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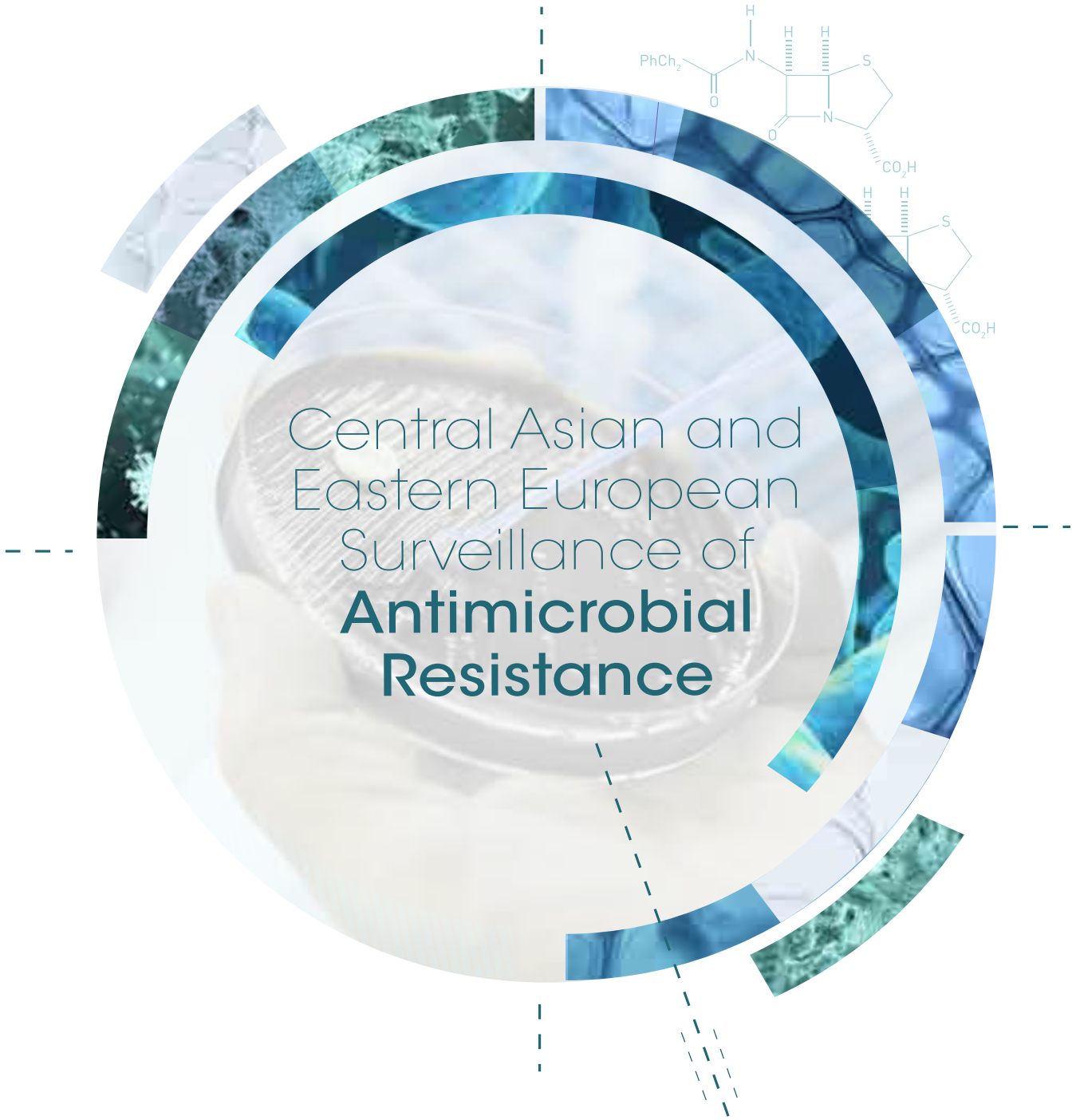

Central Asian and Eastern European Surveillance of **Antimicrobial Resistance**

Annual report 2016

World Health Organization
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Abstract

This report describes resistance data from seven countries and Kosovo (in accordance with United Nations Security Council resolution 1244 (1999)) in the WHO European Region gathered through the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) network. Guidance is provided to the reader on how to interpret the surveillance data with caution, taking conditions outside the direct control of the national antimicrobial resistance surveillance system into account, which may reduce the reliability and representativeness of the data. The aim of this report is to create awareness about the current antibiotic resistance situation and advocate AMR control policies in participating countries . In addition, this report aims to provide guidance and inspiration to countries that are building or strengthening their national antimicrobial resistance surveillance and stimulate the sharing of data internationally. WHO and its partners remain committed to support countries in these endeavours through the activities of the CAESAR network.

Keywords

DRUG RESISTANCE, MICROBIAL
ANTI-INFECTIVE AGENTS
INFECTION CONTROL
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DATA COLLECTION

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Foreword

In September 2011, all 53 Member States of the WHO European Region adopted the European strategic action plan on antibiotic resistance and, in May 2015, the Sixty-eighth World Health Assembly, in resolution WHA68.7, endorsed the global action plan on antimicrobial resistance (document A68/20). The global awareness of the major threat of antimicrobial resistance (AMR) is continuing to grow, and the number of countries engaging actively to control AMR is increasing worldwide. Given its far-reaching implications and the critical need for mounting a multisectoral and whole-of-society response, the United Nations General Assembly discussed AMR as its fourth health subject on 21 September 2016. The outcome was a political declaration urging all countries and stakeholders to accelerate and strengthen their response to AMR and facilitate the implementation of the global action plan on antimicrobial resistance.

Surveillance of antibiotic resistance is considered the backbone of both the European strategic action plan and the global action plan. Many countries in the European Region that are not members of the European Union do not systematically collect and share data on antibiotic resistance. Therefore, the WHO Regional Office for Europe, together with the National Institute for Public Health and the Environment and the European Society of Clinical Microbiology and Infectious Diseases, established the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) network in 2012 to assist countries in setting up or strengthening national AMR surveillance. These efforts will also contribute to the newly established WHO Global Antimicrobial Resistance Surveillance System (GLASS) that was launched in October 2015 in Copenhagen, Denmark, to support a standardized approach to collecting, analysing and sharing data on AMR at the global level.

This second CAESAR report describes the AMR activities undertaken among the countries participating in CAESAR in setting up and strengthening their national AMR surveillance networks. In addition, the results from the three years of external quality assurance exercises of antimicrobial susceptibility testing among laboratories participating in CAESAR and the resistance data from seven countries and Kosovo (in accordance with United Nations Security Council resolution 1244 (1999)) gathered through the CAESAR network is described. Furthermore, for the first time AMR data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) coordinated by the European Centre for Disease Prevention and Control (ECDC) and the CAESAR network are displayed jointly in maps covering the whole WHO European region. Guidance is provided to the reader on how to interpret the surveillance data with caution, taking conditions outside the direct control of the national AMR surveillance system into account, which may reduce the reliability and representativeness of the data.

The aim of this report is to create awareness about the current antibiotic resistance situation and to advocate AMR control policies in participating countries. In addition, this report aims to provide guidance and inspiration to countries that are building or strengthening their national antimicrobial resistance surveillance and to stimulate the sharing of data internationally. WHO and its partners remain committed to support countries in these endeavours through the activities of the CAESAR network.

We would like to thank all the participating countries and areas, our partners and pool of experts for their dedication to the CAESAR network and contributions to this report.

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AMR focal point teams: Perlat Kapisyzi (Albania), Silva Tafaj (Albania), Kristina Gyurjyan (Armenia), Nazifa Mursalova (Azerbaijan), Mais Sailov (Azerbaijan), Leonid Titov (Belarus), Alexander Davydov (Belarus), Amela Dedic-Ljubovic (Bosnia and Herzegovina), Nijaz Tihic (Bosnia and Herzegovina), Maja Ostojic (Bosnia and Herzegovina), Sabina Sestic (Bosnia and Herzegovina), Kanita Dedic (Bosnia and Herzegovina), Pava Dimitrijevic (Bosnia and Herzegovina), Paata Imnadze (Georgia), Lile Malania (Georgia), David Tsereteli (Georgia), Nino Kiknadze (Georgia), Medeia Eloshvili (Georgia), Baktygul Ismailova (Kyrgyzstan), Damira Ashyralieva (Kyrgyzstan), Gordana Mijovic (Montenegro), Milenia Lopicic (Montenegro) Radu Cojocaru (Republic of Moldova), Olga Burduniuc (Republic of Moldova), Roman Kozlov (Russian Federation), Marina Sukhorukova (Russian Federation), Zora Jelesic (Serbia), Mira Mihajlovic Ukropina (Serbia), Andreas Kronenberg (Switzerland), Said Davlatov (Tajikistan), Rahmonali Nasurdinov (Tajikistan), Saranjon Bobjonova (Tajikistan), Firuz Davlyatov (Tajikistan), Musharafa Kilicheva (Tajikistan), Inoyat Kenjaeva (Tajikistan), Aziza Imomberdieva (Tajikistan), Golubinka Bosevska (the former Yugoslav Republic of Macedonia), Biljana Kakaraskoska Boceska (the former Yugoslav Republic of Macedonia), Zaklina Cekovska (the former Yugoslav Republic of Macedonia), Ana Kaftandzieva (the former Yugoslav Republic of Macedonia), Nikola Panovski (the former Yugoslav Republic of Macedonia), Husniye Simsek (Turkey), Serap Suzuk Yesıldız (Turkey), Dilber Aktas (Turkey), Gurbangul Ovliyakulova (Turkmenistan), Azat Ovezov (Turkmenistan), Svetlana Osatshko (Ukraine), Tetiana Glushkevych (Ukraine), Gulnara Abdukhalilova (Ukraine), Lul Raka (Kosovo (in accordance with United Nations Security Council resolution 1244 (1999))), Arsim Kurti (Kosovo (in accordance with United Nations Security Council resolution 1244 (1999))).

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Abbreviations

AMR	antimicrobial resistance
CAESAR	Central Asian and Eastern European Surveillance of Antimicrobial Resistance
CC	clonal complex
CLSI	Clinical and Laboratory Standards Institute
CSF	cerebrospinal fluid
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
ESBL	extended-spectrum beta-lactamase
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GLASS	Global Antimicrobial Resistance Surveillance System
ISO	International Organization for Standardization
MRSA	methicillin-resistant *Staphylococcus aureus*
Susceptibility	susceptibility of a pathogen to an antimicrobial agent
I	intermediate
I+R	intermediate or resistant; non-susceptible
R	resistant
S	sensitive
UK NEQAS	United Kingdom National External Quality Assessment Service for Microbiology
WHONET	WHO microbiology laboratory database software

Summary

The Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) network is a joint initiative of the WHO Regional Office for Europe, the European Society of Clinical Microbiology and Infectious Diseases and the Dutch National Institute for Public Health and the Environment. CAESAR aims to support all countries of the WHO European Region that are not part of the European Antimicrobial Resistance Surveillance Network (EARS-Net) coordinated by the European Centre for Disease Prevention and Control (ECDC) in the European Union (EU).

Currently, Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, the Republic of Moldova, the Russian Federation, Serbia, Switzerland, Tajikistan, the former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, Uzbekistan and Kosovo (in accordance with United Nations Security Council resolution 1244 (1999)) are engaged at various stages of development and participation in CAESAR. So far, seven countries (Belarus, Bosnia and Herzegovina, the Russian Federation, Serbia, Switzerland, the former Yugoslav Republic of Macedonia and Turkey) and Kosovo (in accordance with United Nations Security Council resolution 1244 (1999)) have submitted data to the CAESAR database.

CAESAR collects antibiotic susceptibility testing data from blood and cerebrospinal fluid for eight bacterial species of public health and clinical importance: *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter* species, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecalis* and *Enterococcus faecium*. Chapters 6 and 7 present the trends of resistance observed among these reported pathogens. This year the CAESAR report also includes maps of the European Region displaying the resistance proportions from the CAESAR and EARS-Net countries (Chapter 8).

The CAESAR data clearly show that antibiotic resistance is widespread in the European Region. Although assessing the exact magnitude of resistance is still challenging in many countries, the data clearly indicate the resistance patterns present in clinical settings covered by the surveillance. High levels of carbapenem resistance in *Klebsiella pneumoniae* and high proportions of multidrug-resistant *Acinetobacter* spp. in several countries suggest the dissemination of resistant clones in the healthcare setting. These data provide a basis for taking action to control antimicrobial resistance (AMR).

Limiting conditions outside the direct control of the AMR surveillance systems may reduce the reliability and representativeness of the data because they influence the selection of people eligible for blood culturing or the quality of antibiotic susceptibility testing performed. This report therefore includes a reader's guide that describes several sources of error and bias in data from AMR surveillance (Chapter 5, Annex 1). To further guide the interpretation of the data presented in this report, the authors and the AMR focal points have assessed the level of evidence for their respective country or area.

In addition to the countries and area currently reporting AMR data to CAESAR, many countries are preparing and building the necessary capacity for AMR surveillance, which will also enable them to report AMR data to CAESAR in the near future. Chapter 2 describes the progress being made within the CAESAR network. The necessary steps to set up or strengthen their national AMR surveillance system are being taken by many of the countries, enabling them to get a better insight into the AMR situation in their country and participation in CAESAR. Most of the countries are still facing many challenges, and strong political support is needed to continue the progress being made.

One of the challenges is the limited routine antibiotic susceptibility testing caused by the underutilization of microbiological diagnostics in clinical practice. The proof-of-principle AMR surveillance study was set up, with the aim to stimulate the taking of blood cultures among people with suspected bloodstream infections to start assessing the antibiotic susceptibility of the main pathogens causing community-associated and

hospital-associated bloodstream infections. Chapter 9 describes the preliminary results of the first pilot of the proof-of-principle study initiated in Tbilisi, Georgia in 2015. This proof-of-principle study has laid down a basis for multicentre collaborative surveillance network, and a routine for collecting antibiotic susceptibility testing results from the network laboratories has been developed.

Chapter 10 describes the results from three years of CAESAR external quality assessment. The overall achieved results were good, and the number of countries and laboratories has increased from 131 laboratories in 8 countries in 2013 to 229 laboratories in 15 countries in 2015. Over the years, the antibiotic susceptibility testing results obtained for the bacterial isolates revealed similar problems; detection of borderline susceptibility, interpretation of specific tests and performance of inappropriate techniques. Such problems, when encountered, should not be discouraging but rather motivating to implement necessary measures for improvement. In the past few years, the use of up-to-date European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines increased from 14% in 2013 to 50% in 2015.

In conclusion, this report is meant to provide guidance to countries that are building or strengthening their national AMR surveillance. Even though, for some of the countries, the data displayed in this report should be interpreted with caution, the high percentages of resistance displayed confirm the need for action and emphasize the importance of good clinical practice in reducing the further development of AMR. Using surveillance data to increase awareness among clinicians, policy-makers and the public, is essential in fighting AMR.


CHAPTER
1

Introduction

The discovery of antibiotics and other antimicrobial agents has dramatically changed human and veterinary medicine, preventing and curing infections and saving millions of lives. Bacteria and other microorganisms eventually become resistant to antimicrobial treatment through the natural process of adaptation. However, the overuse and misuse of antimicrobial agents greatly accelerates the rate at which resistance emerges. As currently available antimicrobial agents lose their effectiveness, and very few new drugs are being developed, many types of infection are becoming life-threatening again and surgical procedures hazardous. Without harmonized and immediate action on a global scale, the world is heading towards a post-antibiotic era in which common infections could once again kill *(1)*. In response to this crisis, all 53 Member States in the WHO European Region adopted the European strategic action plan on antibiotic resistance in September 2011, in Baku, Azerbaijan, at the 61st session of the WHO Regional Committee for Europe. This aims to preserve the ability of modern medicine to prevent and treat infections for this and future generations *(2)*. The recent adaptation of the global action plan on antimicrobial resistance at the May 2015 World Health Assembly reflects the growing awareness among national leaders and urges Member States to have in place national action plans aligned with the five strategic objectives of the global action plan on antimicrobial resistance:

1. improve awareness and understanding of antimicrobial resistance (AMR) through effective communication, education and training;

2. strengthen the knowledge and evidence base through surveillance and research;

3. reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures;

4. optimize the use of antimicrobial medicines in human and animal health; and

5. develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions.

The resolutions accompanying the European strategic action plan on antibiotic resistance and the global action plan on AMR urge Member States to ensure political commitment and resources for implementing national strategic action plans. The WHO Regional Office for Europe and its partners are working together with Member State governments to develop and implement these comprehensive strategic action plans.

Continuous AMR surveillance, as described in strategic objective 2 of the global action plan on antimicrobial resistance *(1)*, is crucial in assessing antibiotic resistance rates and targeting adequate action to control the problem and should therefore have a prominent place in the strategic action plans of Member States to combat AMR. About half of the European Region has well established national and international surveillance systems (such as the EU countries), whereas this is often less developed in countries in central Asia and eastern Europe. For this reason, the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) network was established in 2012. CAESAR is a joint initiative of the WHO Regional Office for Europe, the European Society of Clinical Microbiology and Infectious Diseases and the National Institute for Public Health and the Environment of the Netherlands. CAESAR aims to support all countries of the WHO European Region that are not part of the EARS-Net coordinated by the European Centre for Disease Prevention and Control (ECDC) in the European Union (EU).

This second CAESAR report describes the AMR activities that are undertaken among the Member States participating in CAESAR in setting up and strengthening their national AMR surveillance networks. In addition, the results from the three years of external quality assessment exercises of antimicrobial susceptibility testing among laboratories participating in CAESAR and the AMR data for 2014 and 2015 from Belarus, Bosnia and Herzegovina, the Russian Federation, Serbia, Switzerland, the former Yugoslav Republic of Macedonia and Turkey as well as Kosovo[1] are described.

[1] All references to Kosovo in this chapter should be understood as references to Kosovo in accordance with United Nations Security Council resolution 1244 (1999).


CHAPTER
2

Progress in CAESAR

2.1. Objectives of CAESAR

The objectives of CAESAR are to be a network of national surveillance systems that collects relevant data and information to guide national and international action to address AMR and to provide a platform for professionals to share experience and expertise across the European Region.

The methods used in CAESAR are compatible with those used by the ECDC *(1)* to enable comparison of data throughout the whole Region, to provide a pan-European overview of trends and sources of AMR, inform policies and decisions, direct interventions and measure their effectiveness.

2.2 Participation in CAESAR

At present, Kosovo[1] and following 19 countries are engaged in CAESAR at various stages of development and participation: Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, the Republic of Moldova, the Russian Federation, Serbia, Switzerland, Tajikistan, the former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine and Uzbekistan. This report contains AMR surveillance data for 2014 and 2015 submitted to the CAESAR database by seven countries (Belarus, Bosnia and Herzegovina, Serbia, Switzerland, the Russian Federation, the former Yugoslav Republic of Macedonia and Turkey) and Kosovo[1].

2.3 Indicators of progress in CAESAR

Surveillance capacity within the CAESAR network is steadily developing and improving. In addition to the countries currently reporting AMR data to CAESAR, many countries are preparing and building the necessary capacity for AMR surveillance, which will also enable them to report AMR data to CAESAR in the near future.

To get a clear overview of the progress being made, the AMR focal points were asked to fill in a short questionnaire, to report on AMR activities being undertaken and the progress being made. The questionnaire was divided into four main areas: (1) overall coordination; (2) surveillance network and AMR reference laboratory; (3) quality control; and (4) guidelines for antibiotic susceptibility testing. Each area consisted of a set of indicators, reflecting the stepwise approach, needed to develop and strengthen national surveillance of AMR (Table 2.1). The results of the questionnaire are described in this chapter, with final approval from the AMR focal points.

2.3.1 Progress on overall coordination on antimicrobial resistance

As described in the European strategic action plan on antibiotic resistance *(2)* and the global action plan on antimicrobial resistance *(3)*, Member States are encouraged: to establish a sustainable, multisectoral, interdisciplinary and inclusive national committee that monitors the public health risks and impact of AMR in all sectors; to recommend policy options; to secure overall commitment to national strategies for containing antibiotic resistance; to provide technical guidance on national analysis, standards, guidelines, regulations, training and awareness; and to ensure coordination where needed. In addition to representatives of relevant government sectors, this committee should include representatives of national professional associations, authorities and leading scientific institutions. This committee is crucially

[1] All references to Kosovo in this chapter should be understood as references to Kosovo in accordance with United Nations Security Council resolution 1244 (1999).

important for overall coordination and developing a comprehensive national action plan on AMR, and its work could be extended beyond antibiotic resistance to cover the whole field of AMR, including antiviral, antiparasitic or antifungal drugs *(2)*. The global action plan on antimicrobial resistance of 2015 reiterates these recommendations and urges Member States to have a national action plan on AMR in place by June 2017 *(3)*. Table 2.1 presents an overview of the indicators to measure progress in controlling AMR.

Table 2.1 Description of AMR indicators

Area	Indicators	Description
Overall AMR coordination	AMR focal point	AMR focal point officially appointed by health ministry
	International coordinating mechanism	Intersectoral coordinating mechanism to contain AMR has been set up
	AMR action plan	AMR action plan has been developed
	AMR action plan funds	Dedicated funds are available for AMR action plan implementation
	AMR action plan implementation	Active implementation of AMR action plan is ongoing
Surveillance network and AMR reference laboratory	Coordination AMR surveillance	Institute appointed to coordinate national AMR surveillance network
	AMR surveillance team	AMR surveillance team formed
	AMR reference laboratory nominated	AMR reference laboratory nominated
	Functional AMR reference laboratory	Functional AMR reference laboratory
	AMR surveillance	AMR surveillance in place
	Periodic surveillance reports	AMR surveillance report published periodically
	AMR surveillance network meetings	Yearly AMR surveillance network meetings held
	CAESAR reporting	AMR data reported to CAESAR
Quality control	CAESAR external quality assessment	Participation in CAESAR external quality assessment
	Laboratory quality assessment system	Laboratory quality assessment system in place
Antibiotic susceptibility testing guidelines	Current antibiotic susceptibility testing guideline	Antibiotic susceptibility testing guideline based on international standards (European Committee on Antimicrobial Susceptibility Testing (EUCAST), CLSI or other) is currently being used by the majority of laboratories
	Implementation of a recent CLSI or EUCAST guideline	A recent version (2014/2015) of EUCAST or CLSI guidelines is being implemented in the majority of laboratories

Of the 19 countries participating in CAESAR, 18 countries and Kosovo[1] have an AMR focal point appointed, which is a prerequisite for participating in CAESAR (Table 2.2). The AMR focal point represents the institute, nominated by the health ministry, to play a leading role in forming an international coordinating mechanism for containing AMR.

Table 2.2 AMR focal points of CAESAR

Country or area	AMR focal point
Albania	Perlat Kapisyzi (chair, AMR international coordinating mechanism, University Hospital Tirana)
Armenia	Kristina Gyurjyan (Head, Public Health Department, Ministry of Health)
Azerbaijan	Nazifa Mursalova (Sector of Sanitary Epidemiological Surveillance, Ministry of Health)
Belarus	Vladimir Gorbunov (Director, Republican Research and Practical Center for Epidemiology and Microbiology) - Leonid Titov (Head, Laboratory for Clinical and Experimental Microbiology, Republican Research and Practical Center for Epidemiology and Microbiology)
Bosnia and Herzegovina	Mirsada Hukic (Clinical Microbiology Department, Clinical Center, University of Sarajevo) Amela Dedeic-Ljubovic (Head, Clinical Microbiology Department, Clinical Center, University of Sarajevo) Pava Dimitrijevic (Head, Department of Microbiology, Public Health Institute of the Republic of Srpska)
Georgia	Paata Imnadze (Scientific Director, National Center for Disease Control and Public Health)
Kazakhstan	National AMR focal point pending nomination
Kyrgyzstan	Baktygul Ismailova (Chief Specialist, Public Health Department,Ministry of Health)
Montenegro	Gordana Mijovic (Center for Medical Microbiology, Institute of Public Health)
Republic of Moldova	Radu Cojocaru (Deputy Director for Laboratory Activity, National Centre for Public Health, Ministry of Health)
Russian Federation	Roman S. Kozlov (Director, Institute of Antimicrobial Chemotherapy, Smolensk State Medical University)
Serbia	Zora Jelesic (Head, Center for Microbiology, Institute for Public Health of Vojvodina)
Switzerland	Andreas Kronenberg (Swiss Centre for Antibiotic Resistance, Institute for Infectious Diseases, University of Berne)
Tajikistan	Said Davlatov (Deputy Head, State Sanitary Epidemiology Surveillance Service, Ministry of Health and Social Protection of the Population)
The former Yugoslav Republic of Macedonia	Golubinka Bosevska (Head, Laboratory for Virology and Molecular Diagnostics, Institute of Public Health)
Turkey	Husniye Simsek (Microbiology Reference Laboratories Department, Public Health Institution of Turkey)
Turkmenistan	Gurbangul Ovliyakulova (Head, Highly Dangerous Infections Department, State Sanitary Epidemiology Service, Ministry of Health and Medical Industry)
Ukraine	Aidyn Salmanov Hurban Ogly (Head, Department of Microbiology and Epidemiology, Shupyk National Medical Academy of Postgraduate Education)
Uzbekistan	Gulnora Abdukhalilova (Head, Laboratory, Research Institute of Epidemiology, Microbiology and Infectious Diseases)
Kosovo[a]	Lul Raka (Department of Medical Microbiology, Institute of Public Health of Kosovo)

[a] In accordance with United Nations Security Council resolution 1244 (1999).

To date, 11 countries and Kosovo[1], indicated that they have an international coordinating mechanism in place versus nine countries in 2014. In addition, six countries have now indicated that they are in the process of setting up an international coordinating mechanism versus only one country in 2014 (Table 2.3). The international coordinating mechanism is responsible for identifying key areas in which action must be taken and for developing or updating the national strategic action plan on AMR. Continuous AMR surveillance is crucial in assessing major antibiotic resistance rates and targeting adequate actions to control the problem. AMR surveillance should therefore have a prominent place in the strategic action plan to combat AMR. Further, adequate knowledge of (locally) prevailing antibiotic resistance patterns is a basis for empirical antibiotic therapy and prudent use of antibiotics.

Six countries and Kosovo[1] indicated that they have developed an AMR action plan and that active implementation is taking place or is being prepared. An additional ten countries have indicated that they are in the process of developing an AMR action plan versus only two countries in 2014, again showing that progress is being made. At the moment, dedicated funds for implementation are only available in Montenegro, Switzerland and Kosovo[1] (Table 2.3). Together with the 15 action plans among the EU countries, 22 of 53 countries in the WHO European Region currently have a national action plan to address AMR.

2.3.2. Progress on surveillance networks and AMR reference laboratories

A national AMR surveillance network enables a country to identify national antibiotic resistance problems, to set priorities in infection control activities, to develop antibiotic therapy guidelines and to perform sentinel studies. Sharing national AMR data with the international community will enable the comparison of resistance patterns between countries, subregions and regions and inclusion in international activities aiming to control the spread of antibiotic resistance. Fourteen countries and Kosovo[1] have indicated that an institute has formally been appointed to coordinate the AMR surveillance network and that a surveillance coordination team has been formed. Two more country indicated that they were in the process of appointment, taking a leading role in establishing a network of microbiology laboratories to monitor AMR (Table 2.4).

Collaboration among microbiology laboratories and standardization between laboratories are crucial in setting up an AMR surveillance system in a country. Participation in the national surveillance network not only contributes to gathering national resistance data but also greatly improves the quality of routine antibiotic susceptibility testing in participating laboratories by offering national external quality assessment, regular teaching courses, frequent discussions within the laboratory network and during meetings and collaboration with international networks. The national AMR surveillance teams usually include staff members specializing in epidemiology, microbiology and data management and should ideally include staff members with a clinical background to ensure good collaboration with the local teams in the participating hospitals and practical use of information and results.

The national institute assigned to coordinate the national AMR surveillance network often includes the function of being the national AMR reference laboratory. If this is not the case, a national AMR reference laboratory should be appointed as well. Ten countries and Kosovo[1] have nominated an AMR reference laboratory, and six countries are in the process of nomination. Having a functional AMR reference laboratory is a crucial part of the surveillance network, taking the lead in introducing and maintaining standards for antibiotic susceptibility testing and having the capacity and knowledge to perform confirmatory and specialized testing such as determining the minimum inhibitory concentration and phenotypic and molecular detection of resistance mechanisms. Of the appointed AMR reference laboratories, seven have been reported as being a fully functional AMR reference laboratory, whereas seven are still in the process of establishing all required functions (Table 2.4).

Eight countries and Kosovo[1] have an AMR surveillance system in place, of which Montenegro and the Republic of Moldova are still in the progress of aligning their national AMR surveillance system with the CAESAR methods and are planning to report data to CAESAR in 2017. Six countries have indicated they are developing their AMR surveillance system in accordance with CAESAR methods.

Table 2.3 Overall coordination of AMR

Country or area	AMR focal point appointed	Intersectoral coordinating mechanism to contain AMR has been set up	AMR action plan developed	Dedicated funds available for implementing the AMR action plan	Active implementation of the AMR action plan
Albania	✓	✓	✗	✗	✗
Armenia	✓	✓	✓	⚙	⚙
Azerbaijan	✓	⚙	⚙	✗	✗
Bosnia and Herzegovina	✓	⚙	⚙	✗	✗
Belarus	✓	⚙	⚙	⚙	✓
Georgia	✓	✓	✓	✗	⚙
Kazakhstan	⚙	⚙	⚙	✗	✗
Kyrgyzstan	✓	✗	✗	✗	✗
Montenegro	✓	✓	✓	✓	✓
Republic of Moldova	✓	✓	⚙	✗	✗
Russian Federation	✓	✓	✗	✗	⚙
Serbia	✓	⚙	⚙	✗	✗
Switzerland	✓	✓	✓	✓	✓
Tajikistan	✓	✓	⚙	✗	✗
The former Yugoslav Republic of Macedonia	✓	✓	✓	✗	✓
Turkey	✓	✗	✓	⚙	⚙
Turkmenistan	✓	✓	⚙	✗	✗
Ukraine	✓	✓	⚙	✗	✗
Uzbekistan	✓	⚙	⚙	✗	⚙
Kosovo[a]	✓	✓	✓	✓	✓
No	**0**	**2**	**3**	**14**	**10**
In progress	**1**	**6**	**10**	**3**	**5**
Yes	**19**	**12**	**7**	**3**	**5**

[a] In accordance with United Nations Security Council resolution 1244 (1999).

Table 2.4 Overview of progress in countries in the CAESAR network related to AMR surveillance, reference laboratories and quality control

Country or area	Institute appointed to coordinate AMR surveillance network	AMR surveillance team formed	AMR reference laboratory nominated	Functional AMR reference laboratory	AMR surveillance in place
Albania	✖	✖	✖	✖	✖
Armenia	✔	✔	✔	⚙	⚙
Azerbaijan	⚙	✔	✖	✖	✖
Bosnia and Herzegovina	✔	✔	⚙	✔	⚙
Belarus	✔	✔	✔	✔	✔
Georgia	✔	✔	✔	⚙	⚙
Kazakhstan	⚙	⚙	⚙	✖	✖
Kyrgyzstan	✖	✖	✖	✖	✖
Republic of Moldova	✔	✔	✔	✔	✔
The former Yugoslav Republic of Macedonia	✔	✔	✔	⚙	✔
Montenegro	✔	✔	✔	⚙	✔
Russian Federation	✔	✔	✔	✔	✔
Serbia	✔	✔	✔	✔	✔
Switzerland	✔	✔	⚙	⚙	✔
Tajikistan	✔	✔	⚙	✖	⚙
Turkmenistan	✔	✔	⚙	⚙	✖
Turkey	✔	✔	✔	✔	✔
Ukraine	✖	⚙	⚙	⚙	⚙
Uzbekistan	✔	⚙	✔	✖	⚙
Kosovo[a]	✔	✔	✔	✔	✔
No	**3**	**2**	**3**	**6**	**5**
In progress	**2**	**3**	**6**	**7**	**6**
Yes	**15**	**15**	**11**	**7**	**9**

[a] In accordance with United Nations Security Council resolution 1244 (1999).

Country or area	AMR surveillance report published periodically	Yearly AMR surveillance network meetings held	AMR data reported to CAESAR	Participation in CAESAR external quality assessment	Laboratory quality assessment system in place
Albania	✗	✗	✗	✓	✗
Armenia	✗	✗	✗	✓	⚙
Azerbaijan	✗	✗	✗	✓	✗
Bosnia and Herzegovina	✗	✓	⚙	✓	⚙
Belarus	✓	✓	✓	✓	⚙
Georgia	✗	✓	⚙	✓	⚙
Kazakhstan	✗	✗	✗	✗	✗
Kyrgyzstan	✗	✗	⚙	✓	✗
Republic of Moldova	⚙	✓	✗	✓	✓
The former Yugoslav Republic of Macedonia	⚙	✓	✓	✓	⚙
Montenegro	⚙	⚙	⚙	✓	⚙
Russian Federation	✓	✓	✓	✓	✓
Serbia	✓	✓	✓	✓	✗
Switzerland	✓	✓	✓	✗	✓
Tajikistan	✗	✗	✗	✓	✗
Turkmenistan	✗	⚙	✗	✓	⚙
Turkey	✓	✓	✓	✓	✓
Ukraine	✗	✗	✗	✓	✗
Uzbekistan	✗	⚙	✗	✓	⚙
Kosovo[a]	⚙	✓	⚙	✓	⚙
No	**11**	**7**	**9**	**2**	**7**
In progress	**4**	**3**	**5**	**0**	**9**
Yes	**5**	**10**	**6**	**18**	**4**

[a] In accordance with United Nations Security Council resolution 1244 (1999).

Information sharing is a very important aspect of the AMR surveillance network. Obtaining AMR data is only one of the steps in controlling resistance, and surveillance is of little use if these data are not widely shared with all stakeholders that need this information on which to act. AMR results should be distributed to relevant professionals (such as hospital managers, heads of antibiotic or drug committees and heads of infection control committees) to stimulate the use of these data in routine practice (such as treatment regimens, infection, prevention and control programmes and procurement) and for presentations at scientific and professional meetings. Nine countries and Kosovo[1] have indicated that they organize yearly AMR surveillance network meetings, and six countries have indicated that they periodically report AMR data (Table 2.4).

2.3.3. Progress on quality control

A quality assurance system ensures the reliability and reproducibility of laboratory data. Internal quality control should be a routine procedure undertaken by participating laboratories to ensure the quality of testing. Internal quality control should cover all diagnostic tests and procedures, including isolation, identification and sensitivity testing. Internal quality control should also cover media production and equipment maintenance. Only four countries indicated that they have a national laboratory quality assessment system in place to validate the quality of internal quality control. Besides internal quality control, regular external quality control for laboratories in the AMR surveillance network is crucial to enable evaluation of the quality and reliability of data provided for national AMR surveillance. In addition, discussing national external quality assessment results provides guidance for laboratories to implement corrective action and strive for continual improvement. To stimulate setting up an external quality assessment system in a country, CAESAR organizes an annual external quality assessment scheme provided by the United Kingdom National External Quality Assessment Service for Microbiology (UK NEQAS). Participating laboratories are encouraged to store the external quality assessment isolates, which can be used to set up their own external quality assessment and internal quality control. Currently, 17 countries and Kosovo[1] are participating in the CAESAR external quality assessment exercise. Chapter 10 of this report presents the results from the past three years (Table 2.4).

2.3.4. Progress on implementing guidelines on antibiotic susceptibility testing

All laboratories participating in a national AMR surveillance network should follow standard operating procedures for specimen processing, species identification and sensitivity testing. The coordinator of the AMR surveillance network and the AMR reference laboratory have an important task to ensure that these procedures are adequately implemented and to provide regular teaching courses to keep the network up to date on the latest procedures and developments. In recent years, many CAESAR countries have been working on updating and harmonizing the antibiotic susceptibility testing guidelines. CAESAR recommends countries to use EUCAST or CLSI (Clinical and Laboratory Standards Institute) standards. Since EUCAST guidelines are the most widely used in the European Region and all EUCAST documents are freely downloadable in various languages (www.eucast.org), CAESAR provides training in EUCAST methods *(4)*. In accordance with the EUCAST recommendation, CAESAR also advises that a group of experts within the AMR network form the national antibiotic committee or a similar working group that deals with antibiotic susceptibility testing methodology issues and that ensures that all AMR network participants will accept yearly updates of international standards *(5)*. Eight countries have indicated that they use CLSI guidelines, with versions ranging between 2004 and 2015. Four countries and Kosovo[1] have indicated that they use EUCAST 2014–2015. Two countries indicated that they use both CLSI and EUCAST. Six countries could not specify the guidelines used, mostly due to the absence of a national surveillance network or due to the use of outdated local guidelines. Twelve countries and Kosovo[1] indicated that they are in the process of implementing or updating their antibiotic susceptibility testing guidelines to EUCAST 2014–2015, often with support from CAESAR, by means of training and WHO consultants (Table 2.4).

2.4. Conclusions

Seven countries and Kosovo[1] are able to provide AMR surveillance data to CAESAR. This chapter has clearly shown the progress that is being made by the remaining countries in the CAESAR network.

