviral drugs is carried out by only some of these laboratories.

In addition to testing samples and determining sensitivity, the role of microbiology laboratories is to work with clinicians and hospital clinical pharmacists to treat infections, with expert in the prevention and control of healthcare-associated infections, and with public health specialists to manage outbreaks. Monitoring and research on resistance and investigating the accumulation of cases (outbreaks) caused by resistant microbes are also important public health tasks. They require in-depth, and above all molecular microbiological diagnostics, which is the function of reference laboratories. Reference laboratories are essential in human microbiology, as stated in European recommendations (quote from ECDC - Core functions of microbiology reference laboratories for communicable diseases, 2010). They have not yet been designated in Slovenia. They are in the public interest and it is important that they are part of the public health system and of the network of medical microbiology laboratories as defined in the Resolution on the National Healthcare Plan 2016-2025 (ReNPZV16-25).

5.1.2.1 Monitoring resistance in human medicine

In Slovenia, planning and implementation of antimicrobial resistance monitoring in human medicine are carried out in several institutions according to local, regional and international needs, namely in the laboratories of the NLZOH, Slovenian National Antimicrobial Susceptibility Testing Committee (SKUOPZ), the Institute of Microbiology and Immunology of the Faculty of Medicine of the University of Ljubljana and the NIJZ. Monitoring is important to assess the situation (at different levels: local, regional and national), monitor trends, make treatment recommendations, plan infection prevention and control measures, and make a comparison with other countries. In order to ensure a unified way to work in this field, in 2010 the General Advisory Board for Microbiology and Immunology at the Ministry of Health appointed the Slovenian National Antimicrobial Susceptibility Testing Committee (SKUOPZ) informally bringing together representatives of all medical microbiology laboratories in the country and the NIJZ. The SKUOPZ prepares expert guidelines for the use of susceptibility testing methods (since 2014 Slovenian laboratories have been using the European EUCAST guidelines), a basic set of antibiotics and annual reports on the antimicrobial susceptibility of bacteria. The reports cover 19 bacterial groups (including anaerobic bacteria and *Mycobacterium tuberculosis*) and are published online at http://www.imi.si/strokovna-zdruzenja/skuopz.

At the international level, Slovenia has participated in the EEARS-Net since 2010, together with 29 other countries of the European Union and the European Economic Area. Before that, from 2000 to 2010, it participated in the predecessor of this network, the European Antimicrobial Resistance Surveillance System (EARSS). The network is coordinated at the European level by the ECDC and in Slovenia by the NIJZ. The data on the main bacterial pathogens of invasive infections (isolates from blood and cerebrospinal fluid) is collected in the network: *Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus faecalis* and *E. faecium, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and the genus *Acinetobacter spp.* The main objectives are to estimate the prevalence of selected invasive bacteria, monitor trends and make a comparison between countries. The results of the 2016 survey show that the resistance of these bacteria in Slovenia is at the European average. Figure 5 shows the proportion of *E. coli* resistant to third-generation cephalosporins, which is similar to the proportion of ESBL strains, Figure 6 the proportion of MRSA and Figure 7 the differences in multidrug-resistant bacteria. For MRSA, VRE and multidrug-resistant *Klebsiella spp*., resistance rates in Slovenia are lower than the European average, while multidrug-resistant *E. coli* and *Acinetobacter spp.* have higher resistance rates.

The need for a stable, long-term system of resistance monitoring at local, regional, national and international levels coordinated among stakeholders, in addition to a stable network of microbiological laboratories with adequately trained personnel, requires a National Coordination Centre (NCC) with a team of experts to comprehensively plan, coordinate and guide resistance monitoring at all levels. The NCC will be responsible for preparing the reports and making them available to professionals from various fields who need them for their work. The team of experts will work with professionals in other fields and ensure inter-sectoral integration with the veterinary and environmental sectors, as defined in the “One Health” initiative, and with other areas, as appropriate.

Figure 5: *Escherichia coli*. Percentage of invasive isolates resistant to third-generation cephalosporins in the EU/EEA countries (Source: EARS-Net annual report 2016)

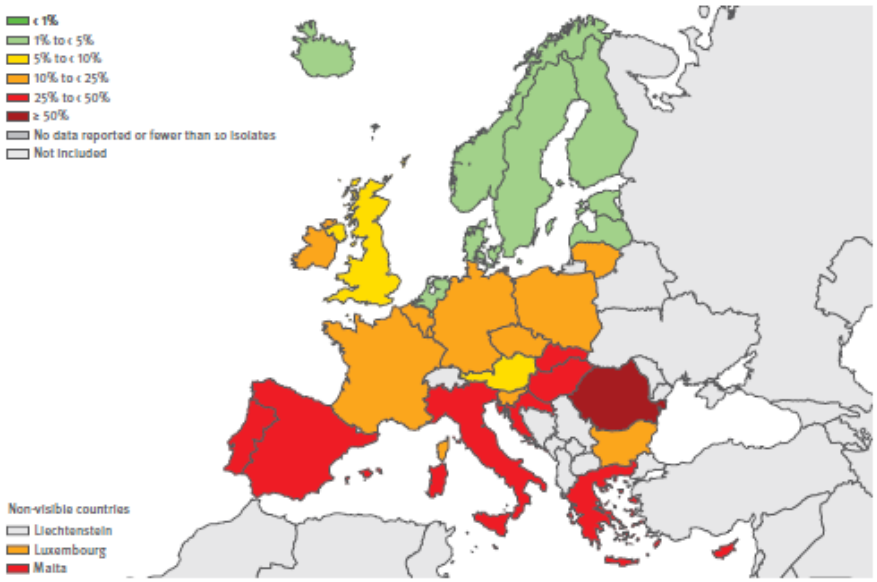

Figure 6: *Staphylococcus aureus*. Percentage of methicillin-resistant invasive isolates (MRSA) in the EU/EEA countries (Source: EARS-Net annual report 2016)

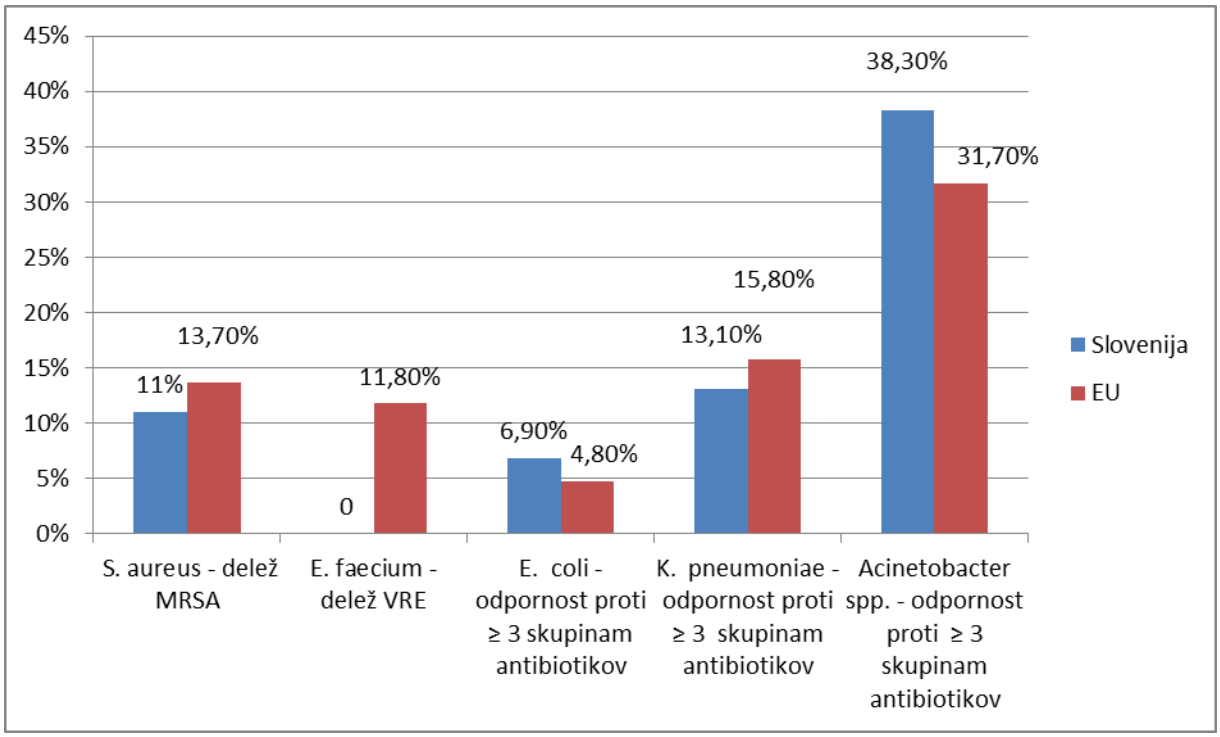

Figure 7: Comparison of multidrug-resistant bacteria in Slovenia and the EU/EEA countries in 2016, data: EARS-Net

S. aureus - delež MRSA	S. aureus - share of MRSA
E. faecium -delež VRE	E. faecium - share of VRE
E. coli-odpornost proti ≥ 3 skupinam antibiotikov	E. coli resistance to ≥ 3 antimicrobial drug classes
K. pneumoniae -odpornost proti ≥ 3 skupinam antibiotikov	K. pneumoniae -resistance to ≥ 3 antimicrobial drug classes
Acinetobacter spp. - odpornost proti ≥ 3 skupinam antibiotikov	Acinetobacter spp. - resistance to ≥ 3 antimicrobial drug classes
Slovenija	Slovenia
EU/EEA	EU/EEA

Comparison with neighbouring countries shows that for most bacteria multidrug resistance is lower in Austria (with the exception of VRE) and higher than in Slovenia in other neighbouring countries, i.e. Italy, Hungary and Croatia.

