MISSION REPORT

ECDC country visit to Romania to discuss antimicrobial resistance issues

6-10 March 2017

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This report of the European Centre for Disease Prevention and Control (ECDC) was coordinated by Anke Kohlenberg.

Contributing authors
Anke Kohlenberg (ECDC), Dominique L. Monnet (ECDC), Andrea Nilsson (ECDC), Michael Borg (Malta), Nandini Shetty (United Kingdom).

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Abbreviations

AMR	antimicrobial resistance
ARHAI	Antimicrobial Resistance and Healthcare-Associated Infections Disease Programme
ARPIM	Romanian Association of International Drug Manufacturers
CDI	*Clostridium difficile* infection
CI	confidence interval
CLSI	Clinical and Laboratory Standards Institute
CPD	continuing professional development
CPE	Carbapenemase-Producing Enterobacteriaceae
EAAD	European Antibiotics Awareness Day
EARS-Net	European Antimicrobial Resistance Surveillance Network
EFPIA	European Federation of Pharmaceutical Industries and Associations
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
ESBL	extended spectrum beta-lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EU/EEA	European Union/European Economic Area
GP	general practitioner
HAI	healthcare-associated infections
ICM	Intersectoral Coordinating Mechanism
ICU	intensive care units
IPC	infection prevention and control
MDRO	multidrug-resistant organisms
MRSA	meticilin-resistant *Staphylococcus aureus*
NDM	New Delhi Metallo-beta-lactamase
NRC	national reference centre
WHO	World Health Organization
TB	tuberculosis

Summary

Rationale and purpose of the country visit

A Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine (2002/77/EC) outlines the threat that antimicrobial resistance (AMR) poses to human health and advocates for a range of actions to be taken for its prevention and control. The Council Conclusions on antimicrobial resistance of 10 June 2008 reiterated this call for action.

To assist Member States in implementing the Council Recommendation, ECDC has developed a process for and is carrying out, upon invitation from national authorities, country visits to specifically discuss and assess the situation of the country regarding prevention and control of AMR through prudent use of antibiotics and infection control. These country visits also help document how Member States have approached this implementation and deployed national activities and support the European Commission in evaluating this implementation.

The main output of the visit is a report from the ECDC Team provided to the inviting national authority. To help the ECDC Team ensure consistency of the visits and follow-up of progress of countries, an assessment tool has been developed. This assessment tool includes ten topics. These topics are regarded as core areas for successful prevention and control of AMR and are based on Council Recommendation 2002/77/EC and on the Council Conclusions of 10 June 2008. The assessment tool is used as a guide for discussions during the visit.

Following an official invitation by the Ministry of Health dated 7 October 2016, an ECDC team conducted visits and meetings to discuss AMR issues in Romania with the overall objective of providing an evidence-based assessment of the situation in Romania regarding prevention and control of AMR through prudent use of antibiotics and infection control.

Conclusions

The current levels of antimicrobial resistance (AMR) in Romania are a serious concern. The reported levels of AMR in key indicator bacteria from humans are very high and/or rising in comparison to most other EU/EEA countries.

Several factors are likely to contribute to the current situation. There is a high consumption rate of antimicrobial agents in human medicine in general and the widespread use of last-line broad-spectrum antimicrobial agents is worrying. There also appear to be constraints in terms of infrastructure in hospitals and a skills shortage in key healthcare personnel.

In addition, Romania lacks robust data on AMR rates, healthcare-associated infections (HAIs) and antimicrobial consumption at the local level to inform treatment guidelines, achieve prudent antibiotic use and target infection prevention and control (IPC) measures. Other contributing factors include inadequate multidisciplinary collaboration between clinicians, microbiologists and epidemiologists and limited collaboration between human and veterinary domains with regard to AMR.

There are, however, several areas of good practice and evidence of change for the better. Most importantly, the recognition that certain areas require improvement is driving the momentum for change. Examples of good practice include the public awareness campaign to limit use of antibiotics and the initiatives to limit the sale of over-the-counter antimicrobial agents. Change is being driven by committed, motivated and knowledgeable healthcare staff who spread the message regarding prudent use of antibiotics and IPC in their everyday work environments. These drivers for change and the staff who strive to achieve this change need to be supported and resourced. They also need to be provided with a structured framework to attain the desired goals.

Romania is at a cross-roads. If the current levels of AMR persist, or even increase, it is likely that untreatable HAIs, especially those caused by *Klebsiella pneumoniae* and *Acinetobacter baumannii*, will become a reality. This would have a serious impact on the ability of hospitals to provide critical medical services such as cancer treatment, major surgical procedures and intensive care.

Recommendations

Based on the observations and conclusions, the ECDC team recommends the following actions:

- Designate AMR as a national public health threat encompassing all regions. This would mandate prioritisation in resource allocation and short- and long-term planning.
- Prioritise the creation of an Intersectoral Coordinating Mechanism. This is essential to facilitate the required improvements and should include the National Insurance House and representatives from each region whose responsibility will be to ensure that information and action is relayed from the national to the regional level. Local groups with a similar composition should be formed in each county to disseminate information and ensure implementation and action at the local level.

- Focus on writing a National Action Plan for AMR with a 'One Health' approach and include the specific needs related to diagnosis, surveillance, prevention and control of multidrug-resistant organisms (MDROs). All these aspects should be included in one single national action plan. Adequately resourced teams should be set up within the Ministry of Health to tackle AMR – i.e. a focal point for AMR, a microbiologist, a clinician and an epidemiologist in each county. They should be provided with intensive training on AMR diagnosis and control, and then formally appointed with clear terms of reference and responsibilities for initiating and coordinating the necessary AMR activities.
- Determine costs of activities at both national and regional level so that appropriate budgets can be made available. Investment in antibiotic stewardship and IPC has been proven to be cost-effective and will usually result in savings that exceed the amount invested. Financial challenges should therefore not be a barrier for implementation of the National Action Plan and its activities.
- Based on the successful *Clostridium difficile* infection (CDI) control programme, launch a similar initiative to include infections caused by other MDROs such as: carbapenem-resistant Enterobacteriaceae (CRE), multidrug-resistant *Acinetobacter* and *Pseudomonas* species, and meticillin-resistant *Staphylococcus aureus* (MRSA). A package of interventions should typically include:
  - a screening strategy for high-risk patients and high-risk units;
  - an alert system to flag positive patients;
  - referral of resistant isolates to the National Reference Laboratory for further characterisation;
  - robust surveillance data capture mechanisms and analyses by the National Public Health Institute (mandatory notification of bacteraemia cases through a simple online reporting system is a possible option);
  - timely and efficient dissemination of information to relevant healthcare staff.
- Consider finding resources for these activities by shifting some of the resources devoted to routine environmental screening in healthcare facilities, known to be of limited value in the control of HAI according to international literature.
- Launch a national campaign on IPC - i.e. hospital hygiene - starting by raising awareness of hand hygiene in hospital and community healthcare facilities, accompanied by increased availability of alcohol hand rub in hospitals, ideally at the end of every hospital bed; surveillance of alcohol hand rub consumption and observation of hand hygiene performance.
- Continue the national public awareness campaign on the prudent use of antibiotics. Considering the low level of awareness of antibiotics and AMR among the public in Romania, the documented levels of non-prescribed antibiotic use and the frequently repeated reference to pressure by the public on doctors and pharmacists, Romania would benefit from continued national antibiotic awareness campaigns. In addition, national communication strategies would benefit from a higher level of cooperation on prudent antibiotic use campaigns in the regions and districts.
  Specific suggestions include:
  - Maintaining public relation activities every year in connection with European Antibiotics Awareness Day (EAAD).
  - Planning a wide-reaching campaign for all the districts (e.g. every two years), focussing on one or two targeted audiences. Another possibility could be to make sure that the districts have an annual plan where information about the topic is fed to the different groups throughout the year.
  - Increasing the number of tools available. This can easily be done by cross-linking websites with the EAAD page in Romanian.
  - Including an adapted version of *the Social Media Strategy Guide for Public Health Communication* available here: http://ecdc.europa.eu/en/publications/Publications/social-media-strategy-guide-for-public-health-communication.pdf. This document can also be used by the national authorities for their social media strategies.
  - Implementing simple performance indicators such as web visits, media clippings, social media reach, event participation, and amount of materials distributed.
  - Organising a training on development, implementation and evaluation of campaigns targeting prudent use of antibiotics. ECDC can provide its training module on the topic and support the development of the training that could be translated into Romanian.
  - Establishing better routines and mailing lists at national level so that the ECDC National Focal Point for communication and its alternate can easily share ECDC's messages.
- Increase the involvement of the National Health Insurance House in campaigns for correct prescribing of antibiotics in ambulatory care as an opportunity to make substantial savings by more prudent use of antibiotics and the subsequent decrease of AMR. Regional branches of the health insurance organisation could start to collate lists of general practitioners (GPs) and their respective prescribing trends that would then be passed on to the public health entities of the region for follow-up. High-end users would be asked to justify their practice and rectify it, if justification was not shown.
- Increase the microbiology laboratory capacity by ensuring sufficient funding of the National Reference Laboratory (Centre of Excellence) for AMR at the Cantacuzino Institute in support of public health activities related to AMR. It should be emphasised that the National Reference Laboratory should support hospital diagnostic laboratories in standardising their methodologies and providing an external quality assurance scheme.