Many countries are taking the necessary steps to set up or strengthen their national AMR surveillance system, enabling them to get better insight into the AMR situation in their country and take appropriate action. Most of the countries are still facing many challenges, and strong political support is needed to continue the progress being made. Challenges that are often observed include:

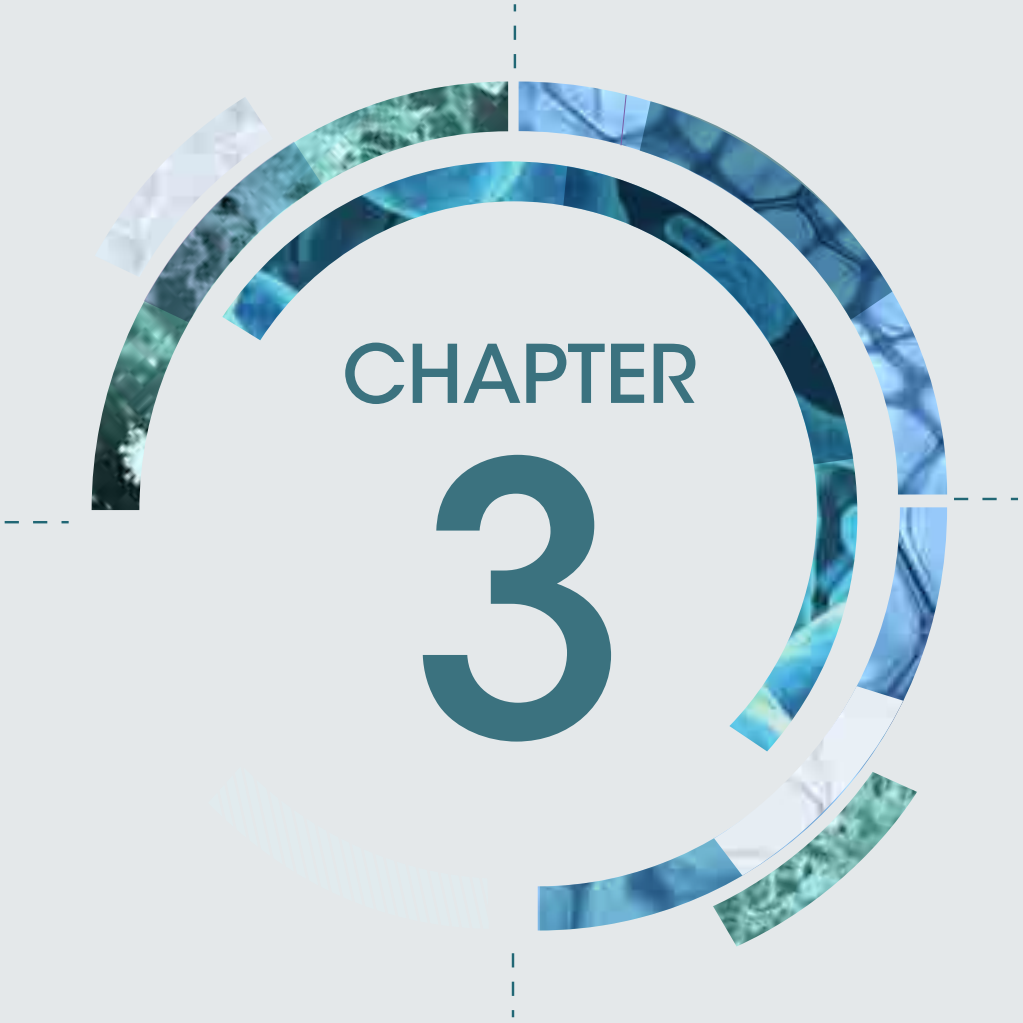
- limited human and financial resources;
- continual need to educate laboratory and hospital personnel and stimulate better collaboration between clinicians and microbiologists;
- the need to improve sampling habits and the use of medical microbiological diagnostics in hospitals;
- the need for standard operating procedures and quality control in laboratory practice;
- the need for quality as a criteria for the tender processes to ensure high-quality consumables;
- the need for implementing updated guidelines on the standardization of antibiotic susceptibility testing laboratory methods for species identification and blood culturing; and
- the need to improve laboratory information management and to set up infrastructure for central data collection at a national reference laboratory.

2.4.1 Support provided to countries

The WHO Regional Office for Europe and its partners and consultants support countries with the stepwise approach towards national coordination and surveillance of AMR. In the majority of countries, a mission to analyse the country situation has been carried out, in collaboration with the European Society of Clinical Microbiology and Infectious Diseases and the National Institute for Public Health and the Environment, to determine the country status regarding preventing and controlling AMR through surveillance, prudent use of antimicrobial agents and infection control, specifically focusing on promoting national coordination and strengthening the surveillance of antimicrobial consumption and resistance. An assessment report is provided to the WHO country office and the health ministry containing observations and recommendations for further action. Follow-up support is provided via multicountry and national AMR workshops and consultancies to set up or strengthening national AMR surveillance systems, focusing on various technical aspects:

- national coordination, stakeholder meetings and development of national AMR action plans;
- CAESAR methods, data collection (among others, WHONET) and data analysis;
- quality control, standard operating procedures, EUCAST guidelines and interpreting antibiotic susceptibility testing data;
- the tasks of an AMR reference laboratory in terms of national coordination of the laboratory network, quality assurance and confirming results; and
- a proof-of-principle study to stimulate sampling habits, routine susceptibility testing and antibiotic stewardship, with Chapter 9 describing the preliminary results from the first proof-of-principle study that is running in Tbilisi, Georgia.

Continued support and collaboration within the CAESAR network among countries and partners is fundamental in the continued process of building a network of national AMR surveillance systems in all countries of the European Region.


CHAPTER
3

Data collection and analysis

3.1. Data collection procedures

CAESAR collects susceptibility test results of invasive isolates and background information about patients from national AMR surveillance networks following a data request to the national AMR focal point. The data are prepared by the national data manager and transferred electronically to the CAESAR international data manager at the National Institute for Public Health and the Environment. The national AMR focal point and national data manager are responsible for collecting data from the laboratories in the national surveillance network. Network laboratories are asked to report antimicrobial susceptibility results for the first isolate from blood or cerebrospinal fluid (CSF) per patient per year, including additional isolate and patient information for a prespecified number of bacterial species and antimicrobial agents. Data are collected and compiled according to the specifications of the CAESAR exchange format *(1)*, which is compatible with the format of the EARS-Net *(2)*.

CAESAR collects antibiotic susceptibility testing data for eight bacterial species of public health and clinical importance:

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Acinetobacter* species
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- *Enterococcus faecalis*
- *Enterococcus faecium*.

The CAESAR manual contains a panel of antimicrobial agents, recommended by EUCAST and the ESCMID Study Group for Antimicrobial Resistance Surveillance to detect resistance mechanisms. Other antimicrobial agents may be collected as well but not analysed.

Once data are submitted to CAESAR, data are analysed and the results are reported back to the AMR focal point by a standardized feedback report. This feedback report gives the proportion of resistance for the important antimicrobial groups, information on pathogens with important or unusual resistance patterns and information on the validity and completeness of the data. Subsequently, the AMR focal point is asked to verify the results and, if needed, update the data. After approval, the data are added to the CAESAR database. The country- and area-specific data presented in Chapters 6 and 7, respectively, have been prepared together with the the respective AMR focal points and published with their final approval.

In addition to the bacterial species listed in the CAESAR manual, countries are encouraged to include pathogen–antibiotic combinations in their surveillance system that are of national concern or relevance.

3.2 Analysis

Antimicrobial susceptibility results are presented as the proportion of isolates of a specific microorganism that are resistant (R) or non-susceptible intermediate and resistant (I+R) to a specific antimicrobial agent: for example, the number of *E. coli* resistant to ciprofloxacin divided by the total number of *E. coli* in which susceptibility to ciprofloxacin was tested. The resistance proportions are rounded off to the nearest whole percentage. The resistance proportions are generally calculated for antibiotic groups or antibiotic classes by combining the results of antibiotics representative for a group or class and basing the outcome on the most resistant result; for example, if *E. coli* susceptibility to imipenem is I and susceptibility to meropenem is R, the susceptibility to carbapenem is set to R. The footnotes to the resistance tables in the country-specific chapters and the CAESAR manual specify which antibiotic combinations are used in analysis.

The R and I+R interpretations are based on the clinical breakpoint criteria used by local laboratories. CAESAR encourages countries to adopt national standards for antibiotic susceptibility testing and promotes the use of internationally accepted guidelines such as EUCAST and CLSI. If fewer than 30 antibiotic susceptibility testing results for a specific microorganism–antimicrobial agent combination have been submitted, the results are marked, indicating that they should be interpreted with caution.


CHAPTER
4

Pathogens under CAESAR surveillance

The following text on pathogens under CAESAR surveillance was adopted from the *Antimicrobial resistance: global report on surveillance 2014* published by WHO *(1)* and the annual report of the EARS-Net published by the ECDC in 2015 *(2)*.

4.1 *Escherichia coli*

E. coli is part of the normal microbiota in the intestine in humans and animals. Nevertheless, it:

- is the most frequent cause of community-acquired and frequent cause of hospital-acquired urinary tract infections (including pyelonephritis);
- is the most frequent cause of bloodstream infection among people of all ages;
- is associated with intra-abdominal infections such as peritonitis;
- causes meningitis in neonates; and
- is one of the leading causes of foodborne infections worldwide.

Infections with *E. coli* usually originate from the person affected (autoinfection), but strains with a particular resistance or disease-causing properties can also be transmitted from animals, through the food chain or between individuals.

4.1.1 Evolution of AMR in *E. coli*

Resistance in *E. coli* readily develops either through mutation, which is often the case for fluoroquinolone resistance, or by acquisition of mobile genetic elements, which has been the case for broad-spectrum penicillins (such as ampicillin or amoxicillin) and resistance to third-generation cephalosporins and carbapenems. Resistance to third-generation cephalosporins is mainly conferred by enzymes known as extended-spectrum beta-lactamases (ESBLs); these enzymes degrade many beta-lactam drugs. ESBLs are transmissible between bacteria of the same species and even between different genera. Because *E. coli* strains that produce ESBL are generally also resistant to several other antibacterial drugs, carbapenems and piperacillin-tazobactam, which resist the effects of ESBLs, might remain as the only available treatment option for severe infections. A recently emerging threat is carbapenem resistance in *E. coli* mediated by a range of carbapenemases, which may confer resistance to virtually all available beta-lactam antibacterial drugs. Colistin is being used with increased frequency for otherwise pan-resistant gram-negative nosocomial infections, and colistin resistance is still very rare. However, of particular concern is the plasmid-mediated resistance to colistin (MCR-1), which was first described in *E. coli* isolated from food animals in China and subsequently found in clinical isolates from hospitalized patients in various parts of the world.

4.2 *Klebsiella pneumoniae*

Like *E. coli*, bacteria of the species *K. pneumoniae* are frequent colonizers of the gut in humans, particularly those with a history of hospitalization, and other vertebrates. Infections with *K. pneumoniae* are

particularly common in hospitals among vulnerable individuals such as preterm infants and patients with impaired immune systems, diabetes or alcohol-use disorders and those receiving advanced health care. Most common are urinary and respiratory tract infections and, among neonates, bloodstream infections. *K. pneumoniae* is a common cause of gram-negative bloodstream infections. Like other bacteria in healthcare settings, *K. pneumoniae* can spread readily between patients, leading to nosocomial outbreaks. This frequently occurs in intensive care units and neonatal care facilities. The mortality rates for hospital-acquired *K. pneumoniae* infections depend on the severity of the underlying condition, even when people are treated with appropriate antibacterial drugs.

4.2.1 Evolution of AMR in *K. pneumoniae*

Similar to *E. coli*, *K. pneumoniae* acquires resistance to multiple antibacterial drugs mainly through horizontal transfer of mobile genetic elements such as transposons or plasmids. In contrast to *E. coli, K. pneumoniae* carries a resistance gene (chromosomally located beta-lactamase) that naturally renders penicillins with an extended spectrum ineffective, such as ampicillin and amoxicillin. Resistance to other widely used and available oral antibacterial drugs such as co-trimoxazole and fluoroquinolones (such as ciprofloxacin) has emerged and spread globally. Thus, few options remain for the oral treatment of *Klebsiella* infections in many parts of the world. Extended-spectrum beta-lactamases and carbapenemases are found more frequently in *K. pneumoniae* than in *E. coli*. Colistin resistance in *K. pneumoniae* is still rare, although colistin-resistant strains have been described to cause outbreaks in settings with high rates of carbapenem resistance.

4.3 *Pseudomonas aeruginosa*

P. aeruginosa is a non-fermentative gram-negative bacterium that is ubiquitous in aquatic environments in nature. It is an opportunistic pathogen for plants, animals and humans and is a major and dreaded cause of infection among hospitalized patients with localized or systemic impairment of immune defences. It commonly causes hospital-acquired pneumonia (including ventilator-associated pneumonia) and bloodstream and urinary tract infections. Because of its ubiquity, enormous versatility and intrinsic tolerance to many detergents, disinfectants and antimicrobial compounds, controlling *P. aeruginosa* in hospitals and institutional environments is difficult. Among people with cystic fibrosis, *P. aeruginosa* causes severe bacterial complication, leading to chronic colonization and intermittent exacerbation of the condition with, for example, bronchiolitis and acute respiratory distress syndrome. Finally, *P. aeruginosa* is common in burn units, where eradicating colonizing strains with classic infection control procedures is almost impossible.

4.3.1 Evolution of AMR in *P. aeruginosa*

P. aeruginosa is intrinsically resistant to most antimicrobial agents because of its selective ability to exclude various molecules from penetrating its outer membrane. The antimicrobial classes that remain active include some fluoroquinolones (such as ciprofloxacin and levofloxacin), aminoglycosides (such as gentamicin, tobramycin and amikacin), some beta-lactams (piperacillin-tazobactam, ceftazidime, cefepime, imipenem, doripenem and meropenem) and polymyxins (polymyxin B and colistin). Resistance of *P. aeruginosa* to these agents can be acquired through one or more mechanism, including modified antimicrobial targets, active efflux, reduced permeability and degrading enzymes. Acquired resistance results from mutational changes in the bacterium and acquisition of plasmid-mediated resistance genes. A growing concern is the emergence and spread of multidrug-resistant *P. aeruginosa* in intensive care units: resistant to three or more classes of antimicrobial agents, often including carbapenems. Such resistance is due partly to the dissemination of carbapenemases in this species. Although still rare, colistin resistance is of particular concern among people with burns and cystic fibrosis.

4.4 *Acinetobacter* spp.

The *Acinetobacter* genus comprises many species that can be roughly divided between the *Acinetobacter baumannii* group (consisting of the species *A. baumannii, A. pittii* and *A. nosocomialis*) and the *Acinetobacter* non-*baumannii* group (consisting of many environmental species with low pathogenicity). The correct identification of isolates at the species level within the *Acinetobacter* genus is challenging and is usually only possible with genotypic methods. Recently, mass spectrometry offers the possibility of at least identifying isolates that belong to the *A. baumannii* group, which is by far the most clinically important group of species within this genus.

Species belonging to the *A. baumannii* group have been identified as pathogens in nosocomial pneumonia (particularly ventilator-associated pneumonia), central line-associated bloodstream infections, urinary tract infections, surgical site infections and other types of wound infection. Although many species of the *Acinetobacter* genus are considered ubiquitous in nature, this is not the case with the species that belong to the *A. baumannii* group. The rates of carrying species belonging to the *A. baumannii* group on the skin and in the faeces have been reported to be very low.

Risk factors for infection with the *A. baumannii* group include advanced age, the presence of serious underlying diseases, immune suppression, major trauma or burn injuries, invasive procedures, presence of indwelling catheters, mechanical ventilation, extended hospital stay and previous administration of antimicrobial agents. The risks for acquiring a multidrug-resistant strain of the *A. baumannii* group are similar and also include prolonged mechanical ventilation, prolonged intensive care unit or hospital stay, exposure to infected or colonized patients, increased frequency of interventions, increased disease severity and receiving broad-spectrum antimicrobial agents, especially third-generation cephalosporins, fluoroquinolones and carbapenems.

4.4.1 Evolution of AMR in *Acinetobacter* spp.

Acinetobacter spp., especially those belonging in the *A. baumannii* group, are intrinsically resistant to most antimicrobial agents due to their selective ability to exclude various molecules from penetrating their outer membrane. The antimicrobial classes that remain active include some fluoroquinolones (such as ciprofloxacin and levofloxacin), aminoglycosides (such as gentamicin, tobramycin and amikacin), carbapenems (imipenem, doripenem and meropenem), polymyxins (polymyxin B and colistin) and, to some extent, sulbactam and tigecycline. The resistance of *Acinetobacter* spp. to these agents can be acquired through one or more of several mechanisms, including modified antimicrobial targets, active efflux, reduced permeability and degrading enzymes. Acquired resistance results from mutational changes in the bacterium and acquisition of plasmid-mediated resistance genes. A growing concern is the emergence and spread of multidrug-resistant *Acinetobacter* spp. in intensive care settings: resistant to three or more classes of antimicrobial agents, most commonly including carbapenems. Multidrug resistance in *Acinetobacter* spp. is frequently due to the dissemination of carbapenemases. In settings with high carbapenem resistance rates, colistin is usually the only effective antibiotic left. With an increase in colistin use, colistin resistance is emerging, mostly among carbapenem-resistant *A. baumannii* strains.

4.5 *Staphylococcus aureus*

S. aureus is a gram-positive bacterium that can be part of the normal microbiota on the skin and in the nose but is another of the most important human pathogens. *S. aureus* can cause a variety of infections, most notably skin, soft tissue, bone and bloodstream infections. It is also the most common cause of postoperative wound infections. Some strains of *S. aureus* produce toxic factors that can cause a variety of specific symptoms, including toxic shock syndrome and food poisoning. Several successful *S. aureus* clones are responsible for most of the international spread and outbreaks in healthcare and community

settings. A recent structured survey showed that the most prevalent clones among methicillin-resistant *S. aureus* (MRSA) in EU countries are ST22 (EMRSA15), ST225 (New York/Japan), ST8 (US300), ST5 (New York/Japan), and ST8 (South German) *(3)*. Among methicillin-susceptible *S. aureus*, the most prevalent clones are ST7, ST15, ST5, ST45 and ST8. The clonal structure of MRSA and methicillin-susceptible *S. aureus* in the CAESAR countries remains to be determined.

4.5.1 Evolution of AMR in *S. aureus*

When penicillin was first introduced in the 1940s, it was an effective treatment for *S. aureus* infections, but resistance had already developed within a few years of its introduction. This resistance was mediated by the production of a beta-lactamase enzyme that inactivates drugs such as penicillin, ampicillin and amoxicillin. Consequently, beta-lactamase-stable drugs (such as methicillin and cloxacillin) as well as beta-lactamase inhibitors (such as clavulanic acid and sulbactam) that could be combined with the antibacterial drugs were developed. Strains of *S. aureus* resistant to these penicillinase-stable antibacterial drugs have acquired a novel gene (*mecA*, recently also *mecC*) that encodes a novel penicillin-binding protein; these strains are termed MRSA.

The first strains of MRSA emerged during the 1960s. Initially, MRSA was mainly a problem in hospital-acquired infections. During the past decade, community-acquired MRSA has increased significantly in several countries. Fortunately, many of these community-acquired MRSA strains have retained susceptibility to several non-beta-lactam antibiotics, whereas most healthcare-associated MRSA infections are caused by difficult-to-treat multidrug-resistant strains. For the latter, the treatment of last resort has been glycopeptides such as vancomycin (since the 1950s) and teicoplanin, which can only be given by injection and also needs careful monitoring to avoid adverse side-effects. New treatment options for MRSA (but also associated with problematic side-effects) have been developed more recently: linezolid (1970s) *(4)* and daptomycin (1980s) are the most recently licensed antibacterial drug classes. In the last few years, some novel cephalosporins with activity against MRSA have also been developed (ceftaroline and ceftobiprole).

4.6 *Streptococcus pneumoniae*

S. pneumoniae is the leading cause of community-acquired pneumonia worldwide, which is among the leading causes of death of children younger than five years. Other diseases caused by *S. pneumoniae* include common, mild, self-limiting infections such as acute otitis media but also extend to cases of invasive disease with high mortality such as meningitis. Among the bacterial causes of meningitis, *S. pneumoniae* is associated with the highest case-fatality rate and is the most likely to leave survivors with permanent residual symptoms. The clinical burden of pneumococcal infection is concentrated among the oldest and youngest sections of the population. According to one estimate, *S. pneumoniae* caused about 826 000 deaths (582 000–926 000) among children 1–59 months old. For HIV-negative children, pneumococcal infection corresponds to 11% of all deaths in this age group *(5)*. Pneumococci are commonly found as asymptomatic nasopharyngeal carriage, where the prevalence varies by age and region. The asymptomatic carriage state is responsible for much of the transmission within populations, such as in childcare centres.

4.6.1 Evolution of AMR in *S. pneumoniae*

Resistance to beta-lactam antibacterial drugs in clinical isolates of *S. pneumoniae* occurs by acquiring mutations in the genes coding for the penicillin-binding proteins, which are essential components of the bacterial cell wall and the main target of beta-lactam antibiotics. The successive acquisition of multiple mutations in the penicillin-binding proteins results in increasing minimum inhibitory concentrations for penicillin and the other beta-lactam drugs. Different clinical breakpoints exist depending on the site of the *S. pneumoniae* infection (meningitis, bloodstream and lungs) as well as dosing regimens. Use of variable

clinical breakpoints to interpret antibiotic susceptibility testing makes combining results and comparing results difficult. If known, tables in this report will state which clinical breakpoints were used to interpret penicillin susceptibility at the laboratory level.

4.7 *Enterococcus faecium* and *Enterococcus faecalis*

Enterococci belong to the normal bacterial microbiota of the gastrointestinal tract of both humans and other animals. Enterococci are usually low-pathogenic but can cause invasive disease under certain circumstances. Recently, the recognition of high-risk clones suggests that some strains can act as true pathogens and not only as opportunistic commensals. Enterococci can cause a variety of infections, including endocarditis, bloodstream and urinary tract infections, and are associated with peritonitis and intra-abdominal abscesses. In the United States of America, enterococci cause 3–4 nosocomial bloodstream infections per 10 000 hospital discharges and contribute to increasing mortality as well as additional hospital stay.

E. faecalis and *E. faecium* cause the vast majority of clinical enterococci infections in humans. Epidemiological data collected over the last two decades have documented the emergence of enterococci as important nosocomial pathogens, exemplified by the expansion of a major hospital-adapted polyclonal subcluster clonal complex 17 (CC17) in *E. faecium* and by CC2 and CC9 in *E. faecalis*. The latter clones have even been isolated from farm animals. The emergence of particular clones and clonal complexes of *E. faecalis* and *E. faecium* was paralleled by increases in resistance to glycopeptides and high-level resistance to aminoglycosides. These two antimicrobial classes represent the few remaining therapeutic options for treating human infections caused by *E. faecium* when resistance has emerged against penicillins. Besides the fact that infections caused by resistant strains are difficult to treat, enterococci are highly tenacious and thus easily disseminate in the hospital setting.

4.7.1 Evolution of AMR in enterococci

Enterococci are intrinsically resistant to a broad range of antimicrobial agents, including cephalosporins, sulphonamides and low concentrations of aminoglycosides. Patient safety in hospitals is challenged by the ability of enterococci to acquire additional resistance by transferring plasmids and transposons and recombining or mutating. By nature, enterococci have low susceptibility to many beta-lactam antibiotics because of their low-affinity penicillin-binding proteins. Resistance to aminopenicillin is currently rare in *E. faecalis*. The first choice for treating infections caused by this microorganism is therefore still an aminopenicillin such as ampicillin. In *E. faecium*, ampicillin resistance has increased significantly in recent years, especially because of the wide dissemination of ampicillin-resistant strains belonging to the polyclonal subcluster CC17.

In addition to the intrinsic mechanism of low-level resistance to aminoglycosides, which causes a low uptake of the drug, enterococci have acquired genes conferring high-level resistance to aminoglycosides. The bifunctional APH(2″)/AAC(6′) enzyme confers high-level resistance to all aminoglycosides except streptomycin and is now widespread across Europe. With high-level resistance, any synergistic effect between beta-lactams and glycopeptides is lost.

Glycopeptide resistance is due to the synthesis of modified cell wall precursors that show a decreased affinity for glycopeptides. Six phenotypes have been identified, of which two have clinical relevance: VanA, with high-level resistance to vancomycin and a variable level of resistance to teicoplanin; and VanB, with a variable level of resistance in most cases to vancomycin only. The VanA and VanB phenotypes, mostly found among *E. faecalis* and *E. faecium*, may be transferred by mobile genetic elements.


CHAPTER
5

Reader's guide

5.1 Data validity

The goal of the AMR surveillance data collected and presented in this report is to provide a valid description of the antimicrobial susceptibility of common bacterial pathogens found in invasive infections to the main antimicrobial groups indicated for treatment of these infections. In other words, the aim is to provide the average susceptibility pattern of bacteria for patients presenting with a bloodstream or central nervous system infection in a country (the target population). The sample of patients included in surveillance should aim to consist of a mix of patient types (such as children or intensive care unit or neurosurgery patients) and infection types (such as community-acquired urosepsis or healthcare-associated bloodstream infections) in proportion to their occurrence in the total population.

The validity of data may be negatively affected at different points in the data generation process: the selection of hospital laboratories that participate in the surveillance programme; the selection of patients for blood culturing in the clinic; the processing of samples in the laboratory; and the aggregation and analysis of the data. In some countries, limiting conditions outside the direct control of the national AMR surveillance system may exist that reduce the validity because they influence the selection of patients eligible for blood or CSF culturing or the quality of antibiotic susceptibility testing performed. Many different healthcare and public health professionals are involved in the many steps of the data generation process, requiring commitment and training at different levels to ensure high-quality data. Several sources of error and bias in AMR surveillance data are presented in Table 5.2 and are discussed in detail in Annex 1.

5.2 Level of evidence

To guide the interpretation of the data, the authors together with the national focal points have come to a qualitative assessment about the level of evidence for each country-specific data chapter.

Level A The data provide an adequate assessment of the magnitude and trends of AMR in the country.

Level B The data provide an indication of the resistance patterns present in clinical settings in the country, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of AMR in the country.

Level C The data do not provide an adequate assessment of the magnitude and trends of AMR in the country. The current surveillance system forms a good basis for improvements needed to enable valid assessment of the AMR situation.

The level of evidence judgement concerns the specific goals of a regional surveillance system such as CAESAR. A country at level A is judged to provide data that enable valid and reproducible assessment of AMR trends in the country. A national surveillance system that aims to provide detailed information to guide policy will have different and more stringent requirements (see below).

Importantly, the results labelled as level B are not necessarily wrong but rather less generalizable to the target population due to errors and biases in the data generation process. Data may not yet be optimal: there are issues leading to biased results. Nevertheless, the authors feel it is important to present the level B data. Publication of level B surveillance data enables the critical appraisal of sources of error and bias, which is important input for improvements. Any suboptimal data presented in this report should be seen as a point of departure for further improvement.

Although level C signifies data that do not adequately assess the magnitude and trends of AMR in a country, this does not mean that there is no value in sharing these data. The purpose of introducing level of evidence C is to invite countries to share data early in the process of setting up national surveillance and to motivate them to improve the quality and representativeness of the data. Nevertheless, the reader is advised to interpret the results with caution while the surveillance system is still improving and to refrain from direct comparison with other countries.

To arrive at the level of evidence, several aspects of each national AMR surveillance system that could negatively affect the validity of the data were assessed.

1. **Surveillance system**
   a. Geographical coverage (Were all major geographical regions represented?)
   b. Selection of surveillance sites (Were all major hospital types represented?)

2. **Sampling procedures**
   a. Selection of patients (Were all major patient groups presenting with suspected invasive infections sampled?)
   b. Sample size (Were at least 30 isolates per pathogen available?)

3. **Laboratory procedures:**
   a. Antibiotic susceptibility testing methods (Were all isolates tested for each relevant antibiotic group and using current methodological standards? Was a national quality assurance system active?)
   b. Antibiotic susceptibility testing breakpoints (Was a harmonized and up-to-date breakpoint system used?)

Table 5.1 provides an overview of the level of evidence for each country and the underlying assessment of the data.

Table 5.1 Level of evidence and scoring of factors affecting data validity for CAESAR 2015

		Belarus	Bosnia and Herzegovina	The former Yugoslav Republic of Macedonia	Russian Federation	Serbia	Switzerland	Turkey	Kosovo[a]
Level of evidence		B	B	B	B	B	A	A	B
Surveillance system	Geographical coverage	+	+	+	+	+	+	+	+/–
	Hospital types	+	+/–	–	–	–	+	+	–
Sampling procedures	Selection of patients	–	+/–	–	–	+/–	+	+/–	–
	Sample size	+	+	–	–	+	+	+	–
Laboratory procedures	Antibiotic susceptibility testing methods	+/–	+	+	+	+	+	+	+
	Antibiotic susceptibility testing breakpoints	+/–	+/–	+	+	+	+	+	+

[a] In accordance with United Nations Security Council resolution 1244 (1999).

The scoring of factors affecting the validity of the data in Table 5.1 also provides important guidance on which elements need to be improved to advance in the level of evidence.

Table 5.2 Sources of error and bias in AMR surveillance data

Type of error or bias		Mechanism	Solution
Random error	Sampling variation	Coincidence	Increase sample size
	Measurement variation	Test-to-test variation in the application of laboratory procedures	Increase sample size Standardize procedures Laboratory staff training Implement laboratory quality management systems
Systematic error	**Bias due to sampling procedures**		
	Selection of participating sites	Sampling special patient populations only, such as tertiary hospitals, intensive care units and urban centres	Select a mixture of hospital types and departments from different geographical regions
	Selection of patients	Sampling only severe cases or after treatment failure	Improve case ascertainment: promote sampling of all cases with signs of bloodstream infection before initiating treatment
	Bias due to laboratory procedures		
	Laboratory standards	Use of non-uniform antibiotic susceptibility testing methods. such as breakpoints from product inserts and out-of-date standards Sequential testing, such as testing carbapenem only if there is resistance to third-generation cephalosporin	Use national standards based on international standards for antibiotic susceptibility testing methods (such as EUCAST) Test susceptibility to all indicator antimicrobial agents (uniform test panel) on all microorganisms
	Measurement error	Improper application of laboratory methods, such as use of too large an inoculum Inadequate laboratory materials, such as use of expired or non-quality-controlled antimicrobial disks Damaged, poorly calibrated, equipment, such as out-of-date firmware used with automated systems	Laboratory staff training Implement laboratory quality management systems Confirmatory testing of highly resistant microorganisms Procurement of high-quality and quality-controlled materials
	Bias from data aggregation and analysis procedures		
		Include repeat isolates from individual patients Use of varying expert rules, such as different rules for deriving resistance used in each laboratory	Collect raw data Use standardized data aggregation and analysis methods

5.3 What do the AMR results mean?

Level A data provide an adequate assessment of the magnitude and trends of AMR in the country. However, because the total sample of patients comprises a mix of community-acquired and healthcare-associated

infections, the proportions of resistance presented in this report should not be used as the sole source for informing empirical treatment choices. To guide empirical treatment, more comprehensive and clinically well characterized local AMR surveillance data are needed, to allow the assessment of resistance patterns in specific patient populations (such as children or intensive care unit patients), specific infection types (such as community-acquired versus healthcare-associated, urosepsis versus central line–associated bloodstream infection versus pyelonephritis versus severe pneumonia) and treatment status (before and after empirical antibiotic treatment).

With level B data, by definition, the magnitude of resistance presented is biased and thus precludes the data from being used for guiding empirical antibiotic treatment choices. However, the data do indicate the presence of highly resistant microorganisms of public health importance in clinical settings in the country. Although additional studies are needed to assess the exact magnitude and spread of these highly resistant microorganisms through the healthcare system, they do indicate that infection prevention and control measures are acutely needed to control the problem.

Level C data should not be used to inform empirical antibiotic treatment choices or AMR control policy, because bias in the data does not provide an adequate assessment of the AMR situation in the country. Despite this, these data may still indicate the presence of resistance and can be used to advocate for further improvements in the laboratory capacity to increase the validity and applicability of the diagnostic results.

5.4 Comparing countries

The resistance proportions for selected pathogen-antibiotic combinations are presented on maps in Chapter 8. Variation in sampling procedures (including selective sampling) and laboratory standards influences the comparability of resistance proportions between countries. The resistance proportions between countries should be compared with care, especially for countries with level B data in which the magnitude of resistance is likely to be biased. Countries providing level B data are shaded in the maps in Chapter 8 to remind the reader to interpret the data cautiously.


CHAPTER
6

Country-specific data on AMR

6.1 Belarus

6.1.1 Surveillance set-up

All the results from routine antibiotic susceptibility testing of clinical bacteriology cultures of 16 (2014) and 50 (2015) clinical microbiology laboratories in Belarus are collected with WHONET software and sent by email on a quarterly basis. Data are collected by the team from the national reference centre for AMR: the Laboratory for Clinical and Experimental Microbiology of the Republican Research and Practical Center for Epidemiology and Microbiology in Minsk. The data received by email are processed; their quality and consistency are checked. Errors are fed back to the laboratories and corrected where applicable. Confirmatory testing of highly resistant microorganisms and unexpected phenotypes is recommended, but the results are not always available due to problems in isolate selection, storage and transferral to the national reference centre for AMR, due to the high workload and for logistical reasons. A subset of antibiotic susceptibility testing results, containing all first isolates from blood and CSF cultures per patient yielding organisms specified by CAESAR for the periods 1 January 2014 to 31 December 2014 and 1 January 2015 to 31 December 2015 were provided to CAESAR.

In 2014, the 16 participating laboratories provided diagnostic support for 70 hospitals, including the national clinical research practical centres. The participating laboratories are geographically spread out, but some large Belarusian urban centres and regions are underrepresented because they use laboratory software incompatible with WHONET. The largest part of the data (about 60%) represents the laboratory of the Minsk City Centre of Hygiene and Epidemiology, which provides diagnostic support for the majority of Minsk clinics (about 30% of the Belarusian population). In 2015, the AMR surveillance network was expanded to cover about 80% of the hospitals and 80% of the Belarusian population.

Antimicrobial susceptibility is mostly tested using the disk diffusion method and automated systems. Some laboratories are able to use gradient tests for selected combinations of microorganisms and antimicrobial agents or for confirmation purposes. All laboratories apply quality management systems and are audited regularly by the responsible organizations (ISO/IEC 17025:2005). Since 2013, eight laboratories from all regions of Belarus take part in the international (CAESAR and UK NEQAS) external quality assessment exercise. Also since 2013, four national laboratories, including the national reference centre for AMR, take part in the WHO globally coordinated external quality assessment programme for the WHO Global Invasive Bacterial Vaccine Preventable Diseases Laboratory Network.

Laboratories are required to follow the national guidelines on bacteriological methods published in 2009. For antibiotic susceptibility testing methods and interpretation, Belarus has adopted CLSI 2004 methods as the national standard. About half the laboratories submitting data to CAESAR use more recent CLSI or EUCAST guidance (2012–2014). Automated systems are configured to use 2009–2012 CLSI or EUCAST guidance in accordance with the manufacturer's updates.

According to national clinical guidelines, blood cultures should be taken from all patients presenting in hospital for which there is reasonable suspicion of bloodstream infections (bacteraemia, sepsis, endocarditis), and CSF cultures should be taken from patients suspected of having meningitis. For all inpatients with pneumonia, sputum culture is mandatory, but a blood culture must be taken only if the patient was hospitalized in an intensive care unit or has severe complications or risk factors (liver cirrhosis, chronic alcoholism, pleural effusion or immunodeficiency). A blood sample is not taken for urinary tract infections, skin infections, enteric infections, central neural system infections or respiratory tract

infections (except pneumonia). Bacteriological cultures and antibiotic susceptibility testing are funded by the national budget. However, logistic issues and lack of funding, laboratory equipment and reagents (blood culture instruments and blood culture bottles) might be the reason for the low number of positive cultures, especially at the regional level, where the laboratories are not equipped with automated blood culture systems.

6.1.2 Results

2014

Table 6.1 shows the patient characteristics of 1361 isolates from Belarus, by pathogen. In *E. coli*, resistance was 37% for aminoglycosides and higher for all tested antimicrobial agents except for carbapenems (2%, Table 6.2). Multidrug resistance was 29% in *E. coli*. Resistance in *K. pneumoniae* ranged from 52% for carbapenems to 90% for third-generation cephalosporins. Multidrug resistance in *K. pneumoniae* was 74%. In *P. aeruginosa*, resistance ranged from 64% for ceftazidime to 91% for fluoroquinolones (Table 6.3). Multidrug resistance was 90% in *P. aeruginosa*. Resistance in *Acinetobacter* spp. was 72% or higher for all agents. Multidrug resistance in *Acinetobacter* spp. was 60%. Forty-five per cent of *S. aureus* isolates were MRSA (Table 6.4). One per cent of the isolates were resistant to linezolid. Based on only 12 *S. pneumoniae* isolates, 50% were resistant to penicillins and 50% to macrolides (Table 6.5). Multidrug resistance in *S. pneumoniae* was 45%. In *E. faecalis*, vancomycin resistance and linezolid non-susceptibility were 1% and 2%, respectively (Table 6.6). In *E. faecium*, 11% were resistant to vancomycin, and 4% linezolid non-susceptibility was found.

2015

Table 6.7 shows the patient characteristics of 1348 isolates from Belarus, by pathogen. In *E. coli*, resistance was 41% for aminoglycosides and higher for all tested antimicrobial agents except for carbapenems (2%, Table 6.8). Multidrug resistance was 38% in *E. coli*. Resistance in *K. pneumoniae* ranged from 58% for carbapenems to 88% for third-generation cephalosporins. Multidrug resistance in *K. pneumoniae* was 69%. In *P. aeruginosa*, resistance ranged from 65% for piperacillin or piperacillin-tazobactam to 86% for fluoroquinolones (Table 6.9). Multidrug resistance was 85% in *P. aeruginosa*. Resistance in *Acinetobacter* spp. was 59% or higher for all agents. Multidrug resistance in *Acinetobacter* spp. was 48%. Forty-eight per cent of *S. aureus* isolates were MRSA (Table 6.10). In *S. pneumoniae*, 47% were resistant to penicillins and 59% to macrolides (Table 6.11). Multidrug resistance in *S. pneumoniae* was 35%. However, because of the relatively low number of isolates, the results for *S. pneumoniae* should be interpreted with caution. In *E. faecalis*, vancomycin resistance and linezolid non-susceptibility were both 3% (Table 6.12). In *E. faecium*, 16% were resistant to vancomycin, and 2% linezolid non-susceptibility was found.

6.1.3 Discussion

The AMR surveillance network of Belarus submitted antibiotic susceptibility testing results for 1361 isolates from blood or CSF in 2014 and the results for 1348 isolates in 2015. Although the surveillance network comprised 16 laboratories in 2014, only 10 provided data on invasive isolates, and 84% of isolates came from two laboratories serving hospitals in Minsk, limiting the national representativeness of the data. In 2015, the number of laboratories providing data on invasive isolates expanded to 18, and 80% were from the two laboratories serving hospitals in Minsk. No national guidance on the minimal set of antimicrobial agents to be tested was implemented in Belarus in 2014 and 2015. Laboratories varied with regard to the antibiotic groups tested, which suggests sequential or selective testing in some laboratories. This may have led to overestimation or underestimation of resistance, depending on the selection and the resistance mechanism. A mix of breakpoints was used to interpret antibiotic susceptibility testing; both CLSI 2004 and more recent (2012–2014) CLSI and EUCAST guidelines were used for interpreting disk diffusion, and CLSI or EUCAST (2012–2014) breakpoints were used for automated antibiotic susceptibility testing. In particular, carbapenem resistance in Enterobacteriaceae may be underestimated when old breakpoint guidelines are used.

Relatively many isolates were from patients admitted to an intensive care unit. Compared with other species, few *E. coli* and many *Acinetobacter* spp. were isolated. In general, high percentages of resistance were found for all pathogens. The combination of an overrepresentation of intensive care unit patients, a skewed distribution of pathogens and high percentages of resistance indicates selective sampling of patients, such as severely ill patients with a history of hospitalization and antibiotic treatment, patients who failed to respond to empirical antimicrobial treatment or patients from wards with high selective pressure of antimicrobial agents and risk of transmission of highly resistant microorganisms. This interpretation is in accordance with low utilization of blood culture diagnostics by Belarusian clinicians, except for severely ill patients admitted to intensive care unit or patients for whom initial antibiotic treatment has failed. The reported percentages of resistance disproportionately reflect nosocomial infections, should be interpreted with caution and are not generalizable to any one patient presenting with invasive infections in Belarus, especially patients with community-acquired infections.