The extent of the problem in Slovenia is also shown by the SKUOPZ data, where the first isolates from all clinical specimens are covered. The results are presented in Table 1. The burden of resistant isolates is the product of the number of total isolates of a bacterial species and the proportion of resistance - due to the high number of isolates, the highest number of resistant isolates, and therefore the highest-burden, is found in *E. coli*.

Table 2: Number and proportion of multidrug-resistant MRSA, *E. faecium VRE*, *E. coli* with ESBL enzymes, *K pneumoniae* with ESBL enzymes and CRAb (carbapenem-resistant *A. baumannii*) in Slovenia, data from SKUOPZ and EARS-Net for 2016

SKUOPZ					EARS-Net
Bacteria	*Number of isolates*	*Types of resistant isolates*	*Number of resistant isolates*	*Share of resistant isolates*	*Share of resistant isolates*
S. aureus	8,373	MRSA	715	8.6%	11%
E. faecium	1,755	VRE	19	1.1%	0%
E. coli	23,835	ESBL	1,952	8.2%	12.5%
K. pneumoniae	4,453	ESBL	664	14.9%	22.8%
A. baumannii	747	CRAb	243	34.1%	*n/a*

5.1.2.2 Trends and major risks for the future

According to EARS-Net, resistance rates remained fairly stable between 2012 and 2016, with two exceptions: the ESBL rate for *E. coli* increased from 9% to 12%, and the rate of carbapenem-resistant isolates of the genus Acinetobacter from 24% to 43.3%.

Infections in Slovenia are on the rise, despite fairly stable resistance rates, as the number of isolates of common bacteria increases: *E. coli* (2012: 1 168 isolates, 2016: 1 420 isolates), *S. aureus* (2012: 445 isolates, 2016: 534 isolates), *Acinetobacter* spp. (2012: 25 isolates, 2016: 60 isolates).

Similar trends are shown by SKUOPZ data. Comparing 2011 and 2016: the percentage of ESBLs in *E. coli* increased from 6.2% to 8.2%, and of carbapenem-resistant isolates of the genus Acinetobacter from 11% to 32.5%. The resistance rates in the SKUOPZ data are generally lower than in the invasive specimens, as they cover a broader patient population.

The frequency of bacteria with ESBLs increases the consumption of carbapenems. The biggest risk for the future will be the isolates with carbapenemases, as they are generally resistant to the vast majority of effective antibiotics. In Slovenia, strains with carbapenemases are currently relatively rare, with 9 isolates of *Pseudomonas aeruginosa*, 25 isolates of *Acinetobacter spp*. and no isolates of *E. coli* and *K. pneumoniae* in 2016, according to the EARS-Net data. We should not be misled by this data, as the situation can change rapidly - in Italy, for example, the proportion of carbapenem-resistant *K. pneumoniae* isolates was only 1% in 2009 and as high as 27% in 2011. An outbreak of carbapenemase-producing Enterobacteriaceae in Slovenia occurred in 2014 and was successfully contained. Patients coming from countries where carbapenemases are common (Serbia, Greece, Italy, Romania and others) constitute the highest risk. Despite the rarity of carbapenemase-producing Enterobacteriaceae in Slovenia, they are potentially the biggest public health risk.

5.1.3 Monitoring, prevention and control of healthcare-associated infections

In 1999, Slovenia adopted the Rules on conditions for the preparation and implementation of hospital-acquired infection prevention and control programme, based on the Communicable Diseases Act, and was published in an updated form in February 2011. In addition to these rules, the Communicable Diseases Act and the Rules on professional supervision of the implementation of the hospital-acquired infection prevention and control programme are also relevant to the control of hospital-acquired and healthcare-associated infections**.**

In Slovenia, we are setting up a network for epidemiological surveillance of healthcare-associated infections (MESBO) in acute care hospitals. Using protocols aligned with those of the ECDC, we are implementing: a) the Slovenian national cross-sectional surveys of hospital-acquired infections (SNPRBO), b) the epidemiological surveillance of surgical site infections (ESOKR) and c) the epidemiological surveillance of *C difficile*-associated infections (ESCDI). In SNPRBO II (2011), we estimated that 6.4% of patients in the 21 participating hospitals had a healthcare-associated infection or were still being treated for a healthcare-associated infection on the day of the survey. The estimate was similar to the estimate of the prevalence of healthcare-associated infections in EU/EEA countries. The ESOKR results (2013-2016) show that in some hospitals the incidence of surgical wound infections (SWI) after certain operations was too high compared to the reference values for EU/EEA countries. Some estimates of the pre-discharge incidence density for surgical wound infections after some of the observed operations (number of pre-discharge surgical wound infections/number of post-operative hospital days × 1 000) were higher than the 90th percentile of the corresponding estimates for EU/EEA countries. The results of the ESCDI pilot showed that the incidence of *C difficile* infections in the three hospitals was similar to that in other EU/EEA countries.

A comparison of the results of the 2011 Slovenian national cross-sectional survey on nosocomial infections with those of other European countries is shown in Figure 8.

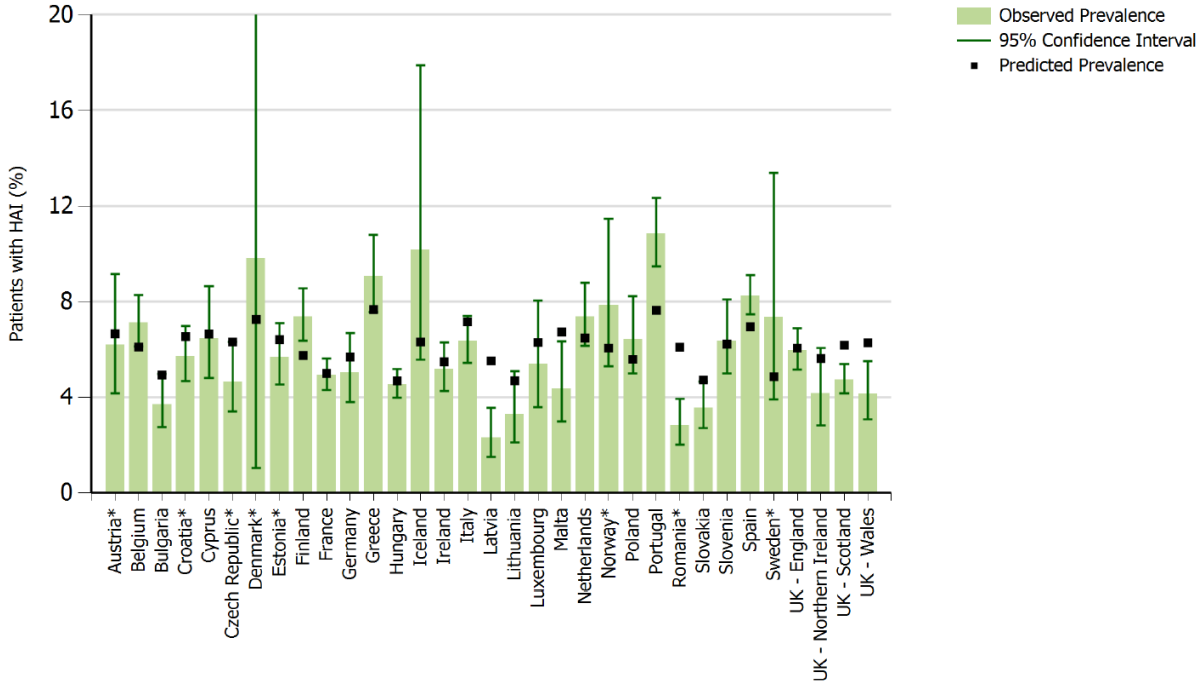

Figure 8: Prevalence of hospital-acquired infections (healthcare-associated infections) in countries of the European Union (Source: ECDC)

In 2017, compared to 2011, the average age of patients was higher, the average length of hospital stays was longer and the proportion of patients undergoing certain invasive procedures was also higher.