- Increase the availability of infectious disease expertise in hospitals and antimicrobial stewardship programmes including pre-authorisation of antibiotics, restricted availability of last-line agents, de-escalation protocols, local evidence-based treatment guidelines and establishment of performance indicators based on antimicrobial consumption in general hospitals.
- Strengthen surveillance data on AMR, both at national and local level. This can be done by improving geographical representativeness and timeliness and increasing the number of tested isolates at each centre/laboratory. It is recommended that available IT expertise is channelled and supported with investment in systems and programmes that can use available data generated by hospitals to study resistance trends nationally and regionally.
- Strengthen surveillance data on antimicrobial consumption. In particular, a commitment is needed to obtain comprehensive antimicrobial consumption data stratified by hospital specialty and community healthcare facilities by working with the National Insurance House, the National Medicines Agency and other relevant bodies.
- Invest in a professional development plan to train future healthcare professionals by updating the educational curricula of undergraduate medical schools, postgraduate medical specialties and colleges of pharmacy and nursing to include modules of microbiology, epidemiology, rational use of antimicrobial agents and IPC. The curriculum on antimicrobial stewardship for infectious disease clinicians, a draft of which has already been submitted to the Ministry, should be instituted and it should be ensured that a sufficient number of IPC nurses with formal national training and IPC certification are available at each hospital. Minimal structure indicators should be agreed for effective IPC, as well as antimicrobial stewardship at hospital level and linked to bed occupancy and type of care provided. This will ensure that the required staff are involved at local level.
- Develop guidelines for diagnosis, management, prevention and control of specific infectious diseases and national guidelines on the correct use of antimicrobial agents in human medicine, based on the local resistance epidemiology. In particular, reduction in the use of broad spectrum antibiotics, such as cephalosporins, and last resort agents, such as carbapenems and colistin, should be addressed in these guidelines.
- Revisit the practice of emergency weekend over-the-counter antibiotics with possible alternative methods of access provided. Supervision of pharmacies to further reduce over-the-counter dispensation of antibiotics should be continued, including measures to reduce the practice by community pharmacies of dispensing injectable agents not covered by the hospital budget.

1. Background

1.1 Rationale for country visits to discuss antimicrobial resistance issues

After the introduction of antibiotics in the 1940s, it soon became clear that antibiotic usage promoted the rise of antibiotic-resistant bacterial strains in common bacteria such as *Staphylococcus aureus* and *Mycobacterium tuberculosis* (TB). In the decades which followed, the increasing number of antibiotic-resistant strains could be managed thanks to the continuous availability of new antibiotics providing new means of treating patients infected with resistant bacteria. However, from the 1990s onwards, development of new antibiotics decreased and at the same time, the emergence of bacteria resistant to multiple antibiotics became an ever-increasing problem in clinical medicine. Treatment guidelines had to be rewritten and the need to take bacteriological samples for antibiotic susceptibility testing became essential.

Once a resistant bacterium has developed, it will spread from a colonised person to another person if appropriate hygienic precautions (e.g. hand hygiene, isolation) are not taken. The risk of resistant bacteria spreading is higher in crowded environments and even greater when people in the surrounding area are receiving antibiotics - a common situation in hospitals and other healthcare facilities.

Today, bacteria that are totally (or almost totally) resistant to antibiotics (i.e. untreatable with antibiotics) are spreading in Europe. This represents a patient safety issue.

In 1998, the Chief Medical Officers of the EU Member States recognised this evolving problem and took the initiative to arrange the first major conference on AMR, which resulted in the Copenhagen Recommendations (Report from the Invitational EU Conference on the Microbial Threat, Copenhagen, Denmark, 9–10 September 1998).

In November 2001, the EU Health Ministers adopted a **Council Recommendation on the prudent use of antimicrobial agents in human medicine (2002/77/EC)**, covering most topics of importance for the prevention and control of AMR. The Commission must report back to the Council on progress implementing the Council Recommendation.

In 2005, the European Commission reported to the Council on progress in Member States in the Report from the Commission to the Council on the basis of Member States reports on the implementation of the Council recommendation (2002/77/EC) on the prudent use of antimicrobial agents in human medicine (COM (2005) 0684). This states that 'ECDC should be able to assist the Commission in the future preparation of implementation reports and of recommendation proposals.'

In June 2008, EU Health Ministers adopted Council Conclusions on antimicrobial resistance (AMR) that reiterated the call for action to contain antimicrobial resistance and called upon Member States 'to ensure that structures and resources for the implementation of the Council recommendation on the prudent use of antimicrobial agents in human medicine are in place and to continue with the implementation of specific strategies targeted towards the containment of the antimicrobial resistance'.

In June 2009, EU Health Ministers adopted a **Council Recommendation on patient safety, including the prevention and control of healthcare-associated infections (2009/C 151/01)**, which further stresses the importance of combating AMR as a patient safety issue.

In April 2010, the European Commission published its second report from the Commission to the Council on the basis of Member States' reports on the implementation of the Council Recommendation (2002/77/EC) on the prudent use of antimicrobial agents in human medicine. While acknowledging that Member States have made significant progress since 2003, this report highlights many areas where implementation is not optimal and identifies directions for future work.

In November 2011, the European Commission published a new five-year **action plan against the rising threats from antimicrobial resistance** with the aim of addressing AMR by implementing a coordinated approach in all those sectors concerned (public health, animal health, food safety, environment, etc.) and strengthening and further developing EU initiatives against AMR and HAI at EU and international levels.

The new cross-sectorial approach has been further strengthened with the adoption of the **Council Conclusions on antimicrobial resistance of 22 June 2012** and the **Council conclusions on the next steps under a One Health approach to combat antimicrobial resistance of 17 June 2016**.

On 29 June 2017, the European Commission published a new **European one health action plan against antimicrobial resistance (AMR)**[1] with concrete actions with EU added value that the European Commission will develop and strengthen as appropriate for a more integrated, comprehensive and effective approach to combating AMR.

[1] https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf

ECDC's mission, as part of its **Founding Regulation No 851/2004**, is (i) to identify, assess and communicate current and emerging threats to human health from communicable diseases; (ii) in the case of other outbreaks of illness of unknown origin which may spread within or to the Community, the Centre shall act on its own initiative until the source of the outbreak is known; and (iii) in the case of an outbreak which clearly is not caused by a communicable disease, the Centre shall act only in cooperation with the competent authority upon request from that authority. As part of this mission, ECDC may be requested, by the European Commission, a Member State, or another country to provide scientific or technical assistance in any field within its mission.

Following the official invitation by the Ministry of Health, dated 7 October 2016, an ECDC Team was in Romania from 6 to 10 March 2017 to conduct visits and meetings to discuss AMR issues with the overall objective of providing an evidence-based assessment of the situation regarding prevention and control of AMR through prudent use of antibiotics and infection control.

1.2 Purpose

The Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine (2002/77/EC) outlines the threat that AMR poses to human health and advocates for a range of actions to be taken for its prevention and control. The Council Conclusions on antimicrobial resistance of 10 June 2008 reiterated this call for action.

To assist Member States in implementing the Council Recommendation, ECDC has developed a process for and is carrying out, upon invitation from national authorities, country visits to specifically discuss and assess the situation of the country regarding prevention and control of AMR through prudent use of antibiotics and infection control. These country visits also help to document how Member States have approached this implementation and deployed national activities, and support the European Commission in evaluating this implementation.

The main output of the visit is a report from the ECDC Team provided to the inviting national authority. To help the ECDC Team ensure consistency of the visits and follow-up of progress of countries, an assessment tool has been developed (see Annex 5.2 of this report). This assessment tool includes ten topics. These topics are regarded as core areas for successful prevention and control of AMR and are based on the Council Recommendation 2002/77/EC and on the Council Conclusions of 10 June 2008. The assessment tool is used as a guide for discussions during the visit.

The ECDC team for the country visit to Romania consisted of Dominique L. Monnet, Head of ECDC's Antimicrobial Resistance and Healthcare-associated infections (ARHAI) Disease Programme, Anke Kohlenberg, ECDC ARHAI expert, and two experts from EU Member States: Michael A. Borg (Malta) and Nandini Shetty (United Kingdom), as well as Andrea Nilsson (ECDC communication expert, only on 6-7 March 2017). At national level, the visit was coordinated for Romania by Dr Amalia Serban, General Director, Healthcare and Public Health Department, Romanian Ministry of Health. For the full list of national experts met during the ECDC country visit, please refer to Annex 5.1 of this report.

2. Overview of the situation in Romania

2.1 Antimicrobial resistance (AMR)

For most of the bacteria-antibiotic combinations reported to the European Antimicrobial Resistance Surveillance Network (EARS-Net), Romania is among the Member States with the highest levels of AMR in Europe. However, time trends are not easy to determine as the proportions of resistant isolates fluctuate significantly from one year to another due to the low number of isolates reported for each bacterium.