Nevertheless, the data suggest that resistance to third-generation cephalosporins, likely mediated by extended-spectrum beta-lactamases (ESBLs), was common in the patient population sampled. The data also suggest the spread of carbapenem-resistant clones of *K. pneumoniae*. The high aminopenicillin resistance in *E. faecalis* may reflect problems with species identification (inclusion of *E. faecium*, which more often is resistant to aminopenicillins). The level of MRSA was similar to that of countries close to Belarus (Fig. 8.6). The 1% linezolid resistance in *S. aureus* in 2014 is an unusual finding, and false-positive automated test results are the most likely explanation. Too few antibiotic susceptibility testing results for *S. pneumoniae* were available to allow interpretation. The high levels of resistance in *P. aeruginosa* and *Acinetobacter* spp. are concerning and may reflect the expansion of resistant clones in the healthcare setting.

The data from Belarus are assessed as level B. The representativeness of the results is limited by the overrepresentation of more severely ill and pretreated patients (selective sampling of patients), the majority from hospitals in Minsk. The interpretation of the antibiotic susceptibility testing results is limited by the absence of harmonized breakpoint guidelines and by sequential testing of isolates in some laboratories. Improvements in this respect are anticipated, following a workshop for representatives of all network laboratories in November 2016. The data indicate the resistance patterns present in clinical settings in the country, but the proportion of resistance should be interpreted with care. Belarus has an active AMR surveillance network. Implementing harmonized antibiotic susceptibility testing methods and breakpoints and increasing blood culturing diagnostic utilization will lead to attaining a more valid assessment of AMR in the country. The readers' guide (Table 5.1) provides additional information on interpreting the data and how the level of evidence was determined.

Chapter 8 displays the proportions of resistance for selected pathogen–antibiotic combinations reported by Belarus in maps of the WHO European Region (Fig. 8.1–8.6). Besides the data from the CAESAR network countries and areas, the maps present data from the EARS-Net at the ECDC.

Table 6.1 Patient characteristics of 1361 isolates from Belarus in 2014, by pathogen

	E. coli	*K. pneumoniae*	*P. aeruginosa*	*Acinetobacter* spp.	*S. aureus*	*S. pneumoniae*	*E. faecalis*	*E. faecium*	**Total number of isolates**
Number of isolates; *n* (%)	57 (4)	234 (17)	79 (6)	346 (25)	395 (29)	12 (1)	158 (12)	80 (6)	**1361**
Isolate source (%)									
Blood	100	98	87	90	97	58	95	95	**1286**
Cerebrospinal fluid	0	2	13	10	3	42	5	5	**75**
Sex (%)									
Male	37	33	49	38	53	42	55	40	**602**
Female	33	18	15	21	30	25	20	29	**319**
Unknown	30	49	35	41	18	33	25	31	**440**
Age in years (%)									
0–4	7	8	5	8	3	0	5	14	**84**
5–19	0	2	4	2	1	8	1	1	**21**
20–64	35	32	43	44	69	58	47	39	**668**
65 and over	30	15	20	12	15	17	28	23	**233**
Unknown	28	44	28	34	12	17	19	24	**355**
Hospital department (%)									
Emergency department	0	0	0	0	0	0	0	3	**2**
Infectious disease ward	2	1	3	1	2	8	0	3	**21**
Internal medicine	0	0	0	0	2	0	0	1	**10**
Surgery	12	17	15	15	12	8	13	21	**196**
Urology	2	0	0	0	1	0	6	1	**13**
Intensive care unit	39	32	32	45	50	67	31	38	**561**
Paediatrics or neonatal	2	6	0	4	0	0	1	3	**33**
Paediatric or neonatal intensive care unit	0	0	0	1	0	0	1	0	**3**
Unknown	44	45	51	34	33	17	48	31	**522**

Table 6.2 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Belarus in 2014

	E. coli		*K. pneumoniae*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (R)	45	87	NA	NA
Aminoglycosides (R)	54	37	211	85
Fluoroquinolones (R)	54	63	190	84
Fluoroquinolones (I+R)	54	63	190	84
Third-generation cephalosporins (R)	55	64	227	90
Third-generation cephalosporins (I+R)	55	71	227	90
Carbapenems (R)	53	2	229	52
Carbapenems (I+R)	53	6	229	56
Multidrug resistance (R)	55	29	172	74

NA: not applicable.
The aminopenicillins group comprises amoxicillin and ampicillin.
The aminoglycosides group comprises amikacin, gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.
The third-generation cephalosporins group comprises cefotaxime, ceftriaxone and ceftazidime.
The carbapenems group comprises imipenem and meropenem.
Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides.

Table 6.3 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Belarus in 2014

	P. aeruginosa		*Acinetobacter* spp.	
	n	Resistance (%)	*n*	Resistance (%)
Aminoglycosides (R)	74	84	292	72
Fluoroquinolones (R)	69	91	294	92
Piperacillin or piperacillin-tazobactam (R)	70	71	NA	NA
Ceftazidime (R)	73	64	NA	NA
Carbapenems (R)	77	90	288	91
Carbapenems (I+R)	77	94	288	92
Multidrug resistance (R)	71	90	272	60

NA = not applicable.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.
The carbapenems group comprises imipenem and meropenem.
For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems.
For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems.

Table 6.4 Percentage of resistance for *S. aureus* among blood and CSF isolates in Belarus in 2014

	S. aureus	
	n	**Resistance (%)**
MRSA (R)	377	45
Fluoroquinolones (R)	385	33
Rifampicin (R)	291	17
Linezolid (R)	331	1

MRSA is calculated as resistance to cefoxitin or, if not available, to one or more of oxacillin, flucloxacillin, methicillin, cloxacillin and dicloxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin, levofloxacin and norfloxacin.

Table 6.5 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Belarus in 2014

	S. pneumoniae	
	n	**Resistance (%)**
Penicillin (R)	10[a]	50[a]
Penicillin (I+R)	10[a]	60[a]
Macrolides (R)	12[a]	50[a]
Macrolides (I+R)	12[a]	50[a]
Fluoroquinolones (R)	12[a]	0[a]
Third-generation cephalosporins (R)	10[a]	10[a]
Third-generation cephalosporins (I+R)	10[a]	10[a]
Multidrug resistance (I+R)	11[a]	45[a]

[a] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.
Penicillin resistance is based on penicillin or, if not available, on oxacillin.
The macrolides group comprises erythromycin, clarithromycin and azithromycin.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
Multidrug resistance is defined as resistance to penicillins and macrolides.

Table 6.6 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Belarus in 2014

	E. faecalis		*E. faecium*	
	n	**Resistance (%)**	*n*	**Resistance (%)**
Aminopenicillins (I+R)	151	75	75	95
High-level gentamicin (R)	8[a]	50[a]	0	No data available
Vancomycin (R)	151	1	72	11
Linezolid (I+R)	143	2	75	4

[a] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.
The aminopenicillins group comprises amoxicillin and ampicillin.

Table 6.7 Patient characteristics of 1348 isolates from Belarus in 2015, by pathogen

	E. coli	*K. pneumoniae*	*P. aeruginosa*	*Acinetobacter* spp.	*S. aureus*	*S. pneumoniae*	*E. faecalis*	*E. faecium*	**Total number of isolates**
Number of isolates; *n* (%)	95 (7)	297 (22)	89 (7)	311 (23)	329 (24)	25 (2)	97 (7)	105 (8)	**1348**
Isolate source (%)									
Blood	99	96	99	94	95	56	97	96	**1282**
Cerebrospinal fluid	1	4	1	6	5	44	3	4	**66**
Sex (%)									
Male	24	28	27	26	27	40	22	26	**357**
Female	25	16	13	21	24	24	11	18	**264**
Unknown	51	57	60	53	49	36	67	56	**727**
Age in years (%)									
0–4	3	6	4	5	4	20	10	9	**75**
5–19	1	0	3	1	2	0	3	1	**17**
20–64	27	31	22	43	49	48	31	30	**508**
65 and older	24	16	17	15	17	8	20	20	**234**
Unknown	44	46	53	36	28	24	36	41	**514**
Hospital department (%)									
Emergency department	0	0	0	0	0	0	0	1	**1**
Infectious disease ward	6	1	1	0	5	4	3	1	**33**
Internal medicine	11	14	11	7	21	8	24	9	**188**
Obstetrics and gynaecology	3	0	0	0	0	0	1	0	**6**
Surgery	15	5	13	5	14	0	12	8	**120**
Intensive care unit	56	73	71	84	53	84	55	77	**925**
Paediatrics or neonatal	3	2	0	2	1	0	1	2	**20**
Paediatric or neonatal intensive care unit	0	0	0	0	0	0	0	1	**2**
Unknown	6	4	3	3	5	4	4	2	**53**

Table 6.8 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Belarus in 2015

	E. coli		*K. pneumoniae*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (R)	53	83	NA	NA
Aminoglycosides (R)	90	41	273	75
Fluoroquinolones (R)	92	53	296	80
Fluoroquinolones (I+R)	92	53	296	80
Third-generation cephalosporins (R)	93	62	273	88
Third-generation cephalosporins (I+R)	93	63	273	88
Carbapenems (R)	86	2	249	58
Carbapenems (I+R)	86	10	249	67
Multidrug resistance (R)	92	38	271	69

NA: not applicable
The aminopenicillins group comprises amoxicillin and ampicillin.
The aminoglycosides group comprises amikacin, gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.
The third-generation cephalosporins group comprises cefotaxime, ceftriaxone and ceftazidime.
The carbapenems group comprises imipenem and meropenem.
Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides.

Table 6.9 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Belarus in 2015

	P. aeruginosa		*Acinetobacter* spp.	
	n	Resistance (%)	*n*	Resistance (%)
Aminoglycosides (R)	66	70	260	59
Fluoroquinolones (R)	83	86	297	90
Piperacillin or piperacillin-tazobactam (R)	81	65	NA	NA
Ceftazidime (R)	44	66	NA	NA
Carbapenems (R)	88	82	262	90
Carbapenems (I+R)	88	86	262	94
Multidrug resistance (R)	55	85	264	48

NA: not applicable.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.
The carbapenems group comprises imipenem and meropenem.
For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems.
For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems.

Table 6.10 Percentage of resistance for *S. aureus* among blood and CSF isolates in Belarus in 2015

	S. aureus	
	n	Resistance (%)
MRSA (R)	299	48
Fluoroquinolones (R)	300	32
Rifampicin (R)	220	25
Linezolid (R)	257	0

MRSA is calculated as resistance to cefoxitin or, if not available, to one or more of oxacillin, flucloxacillin, methicillin, cloxacillin and dicloxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin, levofloxacin and norfloxacin.

Table 6.11 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Belarus in 2015

	S. pneumoniae	
	n	Resistance (%)
Penicillin (R)	15[a]	47[a]
Penicillin (I+R)	15[a]	47[a]
Macrolides (R)	22[a]	59[a]
Macrolides (I+R)	22[a]	68[a]
Fluoroquinolones (R)	16[a]	0[a]
Third-generation cephalosporins (R)	19[a]	16[a]
Third-generation cephalosporins (I+R)	19[a]	21[a]
Multidrug resistance (I+R)	20[a]	35[a]

[a] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.
Penicillin resistance is based on penicillin or, if not available, on oxacillin.
The macrolides group comprises erythromycin, clarithromycin and azithromycin.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
Multidrug resistance is defined as resistance to penicillins and macrolides.

Table 6.12 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Belarus in 2015

	E. faecalis		*E. faecium*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (I+R)	80	57	95	95
High-level gentamicin (R)	14[a]	36[a]	8[a]	38[a]
Vancomycin (R)	93	3	105	16
Linezolid (I+R)	87	3	101	2

[a] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.
The aminopenicillins group comprises amoxicillin and ampicillin.

6.2 Bosnia and Herzegovina

6.2.1 Surveillance set-up

Bosnia and Herzegovina submitted data to CAESAR for the first time in 2016. AMR surveillance activities are conducted by two networks; one in the Federation of Bosnia and Herzegovina and one in Republika Srpska. The surveillance set-up in Bosnia and Herzegovina is described below for each network separately.

Federation of Bosnia and Herzegovina
The AMR focal point and the data manager in the Federation of Bosnia and Herzegovina are responsible for collecting data from the participating laboratories. Laboratories were asked to collect antimicrobial susceptibility results for the first isolate from blood and cerebrospinal fluid for each patient, including patient information for the period 1 January to 31 December 2015. Laboratories check their data for adherence to the CAESAR protocol, microbiological consistency and plausibility and consistency with guidelines (EUCAST or CLSI) before submitting the data. The data are sent electronically from each laboratory in Excel-based data entry forms, previously prepared by the data manager according to the CAESAR protocols. The data manager and AMR focal point approve the data before electronic submission to CAESAR.

The five participating laboratories (of 12 laboratories in the Federation of Bosnia and Herzegovina) provide diagnostic support for three tertiary care and two secondary care hospitals. The laboratories are geographically and demographically spread across the Federation of Bosnia and Herzegovina, including urban and rural areas. AMR surveillance in the Federation of Bosnia and Herzegovina covers about two thirds of the population of Bosnia and Herzegovina.

Antimicrobial susceptibility in the tertiary level of care is mostly tested using automated systems and, secondarily, by gradient tests or disk diffusion. If highly resistant microorganisms or exceptional phenotypes are found, strains are usually sent to a clinical microbiology laboratory at a university hospital in the capital for confirmation. All laboratories have applied an internal quality management system and take part in international external quality control programmes (the UK NEQAS). Laboratories are required to follow EUCAST standards in testing and interpreting antibiotic susceptibility testing, and these standards are now being implemented in three of the five laboratories that are still using CLSI guidelines.

According to clinical guidelines, blood samples are collected from all patients presenting with signs of a bloodstream infection (sepsis) and CSF from patients with meningitis. In 2015, the number of blood cultures taken in the Federation of Bosnia and Herzegovina ranged from 3 to 24 per 1000 patient-days in the five participating hospitals.

Republika Srpska
The AMR focal point and data manager of Republika Srpska are responsible for collecting data from the University Clinical Centre of Republika Srpska, the largest and main hospital in Republika Srpska. All results from the routine antibiotic susceptibility testing of clinical bacteriology cultures are collected electronically from the clinical information system. Almost all patients from Republika Srpska suspected of having sepsis or meningitis are hospitalized in the University Clinical Centre of Republika Srpska. Other microbiology laboratories in hospitals in Republika Srpska (Doboj, Prijedor, Bijeljina and Istocno Sarajevo) have less than 100–200 invasive samples per year, since patients suspected of having sepsis or meningitis are transported to the University Clinical Centre of Republika Srpska. AMR surveillance covers at least 75% of the population of Republika Srpska.

Confirmatory testing (phonotypical) of highly resistant microorganisms is done before the results are included in the final dataset. A subset of antibiotic susceptibility testing results, containing all first isolates from blood and CSF cultures yielding organisms specified by CAESAR for the period 1 January to 31 December 2015, were reported to CAESAR.

The antibiotic susceptibility of gram-negative bacteria and *S. aureus* is mostly tested using automated systems. If highly resistant microorganisms or exceptional phenotypes are found, the results are confirmed by gradient tests or disk diffusion. Gram-positive bacteria are mostly tested using disk diffusion. All laboratories

have applied quality management systems, with internal (in the University Clinical Centre laboratory) and external international (UK NEQAS) quality control programmes. Laboratories are required to follow guidelines on bacteriological methods for testing special resistance. For methods and interpretation of antibiotic susceptibility testing, Republika Srpska has adopted EUCAST methods as the standard.

According to clinical guidelines, blood cultures are taken from all patients with suspected bloodstream infections (sepsis) presenting in the University Clinical Centre of Republika Srpska, and CSF cultures are taken from patients suspected of having meningitis. Bacteriology cultures are reimbursed through the universal health insurance scheme. In 2015, 11 blood cultures per 1000 patient-days were taken in Republika Srpska.

6.2.2 Results

Table 6.13 shows the patient characteristics of 858 isolates from Bosnia and Herzegovina in 2015, by pathogen. In *E. coli*, apart from aminopenicillins (80%), resistance ranged from 0% (carbapenems) to 22% (fluoroquinolones, Table 6.14). Multidrug resistance was 7% in *E. coli*. In *K. pneumoniae*, resistance ranged from 38% to 76% for all tested agents except for carbapenems (6%). Multidrug resistance in *K. pneumoniae* was 34%. In *P. aeruginosa*, resistance ranged from 11% for ceftazidime to 37% for aminoglycosides (Table 6.15). Multidrug resistance was 17% in *P. aeruginosa*. Resistance in *Acinetobacter* spp. was 89–92% for all antibiotics tested. Multidrug resistance in *Acinetobacter* spp. was 84%. Twenty-three per cent of *S. aureus* isolates were MRSA (Table 6.16). In *S. pneumoniae*, penicillin resistance was 27% (Table 6.17). Six per cent of *S. pneumoniae* isolates were multidrug resistant. However, because of the relatively few isolates, the results for *S. pneumoniae* should be interpreted with caution. In *E. faecalis*, vancomycin resistance was 4%, and 3% were non-susceptible to linezolid (Table 6.18). Based on only 17 isolates, vancomycin resistance was 65%, and linezolid non-susceptibility was 19% in *E. faecium*.

6.2.3 Discussion

The AMR surveillance networks of Bosnia and Herzegovina submitted the antibiotic susceptibility testing results of 858 isolates from blood or CSF in 2015. The network laboratories provide good geographical coverage of Bosnia and Herzegovina. Blood samples are generally taken before initial antibiotic treatment. A relatively large number of isolates were from patients admitted to intensive care units (30%), and a relatively high number of *Acinetobacter* spp. and a relatively low number of *E. coli* isolates were seen. The percentages of resistance were high for *K. pneumoniae*, *Acinetobacter* spp., *E. faecalis* and *E. faecium.* The combination of a skewed distribution of pathogens and high percentages of resistance suggests that the results disproportionately reflect nosocomial infections and that community-acquired infections are underrepresented. The reported percentages of resistance should be interpreted with caution and may not be generalizable to any one patient presenting with an invasive infection in Bosnia and Herzegovina.

Nevertheless, percentages of resistance in *E. coli* were not very high, and although no information was available to differentiate nosocomial from community-acquired infections, this may suggest that resistance in community-acquired infections is limited. The level of MRSA was similar to countries close to Bosnia and Herzegovina (Fig. 8.6). Although based on a low number of isolates tested, penicillin resistance in *S. pneumoniae* was high. The percentages of resistance in *P. aeruginosa* were not very high. The high levels of resistance in *K. pneumoniae*, *Acinetobacter* spp., *E. faecalis* and *E. faecium* are concerning and suggest the dissemination of resistant clones in the healthcare setting.

The data from Bosnia and Herzegovina are assessed as level B. The generalizability of the data is limited by disproportionate inclusion of patients from intensive care units and patients with healthcare-associated infections. The antibiotic susceptibility testing results seem to be reliable, but comparability is limited by applying a mix of antibiotic susceptibility testing standards. The data provide a good indication of resistance patterns present in clinical settings in the country, but the proportion of resistance should be interpreted with care. The readers' guide (Table 5.1) provides additional information on interpreting the data and how the level of evidence was determined.

Chapter 8 displays the proportions of resistance for selected pathogen–antibiotic combinations reported by Bosnia and Herzegovina in maps of the WHO European Region (Fig. 8.1–8.6). Besides the data from the CAESAR countries and areas, the maps present data from the EARS-Net at the ECDC.

Table 6.13 Patient characteristics of 858 isolates from Bosnia and Herzegovina in 2015, by pathogen

	E. coli	*K. pneumoniae*	*P. aeruginosa*	*Acinetobacter* spp.	*S. aureus*	*S. pneumoniae*	*E. faecalis*	*E. faecium*	**Total number of isolates**
Number of isolates; *n* (%)	175 (20)	177 (21)	71 (8)	180 (21)	160 (19)	22 (3)	56 (7)	17 (2)	**858**
Isolate source (%)									
Blood	99	98	94	94	98	45	100	100	**822**
Cerebrospinal fluid	1	2	6	6	3	55	0	0	**36**
Sex (%)									
Male	37	60	59	63	61	55	57	65	**479**
Female	62	40	41	37	38	45	43	35	**374**
Unknown	1	1	0	0	1	0	0	0	**5**
Age in years (%)									
0–4	10	17	17	23	6	9	32	18	**134**
5–19	1	2	3	3	4	18	4	0	**24**
20–64	40	31	42	44	50	32	29	41	**345**
65 and over	42	28	38	25	38	23	30	41	**283**
Unknown	8	23	0	4	2	18	5	0	**72**
Hospital department (%)									
Emergency department	0	1	3	4	0	0	0	0	**10**
Haematology or oncology	9	7	3	3	9	18	2	6	**55**
Infectious disease ward	23	4	3	2	9	50	5	0	**81**
Internal medicine	26	15	28	7	28	0	25	18	**165**
Obstetrics and gynaecology	6	1	0	2	1	0	0	0	**16**
Surgery	2	7	11	8	6	0	4	6	**52**
Urology	12	2	0	1	1	0	2	6	**29**
Intensive care unit	8	23	42	62	27	0	18	47	**256**
Paediatrics or neonatal	9	37	6	11	8	14	38	18	**143**
Other	4	4	3	2	11	18	7	0	**45**
Unknown	1	1	1	0	1	0	0	0	**6**

Table 6.14 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Bosnia and Herzegovina in 2015

	E. coli		*K. pneumoniae*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (R)	172	80	NA	NA
Aminoglycosides (R)	175	17	177	72
Fluoroquinolones (R)	171	22	176	38
Fluoroquinolones (I+R)	171	22	176	39
Third-generation cephalosporins (R)	173	21	177	76
Third-generation cephalosporins (I+R)	173	23	177	77
Carbapenems (R)	175	0	177	6
Carbapenems (I+R)	175	0	177	8
Multidrug resistance (R)	173	7	176	34

NA: not applicable.
The aminopenicillins group comprises amoxicillin and ampicillin.
The aminoglycosides group comprises amikacin, gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.
The third-generation cephalosporins group comprises cefotaxime, ceftriaxone and ceftazidime.
The carbapenems group comprises imipenem and meropenem.
Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides.

Table 6.15 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Bosnia and Herzegovina in 2015

	P. aeruginosa		*Acinetobacter* spp.	
	n	Resistance (%)	*n*	Resistance (%)
Aminoglycosides (R)	71	37	180	92
Fluoroquinolones (R)	65	25	180	91
Piperacillin or piperacillin-tazobactam (R)	60	17	NA	NA
Ceftazidime (R)	55	11	NA	NA
Carbapenems (R)	71	17	180	89
Carbapenems (I+R)	71	20	180	89
Multidrug resistance (R)	64	17	180	84

NA: not applicable.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.
The carbapenems group comprises imipenem and meropenem.
For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems.
For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems.

Table 6.16 Percentage of resistance for *S. aureus* among blood and CSF isolates in Bosnia and Herzegovina in 2015

	S. aureus	
	n	Resistance (%)
MRSA (R)	160	23
Fluoroquinolones (R)	131	14
Rifampicin (R)	84	4
Linezolid (R)	109	0

MRSA is calculated as resistance against cefoxitin or, if not available, against one or more of oxacillin, flucloxacillin, methicillin, cloxacillin and dicloxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin, levofloxacin and norfloxacin.

Table 6.17 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Bosnia and Herzegovina in 2015

	S. pneumoniae	
	n	Resistance (%)
Penicillin (R)	22[a]	27[a]
Penicillin (I+R)	22[a]	27[a]
Macrolides (R)	12[a]	17[a]
Macrolides (I+R)	12[a]	17[a]
Fluoroquinolones (R)	15[a]	0[a]
Third-generation cephalosporins (R)	21[a]	5[a]
Third-generation cephalosporins (I+R)	21[a]	5[a]
Multidrug resistance (I+R)	18[a]	6[a]

[a] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.
Penicillin resistance is based on penicillin or, if not available, on oxacillin.
The macrolides group comprises erythromycin, clarithromycin and azithromycin.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
Multidrug resistance is defined as resistance to penicillins and macrolides.

Table 6.18 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Bosnia and Herzegovina in 2015

	E. faecalis		*E. faecium*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (I+R)	56	23	17[a]	100[a]
High-level gentamicin (R)	55	53	17[a]	100[a]
Vancomycin (R)	56	4	17[a]	65[a]
Linezolid (I+R)	31	3	16[a]	19[a]

[a] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.
The aminopenicillins group comprises amoxicillin and ampicillin.

6.3 Russian Federation

6.3.1 Surveillance set-up

Antibiotic susceptibility testing results are obtained from an annual national surveillance study on AMR of bacterial pathogens causing infections among hospitalized patients. Clinical bacterial isolates are collected from 30 laboratories, each serving one tertiary care or specialized hospital, in 20 cities. Each laboratory is requested to submit a maximum of 150 consecutive, non-duplicate isolates (one isolate of each species per patient or case of infection) annually. Non-clinical (screening) isolates are spared. Isolates are sent to the central laboratory of the Institute of Antimicrobial Chemotherapy of Smolensk State Medical University together with case report forms containing basic patient demographic data, clinical data (including the type and location of infection), source (nosocomial or community-acquired), type of hospital ward and the type and date of clinical specimen.

All isolates submitted to the laboratory of the Institute of Antimicrobial Chemotherapy and meeting the criteria of the study are reidentified at the species level by means of matrix-assisted laser desorption and ionization–time of flight (MALDI-TOF) mass spectrometry and tested for antibiotic susceptibility using the broth microdilution method according to the EUCAST recommendations. The quality of antibiotic susceptibility testing is controlled by testing reference ATCC strains in parallel with clinical isolates. Organisms revealing rare resistance phenotypes or specific resistance of clinical and epidemiological significance (such as MRSA, ESBL or carbapenemase-producing Enterobacteriaceae) are further characterized using molecular methods. All antibiotic susceptibility testing results are fed back to the participating laboratories.

A subset of antibiotic susceptibility testing results, containing all first isolates from blood and CSF cultures yielding organisms specified by CAESAR for the periods 1 January to 31 December 2014 and 1 January to 31 December 2015 was provided for CAESAR. Isolates included in this subset were obtained from 18 geographically distinct laboratories in 2014 and 22 laboratories in 2015, mostly representing large urban tertiary hospitals.

According to current practices, blood cultures are taken from patients with severe infections and suspected sepsis, and more often from patients with hospital-onset infections and in the cases of ineffective primary or empirical therapy. CSF cultures are taken from all patients with suspected primary or secondary meningitis presenting in hospital. Bacteriology cultures are reimbursed through the universal health insurance scheme.

6.3.2 Results

2014

Table 6.19 shows the patient characteristics of 347 isolates from the Russian Federation in 2014, by pathogen. No data on *S. pneumoniae* were available. In *E. coli*, resistance was 59% or higher for all tested antimicrobial agents except for aminoglycosides (31%) and carbapenems (3%, Table 6.20). Multidrug resistance was 28% in *E. coli*. In *K. pneumoniae*, resistance ranged from 84% to 89% for all tested agents except for carbapenems (10%). Multidrug resistance in *K. pneumoniae* was 77%. Resistance in *P. aeruginosa* was 74% or higher for all tested agents (Table 6.21). Multidrug resistance was 74% in *P. aeruginosa*. In *Acinetobacter* spp., resistance ranged from 53% for carbapenems to 96% for fluoroquinolones. Multidrug resistance in *Acinetobacter* spp. was 49%. Eighteen per cent of *S. aureus* isolates were MRSA (Table 6.22). Vancomycin resistance was 5% in *E. faecalis* and 7% in *E. faecium* (Table 6.23).

2015

Table 6.24 shows the patient characteristics of 322 isolates from the Russian Federation in 2015, by pathogen. No data on *S. pneumoniae* were available. In *E. coli*, resistance ranged from 43% to 80% for all tested agents except for carbapenems (0%, Table 6.25). Multidrug resistance was 38% in *E. coli*. In *K. pneumoniae*, resistance ranged from 91% to 95% for all antibiotic groups except for carbapenems (7%).

Multidrug resistance in *K. pneumoniae* was 84%. Resistance in *P. aeruginosa* ranged from 46% to 71% for all tested agents (Table 6.26). Multidrug resistance was 50% in *P. aeruginosa*. In *Acinetobacter* spp., resistance was 56% for carbapenems and higher for all other agents. Multidrug resistance in *Acinetobacter* spp. was 56%. Twenty-two per cent of *S. aureus* isolates were MRSA (Table 6.27). Vancomycin resistance was 0% in both *E. faecalis* and *E. faecium* (Table 6.28).

6.3.3 Discussion

The AMR surveillance network of the Russian Federation submitted antibiotic susceptibility testing results for 347 isolates from blood or CSF in 2014 and the results for 322 isolates in 2015.

The laboratories in the network are distributed throughout the western part of the Russian Federation. The laboratories in the surveillance network mainly include tertiary care facilities. The overall low number of blood isolates (about 5% of total number of isolates collected) reflects the low utilization of blood culture diagnostics by clinicians, except among severely ill patients or following treatment failure. This is reflected in the large proportion of results coming from patients admitted to intensive care units. Community-acquired infections are generally not cultured, which may explain the relatively low number of *E. coli* and absence of *S. pneumoniae* isolates. The reported percentages of resistance disproportionately represent nosocomial infections. Besides reflecting selective sampling, few isolates makes the observed resistance proportions more sensitive to random variation, such as due to nosocomial outbreaks. The proportions of resistance should be interpreted with caution and are not generalizable to any one patient presenting with invasive infection in the Russian Federation, especially patients with community-acquired infections.

Nevertheless, Enterobacteriaceae had high resistance to aminoglycosides, fluoroquinolones and third-generation cephalosporins. Resistance to carbapenems was 7% in *K. pneumoniae* and 0% in *E. coli* in 2015. This finding could be explained by the fact that carbapenems were only recently introduced in the Russian Federation, whereas the former classes of antimicrobial agents have been used for a longer time. The MRSA level was moderate and similar to surrounding countries (Fig. 8.6). The high percentages of resistance in the pathogens *P. aeruginosa* and *Acinetobacter* spp. are concerning and may reflect dissemination of resistant clones in the healthcare setting.

The data from the Russian Federation are assessed as level B. The generalizability of the results is limited by the overrepresentation of more severely ill and pretreated patients (selective sampling), the limited coverage of hospital types in the surveillance system and the low overall number of isolates (low utilization of blood culture diagnostics). Because all isolates were (re)tested at the national AMR reference laboratory using standardized methods, the antibiotic susceptibility testing results are considered reliable. The data indicate the resistance patterns present in clinical settings in the country, but the proportion of resistance should be interpreted with care. The Russian Federation has an active AMR surveillance network that has recently been working on updating national guidance on antibiotic susceptibility testing methods and breakpoints to EUCAST. Improving the use of blood culture diagnostics and expanding the network to include a variety of different types of hospitals will lead to more valid assessment of the magnitude of AMR in the country. The readers' guide (Table 5.1) provides additional information on interpreting the data and how the level of evidence was determined.

Chapter 8 displays the proportions of resistance for selected pathogen–antibiotic combinations reported by the Russian Federation in maps of the WHO European Region (Fig. 8.1–8.6). Besides the data from the CAESAR countries and areas, the maps present data from the EARS-Net at the ECDC.

Table 6.19 Patient characteristics of 347 isolates from the Russian Federation in 2014, by pathogen

	E. coli	*K. pneumoniae*	*P. aeruginosa*	*Acinetobacter* spp.	*S. aureus*	*S. pneumoniae*	*E. faecalis*	*E. faecium*	**Total number of isolates**
Number of isolates; *n* (%)	29 (8)	96 (28)	27 (8)	53 (15)	105 (30)	0 (0)	22 (6)	15 (4)	**347**
Isolate source (%)									
Blood	100	96	100	85	96	0	100	100	**331**
Cerebrospinal fluid	0	4	0	15	4	0	0	0	**16**
Sex (%)									
Male	62	63	52	58	48	0	73	33	**194**
Female	38	34	44	38	50	0	27	67	**145**
Unknown	0	3	4	4	2	0	0	0	**8**
Age in years (%)									
0–4	3	5	11	4	3	0	5	13	**17**
5–19	0	0	0	2	2	0	0	13	**5**
20–64	52	68	74	68	82	0	64	47	**243**
65 and over	45	25	15	25	13	0	32	27	**79**
Unknown	0	2	0	2	0	0	0	0	**3**
Hospital department (%)									
Haematology or oncology	10	1	4	4	3	0	0	7	**11**
Internal medicine	28	9	19	4	24	0	36	13	**59**
Obstetrics and gynaecology	0	1	0	0	2	0	0	0	**3**
Surgery	3	19	11	13	17	0	23	20	**55**
Urology	3	4	4	2	3	0	0	0	**10**
Intensive care unit	55	60	56	74	50	0	36	47	**195**
Paediatric or neonatal intensive care unit	0	4	4	2	2	0	0	13	**10**
Unknown	0	1	4	2	0	0	5	0	**4**

Table 6.20 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in the Russian Federation in 2014

	E. coli		*K. pneumoniae*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (R)	29[a]	79[a]	NA	NA
Aminoglycosides (R)	29[a]	31[a]	96	84
Fluoroquinolones (R)	29[a]	69[a]	96	87
Fluoroquinolones (I+R)	29[a]	69[a]	96	89
Third-generation cephalosporins (R)	29[a]	66[a]	96	89
Third-generation cephalosporins (I+R)	29[a]	66[a]	96	90
Carbapenems (R)	29[a]	3[a]	96	10
Carbapenems (I+R)	29[a]	3[a]	96	16
Multidrug resistance (R)	29[a]	28[a]	96	77

NA: not applicable.

[a] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.

The aminopenicillins group comprises amoxicillin and ampicillin.

The aminoglycosides group comprises amikacin, gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

The third-generation cephalosporins group comprises cefotaxime, ceftriaxone and ceftazidime.

The carbapenems group comprises imipenem and meropenem.

Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides.

Table 6.21 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in the Russian Federation in 2014

	P. aeruginosa		*Acinetobacter* spp.	
	n	Resistance (%)	*n*	Resistance (%)
Aminoglycosides (R)	27[a]	85[a]	53	92
Fluoroquinolones (R)	27[a]	74[a]	53	96
Piperacillin or piperacillin-tazobactam (R)	27[a]	74[a]	NA	NA
Ceftazidime (R)	27[a]	74[a]	NA	NA
Carbapenems (R)	27[a]	74[a]	53	53
Carbapenems (I+R)	27[a]	89[a]	53	62
Multidrug resistance (R)	27[a]	74[a]	53	49

NA: not applicable.

[a] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.

The aminoglycosides group comprises gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin and levofloxacin.

The carbapenems group comprises imipenem and meropenem.

For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems.

For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems.

Table 6.22 Percentage of resistance for *S. aureus* among blood and CSF isolates in the Russian Federation in 2014

	S. aureus	
	n	**Resistance (%)**
MRSA (R)	105	18
Fluoroquinolones (R)	105	22
Rifampicin (R)	0	No data available
Linezolid (R)	105	0

MRSA is calculated as resistance to cefoxitin or, if not available, to one or more of oxacillin, flucloxacillin, methicillin, cloxacillin and dicloxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin, levofloxacin and norfloxacin.

Table 6.23 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in the Russian Federation in 2014

	E. faecalis		*E. faecium*	
	n	**Resistance (%)**	*n*	**Resistance (%)**
Aminopenicillins (I+R)	22[a]	0[a]	15[a]	93[a]
High-level gentamicin (R)	22[a]	64[a]	15[a]	60[a]
Vancomycin (R)	21[a]	5[a]	15[a]	7[a]
Linezolid (I+R)	22[a]	0[a]	15[a]	0[a]

[a] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.
The aminopenicillins group comprises amoxicillin and ampicillin.

Table 6.24 Patient characteristics of 322 isolates from the Russian Federation in 2015, by pathogen

	E. coli	*K. pneumoniae*	*P. aeruginosa*	*Acinetobacter* spp.	*S. aureus*	*S. pneumoniae*	*E. faecalis*	*E. faecium*	**Total number of isolates**
Number of isolates; *n* (%)	40 (12)	95 (30)	28 (9)	61 (19)	65 (20)	0 (0)	19 (6)	14 (4)	**322**
Isolate source (%)									
Blood	98	93	79	84	100	0	100	100	**298**
Cerebrospinal fluid	3	7	21	16	0	0	0	0	**24**
Sex (%)									
Male	60	60	57	62	63	0	47	43	**191**
Female	35	32	39	30	37	0	37	50	**111**
Unknown	5	8	4	8	0	0	16	7	**20**
Age in years (%)									
0–4	0	1	0	0	2	0	0	7	**3**
5–19	0	3	4	2	3	0	0	7	**8**
20–64	55	49	61	69	71	0	68	43	**193**
65 and over	40	33	29	20	22	0	21	43	**91**
Unknown	5	14	7	10	3	0	11	0	**27**
Hospital department (%)									
Haematology or oncology	3	0	0	0	3	0	0	0	**3**
Internal medicine	18	5	11	11	34	0	21	7	**49**
Surgery	20	15	7	18	18	0	5	21	**51**
Urology	3	3	0	0	0	0	5	0	**5**
Intensive care unit	50	57	75	61	38	0	47	64	**175**
Paediatric or neonatal intensive care unit	0	4	4	0	0	0	5	0	**6**
Unknown	8	16	4	10	6	0	16	7	**33**

Table 6.25 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in the Russian Federation in 2015

	E. coli		*K. pneumoniae*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (R)	40	80	NA	NA
Aminoglycosides (R)	40	43	95	93
Fluoroquinolones (R)	40	60	95	91
Fluoroquinolones (I+R)	40	60	95	92
Third-generation cephalosporins (R)	40	77	95	95
Third-generation cephalosporins (I+R)	40	77	95	95
Carbapenems (R)	40	0	95	7
Carbapenems (I+R)	40	0	95	22
Multidrug resistance (R)	40	38	95	84

NA: not applicable.
The aminopenicillins group comprises amoxicillin and ampicillin.
The aminoglycosides group comprises amikacin, gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.
The third-generation cephalosporins group comprises cefotaxime, ceftriaxone and ceftazidime.
The carbapenems group comprises imipenem and meropenem.
Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides.

Table 6.26 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in the Russian Federation in 2015

	P. aeruginosa		*Acinetobacter* spp.	
	n	Resistance (%)	*n*	Resistance (%)
Aminoglycosides (R)	28[a]	46[a]	61	85
Fluoroquinolones (R)	28[a]	46[a]	61	95
Piperacillin or piperacillin-tazobactam (R)	28[a]	71[a]	NA	NA
Ceftazidime (R)	28[a]	61[a]	NA	NA
Carbapenems (R)	28[a]	54[a]	61	56
Carbapenems (I+R)	28[a]	64[a]	61	61
Multidrug resistance (R)	28[a]	50[a]	61	56

NA: not applicable.
[a] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.
The carbapenems group comprises imipenem and meropenem.
For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems.
For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems.