From 2013-2016, three-member teams of experts from the National Commission for the Control and Prevention of Hospital-Acquired Infections (NAKOBO) carried out professional supervision of the implementation of the hospital-acquired infection prevention and control programme in the majority of Slovenian hospitals. These supervisions showed the same pattern as the two national cross-sectional surveys, namely an insufficient number of healthcare professionals to control hospital-acquired infections in relation to the number of beds in Slovenian hospitals, and a lack of single rooms for isolation as well as a poor hospital environment for patients. Slovenia is at the bottom of the EU countries in terms of the possibility of isolating patients, with single-room beds accounting for less than 5% of all beds, as shown in Figure 9 (ECDC point prevalence survey indicators).

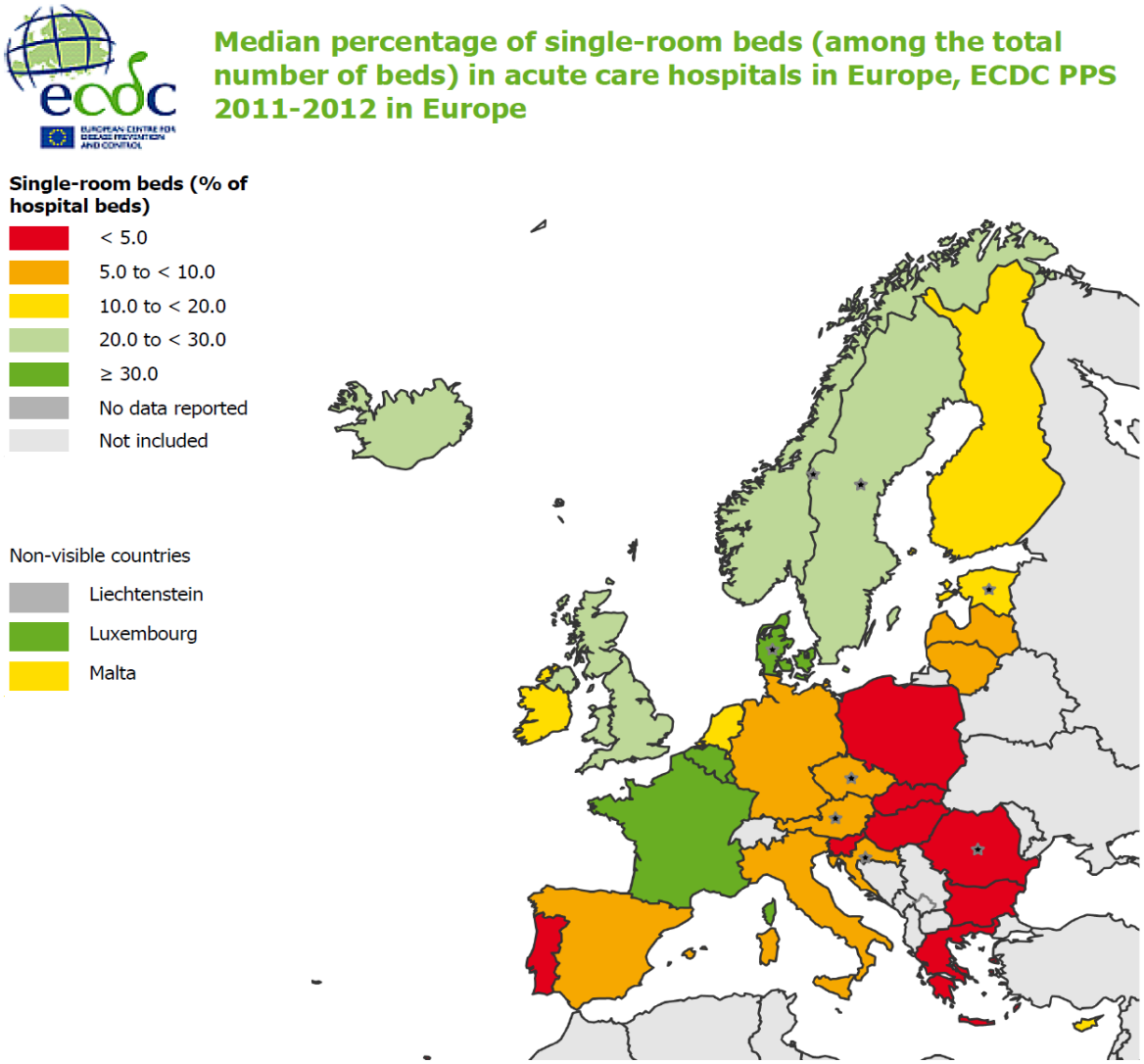

Figure 9: Percentage of single-room beds in acute care hospitals in Europe in 2011 and 2012 (Source: ECDC)

5.2 SITUATION IN THE FIELD OF VETERINARY MEDICINE AND AGRICULTURE

5.2.1 Consumption of antimicrobials in veterinary medicine

According to statistics from the ESVAC (European Surveillance of Veterinary Antimicrobial Consumption) project, the estimated total sales of antimicrobials for use in veterinary medicine in Slovenia fell between 2010 and 2016 from 8.8 to 5.8 tonnes. The calculated sales of these medicines for food-producing animals in mg/PCU (Population Correction Unit) decreased from 46.9 mg/PCU in 2010 to 30.3 mg/PCU in 2016 (-35%) according to the ESVAC project. According to the ESVAC project, the highest estimated sales of antimicrobial medicines in the 30 EU/EEA countries in 2015 were 434 mg/PCU and the lowest was 2.9 mg/PCU (Slovenia 26.4 mg/PCU) (ESVAC Reports). There are large differences between countries, but not only in terms of the estimated sales in mg/PCU but also demographic differences in the animal population and differences in sales between classes of antimicrobials, so cautious interpretation is needed as the situation may change. In Slovenia, penicillins, sulphonamides, fluoroquinolones and tetracyclines were the top-selling antimicrobials for use in food-producing animals in 2016. Among the 30 EU/EEA countries, only Finland, Iceland, Norway and Sweden had lower estimated sales in mg/PCU for food-producing animals than Slovenia in 2015 (Figure 10).