Table 1. AMR of key indicator bacteria in Romania, 2013–2015

Bacterium-antibiotic combination	2013			2014			2015		
	N	% R	95% CI	N	% R	95% CI	N	% R	95% CI
Staphylococcus aureus - meticillin	383	64.5	59-69	316	56.0	50-62	297	57.2	51-63
Enterococcus faecium - vancomycin	54	11.1	4-23	56	25.0	14-38	72	25.0	16-37
Escherichia coli - 3rd-generation cephalosporins	298	22.8	18 – 28	306	29.4	24-35	369	26.8	22 - 32
E. coli - carbapenems	299	0.0	0-1	305	0.7	0-2	368	1.9	1-4
Klebsiella pneumoniae - 3rd-generation cephalosprins	214	67.3	61-74	256	73.8	68-79	270	70.7	65-76
K. pneumoniae - carbapenems	215	20.5	15-26	257	31.5	26-38	271	24.7	20-30
Acinetobacter spp. - carbapenems	137	85.4	78-91	123	81.3	73-88	189	81.5	75-87

Source: EARS-Net

N - number of tested isolates;

% R - percentage of resistant isolates

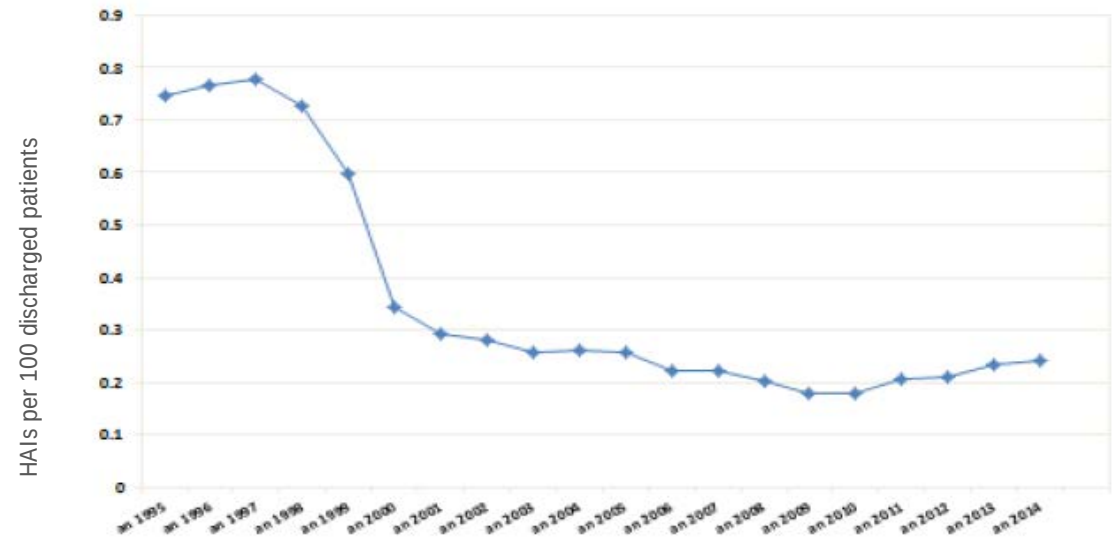
CI, confidence interval.

The high levels of carbapenem resistance in gram-negative bacteria, especially *Acinetobacter* spp. and *K. pneumoniae* are especially worrying. All major classes of carbapenemases have been detected in *K. pneumoniae* isolates from Romania and the analysis of pulse-field gel-electrophoresis profiles of OXA-48- and NDM-1-producing *K. pneumoniae* isolates suggested inter-hospital and regional transmission of epidemic clones (Lixandru *et al*, PLoS One 2015).

2.2 Healthcare-associated infections (HAIs)

The reported level of HAIs in the national passive surveillance system was less than 1% in the last 20 years, and less than 0.25% in the past 10 years (Figure 1). Given that the ECDC point prevalence survey performed in ten Romanian hospitals in 2012 indicated a ten-fold higher prevalence of HAIs (at least 2.8%, but probably over 5%, as reported in the revalidated data for five hospitals), it appears that HAIs are largely underreported in Romania.

Figure 1. Reported incidence of HAIs, Romania, 1995–2014



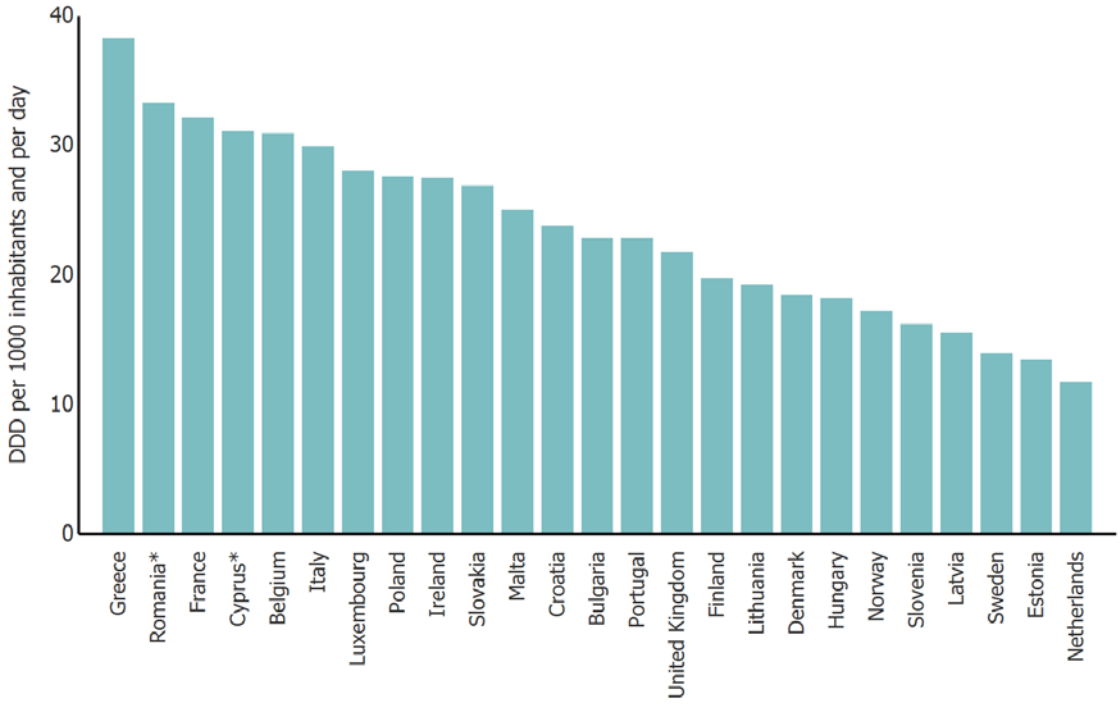
Source: National passive surveillance system, 2016)

The extent of transmission of MDROs in Romanian hospitals became public and received media attention after a fire at a nightclub in Bucharest in October 2015 when burn patients were rapidly colonised and developed HAIs with extensively drug-resistant and even pandrug-resistant strains of *Enterobacteriaceae* and *Acinetobacter baumannii*.

2.3 Antimicrobial consumption

In 2015, Romania was the country with the second highest consumption of antibacterials for systemic use in Europe (Figure 2), as reported to the European Surveillance of Antimicrobial Consumption Network (ESAC-Net).

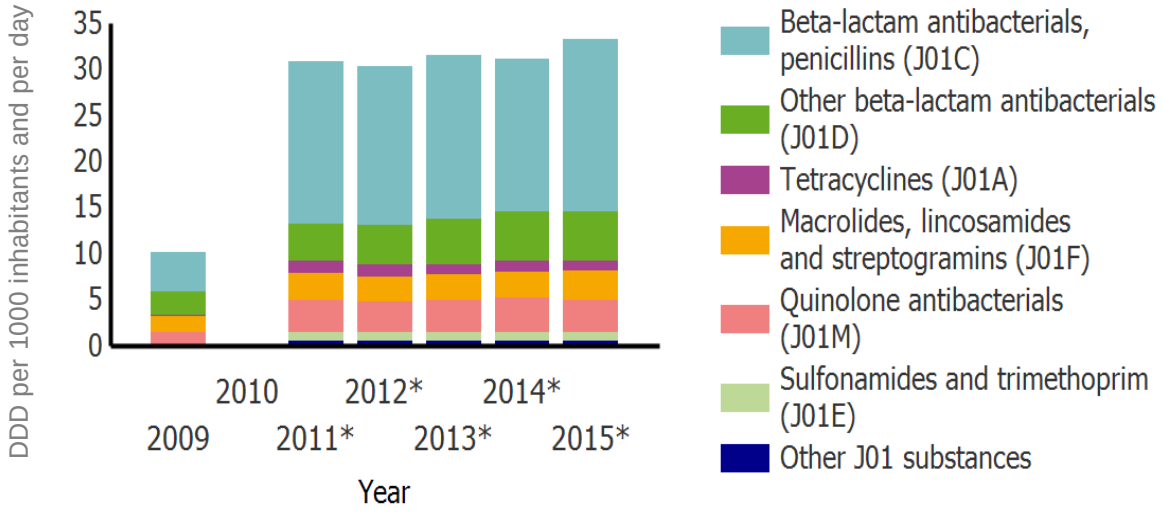
Figure 2. Consumption of antibacterials for systemic use (ATC group J01) in the community and hospital sector combined, EU/EEA countries, 2015



Source: ESAC-Net

Romania reports data for antimicrobial consumption only for total care, therefore differentiation of consumption in the hospital and community sector is not possible. Consumption remained at the same level for the years 2011–2015 (Figure 3).

Figure 3. Trend in consumption of antibacterials for systemic use (ATC group J01) in the community, Romania, 2009–2015



Source: ESAC-Net

* Only total care data provided.