Table 6.27 Percentage of resistance for *S. aureus* among blood and CSF isolates in the Russian Federation in 2015

	S. aureus	
	n	Resistance (%)
MRSA (R)	64	22
Fluoroquinolones (R)	65	35
Rifampicin (R)	65	8
Linezolid (R)	65	0

MRSA is calculated as resistance to cefoxitin or, if not available, to one or more of oxacillin, flucloxacillin, methicillin, cloxacillin and dicloxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin, levofloxacin and norfloxacin.

Table 6.28 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in the Russian Federation in 2015

	E. faecalis		*E. faecium*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (I+R)	19[a]	0[a]	14[a]	100[a]
High-level gentamicin (R)	19[a]	47[a]	14[a]	93[a]
Vancomycin (R)	19[a]	0[a]	14[a]	0[a]
Linezolid (I+R)	19[a]	0[a]	14[a]	0[a]

[a] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.
The aminopenicillins group comprises amoxicillin and ampicillin.

6.4 Serbia

6.4.1 Surveillance set-up

All results from routine antibiotic susceptibility testing of the first isolates from blood and CSF cultures for each patient yielding organisms specified by CAESAR are collected twice a year (for the six-month periods 1 January–30 June and 1 July–31 December) from the laboratory network of microbiology laboratories in Serbia.

Data are collected by the national reference laboratory for AMR: the Center for Microbiology of the Institute for Public Health of Vojvodina in Novi Sad, Serbia. As data come in, their quality and consistency are checked, errors are fed back to the laboratories and corrected where applicable, and then the data are uploaded into the national WHONET database.

In 2014 and 2015, 14 laboratories participated in the national AMR surveillance. They provide diagnostic support for 21 hospitals: about 30% of the general hospitals and more than 50% of the academic and top clinical hospitals, including the largest clinical centres in the country. They are geographically dispersed and cover about 50% of the population.

Antimicrobial susceptibility is mostly tested using the disk diffusion method; some laboratories use a combination of an automated system and disk diffusion, and gradient tests when needed, according to 2014 CLSI guidelines. In 2015, some laboratories switched to EUCAST, and the remainder plan to switch in 2016.

Several laboratories are accredited according to International Organization for Standardization (ISO)/ International Electrotechnical Commission standard 17025:2005, and some according to ISO 9001 and ISO 14001 standards. All laboratories have internal quality control schemes and took part in the national and international (CAESAR and UK NEQAS) external quality assessment exercise. There is no regular national external quality assessment programme. The Ministry of Health nominates reference laboratories, but funding is insufficient, no additional staff could be allocated and the sending of reports and bacterial strains to reference laboratories is not regulated, but done voluntarily. There are no published national guidelines on bacteriological methods for testing antimicrobial susceptibility.

Blood cultures are taken from all patients with suspected bloodstream infections (sepsis), and CSF cultures are taken from patients suspected of having meningitis. Bacteriology cultures are reimbursed through the National Health Insurance Fund.

6.4.2 Results

2014

Table 6.29 shows the patient characteristics of 1550 isolates from Serbia in 2014, by pathogen. In *E. coli*, resistance was 30% for fluoroquinolones and higher for all tested antimicrobial agents except for carbapenems (1%, Table 6.30). Multidrug resistance was 14% in *E. coli*. In *K. pneumoniae*, resistance ranged from 34% for carbapenems to 89% for third-generation cephalosporins. Multidrug resistance in *K. pneumoniae* was 59%. In *P. aeruginosa*, resistance ranged from 21% for piperacillin or piperacillin-tazobactam to 57% for aminoglycosides (Table 6.31). Multidrug resistance was 51% in *P. aeruginosa*. Resistance in *Acinetobacter* spp. was 92–93% for all antibiotics tested. Multidrug resistance in *Acinetobacter* spp. was 85%. Thirty-three per cent of *S. aureus* isolates were MRSA (Table 6.32). In *S. pneumoniae*, 30% resistance was found for penicillin (Table 6.33), and resistance was highest for macrolides (31%). Twenty-three per cent of *S. pneumoniae* isolates were multidrug resistant. However, because of the relatively few isolates, the results for *S. pneumoniae* should be interpreted with caution. Vancomycin resistance was 2% in *E. faecalis* and 61% in *E. faecium* (Table 6.34). Three per cent of *E. faecium* isolates were non-susceptible to linezolid.

2015

Table 6.35 shows the patient characteristics of 1877 isolates from Serbia in 2015 by pathogen. In *E. coli*, resistance was 27% for fluoroquinolones and higher for all tested antimicrobial agents except for carbapenems (1%, Table 6.36). Multidrug resistance was 16% in *E. coli*. In *K. pneumoniae*, resistance ranged from 39% for carbapenems to 90% for third-generation cephalosporins. Multidrug resistance in *K. pneumoniae* was 65%. In *P. aeruginosa*, resistance ranged from 28% for piperacillin or piperacillin-tazobactam to 64% for aminoglycosides (Table 6.37). Multidrug resistance was 54% in *P. aeruginosa*. Resistance in *Acinetobacter* spp. was high (94–95%) for all antibiotics tested. Multidrug resistance in *Acinetobacter* spp. was 90%. Thirty-three per cent of *S. aureus* isolates were MRSA (Table 6.38). In *S. pneumoniae,* 14% resistance was found for penicillin (Table 6.39), and resistance was highest for macrolides (54%). Eighteen per cent of *S. pneumoniae* isolates were multidrug resistant. Vancomycin resistance was 8% in *E. faecalis* and 53% in *E. faecium* (Table 6.40).

6.4.3 Discussion

The AMR surveillance network submitted antibiotic susceptibility testing results for 1550 isolates from blood or CSF in Serbia in 2014 and the results for 1877 isolates in 2015. The network laboratories provide good geographical coverage. However, large clinical centres are overrepresented, likely resulting in a disproportionate contribution of severely ill patients referred from smaller general hospitals, often following initial antibiotic treatment. This is also reflected in the relatively large number of isolates from patients admitted to intensive care units and the relatively low number of *E. coli* isolates. In general, high percentages of resistance were seen. The combination of a skewed distribution of pathogens and high percentages of resistance suggests that the results disproportionately reflect nosocomial infections and that community-acquired infections are underrepresented. The reported percentages of resistance should be interpreted with caution and are not generalizable to any one patient presenting with invasive infection in Serbia, especially patients with community-acquired infections.

Nevertheless, a high level of carbapenem resistance was seen in *K. pneumoniae* and both *K. pneumoniae* and *E. coli* had high third-generation cephalosporin resistance in the specific patient population sampled. The Center for Microbiology of the Institute for Public Health confirmed that most carbapenem-resistant Enterobacteriaceae were carbapenemase producers using molecular methods. New Delhi metallo-beta-lactamase-1 was the most frequent gene in both species, and clonal spread of *K. pneumoniae* is suspected. The level of MRSA was similar to countries close to Serbia (Fig. 8.6). Penicillin and macrolide resistance in *S. pneumoniae* was high. The high percentages of resistance in *P. aeruginosa* and *Acinetobacter* spp. are concerning and may reflect the dissemination of resistant clones in the healthcare setting. The unusual finding of 3% linezolid resistance in *E. faecium* in 2014 (two isolates) was not confirmed. A false-positive automated test result for linezolid is the most likely explanation.

The data from Serbia are assessed as level B. The limited coverage of small general hospitals in the surveillance system leads to an overrepresentation of more severely ill and pretreated patients, constraining the generalizability of the results. The antibiotic susceptibility testing results seem to be reliable and comparable. The data provide a good indication of resistance patterns present in clinical settings in the country, but the proportion of resistance should be interpreted with care. Serbia has an active AMR surveillance network that has been working on implementing harmonized antibiotic susceptibility testing methods and breakpoints and will expand the network with eight small general hospitals to improve coverage and generalizability. The readers' guide (Table 5.1) provides additional information on interpreting the data and how the level of evidence was determined.

Chapter 8 displays the proportions of resistance for selected pathogen–antibiotic combinations reported by Serbia in maps of the WHO European Region (Fig. 8.1–8.6). Besides the data from the CAESAR countries and areas, the maps present data from the EARS-Net at the ECDC.

Table 6.29 Patient characteristics of 1550 isolates from Serbia in 2014, by pathogen

	E. coli	*K. pneumoniae*	*P. aeruginosa*	*Acinetobacter* spp.	*S. aureus*	*S. pneumoniae*	*E. faecalis*	*E. faecium*	**Total number of isolates**
Number of isolates; *n* (%)	245 (16)	325 (21)	95 (6)	343 (22)	350 (23)	33 (2)	98 (6)	61 (4)	**1550**
Isolate source (%)									
Blood	98	97	98	93	97	45	98	98	**1478**
Cerebrospinal fluid	2	3	2	7	3	55	2	2	**72**
Sex (%)									
Male	50	65	65	61	65	52	67	57	**949**
Female	49	32	32	38	32	45	29	41	**566**
Unknown	1	3	3	1	3	3	4	2	**35**
Age in years (%)									
0–4	10	9	5	6	3	0	9	7	**103**
5–19	6	4	5	3	4	6	5	5	**70**
20–64	37	44	37	41	41	61	39	46	**638**
65 and over	35	31	27	29	35	30	37	31	**498**
Unknown	12	12	25	20	17	3	10	11	**241**
Hospital department (%)									
Emergency department	5	14	14	24	9	0	7	11	**198**
Haematology or oncology	16	5	13	6	8	3	1	15	**125**
Infectious disease ward	19	5	12	5	17	58	13	13	**191**
Internal medicine	16	9	6	5	23	9	28	10	**207**
Obstetrics and gynaecology	4	2	0	0	1	0	4	0	**24**
Surgery	7	11	8	17	9	6	7	8	**165**
Urology	6	7	3	1	3	3	3	2	**62**
Intensive care unit	6	22	24	26	10	9	18	23	**266**
Paediatrics or neonatal	11	9	4	2	5	3	8	5	**97**
Other	11	15	12	12	14	6	9	13	**197**
Unknown	0	1	4	2	1	3	1	0	**18**

Table 6.30 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Serbia in 2014

	E. coli		*K. pneumoniae*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (R)	224	74	NA	NA
Aminoglycosides (R)	243	33	288	77
Fluoroquinolones (R)	240	30	305	71
Fluoroquinolones (I+R)	240	33	305	75
Third-generation cephalosporins (R)	245	33	324	89
Third-generation cephalosporins (I+R)	245	36	324	89
Carbapenems (R)	244	1	325	34
Carbapenems (I+R)	244	1	325	37
Multidrug resistance (R)	243	14	285	59

NA: not applicable.
The aminopenicillins group comprises amoxicillin and ampicillin.
The aminoglycosides group comprises amikacin, gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.
The third-generation cephalosporins group comprises cefotaxime, ceftriaxone and ceftazidime.
The carbapenems group comprises imipenem and meropenem.
Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides.

Table 6.31 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Serbia in 2014

	P. aeruginosa		*Acinetobacter* spp.	
	n	Resistance (%)	*n*	Resistance (%)
Aminoglycosides (R)	95	57	300	93
Fluoroquinolones (R)	95	47	318	92
Piperacillin or piperacillin-tazobactam (R)	95	21	NA	NA
Ceftazidime (R)	95	49	NA	NA
Carbapenems (R)	95	45	343	93
Carbapenems (I+R)	95	47	343	93
Multidrug resistance (R)	95	51	298	85

NA: not applicable.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.
The carbapenems group comprises imipenem and meropenem.
For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems.
For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems.

Table 6.32 Percentage of resistance for *S. aureus* among blood and CSF isolates in Serbia in 2014

	S. aureus	
	n	Resistance (%)
MRSA (R)	350	33
Fluoroquinolones (R)	347	27
Rifampicin (R)	288	13
Linezolid (R)	306	0

MRSA is calculated as resistance to cefoxitin or, if not available, to one or more of oxacillin, flucloxacillin, methicillin, cloxacillin and dicloxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin, levofloxacin and norfloxacin.

Table 6.33 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Serbia in 2014

	S. pneumoniae	
	n	Resistance (%)
Penicillin (R)	27[a]	30[a]
Penicillin (I+R)	27[a]	30[a]
Macrolides (R)	29[a]	31[a]
Macrolides (I+R)	29[a]	31[a]
Fluoroquinolones (R)	14[a]	0[a]
Third-generation cephalosporins (R)	27[a]	0[a]
Third-generation cephalosporins (I+R)	27[a]	4[a]
Multidrug resistance (I+R)	31	23

[a] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.
Penicillin resistance is based on penicillin or, if not available, on oxacillin.
The macrolides group comprises erythromycin, clarithromycin and azithromycin.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
Multidrug resistance is defined as resistance to penicillins and macrolides.

Table 6.34 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Serbia in 2014

	E. faecalis		*E. faecium*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (I+R)	97	23	60	97
High-level gentamicin (R)	88	60	54	85
Vancomycin (R)	98	2	61	61
Linezolid (I+R)	90	0	59	3

The aminopenicillins group comprises amoxicillin and ampicillin.

Table 6.35 Patient characteristics of 1877 isolates from Serbia in 2015, by pathogen

	E. coli	*K. pneumoniae*	*P. aeruginosa*	*Acinetobacter* spp.	*S. aureus*	*S. pneumoniae*	*E. faecalis*	*E. faecium*	**Total number of isolates**
Number of isolates; *n* (%)	272 (14)	365 (19)	148 (8)	457 (24)	366 (19)	45 (2)	138 (7)	86 (5)	**1877**
Isolate source (%)									
Blood	98	98	96	95	99	47	97	94	**1798**
Cerebrospinal fluid	2	2	4	5	1	53	3	6	**79**
Sex (%)									
Male	43	65	70	58	67	62	64	59	**1138**
Female	55	28	29	41	32	38	36	41	**705**
Unknown	1	6	1	0	1	0	0	0	**34**
Age in years (%)									
0–4	7	11	3	5	3	2	4	10	**110**
5–19	8	5	5	3	7	20	9	3	**110**
20–64	39	43	49	44	43	49	42	50	**819**
65 and over	39	34	32	37	38	29	41	33	**684**
Unknown	8	7	11	10	9	0	5	3	**154**
Hospital department (%)									
Emergency department	6	13	12	15	5	4	2	6	**178**
Haematology or oncology	11	7	16	2	9	7	4	8	**137**
Infectious disease ward	21	5	7	9	12	40	7	5	**200**
Internal medicine	25	13	8	10	37	18	34	27	**386**
Obstetrics and gynaecology	2	3	0	0	2	2	1	2	**28**
Surgery	6	24	22	29	11	2	22	19	**358**
Urology	4	2	1	2	2	0	1	1	**36**
Intensive care unit	12	19	32	29	14	11	22	23	**388**
Paediatrics or neonatal	8	8	1	3	3	9	4	7	**91**
Other	5	5	1	2	5	7	4	2	**70**
Unknown	1	0	0	0	0	0	0	0	**5**

Table 6.36 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Serbia in 2015

	E. coli		*K. pneumoniae*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (R)	259	68	NA	NA
Aminoglycosides (R)	270	35	332	83
Fluoroquinolones (R)	266	27	355	75
Fluoroquinolones (I+R)	266	28	355	77
Third-generation cephalosporins (R)	272	28	364	90
Third-generation cephalosporins (I+R)	272	31	364	91
Carbapenems (R)	272	1	365	39
Carbapenems (I+R)	272	1	365	44
Multidrug resistance (R)	270	16	326	65

NA: not applicable.
The aminopenicillins group comprises amoxicillin and ampicillin.
The aminoglycosides group comprises amikacin, gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.
The third-generation cephalosporins group comprises cefotaxime, ceftriaxone and ceftazidime.
The carbapenems group comprises imipenem and meropenem.
Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides.

Table 6.37 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Serbia in 2015

	P. aeruginosa		*Acinetobacter* spp.	
	n	Resistance (%)	*n*	Resistance (%)
Aminoglycosides (R)	148	64	440	94
Fluoroquinolones (R)	145	52	442	95
Piperacillin or piperacillin-tazobactam (R)	139	28	NA	NA
Ceftazidime (R)	145	50	NA	NA
Carbapenems (R)	148	54	457	95
Carbapenems (I+R)	148	56	457	95
Multidrug resistance (R)	147	54	429	90

NA: not applicable.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.
The carbapenems group comprises imipenem and meropenem.
For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems.
For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems.

Table 6.38 Percentage of resistance for *S. aureus* among blood and CSF isolates in Serbia in 2015

	S. aureus	
	n	Resistance (%)
MRSA (R)	366	33
Fluoroquinolones (R)	359	29
Rifampicin (R)	314	19
Linezolid (R)	311	0

MRSA is calculated as resistance to cefoxitin or, if not available, to one or more of oxacillin, flucloxacillin, methicillin, cloxacillin and dicloxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin, levofloxacin and norfloxacin.

Table 6.39 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Serbia in 2015

	S. pneumoniae	
	n	Resistance (%)
Penicillin (R)	44	14
Penicillin (I+R)	44	23
Macrolides (R)	41	54
Macrolides (I+R)	41	54
Fluoroquinolones (R)	42	0
Third-generation cephalosporins (R)	43	0
Third-generation cephalosporins (I+R)	43	2
Multidrug resistance (I+R)	44	18

Penicillin resistance is based on penicillin or, if not available, on oxacillin.
The macrolides group comprises erythromycin, clarithromycin and azithromycin.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
Multidrug resistance is defined as resistance to penicillins and macrolides.

Table 6.40 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Serbia in 2015

	E. faecalis		*E. faecium*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (I+R)	137	10	86	97
High-level gentamicin (R)	122	63	80	91
Vancomycin (R)	137	8	86	53
Linezolid (I+R)	129	0	84	0

The aminopenicillins group comprises amoxicillin and ampicillin.

6.5 Switzerland

6.5.1 Surveillance set-up

The Swiss Centre for Antibiotic Resistance was set up in 2004 in the framework of a national research programme. It is run by the Institute for Infectious Diseases, University of Berne and funded by the Swiss Federal Office of Public Health, the Swiss Conference of the Cantonal Ministers of Public Health and the University of Berne.

Twenty laboratories send all results from routine antibiotic susceptibility testing of all clinical bacteriology cultures on a regular basis (weekly or monthly) to a central database. There is no central collection of isolates or central confirmatory testing of isolates. A subset of antibiotic susceptibility testing results was provided to CAESAR, containing all first isolates from blood and CSF cultures per patient yielding organisms specified by CAESAR, for the periods 1 January to 31 December 2014 and 1 January to 31 December 2015.

The 20 participating laboratories provide services to about 70% of hospitalized patients and one third of ambulatory practitioners. The laboratories are geographically spread over all regions and include university and general hospital laboratories as well as private laboratories.

There are no national antibiotic susceptibility testing guidelines. Most laboratories changed from CLSI to EUCAST guidelines between 2011 and 2013. Most laboratories use automated systems; unusual antibiotic susceptibility testing results are confirmed locally, and invasive *S. pneumoniae* isolates are sent to a national reference centre for antibiotic susceptibility testing and serotyping. All laboratories are participating in at least one national or international external quality assurance programme. Switzerland therefore decided not to participate in the CAESAR external quality assessment exercise. Blood cultures are taken from all patients with suspected bloodstream infections presenting in a hospital, and CSF cultures are taken from patients suspected of having meningitis. Bacteriological cultures are reimbursed through the universal health insurance scheme.

6.5.2 Results

2014

Table 6.41 shows the patient characteristics of 9148 isolates from Switzerland, by pathogen. In *E. coli*, resistance ranged from 0% for carbapenems to 49% for aminopenicillins (Table 6.42). Multidrug resistance was 3% in *E. coli*. Resistance in *K. pneumoniae* was 1% for carbapenems and was highest for third-generation cephalosporins (8%). Multidrug resistance in *K. pneumoniae* was 3%. In *P. aeruginosa*, resistance was highest for piperacillin or piperacillin-tazobactam (11%, Table 6.43). Four per cent of *P. aeruginosa* isolates were multidrug resistant. The percentages of resistance in *Acinetobacter* spp. ranged from 5% for carbapenems to 11% for aminoglycosides and fluoroquinolones. Multidrug resistance in *Acinetobacter* spp. was 5%. Five per cent of *S. aureus* isolates were MRSA (Table 6.44). In *S. pneumoniae*, penicillin resistance was 2% and resistance was highest for macrolides (13%, Table 6.45). Three per cent of *S. pneumoniae* isolates were multidrug resistant. In *E. faecalis*, vancomycin had 0% resistance, and 1% were non-susceptible to linezolid (Table 6.46). Vancomycin resistance in *E. faecium* was 1%; none were non-susceptible to linezolid.

2015

Table 6.47 shows the patient characteristics for 9950 isolates from Switzerland, by pathogen. In *E. coli*, resistance ranged from 0% for carbapenems to 49% for aminopenicillins (Table 6.48). Multidrug resistance was 3% in *E. coli*. Resistance in *K. pneumoniae* was 0% for carbapenems and was highest for third-generation cephalosporins (7%). Multidrug resistance in *K. pneumoniae* was 3%. In *P. aeruginosa*, resistance was highest for piperacillin or piperacillin-tazobactam (12%, Table 6.49). Five per cent of *P. aeruginosa* isolates were multidrug resistant. The percentages of resistance in *Acinetobacter* spp. ranged from 6% for carbapenems to 8% for aminoglycosides and fluoroquinolones. Multidrug resistance in *Acinetobacter* spp. was 5%.

Four per cent of *S. aureus* isolates were MRSA (Table 6.50). In *S. pneumoniae*, penicillin resistance was 4% and resistance was highest for macrolides (8%, Table 6.51). Three per cent of *S. pneumoniae* isolates were multidrug resistant. Vancomycin resistance was 0% in *E. faecalis* and 1% in *E. faecium* (Table 6.52). In *E. faecium*, 1% of the isolates were non-susceptible to linezolid.

6.5.3 Discussion

The AMR surveillance network submitted antibiotic susceptibility testing results for 9148 isolates from blood or CSF in Switzerland in 2014 and the results for 9950 isolates in 2015. *E. coli* was the main pathogen isolated (50%), followed by *S. aureus* (18%) and *K. pneumoniae* (9%). About 7% of the isolates were from patients admitted to intensive care units. Based on the large number of isolates and the distribution of pathogens, there is no indication of selective sampling of patients. The reported percentages of resistance are therefore expected to be generalizable to the overall patient population presenting with invasive infections in Switzerland.

The data from Switzerland are assessed as level A. The data presented are judged to be generalizable to the target population, and the antibiotic susceptibility testing results seem to be reliable. The data provide a valid assessment of the magnitude and trends of AMR in the country. The readers' guide (Table 5.1) provides additional information on interpreting the data and how the level of evidence was determined.

Chapter 8 displays the proportions of resistance for selected pathogen–antibiotic combinations reported by Switzerland in maps of the WHO European Region (Fig. 8.1–8.6). Besides the data from the CAESAR countries and areas, the maps present data from the EARS-Net at the ECDC. For all pathogens, the percentages of resistance are comparable with those in countries close to Switzerland and comparable or slightly higher than in 2013 *(1)*.

Table 6.41 Patient characteristics of 9148 isolates from Switzerland in 2014, by pathogen

	E. coli	*K. pneumoniae*	*P. aeruginosa*	*Acinetobacter* spp.	*S. aureus*	*S. pneumoniae*	*E. faecalis*	*E. faecium*	**Total number of isolates**
Number of isolates; *n* (%)	4550 (50)	852 (9)	431 (5)	77 (1)	1656 (18)	551 (6)	634 (7)	397 (4)	**9148**
Isolate source (%)									
Blood	100	100	99	95	100	97	100	100	**9117**
Cerebrospinal fluid	0	0	1	5	0	3	0	0	**31**
Sex (%)									
Male	45	63	69	69	63	54	68	64	**4965**
Female	55	37	31	31	37	46	32	36	**4180**
Unknown	0	0	0	0	0	0	0	0	**3**
Age in years (%)									
0–4	2	3	3	5	3	5	6	3	**275**
5–19	1	1	1	6	3	3	1	1	**137**
20–64	28	29	30	40	35	29	26	37	**2721**
65 and over	69	67	66	48	59	63	67	59	**6015**
Hospital department (%)									
Emergency department	29	20	16	10	23	34	14	7	**2270**
Haematology or oncology	2	4	3	4	1	2	0	3	**172**
Internal medicine	13	19	18	18	17	9	21	31	**1461**
Obstetrics and gynaecology	1	1	0	0	0	0	0	0	**67**
Surgery	5	8	13	6	9	1	12	16	**645**
Urology	1	1	1	0	0	0	1	1	**83**
Intensive care unit	4	6	9	8	7	7	8	16	**554**
Paediatrics or neonatal	1	2	1	1	2	1	2	1	**113**
Paediatric or neonatal intensive care unit	0	0	0	3	1	1	0	1	**55**
Other	43	40	36	49	38	45	41	25	**3728**

Table 6.42 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Switzerland in 2014

	E. coli		*K. pneumoniae*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (R)	4210	49	NA	NA
Aminoglycosides (R)	4543	8	850	6
Fluoroquinolones (R)	4541	17	850	6
Fluoroquinolones (I+R)	4541	18	850	9
Third-generation cephalosporins (R)	4547	8	848	8
Third-generation cephalosporins (I+R)	4547	9	848	10
Carbapenems (R)	4539	0	851	1
Carbapenems (I+R)	4539	0	851	1
Multidrug resistance (R)	4550	3	850	3

NA: not applicable.
The aminopenicillins group comprises amoxicillin and ampicillin.
The aminoglycosides group comprises amikacin, gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.
The third-generation cephalosporins group comprises cefotaxime, ceftriaxone and ceftazidime.
The carbapenems group comprises imipenem and meropenem.
Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides.

Table 6.43 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Switzerland in 2014

	P. aeruginosa		*Acinetobacter* spp.	
	n	Resistance (%)	*n*	Resistance (%)
Aminoglycosides (R)	430	3	62	11
Fluoroquinolones (R)	429	8	75	11
Piperacillin or piperacillin-tazobactam (R)	414	11	NA	NA
Ceftazidime (R)	403	9	NA	NA
Carbapenems (R)	427	10	75	5
Carbapenems (I+R)	427	12	75	8
Multidrug resistance (R)	427	4	77	5

NA: not applicable.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.
The carbapenems group comprises imipenem and meropenem.
For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems.
For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems.

Table 6.44 Percentage of resistance for *S. aureus* among blood and CSF isolates in Switzerland in 2014

	S. aureus	
	n	Resistance (%)
MRSA (R)	1643	5
Fluoroquinolones (R)	1645	8
Rifampicin (R)	1605	1
Linezolid (R)	880	0

MRSA is calculated as resistance to cefoxitin or, if not available, to one or more of oxacillin, flucloxacillin, methicillin, cloxacillin and dicloxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin, levofloxacin and norfloxacin.

Table 6.45 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Switzerland in 2014

	S. pneumoniae	
	n	Resistance (%)
Penicillin (R)	519	2
Penicillin (I+R)	519	7
Macrolides (R)	454	13
Macrolides (I+R)	454	13
Fluoroquinolones (R)	410	1
Third-generation cephalosporins (R)	351	0
Third-generation cephalosporins (I+R)	351	1
Multidrug resistance (I+R)	532	3

Penicillin resistance is based on penicillin or, if not available, on oxacillin.
The macrolides group comprises erythromycin, clarithromycin and azithromycin.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
Multidrug resistance is defined as resistance to penicillins and macrolides.

Table 6.46 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates Switzerland in 2014

	E. faecalis		*E. faecium*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (I+R)	579	0	327	80
High-level gentamicin (R)	214	12	137	34
Vancomycin (R)	576	0	347	1
Linezolid (I+R)	415	1	271	0

The aminopenicillins group comprises amoxicillin and ampicillin.

Table 6.47 Patient characteristics of 9950 isolates from Switzerland in 2015, by pathogen

	E. coli	*K. pneumoniae*	*P. aeruginosa*	*Acinetobacter* spp.	*S. aureus*	*S. pneumoniae*	*E. faecalis*	*E. faecium*	**Total number of isolates**
Number of isolates; *n* (%)	4914 (49)	907 (9)	490 (5)	64 (1)	1729 (17)	640 (6)	723 (7)	483 (5)	**9950**
Isolate source (%)									
Blood	100	100	99	98	100	98	100	100	**9932**
Cerebrospinal fluid	0	0	1	2	0	2	0	0	**18**
Sex (%)									
Male	46	58	68	45	66	52	58	61	**5311**
Female	54	42	32	55	34	48	42	39	**4635**
Unknown	0	0	0	0	0	0	0	0	**4**
Age in years (%)									
0–4	4	2	2	9	2	3	20	4	**437**
5–19	1	1	1	3	3	2	1	1	**125**
20–64	27	29	32	27	33	36	20	32	**2852**
65 and over	69	69	64	61	61	59	59	63	**6536**
Hospital department (%)									
Emergency department	30	23	16	13	25	35	17	11	**2577**
Haematology or oncology	1	3	4	0	2	0	1	4	**172**
Internal medicine	12	15	16	16	16	9	14	25	**1364**
Obstetrics and gynaecology	1	0	1	0	1	0	1	1	**93**
Surgery	5	10	9	3	8	1	8	14	**668**
Urology	1	1	1	0	0	0	1	1	**75**
Intensive care unit	4	6	10	13	7	5	8	16	**578**
Paediatrics or neonatal	2	2	2	3	3	2	2	1	**181**
Paediatric or neonatal intensive care unit	0	0	0	0	1	0	1	0	**38**
Other	44	40	40	53	39	47	46	27	**4204**

Table 6.48 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Switzerland in 2015

	E. coli		*K. pneumoniae*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (R)	4459	49	NA	NA
Aminoglycosides (R)	4893	9	905	5
Fluoroquinolones (R)	4870	17	904	6
Fluoroquinolones (I+R)	4870	19	904	8
Third-generation cephalosporins (R)	4894	10	905	7
Third-generation cephalosporins (I+R)	4894	10	905	8
Carbapenems (R)	4909	0	907	0
Carbapenems (I+R)	4909	0	907	0
Multidrug resistance (R)	4909	3	906	3

NA: not applicable.
The aminopenicillins group comprises amoxicillin and ampicillin.
The aminoglycosides group comprises amikacin, gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.
The third-generation cephalosporins group comprises cefotaxime, ceftriaxone and ceftazidime.
The carbapenems group comprises imipenem and meropenem.
Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides.

Table 6.49 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Switzerland in 2015

	P. aeruginosa		*Acinetobacter* spp.	
	n	Resistance (%)	*n*	Resistance (%)
Aminoglycosides (R)	488	3	60	8
Fluoroquinolones (R)	484	7	63	8
Piperacillin or piperacillin-tazobactam (R)	476	12	NA	NA
Ceftazidime (R)	474	10	NA	NA
Carbapenems (R)	485	10	64	6
Carbapenems (I+R)	485	12	64	11
Multidrug resistance (R)	485	5	64	5

NA: not applicable.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.
The carbapenems group comprises imipenem and meropenem.
For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems.
For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems.

Table 6.50 Percentage of resistance for *S. aureus* among blood and CSF isolates in Switzerland in 2015

	S. aureus	
	n	**Resistance (%)**
MRSA (R)	1724	4
Fluoroquinolones (R)	1724	6
Rifampicin (R)	1627	0
Linezolid (R)	768	0

MRSA is calculated as resistance to cefoxitin or, if not available, to one or more of oxacillin, flucloxacillin, methicillin, cloxacillin and dicloxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin, levofloxacin and norfloxacin.

Table 6.51 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Switzerland in 2015

	S. pneumoniae	
	n	**Resistance (%)**
Penicillin (R)	624	4
Penicillin (I+R)	624	6
Macrolides (R)	561	8
Macrolides (I+R)	561	9
Fluoroquinolones (R)	475	1
Third-generation cephalosporins (R)	408	0
Third-generation cephalosporins (I+R)	408	0
Multidrug resistance (I+R)	635	3

Penicillin resistance is based on penicillin or, if not available, on oxacillin.
The macrolides group comprises erythromycin, clarithromycin and azithromycin.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
Multidrug resistance is defined as resistance to penicillins and macrolides.

Table 6.52 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates Switzerland in 2015

	E. faecalis		*E. faecium*	
	n	**Resistance (%)**	*n*	**Resistance (%)**
Aminopenicillins (I+R)	682	0	407	80
High-level gentamicin (R)	240	13	181	44
Vancomycin (R)	653	0	426	1
Linezolid (I+R)	380	0	318	1

The aminopenicillins group comprises amoxicillin and ampicillin.

6.6 The former Yugoslav Republic of Macedonia

6.6.1 Surveillance set-up

All results from the routine antibiotic susceptibility testing of clinical bacteriology cultures were collected on paper monthly from six (2014) and 12 (2015) microbiology laboratories in the former Yugoslav Republic of Macedonia. The CAESAR national data team collected data independently from the national AMR surveillance system managed by the Institute for Public Health. As data came in, their quality and consistency were checked, and errors were fed back to the laboratories and corrected where applicable. Confirmatory testing of highly resistant microorganisms is required before the results are included in the final dataset. A subset of antibiotic susceptibility testing results, containing all first isolates from blood and CSF cultures yielding organisms specified by CAESAR, for the periods 1 January to 31 December 2014 and 1 January to 31 December 2015 were provided to CAESAR.

In 2014, six laboratories (of 29 public and private) participated in national AMR surveillance. These provide diagnostic support for about 65% of hospitals, including academic, clinical and general hospitals. The six laboratories are located in the capital city of Skopje and in the south-western part of the country. No data are available from laboratories in the eastern, western, central and northern parts of the country. In 2015, 12 laboratories participated in national AMR surveillance, covering about 79% of hospitals. The laboratories are geographically spread out in the capital city of Skopje and the south-western, western, central and eastern parts of the country. Regarding coverage of the population, almost half the population lives and uses health services in Skopje, which is well covered with public and private microbiological laboratories reporting to CAESAR as well as referral of patients from other hospitals in the country to the University Clinical Center in Skopje.

Antimicrobial susceptibility is routinely tested using disk diffusion tests and automated systems. There are laboratories that use gradient tests for minimum inhibitory concentrations to confirm highly resistant microorganisms or exceptional phenotypes. Sixteen microbiological laboratories in 2014 and in 2015 took part in the international (CAESAR and UK NEQAS) external quality control exercise.

Laboratories are required to follow national guidelines on bacteriological methods for testing special resistance. For methods and interpretation of antibiotic susceptibility testing, most laboratories still use the CLSI system but are in the process of adopting EUCAST methods as the national standard. EUCAST guidelines were translated and distributed to all laboratories in 2013, and workshops for implementing EUCAST methods were held. In November 2014, a second Combating Bacterial Resistance Europe – Networks (COMBACTE) LAB-Net workshop on antibiotic resistance was organized with participants from all microbiological laboratories in the country and representatives from five neighbouring countries (Albania, Bosnia, Bulgaria, Montenegro and Serbia) and Kosovo[1] with practical sessions on detecting multidrug-resistant organisms and discussions about switching from CLSI to EUCAST. New copies of translated EUCAST guidelines were delivered to all participants from the former Yugoslav Republic of Macedonia with a kind reminder to start the process of implementing EUCAST. The laboratories are still in the process of procuring media and antimicrobial discs in accordance with EUCAST standards. According to national clinical guidelines, blood cultures should be taken from all patients with suspected bloodstream infections (sepsis) presenting in hospital, and CSF cultures are taken from patients suspected of having meningitis. Bacteriology cultures are reimbursed through the national health insurance fund for outpatients. The number of blood cultures from hospitals is low due to lack of money.

6.6.2 Results

2014

Table 6.53 shows the patient characteristics of 221 isolates from the former Yugoslav Republic of Macedonia in 2014, by pathogen. In *E. coli*, resistance was 64% for aminoglycosides and higher for all tested antimicrobial

[1] All references to Kosovo in this chapter should be understood as references to Kosovo in accordance with United Nations Security Council resolution 1244 (1999).

agents except for carbapenems (0%, Table 6.54). Multidrug resistance was 48% in *E. coli*. Resistance in *K. pneumoniae* was 32% for fluoroquinolones and higher for all other agents except for carbapenems (0%). Multidrug resistance in *K. pneumoniae* was 26%. Resistance in only eight *P. aeruginosa* isolates ranged from 38% for carbapenems to 100% for ceftazidime (Table 6.55). Multidrug resistance was 57% in *P. aeruginosa*. In *Acinetobacter* spp., resistance was 65% for carbapenems and higher for all other agents. Multidrug resistance in *Acinetobacter* spp. was 65%. Thirty-seven per cent of *S. aureus* isolates were MRSA, and linezolid resistance was 2% (Table 6.56). Based on only six *S. pneumoniae* isolates, no resistance was found except for macrolides (17%, Table 6.57). Vancomycin resistance was 5% in *E. faecalis* and 65% in *E. faecium*, respectively (Table 6.58).

2015

Table 6.59 shows the patient characteristics of 217 isolates from the former Yugoslav Republic of Macedonia in 2015, by pathogen. In *E. coli*, resistance was 59% for aminoglycosides and higher for all tested antimicrobial agents except for carbapenems (0%, Table 6.60). Multidrug resistance was 47% in *E. coli*. Resistance in *K. pneumoniae* was 33% for fluoroquinolones and higher for all other agents except for carbapenems (0%). Multidrug resistance in *K. pneumoniae* was 33%. Resistance in only 12 *P. aeruginosa* isolates ranged from 33% for aminoglycosides and piperacillin or piperacillin-tazobactam to 42% for carbapenems (Table 6.61). Multidrug resistance was 30% in *P. aeruginosa*. In *Acinetobacter* spp., resistance was 84% for aminoglycosides and carbapenems and 93% for fluoroquinolones. Multidrug resistance in *Acinetobacter* spp. was 73%. Forty-three per cent of *S. aureus* isolates were MRSA (Table 6.62), and 2% were resistant to linezolid. Based on only five *S. pneumoniae* isolates, resistance to penicillin, as well as multidrug resistance, was 20% (Table 6.63). Vancomycin resistance was 0% in *E. faecalis* and 50% in *E. faecium*, respectively (Table 6.64).

6.6.3 Discussion

CAESAR laboratories in the former Yugoslav Republic of Macedonia submitted antibiotic susceptibility testing results for 221 isolates from blood or CSF in 2014 and results for 217 isolates in 2015. The 12 network laboratories provide good geographical coverage, except for the eastern part of the country. However, most isolates (about 70%) were processed at the Department of Microbiology and Parasitology of the Medical Faculty in Skopje, which provides diagnostic support for the main tertiary care hospital in the country. The predominance of isolates from referred patients may have led to a disproportionate contribution of more severely ill patients and patients sampled following initial antibiotic treatment provided at a peripheral hospital before referral. The low overall number of isolates reflects the low utilization of blood culture diagnostics in general, which is thought to result from financial constraints. Besides bias towards higher resistance caused by selective sampling, few isolates make the observed proportions of resistance more sensitive to random variation, such as from nosocomial outbreaks. The reported percentages of resistance should be interpreted with caution and are not necessarily generalizable to any one patient presenting with invasive infection in the former Yugoslav Republic of Macedonia, especially patients with community-acquired infections.