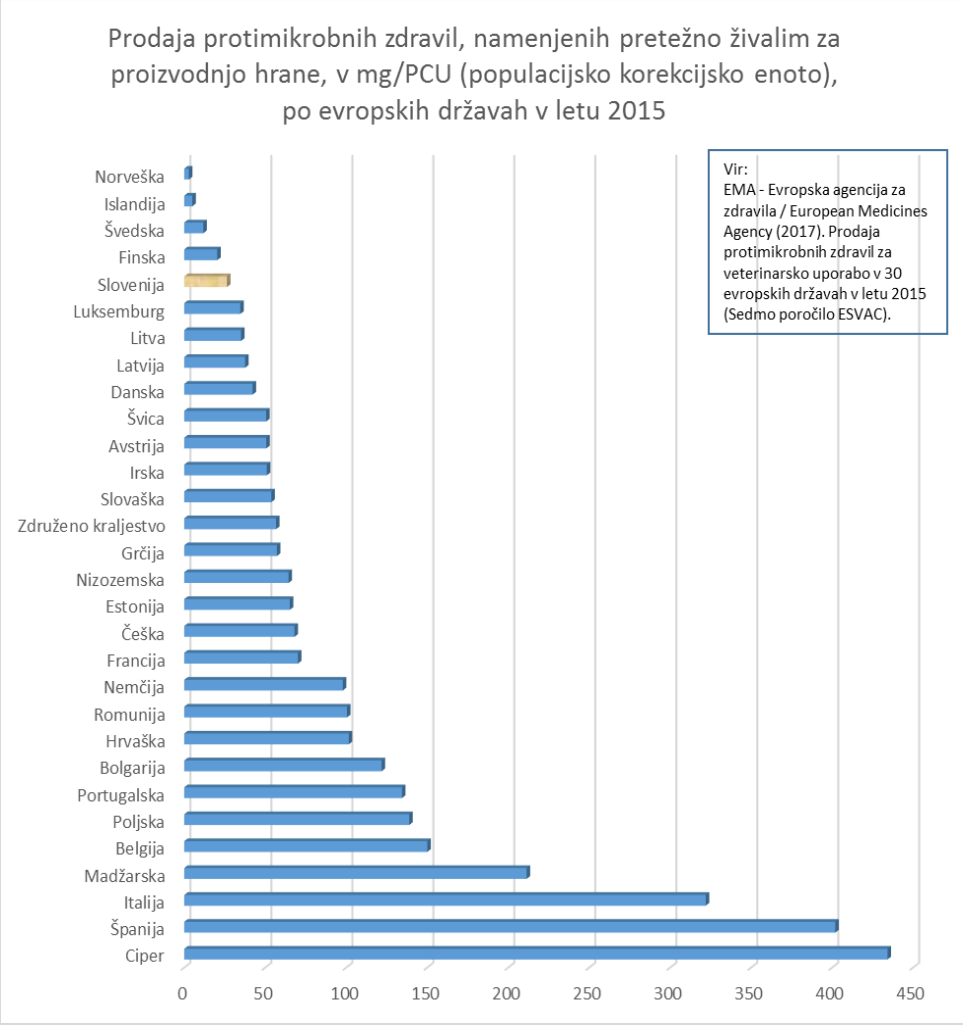

Figure 10: Sales of antimicrobial medicinal products by European country

	Sales of antimicrobial medicinal products predominantly intended for food-producing animals in mg/PCU (Population Correction Unit) by European country in 2015
	Norway
	Iceland
	Sweden
	Finland
	Slovenia
	Luxembourg
	Lithuania
	Latvia
	Denmark
	Switzerland
	Austria
	Ireland
	Slovakia
	United Kingdom
	Greece
	Netherlands
	Estonia
	Czech Republic
	France
	Germany
	Romania
	Croatia
	Bulgaria
	Portugal
	Poland
	Belgium
	Hungary
	Italy
	Spain
	Cyprus
	Source: EMA - European Medicines Agency (2017). Sales of veterinary antimicrobial medicinal products in 30 European countries in 2015 (Seventh ESVAC Report).

As regards the sales of antimicrobials in the form of tablets, mainly to companion animals, ESVAC monitoring shows that sales remained almost unchanged between 2010 and 2016 at around 0.4 tonnes per year, with the share of tablets in total sales increasing from 4.5% to 7.7% over the same period. Meanwhile, the number of registered dogs increased from 202,643 (2010) to 225,716 (2016). The use of antibiotics to treat animals should also follow the EU guidelines for the prudent use of antimicrobials in veterinary medicine (Guidelines for the prudent use of antimicrobials in veterinary medicine (2015/C 299/04)) and the strategy and definitions published by the World Organisation for Animal Health, Office International des Epizooties (WOAHOIE) for this purpose.

The available data on fluoroquinolone sales suggest, inter alia, that there is a particular need to strengthen the responsible and restrictive use (where permissible to preserve animal health and welfare) of these and

other antibiotics on the list of Critically Important Antimicrobials (CIAs) for human use published by the World Health Organisation (WHO).

The following figures (Figures 11 to 13) show the distribution of sales of antimicrobials for food-producing animals in Slovenia in 2015 and by antimicrobial class between 2010 and 2015 (Source: EMA – Seventh ESVAC report, 2017; European Medicines Agency (2017) ESVAC Reports).

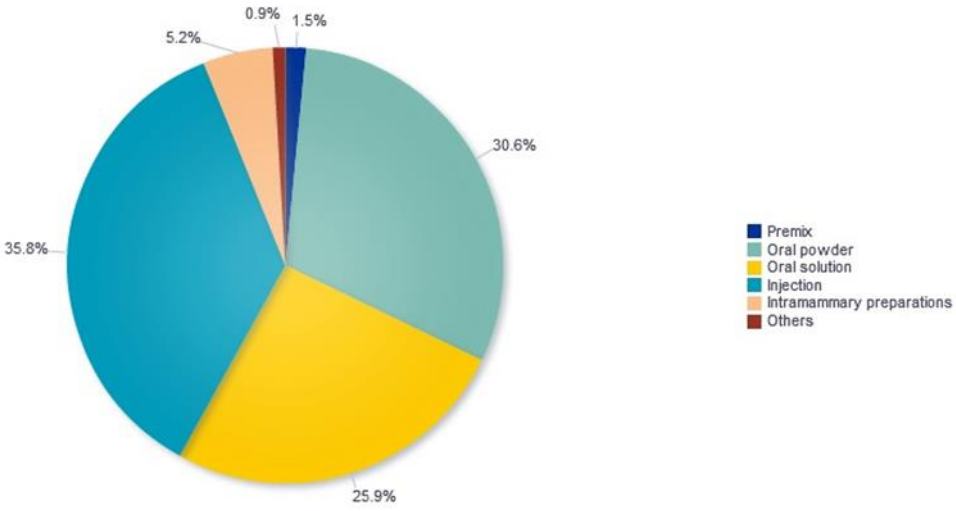

Figure 11: Proportions of the sales of various forms of pharmaceutical veterinary antimicrobial agents for food-producing animals, in mg/PCU, in Slovenia in 2015 (Source: EMA-Seventh ESVAC report, 2017)

In Slovenia, throughout the observation period (2010-2015), greater fluctuations were noted for sales of fluoroquinolones, ranging between 1.8 and 5.9 mg/PCU, compared to the other classes (Figure 13). In 2013, sales of fluoroquinolones were significantly lower than in other years.

Sales of 3rd- and 4th-generation cephalosporins were relatively stable from 2010 to 2015 in Slovenia. In 2015, sales of 3rd- and 4th-generation cephalosporins were 0.17 mg/PCU (Figure 12).

Sales of polymyxins were relatively stable from 2010 to 2015. In 2015, sales of polymyxins for veterinary use amounted to 0.1 mg/PCU.

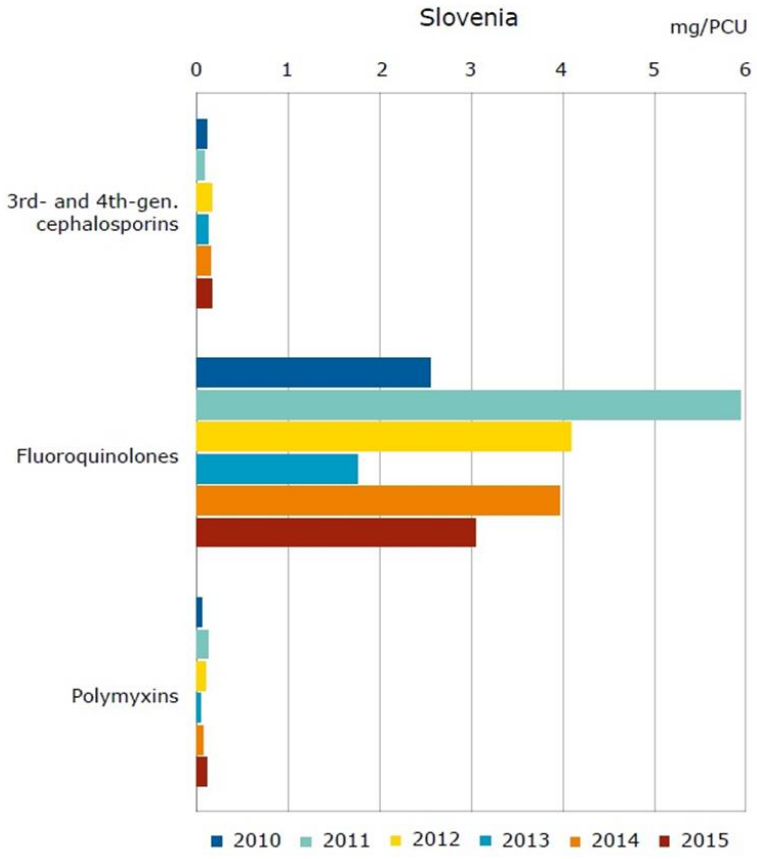

Figure 12: Sales (mg/PCU) of third- and fourth-generation cephalosporins, fluoroquinolones and polymyxins for food-producing animals in Slovenia, 2010-2015 (Source: EMA – Seventh ESVAC report, 2017)