3. Observations

3.1 Development of an Intersectoral Coordinating Mechanism (ICM)

At present, there is no Intersectoral Coordinating Mechanism (ICM) as defined in Council Recommendation 2002/77/EC. There is a plan to create such an ICM with a 'One Health' perspective, as reflected in a government decision that was delivered to the Ministry of Health in November 2016 and is currently awaiting public consultation before possible approval. This ICM will likely include representatives of the Ministry of Health, Ministry of Agriculture, Ministry of Environment, Ministry of Education, the National Institute of Public Health, the National Sanitary Veterinary and Food Safety Authority, the National Agency of Medicines, the College of Physicians, the College of Pharmacists, the College of Veterinarians, professional organisations, non-governmental organisations (NGOs) and patient associations.

Although there is a national strategy on AMR in veterinary medicine that was adopted in 2016 for the period 2016 to 2018, as yet there is no equivalent national strategy and/or national action plan for AMR in human medicine. There are plans to develop this national strategy/action plan once the ICM is established. So far, there has been limited cross-sectoral collaboration between the human and veterinary authorities on strategies and/or action plans.

In a previous ECDC country visit that took place on 4–7 July 2016, the visiting team was provided with various drafts of national plans for prevention, reduction and control of healthcare-associated infections (HAIs), including short- and medium-term actions in the following areas: improving staff training and staff professional development; increasing the quality of HAI surveillance at national level, and improving communication with the general public – both at national and local/hospital levels. It appears that this national plan was not published because it was considered that most actions had already been implemented. However, ECDC's visiting team was not in a position to ascertain the level of implementation of these actions.

3.2 Organised multidisciplinary and multisectoral collaboration at local level

In the counties visited, there were no local or health-facility-based activities to reduce antimicrobial consumption or improve information sharing to medical professionals. Specific multidisciplinary committees or working groups related to AMR were not in place within county public health authorities.

In one hospital visited, there was an infection control committee, consisting of an epidemiologist, an infection control nurse, a pharmacist, heads of clinical departments and an infectious diseases advisor. No systematic collaboration between microbiologists, pharmacists, epidemiologists and clinicians was evident in hospitals or within the public health authorities.

In one county, general practitioners (GPs) held monthly meetings to discuss difficult cases and other issues, but these meetings were not specifically related to AMR. No further evidence was found of local multidisciplinary or multisectoral collaboration relating to AMR.

3.3 Laboratory capacity

Microbiology laboratory capacity for standardised testing of antimicrobial susceptibility was available at the National Reference/Research Laboratory at the Cantacuzino Institute and at the two hospital laboratories visited. All laboratories were accredited by a national accreditation authority and the National Reference Laboratory participated in an external quality assurance scheme. Semi-automated equipment was in use and standardised methodology for testing was evident using European Committee on Antimicrobial Susceptibility testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI) standards. All laboratories had standard operating procedures and were staffed by medical and scientific microbiologists.

In the hospital microbiology laboratories that we visited, the number of specimens received each day varied between 100 and 250 and originated mainly from intensive care unit (ICU) patients. The most frequently submitted specimens were pus/fluid. Organism-specific susceptibility data for all antimicrobials tested were reported as detected, without clinical interpretation. There was no selective reporting of susceptibility results. The hospital laboratories had facilities for computerised registration of specimens.

Computer-generated antimicrobial susceptibility data from the semi-automated equipment were transcribed by hand into a paper-based register and re-entered into a local database. One laboratory was using the WHONET

software to monitor AMR. There was no computerised interface to link equipment-generated antimicrobial susceptibility data to the local hospital information system. Hospital epidemiologists in both the hospitals visited had access to AMR data from the microbiology laboratory.

Romania does not have a nationally agreed standardised laboratory protocol for antimicrobial susceptibility testing. To date, there is no national antibiotic committee, as recommended by EUCAST, however, a plan to establish such a committee under the National Society of Microbiology was mentioned.

The National Reference Laboratory had recently introduced whole genome sequencing for verotoxin-producing *E. coli*, but no bioinformatics or informatics pipelines were currently in place. Once fully established, this technology could be used for the typing of MDROs in the future.

3.4 Monitoring of antibiotic resistance

At national level, Romania provides data for EARS-Net received mainly from specialised infectious disease hospitals, academic and tertiary hospitals. Data collection is managed by the National Public Health Institute with no involvement of the National Reference Laboratory. Data on invasive isolates has increased in recent years, however, the numbers of isolates for specific pathogen-antimicrobial resistance combinations reported each year are too low to ascertain time trends.

The National Reference Laboratory receives isolates only occasionally, either in connection with specific research projects or occasional outbreak investigations. There is no systematic submission of specific resistant-phenotype bacteria for further analysis. One reason for this might be that regional authorities or hospitals have to pay for analysis and for molecular typing performed at the National Reference Laboratory. Moreover, there is no obligation for the laboratory to report significant findings related to MDROs or outbreaks to the national authorities.

While HAIs are reported monthly by hospitals to the county public health authorities, these authorities currently do not collect data on AMR. Since October 2016, reporting of AMR for pathogens associated with HAIs is mandatory. However, these data were not yet available at the county public health authorities at the time of our visit. AMR statistics were available in hospitals, but were not analysed regularly in order to inform treatment strategies.

At GP level, AMR data for the respective county or the whole of Romania were not available to guide antimicrobial treatment. International protocols or information from textbooks were applied to guide antimicrobial treatment instead. The lack of data on AMR was perceived as an obstacle to drafting locally-adapted treatment guidelines.

3.5 Monitoring of antibiotic use

Romania reports national antimicrobial consumption in humans to ESAC-Net for all sectors collectively (i.e. community and hospital data are combined). The data provided to ESAC-Net are total sales data received via a personal connection with a commercial service provider. Data for the subgroup of reimbursed prescriptions are also available at the National Insurance House. The National Medicines Agency has access to comprehensive antimicrobial consumption data from wholesalers, but resources for data extraction and systematic analysis are lacking.

Currently, distributors of pharmaceutical products are only required to report if medicines are sold by a wholesaler or a pharmacy. Separation of antimicrobial consumption between the community and the hospital sector would therefore require a change in legislation and effort by the sellers to change their reporting procedures. This issue is further complicated by the fact that, in some instances, certain antimicrobial agents that are not available in hospitals (including intravenous and last-line antimicrobials, such as colistin) could be purchased by patients or their relatives, with a prescription, from community pharmacies. However, there was no clear information on the extent of this practice.

At the county public health authorities, there is no routine monitoring of antimicrobial consumption, although national consumption data can be accessed by written request and have been requested in a few specific instances. The hospitals visited had data available on their hospital-specific consumption of antimicrobials, but did not analyse them systematically or use them to reduce antimicrobial consumption or improve antimicrobial prescribing practices. There is no system for providing feedback to individual prescribers on their antimicrobial prescribing practices.

3.6 Antibiotic utilisation and treatment guidance

International recommendations and guidelines were the most frequently mentioned sources consulted by physicians for advice on antimicrobial treatment. National guidelines exist only for diagnosis and treatment of a few specific pathogens and indications, including meticillin-resistant *S. aureus* (MRSA), *Clostridium difficile* infection (CDI) and surgical prophylaxis. During the period April 2013 – November 2014, there was a multidisciplinary

subcommittee at the Ministry of Health to establish or revise national recommendations, but this subcommittee was dissolved.

With regard to hospital-specific treatment guidelines, the situation differed by hospital: one hospital reported having no guidelines, another hospital stated that guidelines were available on their intranet. In one hospital visited, an infectious disease consultant (medical doctor) had been recruited for one week to review the local AMR statistics and develop hospital-specific treatment recommendations. In all hospitals, we were informed that antimicrobial treatment was not prescribed by junior doctors in training, but only by senior doctors who had completed their specialty training, even out of normal working hours. These senior doctors could prescribe antimicrobial treatment without restriction. Authorisation of prescriptions by the head of department or the medical director was only sought if an expensive antimicrobial agent was to be prescribed.

The hospitals visited did not have infectious disease physicians and there was no systematic review of antimicrobial treatment. This was perceived by other medical staff as hampering appropriate antimicrobial treatment. Clinical microbiologists and/or pharmacists neither routinely reviewed antimicrobial treatment in the wards, nor performed antibiotic stewardship rounds.

Legislation prohibits over-the-counter sale of antibiotics without prescription. However, it is unclear whether this is universally complied with. This was exemplified by data for Romania from Special Eurobarometer 445 on AMR which showed that in 2016, 13% of the antibiotics used during the past year were obtained directly at a pharmacy without a medical prescription. As an exception to the legislation, there is a currently accepted practice, endorsed by the College of Pharmacists, that the amount of antibiotics necessary for one or two days of treatment can be dispensed without prescription during the weekends.

3.7 Infection control

Infection control organisation and procedures are detailed in a Ministerial Order and adapted by each hospital to the local situation. In the two county hospitals visited, infection prevention and control (IPC) functions were performed by specialist staff who were known as hospital epidemiologists. The hospital epidemiologists had access to antimicrobial susceptibility data from the microbiology laboratories. They monitored cases of HAIs and the prevalence of MDROs in their hospitals. There is a national drive to reduce the incidence of CDI. As a result of this focus, the most common HAI reported by hospitals is CDI.

The standard of IPC varied among the hospitals visited. Alcohol-based hand rub was available in the hospitals visited, however it was not always conveniently located for easy access during patient handling. In one ward, hand washing facilities and alcohol-based hand rub were not available at or near the patient bedside. Alcohol-based hand rub was only available on a treatment trolley, meaning that it was only used when changing dressings or drawing blood.