Nevertheless, the patient population sampled had very high levels of resistance to third-generation cephalosporins, aminoglycosides and fluoroquinolones in *E. coli* and *K. pneumoniae*. Carbapenem resistance in *E. coli* and *K. pneumoniae* from blood and CSF was 0% in 2014 and 2015, although carbapenem resistance reportedly has been seen in other specimen types in the country (such as wounds). The level of MRSA was similar to countries close to the former Yugoslav Republic of Macedonia (Fig. 8.6). Although based on few isolates, in *S. aureus*, linezolid resistance (2% in both 2014 and 2015) is an unusual finding. False-positive automated test results are the most likely explanation. Too few antibiotic susceptibility testing results for *P. aeruginosa* and *S. pneumoniae* were available to allow interpretation. Although based on few isolates tested, the high levels of resistance in *Acinetobacter* spp. and the high proportion of *E. faecium* resistant to vancomycin (50–64%) are concerning and may reflect the dissemination of resistant clones in the healthcare setting.

The data from the former Yugoslav Republic of Macedonia are assessed as level B. The overrepresentation of more severely ill and pretreated patients (selective sampling) and an overall low number of isolates (low utilization of blood culture diagnostics) constrain the representativeness of the results. The antibiotic susceptibility testing results seem to be reliable and comparable. The data indicate the resistance patterns present in clinical settings in the country, but the proportion of resistance should be interpreted with care. The country has an active AMR surveillance network that has been working on implementing harmonized antibiotic susceptibility testing methods and breakpoints and has expanded the coverage of the network. Increasing diagnostic utilization of blood cultures, especially in regional hospitals, will lead more valid assessment of AMR in the country. The readers' guide (Table 5.1) provides additional information on interpreting the data and how the level of evidence was determined.

Chapter 8 displays the proportions of resistance for selected pathogen–antibiotic combinations reported by the former Yugoslav Republic of Macedonia in maps of the WHO European Region (Fig. 8.1–8.6). Besides the data from the CAESAR countries and areas, the maps present data from the EARS-Net at the ECDC.

Table 6.53 Patient characteristics of 221 isolates from the former Yugoslav Republic of Macedonia in 2014, by pathogen

	E. coli	*K. pneumoniae*	*P. aeruginosa*	*Acinetobacter* spp.	*S. aureus*	*S. pneumoniae*	*E. faecalis*	*E. faecium*	**Total number of isolates**
Number of isolates; *n* (%)	56 (25)	38 (17)	8 (4)	26 (12)	45 (20)	6 (3)	19 (9)	23 (10)	**221**
Isolate source (%)									
Blood	100	97	88	92	98	33	95	96	**210**
Cerebrospinal fluid	0	3	13	8	2	67	5	4	**11**
Sex (%)									
Male	46	47	75	46	56	50	58	74	**118**
Female	45	16	25	46	38	50	42	26	**79**
Unknown	9	37	0	8	7	0	0	0	**24**
Age in years (%)									
0–4	16	63	38	23	18	0	5	0	**51**
5–19	5	5	0	4	4	0	0	9	**10**
20–64	36	18	25	35	38	50	37	70	**81**
65 and over	34	13	25	19	33	17	26	9	**54**
Unknown	9	0	13	19	7	33	32	13	**25**
Hospital department (%)									
Haematology or oncology	2	0	0	0	2	0	0	9	**4**
Infectious disease ward	18	3	13	4	2	83	16	0	**22**
Internal medicine	25	8	25	4	9	0	11	43	**36**
Obstetrics and gynaecology	7	8	0	4	0	0	0	0	**8**
Surgery	9	11	25	27	7	0	32	26	**33**
Urology	30	11	13	23	53	17	32	9	**61**
Intensive care unit	0	24	0	15	0	0	5	9	**16**
Paediatrics or neonatal	5	8	13	8	11	0	0	0	**14**
Paediatric or neonatal intensive care unit	4	29	13	15	7	0	5	4	**23**
Unknown	0	0	0	0	9	0	0	0	**4**

Table 6.54 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in the former Yugoslav Republic of Macedonia in 2014

	E. coli		*K. pneumoniae*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (R)	28[a]	86[a]	NA	NA
Aminoglycosides (R)	56	64	37	78
Fluoroquinolones (R)	55	73	38	32
Fluoroquinolones (I+R)	55	73	38	32
Third-generation cephalosporins (R)	56	73	38	82
Third-generation cephalosporins (I+R)	56	75	38	82
Carbapenems (R)	56	0	38	0
Carbapenems (I+R)	56	2	38	0
Multidrug resistance (R)	56	48	38	26

NA: not applicable.

[a] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.

The aminopenicillins group comprises amoxicillin and ampicillin.

The aminoglycosides group comprises amikacin, gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

The third-generation cephalosporins group comprises cefotaxime, ceftriaxone and ceftazidime.

The carbapenems group comprises imipenem and meropenem.

Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides.

Table 6.55 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in the former Yugoslav Republic of Macedonia in 2014

	P. aeruginosa		*Acinetobacter* spp.	
	n	Resistance (%)	*n*	Resistance (%)
Aminoglycosides (R)	8[a]	50[a]	26[a]	88[a]
Fluoroquinolones (R)	8[a]	50[a]	26[a]	85[a]
Piperacillin or piperacillin-tazobactam (R)	7[a]	43[a]	NA	NA
Ceftazidime (R)	3[a]	100[a]	NA	NA
Carbapenems (R)	8[a]	38[a]	26[a]	65[a]
Carbapenems (I+R)	8[a]	38[a]	26[a]	69[a]
Multidrug resistance (R)	7[a]	57[a]	26[a]	65[a]

NA: not applicable.

[a] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.

The aminoglycosides group comprises gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin and levofloxacin.

The carbapenems group comprises imipenem and meropenem.

For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems.

For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems.

Table 6.56 Percentage of resistance for *S. aureus* among blood and CSF isolates in the former Yugoslav Republic of Macedonia in 2014

	S. aureus	
	n	Resistance (%)
MRSA (R)	43	37
Fluoroquinolones (R)	43	9
Rifampicin (R)	39	3
Linezolid (R)	43	2

MRSA is calculated as resistance to cefoxitin or, if not available, to one or more of oxacillin, flucloxacillin, methicillin, cloxacillin and dicloxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin, levofloxacin and norfloxacin.

Table 6.57 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in the former Yugoslav Republic of Macedonia in 2014

	S. pneumoniae	
	n	Resistance (%)
Penicillin (R)	5[a]	0[a]
Penicillin (I+R)	5[a]	0[a]
Macrolides (R)	6[a]	17[a]
Macrolides (I+R)	6[a]	17[a]
Fluoroquinolones (R)	5[a]	0[a]
Third-generation cephalosporins (R)	6[a]	0[a]
Third-generation cephalosporins (I+R)	6[a]	0[a]
Multidrug resistance (I+R)	5[a]	0[a]

[a] Few isolates were tested (*n* < 30), and the percentage of resistance should be interpreted with caution.
Penicillin resistance is based on penicillin or, if not available, on oxacillin.
The macrolides group comprises erythromycin, clarithromycin and azithromycin.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
Multidrug resistance is defined as resistance to penicillins and macrolides.

Table 6.58 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in the former Yugoslav Republic of Macedonia in 2014

	E. faecalis		*E. faecium*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (I+R)	19[a]	11[a]	23[a]	87[a]
High-level gentamicin (R)	19[a]	89[a]	22[a]	86[a]
Vancomycin (R)	19[a]	5[a]	23[a]	65[a]
Linezolid (I+R)	19[a]	0[a]	22[a]	0[a]

[a] Few isolates were tested (*n* < 30), and the percentage of resistance should be interpreted with caution.
The aminopenicillins group comprises amoxicillin and ampicillin.

Table 6.59 Patient characteristics of 217 isolates from the former Yugoslav Republic of Macedonia in 2015, by pathogen

	E. coli	*K. pneumoniae*	*P. aeruginosa*	*Acinetobacter* spp.	*S. aureus*	*S. pneumoniae*	*E. faecalis*	*E. faecium*	**Total number of isolates**
Number of isolates; *n* (%)	56 (26)	24 (11)	12 (6)	31 (14)	56 (26)	5 (2)	23 (11)	10 (5)	**217**
Isolate source (%)									
Blood	100	92	75	90	96	40	91	100	**202**
Cerebrospinal fluid	0	8	25	10	4	60	9	0	**15**
Sex (%)									
Male	57	33	67	55	61	60	74	80	**127**
Female	41	33	33	39	36	40	26	20	**77**
Unknown	2	33	0	6	4	0	0	0	**13**
Age in years (%)									
0–4	5	58	17	35	29	40	0	20	**50**
5–19	4	4	0	0	5	0	0	20	**8**
20–64	34	8	33	42	43	60	35	20	**75**
65 and over	43	25	42	19	16	0	57	30	**66**
Unknown	14	4	8	3	7	0	9	10	**18**
Hospital department (%)									
Haematology or oncology	20	0	8	6	4	0	0	0	**16**
Infectious disease ward	20	0	25	23	11	60	17	10	**35**
Internal medicine	9	4	0	3	9	20	22	20	**20**
Obstetrics and gynaecology	4	13	0	0	0	0	0	0	**5**
Surgery	5	13	8	26	4	0	13	30	**23**
Urology	36	13	17	3	34	0	43	20	**57**
Intensive care unit	0	8	17	3	4	0	0	0	**7**
Paediatrics or neonatal	5	17	17	19	25	20	4	10	**32**
Paediatric or neonatal intensive care unit	0	33	8	16	5	0	0	10	**18**
Unknown	2	0	0	0	5	0	0	0	**4**

Table 6.60 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in the former Yugoslav Republic of Macedonia in 2015

	E. coli		*K. pneumoniae*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (R)	12[a]	83[a]	NA	NA
Aminoglycosides (R)	56	59	24[a]	79[a]
Fluoroquinolones (R)	55	69	24[a]	33[a]
Fluoroquinolones (I+R)	55	69	24[a]	42[a]
Third-generation cephalosporins (R)	56	66	24[a]	87[a]
Third-generation cephalosporins (I+R)	56	70	24[a]	87[a]
Carbapenems (R)	56	0	24[a]	0[a]
Carbapenems (I+R)	56	0	24[a]	0[a]
Multidrug resistance (R)	55	47	24[a]	33[a]

NA: not applicable.

[a] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.

The aminopenicillins group comprises amoxicillin and ampicillin.

The aminoglycosides group comprises amikacin, gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

The third-generation cephalosporins group comprises cefotaxime, ceftriaxone and ceftazidime.

The carbapenems group comprises imipenem and meropenem.

Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides.

Table 6.61 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in the former Yugoslav Republic of Macedonia in 2015

	P. aeruginosa		*Acinetobacter spp.*	
	n	Resistance (%)	*n*	Resistance (%)
Aminoglycosides (R)	12[a]	33[a]	31	84
Fluoroquinolones (R)	11[a]	36[a]	30	93
Piperacillin or piperacillin-tazobactam (R)	6[a]	33[a]	NA	NA
Ceftazidime (R)	3[a]	0[a]	NA	NA
Carbapenems (R)	12[a]	42[a]	31	84
Carbapenems (I+R)	12[a]	42[a]	31	87
Multidrug resistance (R)	10[a]	30[a]	30	73

NA: not applicable.

[a] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.

The aminoglycosides group comprises gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin and levofloxacin.

The carbapenems group comprises imipenem and meropenem.

For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems.

For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems.

Table 6.62 Percentage of resistance for *S. aureus* among blood and CSF isolates in the former Yugoslav Republic of Macedonia in 2015

	S. aureus	
	n	Resistance (%)
MRSA (R)	54	43
Fluoroquinolones (R)	52	8
Rifampicin (R)	53	6
Linezolid (R)	53	2

MRSA is calculated as resistance to cefoxitin or, if not available, to one or more of oxacillin, flucloxacillin, methicillin, cloxacillin and dicloxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin, levofloxacin and norfloxacin.

Table 6.63 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in the former Yugoslav Republic of Macedonia in 2015

	S. pneumoniae	
	n	Resistance (%)
Penicillin (R)	5[a]	20[a]
Penicillin (I+R)	5[a]	20[a]
Macrolides (R)	5[a]	60[a]
Macrolides (I+R)	5[a]	60[a]
Fluoroquinolones (R)	4[a]	0[a]
Third-generation cephalosporins (R)	5[a]	0[a]
Third-generation cephalosporins (I+R)	5[a]	0[a]
Multidrug resistance (I+R)	5[a]	20[a]

[a] Few isolates were tested (*n* < 30), and the percentage of resistance should be interpreted with caution.
Penicillin resistance is based on penicillin or, if not available, on oxacillin.
The macrolides group comprises erythromycin, clarithromycin and azithromycin.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
Multidrug resistance is defined as resistance to penicillins and macrolides.

Table 6.64 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in the former Yugoslav Republic of Macedonia in 2015

	E. faecalis		*E. faecium*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (I+R)	22[a]	27[a]	7[a]	57[a]
High-level gentamicin (R)	22[a]	64[a]	6[a]	67[a]
Vancomycin (R)	22[a]	0[a]	10[a]	50[a]
Linezolid (I+R)	22[a]	0[a]	10[a]	0[a]

[a] Few isolates were tested (*n* < 30), and the percentage of resistance should be interpreted with caution.
The aminopenicillins group comprises amoxicillin and ampicillin.

6.7 Turkey

6.7.1 Surveillance set-up

The Turkish national AMR surveillance system was established in 2011. The national reference laboratory collects data on AMR at the Public Health Institution of Turkey of the Ministry of Health. Antibiotic susceptibility testing results from blood and CSF culture isolates are collected into a standard database in six-month intervals from participating laboratories. As data come in, their quality and consistency are checked; errors are fed back to the laboratories and corrected where applicable. After these processes, the data are converted into CAESAR data format via Backlink in WHONET. A subset of antibiotic susceptibility testing results was provided to CAESAR, containing all first isolates from blood and CSF cultures per patient yielding organisms specified by CAESAR, for the periods 1 January to 31 December 2014 and 1 January to 31 December 2015.

The participating laboratories were selected from different geographical regions of the country to reflect the distribution of the population. In 2014, data from 47 laboratories were included: 25 clinical microbiology laboratories of university hospitals and 22 clinical microbiology laboratories of state hospitals. These hospitals cover about 33% of the hospital beds in Turkey. In 2015, data from 77 laboratories were included: 35 clinical microbiology laboratories of university hospitals, 39 clinical microbiology laboratories of state hospitals and three clinical microbiology laboratories of private hospitals. These hospitals cover about 37% of the hospital beds in Turkey.

Antimicrobial susceptibility is mostly tested using automated systems (33 laboratories in 2014 and 46 laboratories in 2015). Three laboratories used disk diffusion in 2014 and 11 in 2015. Eleven laboratories used a combination of automated systems and disk diffusion in 2014 and 20 in 2015.

All laboratories have implemented internal quality control. The Public Health Institution of Turkey has applied the national external quality control programme to participating laboratories once a year since 2011. The laboratories participating in CAESAR also participate in an international external quality assessment (UK NEQAS). Turkey has published national guidelines on bacteriological methods for testing antimicrobial susceptibility, which were updated in 2014. The methods of the AMR surveillance system are compatible with CAESAR methods. In 2014 and most of 2015, all laboratories used CLSI standards, but in late 2015, the new EUCAST-based standard was implemented in 52 laboratories. EUCAST documents were translated into Turkish in 2014 and are updated yearly.

According to national clinical guidelines, blood cultures are taken from all patients with suspected bloodstream infections presenting in hospital, and CSF cultures are taken from patients suspected of having meningitis. If unusual resistance is detected, isolates are to be sent to the reference centre for confirmation. Bacteriology cultures are reimbursed through the National Health Insurance Fund.

6.7.2 Results

2014

Table 6.65 shows the patient characteristics of 10 668 isolates from Turkey in 2014, by pathogen. In *E. coli*, resistance ranged from 29% to 76% for all antibiotic groups except for carbapenems (1%, Table 6.66). Multidrug resistance in *E. coli* was 14%. Resistance in *K. pneumoniae* was 28% for carbapenems and higher for all other antibiotic groups. Multidrug resistance was 20% in *K. pneumoniae*. In *P. aeruginosa*, resistance was lowest for aminoglycosides (18%) and highest for carbapenems (24%, Table 6.67). Multidrug resistance in *P. aeruginosa* was 17%. Resistance in *Acinetobacter* spp. was 74% for aminoglycosides and higher for the other antibiotic groups. Multidrug resistance was 66% in *Acinetobacter* spp. Twenty-seven per cent of *S. aureus* were MRSA (Table 6.68). In *S. pneumoniae*, penicillin resistance was 48%, and resistance to other agents ranged from 8% (third-generation cephalosporins) to 42% (macrolides, Table 6.69). Multidrug resistance was 24% in *S. pneumoniae*. Three per cent of *E. faecalis* isolates were resistant to

vancomycin, and 3% showed non-susceptibility to linezolid (Table 6.70). For *E. faecium*, these levels were 16% for vancomycin and 4% for linezolid.

2015

Table 6.71 shows the patient characteristics of 16 423 isolates from Turkey in 2015, by pathogen. In *E. coli*, resistance ranged from 28% to 78% for all antibiotic groups except for carbapenems (2%, Table 6.72). Multidrug resistance in *E. coli* was 16%. Resistance in *K. pneumoniae* was 30% for carbapenems and higher for all other antibiotic groups. Multidrug resistance was 32% in *K. pneumoniae*. In *P. aeruginosa*, resistance ranged from 17% to 32% for all antibiotic groups (Table 6.73). Multidrug resistance in *P. aeruginosa* was 21%. Resistance in *Acinetobacter* spp. was 80% for aminoglycosides and higher for the other antibiotic groups. Multidrug resistance was 77% in *Acinetobacter* spp. Twenty-five per cent of *S. aureus* were MRSA, and 1% of the isolates were resistant to linezolid (Table 6.74). In *S. pneumoniae*, penicillin resistance was 55%, and resistance to other agents ranged from 8% (fluoroquinolones) to 36% (macrolides, Table 6.75). Multidrug resistance was 11% in *S. pneumoniae*. Three per cent of *E. faecalis* isolates were resistant to vancomycin, and 2% showed non-susceptibility to linezolid (Table 6.76). For *E. faecium*, these levels were 16% for vancomycin and 4% for linezolid.

6.7.3 Discussion

The AMR surveillance network of Turkey submitted antibiotic susceptibility testing results for 10 668 isolates from blood or CSF in 2014 and 16 423 isolates in 2015. The large number of isolates and the distribution of pathogens, with *E. coli* being the most common pathogen isolated (26% in 2014 and 2015), suggest that the data represent a mix of community-acquired and healthcare-associated infections. However, the relatively large proportion of isolates coming from patients admitted to intensive care units (34% in 2014 and 40% in 2015) and the relatively large proportions of *K. pneumoniae*, *P. aeruginosa*, *Acinetobacter* spp. and *Enterococcus* spp. suggest that the data disproportionately reflect severely ill (pretreated) patients and patients with nosocomial infections. This could be explained by the tendency of clinicians to more often take blood cultures from patients admitted to an intensive care unit compared with patients in the emergency department.

E. coli and *K. pneumoniae* had high resistance to third-generation cephalosporins, aminoglycosides and fluoroquinolones. Compared with 2014, carbapenem resistance was slightly higher in 2015 in both *E. coli* and *K. pneumoniae*. The high level of carbapenem-resistant *K. pneumoniae* and the relatively high number of *Acinetobacter* spp. and their high percentages of resistance are of concern and likely reflect the dissemination of resistant clones in the healthcare setting. The level of MRSA was similar to countries close to Turkey (Fig. 8.6). The relatively low number of *S. pneumoniae* isolates and their high percentages of resistance may indicate infrequent routine blood culturing of severe pneumonia cases and selective sampling of treatment failures. Resistance in *P. aeruginosa* in general, and vancomycin resistance in *E. faecium*, was moderately high. Aminopenicillin non-susceptibility in *E. faecalis* was higher than expected. Methodological issues in determining species or antimicrobial susceptibility testing may have influenced these results. The findings of linezolid non-susceptibility in *S. aureus* (2015), *E. faecalis* and *E. faecium* are unusual. The national reference laboratory has confirmed resistance in 30% of these isolates. The remainder were mostly false-positive results obtained by automated antimicrobial susceptibility testing systems.

The data from Turkey are assessed as level A. The large quantity of high-quality antibiotic susceptibility testing data from a geographically representative network adequately assesses the trends of AMR in the country. However, there are indications that more severely ill patients and patients with healthcare-associated infections are overrepresented in the data, and this case mix should be taken into account when interpreting the data. The readers' guide (Table 5.1) provides additional information on interpreting the data and how the level of evidence was determined.

Chapter 8 displays the proportions of resistance for selected pathogen–antibiotic combinations reported by Turkey in maps of the WHO European Region (Fig. 8.1–8.6). Besides the data from the CAESAR countries and areas, the maps present data from the EARS-Net at the ECDC.

Table 6.65 Patient characteristics of 10 668 isolates from Turkey in 2014, by pathogen

	E. coli	*K. pneumoniae*	*P. aeruginosa*	*Acinetobacter* spp.	*S. aureus*	*S. pneumoniae*	*E. faecalis*	*E. faecium*	**Total number of isolates**
Number of isolates; *n* (%)	2 794 (26)	1 617 (15)	987 (9)	1 482 (14)	1 919 (18)	142 (1)	913 (9)	814 (8)	**10 668**
Isolate source (%)									
Blood	99	99	97	96	98	85	98	97	**10 420**
Cerebrospinal fluid	1	1	3	4	2	15	2	3	**248**
Sex (%)									
Male	52	57	60	54	58	64	50	51	**5 835**
Female	48	43	40	46	42	35	50	49	**4 825**
Unknown	0	0	0	0	0	1	0	0	**8**
Age in years (%)									
0–4	4	14	7	6	9	12	7	8	**835**
5–19	4	4	7	6	5	9	4	3	**495**
20–64	36	33	36	37	39	40	30	30	**3 744**
65 and over	40	29	34	36	36	30	48	41	**3 972**
Unknown	15	21	16	15	11	9	11	18	**1 622**
Hospital department (%)									
Emergency department	13	5	6	2	7	28	5	3	**757**
Haematology or oncology	14	9	7	3	6	4	4	8	**871**
Infectious disease ward	5	2	3	1	6	9	3	2	**392**
Internal medicine	24	18	17	14	27	15	19	18	**2 202**
Obstetrics and gynaecology	0	0	0	0	0	0	0	0	**35**
Surgery	14	13	18	14	11	8	13	11	**1 412**
Intensive care unit	18	36	35	57	26	18	46	47	**3 589**
Paediatrics or neonatal	3	7	7	4	6	13	4	5	**560**
Paediatric or neonatal intensive care unit	1	5	2	3	3	3	3	3	**291**
Unknown	6	6	5	2	8	1	3	2	**559**

Table 6.66 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Turkey in 2014

	E. coli		*K. pneumoniae*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (R)	1494	76	NA	NA
Aminoglycosides (R)	2738	29	1587	45
Fluoroquinolones (R)	2676	47	1454	42
Fluoroquinolones (I+R)	2676	48	1454	48
Third-generation cephalosporins (R)	2506	36	1407	52
Third-generation cephalosporins (I+R)	2506	39	1407	61
Carbapenems (R)	2486	1	1493	28
Carbapenems (I+R)	2486	2	1493	31
Multidrug resistance (R)	2723	14	1504	20

NA: not applicable.
The aminopenicillins group comprises amoxicillin and ampicillin.
The aminoglycosides group comprises amikacin, gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.
The third-generation cephalosporins group comprises cefotaxime, ceftriaxone and ceftazidime.
The carbapenems group comprises imipenem and meropenem.
Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides.

Table 6.67 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates Turkey in 2014

	P. aeruginosa		*Acinetobacter spp.*	
	n	Resistance (%)	*n*	Resistance (%)
Aminoglycosides (R)	961	18	1466	74
Fluoroquinolones (R)	886	19	1262	89
Piperacillin or piperacillin-tazobactam (R)	900	21	NA	NA
Ceftazidime (R)	828	19	NA	NA
Carbapenems (R)	914	24	1401	89
Carbapenems (I+R)	914	30	1401	90
Multidrug resistance (R)	878	17	1264	66

NA: not applicable.
The aminoglycosides group comprises gentamicin and tobramycin
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.
The carbapenems group comprises imipenem and meropenem.
For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems.
For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems.

Table 6.68 Percentage of resistance for *S. aureus* among blood and CSF isolates Turkey in 2014

	S. aureus	
	n	**Resistance (%)**
MRSA (R)	1575	27
Fluoroquinolones (R)	1470	15
Rifampicin (R)	105	14
Linezolid (R)	1681	0

MRSA is calculated as resistance to cefoxitin or, if not available, to one or more of oxacillin, flucloxacillin, methicillin, cloxacillin and dicloxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin, levofloxacin and norfloxacin.

Table 6.69 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Turkey in 2014

	S. pneumoniae	
	n	**Resistance (%)**
Penicillin (R)	99	48
Penicillin (I+R)	99	48
Macrolides (R)	109	42
Macrolides (I+R)	109	43
Fluoroquinolones (R)	109	22
Third-generation cephalosporins (R)	52	8
Third-generation cephalosporins (I+R)	52	25
Multidrug resistance (I+R)	104	24

Penicillin resistance is based on penicillin or, if not available, on oxacillin.
The macrolides group comprises erythromycin, clarithromycin and azithromycin.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
Multidrug resistance is defined as resistance to penicillins and macrolides.

Table 6.70 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Turkey in 2014

	E. faecalis		*E. faecium*	
	n	**Resistance (%)**	*n*	**Resistance (%)**
Aminopenicillins (I+R)	746	8	655	82
High-level gentamicin (R)	450	22	391	43
Vancomycin (R)	860	3	780	16
Linezolid (I+R)	806	3	721	4

The aminopenicillins group comprises amoxicillin and ampicillin.

Table 6.71 Patient characteristics of 10 668 isolates from Turkey in 2015, by pathogen

	E. coli	*K. pneumoniae*	*P. aeruginosa*	*Acinetobacter* spp.	*S. aureus*	*S. pneumoniae*	*E. faecalis*	*E. faecium*	**Total number of isolates**
Number of isolates; *n* (%)	4 159 (25)	2 570 (16)	1 344 (8)	2 418 (15)	2 591 (16)	186 (1)	1 664 (10)	1 491 (9)	**16 423**
Isolate source (%)									
Blood	99	98	97	96	98	86	98	98	**16 063**
Cerebrospinal fluid	1	2	3	4	2	14	2	2	**360**
Sex (%)									
Male	50	54	55	54	55	62	50	48	**8 567**
Female	45	45	41	40	40	33	45	44	**7 063**
Unknown	5	2	4	6	5	5	6	8	**793**
Age in years (%)									
0–4	5	16	9	10	9	12	10	11	**1 565**
5–19	4	6	7	5	7	13	3	4	**869**
20–64	44	40	42	42	43	42	34	35	**6 718**
65 and over	45	35	39	40	36	32	49	47	**6 764**
Unknown	3	3	2	4	3	1	3	3	**507**
Hospital department (%)									
Emergency department	3	2	2	0	3	5	1	1	**332**
Haematology or oncology	4	3	3	2	1	3	1	2	**418**
Infectious disease ward	0	0	0	0	0	2	0	0	**49**
Internal medicine	5	3	3	1	5	3	3	3	**619**
Obstetrics and gynaecology	0	0	0	0	0	0	0	0	**9**
Surgery	2	1	2	1	1	0	1	2	**265**
Intensive care unit	4	9	11	15	5	4	9	8	**1 313**
Paediatrics or neonatal	1	2	2	1	1	3	1	1	**211**
Paediatric or neonatal intensive care unit	0	1	0	1	1	0	1	1	**94**
Unknown	80	78	78	78	81	81	83	82	**13 113**

Table 6.72 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Turkey in 2015

	E. coli		*K. pneumoniae*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (R)	2730	78	NA	NA
Aminoglycosides (R)	4108	28	2550	44
Fluoroquinolones (R)	3996	48	2518	48
Fluoroquinolones (I+R)	3996	49	2518	52
Third-generation cephalosporins (R)	3852	51	2489	68
Third-generation cephalosporins (I+R)	3852	53	2489	70
Carbapenems (R)	3914	2	2533	30
Carbapenems (I+R)	3914	5	2533	35
Multidrug resistance (R)	4054	16	2510	32

NA: not applicable.
The aminopenicillins group comprises amoxicillin and ampicillin.
The aminoglycosides group comprises amikacin, gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.
The third-generation cephalosporins group comprises cefotaxime, ceftriaxone and ceftazidime.
The carbapenems group comprises imipenem and meropenem.
Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides.

Table 6.73 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates Turkey in 2015

	P. aeruginosa		*Acinetobacter* spp.	
	n	Resistance (%)	*n*	Resistance (%)
Aminoglycosides (R)	1333	17	2373	80
Fluoroquinolones (R)	1307	24	2372	89
Piperacillin or piperacillin-tazobactam (R)	1251	30	NA	NA
Ceftazidime (R)	1297	24	NA	NA
Carbapenems (R)	1314	32	2381	89
Carbapenems (I+R)	1314	37	2381	90
Multidrug resistance (R)	1303	21	2347	77

NA: not applicable.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.
The carbapenems group comprises imipenem and meropenem.
For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems.
For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems.

Table 6.74 Percentage of resistance for *S. aureus* among blood and CSF isolates Turkey in 2015

	S. aureus	
	n	**Resistance (%)**
MRSA (R)	795	25
Fluoroquinolones (R)	2084	14
Rifampicin (R)	0	No data available
Linezolid (R)	2354	1

MRSA is calculated as resistance to cefoxitin or, if not available, to one or more of oxacillin, flucloxacillin, methicillin, cloxacillin and dicloxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin, levofloxacin and norfloxacin.

Table 6.75 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Turkey in 2015

	S. pneumoniae	
	n	**Resistance (%)**
Penicillin (R)	44	55
Penicillin (I+R)	44	55
Macrolides (R)	166	36
Macrolides (I+R)	166	36
Fluoroquinolones (R)	156	8
Third-generation cephalosporins (R)	121	10
Third-generation cephalosporins (I+R)	121	25
Multidrug resistance (I+R)	123	11

Penicillin resistance is based on penicillin or, if not available, on oxacillin.
The macrolides group comprises erythromycin, clarithromycin and azithromycin.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
Multidrug resistance is defined as resistance to penicillins and macrolides.

Table 6.76 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Turkey in 2015

	E. faecalis		*E. faecium*	
	n	**Resistance (%)**	*n*	**Resistance (%)**
Aminopenicillins (I+R)	1563	9	1405	87
High-level gentamicin (R)	805	54	851	69
Vancomycin (R)	1536	3	1435	16
Linezolid (I+R)	1465	2	1395	4

The aminopenicillins group comprises amoxicillin and ampicillin.


CHAPTER
7

Area-specific data on antimicrobial resistance

7.1. Kosovo (in accordance with United Nations Security Council resolution 1244(1999)

7.1.1 Surveillance set-up

In Kosovo[1], all results from the routine antibiotic susceptibility testing of clinical bacteriology cultures were collected electronically at the Institute of Public Health of Kosovo and on paper at the six microbiology laboratories within the regional institutes of public health on a monthly basis. The AMR surveillance network managed by the Institute for Public Health of Kosovo collected the data. As data came in, their quality and consistency were checked, and errors were fed back to the laboratories and corrected where applicable. Confirmatory testing of highly resistant microorganisms was required before the results were included in the final dataset; the Institute of Public Health of Kosovo performed these tests. A subset of antibiotic susceptibility testing results was provided to CAESAR, containing all first isolates from blood and CSF cultures per patient yielding organisms specified by CAESAR for the periods 1 January to 31 December 2014 and 1 January to 31 December 2015. Only data from the Institute of Public Health of Kosovo were provided, since data from regional laboratories were not available electronically.

The seven participating public laboratories provide diagnostic support for seven hospitals (about 90% of the hospitals), including academic, clinical and general hospitals with a range of 120 to 2167 beds. The participating laboratories are geographically spread throughout Kosovo[1] and cover about 90% of the population.

Antimicrobial susceptibility at the Institute of Public Health of Kosovo is tested using automated systems and disk diffusion tests, whereas regional laboratories use disk diffusion tests in their work. If highly resistant microorganisms or exceptional phenotypes are found, the Institute of Public Health of Kosovo confirms the results. Laboratories (for clinical microbiology) in Kosovo[1] are not yet accredited by a accreditation institute, but they all took part in the international external quality control programmes (UK NEQAS and University of Antwerp, 2013 and 2014).

Laboratories are required to follow guidelines on bacteriological methods for testing special resistance. All laboratories in Kosovo[1] have been using EUCAST methods as the standard for performing and interpreting antibiotic susceptibility testing since 2013. Part of the EUCAST guidelines was translated into Albanian and distributed to all laboratories. Workshops for implementing EUCAST methods were held. All antimicrobial discs and media were procured according to EUCAST standards. Blood cultures are not taken from all patients with suspected bloodstream infections (sepsis) presenting in hospital; CSF cultures are taken from patients suspected of having meningitis. Kosovo[1] has not established a health insurance system yet. The number of blood cultures in regional hospitals is low due to lack of money and insufficient awareness among clinicians.

7.1.2 Results

2014

Table 7.1 shows the patient characteristics of 179 isolates from Kosovo[1], by pathogen. In *E. coli*, resistance ranged from 0% for carbapenems to 52% for aminopenicillins (Table 7.2). Multidrug resistance was 4% in *E. coli*. Resistance in *K. pneumoniae* was 91% or higher for all antibiotic groups except for

[1] All references to Kosovo in this chapter should be understood as references to Kosovo in accordance with United Nations Security Council resolution 1244 (1999).

fluoroquinolones (6%) and carbapenems (0%). Multidrug resistance in *K. pneumoniae* was 6%. In *P. aeruginosa*, resistance was 7% for fluoroquinolones but ranged from 36% to 64% for all other agents (Table 7.3). Multidrug resistance was 36% in *P. aeruginosa*. Resistance in *Acinetobacter* spp. was 88% or higher for all agents. Multidrug resistance in *Acinetobacter* spp. was 82%. Thirty-eight per cent of *S. aureus* isolates were MRSA (Table 7.4). Based on only six *S. pneumoniae* isolates, resistance was observed for penicillins (33%) but not for other agents (Table 7.5). The percentages of resistance for vancomycin and high-level gentamicin were 0% and 25%, respectively, in the 12 *E. faecalis* isolates tested and 50% and 100%, respectively, in the four *E. faecium* isolates tested (Table 7.6).

2015

Table 7.7 shows the patient characteristics of 122 isolates from Kosovo[1], by pathogen. In *E. coli*, resistance ranged from 0% for carbapenems to 69% for aminopenicillins (Table 7.8). Multidrug resistance was 24% in *E. coli*. Resistance in 18 *K. pneumoniae* isolates was 83% or higher except for fluoroquinolones (6%) and carbapenems (0%). Multidrug resistance in *K. pneumoniae* was 6%. Based on only 11 *P. aeruginosa* isolates, resistance ranged from 9% for fluoroquinolones to 55% for aminoglycosides (Table 7.9). Multidrug resistance was 9% in *P. aeruginosa*. Resistance in *Acinetobacter* spp. was 83% or higher for all agents. Multidrug resistance in *Acinetobacter* spp. was 83%. Forty-one per cent of *S. aureus* isolates were MRSA (Table 7.10). The results were available for only one *S. pneumoniae* isolate. It was resistant to penicillin and macrolides and therefore multidrug resistant (Table 7.11). Based on only six *E. faecalis* isolates, vancomycin resistance was not observed, but high-level gentamicin resistance was 67% (Table 7.12). The results for *E. faecium* were not available in 2015.

7.1.3 Discussion

The AMR surveillance network of Kosovo[1] submitted antibiotic susceptibility testing results for 179 isolates from blood or CSF in 2014 and 122 isolates were submitted in 2015. Although the network comprises seven public laboratories, only results from isolates processed at the Institute of Public Health of Kosovo, which provides microbiological diagnostic support for the main tertiary care hospital, were included in this report. Importantly, the majority of isolates (76% in 2014 and 67% in 2015) were from children 0–4 years of age, reflecting high utilization of blood culture diagnostics in the neonatal department. The low number of isolates from older children and adults reflects the low utilization of blood culture diagnostics otherwise, which is thought to be due to low perceived benefits by clinicians. The low number of blood cultures and the tertiary care setting suggest that the results disproportionately represent more severely ill patients and patients failing empirical antibiotic treatment preceding referral. In addition, low numbers of isolates make the observed resistance proportions more sensitive to random variation, for example due to nosocomial outbreaks. The reported percentages of resistance should be interpreted with caution and are not necessarily generalizable to any one patient presenting with invasive infection, especially patients with community-acquired infections.

Nevertheless, the patient population sampled had high levels of resistance to third-generation cephalosporins and aminoglycosides in *E. coli* and very high levels in *K. pneumoniae*. No carbapenem-resistant *K. pneumoniae* and *E. coli* were seen in blood and CSF, although carbapenem-resistant *K. pneumoniae* has been seen in other specimen types (such as tracheal aspirate). The level of MRSA was similar to that of nearby countries (Fig. 8.6). Too few antibiotic susceptibility testing results for *S. pneumoniae*, E. faecalis, and *E. faecium* were available to allow interpretation. The high levels of resistance in *P. aeruginosa* and *Acinetobacter* spp. are concerning and may reflect the dissemination of resistant clones in the healthcare setting.

The data from Kosovo[1] are assessed as level B. The representativeness of the results is limited by the inclusion of only a single laboratory providing diagnostic support to a specific patient population (tertiary care, neonatal patients), overrepresentation of more severely ill and pretreated patients (selective sampling) and a low overall number of isolates (low utilization of blood culture diagnostics). The antibiotic susceptibility testing results seem to be reliable. The data indicate the resistance patterns present in clinical settings,

but the proportion of resistance should be interpreted with care. Kosovo[1] has an active AMR surveillance network that has been working on implementing harmonized antibiotic susceptibility testing methods and breakpoints. Including data from regional hospitals and increasing the diagnostic utilization of blood cultures will lead to more valid assessment of the magnitude of AMR. The readers' guide (Table 5.1) provides additional information on interpreting the data and how the level of evidence was determined.

Chapter 8 displays the proportions of resistance for selected pathogen–antibiotic combinations reported by Kosovo[1] in maps of the WHO European Region (Fig. 8.1–8.6). Besides the data from the CAESAR countries and areas, the maps present data from the EARS-Net at the ECDC.