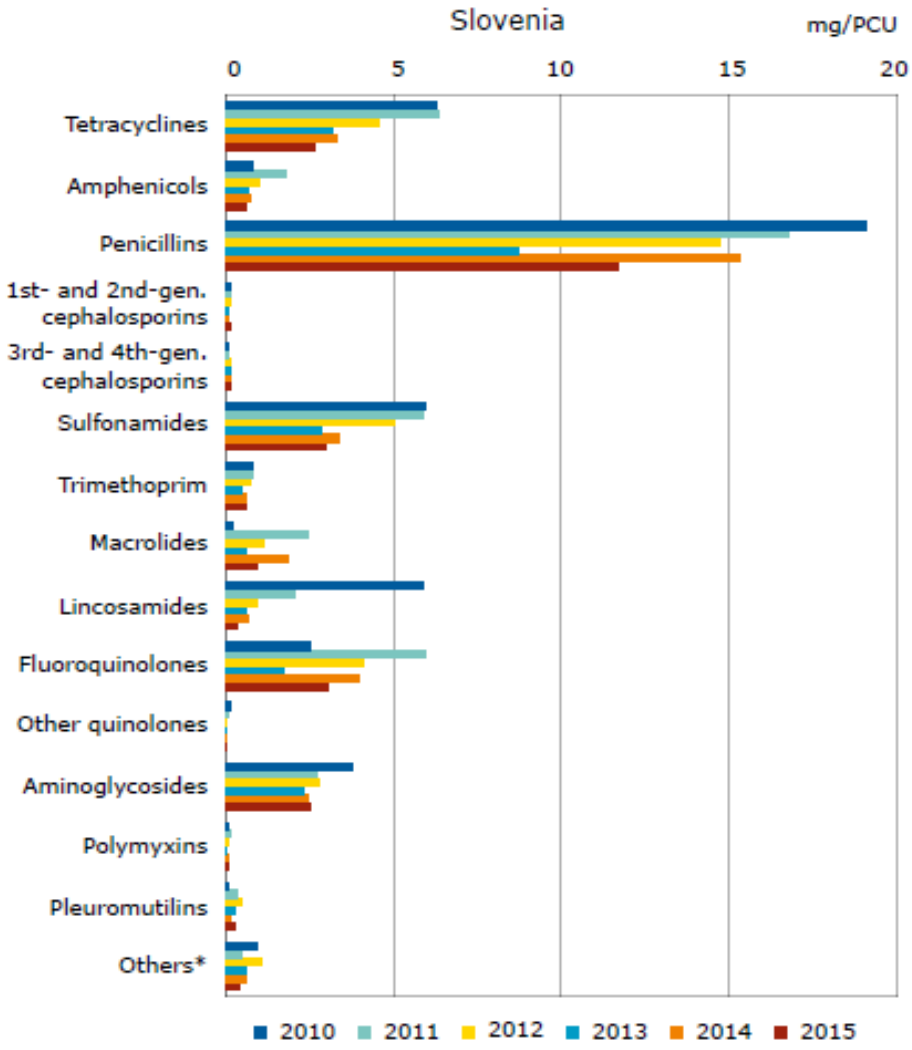

Figure 13: Sales (mg/PCU) by class of antimicrobials for food-producing animals in Slovenia for the years 2010-2015 (Source: EMA – Seventh ESVAC report, 2017)

For the time being, we can only report to the WOAH on the extent of antimicrobial consumption in animals based on the sales of antimicrobials reported to us by wholesalers. In 2015, the WOAH introduced the annual collection of data on the use of antimicrobials in animals in WOAH member states. The WOAH-AMR database is specifically designed to monitor the type of antimicrobial use and consumption in animals, trends over time, and the circulation and use patterns of antimicrobials worldwide, as well as to evaluate the quality of antimicrobials in use. By 2024, the overall consumption of antimicrobials in animals is expected to be reduced by 50% (compared to 2009) and maintained at or below this level. The use of CIAs (especially fluoroquinolones) and medicated feed (for group treatment of animals) should be reduced.

5.2.2 Resistance of bacteria isolated from animals

Tests for the detection of bacterial resistance to antimicrobials in veterinary medicine, which are carried out within the framework of the zoonoses and zoonotic agents monitoring programme (hereinafter referred to

as the zoonoses monitoring programme) and financed from the state budget, are carried out by official laboratories designated by the director-general of the Food Safety, Veterinary and Plant Protection Administration of the Republic of Slovenia (UVHVVR). These are the National Veterinary Institute (NVI) at the Faculty of Veterinary Medicine (VF) and the National Laboratory of Health, Environment and Food. The National Reference Laboratory (NRL) for antimicrobial resistance of bacteria is part of the NVI and performs most of the AMR tests in the framework of the zoonoses monitoring programme. The NRL is integrated into the official network of European veterinary laboratories following the guidelines of the European Reference Laboratory for Antimicrobial Resistance (EU-RL AMR) and has been participating in the EU-RL AMR interlaboratory controls for specific bacterial species since 2006.

Resistance testing of clinical isolates is not part of the zoonoses monitoring programme and is not carried out systematically, but only when ordered by a veterinary organisation for direct treatment of sick animals. They can be conducted in any laboratory in Slovenia or abroad, as there are no legal rules in this area. In Slovenia, testing of clinical isolates is carried out in the laboratory of the Institute of Microbiology and Parasitology of the National Institute of Infectious Diseases (IMP NVI) in Ljubljana and in the laboratories of the regional units of the National Institute of Infectious Diseases (NVI) in Murska Sobota, Maribor, Celje, Novo mesto, Nova Gorica and Kranj, which test a limited number of specific types of specimens from their region.

5.2.3 Resistance of bacterial isolates in farm animals and foodstuffs

The veterinary antimicrobial resistance monitoring programme, which is part of the zoonoses monitoring programme, is prepared annually by the UVHVVR in cooperation with NRLs. Resistance monitoring includes bacterial isolates from certain food-producing animal species and foodstuffs for which monitoring is mandatory under the EU Implementing Decision on the monitoring and reporting of antimicrobial resistance of zoonotic and commensal bacteria. In particular, isolates of certain bacteria from broilers and fattening pigs are included in the resistance monitoring, and testing for most bacteria is carried out on a rotational basis. To a lesser extent, however, bacterial isolates for which resistance and trend monitoring has been carried out for several years or are recommended by various scientific opinions are also included in resistance monitoring at the national level.

The results of the testing of isolates obtained under the zoonoses monitoring programme shall be collected by the UVHVVR in collaboration with the NRLs and sent to the European Food Safety Authority (EFSA). The EFSA, together with the ECDC, prepares a joint EU report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food. A national report, including results on monitoring antimicrobial resistance and assessment of trends in the emergence of resistance at the level of the Republic of Slovenia, is prepared by the NRL. National reports have been published on the UVHVVR website since 2013. The collection and analysis of clinical isolate test results are currently not carried out systematically, but only at the specific request of the test sponsor or for research purposes.

The results of the resistance monitoring performed under the EU Implementing Decision in all Member States are suitable for international comparisons.

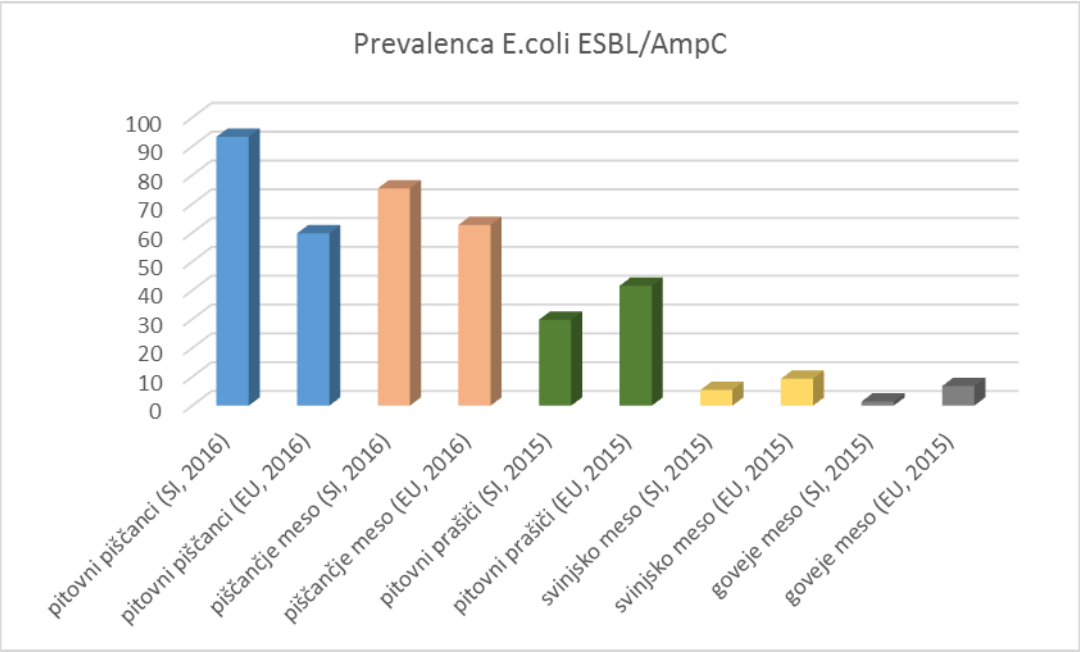

Figure 14: Prevalence of *E.coli* ESBL/AmpC in fattening pigs, in pork, beef, and chickens for fattening and in chicken meat in Slovenia and the EU (results of tests carried out according to the protocol for the selective isolation of *E-coli* ESBL/Ampc)

	Prevalence of *E.coli* ESBL/AmpC
	Broilers (SI, 2016)
	Broilers (EU, 2016)
	Chicken meat (SI, 2016)
	Chicken meat (EU, 2016)
	Fattening pigs (SI, 2015)
	Fattening pigs (EU, 2015)
	Pork (SI, 2015)
	Pork (EU, 2015)
	Beef (SI, 2015)
	Beef (EU, 2015)

The results of the monitoring show that in Slovenia the prevalence of *E. coli* ESBL/AmpC is high in chickens and fresh poultry, and also higher than the average prevalence in the EU (Figure 14). In Slovenia, the prevalence of *E.coli* ESBL/AmpC in pigs and in pork and beef is significantly lower compared to poultry and is also lower than the average prevalence in the EU.