Areas of good practice included safe disposal of sharps and awareness of international guidelines for preventing ventilator-associated pneumonia and communication between the hospital epidemiologist and the clinical staff in matters regarding IPC and management of patients with MDROs.

The infrastructure in older Romanian hospitals makes it difficult to isolate patients with MDROs and ensure appropriate disinfection. In one of the hospitals visited, beds were placed at very close proximity to one another. Overcrowding of hospitals and lack of specialists in hospital epidemiology/hygiene were highlighted as limiting factors to achieving appropriate IPC and control of the emergence of AMR in hospitals.

Patients were not routinely screened for MDROs in the hospitals visited. A substantial amount of staff time and financial resources in hospital epidemiology departments is devoted to routine microbiological screening of the hospital environment. There is a legal obligation to undertake this sampling in Romanian hospitals. However, with the exception of specific situations, it is internationally recognised that this practice is of limited value.

3.8 Educational programmes on AMR

In the undergraduate curriculum, microbiology, pharmacology and infectious diseases are taught in the second and sixth years of study. AMR, HAIs and epidemiology are also covered in the curriculum. Postgraduate training courses in infectious diseases, pharmacy and laboratory medicine are also available. The infectious diseases curriculum includes modules in microbiology and epidemiology but no specific module on antimicrobial prescribing and prudent use of antibiotics. Postgraduate curricula for the other clinical specialties do not focus on microbiology, antimicrobial prescribing, HAI or IPC.

In 2016, a new clinical microbiology specialty was established with a focus on antibiotics, AMR and IPC. A clinical pharmacology curriculum would also need to be developed as there are too few clinical pharmacologists to meet the needs of the country. The College of Nursing had introduced an IPC course as part of the two-year nursing training

course, however, this course was later discontinued. The postgraduate course on family medicine has a one-month training module in infectious diseases.

All doctors, nurses and pharmacists were expected to fulfil a mandatory continuing professional development (CPD) programme, worth at least 200 points, each year by attending courses or seminars. In 2016, for the first time in Romania, one of the CPD courses offered focused on microbiology/epidemiology, prudent use of antibiotics and development of clinical policies and guidelines. A similar course (including surveillance and inspection) is planned for nurses and for the county epidemiologists in 2017. There is also a plan to access European funds to expand this training to doctors at all hospitals in Romania and to nurses to meet the skills shortages in hospitals and to give specific information to all staff working on HAI, AMR and antimicrobial stewardship as well as to clinicians and microbiologists, to be able to build functional teams. This national programme began with 114 hospitals offering a training designed for epidemiologists, microbiologists and clinicians, especially those working in ICUs. The training was structured as a team work exercise. For the future, the aim is to train staff at all hospitals and to run similar training courses for nurses and other medical staff.

It was stated that none of the courses were sponsored by commercial companies as this is not legal.

Hospitals do not have a specific induction programme on antimicrobial use or IPC for new doctors, other than a general induction on occupational health, legislation and standard precautions.

3.9 Public information related to AMR

Every year since 2008, the Ministry of Health, the Public Health Institute and other health-related organisations have had public relations activities (e.g. conferences, press releases, TV and radio broadcasts) surrounding European Antibiotic Awareness Day (EAAD).

In November 2016, Romania launched a first national public awareness campaign on prudent antibiotic use called 'Nu antibiotice la-ntamplare' ('No antibiotics randomly'), including a TV broadcast, posters and a 'Nu antibiotice la-ntamplare' medication box containing a leaflet with information on prudent use of antibiotics. During our visit, posters for the campaign and other materials were visible at the entrance of one hospital and in the office of the GP visited.

In addition, public information campaigns have been launched in some districts. Each year, the Ministry of Health provides funds to the 40 districts and to Bucharest for communication campaigns. Districts have the freedom to choose up to five campaigns to implement and prudent use of antibiotics is not always among them. Districts can also choose their target audiences for these campaigns. In 2016, eleven districts had activities targeting prudent use of antibiotics, covering a wide range of audiences.

The Health Promotion Department at the National Institute of Public Health is in charge of providing the districts and Bucharest with suggestions of topics for campaigns, as well as related materials. In recent years, this department has produced a media toolkit (similar to the one provided by ECDC) including an analysis of the situation, draft press releases, event suggestions, possible partnerships, presentations and other template communication materials. This initiative was greatly appreciated by the recipients and further adapted to respond to regional and local needs. In the past, training has been arranged for the organisers of the campaigns - e.g. on how to use data for communication purposes. After EAAD, each district submits a list of activities targeting prudent antibiotic use to the Health Promotion Department at the National Institute of Public Health.

3.10 Marketing related issues

Independent - i.e. not supported by industry - drug information is available from the website of the National Agency for Medicines.

There are regulations (ministerial orders) regarding advertising for medicines. Prescription-only medicines such as antibiotics, can only be advertised to professionals.

Pharmaceutical companies must follow the ethical code of the Romanian Association of International Drug Manufacturers (ARPIM) which is similar to that of the European Federation of Pharmaceutical Industries and Associations (EFPIA), and are obliged to declare to the National Agency of Medicines which doctors have received sponsorship, including the reason and the amount. Each doctor and pharmacist must report the same information to the National Agency of Medicines. A company that would like to sponsor a meeting or event must first ask for authorisation from the National Agency of Medicines.

It is illegal for the pharmaceutical industry to give personal gifts to physicians. However, pharmaceutical representatives commonly have easy access to doctors, particularly in hospitals, and this is poorly regulated. In one hospital visited, the consequence of these visits was reportedly reflected in the prescribing of specific antibiotics.

4 Conclusion and recommendations

4.1 Conclusions

The current levels of antimicrobial resistance (AMR) in Romania are a serious concern. The reported levels of AMR in key indicator bacteria from humans are very high and/or rising in comparison to most other EU/EEA countries.

Several factors are likely to contribute to the current situation. There is a high consumption rate of antimicrobial agents in human medicine in general and the widespread use of last-line broad-spectrum antimicrobial agents is worrying. There also appear to be constraints in terms of infrastructure in hospitals and a skills shortage in key healthcare personnel.

In addition, Romania lacks robust data on AMR rates, healthcare-associated infections (HAIs) and antimicrobial consumption at the local level to inform treatment guidelines, achieve prudent antibiotic use and target infection prevention and control (IPC) measures. Other contributing factors include inadequate multidisciplinary collaboration between clinicians, microbiologists and epidemiologists and limited collaboration between human and veterinary domains with regard to AMR.

There are, however, several areas of good practice and evidence of change for the better. Most importantly, the recognition that certain areas require improvement is driving the momentum for change. Examples of good practice include the public awareness campaign to limit use of antibiotics and the initiatives to limit the sale of over-the-counter antimicrobial agents. Change is being driven by committed, motivated and knowledgeable healthcare staff who spread the message regarding prudent use of antibiotics and IPC in their everyday work environments. These drivers for change and the staff who strive to achieve this change need to be supported and resourced. They also need to be provided with a structured framework to attain the desired goals.

Romania is at a cross-roads. If the current levels of AMR persist, or even increase, it is likely that untreatable HAIs, especially those caused by *Klebsiella pneumoniae* and *Acinetobacter baumannii*, will become a reality. This would have a serious impact on the ability of hospitals to provide critical medical services such as cancer treatment, major surgical procedures and intensive care.

4.2 Recommendations

Based on the observations and conclusions, the ECDC team recommends the following actions:

- Designate AMR as a national public health threat encompassing all regions. This would mandate prioritisation in resource allocation and short- and long-term planning.
- Prioritise the creation of an Intersectoral Coordinating Mechanism. This is essential to facilitate the required improvements and should include the National Insurance House and representatives from each region whose responsibility will be to ensure that information and action is relayed from the national to the regional level. Local groups with a similar composition should be formed in each county to disseminate information and ensure implementation and action at the local level.
- Focus on writing a National Action Plan for AMR with a 'One Health' approach and include the specific needs related to diagnosis, surveillance, prevention and control of multidrug-resistant organisms (MDROs). All these aspects should be included in one single national action plan. Adequately resourced teams should be set up within the Ministry of Health to tackle AMR – i.e. a focal point for AMR, a microbiologist, a clinician and an epidemiologist in each county. They should be provided with intensive training on AMR diagnosis and control, and then formally appointed with clear terms of reference and responsibilities for initiating and coordinating the necessary AMR activities.
- Determine costs of activities at both national and regional level so that appropriate budgets can be made available. Investment in antibiotic stewardship and IPC has been proven to be cost-effective and will usually result in savings that exceed the amount invested. Financial challenges should therefore not be a barrier for implementation of the National Action Plan and its activities.
- Based on the successful *Clostridium difficile* infection (CDI) control programme, launch a similar initiative to include infections caused by other MDROs such as: carbapenem-resistant Enterobacteriaceae (CRE), multidrug-resistant *Acinetobacter* and *Pseudomonas* species, and meticillin-resistant *Staphylococcus aureus* (MRSA). A package of interventions should typically include:
  - a screening strategy for high-risk patients and high-risk units;
  - an alert system to flag positive patients;
  - referral of resistant isolates to the National Reference Laboratory for further characterisation;
  - robust surveillance data capture mechanisms and analyses by the National Public Health Institute (mandatory notification of bacteraemia cases through a simple online reporting system would be a possible option);
  - timely and efficient dissemination of information to relevant healthcare staff.