Table 7.1 Patient characteristics of 179 isolates from Kosovo[a] in 2014, by pathogen

	E. coli	*K. pneumoniae*	*P. aeruginosa*	*Acinetobacter* spp.	*S. aureus*	*S. pneumoniae*	*E. faecalis*	*E. faecium*	**Total number of isolates**
Number of isolates; *n* (%)	23 (13)	34 (19)	14 (8)	49 (27)	37 (21)	6 (3)	12 (7)	4 (2)	**179**
Isolate source (%)									
Blood	96	94	71	86	95	50	83	100	**158**
Cerebrospinal fluid	4	6	29	14	5	50	17	0	**21**
Sex (%)									
Male	35	3	21	2	30	0	0	50	**26**
Female	65	97	79	98	70	100	100	50	**153**
Age in years (%)									
0–4	30	100	71	90	68	67	83	25	**135**
5–19	4	0	7	0	11	17	0	50	**9**
20–64	48	0	21	6	16	17	0	25	**25**
65 and over	17	0	0	4	5	0	17	0	**10**
Hospital department (%)									
Infectious disease ward	17	0	21	2	32	50	8	50	**26**
Intensive care unit	4	0	0	8	3	0	8	25	**8**
Paediatrics or neonatal	26	100	79	90	65	50	83	25	**133**
Other	52	0	0	0	0	0	0	0	**12**

[a] In accordance with United Nations Security Council resolution 1244 (1999).

Table 7.2 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Kosovo[a] in 2014

	E. coli		*K. pneumoniae*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (R)	23[b]	52[b]	NA	NA
Aminoglycosides (R)	23[b]	39[b]	34	94
Fluoroquinolones (R)	23[b]	4[b]	34	6
Fluoroquinolones (I+R)	23[b]	4[b]	34	6
Third-generation cephalosporins (R)	23[b]	48[b]	34	91
Third-generation cephalosporins (I+R)	23[b]	52[b]	34	94
Carbapenems (R)	23[b]	0[b]	34	0
Carbapenems (I+R)	23[b]	0[b]	34	0
Multidrug resistance (R)	23[b]	4[b]	34	6

NA: not applicable.

[a] In accordance with United Nations Security Council resolution 1244 (1999).

[b] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.

The aminopenicillins group comprises amoxicillin and ampicillin.

The aminoglycosides group comprises amikacin, gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

The third-generation cephalosporins group comprises cefotaxime, ceftriaxone and ceftazidime.

The carbapenems group comprises imipenem and meropenem.

Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides.

Table 7.3 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Kosovo[a] in 2014

	P. aeruginosa		*Acinetobacter* spp.	
	n	Resistance (%)	*n*	Resistance (%)
Aminoglycosides (R)	14[b]	57[b]	49	96
Fluoroquinolones (R)	14[b]	7[b]	49	88
Piperacillin or piperacillin-tazobactam (R)	14[b]	36[b]	NA	NA
Ceftazidime (R)	14[b]	50[b]	NA	NA
Carbapenems (R)	14[b]	64[b]	49	90
Carbapenems (I+R)	14[b]	71[b]	49	90
Multidrug resistance (R)	14[b]	36[b]	49	82

NA: not applicable.

[a] In accordance with United Nations Security Council resolution 1244 (1999).

[b] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.

The aminoglycosides group comprises gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin and levofloxacin.

The carbapenems group comprises imipenem and meropenem.

For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems.

For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems.

Table 7.4 Percentage of resistance for *S. aureus* among blood and CSF isolates in Kosovo[a] in 2014

	S. aureus	
	n	Resistance (%)
MRSA (R)	37	38
Fluoroquinolones (R)	37	22
Rifampicin (R)	37	8
Linezolid (R)	37	0

[a] In accordance with United Nations Security Council resolution 1244 (1999).
MRSA is calculated as resistance to cefoxitin or, if not available, to one or more of oxacillin, flucloxacillin, methicillin, cloxacillin and dicloxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin, levofloxacin and norfloxacin.

Table 7.5 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Kosovo[a] in 2014

	S. pneumoniae	
	n	Resistance (%)
Penicillin (R)	6[b]	33[b]
Penicillin (I+R)	6[b]	33[b]
Macrolides (R)	6[b]	0[b]
Macrolides (I+R)	6[b]	0[b]
Fluoroquinolones (R)	0	No data available
Third-generation cephalosporins (R)	6[b]	0[b]
Third-generation cephalosporins (I+R)	6[b]	0[b]
Multidrug resistance (I+R)	6[b]	0[b]

[a] In accordance with United Nations Security Council resolution 1244 (1999).
[b] Few isolates were tested (*n* < 30), and the percentage of resistance should be interpreted with caution.
Penicillin resistance is based on penicillin or, if not available, on oxacillin.
The macrolides group comprises erythromycin, clarithromycin and azithromycin.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
Multidrug resistance is defined as resistance to penicillins and macrolides.

Table 7.6 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Kosovo[a] in 2014

	E. faecalis		*E. faecium*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (I+R)	12[b]	17[b]	4[b]	100[b]
High-level gentamicin (R)	12[b]	25[b]	4[b]	100[b]
Vancomycin (R)	12[b]	0[b]	4[b]	50[b]
Linezolid (I+R)	12[b]	0[b]	4[b]	0[b]

[a] In accordance with United Nations Security Council resolution 1244 (1999).
[b] Few isolates were tested (*n* < 30), and the percentage of resistance should be interpreted with caution.
The aminopenicillins group comprises amoxicillin and ampicillin.

Table 7.7 Patient characteristics of 122 isolates from Kosovo[a] in 2015, by pathogen

	E. coli	*K. pneumoniae*	*P. aeruginosa*	*Acinetobacter* spp.	*S. aureus*	*S. pneumoniae*	*E. faecalis*	*E. faecium*	**Total number of isolates**
Number of isolates; *n* (%)	29 (24)	18 (15)	11 (9)	30 (25)	27 (22)	1 (1)	6 (5)	0 (0)	**122**
Isolate source (%)									
Blood	97	94	82	80	100	100	100	0	**112**
Cerebrospinal fluid	3	6	18	20	0	0	0	0	**10**
Sex (%)									
Male	31	33	0	0	30	100	50	0	**27**
Female	34	67	0	0	70	0	50	0	**44**
Unknown	34	0	100	100	0	0	0	0	**51**
Age in years (%)									
0–4	45	94	82	87	67	100	50	0	**87**
5–19	0	0	0	3	11	0	33	0	**6**
20–64	31	6	18	10	22	0	17	0	**22**
65 and over	24	0	0	0	0	0	0	0	**7**
Hospital department (%)									
Haematology or oncology	7	6	9	3	4	0	0	0	**6**
Infectious disease ward	34	0	9	10	37	100	50	0	**28**
Internal medicine	14	0	0	0	0	0	0	0	**4**
Surgery	0	0	0	0	0	0	17	0	**1**
Intensive care unit	0	0	0	3	4	0	0	0	**2**
Paediatrics or neonatal	45	94	82	83	56	0	33	0	**81**

[a] In accordance with United Nations Security Council resolution 1244 (1999).

Table 7.8 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Kosovo[a] in 2015

	E. coli		*K. pneumoniae*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (R)	29[b]	69[b]	NA	NA
Aminoglycosides (R)	29[b]	52[b]	18[b]	89[b]
Fluoroquinolones (R)	29[b]	24[b]	18[b]	6[b]
Fluoroquinolones (I+R)	29[b]	24[b]	18[b]	6[b]
Third-generation cephalosporins (R)	29[b]	45[b]	18[b]	83[b]
Third-generation cephalosporins (I+R)	29[b]	45[b]	18[b]	83[b]
Carbapenems (R)	29[b]	0[b]	18[b]	0[b]
Carbapenems (I+R)	29[b]	0[b]	18[b]	0[b]
Multidrug resistance (R)	29[b]	24[b]	18[b]	6[b]

NA: not applicable.

[a] In accordance with United Nations Security Council resolution 1244 (1999).

[b] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.

The aminopenicillins group comprises amoxicillin and ampicillin.

The aminoglycosides group comprises amikacin, gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

The third-generation cephalosporins group comprises cefotaxime, ceftriaxone and ceftazidime.

The carbapenems group comprises imipenem and meropenem.

Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides.

Table 7.9 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Kosovo[a] in 2015

	P. aeruginosa		*Acinetobacter* spp.	
	n	Resistance (%)	*n*	Resistance (%)
Aminoglycosides (R)	11[b]	55[b]	30	100
Fluoroquinolones (R)	11[b]	9[b]	30	83
Piperacillin or piperacillin-tazobactam (R)	11[b]	36[b]	NA	NA
Ceftazidime (R)	11[b]	18[b]	NA	NA
Carbapenems (R)	11[b]	45[b]	30	87
Carbapenems (I+R)	11[b]	64[b]	30	90
Multidrug resistance (R)	11[b]	9[b]	30	83

NA: not applicable.

[a] In accordance with United Nations Security Council resolution 1244 (1999).

[b] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.

The aminoglycosides group comprises gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin and levofloxacin.

The carbapenems group comprises imipenem and meropenem.

For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems.

For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems.

Table 7.10 Percentage of resistance for *S. aureus* among blood and CSF isolates in Kosovo[a] in 2015

	S. aureus	
	n	Resistance (%)
MRSA (R)	27[b]	41[b]
Fluoroquinolones (R)	27[b]	26[b]
Rifampicin (R)	27[b]	4[b]
Linezolid (R)	27[b]	0[b]

[a] In accordance with United Nations Security Council resolution 1244 (1999).
[b] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.
MRSA is calculated as resistance to cefoxitin or, if not available, to one or more of oxacillin, flucloxacillin, methicillin, cloxacillin and dicloxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin, levofloxacin and norfloxacin.

Table 7.11 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Kosovo[a] in 2015

	S. pneumoniae	
	n	Resistance (%)
Penicillin (R)	1[b]	100[b]
Penicillin (I+R)	1[b]	100[b]
Macrolides (R)	1[b]	100[b]
Macrolides (I+R)	1[b]	100[b]
Fluoroquinolones (R)	0	No data available
Third-generation cephalosporins (R)	1[b]	0[b]
Third-generation cephalosporins (I+R)	1[b]	0[b]
Multidrug resistance (I+R)	1[b]	100[b]

[a] In accordance with United Nations Security Council resolution 1244 (1999).
[b] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.
Penicillin resistance is based on penicillin or, if not available, on oxacillin
The macrolides group comprises erythromycin, clarithromycin and azithromycin
The fluoroquinolones group comprises levofloxacin and moxifloxacin
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone
Multidrug resistance is defined as resistance to penicillins and macrolides

Table 7.12 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Kosovo[a] in 2015

	E. faecalis		*E. faecium*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (I+R)	6[b]	0[b]	0	No data available
High-level gentamicin (R)	6[b]	67[b]	0	No data available
Vancomycin (R)	6[b]	0[b]	0	No data available
Linezolid (I+R)	6[b]	0[b]	0	No data available

[a] In accordance with United Nations Security Council resolution 1244 (1999).
[b] Few isolates were tested ($n < 30$), and the percentage of resistance should be interpreted with caution.
The aminopenicillins group comprises amoxicillin and ampicillin.


CHAPTER
8

Antimicrobial resistance maps of the WHO European Region

8.1 Introduction

This chapter presents the 2015 AMR data from the CAESAR countries together with the 2015 data from EARS-Net, which are provided by the ECDC. For 2015, 30 countries, including all EU countries and two European Economic Area countries (Iceland and Norway), reported their data to EARS-Net. CAESAR and EARS-Net apply the same methods; this enables comparison between countries across the two networks and provides an overview of the AMR situation based on all the available data from the European Region. Several countries in the CAESAR network are not yet able to report level A or level B data to CAESAR, but they are actively setting up and strengthening their national AMR surveillance systems, which will give further colour to the maps in the foreseeable future.

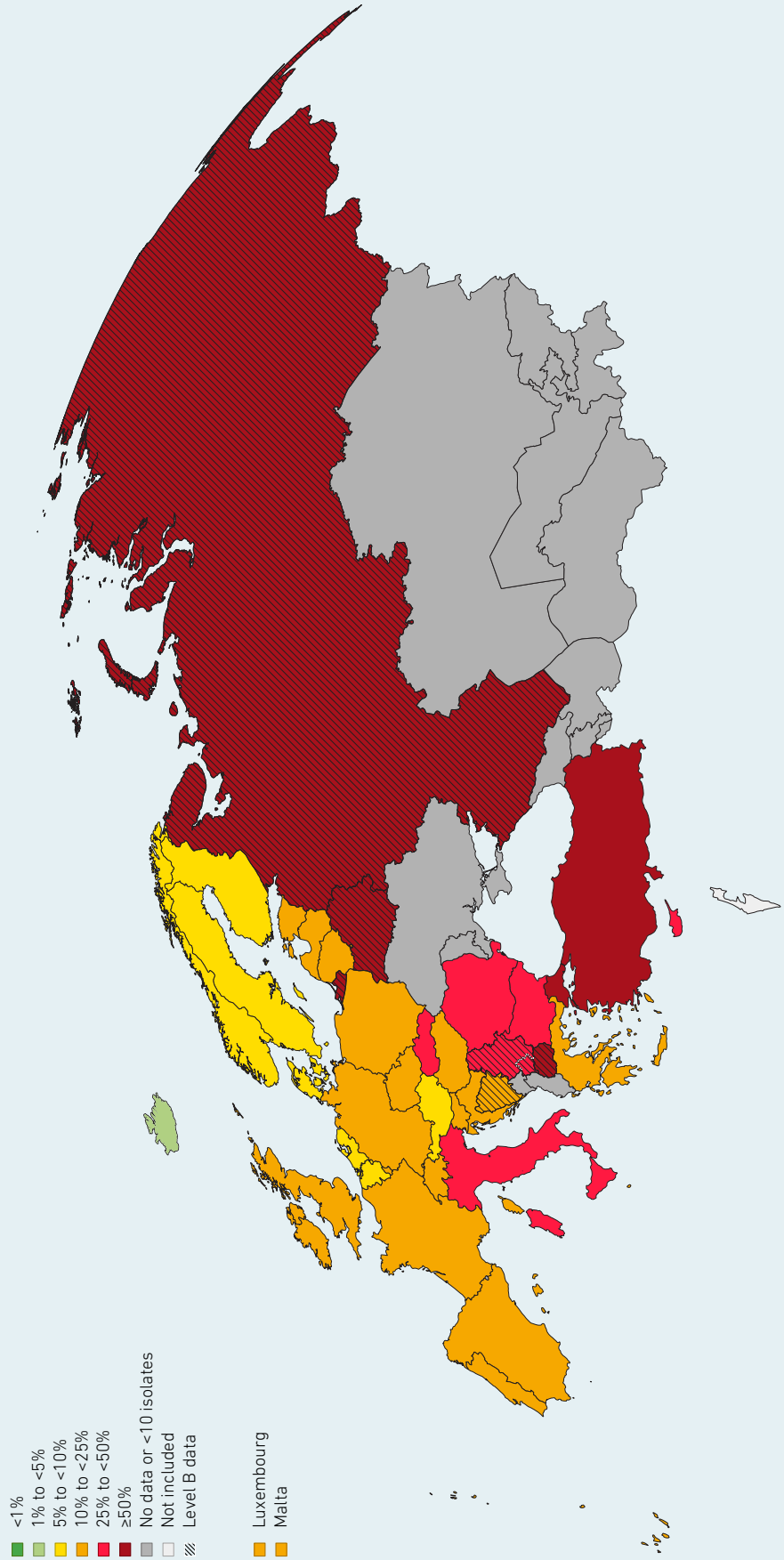
The legends of the maps indicate the countries participating in EARS-Net or CAESAR. Since data vary with regard to the representativeness of the underlying population, the CAESAR network assigns levels of evidence to guide the reader in interpreting the presented data, whereas EARS-Net does not make this distinction. For CAESAR countries and areas with level B data, the colour in the maps is shaded, indicating that the proportion of resistance should be interpreted with caution. Improvements are needed to attain more valid assessment of the magnitude of antimicrobial resistance in the country. Level A data, presented without shading, provide an adequate assessment of the magnitude of antimicrobial resistance in the country. Chapter 5 presents more information about the different levels of evidence. For more details on EARS-Net, see to the EARS-Net annual report 2014 *(1)*. The latest EARS-Net data from 2015 can be found on the ECDC Surveillance Atlas of Infectious Diseases *(2)*. This chapter was prepared in collaboration with the ECDC in our efforts to provide an overview of AMR in the European Region.

8.2 Description of the maps

Escherichia coli

E. coli is the most frequent cause of bloodstream infections and urinary tract infections. EARS-data has shown a significant increase in third-generation cephalosporin resistance in EU and EEA countries *(3)*. This has reached 13% in 2015, varying between 1.7% in Iceland and 38.5% in Bulgaria. Among the CAESAR countries, Belarus, the Russian Federation, the former Yugoslav Republic of Macedonia and Turkey reported resistance levels exceeding 50%, whereas the proportions of resistance in, for example, Serbia are more comparable to their neighbouring EARS-Net countries (25–50%), as are the resistance proportions in Bosnia and Herzegovina and Switzerland (10–25%) (Fig. 8.1). The recently emerging threat of resistance to carbapenems remains low (EU/EEA population-weighted mean < 0.1%), with only two EARS-Net countries reporting resistance level above 1 % (Greece 1.2%, Romania 1.9 %) *(3)*. Of serious concern are the also slightly elevated resistance proportions reported by some of the CAESAR countries: Belarus (2%), Serbia (1%) and Turkey (2%) (Fig. 8.2).

Fig. 8.1. Third-generation cephalosporin-resistant *E. coli* in the European Region (EARS-Net and CAESAR), 2015

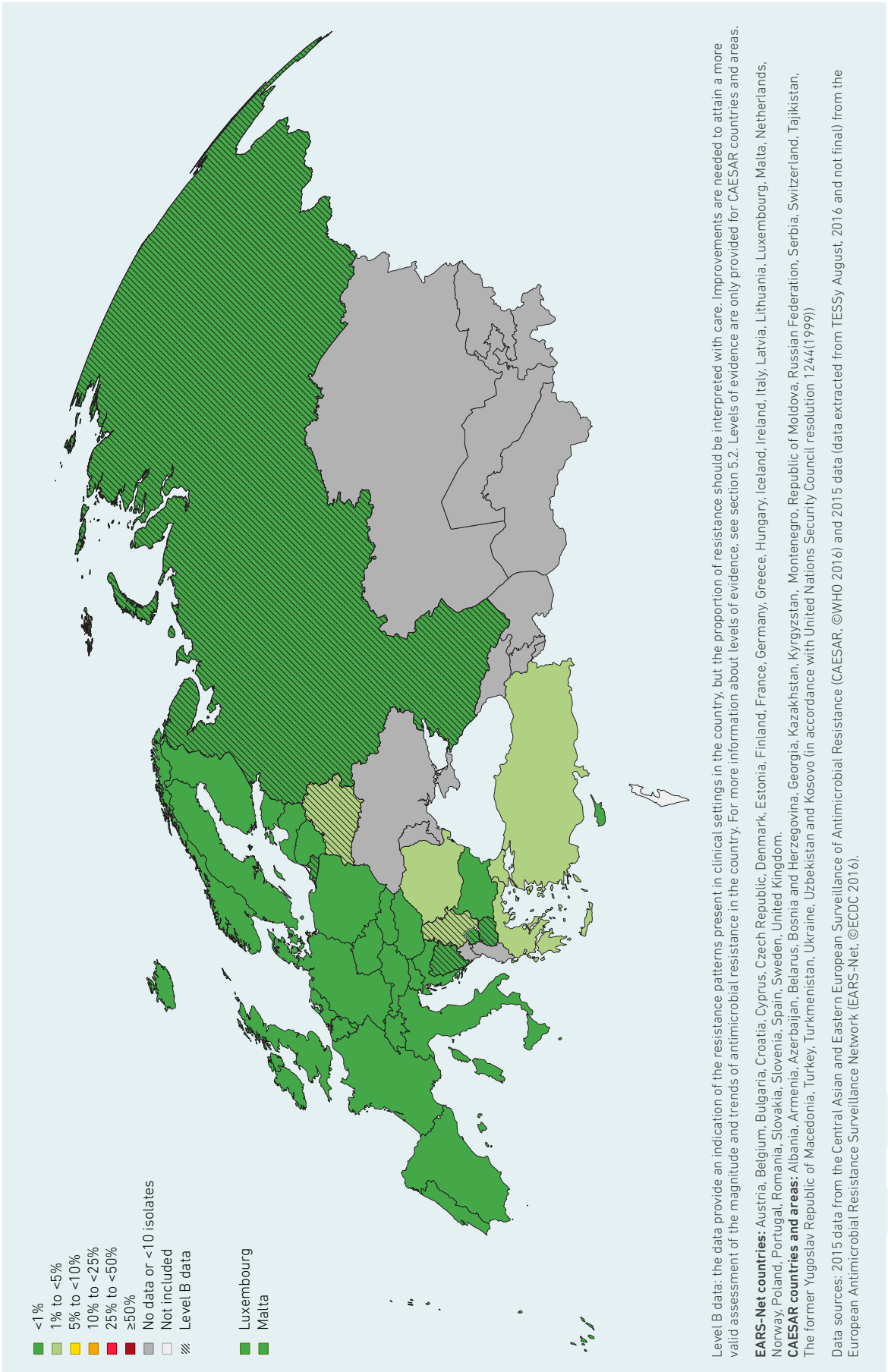


Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of antimicrobial resistance in the country. For more information about levels of evidence, see section 5.2. Levels of evidence are only provided for CAESAR countries and areas.

EARS-Net countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom.
CAESAR countries and areas: Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, Republic of Moldova, Russian Federation, Serbia, Switzerland, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, Uzbekistan and Kosovo (in accordance with United Nations Security Council resolution 1244(1999))

Data sources: 2015 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2016) and 2015 data (data extracted from TESSy August, 2016 and not final) from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2016).

Fig. 8.2. Carbapenem-resistant *E. coli* in the European Region (EARS-Net and CAESAR), 2015



Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of antimicrobial resistance in the country. For more information about levels of evidence, see section 5.2. Levels of evidence are only provided for CAESAR countries and areas.

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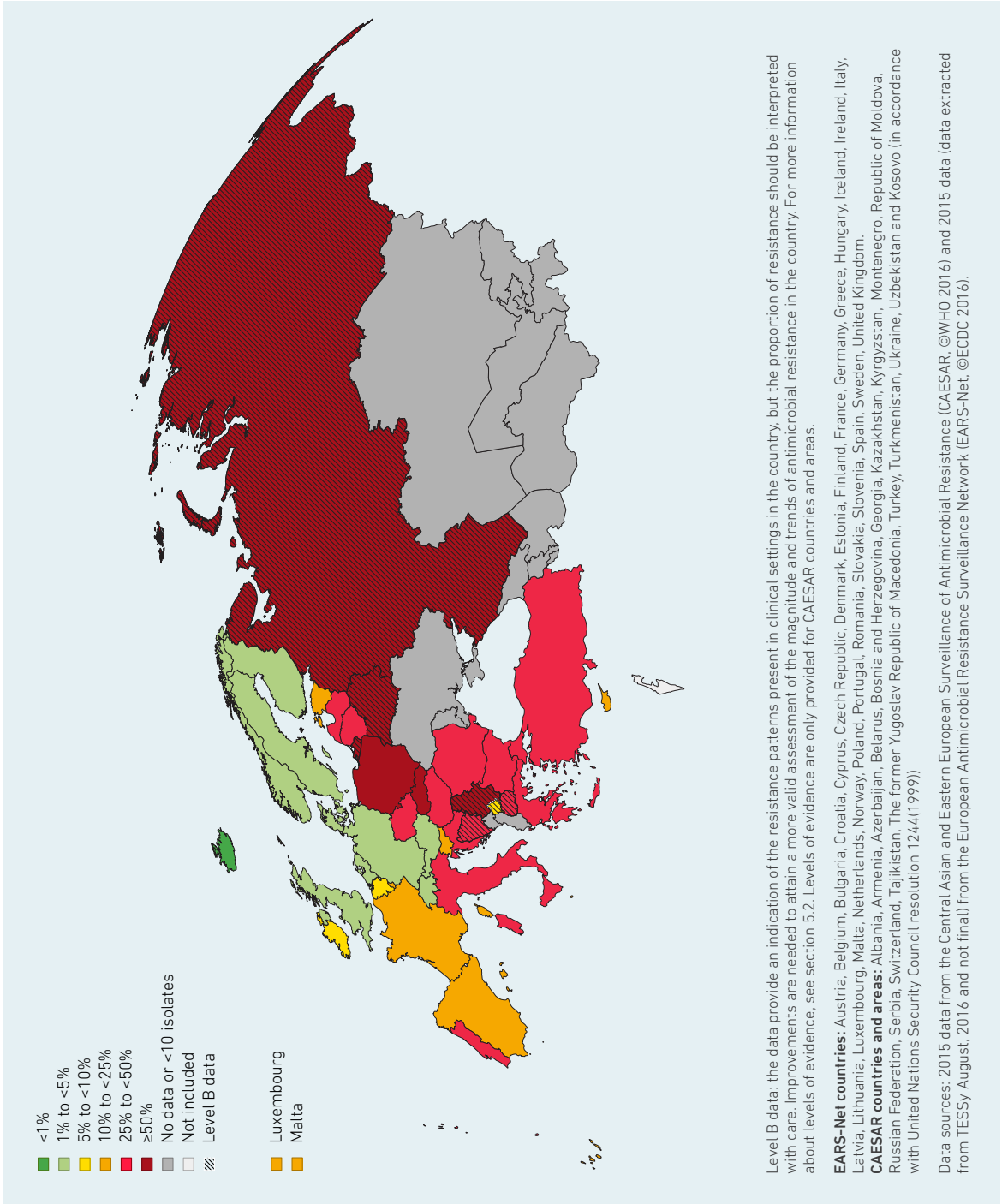
Data sources: 2015 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2016) and 2015 data (data extracted from TESSy August, 2016 and not final) from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2016).

Klebsiella pneumoniae

Like *E. coli*, *K. pneumoniae* is a common cause of bloodstream infections and of urinary and respiratory tract infections and can spread readily between patients, leading to nosocomial outbreaks. Multidrug resistance has become quite common in the European Region. In general, lower percentages are reported from northern European countries and much higher percentages from the southern, eastern and central Asian parts of the European Region, even exceeding 50% in Belarus, Poland, the Russian Federation, Serbia and Slovakia (Fig. 8.3). Compared to *E. coli*, carbapenem resistance is more frequently found in *K. pneumoniae*, with high proportions (>25%) reported by Belarus (58%), Greece (61.9%), Italy (33.5%), Serbia (39%) and Turkey (30%) (Fig 8.4).

Fig. 8.3 Multidrug-resistant (combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides) *K. pneumoniae* in the European Region (EARS-Net and CAESAR), 2015



Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of antimicrobial resistance in the country. For more information about levels of evidence, see section 5.2. Levels of evidence are only provided for CAESAR countries and areas.

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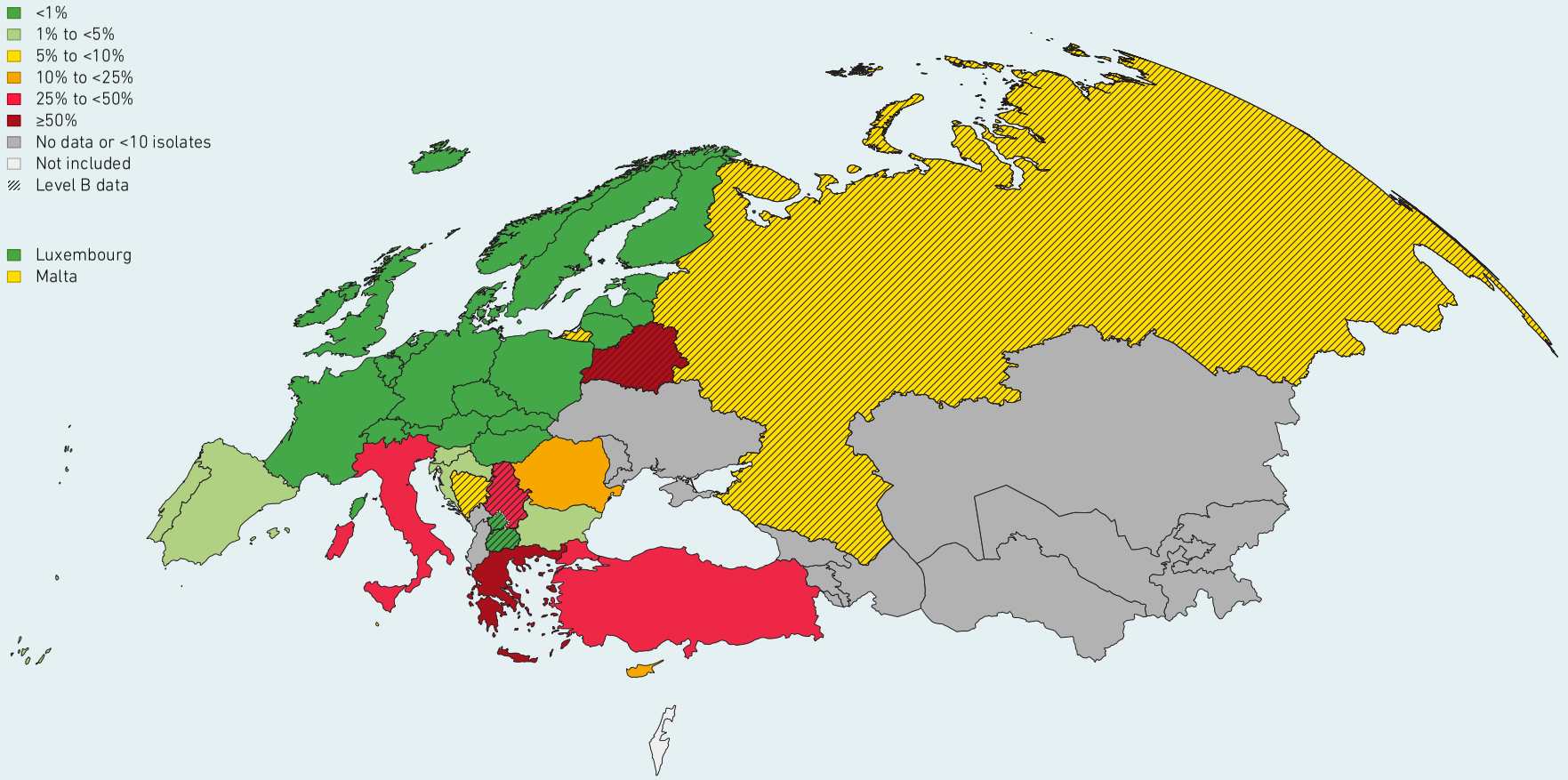
Data sources: 2015 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2016) and 2015 data (data extracted from TESSy August, 2016 and not final) from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2016).



Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of antimicrobial resistance in the country. For more information about levels of evidence, see section 5.2. Levels of evidence are only provided for CAESAR countries and areas.

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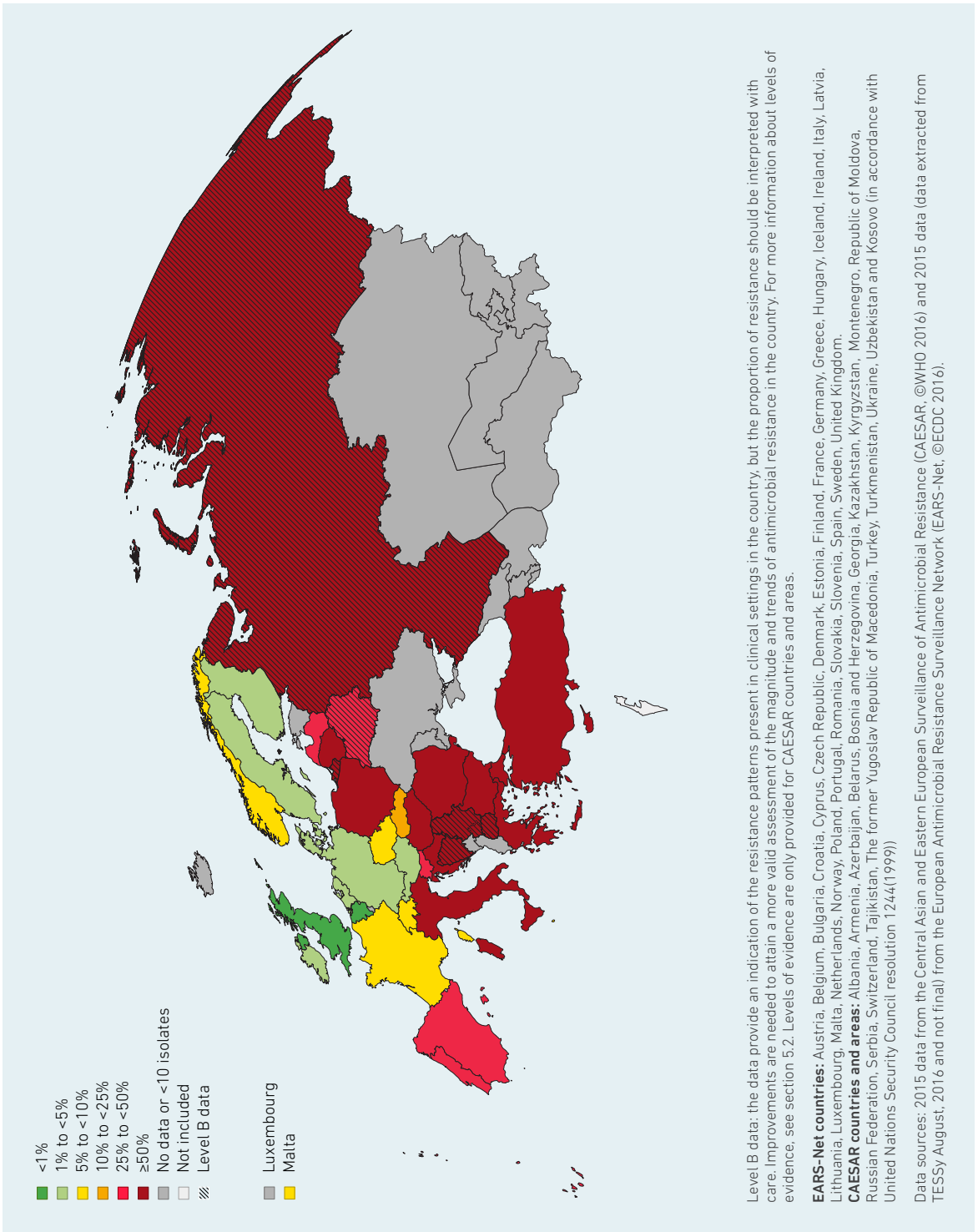
Data sources: 2015 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2016) and 2015 data (data extracted from TESSy August, 2016 and not final) from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2016).

Fig. 8.4 Carbapenem-resistant *K. pneumoniae* in the European Region (EARS-Net and CAESAR), 2015

Acinetobacter spp.

The presence of multidrug-resistant *Acinetobacter* spp. varies widely within the European Region and clearly shows very high resistance proportions exceeding 50% in countries in southern and eastern Europe. These high percentages are concerning, may reflect the dissemination of resistant clones in the healthcare settings and indicate the serious limitation in treatment options for patients with (invasive) infections with *Acinetobacter* spp. in these countries.

Fig. 8.5 Multidrug-resistant (combined resistance to fluoroquinolones, aminoglycosides and carbapenems) *Acinetobacter* spp. in the European Region (EARS-Net and CAESAR), 2015



Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of antimicrobial resistance in the country. For more information about levels of evidence, see section 5.2. Levels of evidence are only provided for CAESAR countries and areas.

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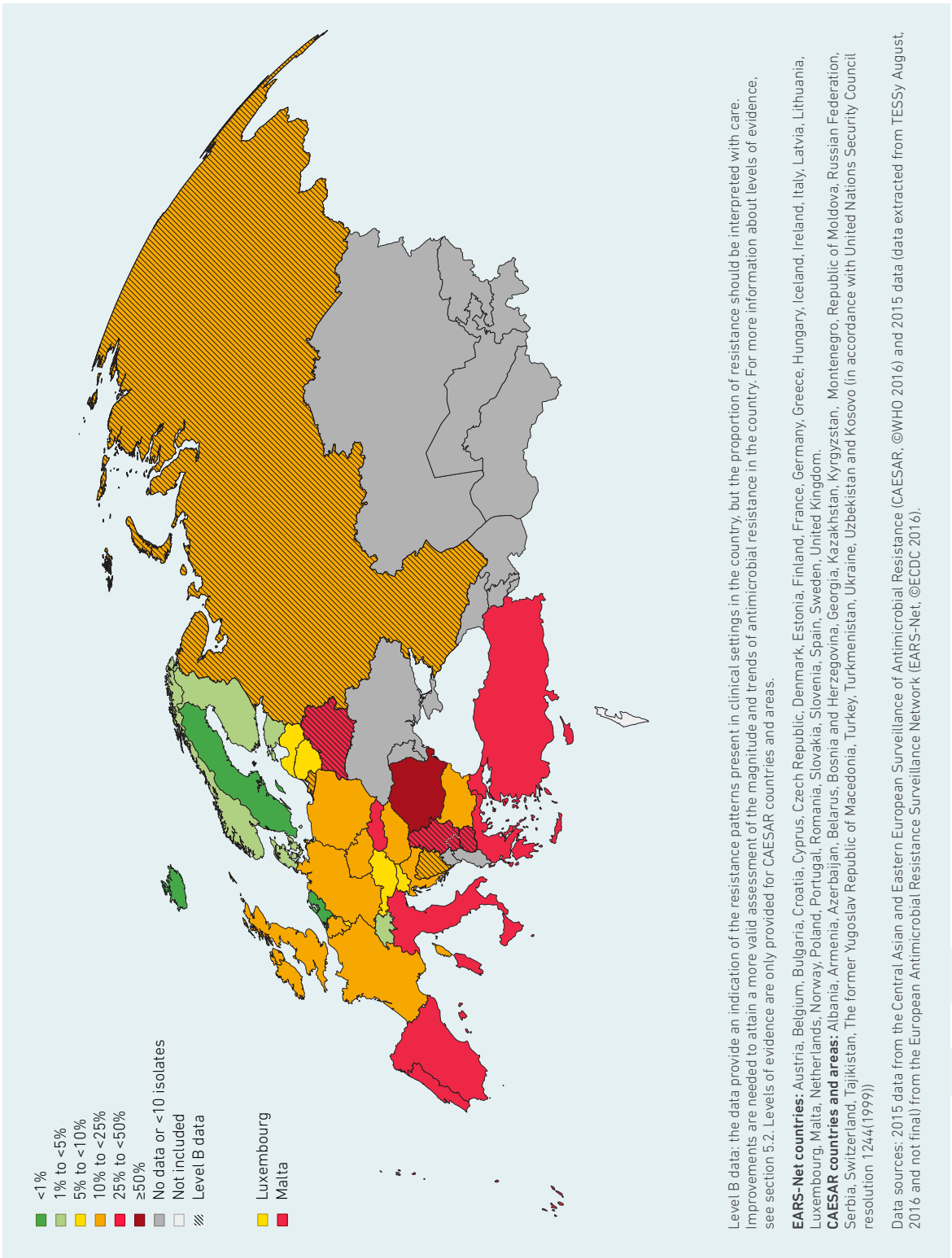
CAESAR countries and areas: Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, Republic of Moldova, Russian Federation, Serbia, Switzerland, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, Uzbekistan and Kosovo (in accordance with United Nations Security Council resolution 1244(1999))

Data sources: 2015 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2016) and 2015 data (data extracted from TESSy August 2016 and not final) from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2016).