The presence of *E.coli* ESBL/AmpC was also monitored in certain food of non-animal origin (leafy vegetables, pre-cut fruit, pre-cut vegetables, sprouts) in the period 2013-2015. The results showed that the contamination of these foodstuffs is low, as *E.coli* ESBL/AmpC was only detected in 2.4% of fresh leafy vegetables in 2013.

No carbapenemase-producing *E.coli* isolates have so far been identified during monitoring.

The results of the 2015 monitoring of indicator *E.coli* in fattening pigs show that Slovenia has a lower resistance rate for all antibiotics tested compared to the EU average. The highest resistance rate was identified for tetracyclines (40%) and ampicillin (22.4%), while resistance to quinolones was low. The percentage of multidrug-resistant isolates amounted to approximately 18%. In particular, a high resistance

rate to quinolones and ampicillin, tetracyclines, sulphonamides and trimethoprim was identified in indicator *E.coli* isolates from broilers in 2016. Compared to the EU average, Slovenia had a higher percentage of ampicillin-, quinolone- and cephalosporin-resistant isolates. The percentage of multidrug-resistant isolates was approximately 43%.

The results of resistance testing of *C. jejuni* isolates from poultry meat show a particularly high resistance rate to quinolones and tetracyclines. *C.coli* isolates from poultry and pigs also show high rates of resistance to quinolones and tetracyclines, as well as to streptomycin.

In 2014, *E. faecium* and *E. faecalis* isolates from the caecum of broilers and fresh chicken meat were included in resistance testing under the zoonoses monitoring programme. For both enterococci species and both matrices (caecum and meat), the highest resistance rates were found to tetracyclines and macrolides (erythromycin). Moreover, we isolated vancomycin-resistant *E. faecium* (VRE) from one meat and one faeces sample.

MRSA monitoring in farm animals was only included in the zoonoses monitoring programme in 2008 when MRSA was identified on breeding pig farms. The contamination on Slovenian farms was found to be less than 10%, placing us among the countries with a low risk of human infections. The strains belonged to the three most common spa types (t011, t034, t108) and all were resistant to tetracycline. MRSA contamination of fresh pork was detected between 2011 and 2013, with the percentage of samples found to be contaminated with MRSA ranging from 33.3% (2011) to 17.6% (2013). As part of our research activities, we are also monitoring MRSA with the *mecC* gene in animals, where it has not yet been identified.

Salmonella susceptibility at the EU level has remained fairly stable in recent years, with increasing trends in resistance to individual antibiotic classes at the national level.

In Slovenia, Salmonellae have maintained relatively good antibiotic susceptibility, with the exception of serovar Infantis in broilers, where a high percentage of multidrug-resistant isolates to quinolones, sulphonamides and tetracyclines has been identified.

The results of resistance monitoring in farm animals show that the resistance rate of bacterial isolates is high, especially in poultry, and that a high proportion of ESBL/AmpC-producing *E.coli* has also been identified in poultry.

5.2.4 Antimicrobial resistance in bacterial isolates from pets

Health problems in pets are becoming very similar to those in humans. Testing for resistance of bacterial isolates is mainly carried out on the basis of orders of individual veterinary organisations for the direct treatment of sick animals. Coagulase-positive staphylococci (CPS) are the most clinically relevant. MRSA infection or colonisation is relatively rare in dogs and cats. In Slovenia, isolated cases of MRSA have so far been identified in cats belonging to the type (ST 1327, spa t005) normally found in humans.

Methicillin-resistant *S. pseudintermedius* (MRSP) is very important in dogs and cats and is of the same importance in animals as MRSA in humans. Different resistance patterns have been identified in strains isolated so far in Slovenia. The most common are strains which, in addition to beta-lactams, are also resistant to quinolone, macrolides, lincosamides, aminoglycosides, the combination of trimethoprim with a sulphonamide, and some to tetracyclines other than doxycycline.

Among enterobacteria, *E. coli* strains secreting plasmid-encoded extended-spectrum beta-lactamases (ESBLs and AmpC) are the most problematic. The majority of such strains isolated from animals are also resistant to quinolones. Most strains of *P. aeruginosa* are resistant to at least one class of antibiotics commonly used for treatment. Recently, there has been an increase in resistance to fluoroquinolones, from a maximum of 5% in the past to 25% for ciprofloxacin and even over 40% for enrofloxacin since 2009.

Animal infections with *A. baumannii* are very rarely described and their role in veterinary medicine is still very unclear.

5.3 IMPACT OF THE EVOLUTION OF MICROBIAL RESISTANCE ON THE ENVIRONMENT

The environment is part of nature that is or could be affected by human activities. The purpose of environmental protection is to promote and guide the kind of social development that secures long-term conditions for human health, well-being and quality of life, and the preservation of biodiversity.

Environmental protection indirectly contributes to health protection, as actions to improve the environment have an impact on health at the national and local level. Even though environmental protection policies do not directly regulate the prudent use of antimicrobials and the control of antimicrobial resistance in human and veterinary medicine, the environmental protection measures taken also contribute to the control of antimicrobial resistance. The measures taken so far may also have an impact on reducing the occurrence of antimicrobial agents in the environment.

In particular, reducing the discharge and release of antimicrobials and resistant bacteria into the environment, as well as some other chemicals and hazardous substances that can cause antimicrobial resistance, such as biocides and heavy metals, is important for managing antimicrobial resistance.

The main sources and pathways through which chemicals that cause antimicrobial resistance enter the environment are:

- Inappropriate handling of medicines that are no longer needed. Waste medicines disposed of by individuals as mixed municipal waste may end up in landfills due to their physical properties, despite the mandatory treatment of all mixed municipal waste. If they are discarded without immediate packaging or if it is punctured or destroyed, the waste medicines are dissolved by the moisture that is always present in the waste, or under the influence of precipitation water. In this way, antimicrobial active substances enter the environment through landfill leachate. This can lead to pollution of soil and groundwater. Antimicrobials can also enter the environment in wastewater if medicines are flushed down the toilet.
- Significant amounts of antimicrobials used are still biologically active when they are eliminated from the body. They can enter the environment through excreta via urban wastewater. This is also how resistant intestinal bacteria enter the environment. Even though a network of wastewater treatment plants has been set up for municipal wastewater treatment, these systems cannot effectively remove all antimicrobial agents and resistant bacteria from wastewater.
- In agriculture, antimicrobials are used for veterinary treatment. Animals still excrete biologically active substances in their urine and faeces, which can enter the soil and groundwater through fertilisation with livestock manure or through leaching or seepage from livestock manure storage facilities.
- In animal husbandry, antimicrobials (active substances) are used to treat infections. As much as 70-90% of the antimicrobial agents (antibiotics) used are excreted in faeces and urine, either unchanged or as active metabolites (Massé et al., 2014). Through fertilisation of agricultural land with livestock manure, the use of sludge from urban wastewater treatment plants in agriculture and the use of compost or digestate derived from waste, antimicrobial agents or resistant bacteria, if present in these substances, may be transferred to humans and animals by ingesting the plants or products intended for human and animal consumption.
- Antimicrobial and active pharmaceutical substances may also enter waterways via industrial wastewater from production plants.

5.3.1 Separate collection of waste medicines

In Slovenia, a separate collection of waste medicines from households has been established since 2002 as part of the mandatory municipal public utility service for the collection of municipal waste. Waste medicines can be disposed of at municipal waste collection centres or mobile collection units for the collection of hazardous municipal waste. Public service operators must collect municipal waste from

collection centres at least 30 hours per week, including at least 10 hours after 3 p.m. and at least two Saturdays per month for four hours each. As part of the collection of municipal hazardous waste, waste medicines are collected at least once a year in mobile collection units in all settlements with at least 500 inhabitants. If the population density in these settlements is at the same time higher than 500 inhabitants per km^2, municipal hazardous waste shall be collected in a mobile collection unit at least twice a year. Collection of waste at a mobile collection unit must take at least 60 minutes per site.