- Consider finding resources for these activities by shifting some of the resources devoted to routine environmental screening in healthcare facilities, known to be of limited value in the control of HAI according to international literature.
- Launch a national campaign on IPC - i.e. hospital hygiene - starting by raising awareness of hand hygiene in hospital and community healthcare facilities, accompanied by increased availability of alcohol hand rub in hospitals, ideally at the end of every hospital bed; surveillance of alcohol hand rub consumption and observation of hand hygiene performance.
- Continue the national public awareness campaign on the prudent use of antibiotics. Considering the low level of awareness of antibiotics and AMR among the public in Romania, the documented levels of non-prescribed antibiotic use and the frequently repeated reference to pressure by the public on doctors and pharmacists, Romania would benefit from continued national antibiotic awareness campaigns. In addition, national communication strategies would benefit from a higher level of cooperation on prudent antibiotic use campaigns in the regions and districts.
  Specific suggestions include:
  - Maintaining public relation activities every year in connection with European Antibiotics Awareness Day (EAAD).
  - Planning a wide-reaching campaign for all the districts (e.g. every two years), focussing on one or two targeted audiences. Another possibility could be to make sure that the districts have an annual plan where information about the topic is fed to the different groups throughout the year.
  - Increasing the number of tools available. This can easily be done by cross-linking websites with the EAAD page in Romanian.
  - Including an adapted version of *the Social Media Strategy Guide for Public Health Communication* available here: http://ecdc.europa.eu/en/publications/Publications/social-media-strategy-guide-for-public-health-communication.pdf. This document can also be used by the national authorities for their social media strategies.
  - Implementing simple performance indicators such as web visits, media clippings, social media reach, event participation, and amount of materials distributed.
  - Organising a training on development, implementation and evaluation of campaigns targeting prudent use of antibiotics. ECDC can provide its training module on the topic and support the development of the training that could be translated into Romanian.
  - Establishing better routines and mailing lists at national level so that the ECDC National Focal Point for communication and its alternate can easily share ECDC's messages.
- Increase the involvement of the National Health Insurance House in campaigns for correct prescribing of antibiotics in ambulatory care as an opportunity to make substantial savings by more prudent use of antibiotics and the subsequent decrease of AMR. Regional branches of the health insurance organisation could start to collate lists of general practitioners (GPs) and their respective prescribing trends that would then be passed on to the public health entities of the region for follow-up. High-end users would be asked to justify their practice and rectify it, if justification was not shown.
- Increase the microbiology laboratory capacity by ensuring sufficient funding of the National Reference Laboratory (Centre of Excellence) for AMR at the Cantacuzino Institute in support of public health activities related to AMR. It should be emphasised that the National Reference Laboratory should support hospital diagnostic laboratories in standardising their methodologies and providing an external quality assurance scheme.
- Increase the availability of infectious disease expertise in hospitals and antimicrobial stewardship programmes including pre-authorisation of antibiotics, restricted availability of last-line agents, de-escalation protocols, local evidence-based treatment guidelines and establishment of performance indicators based on antimicrobial consumption in general hospitals.
- Strengthen surveillance data on AMR, both at national and local level. This can be done by improving geographical representativeness and timeliness and increasing the number of tested isolates at each centre/laboratory. It is recommended that available IT expertise is channelled and supported with investment in systems and programmes that can use available data generated by hospitals to study resistance trends nationally and regionally.
- Strengthen surveillance data on antimicrobial consumption. In particular, a commitment is needed to obtain comprehensive antimicrobial consumption data stratified by hospital specialty and community healthcare facilities by working with the National Insurance House, the National Medicines Agency and other relevant bodies.
- Invest in a professional development plan to train future healthcare professionals by updating the educational curricula of undergraduate medical schools, postgraduate medical specialties and colleges of pharmacy and nursing to include modules of microbiology, epidemiology, rational use of antimicrobial agents and IPC. The curriculum on antimicrobial stewardship for infectious disease clinicians, a draft of which has already been submitted to the Ministry, should be instituted and it should be ensured that a sufficient number of IPC nurses with formal national training and IPC certification are available at each hospital. Minimal structure indicators should be agreed for effective IPC, as well as antimicrobial stewardship at hospital level and linked to bed occupancy and type of care provided. This will ensure that the required staff are involved at local level.

- Develop guidelines for diagnosis, management, prevention and control of specific infectious diseases and national guidelines on the correct use of antimicrobial agents in human medicine, based on the local resistance epidemiology. In particular, reduction in the use of broad spectrum antibiotics, such as cephalosporins, and last resort agents, such as carbapenems and colistin, should be addressed in these guidelines.
- Revisit the practice of emergency weekend over-the-counter antibiotics with possible alternative methods of access provided. Supervision of pharmacies to further reduce over-the-counter dispensation of antibiotics should be continued, including measures to reduce the practice by community pharmacies of dispensing injectable agents not covered by the hospital budget.

5. Annexes

5.1 Country visit team and people met during the ECDC country visit to Romania

ECDC Team

- Dominique L. Monnet, Antimicrobial Resistance and Healthcare-Associated Infections (ARHAI) Disease Programme, ECDC, Stockholm, Sweden
- Anke Kohlenberg, Expert, Antimicrobial Resistance and Healthcare-Associated Infections, ECDC, Stockholm, Sweden
- Michael A. Borg, External expert, National Focal Point for AMR, Malta (only 6-8 March 2017)
- Nandini Shetty, External expert, Consultant microbiologist, Public Health England; Deputy Head of WHO Collaborating Centre for AMR, United Kingdom
- Andrea Nilsson, Communication expert, ECDC, Stockholm, Sweden (only 6-7 March 2017)
- Observer: Rex Horgan, European Commission, DG SANTE Directorate F.

Persons met

Monday 6 March 2017

Meeting at the Ministry of Health, Bucharest

- Florian-Dorel Bodog, Minister of Health
- Amalia Serban, General Director, Healthcare and Public Health Department, Ministry of Health
- Christian Iordache, Senior Epidemiologist and Counsellor for European Affairs, Ministry of Health
- Monica Lazar, Pharmaceutical Department, Ministry of Health
- Gabriel-Adrian Popescu, Professor of Infectious Diseases, INBI Matei Bals, former Advisor to the Minister of Health
- Rodica Morcov, Counsellor Veterinary Medical Products Service, National Sanitary Veterinary and Food Safety Authority
- Roxana Serban, National Institute of Public Health, National Focal Point for HAIs
- Andreea Niculcea, Epidemiologist, National Institute of Public Health, Data manager EARS-Net and HAI-Net (HAICDI, HAIICU, HAISSI)

Meeting at the National Institute of Public Health, Bucharest

- Mihai-Marius Dan, Director
- Adriana Pistol, Director of the National Centre for Surveillance and Control, and National Coordinator (Coordinating Competent Body)
- Florin Popovici, Senior Epidemiologist, Member of ECDC Advisory Forum
- Roxana Serban, National Focal Point for HAIs
- Livia Cioran, Health Promotion Department
- Claudia Dima, Health Promotion Department
- Andreea Niculcea, Epidemiologist, Data manager EARS-Net and HAI-Net (HAICDI, HAIICU, HAISSI)
- Also present: Amalia Serban, General Director, Healthcare and Public Health Department, Ministry of Health.

Meeting at the National Institute Ion Cantacuzino, Bucharest

- Alexandru-Filip Vladimirescu, Director
- Irina Codita, Head of National Reference Laboratory for Antimicrobial Resistance and Nosocomial Infections
- Adriana Simona Ciontea, Principal Biologist, Head of the Bacterial Enteric Laboratory
- Cerasella Dragomirescu, Head of the Department of Microbiology for Public Health
- Elena-Carmina Dragulescu, Researcher-Biologist, National Reference Laboratory for Antimicrobial Resistance and Nosocomial Infections
- Brandusa Elena Lixandru, Researcher-Biologist, National Reference Laboratory for Antimicrobial Resistance and Nosocomial Infections
- Monica Straut, Molecular Epidemiology Laboratory
- Also present: Amalia Serban, General Director, Healthcare and Public Health Department, Ministry of Health.

Tuesday 7 March 2017

Separate meeting about European Antibiotic Awareness Day, national campaigns and communication issues related to AMR (with ECDC communication expert Andrea Nilsson), National Institute of Public Health, Bucharest

- Livia Cioran, Health Promotion Department,
- Claudia Dima, Health Promotion Department
- Roxana Serban, National Focal Point for HAIs
- Amalia Serban, General Director, Healthcare and Public Health Department, Ministry of Health

Visit to the county public health authority, Cluj-Napoca

- Mihai Moisescu-Goia, Director
- Alexandru Coman, Epidemiologist, Polaris Hospital

Visit to the Institute of Gastroenterology and Hepatology, Prof. Dr. Octavian Fodor, Cluj-Napoca

- Mihai Adrian Mlesnite, Manager
- Adriana Cavasi, ICU physician
- Erszebet Kalman, Hospital epidemiologist
- Lucia Stanca Pandrea, Microbiologist
- Mariana Andries, Pharmacist.