Staphylococcus aureus

The Scandinavian countries, the Netherlands and Switzerland have the lowest percentages of MRSA. Even though EARS-Net reports a significant decrease in the population-weighted mean percentage from 18.8% in 2012 to 16.8% in 2015 *(3)*, resistance proportions of more than 25% are still found in many of the countries in the southern and eastern parts of the European Region (Fig. 8.6).

Fig. 8.6 MRSA in the European Region (EARS-Net and CAESAR), 2015



Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of antimicrobial resistance in the country. For more information about levels of evidence, see section 5.2. Levels of evidence are only provided for CAESAR countries and areas.

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CHAPTER
9

Preliminary results from the proof-of-principle study to promote routine diagnostics in Georgia

9.1 Background

AMR threatens adequate treatment and prevention of infectious diseases in individual patients. Infections with resistant microorganisms have been associated with higher morbidity, mortality and healthcare costs, and thus, besides the negative effect on the individual patient, affect society as a whole. Reliable surveillance programmes are needed to tackle the AMR threat, by creating awareness and supporting the development of clinical guidelines and AMR control policies.

In parts of the WHO European Region, the implementation of a national AMR surveillance system based on routine antibiotic susceptibility testing is limited by the underutilization of microbiological diagnostics in routine clinical practice. The main reasons reported for this low utilization are the lack of resources for microbiological diagnostics and clinicians' perception of a lack of clinical utility. The proof-of-principle AMR surveillance study was set up, with the aim of stimulating the taking of blood samples in patients with suspected bloodstream infections by providing materials and starting to assess the antibiotic susceptibility patterns in the main pathogens causing community-acquired and hospital-acquired bloodstream infections, thereby:

- demonstrating the value of clinical microbiological diagnostics in routine patient care by providing timely feedback of laboratory results to clinicians to guide the antibiotic treatment of bloodstream infection; and
- establishing good clinical practice for routine clinical work-up in hospitals and strengthening the AMR reference and surveillance capacity at the national reference laboratory;
- establishing and supporting a surveillance infrastructure as a point of departure for a national sentinel laboratory-based surveillance system for AMR.

9.2 Methods

In Georgia, the proof-of-principle AMR surveillance study was started as a pilot project in July 2015. The preliminary data for the first year of the ongoing study are presented here. Data were collected between 1 July 2015 and 7 July 2016 in three general hospitals: the Gudushauri National Medical Center (240 beds), the High Medical Technology Center (250 beds) and the Iashvili Children's Central Clinic (290 beds). The study is coordinated by the Richard Lugar Center for Public Health Research of the National Center for Disease Control and Public Health of Georgia. The study team at the National Center for Disease Control and Public Health comprises a project manager, a research coordinator, a bacteriologist, an epidemiologist and support personnel. The study team made weekly visits to the research sites to support implementation of the study. The study team is supported by the WHO Regional Office for Europe AMR team, AMR surveillance experts from the National Institute for Public Health and the Environment in the Netherlands and microbiology experts from the University Hospital of Infectious Disease in Zagreb, Croatia.

Before the study started, the National Center for Disease Control and Public Health team trained the participating laboratories in blood culturing procedures and techniques and antibiotic susceptibility testing following EUCAST methods. All blood culture materials and laboratory consumables for species identification and antibiotic susceptibility testing and confirmatory testing at the Lugar Centre for a maximum of 1800 patients were provided free of charge for the study by the WHO Regional Office for Europe.

At each study site, a local team, comprising a clinician, a hospital epidemiologist and a bacteriologist, were responsible for conducting the study. Clinicians were instructed to recruit patients through active case finding, from hospital departments admitting patients with suspected bloodstream infection from the community (such as emergency departments) and wards where patients are at risk of developing hospital-acquired bloodstream infections (such as intensive care units and departments of urology or surgery). Patients fulfilling the criteria for systemic inflammatory response syndrome *(1)* were eligible for blood culturing. For children, the local clinicians adapted the criteria for systemic inflammatory response syndrome. For each patient included, the study team completed a clinical data form and, for each positive blood culture, a laboratory data form. Data forms were collected at the weekly study meetings and entered into an electronic database at the National Center for Disease Control and Public Health.

Blood cultures were processed at the hospital's bacteriology laboratory. One hospital did not have bacteriology laboratory capabilities, and blood cultures were transported to the national AMR reference laboratory at the Lugar Centre for full processing, directly following the blood draw. Bacteriologists were advised to actively report preliminary results (gram stain of a positive blood culture) and final reports (species identification and antibiotic susceptibility testing) back to the clinician as soon as these were available, to allow clinicians to adjust the (empirical) antibiotic therapy. All positive blood culture isolates were sent to the Lugar Center for quality assurance and confirmatory antibiotic susceptibility testing.

Blood culturing was done using a manual blood culture system according to standard operating procedures. Culture bottles were checked for growth daily. Blind subcultures were made at 24 hours, 48 hours, 72 hours and 7 days if no growth was seen. Antibiotic susceptibility was tested by disk diffusion according to EUCAST standards. The tested bacterium–drug combinations were based on the recommendations in the CAESAR manual *(2)*, including indicator antibiotics for the main antibiotic groups plus some empirical treatment options not in the CAESAR manual.

This chapter was prepared together with the study team at the National Center for Disease Control and Public Health in Tbilisi, Georgia.

9.3 Results

Blood samples were collected from 1162 patients with suspected bloodstream infection. Tables 9.1 and 9.2 show the characteristics of these patients. The most common clinical diagnoses were respiratory distress syndrome (65%) among neonates, fever (24%) among children and pneumonia (15%) among adults. The overall rate of blood culture was 5.8 blood cultures per 1000 patient-days, which was a significant increase compared with the year before implementation of the proof-of-principle study (1.8 per 1000 patient-days). Of all blood cultures, 74% and 84% were taken in duplicate, among children and adults respectively. For neonates, only 18% of blood cultures were taken in duplicate. Most blood cultures were taken among patients admitted to an intensive care unit (72% of blood cultures, rate 28.4 per 1000 patient-days), in particular in neonatal or paediatric intensive care units (57% of blood cultures, rate 38.0 per 1000 patient-days). Relatively few blood cultures were taken in non-intensive care unit departments (28% of blood cultures, rate 1.9 per 1000 patient-days).

At the time of taking a blood culture, antibiotics were already administered in 367 (32%) of the patients suspected of bloodstream infection. Of these patients, 85% were characterized as having a suspected nosocomial infection: having been admitted for more than 48 hours (including transfer from another hospital) and children born in the hospital. In the patient group with a suspected community-acquired

infection, 21% had taken antibiotics in the seven days before the blood culture. The most commonly prescribed combination of antibiotics was a carbapenem and glycopeptide. Table 9.3 presents the top three most frequently given antibiotics for each age category.

Of the 1162 blood culture sets taken, in 165 (14%) at least one was positive. Table 9.4 shows the patient characteristics of the positive isolates by pathogen. For this report, we only present antibiotic susceptibility for the eight pathogens under CAESAR surveillance. Except for *K. pneumoniae*, few isolates of each pathogen were available ($n < 30$), and the percentage of resistance should be interpreted with caution. In *E. coli* and *K. pneumoniae*, resistance to aminoglycosides, third-generation cephalosporins and aminopenicillins exceeded 50%. Resistance to carbapenems was 0% and 10% and multidrug resistance 33% and 28% in *E. coli* and *K. pneumoniae* respectively (Table 9.5). In *P. aeruginosa* and *Acinetobacter* spp., carbapenem resistance reached 56% and 86%, respectively (Table 9.6). Multidrug resistance was present in 46% of *P. aeruginosa*. For *Acinetobacter* spp., multidrug resistance could not be assessed because fluoroquinolone susceptibility was only tested on one isolate. In *S. aureus*, 21% of the isolates were characterized as MRSA (Table 9.7). Too few *Enterococcus* and *S. pneumonia* isolates were available to draw conclusions about their antibiotic susceptibility.

Table 9.1 Demographic characteristics of all patients who had a blood culture taken

		n	%	mean
Sex	Male	690	59	
	Female	472	41	
Age	<1 month	591	51	4.7 (±6.7) days
	1–11 months	151	13	3.4 (±3.1) months
	1–16 years	163	14	6.3 (±4.5) years
	17–35 years	66	6	26.7 (±5.0) years
	>35 years	190	16	59.2 (±12.2) years

Table 9.2 Patient characteristics of all patients who had a blood culture taken

		n	%
Ward	Adult intensive care unit	170	15
	Neonatal intensive care unit	569	49
	Paediatric intensive care unit	111	10
	Other adult departments	145	12
	Other neonatal departments	96	8
	Other paediatric department	34	3
	Emergency department	37	3
Source of infection[a]	Community	254	22
	Nosocomial	908	78

[a] Nosocomial source defined as patients admitted to hospital more than 48 hours (including patients transferred from other hospitals) and children born in the hospital. Community source defined as patients developing signs of infection within 48 hours of admission to hospital.

Table 9.3 Top three antibiotic combinations among patients receiving antibiotics before a blood sample was taken

Total	*n* (%) (of 366)[a]	Neonates	*n* (%) (of 83)[a]	Child[b]	*n* (%) (of 72)[a]	Adult	*n* (%) (of 211)[a]
1. Carbapenem and glycopeptide	47 (13%)	Aminoglycoside and penicillin + β-lactamase inhibitor	38 (46%)	Third-generation cephalosporin	15 (21%)	Carbapenem and glycopeptide	28 (13%)
2. Aminoglycoside and penicillin + β-lactamase inhibitor	40 (11%)	Carbapenem and glycopeptide	6 (7%)	Carbapenem and glycopeptide	13 (18%)	Carbapenem	18 (9%)
3. Third-generation cephalosporin	29 (8%)	Penicillin + β-lactamase inhibitor	5 (6%)	Carbapenem and polymyxin and glycopeptide	9 (13%)	Fourth-generation cephalosporin and metronidazole	11 (5%)

[a] Number of patients who received antibiotics before blood culture. [b] Child: >1 month and younger than 17 years old and not in a neonatal department.

Table 9.4 Patient characteristics by pathogen

Pathogen	Number of isolates	Sex (%)		Age (years) (%)					Hospital department (%)		Source of the infection[a] (%)	
		Male	Female	0–4	5–19	20–64	>64	Unknown	Intensive care unit	Non-intensive care unit	Nosocomial	Community
E. coli	13	54	46	69	8	15	0	8	62	39	85	15
K. pneumoniae	49	63	37	84	4	8	0	4	84	16	84	16
P. aeruginosa	16	50	50	75	6	19	0	0	94	6	94	6
Acinetobacter spp.	7	57	43	14	0	57	0	29	100	0	100	0
S. aureus	20	65	35	65	5	25	0	5	70	30	70	30
S. pneumoniae	2	100	0	50	50	0	0	0	50	50	50	50
E. faecalis	2	50	50	100	0	0	0	0	100	0	100	0
E. faecium	–											
Coagulase-negative Staphylococcus	16	63	38	44	0	56	0	0	94	6	69	31
Enterococcus spp.	5	60	40	80	0	20	0	0	80	20	100	0
Burkholderia cepacia	4	50	50	75	0	0	0	25	100	0	100	0
Enterobacter cloacae	3	33	67	100	0	0	0	0	100	0	100	0
Providencia stuartii	3	67	33	33	0	67	0	0	67	33	100	0
Klebsiella oxytoca	2	100	0	50	0	50	0	0	100	0	50	50
Serratia liquefaciens	2	100	0	100	0	0	0	0	100	0	100	0
Serratia marcescens	2	50	50	50	50	0	0	0	100	0	50	50
Flavimonas oryzihabitans	2	50	50	50	0	50	0	0	100	0	100	0
Other	13	69	31	54	0	23	0	23	85	15	85	15

[a] Nosocomial source defined as patients admitted to hospital for more than 48 hours (including patients transferred from other hospitals) and children born in the hospital. A community source is defined as patients developing signs of infection within 48 hours of admission to hospital.
[b] Coagulase-negative *Staphylococcus* is considered clinically relevant (two or more blood cultures positive).

Table 9.5 Percentage of resistance for *E. coli* and *K. pneumoniae*

Antibiotic class	*E. coli*		*K. pneumoniae*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (R)	13	85	NA	NA
B-lactam and B-lactamase inhibitor combinations (R)	13	39	49	94
Aminoglycosides (R)	13	62	49	90
Fluoroquinolones (R)	12	33	45	29
Fluoroquinolones (I+R)	12	33	45	33
Third-generation cephalosporins (R)	13	54	49	96
Third-generation cephalosporins (I+R)	13	62	49	96
Cefotaxime and cetriaxone (R)	13	55	49	94
Ceftazidime (R)	13	39	49	94
Carbapenems (R)	13	0	49	10
Carbapenems (I+R)	13	8	49	20
Ertapenem (R)	5	0	28	11
Colistin (R)	13	0	47	4
Multidrug resistance (R)	12	33	45	29

NA: not applicable.
The aminopenicillins group comprises amoxicillin and ampicillin.
The aminoglycosides group comprises amikacin, gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.
The third-generation cephalosporins group comprises cefotaxime, ceftriaxone and ceftazidime.
The carbapenems group comprises imipenem and meropenem.
Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides.

Table 9.6 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp.

Antibiotic class	*P. aeruginosa*		*Acinetobacter* spp.	
	n	Resistance (%)	*n*	Resistance (%)
Aminoglycosides (R)	16	44	7	71
Fluoroquinolones (R)	15	27	1	100
Piperacillin and piperacillin-tazobactam (R)	16	25	NA	NA
Ceftazidime (R)	16	44	NA	NA
Carbapenems (R)	16	56	7	86
Carbapenems (I+R)	16	56	7	86
Colistin (R)	16	19	7	0
Multidrug resistance (R)	11	46	1	0

NA: not applicable.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.
The carbapenems group comprises imipenem and meropenem.
For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems.
For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides, and carbapenems.

Table 9.7 Percentage of resistance for *S. aureus*

Antibiotic class	*S. aureus*	
	n	Resistance (%)
MRSA	19	21
Fluoroquinolones (R)	15	20
Vancomycin (R)	20	0
Rifampicin (R)	20	10
Linezolid (R)	20	0

MRSA is calculated as resistance to cefoxitin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin, levofloxacin and norfloxacin.

Table 9.8 Percentage of resistance for *E. faecalis* and *E. faecium*

Antibiotic class	*E. faecalis*		*E. faecium*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (R)	2	0	No data available	
High-level gentamicin (R)	No data available		No data available	
Vancomycin (R)	2	0	No data available	
Linzeolid (I+R)	2	50	No data available	

Penicillin resistance is based on penicillin or, if not available, on oxacillin.
The macrolides group comprises erythromycin, clarithromycin and azithromycin.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
Multidrug resistance is defined as resistance to penicillins and macrolides.

Table 9.9 Percentage of resistance for *S. pneumoniae*

Antibiotic class	*S. pneumoniae*	
	n	Resistance (%)
Penicillins (R)	2	50
Penicillins (I+R)	2	50
Macrolides (R)	2	0
Macrolides (I+R)	2	0
Fluoroquinolones (R)	2	0
Third-generation cephalosporins (R)	2	0
Third-generation cephalosporins (I+R)	2	0
Multidrug resistance (I+R)	2	0

The aminopenicillins group comprises amoxicillin and ampicillin.

9.4 Discussion

The use of blood culture diagnostics improved significantly in all three participating clinics. This improvement was most apparent in intensive care units. The increase in blood cultures taken was achieved by providing blood culturing materials free of charge and improving local laboratory capacity for processing blood cultures in two hospitals with an in-house bacteriology laboratory and setting up a service-level agreement between the third hospital and the AMR reference laboratory. Although an important improvement, the overall average rate of blood culture taking (5.8 per 1000 patient-days) was lower than that of hospitals in most countries in the EU; median 30 per 1000 patient-days (range 6.6–66.2) *(3)*. This observation together with the fact that the blood culture rate in

non-intensive care unit patients remained low (1.9 per 1000 patient-days) and that most blood cultures were taken in patients already admitted to hospital for more than 48 hours suggests that patients, especially those with community-acquired infections, may have been missed. This may have been due to difficulty in changing current clinical practice throughout the hospital (active case-finding was not effectively introduced in all wards) and that establishing trust and a working relationship between clinicians and the laboratory may have required more time. More extensive awareness-raising and training to improve active case-finding of patients with suspected bloodstream infection and sepsis in departments in which patients with suspected bloodstream infection are less common may lead to additional improvements in the use of blood culture diagnostics.

The working relationship between clinicians and the bacteriology laboratory improved in several participating hospitals. Clinicians are provided timely and reliable feedback from the laboratory, which has resulted in a better approach to prescribing antibiotic treatment for bloodstream infections. Detailed analysis of the timeliness and quality of laboratory work, the effects of laboratory results on antibiotic prescribing and the cost aspects of sustaining blood culture diagnostics in routine care are currently being performed. These results will be presented elsewhere.

This proof-of-principle study prompted the implementation of EUCAST standards in three clinics and at the central level. The increased number of isolates from the proof-of-principle study allowed laboratories to gain experience using state-of-the-art antibiotic susceptibility testing methods. An important logistical challenge delaying implementation of this new laboratory standard was the need for procuring new laboratory materials through lengthy tendering procedures, in accordance with national regulations.

During the proof-of-principle study, the Lugar Center was introduced as reference laboratory for AMR. All blood culture isolates were retested at the Lugar Center, the national AMR reference laboratory. Discrepancies in laboratory results between the Lugar Center and hospital laboratories provide important input for quality improvements, such as (1) implementing a harmonized approach to identifying species and (2) implementing a laboratory quality management system, including daily quality assurance using ATCC strains.

This proof-of-principle study laid down a solid basis for a multicentre collaborative surveillance network. A routine for standardized collection of antibiotic susceptibility testing results from the network laboratories has been developed. In its role as an AMR reference centre, the Lugar Center provides technical support and receives isolates for confirmatory testing and further characterization from clinics throughout Georgia.

9.5 Conclusions

This proof-of-principle study gives initial systematic insight into the pathogens causing bloodstream infections and their antibiotic susceptibility in Georgia. Even though the number of blood cultures taken and processed significantly improved during the study period, the absolute number of isolates per species was low, and the results should thus be interpreted with care. Most isolates were from patients with a suspected bloodstream infection with a nosocomial origin, precluding the generalization of results to patients with community-acquired infections. The percentages of resistance were high in general, which suggests nosocomial spread of (multi-)drug-resistant pathogens. An important exception was *S. aureus*, of which a moderate 20% was characterized as MRSA. This opens possibilities for reducing the use of vancomycin, which was among the most frequently used antibiotics among the patients included in the proof-of-principle study.

This proof-of-principle study has benefited Georgia, since it provided baseline AMR data for the main pathogens causing bloodstream infection in the country. Further, laboratory capacity was strengthened for species identification and antibiotic susceptibility testing at the local laboratories and the national AMR reference laboratory. A basis was established for a national AMR surveillance network and participation in CAESAR. Finally, the laboratories have the capacity to take samples according to standard protocols and to provide microbiological diagnostic information to guide appropriate treatment decisions. Additional analyses on how diagnostic results affect antibiotic prescribing and the cost and benefit aspects of sustaining blood culture diagnostics are improving and will be presented elsewhere. The National Center for Disease Control and Public Health is currently working on expanding the number of hospitals in the surveillance network, including all regions of Georgia.


CHAPTER
10

CAESAR external quality assessment

10.1 Introduction

The objective of the CAESAR external quality assessment is to assess whether the data collected by participating laboratories from all countries and areas is valid and can be pooled and analysed collectively. Further, the external quality assessment results can also be used to assess capacity-building needs in countries and areas. The external quality assessment is a joint exercise with the EARS-Net coordinated by the ECDC. The UK NEQAS based at the Public Health England National Infection Service in Colindale, London coordinates the preparation and quality control of the samples, organizes logistics and arranges the shipment to the countries and areas in collaboration with the AMR focal points and external quality assessment coordinator.

This chapter describes the results from the CAESAR external quality assessment 2015 in detail and summarizes the CAESAR external quality assessment that was performed in 2014. The conclusions discuss the overall results from three years of CAESAR external quality assessment. This chapter was shared with all AMR focal points for their final approval.

10.2 CAESAR external quality assessment in 2015

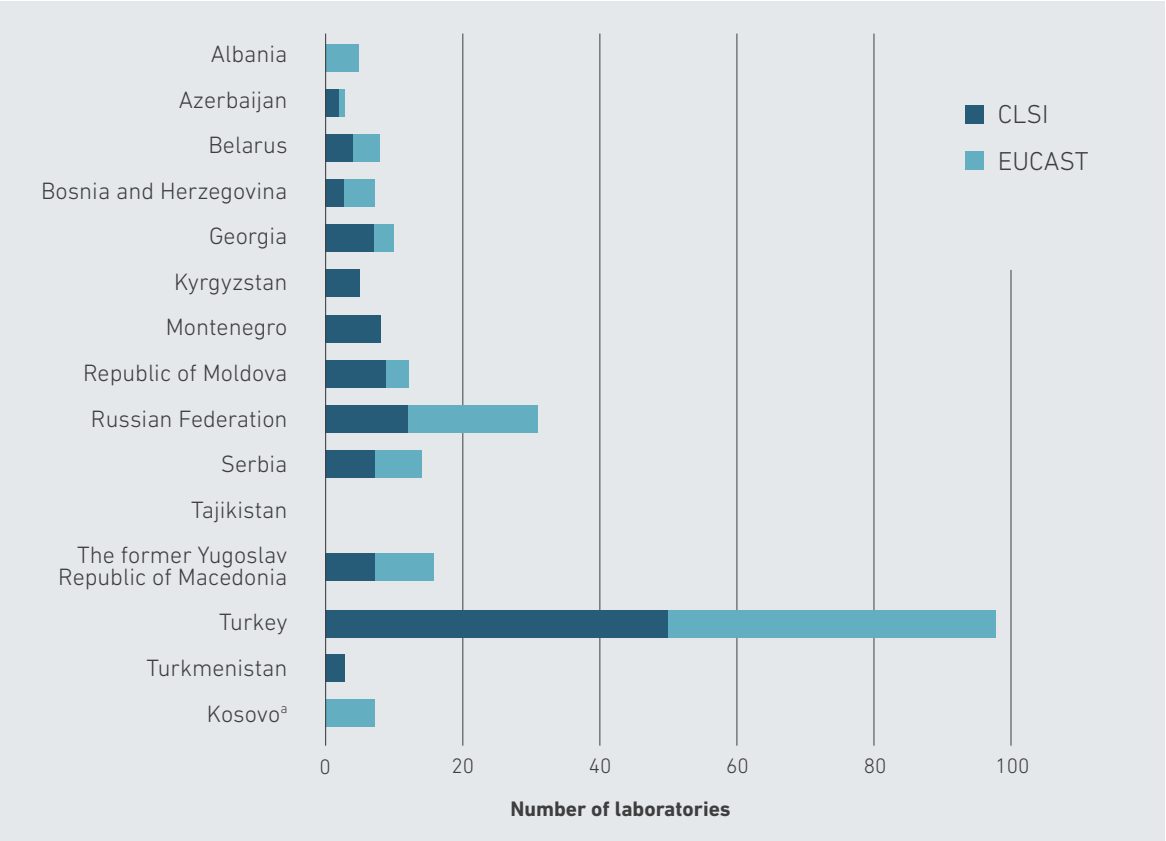
A panel of six lyophilized isolates was prepared and found fully compliant in quality control testing by the UK NEQAS, and the results were confirmed in two expert reference laboratories. The panel included the following strains: *E. faecalis* (specimen 3088), *K. pneumoniae* (specimen 3089), *S. aureus* (specimen 3090), *S. pneumoniae* (specimen 3091), *E. coli* (specimen 3092) and *P. aeruginosa* (specimen 3093). The external quality assessment panels were dispatched on 7 September 2015 to 252 participants in 15 of the 19 countries or areas participating in the CAESAR network. The participants were requested to return the results within 10 weeks. Results were returned from 15 countries and areas by 229 of 252 (91%) participants: 6 of 7 laboratories from Albania, 3 of 3 from Azerbaijan, 8 of 8 from Belarus, 7 of 7 from Bosnia and Herzegovina, 10 of 10 from Georgia, 5 of 5 from Kyrgyzstan, 8 of 9 from Montenegro, 12 of 12 from the Republic of Moldova, 31 of 39 from the Russian Federation, 14 of 14 from Serbia, 1 of 5 from Tajikistan, 16 of 17 from the former Yugoslav Republic of Macedonia, 98 of 106 from Turkey, 3 of 3 from Turkmenistan and 7 of 7 from Kosovo.[1]

10.2.1 Methods and guidelines used

Fig. 10.1 presents a breakdown of the methods and guidelines used by participants examining the external quality assessment specimens. All participants followed international guidelines: CLSI (50%) and EUCAST (50%). In most of the countries and areas (80%), both guidelines were stated to be in use among the participating laboratories, whereas in three countries and areas, Albania (EUCAST), Turkmenistan (CLSI) and Kosovo[1] (EUCAST), all participating laboratories homogeneously used the same guideline. A breakdown of the susceptibility testing methods used revealed that 50% of laboratories used the disk diffusion susceptibility testing method and 47% used an automated instrument; of the remaining participants, three performed minimum inhibitory concentration testing, two used gradient tests and two participants did not specify a method (Fig. 10.2).

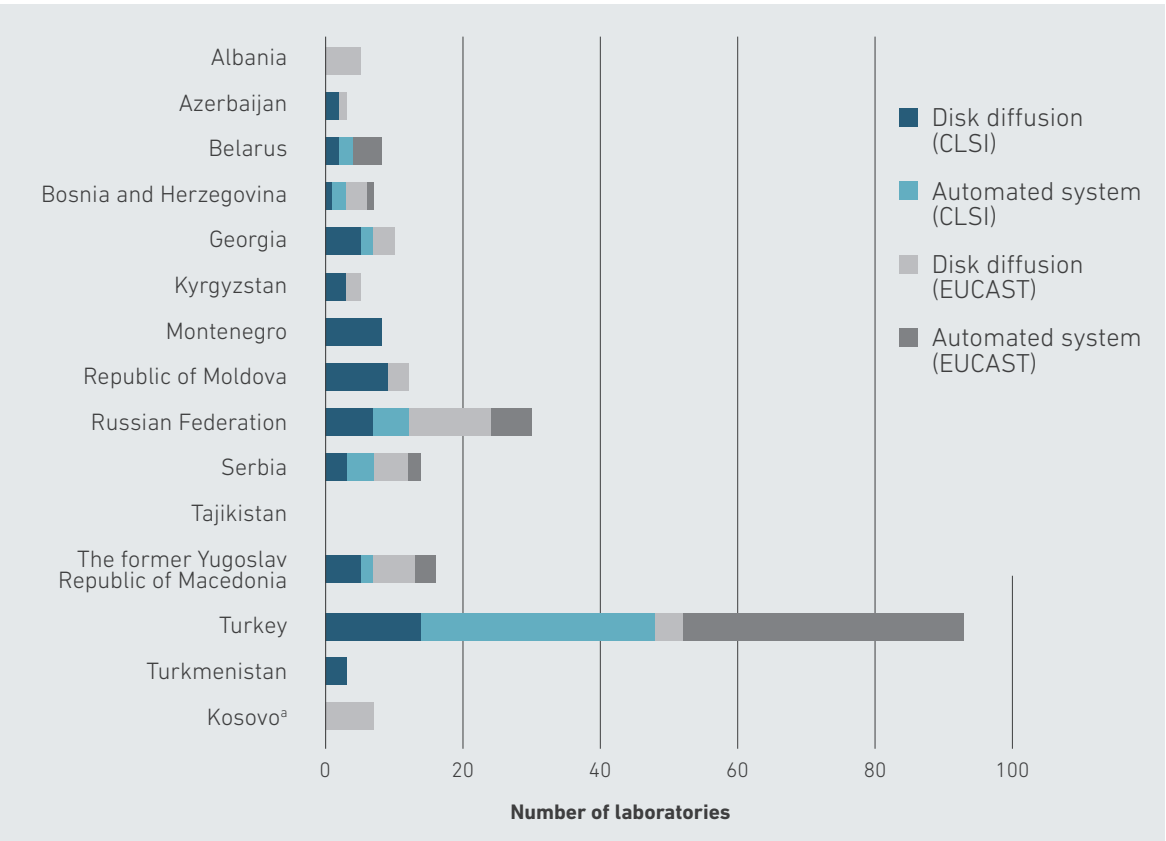
[1] All references to Kosovo in this chapter should be understood as references to Kosovo in accordance with United Nations Security Council resolution 1244 (1999).

Fig. 10.1 Number of laboratories and type of guideline used per country or area



[a] In accordance with United Nations Security Council resolution 1244 (1999).

Fig. 10.2 Number of laboratories and type of susceptibility testing method per country or area



[a] In accordance with United Nations Security Council resolution 1244 (1999).

10.2.2 Antimicrobial susceptibility test results

In general, performance was very good and consistent with that seen in previous external quality assessment surveys among participants in the European Region. Problems, where experienced, were mostly related to borderline susceptibility. External quality assessment is a valuable tool in the quality assurance of antimicrobial susceptibility testing and indicates the validity of comparing collated data between laboratories in resistance surveillance studies. The different isolates are described in more detail on the next pages, and the results by country or area are in Tables 10.1–10.6. The susceptibility of the pathogens isolated against the antimicrobial agents tested was defined as intermediate (I), resistant (R) or susceptible (S).

Specimen 3088 was an *E. faecalis* that was resistant to vancomycin and high-level resistant to gentamicin (Table 10.1). All laboratories correctly identified at the species level by using an automated instrument and 92% of the laboratories by using conventional methods, among which five laboratories identified the strain as *Enterococcus* spp. and two laboratories as *E. faecium*.

Table 10.1 *E. faecalis* (specimen 3088): minimum inhibitory concentration and intended results reported by the reference laboratories and the percentage of laboratories giving the correct result per country or area

Agent	Minimum inhibitory concentration range (mg/L), reference laboratory	Intended interpretation EUCAST/ CLSI	Percentage of laboratories giving the correct result														
			Albania (6)	Azerbaijan (3)	Bosnia and Herzegovina (7)	Belarus (8)	Georgia (10)	Kyrgyzstan (5)	Montenegro (8)	Republic of Moldova (12)	Serbia (14)	Russian Federation (31)	Tajikistan (1)	The former Yugoslav Republic of Macedonia (16)	Turkey (98)	Turkmenistan (3)	Kosovo[a] (7)
Identification			100%	33%	100%	100%	100%	100%	88%	100%	93%	100%	100%	94%	100%	33%	57%
Amoxicillin	–	S/S	33%	67%	100%	100%	80%	–	100%	78%	100%	100%	–	100%	–	100%	100%
Ampicillin	1	S/S	50%	33%	86%	88%	80%	–	100%	92%	100%	97%	–	100%	96%	100%	100%
Gentamicin (high level)	>512	R/R	83%	67%	67%	75%	88%	–	100%	91%	85%	67%	–	73%	98%	–	50%
Teicoplanin	0.25–0.5	S/S	67%	–	100%	100%	100%	–	–	–	100%	–	–	100%	93%	–	–
Vancomycin	8	R/I	50%	33%	50%	50%	70%	0%	13%	25%	100%	62%	–	75%	53%	–	71%

[a] In accordance with United Nations Security Council resolution 1244 (1999).
The results are only given when ≥50% of the laboratories in a country or area provided a result.

The minimum inhibitory concentration for vancomycin can be low for *Enterococcus* spp. harbouring the *vanB* gene and was 8 mg/L in this case. The isolate should be interpreted as resistant by EUCAST breakpoints but intermediate by CLSI breakpoints. The borderline susceptibility makes detecting reduced susceptibility more difficult, especially with disk diffusion methods, where the difference in zone diameter between susceptible and resistant isolates may be small and the appearance of a fuzzy zone edge or colonies just within the zone edge may be the best indication of resistance. Reduced susceptibility to vancomycin was detected by 79% of 219 participants (21% reported susceptible, 12% intermediate and 67% resistant).

Overall, there were few incorrect reports of intermediate or resistant to ampicillin (7% non-susceptible) and amoxicillin (9% non-susceptible). Resistance to ampicillin and amoxicillin in *E. faecalis* is very rare worldwide; any isolate of *E. faecalis* appearing resistant to ampicillin or amoxicillin should be retested for identification and antimicrobial susceptibility, and the isolate should be sent to a reference laboratory if resistance is confirmed.

The isolate was also high-level resistant to gentamicin. Among 229 laboratories that returned results for the survey, only 190 (83%) reported results for high-level resistance to gentamicin, and the correct answer rate was 86%. The relatively low response rate might indicate that this antimicrobial agent is not routinely tested for enterococci. The testing of high-level aminoglycoside resistance in enterococci is particularly important since aminoglycosides and cell wall–active agents, such as beta-lactams and glycopeptides, can be used in combination for life-threatening infections. There is likely to be synergy between aminoglycosides and penicillins or glycopeptides against enterococci without acquired high-level resistance.

Table 10.2 *K. pneumoniae* (specimen 3089): minimum inhibitory concentration and intended results reported by the reference laboratories and the percentage of laboratories giving the correct result per country or area

Agent	Minimum inhibitory concentration range (mg/L), reference laboratory	Intended interpretation EUCAST/ CLSI	Percentage of laboratories giving the correct result														
			Albania (6)	Azerbaijan (3)	Bosnia and Herzegovina (7)	Belarus (8)	Georgia (10)	Kyrgyzstan (5)	Montenegro (8)	Republic of Moldova (12)	Serbia (14)	Russian Federation (31)	Tajikistan (1)	The former Yugoslav Republic of Macedonia (16)	Turkey (98)	Turkmenistan (3)	Kosovo[a] (7)
Identification			100%	100%	86%	100%	100%	100%	100%	100%	93%	97%	0%	100%	100%	33%	71%
Amikacin	1	S/S	50%	67%	100%	100%	100%	67%	100%	100%	100%	100%	100%	100%	100%	–	100%
Amoxicillin	≥128	R/R	100%	100%	100%	100%	100%	–	100%	78%	100%	–	–	100%	–	100%	100%
Amoxicillin-clavulanic acid	≥128 (≥128)	R/R	100%	100%	100%	100%	100%	–	100%	82%	100%	100%	–	100%	100%	100%	100%
Ampicillin	≥128	R/R	83%	100%	100%	100%	100%	–	100%	100%	100%	100%	–	100%	100%	100%	100%
Cefotaxime	1	S/S	67%	33%	60%	50%	90%	100%	13%	50%	46%	69%	–	29%	–	50%	57%
Ceftazidime	0.5–1	S/S	33%	50%	71%	75%	100%	100%	63%	50%	64%	83%	–	56%	64%	–	43%
Ceftriaxone	1	S/S	50%	33%	67%	86%	90%	100%	25%	90%	57%	79%	0%	15%	59%	50%	86%
Ciprofloxacin	0.03	S/S	100%	100%	100%	100%	100%	67%	100%	100%	100%	97%	100%	100%	98%	100%	100%
Ertapenem	8	R/R	100%	–	50%	33%	80%	–	100%	–	100%	89%	–	89%	99%	–	100%
Gentamicin	0.25–0.5	S/S	83%	50%	100%	100%	100%	100%	100%	92%	100%	97%	100%	100%	100%	100%	86%
Imipenem	4–8	I/R	20%	50%	43%	25%	30%	50%	50%	9%	36%	23%	0%	38%	57%	–	29%
Levofloxacin	–	S/S	100%	100%	–	100%	100%	100%	–	100%	100%	100%	100%	100%	100%	–	–
Meropenem	2–4	I/I–R	40%	–	67%	25%	40%	–	100%	18%	21%	33%	–	57%	70%	–	40%
Ofloxacin	–	S/S	–	100%	–	100%	–	100%	100%	100%	92%	–	–	100%	–	67%	100%
Piperacillin-tazobactam	≥128	R/R	100%	–	100%	100%	90%	–	100%	89%	100%	100%	–	93%	100%	–	100%
Tobramycin	0.25–0.5	S/S	67%	67%	100%	100%	88%	100%	100%	91%	100%	100%	–	93%	–	–	100%

[a] In accordance with United Nations Security Council resolution 1244 (1999).

The results are only given when ≥50% of the laboratories in a country or area provided a result.

Specimen 3089 was a *K. pneumoniae*, which produces an OXA-48 carbapenemase, conferring reduced susceptibility to carbapenems (Table 10.2). All laboratories correctly identified the strain at the species level by using an automated instrument. However, 93% of the laboratories using conventional methods for identification could correctly identify the strain as *K. pneumoniae*, whereas three laboratories identified the strain as *Klebsiella* spp., one laboratory *E. coli* and one laboratory *P. aeruginosa*. Resistance to amoxicillin, ampicillin and amoxicillin-clavulanic acid was obvious, with 95%, 99% and 99.5%, respectively, of participants reporting that the isolate was resistant to these agents.

Isolates producing OXA-48 enzymes frequently show borderline resistance to carbapenems and may appear fully susceptible to cephalosporins. Susceptibility to third-generation cephalosporins was reduced compared with wild-type isolates, but the minimum inhibitory concentrations were within the susceptible category, although they were borderline. The borderline susceptibility was reflected in the high discrepancy rates for cefotaxime: 55% of 156 participants reported susceptible, 21% intermediate and 24% resistant, ceftriaxone (62% of 204 participants reported susceptible, 26% intermediate and 12% resistant) and ceftazidime (66% of 217 participants reported susceptible, 22% intermediate and 12% resistant). OXA-48 carbapenemases generally hydrolyse carbapenems weakly. In the presence of OXA-48, the minimum inhibitory concentrations of carbapenems are commonly elevated, often resulting in resistance to ertapenem, whereas the effect on other carbapenems is much less, sometimes resulting in reports of intermediate or even susceptible. This organism was resistant to ertapenem (minimum inhibitory concentration 8 mg/L), and 93% of participants reported resistant. The organism was borderline intermediate-resistant to imipenem (minimum inhibitory concentration 4–8 mg/L) by EUCAST breakpoints and resistant by CLSI breakpoints, and this was reflected in the variable reporting (overall 26% of 212 participants reported susceptible, 34% intermediate and 39% resistant). Notably, many participants incorrectly reported the isolate as being susceptible to imipenem.