Public waste collection service providers have an ongoing task to inform service users about the correct separation of waste and the need to separate waste at the source. They are informed about the objectives, advantages and benefits of separate waste collection. They organise practical waste separation demonstrations for users and carry out awareness-raising activities in schools and kindergartens. Waste separation instructions are usually published on their websites. Public service operators also provide notices and instructions on how to store hazardous and non-hazardous waste properly at home so that it does not endanger human health or the environment, and on how to dispose of municipal waste. They inform users about the locations of collection centres and the dates and times when waste can be dropped off, about the collection of waste at mobile collection units and about the types of municipal waste collected at mobile collection units and collection centres.

Since 2010, citizens have also been able to return unused and residual medicines sealed in their original immediate packaging to marketing authorisation holders for medicinal products for retail trade (public pharmacies, pharmacists and other persons in accordance with the Medicinal Products Act) or hand them over to collectors during collection campaigns for waste medicines.

All healthcare and veterinary services providers are also obliged to collect waste medicines separately. This waste is collected by collectors of waste medicines, or, if so agreed, by wholesalers of medicines or marketing authorisation holders for medicinal products for retail trade.

5.3.2 Separate collection of other waste arising from the provisions of healthcare and veterinary services

The regulation of the management of waste from healthcare activities dates back to the 1980s (Rules on the management of special waste containing hazardous substances). The rules on the management of this waste have been amended several times and, in order to align the waste management legislation with the EU law, the Rules on the management of waste from healthcare activities and related research were adopted in 2004. They were in force until 2008 when they were replaced by the Decree on the management of waste generated by health and veterinary services and related research activities, which extended the separate collection of such waste to veterinary services providers. In order to protect the environment and human health, separate collection of sharp waste, waste requiring special handling in collection and disposal to prevent contamination, and chemicals is mandatory. Nevertheless, in line with the prevention, precaution and polluter-pays principles the requirement for separate waste collection also applies to linen, plaster casts, nappies, disposable clothing and other similar waste that is not otherwise required to be handled separately in order to prevent hospital-acquired infections. All this waste must be separated already in outpatient clinics and kept separate from other waste in the prescribed manner until handed over to collectors. Collectors must provide for adequate processing or disposal of all collected waste from the healthcare and veterinary services. If such waste is disposed of in landfills, it must first be disinfected and treated in such a way as to meet the requirements for the disposal of waste with a high level of biodegradable matter.

5.3.3 Use of sludge from sewage plants in agriculture

To improve crop production, sludge from sewage plants is sometimes used in agriculture as a fertiliser alongside other types of fertilisers. However, this "natural fertiliser" can also contain antimicrobials in addition to nutrients and organic matter.

The decree on the management of sewage sludge from urban wastewater treatment plants in agriculture, complying with Directive 86/278/EEC, lays down the rules, measures and management of sludge from sewage plants when it is used as a fertiliser in agriculture, in order to prevent its harmful effects on soil, vegetation, surface water and groundwater, and thereby endangering human and animal health.

The use of sewage sludge in agriculture must comply with the “due diligence” principle, take into account the regulatory limits regarding the amount that can be applied to or in the soil and recommendations from experts. One of the recommendations of the experts is that antimicrobials should be removed (neutralised) before sewage sludge is used as a fertiliser.

Sludge from urban wastewater treatment plants can only be used in agriculture if it meets the regulatory requirements while ensuring that the environment is protected from its harmful effects. Accordingly, at the current level of technology, the use of sewage sludge is not explicitly encouraged; if it is used for fertilisation, the top priority is to avoid its negative effects on the environment (available from: ec.europa.eu/environment/integration/research/newsalert/pdf/applying_sewage_sludge_soil_may_spread_antibiotic resistance_472na1_en.pdf).

5.3.4 Recycling of biodegradable waste and use of compost or digestate

In 2010, the Decree on biodegradable kitchen waste and garden waste management came into force, making the separate collection of biodegradable kitchen waste from households and the catering industry mandatory. Due to the increase in the amount of separately collected biodegradable waste and the growing demand for its recovery into useful raw materials, in 2013 the Decree on the recovery of biodegradable waste and the use of compost or digestate laid down rules on the treatment of biodegradable waste and other conditions for its recovery.

Separately collected biodegradable waste is treated aerobically in composting plants or anaerobically in biogas plants. The product of the processing is a useful material, i.e. compost or digestate, suitable for fertilisation of agricultural and non-agricultural land. The decree introduces a quality management procedure for the entire recovery process of biodegradable waste, including the control and determination of the quality grade of the compost or digestate (distinguishing between the recovery product which is waste and that which is a product).

Most antimicrobials (antibiotics) form complexes with metals and soluble organic matter in the fertiliser and remain unchanged during storage of biodegradable wastes (e.g. animal faeces, urine), but can be degraded during aerobic and anaerobic digestion. The degradation of antimicrobial agents varies, depending mainly on the concentration and type of antimicrobial agent, the type of aerobic/anaerobic plant, the conditions of aerobic/anaerobic digestion, the type of biodegradable waste entering the digestion process, as well as the time and conditions of maturation and storage of the compost or digestate.

Despite the high quality of compost and digestate required, the decree also restricts the application of compost and digestate to or in the soil. The values given are considered as general limit values for the sustainable and regular use of compost or digestate in agriculture for food and feed production and hobby gardening.

5.3.5 Restrictions on the handling of fertilisers

Fertilisation with organic fertilisers, including livestock manures (farmyard manure, slurry, manure and excreta excreted by animals during grazing) and mineral fertilisers containing nitrogen, as well as the storage of livestock manures, including slurry pits, is regulated by the Decree on the protection of waters against pollution caused by nitrates from agricultural sources in accordance with Directive 91/676/EEC. The regulation sets out restrictions on the handling of fertilisers and prescribes requirements for the management of fertilisers with a view to preventing nitrate pollution of surface water and groundwater. It sets maximum annual intake of nitrogen/ha from livestock and organic fertilisers, time bans on fertilisation

when plants do not need nutrients for development and growth (late autumn and winter), and restrictions on fertilisation of farmland where fertiliser runoff or leaching into watercourses could occur. Fertilisation of frozen, water-saturated or snow-covered soils is prohibited, as is fertilisation in certain cases and in varying widths directly on land in coastal areas and on overgrown agricultural land, on infertile land and on water land. Until a water protection regime has been established for the drinking water catchment stations included in the public drinking water supply system, the application of liquid organic fertilisers on the surface of the land or below and ploughing of permanent grassland are prohibited in their vicinity.

Livestock manure storage facilities must be watertight, stable and resistant to mechanical, thermal and chemical influences. They must be regularly maintained to prevent uncontrolled leaching of these fertilisers into the environment. In the event of damage, the livestock manure or biogas slurry must be quickly and safely used or stored elsewhere in a manner that prevents the pollution of water or soil. The storage capacity for livestock manure must be adapted to the number and type of animals on an agricultural holding and provide storage capacity for at least six months in the continental part of Slovenia or four months in the sub-Mediterranean area of Slovenia. Flow channels and pipelines connecting stables with storage facilities for livestock manure or several such storage facilities must be regularly maintained. They must be watertight, stable and resistant to mechanical, thermal or chemical damage.

The Agricultural Institute of Slovenia carried out a study for the Ministry of the Environment and Spatial Planning on the possibility of using hygienisation of livestock manure in the narrowest water protection areas (Agricultural Institute of Slovenia, 2013-2015). Extended slurry storage, aerobic and anaerobic treatment of slurry, slurry additives and hygienisation in slurry storage were analysed. The results of the analyses showed that the risk of drinking water contamination by micro-organisms (*E. coli*, Int enterococci and *C. perfringens*) is reduced by the hygienisation of livestock manure (more so for livestock manure than for slurry), but cannot be completely prevented.