Visit to the private Polaris Rehabilitation Hospital, Suceagu

- Mihai Casu, Medical Director
- Alexandru Coman, Epidemiologist
- Ramona Ionescu, Consultant ID physician
- Damian Popescu, Physician, Neurology Service
- Mihaela Popescu, Pharmacist
- Hella Popovic, Pharmacist

Wednesday 8 March 2017

Visit to the county public health authorities, Braşov

- Lavinia Buvnariu, Executive Director, Regional Public Health Department
- Camelia Defta, Epidemiologist
- Raluca Pintea, Medical Epidemiologist, Prevention and Control of Transmissible Diseases
- Veronica Cristea, Resident Epidemiologist

Visit to a general practitioner, Braşov

- Simina Diaconu, General practitioner

Visit to a private pharmacy, Braşov

- Sorina Crisan, Pharmacist

Visit to the 'Spitalul Clinic Judetean de Urgenta Braşov' public hospital

- Carmen-Daniela Neculoiu, Hospital manager
- Adrian Baracan, Physician, Head, Intensive Care Unit
- Dan Grigorescu, Head, Plastic surgery Department
- Cristina Cupsa, Head, Microbiology laboratory
- Gabriela Gavrila, Microbiologist
- Emilia Rodica Guth, Microbiologist
- Mihaela Idomir, Microbiologist
- Dora Ana Godri, Epidemiologist

Thursday 9 March 2017

Meeting with representatives from the National Sanitary Veterinary and Food Safety Authority

- Mihaela Dumitrache, Director Veterinary Medical Products and Animal Nutrition Directorate
- Ramona Anton, Counsellor
- Florica Durlea, Head of Service Veterinary Medical Products
- Rodica Morcov, Counsellor Veterinary Medical Products Service
- Camelia Voicu, Institute for the Control of Biological Products and Medicaments for Veterinary Use
- Also present: Christian Iordache, Senior Epidemiologist and Counsellor for European Affairs, Ministry of Health.

Meeting at the National Agency for Medicines and Medical Devices

- Marius Tanasa, Vice-President and Head of the Medical Devices Unit
- Simona Badoi, Head of the National Procedure Department
- Roxana Dondera, Deputy Head, Pharmacovigilance and Risk Management Unit
- Gabriela Ruja, GMP Inspector, Pharmaceutical Inspection Department
- Mihaela Tavakol, Head of Biological Products Evaluation and Control Department
- Nela Vilceanu, Coordinator, European Procedures Department
- Also present: Christian Iordache, Senior Epidemiologist and Counsellor for European Affairs, Ministry of Health.

Meeting with representatives of professional associations and institutions in the area of pharmacy and medicine, key stakeholders in the area of AMR, professionals and NGO representatives at the National Infectious Diseases Institute (INBI) Matei Bals, Bucharest

- Gheorghe Borcean, President, Romanian College of Physicians
- M. Mardarescu, National Infectious Diseases Institute (INBI) Matei Bals, Romanian Society for HIV/AIDS, National Focal Point for HIV/AIDS
- Adriana Pistol, National Society of Epidemiology
- Alexandru Rafila, President, National Microbiology Society, Head of Microbiology Laboratory, INBI Matei Bals
- Razvan Prisada, Vice-President, Romanian College of Pharmacists
- Gabriel-Adrian Popescu, Infectious Diseases Department, INBI Matei Bals, former Advisor to the Minister of Health
- Sorin Petrea, Medical Director, INBI Matei Bals, Romanian Society for Infectious Diseases & HIV
- Oana Sandulescu, INBI Matei Bals, Romanian Society for HIV/AIDS
- Daniela Pitigoi, INBI Matei Bals
- Anca Streinu-Cercel, INBI Matei Bals
- Maria Nica, Clinic of Infectious and Tropical Diseases Victor Babes, Bucharest
- Also present: Amalia Serban, General Director, Healthcare and Public Health Department, Ministry of Health; Christian Iordache, Counsellor, Ministry of Health, Senior Epidemiologist and Counsellor for European Affairs

Friday 10 March 2017

Preliminary report from the ECDC team to representatives of the Ministry of Health

- Cristian Grasu, Secretary of State, Ministry of Health
- Amalia Serban, General Director, Healthcare and Public Health Department, Ministry of Health
- Christian Iordache, Senior Epidemiologist and Counsellor for European Affairs, Ministry of Health
- Gabriel-Adrian Popescu, Professor of Infectious Diseases and former Advisor to the Ministry of Health
- Irina Codita, National Reference Laboratory for Antimicrobial Resistance and Nosocomial Infections, Institute Ion Cantacuzino, National Focal Point for AMR
- Roxana Serban, National Institute of Public Health, Focal point Healthcare-associated infections, national coordinator for AMR
- Marius Tanasa, Vice-President and Head of Medical Devices Unit, National Agency for Medicines and Medical Devices
- Rodica Morcov, Counsellor Veterinary Medical Products Service, National Sanitary Veterinary and Food Safety Authority.

5.2 Assessment tool for ECDC country visits to discuss AMR issues

The mechanisms behind emerging antimicrobial resistance (AMR) are complex. However, two main issues that stand out offering opportunity for control efforts are: the use of antibiotics and the epidemiological spread of resistant microbes.

The complexity of the problem makes it difficult to grade which interventions are most successful. Where interventions have been introduced few of them have been evaluated. This may partly be because few systematic interventions have been used.

The Council Recommendation on the prudent use of antimicrobial agents in human medicine (2002/77/EC) lists a number of areas that have an impact on controlling AMR. Most of the following tentative indicators are based on the Council Recommendation. Some are based on experience from different countries. These indicators are either structure- or process-related. Outcome indicators are collected by dedicated surveillance networks.

1. Development of an Intersectoral Coordinating Mechanism (ICM)

Due to the complexity of the issue there is a need for coordination to make an interventional strategy work. There is also a need for close cooperation from fields such as epidemiology, microbiology clinical medicine, infection control, veterinary medicine, pharmacology and behavioural sciences. It also requires cooperation from practitioners working in different medical specialities as well as government departments and healthcare providers.

In the Council Recommendation on the prudent use of antimicrobial agents in human medicine (2002/77/EC) and the World Health Organization (WHO) Global Strategy for Containment of Antimicrobial Resistance (WHO/CDS/CSR/DRS/2001.2) the establishment of a coordinating group is regarded as essential.

Member States have different administrative organisations. There should be a group at the highest administrative level where representatives from regulatory bodies and professionals from the different sectors coordinate.

Tentative indicators for 1

Structures

- Multidisciplinary composition
- Regular meetings
- Minutes from meetings
- National strategy plan available
- Defined governmental mandate
- Financially supported by government.

Functions

- Coordinates analysis of consumption and plans and supports interventions
- Proposes national objectives and policies
- Proposes, plans and supports interventions
- Provides policymakers, media and public with continues updated and structured data
- Provides support to local working groups.

2. Organised multidisciplinary and multisectoral collaboration at local level

One of the main elements for control strategies is to lower the selective pressure of antibiotics by restricting usage to appropriate indications. There is much evidence showing that antibiotics are overused. Prescribers need to be well acquainted with the AMR problem and the rational of using antibiotics appropriately.

A non-regulatory intervention that has had some influence on prescribing habits is a local activity whereby practising physicians discuss local data on consumption and bacterial resistance patterns, supported by epidemiologists, pharmacists and infection control. This proves to be an appropriate opportunity to revise local usage patterns, develop local guidelines (based on national guidelines) and organise local meetings with prescribers to promote rational use of antibiotics. In addition, topical issues can be discussed, such as problems related to MRSA or *Clostridium difficile* 027.

Practising doctors have limited time available. It is essential that there is a good collaboration with and support from the national/regional group to provide background data and help with scientific updates.

Tentative indicators for 2

General

Structures

- Are there local activities in some places?
- Are there nationally disseminated local activities?
- Are activities in hospitals and primary healthcare coordinated at the local level?

Primary health care

Structures

- Are there local activities in primary health care?
  - If yes:
  - Mostly multidisciplinary
  - Private practitioners are taking part
  - Have access to local surveillance data on AMR
  - Have access to local antibiotic consumption data
  - Have public funding
  - Meet regularly.

Functions

Primary areas of work are:

- Infection control
- Diagnostic practices/habits
- Analysis of local consumption and resistance data
- Educational activities
- Coordination of interventions
- Provide local guidelines
- Convene local meetings with prescribers at least once a year.

Hospitals

Structures

- Are there local activities in hospital health care?
  - If yes:
  - Mostly multidisciplinary
  - Have access to local surveillance data on AMR
  - Have access to local antibiotic consumption data
  - Have public funding
  - Meet regularly.

Functions

Primary areas of work are:

- Infection control
- Diagnostic practices/habits
- Analysis of local consumption and resistance data
- Educational activities
- Coordination of interventions
- Provide local guidelines
- Convene local meetings with prescribers at least once a year.

3. Laboratory capacity

Laboratory capacity is essential for many reasons:

- To be able to follow trends in antimicrobial resistance;
- To discover newly emergent resistant strains;
- To enable prescribers to make informed antibiotic choices. For this there is a need for timely feedback to clinicians.

It is important to characterise isolates that may have clinical importance. Often this cannot be done in all laboratories so a referral system to specialised laboratories should exist.

All laboratory work should be quality assessed regularly.

Tentative indicators for 3

General

Structures

- How many diagnostic laboratories are appropriately equipped for microbiological diagnostic work (minimum requirement: performance of gram-stain, aerobe culture and antimicrobial susceptibility testing)?
- What proportion of microbiological laboratories have at least one specialist clinical/medical microbiologist?
- Is there a formal referral structure to reference laboratories supported by public (alternatively through insurance system or equivalent) funding?
- Does a national external quality assessment scheme exist?
- Does an accreditation system exist for microbiological laboratories that requires regular QC and EQA?