6. PRINCIPLES AND DEFINITIONS

- **One Health** is a term used to describe a principle that recognises that human and animal health are interconnected, that diseases are transmitted from humans to animals and vice versa and must therefore be tackled in both. The One Health approach also covers the environment, linking both humans and animals and is a potential source of new resistant micro-organisms.
- **Antimicrobial resistance:** is the ability of microorganisms (bacteria, viruses, fungi, parasites) to prevent the action of an antimicrobial drug (e.g. antibiotic, antiviral, etc.). Treatment with a drug to which the microbe is resistant is not effective, the infection continues and the pathogen can be transmitted to other people. Resistance can be natural (primary) or acquired (secondary). The latter is most often the result of inappropriate use of antibiotics and other antimicrobial drugs in human and veterinary medicine and agriculture, poor hygiene conditions, and poor practices in healthcare facilities and the food chain that facilitate the transmission of resistant micro-organisms.
- **Healthcare-associated infections**: infections where there is a direct causal link with exposure in diagnostic, therapeutic, nursing, rehabilitation or other healthcare-related procedures in healthcare.
- **Antimicrobial stewardship**: is a set of coordinated measures to ensure the appropriate and responsible prescribing of antimicrobials. Responsible prescribing is important for the sustainable use of antimicrobials. Appropriate prescribing of antimicrobial drugs includes drug selection, dosage, route of administration and duration of treatment.
- **Extreme antibiotic resistance**: in some cases, bacterial infections are difficult to treat because the bacterium is resistant to the vast majority or even all available antibiotics. It occurs mainly in enterobacteria with carbapenemases (*Escherichia coli* and *Klebsiella sp*.), but can also occur in other bacteria (*Pseudomonas aeruginosa, Acinetobacter baumannii*). Infections with these bacteria have been shown to increase mortality (ECDC, 2018). Early detection of extreme resistance, appropriate

treatment of infections, rapid action to prevent the spread of these bacteria and monitoring are very important.

- **A bacterial isolate** is a bacterium isolated from a sample or culture.
- **A bacterial strain or strain of bacteria** is a bacterium or a culture group of bacteria of the same species, that shares certain characteristic properties and differs from other isolates in phenotypic or genotypic features.
- **Hospital-acquired infections** are infections that occur in connection with hospital treatment.
- **Carbapenems** are broad-spectrum antibiotics (acting on many types of bacteria) used to treat the most serious infections.
- **Carbapenemases** are enzymes secreted by bacteria that break down carbapenem antibiotics. The action of carbapenemases can make bacteria resistant to carbapenems (see also carbapenem resistance).
- **Carbapenem resistance** in *E. coli*, Klebsiella, *P. aeruginosa*, *A. baumannii* can be due to different mechanisms, one of them being carbapenemase enzymes. Carbapenem resistance genes often co-occur with resistance genes for other antibiotics. This makes infections with these bacteria extremely difficult to treat.
- **Multiple antibiotic resistance** means that a bacterial isolate is simultaneously resistant to several antibiotics from different groups, usually three or more antibiotic groups.
- **Multidrug-resistant bacteria** are simultaneously resistant to three or more different groups of antimicrobial drugs. Ineffective initial (experiential) therapy results in longer treatment times, more complications, and higher mortality and treatment costs compared to infections caused by antibiotic-sensitive bacteria. The most common multidrug-resistant bacteria are MRSA, ESBL-producing bacteria, carbapenem-resistant bacteria and VRE.

7. LIST OF ABBREVIATIONS

Abbreviation	Meaning	Translation/explanation
AMR	Antimicrobial resistance	Resistance to antimicrobial drugs
ATC	Anatomical Therapeutic Chemical Classification System for human medicinal products	Anatomical Therapeutic Chemical Classification System for human medicinal products
ATCvet	Anatomical Therapeutic Chemical Classification System for veterinary medicinal product	Anatomical Therapeutic Chemical Classification System for veterinary medicinal product
CDI	Clostridium difficile infection	*Clostridium difficile* infection
CIA	Critically Important Antimicrobials	Critically Important Antimicrobials
DDD	Defined Daily Dose	Defined Daily Dose
EARS-Net	European Antimicrobial Resistance Surveillance Network	It is a European network for epidemiological monitoring of the resistance of selected bacterial

		pathogens responsible for invasive infections isolated from blood and/or CSF. It aims to collect reliable and comparable data on the prevalence and spread of the main invasive bacteria with clinically and epidemiologically relevant antibiotic resistance for public health purposes. It is comprised of the ECDC networks of the Member States of the European Union.
EARS-net Slovenia	European Antimicrobial Resistance Surveillance Network Slovenia	The Slovenian part of the EARS-Net collects national data and submits it to the EARS-Net and prepares annual reports, which are published on the NIJZ website as part of the report on epidemiological surveillance of infectious diseases in Slovenia.
EARSS	European Antimicrobial Resistance Surveillance System	The European Antimicrobial Resistance Surveillance System operated between 1999 and 2010 and is the predecessor of EARS-Net. Slovenia participated in the system from 2000 to 2010.
ECDC	European Centre for Disease Prevention and Control	European Centre for Disease Prevention and Control
EFSA	European Food Safety Authority	European Food Safety Authority
EC		European Commission
EMA	European Medicines Agency	European Medicines Agency
ESAC	Net European Surveillance of Antimicrobial Consumption Network	Net European Surveillance of Antimicrobial Consumption Network
ESBL	Extended-Spectrum Beta Lactamases	Extended-Spectrum Beta Lactamases
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption	European Surveillance of Veterinary Antimicrobial Consumption
EUCAST	European Committee on Antimicrobial Susceptibility Testing	European Committee on Antimicrobial Susceptibility Testing
EU/EEA		European Union/European Economic Area
FAO	Food and Agriculture Organization of the United Nations	Food and Agriculture Organization of the United Nations

JAZMP		Agency for Medicinal Products and Medical Devices of the Republic of Slovenia
KGZS		Chamber of Agriculture and Forestry of Slovenia
MRSA	Methicillin-resistant *Staphylococcus aureus*	Methicillin-resistant *Staphylococcus aureus*
MZ		Ministry of Health
NAKOBO		National Commission for the Control and Prevention of Hospital-Acquired Infections
NDM	New Delhi Metallo-beta-lactamase	New Delhi Metallo-beta-lactamase
NIJZ		National Institute of Public Health
NLZOH		National Laboratory for Health, Environment and Food
NKC		National Coordination Centre
NVI		National Veterinary Institute at the Veterinary Faculty
OECD	Organisation for Economic Co-operation and Development	Organisation for Economic Co-operation and Development
OIE	World Organisation for Animal Health	World Organisation for Animal Health
OLTP		
PCU	Population Correction Unit	Population Correction Unit
SKUOPZ		Slovenian National Antimicrobial Susceptibility Testing Committee
VF		Veterinary Faculty of the University of Ljubljana
MDRB		Multidrug-resistant bacteria
VRE	Vancomycin Resistant Enterococcus	Vancomycin Resistant *Enterococcus Faecalis* and *Enterococcus Faecium*
SRIP		Strategic Research and Innovation Partnerships
WHO	World Health Organization	World Health Organization

UVHVVR		Food Safety, Veterinary and Plant Protection Administration of the Republic of Slovenia
ZZZS		Health Insurance Institute of Slovenia

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I. ABBREVIATIONS

ARSO – Slovenian Environment Agency,

BF - Faculty of Biotechnology,

BO- Hospital-acquired infections,

ECDC - European Centre for Disease Prevention and Control,

EK-BTSF - BTSF initiative (training for the implementation of food safety programmes),

EMA – European Medicines Agency,

ESVAC - European Surveillance of Veterinary Antimicrobial Consumption,

FZZ - Faculty of Health Sciences,

IMI - Institute of Microbiology and Immunology at the University of Ljubljana's Faculty of Medicine,

JAZMP - Agency for Medicinal Products and Medical Devices of the Republic of Slovenia,

KGZS - Chamber of Agriculture and Forestry of Slovenia,

KIBIVS - Department of Infectious Diseases and Febrile Illnesses at the Ljubljana University Medical Centre,

KOBO - Commission for the control of hospital-acquired infections,

MDDSZ - Ministry of Labour, Family and Social Affairs,

MF LJ - Faculty of Medicine of the University of Ljubljana,

MF MB - Faculty of Medicine of the University of Maribor,

MIZŠ - Ministry of Education, Science and Sport,

MKGP - Ministry of Agriculture, Forestry and Food,

MOP - Ministry of the Environment and Spatial Planning,

MZ - Ministry of Health,

NAKOBO - National Commission for the Control and Prevention of Hospital-Acquired Infections,

NVI - National Veterinary Institute,

OIE - World Organisation for Animal Health,

HAI - healthcare-associated infections,

RSK – expanded expert committees, General Advisory Board at the Ministry of Health

SVZ- social care homes providing healthcare services (e.g. nursing homes)

SZD - Slovenian Medical Society,

SKUOPZ - Slovenian National Antimicrobial Susceptibility Testing Committee,

SOS - Alert monitoring group,

SZPK - Society of Antimicrobial Chemotherapy,

UVHVVR - Food Safety, Veterinary and Plant Protection Administration of the Republic of Slovenia,

VF - Veterinary Faculty,

VZb - Veterinary Chamber,

ZRSŠ – National Education Institute of the Republic of Slovenia,

ZZS – Medical Chamber of Slovenia,

ZZNS – Nurses Association of Slovenia,

ZZZS – Health Insurance Institute of Slovenia.