Hospitals

Functions

- What proportion of microbiological laboratories provide preliminary and individual feedback (gram stain, rapid tests, culture results) via telephone or clinical rounds to the submitting clinician within the first 12 hours of receiving a diagnostic specimen?
- What proportion of microbiological laboratories provide preliminary and individual feedback (gram stain, rapid tests, culture results) via telephone or clinical rounds to the submitting clinician within the first 24 hours of receiving a diagnostic specimen?
- What proportion of microbiological laboratories provides susceptibility test results to the submitting clinician within 48 hours of receiving a diagnostic specimen?
- What proportion of microbiological laboratories provides species identification of blood culture isolates to the submitting clinician?
- Who pays for the analysis of samples sent in?

Out patients

Functions

- What proportion of general practitioners can submit clinical specimen for microbiological investigation to an appropriately equipped microbiological laboratory within 12 hours?
- What proportion of microbiological laboratories provide preliminary and individual feedback (gram stain, rapid tests, culture results) to the submitting clinician within the first 24 hours of receiving diagnostic specimen?
- What proportion of microbiological laboratories provides susceptibility test results to the submitting clinician within 48 hours of receiving a diagnostic specimen?
- Who pays for sent in sample analysis?

4. Monitoring of antibiotic resistance

Resistance patterns should regularly be followed. This should be done using a standardised method. The method should be quality assessed on a regular basis.

To be able to guide prescribers in prudent usage of antibiotics, surveys of different clinical conditions should be carried out to define which pathogens and their susceptibility profiles for antibiotics. The resistance pattern may vary from area to area so local monitoring may be needed.

Data should be gathered nationally and internationally to follow long term trends.

Tentative indicators for 4

- Local, time limited studies have been performed
- Local continuous, monitoring is done in a few laboratories
- Are duplicates excluded?
- National monitoring with standardised methodology on clinically and epidemiologically relevant bacterial pathogens is on-going
- Country wide local monitoring with standardized methodology in communities and hospital unites is on-going
- Data from hospitals and out-patient settings are treated separately
- Data collection is financially supported by government
- Regular surveys of resistance patterns for pathogens in population based syndromes are performed
- Regular feedback of resistance patterns to prescribers and local groups is given.

5. Monitoring of antibiotic usage

As antibiotic usage is the driving force for emerging resistance it is important to monitor usage. Therefore, reliable surveillance systems of antibiotic consumption are essential to complement antibiotic resistance data and develop instruments for assessing effective strategies to foster appropriate antibiotic use in all European countries.

Current antibiotic use surveillance systems are mostly monitoring trends and shifts in usage patterns. However, to deepen our understanding of antibiotic prescribing, more detailed information is needed on patients' age and gender, the prescriber, the indication and pathogen. Although prescriber data are felt as sensitive, this kind of data can be used for the self-assessment. Aggregated data may be used for local group discussions.

Tentative indicators for 5

- Are valid national data on outpatient antibiotic use available?
- Are valid national (or at least representative sample) data on hospital antibiotic use available?
- Is collection of data on antibiotic use legally supported?
- Is data collection financially supported by the government?
- Are data available per prescriber/ clinical diagnosis/micro-organism?
- Is there regular feedback of prescription patterns to prescribers?
- Are anonymous data fed back to local groups?

6. Antibiotic utilisation and treatment guidance

Antibiotics should be used properly. 'Proper use' is a difficult term both in human and veterinary medicine. There is still a need to find some common view on what is 'proper'. Guidelines are a way of agreeing locally or nationally.

Antibiotics allow treatment of serious bacterial infections. The largest volume of antibiotics is prescribed in ambulatory care. This use is increasingly recognised as the major selective pressure driving resistance, which in turn makes them ineffective. Therefore antibiotics should be used appropriately - i.e. (no) antibiotics for those who will (not) benefit from the treatment. In addition, unnecessary use of antibiotics requires more resources, motivates patients to re-consult and exposes them to the additional risk of side effects, whereas under-prescribing could be associated with higher risk of complications of untreated infections.

A 'proper' level of usage is difficult to define. The levels are mostly for following trends and shifts in usage patterns. With these data related to other data there might be a way of defining a 'proper' range of usage. One benchmark value at European level cannot be given, because for different countries the demographical characteristics and epidemiological situation can influence this indicator. Individual countries should position themselves and define their own benchmark, This should be based on the epidemiology of infectious diseases and national guidelines. A range of acceptable antibiotic use should be defined rather than one threshold value. If the use is outside the limits of the range, more detailed assessment is recommended in order to define the action required. For any action planned explicit targets should be set.

Most guidelines define treatment for specific diagnosis. This means that the diagnosis has to be made correctly before guidelines are applicable.

That also means that antibiotic usage must be directed by medical diagnosis and decisions. This is why systemic antibiotics are prescription-only medicines in the European Union.

Tentative indicators for 6

- Availability of OTC (over-the-counter) antibiotics
- Availability of national treatment guidelines
- Availability of locally adapted treatment guidelines
- Has the compliance to guidelines been assessed?
- Defined standardised criteria for clinical diagnosis
- What is the rate of laboratory diagnostics use before deciding on use of antibiotics for sore throat (% of patients)?
- What is the rate of blood cultures before use of antibiotics for perceived bacteraemia with sepsis (% of patients)?

7. Infection control

Healthcare and hospitals in particular have historically been a major source of spread for epidemics. This has been shown for a wide variety of microbes – for example smallpox and early outbreaks of Lassa fever. A recent well-known example is SARS. Another very well-known bacterium that spreads in healthcare settings is MRSA.

All hospitals have defined procedures and hygienic principles although these may not always be based on the latest scientific knowledge. Implementation of guidelines and adherence to procedures is another problem. Surveys have shown that adherence to infection control guidelines many times is poor.

More and more people with complicated medical conditions are given home-based care. Many of them are elderly. Such patients may have indwelling catheters, a lower immunity and often use antibiotics. Infection control guidelines are difficult to follow in a home setting and many of the care staff have little or no training in infection control. Increasingly MRSA is reported to also be a problem in these settings.

Tentative indicators for 7

General

- Is there a national committee on issues related to infection control?

Hospitals

- Alcohol-based hand disinfection recommended for non-diarrhoeal disease
- Guidelines for hygienic procedures including standardized barrier precautions in >90% of hospitals
- Specific guidelines for MRSA in >90% of hospitals
- At least one infection control nurse/doctor per hospital
- Time allocated for infection control?
- What numbers of hospitals do surveillance of healthcare acquired infections (HAI) regularly in ICUs? (% of hospitals)
- What numbers of hospitals do surveillance of healthcare acquired infections (HAI) regularly in surgical wards? (% of hospitals)
- What numbers of hospitals do surveillance of healthcare acquired infections (HAI) regularly in internal medicine wards? (% of hospitals)
- Are there legal requirements for infection control system in hospitals?
- Is implementation of infection control practice regularly evaluated?

Healthcare settings outside hospitals

- Alcohol-based hand disinfection recommended for non-diarrhoeal disease
- Alcohol-based hand disinfection available in >90% of outpatient clinics
- Alcohol-based hand disinfection available in >90% of health care settings for elderly
- Guidelines for infection control are available for elderly and long term care staff
- Implementation of infection control practice in elderly and long term care is regularly evaluated.

8. Educational programmes on AMR

Understanding the problem with AMR is the basis for having an impact with interventional programmes. This can partially be achieved with educational programmes. Educational programmes should be an integrated part of undergraduate studies. All healthcare-related professionals need to have an understanding of the AMR problem.

'Education' in the context of AMR is more than just pharmacology of antibiotics or resistance patterns in microbes. It encompasses the relationship between microbes, antibiotics and the epidemiology of resistant strains. It describes the complex interrelation between all aspects brought up in this document.

Regular, repetitive, independent educational material best provided by locally-based colleagues in discussion groups seems to be one of the better success factors.

Tentative indicators for 8

- Doctors have in their curriculum AMR as undergraduate course
- Hospital health care workers have some education on AMR
- Community health care workers have some education on AMR
- Specific post-graduate courses for doctors in antibiotic resistance are provided
- Regular educational programmes in antibiotic resistance are provided for health staff
- It is compulsory for all prescribers to take part regularly in a session on AMR
- <60% of information on AMR is industry sponsored.

9. Public information related to AMR

Many prescribers blame patients for demanding antibiotics irrespective of their condition. This can only be changed if the public is well informed about what antibiotics can and cannot do. Hence, educational activities for the wider public are important.

Tentative indicators for 9

- No information provided
- Topic sometimes covered in media
- Some material for media and/or internet from official sources
- Occasional national campaigns
- Repeated, structured national campaigns
- Regular, structured information provided by professional bodies
- Public perception assessed.

10. Marketing related issues

Economics also have an impact on prescribing habits, irrespective of diagnosis or best practice. This should be discouraged.

Tentative indicators for 10

- Independent (not industry supported) drug information is available
- Ethical guidelines for interrelation between physicians and industry are in place
- Physician's prescriptions do not influence on physician's salary
- Personal gifts from industry to physicians are illegal.

European Centre for Disease Prevention and Control (ECDC)

Address:
Gustav III:s boulevard 40, SE-169 73 Solna, Sweden

Tel. +46 858601000
Fax +46 858601001
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