The organism was borderline susceptible-intermediate to meropenem (minimum inhibitory concentration 2–4 mg/L) by EUCAST breakpoints and intermediate-resistant by CLSI breakpoints, and this was again reflected in the variable reporting (30% of 207 participants reported susceptible, 34% intermediate and 36% resistant).

Specimen 3090 was an MRSA (Table 10.3). All laboratories correctly identified the strain at the genus level. Only two laboratories misidentified the strain, one using an automated identification system that reported the strain as *Staphylococcus sciuri* and the other using conventional methods that reported the strain as *Staphylococcus* spp. without further differentiation.

Table 10.3 *S. aureus* (specimen 3090): minimum inhibitory concentration and intended results reported by the reference laboratories and the percentage of laboratories giving the correct result per country or area

Agent	Minimum inhibitory concentration range (mg/L), reference laboratory	Intended interpretation	Percentage of laboratories giving the correct result														
		EUCAST/ CLSI	Albania (6)	Azerbaijan (3)	Bosnia and Herzegovina (7)	Belarus (8)	Georgia (10)	Kyrgyzstan (5)	Montenegro (8)	Republic of Moldova (12)	Serbia (14)	Russian Federation (31)	Tajikistan (1)	The former Yugoslav Republic of Macedonia (16)	Turkey (98)	Turkmenistan (3)	Kosovo[a] (7)
Identification			100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	100%	99%	67%	100%
Cefoxitin	≥128	R/R	67%	100%	100%	100%	100%	–	100%	83%	100%	100%	–	100%	100%	–	100%
Ciprofloxacin	16	R/R	67%	100%	83%	88%	100%	50%	86%	25%	93%	100%	–	100%	100%	33%	100%
Clindamycin	≥128	R/R	100%	–	100%	100%	100%	100%	100%	91%	100%	100%	–	100%	99%	–	100%
Erythromycin	≥128	R/R	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	–	100%	100%	–	100%
Fusidic acid	0.06–0.12	S/–	100%	–	100%	–	–	–	–	–	100%	–	–	100%	–	–	100%
Gentamicin	128–256	R/R	100%	100%	100%	88%	100%	75%	100%	100%	100%	96%	–	100%	99%	33%	100%
Oxacillin	≥128	R/R	100%	67%	100%	100%	100%	–	100%	100%	100%	100%	–	100%	100%	100%	100%
Penicillin	64	R/R	100%	100%	100%	100%	100%	–	100%	100%	100%	100%	–	100%	100%	–	100%
Rifampicin	≥128	R/R	100%	100%	100%	100%	100%	–	100%	90%	100%	100%	–	100%	100%	–	100%
Teicoplanin	8–16	R/S–I	–	–	100%	86%	–	–	–	–	45%	–	–	80%	84%	–	–
Tetracycline	64	R/R	100%	–	100%	88%	100%	75%	100%	50%	100%	100%	–	100%	97%	67%	100%
Vancomycin	4	R/I	0%	33%	0%	0%	22%	–	–	8%	43%	25%	–	69%	35%	–	57%

[a] In accordance with United Nations Security Council resolution 1244 (1999).
The results are only given when ≥50% of the laboratories in a country or area provided a result.

This organism was an *S. aureus* with low-level resistance to vancomycin and teicoplanin. It is the same strain of vancomycin-intermediate *S. aureus* that was distributed in the CAESAR external quality assessment exercise in 2014, and little evidence indicates change in the performance of participants. Reduced susceptibility to glycopeptides in *S. aureus* is difficult to detect, and this was again reflected in the failure of many participants to detect reduced susceptibility. Of 206 participants reporting vancomycin susceptibility, only 27% reported resistant and 13% intermediate, while 60% incorrectly reported susceptible. This is very similar to reports in 2014, when 10% of 127 participants reported resistant, 28% intermediate and 61% reported susceptible. Reports of susceptible were less frequent among 105 participants following EUCAST guidelines than among 99 following CLSI guidelines and, in accordance with breakpoints, most non-susceptible reports with CLSI guidelines were in the intermediate category, whereas with EUCAST guidelines, most were in the resistant category to vancomycin.

Reduced susceptibility to glycopeptides in *S. aureus* cannot be reliably detected by disk diffusion methods, and EUCAST and CLSI disk diffusion methods state that disk diffusion should not be used for *S. aureus*.

Of the 98 participants reporting use of an automated method, 65 (66%) reported the isolate to be susceptible to vancomycin. As seen in 2014, minimum inhibitory concentration methods were clearly most reliable in detecting reduced susceptibility. There continue to be serious concerns regarding the ability of many participants to detect vancomycin resistance in isolates of vancomycin-intermediate *S. aureus*.

Specimen 3091 was an *S. pneumoniae* with reduced susceptibility to penicillin (minimum inhibitory concentration 0.25 mg/L) (Table 10.4). None of the laboratories had any difficulty in identifying the strain, and laboratories using both automated systems (44%) and conventional methods (56%) correctly identified the strain as *S. pneumoniae*.

Table 10.4 *S. pneumoniae* (specimen 3091): minimum inhibitory concentration and intended results reported by the reference laboratories and the percentage of laboratories giving the correct result per country or area

Agent	Minimum inhibitory concentration range (mg/L), reference laboratory	Intended interpretation	Percentage of laboratories giving the correct result														
		EUCAST/ CLSI	Albania (6)	Azerbaijan (3)	Bosnia and Herzegovina (7)	Belarus (8)	Georgia (10)	Kyrgyzstan (5)	Montenegro (8)	Republic of Moldova (12)	Serbia (14)	Russian Federation (31)	Tajikistan (1)	The former Yugoslav Republic of Macedonia (16)	Turkey (98)	Turkmenistan (3)	Kosovo[a] (7)
Identification			100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	100%	100%	100%	100%
Cefotaxime	0.12–0.25	S/S	83%	33%	100%	100%	100%	100%	100%	100%	100%	94%	–	86%	94%	–	71%
Cefotaxime (meningitis)		S/S	–	50%	80%	100%	–	100%	–	–	100%	–	–	–	–	–	67%
Cefotaxime (pneumonia)		S/S	100%	–	100%	100%	–	100%	–	–	100%	94%	–	–	–	–	67%
Ceftriaxone	0.25–0.5	S/S	50%	33%	100%	100%	100%	100%	–	89%	100%	95%	–	87%	98%	100%	71%
Ceftriaxone (meningitis)		S/S	–	50%	75%	100%	100%	100%	–	–	100%	88%	–	75%	–	100%	67%
Ceftriaxone (pneumonia)		S/S	100%	–	100%	100%	100%	100%	–	–	100%	95%	–	88%	–	100%	60%
Clindamycin	–	S/S	100%	–	100%	88%	100%	100%	100%	91%	100%	100%	–	100%	93%	–	100%
Erythromycin	4–8	R/R	67%	100%	71%	100%	90%	50%	50%	25%	86%	89%	–	73%	97%	100%	80%
Levofloxacin	1	S/S	100%	33%	100%	100%	90%	100%	–	91%	100%	100%	–	93%	97%	–	–
Moxifloxacin	0.12	S/S	100%	–	–	100%	100%	–	–	–	100%	100%	–	100%	–	–	–
Norfloxacin	–	S/S	75%	–	100%	100%	100%	–	–	89%	100%	–	–	91%	–	–	–
Oxacillin	–	R/R	100%	100%	100%	71%	90%	100%	100%	83%	100%	88%	–	89%	94%	67%	100%
Penicillin	0.25	–/–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Penicillin (meningitis)		R/R	80%	–	83%	100%	80%	–	–	–	77%	95%	–	92%	97%	–	–
Penicillin (pneumonia)		S/S	–	–	100%	86%	100%	–	–	–	85%	41%	–	73%	51%	–	–

[a] In accordance with United Nations Security Council resolution 1244 (1999).

The results are only given when ≥50% of the laboratories in a country or area provided a result.

For *S. pneumoniae* with no mechanism of resistance to penicillin, the minimum inhibitory concentrations are ≤0.06 mg/L. For isolates with higher minimum inhibitory concentrations, the interpretation of susceptibility to penicillin depends on the site of infection and route of administration. Patients with pneumonia caused by strains with intermediate susceptibility (minimum inhibitory concentration 0.12–2 mg/L) are treatable with penicillin, ampicillin or amoxicillin, depending on the parenteral dosage. Hence, such strains may be reported susceptible if they are from pneumonia. Patients with meningitis caused by strains with penicillin minimum inhibitory concentration >0.06 mg/L are unlikely to respond to therapy, and such strains should be reported as resistant in this situation. Both EUCAST and CLSI guidelines include options for reporting susceptibility depending on the site of infection.

Of the 163 participants reporting a result for oxacillin (screening test for penicillin resistance), 92% (*n* = 150) reported resistant, 1% (*n* = 2) intermediate and 7% (*n* = 11) susceptible. EUCAST and CLSI guidelines do not include an intermediate category for oxacillin, since the oxacillin screening test is not considered to distinguish reliably between isolates with different degrees of reduced susceptibility; so reports of intermediate are inappropriate.

If the isolate was from a case of pneumonia, 63% (*n* = 80) of 129 participants would report penicillin susceptible, 27% (*n* = 35) intermediate and only 11% (*n* = 14) resistant. As seen in previous CAESAR external quality assessment distributions, participants following CLSI guidelines were more likely to report an isolate being susceptible to penicillin when the infection was pneumonia. The differences in reporting for pneumonia again may partly relate to differences in reporting practices. Some participants may apply the guidelines for isolates other than meningitis without allowance for the high doses used to treat pneumonia. Some may report susceptible because higher doses are always used to treat pneumonia, and variation in dosing listed by EUCAST would not affect reporting if the minimum inhibitory concentration is 0.25 mg/L. Some may report intermediate because susceptibility is dose dependent and clinicians are left to interpret based on the dose they use.

If the isolate was from a case of meningitis 91% of 137 participants would report resistant, 0% intermediate and 9% susceptible. EUCAST and CLSI guidelines both indicate that the isolate should be reported resistant to penicillin, and there was little difference in reporting between participants following EUCAST guidelines and those following CLSI guidelines.

Specimen 3092 was an *E. coli* with a TEM-3 ESBL (Table 10.5). The laboratories using automated identification systems (60%) did not have any difficulty in identifying this strain, except for two laboratories reporting *P. aeruginosa* and *Salmonella* species. The laboratories using conventional methods for identification, however, exhibited rather poor performance for the *E. coli* strain, which is among the most frequently encountered clinical isolates in a diagnostic microbiology laboratory. Among 89 (40%) laboratories using conventional methods, 11 laboratories failed to correctly identify the strain and reported the following results: *Yersinia enterocolitica* (*n* = 3), *Shigella flexneri* (*n* = 3), *Acinetobacter* spp. (*n* = 2), *Hafnia alvei* (*n* = 1), *Klebsiella* spp. (*n* = 1) and *Shigella sonnei* (*n* = 1). The frequent misidentification of enteric pathogens might be explained by use of the diagnostic algorithms designed primarily to identify intestinal bacteria. Resistance to aminopenicillins and third-generation cephalosporins was clear, and there were no significant problems in detecting resistance.

Susceptibility to amoxicillin-clavulanic acid (minimum inhibitory concentration 16 mg/L) was borderline, and the isolate was resistant by EUCAST breakpoints (S ≤ 8, R > 8 mg/L) and intermediate by CLSI breakpoints (S ≤ 8, R ≥ 32 mg/L). Overall, 14% of 202 participants reported the organism susceptible to amoxicillin-clavulanic acid, 15% intermediate and 71% resistant. The difference in breakpoints was reflected in the reported results since the participants following EUCAST breakpoints were most likely to report resistant, whereas those following CLSI breakpoints were most likely to report intermediate.

The organism was susceptible to piperacillin-tazobactam (minimum inhibitory concentration 4 mg/L) by both EUCAST and CLSI breakpoints. Overall, 81% of 193 participants reported the organism susceptible to piperacillin-tazobactam, 12% intermediate and 6% resistant. There was no particular association

Table 10.5 *E. coli* (specimen 3092): minimum inhibitory concentration and intended results reported by the reference laboratories and the percentage of laboratories giving the correct result per country or area

Agent	Minimum inhibitory concentration range (mg/L), reference laboratory	Intended interpretation EUCAST/CLSI	Percentage of laboratories giving the correct result														
			Albania (6)	Azerbaijan (3)	Bosnia and Herzegovina (7)	Belarus (8)	Georgia (10)	Kyrgyzstan (5)	Montenegro (8)	Republic of Moldova (12)	Russian Federation (31)	Serbia (14)	Tajikistan (1)	The former Yugoslav Republic of Macedonia (16)	Turkey (98)	Turkmenistan (3)	Kosovo[a] (7)
Identification			100%	0%	100%	100%	80%	40%	100%	100%	100%	100%	0%	100%	98%	0%	57%
Amikacin	8	S/S	0%	33%	43%	63%	50%	100%	100%	64%	58%	43%	0%	13%	54%	–	57%
Amoxicillin	≥128	R/R	100%	100%	100%	100%	100%	–	100%	100%	–	100%	100%	100%	–	67%	100%
Amoxicillin-clavulanic acid	16 (16)	R/R	100%	100%	71%	50%	75%	75%	100%	64%	58%	54%	–	56%	76%	50%	80%
Ampicillin	≥128	R/R	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	–	100%	100%	67%	100%
Cefotaxime	32	R/R	100%	100%	100%	100%	90%	80%	100%	58%	96%	100%	–	100%	–	–	100%
Ceftazidime	64	R/R	100%	100%	100%	100%	100%	100%	100%	92%	90%	100%	–	100%	98%	–	100%
Ceftriaxone	32	R/R	100%	100%	86%	100%	90%	60%	100%	70%	89%	100%	–	93%	99%	50%	100%
Ciprofloxacin	0.25	S/S	83%	67%	100%	100%	100%	100%	100%	92%	87%	93%	0%	94%	98%	33%	86%
Ertapenem	0.06	S/S	50%	–	100%	86%	100%	–	100%	–	85%	93%	–	100%	95%	–	25%
Gentamicin	0.5–1	S/S	67%	33%	100%	100%	100%	100%	100%	92%	97%	93%	0%	94%	97%	67%	100%
Imipenem	0.25	S/S	33%	–	100%	100%	100%	100%	100%	100%	100%	100%	0%	100%	98%	–	86%
Levofloxacin	–	S/S	50%	33%	–	100%	100%	75%	–	91%	82%	92%	0%	90%	100%	–	–
Meropenem	0.03	S/S	50%	–	100%	100%	100%	100%	100%	91%	100%	100%	–	100%	97%	–	100%
Ofloxacin	–	S/S	–	50%	–	57%	–	100%	100%	75%	–	90%	–	70%	–	50%	80%
Piperacillin-tazobactam	4	S/S	75%	–	83%	100%	100%	–	100%	89%	88%	86%	–	64%	77%	–	–
Tobramycin	8–16	R/I–R	100%	100%	67%	88%	100%	–	–	27%	81%	82%	–	100%	–	–	60%

[a] In accordance with United Nations Security Council resolution 1244 (1999).
The results are only given when ≥50% of the laboratories in a country or area provided a result.

between guidelines or methods and reported susceptibility. Some participants may have edited susceptible test results to intermediate or resistant because of the presence of the ESBL, but guidelines from both EUCAST and CLSI recommend reporting beta-lactamase inhibitor combinations "as found" in routine tests. The current EUCAST expert rules do recommend that, when an organism is intermediate or resistant to any third-generation (cefotaxime, ceftriaxone or ceftazidime) or fourth-generation (cefepime) oxyimino-

cephalosporin, reports of susceptible to beta-lactamase inhibitor combinations should include a warning of uncertain therapeutic outcome for infections other than urinary tract infections.

Aminoglycoside susceptibility was typical for an organism producing AAC(6')-I since the organism was susceptible to gentamicin (minimum inhibitory concentration 0.5–1 mg/L), borderline susceptible to amikacin (minimum inhibitory concentration 8 mg/L) and borderline resistant to tobramycin (minimum inhibitory concentration 8–16 mg/L; resistant by EUCAST breakpoints, intermediate-resistant by CLSI breakpoints). For tobramycin, 72% of 141 participants reported resistant, 14% intermediate and 14% susceptible. In accordance with the differences in breakpoints between EUCAST and CLSI, participants using CLSI guidelines more commonly reported intermediate than those following EUCAST guidelines.

For amikacin, 52% of 223 participants reported susceptible, 37% intermediate and 11% resistant. In accordance with the differences in breakpoints between EUCAST and CLSI, reports of susceptible were most common among those following CLSI guidelines and reports of intermediate were most common among participants using EUCAST guidelines.

The ciprofloxacin minimum inhibitory concentration (0.25 mg/L) was elevated slightly compared with wild-type *E. coli*, but the organism was within the susceptible category according to both EUCAST and CLSI breakpoints. Most of the 228 participants reported susceptible (93%), with 5% reporting intermediate and 2% resistant.

Specimen 3093 was a *P. aeruginosa* resistant to ciprofloxacin, gentamicin, tobramycin, carbapenems and piperacillin-tazobactam (Table 10.6). The laboratories using an automated identification system (59%) had no difficulty in identifying this strain, except for a laboratory that reported *Burkholderia cepacia*. The laboratories using conventional methods (41%) also performed well and, except for two laboratories that reported *Pseudomonas* spp. and *Proteus mirabilis*, all successfully identified the strain as *P. aeruginosa*.

There were no problems in detecting the carbapenem resistance, which is likely to be mediated by porin loss and efflux, since no carbapenemase enzyme was present.

The ceftazidime minimum inhibitory concentration (8 mg/L) was borderline susceptible with both EUCAST (S ≤ 8, R > 8 mg/L) and CLSI (S ≤ 8, R ≥ 32 mg/L) breakpoints. Overall, 24% of 221 participants reported resistant, 24% intermediate and 53% susceptible. Of 111 participants following EUCAST guidelines, 37% reported ceftazidime resistant, with 9% reporting intermediate and 54% susceptible. Among 108 participants following CLSI guidelines, reports of susceptible (49%) or intermediate (39%) were more common, with 12% reporting resistant. The CLSI guidelines include an intermediate category but EUCAST guidelines do not, and many laboratories following CLSI guidelines (39%) reported intermediate, whereas few following EUCAST guidelines (9.0%) reported intermediate.

The minimum inhibitory concentration for piperacillin-tazobactam (64 mg/L) was clearly in the resistant category by EUCAST breakpoints (S ≤ 16, R > 16 mg/L) but intermediate by CLSI breakpoints (S ≤ 16, R ≥ 128 mg/L). Overall, 53% of 197 participants reported resistant, 28% intermediate and 19% susceptible. In accordance with the differences in breakpoints, the participants following CLSI guidelines were more likely to report intermediate (49% of 96) or susceptible (28%) than those following EUCAST guidelines (7% of 100 reported intermediate and 11% reported susceptible). There was no clear correlation of methods with results.

Table 10.6 *P. aeruginosa* (specimen 3093): minimum inhibitory concentration and intended results reported by the reference laboratories and the percentage of laboratories giving the correct result per country or area

Agent	Minimum inhibitory concentration range (mg/L), reference laboratory	Intended interpretation	Percentage of laboratories giving the correct result														
		EUCAST/CLSI	Albania (6)	Azerbaijan (3)	Bosnia and Herzegovina (7)	Belarus (8)	Georgia (10)	Kyrgyzstan (5)	Montenegro (8)	Republic of Moldova (12)	Russian Federation (31)	Serbia (14)	Tajikistan (1)	The former Yugoslav Republic of Macedonia (16)	Turkey (98)	Turkmenistan (3)	Kosovo[a] (7)
Identification			100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	100%	99%	100%	86%
Amikacin	4	S/S	100%	100%	100%	100%	100%	100%	100%	100%	97%	93%	100%	87%	98%	–	86%
Ceftazidime	8	S/S	20%	50%	50%	13%	40%	25%	38%	67%	65%	43%	–	38%	58%	–	57%
Ciprofloxacin	32	R/R	100%	100%	100%	100%	100%	100%	100%	83%	97%	100%	–	100%	99%	33%	100%
Gentamicin	≥128	R/R	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	–	100%	99%	100%	100%
Imipenem	32	R/R	100%	100%	100%	88%	100%	100%	100%	91%	97%	100%	–	100%	99%	–	100%
Levofloxacin	–	R/R	80%	100%	100%	100%	100%	100%	100%	100%	100%	100%	–	100%	100%	50%	100%
Meropenem	32	R/R	100%	100%	100%	100%	100%	100%	100%	91%	97%	100%	–	100%	100%	–	100%
Piperacillin-tazobactam	64	R/R	17%	100%	83%	43%	30%	–	0%	44%	67%	43%	–	64%	58%	–	40%
Tobramycin	≥128	R/R	100%	100%	100%	100%	100%	100%	100%	55%	100%	100%	–	100%	100%	100%	100%

[a] In accordance with United Nations Security Council resolution 1244 (1999).

The results are only given when ≥50% of the laboratories in a country or area provided a result.

10.3 CAESAR external quality assessment in 2014

In 2014, six lyophilized isolates including the following strains: *E. coli* (specimen 2496), *K. pneumoniae* (specimen 2497), *S. aureus* (specimen 2498), *S. pneumoniae* (specimen 2499), *E. faecium* (specimen 2500) and *A. baumannii* complex (specimen 2501) were sent to participant laboratories in 12 countries and areas. A total of 161 participants returned results: two laboratories from Albania, three from Azerbaijan, six from Belarus, four from Bosnia and Herzegovina, five from Georgia, five from Kyrgyzstan, six from Montenegro, 28 from the Russian Federation, 14 from Serbia, 13 from the former Yugoslav Republic of Macedonia, 68 from Turkey, and seven from Kosovo[1].

All participants followed international guidelines: CLSI (78%) and EUCAST (22%). Seven countries or areas stated that the participating laboratories used both guidelines, whereas in five countries or areas, all participating laboratories used the same guideline: Albania (EUCAST), Azerbaijan (CLSI), Kyrgyzstan (CLSI), Montenegro (CLSI) and Kosovo[1] (EUCAST). The antimicrobial susceptibility testing methods the laboratories used for the external quality assessment strains were the disk diffusion method (53%) and an automated instrument (46%); of the remaining two, one used gradient tests and one did not specify a method.

The participants generally performed very well in identifying and in testing the antimicrobial susceptibility of the external quality assessment strains. Overall, no problems were observed with identifying the strains, indicating the diagnostic capability of the laboratories. The only organism for which the laboratories exhibited relatively poor performance was the *E. faecium* strain. For this strain, the correct identification rate among all participating laboratories was 87%, but the breakdown of the identification methods revealed that laboratories using an automated identification system performed satisfactorily (correct identification rate 96%), whereas laboratories using conventional methods had a correct identification rate of 67%, indicating the need for improvement of the diagnostic test capacity. For antimicrobial susceptibility testing, the problems, where experienced, were almost exclusively related to borderline susceptibility and interpretation and/or reporting of penicillin, cefotaxime and ceftriaxone susceptibility in *S. pneumoniae*. Table 10.7 presents the external quality assessment isolates and their important features related to antimicrobial susceptibility.

Table 10.7 Specimens distributed in the CAESAR external quality assessment survey in 2014 and their important antimicrobial susceptibility features

Specimen number	Organism	Correct identification among participating laboratories (*n* = 161) (%)	Important antimicrobial susceptibility features of the strain
2496	*Escherichia coli*	100	Extended-spectrum beta-lactamase (CTX-M-15) positive Low-level resistance to piperacillin-tazobactam
2497	*Klebsiella pneumoniae*	92	VIM carbapenemase positive Borderline to amikacin
2498	*Staphylococcus aureus*	99	MRSA Low-level resistance to vancomycin and teicoplanin
2499	*Streptococcus pneumoniae*	99	Reduced susceptibility to penicillin Different interpretation of susceptibility to penicillin, cefotaxime and ceftriaxone in meningitis and pneumonia
2500	*Enterococcus faecium*	87	High-level resistance to gentamicin
2501	*Acinetobacter baumannii* complex	98	GES-12 carbapenemase positive

10.4 Summary of three years of external quality assessment in CAESAR

The CAESAR external quality assessment survey has been conducted since 2013 in collaboration with the UK NEQAS. It has distributed six lyophilized isolates per year to laboratories in countries and areas participating in CAESAR. The number of laboratories participating in the CAESAR external quality assessment has steadily increased by involving new countries and areas in CAESAR or by adding new laboratories to existing national networks. The survey started in 2013 with 131 laboratories from eight countries and areas (Belarus, Georgia, Kyrgyzstan, Montenegro, Serbia, the former Yugoslav Republic of Macedonia, Turkey and Kosovo[1]). With the involvement of four national networks (Albania, Azerbaijan, Bosnia and Herzegovina and the Russian Federation), the number of countries and areas participating in the external quality assessment survey has increased to 12 and the number of laboratories to 161. In 2015, three new countries (Republic of Moldova, Tajikistan and Turkmenistan) started to participate in the external quality assessment survey, and the number of participating laboratories reached 252, of which 229 returned results.

The results obtained from the external quality assessment survey enable the laboratory capacity of the participating laboratories to be assessed, both at the individual laboratory level and also at the country or area level, and this is thus a very useful activity for developing policies to improve the existing network. The CAESAR external quality assessment survey can obtain information on the capacity to perform correct identification, the antimicrobial susceptibility testing method used, adherence to international standards for antimicrobial susceptibility testing, correct interpretation of the susceptibility test results and ability to perform additional or confirmatory tests to identify special resistance mechanisms. The isolates with well characterized antimicrobial susceptibility profiles give the participating laboratories the opportunity to compare their performance with that of other laboratories at the national and international levels, identify the weaknesses and develop action plans to improve.

The accumulated data from the CAESAR external quality assessment results show an increasing number of laboratories participating in the CAESAR network implement EUCAST methods. In 2013, 88% of the participants indicated that they used CLSI guidelines, and 14% were using the EUCAST guideline. In 2014, the use of EUCAST methods increased to 22%. The shift became more evident in 2015, as the use of EUCAST methods increased to 50%. Most importantly, this shift has resulted in the use of up-to-date guidelines for antibiotic susceptibility testing in more countries.

Even though the guideline being followed among the CAESAR laboratories shifted strikingly, the antibiotic susceptibility testing methods used by the laboratories did not change. In 2013, 49% of the laboratories used an automated instrument and 47% used the disk diffusion method. Similarly in 2014, 46% of the laboratories used an automated instrument and 53% used the disk diffusion method. No change in the preferred method was observed in 2015; 47% of the laboratories used an automated instrument and 50% used the disk diffusion susceptibility testing method.

The antibiotic susceptibility testing results obtained for the bacterial isolates revealed similar problems; detection of borderline susceptibility (such as piperacillin-tazobactam and aminoglycosides in gram-negative bacteria, vancomycin in *S. aureus*), interpretation of specific tests (such as the oxacillin-screen test in *S. pneumoniae*, interpreting and reporting penicillin, cefotaxime and ceftriaxone susceptibility results in *S. pneumoniae* in meningitis and pneumonia cases and high-level gentamicin resistance in *Enterococcus* spp.), performance of inappropriate techniques (such as using the disk diffusion method for testing vancomycin in *S. aureus*). Such problems, when encountered, should not be discouraging but motivating to implement necessary measures for improvement.

A good example of improvement among the network laboratories is the detection of carbapenem resistance in Enterobacteriaceae. As an important emerging resistance mechanism, laboratory capacity to detect carbapenem resistance in carbapenemase-producing Enterobacteriaceae was tested in all previous surveys. OXA-48-producing *K. pneumoniae* with low-level meropenem resistance isolates were sent to laboratories in both 2013 and 2015 (minimum inhibitory concentration of meropenem: 4 mg/L in 2013 and 2–4 mg/L in 2015). The susceptibility results in 2013 showed correct results for meropenem, ranging between 0% and 50% among participating laboratories; the results obtained in 2015, however, exhibited correct susceptibility results ranging between 18% and 100%. This improvement emphasizes the contribution of external quality assessment practice to continuous development of laboratory performance.


CHAPTER
11

Concluding remarks

Since it started in 2012, the CAESAR network has grown into an important network for exchanging knowledge, expertise and experience related to surveillance for AMR. The network has become a platform for capacity-building efforts to improve AMR surveillance and AMR control among the countries in the WHO European Region that are not included in EARS-Net. The main activities of the CAESAR network include yearly CAESAR network meetings at ECCMID, twice-yearly multicountry AMR workshops, national training workshops and capacity-building activities, national AMR surveillance network meetings and the CAESAR external quality assessment exercises. All countries participating in the CAESAR network are making progress towards implementing the basic building blocks to gain insight into their current AMR situation and to coordinate the control of AMR (Chapter 2).

The number of countries submitting AMR data to CAESAR has grown from five countries presented in the first CAESAR annual report in 2014 to seven countries and Kosovo[1] in this report (Chapters 6 and 7). With this, a first step is being made towards pan-European surveillance of AMR as represented in the maps in Chapter 8, combining data from EARS-Net (ECDC) and CAESAR. Many countries within the CAESAR network are working on setting up and improving their national AMR surveillance capacity to improve insight into the AMR situation in their country. This will enable them to take appropriate action to control AMR and to submit data to the CAESAR database to be shared with the international community. The CAESAR network strives to continually progress towards full coverage of functional national surveillance systems in the European Region. This vision is further strengthened by the aim of all CAESAR countries to contribute to the Global Antimicrobial Resistance Surveillance System (GLASS).

This CAESAR report gives important insights into the resistance patterns in participating countries. However, the use of the data for developing treatment guidelines and assessing time trends are limited because of several methodological factors that influence the observed magnitude of resistance (Chapter 5). Several of these limiting factors, such as implementing harmonized antibiotic susceptibility testing methods, internal and external quality assurance in the laboratories and expanding coverage to improve the representativeness of the country, can be improved with some effort through the active AMR surveillance network of laboratories present in all participating countries.

A more challenging improvement that is needed is increasing the use of blood culture diagnostics and microbiological diagnostics in general. The underrepresentation of data from less severely ill patients and treatment-naive patients (because of selective sampling) is a main factor leading to overestimation of the proportion of resistance, limiting their usefulness for informing treatment guidelines. The proof-of-principle pilot study to stimulate blood sampling and antimicrobial susceptibility testing being conducted in Georgia is a good example of how improvements can be achieved (Chapter 9). Improving the use of microbiological diagnostics requires involving various clinical specialties and/or the health ministry to incorporate microbiological culturing in clinical guidelines and hospital administration and/or insurance companies to secure financial means. We strongly urge the participating surveillance networks to build a case and push for the increased use of microbiological diagnostics and blood culturing in particular. Blood culturing before starting antibiotic therapy is an essential component of the clinical care of patients with bloodstream infections and sepsis, in accordance with international guidelines.

Indeed, reliable and valid AMR surveillance is the basis for implementing targeted measures to control AMR. Nevertheless, the development and further improvement of AMR surveillance should not delay the implementation of control measures. Although the exact magnitude of resistance is still difficult to assess in many countries, the current CAESAR data clearly indicate the presence of multidrug resistance, high levels of carbapenem resistance in *Klebsiella pneumoniae* and high proportions of multidrug-resistant

1 In accordance with United Nations Security Council resolution 1244 (1999).

Acinetobacter spp. in clinical settings in several countries and suggest that resistant clones are being disseminated in the healthcare setting. These strong indications should already lead to prompt action to improve antibiotic stewardship and infection prevention and control in clinical settings, including in the countries in which these data are not yet available. Ideally, these control measures are accompanied with the development of local surveillance to target and evaluate the effect of control measures. Ample guidance on antibiotic stewardship and infection prevention and control is available, although implementation requires additional and tailored support.

With the control of AMR being one of the main priorities of WHO, the WHO Regional Office for Europe and its partners remain dedicated to providing the support needed to equip countries with the skills and knowledge to successfully address AMR in healthcare settings and the community.

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ANNEX
1

Sources of errors and bias in antimicrobial resistance surveillance data

When interpreting results from surveillance or any other form of research, one should always assess whether the results reflect the truth. Every measurement of reality has a risk of deviating from the truth, because of either random or systematic error. Random deviation results from chance variation occurring during sampling or measurement. Systematic deviation is caused by systematic errors in collecting, processing and analysing the data. Systematic deviation is also called bias. In particular, systematic deviation may occur because of choices made when taking patient samples (such as sampling bias), when processing samples in the laboratory (such as measurement error) or when aggregating data for analysis (such as duplicate isolates).

Random error will always occur, and the investigators can reduce the amount of error somewhat. In contrast, the investigators can reduce systematic error significantly by paying attention to details of and improving the data generation process.

Random error

Sampling variation
Random error may occur by chance whenever a sample of individuals is taken from a population. For example, counting the number of patients presenting with signs of a bloodstream infection from whom a blood culture is obtained each week over the period of four consecutive weeks means submitting a different number each week, such as 9, 13, 10 and 11 during the first, second, third and fourth week, respectively. This is consistent with a true average of 11 blood cultures per week, but the observed number of blood cultures varies per week by chance. Random variation may result in either over- or underestimating a resistance proportion. The amount of deviation from reality expected from random error, or the statistical precision of a measurement, depends on sample size. The smaller the sample size, the larger the potential deviation from reality; the larger the sample size, the smaller the potential variation.

Measurement variation
Random error also occurs whenever measurements are taken and will result from slight variation in how measurement procedures are applied from measurement to measurement. For example, the concentration of an inoculum that is prepared varies every time. Random variation will result in either over- or underestimating a resistance proportion. In general, this deviation will be a mix of over- or underestimation, and the values will cancel each other out when results are combined. Again, sample size will reduce the effect of random highs and lows. The amount of error in automated measuring systems is generally small and acceptable. With human procedures, the amount of error depends on the experience of the person doing the test and the care taken during the measurement procedures. Standardizing procedures, training laboratory staff and quality assurance will minimize random measurement variation.

Systematic error

Bias from sampling procedures – selecting participating sites
In order to obtain a nationally representative assessment of AMR the hospital laboratories selected for participation in the national surveillance should be from different geographical and climatic regions,

include both rural and urban areas and provide samples from different patient populations (hospital types / departments). Sampling only special populations will only allow the generalization of results to that specific population, but not necessarily to the overall patient population.

Bias from sampling procedures – selecting patients

When surveillance is based on routine diagnostic testing, as in this report, data should be interpreted with extra caution. Because the data used in passive surveillance is not generated with surveillance as the primary objective but instead has patient care as the aim, these data are inherently biased towards more ill patients, patients among whom treatment is problematic or patients for whom there is high suspicion of resistant infections: that is, clinical predictions are included in the decision on whether or not to test. In active surveillance, in contrast, clear case definitions are generally used to identify patients that need to be sampled, and specific efforts are made to attain a representative sample of the target population.

Obtaining results that are representative of the target population requires making certain that all patients fitting the case-definition are sampled; in the case of CAESAR, all patients presenting with signs of a bloodstream infection (signs of systematic inflammatory response syndrome) should be sampled. Including only special patient categories (such as only intensive care units or tertiary care institutions) or patients with chronic or recurring infection, relapses or treatment failure will overestimate the resistance proportion, because these patients were subjected to selective pressure of antimicrobial agents. The use of microbiological diagnostics is subject to financial and logistical constraints outside the control of the surveillance system. For example, few blood cultures may be taken in routine clinical care if bacteriological sampling is not reimbursed through health insurance or if physicians are not used to sampling every patient because little laboratory capacity is available. Further, sampling of patients may be frequent after antimicrobial therapy has already been started or after self-treatment fails if no legislation bans over-the-counter sales of antimicrobial agents.

When the samples are collected may also influence the resistance proportions found. Any seasonal variation can be overcome by sampling throughout the year. Ad hoc or convenience sampling for a limited time period, especially during outbreaks, will bias results.

Bias from laboratory procedures – measurement error

As mentioned above, random variation occurs whenever measurements are taken. Besides random variation, systematic error in measurement may occur and lead to false-negative or false-positive results. Systematic error generally results in either over- or underestimating the overall proportion of resistance. Systematic measurement error occurs when laboratory procedures are improperly applied, such as plating a too large inoculum; when inadequate laboratory materials are used, such as poor-quality growth media or expired antimicrobial disks; or when automatic systems are damaged or not properly calibrated.

Correctly identifying species may be important for interpreting the percentages of resistance, since some species are more clinically relevant than others and their capacity to acquire resistance or to be intrinsically resistant varies. Sometimes telltale signs indicate problems with species identification. For example, a high proportion (>5%) of ampicillin resistance in *E. faecalis* suggests that *E. faecium* is being misclassified as *E. faecalis*.

A laboratory quality management system and regular application of internal quality assurance procedures allows the timely detection and correction of systematic error in laboratory procedures. National auditing and accreditation schemes in conjunction with external quality assurance programmes ensure that laboratories conform to national quality standards.

Importantly, specific highly resistant microorganisms or exceptional antimicrobial resistant phenotypes (such as carbapenem-resistant Enterobacteriaceae) may need to be confirmed by additional testing, to assess whether they are true findings or may result from laboratory error. This double checking of results is important because the finding of these types of organisms may have serious consequences for empirical antimicrobial therapy and for infection prevention and control policies.

Bias from laboratory procedures – laboratory standards

To ensure reliable results, antibiotic susceptibility testing must be done according to well developed and scientifically grounded standards. Both EUCAST and CLSI provide comprehensive methodological standards for routine antibiotic susceptibility testing, confirmatory testing and its interpretation. Because the laboratory methods and interpretive criteria (clinical breakpoints) may differ between standards and change over time, they may lead to incomparable results when assessing trends, and comparing results from laboratories or countries using different standards may be problematic.

Importantly, susceptibility to all indicated antimicrobial agents should be tested for each isolate included in surveillance. Differential or sequential test ordering, such as only testing carbapenems if there is resistance to third-generation cephalosporins, will lead to overestimating resistance proportions.

Bias from data aggregation and analysis procedures

Individual patients are often sampled repeatedly during their illness, for diagnostic purpose or to assess therapeutic response. Patients with infections caused by resistant microorganisms are more likely to be cultured more than once. Inclusion of repeat isolates from an individual patient when calculating the proportion of resistance will result in overestimation, since the resistant isolates are overrepresented. To prevent this, CAESAR collects the first isolate per microorganism per person per year, the convention when doing surveillance.

Expert rules are often used in interpreting antibiotic susceptibility testing results in practice, for the purpose of reporting results to the clinic. For example, if *S. aureus* is resistant to cefoxitin, it is reported as resistant to all beta-lactam antimicrobial agents. Different laboratories or national surveillance systems may use different expert rules, which may make comparison between laboratories or countries problematic. To prevent varying practice from biasing the results and to standardize the interpretation, we collect systematic inflammatory response results for all bacterium–antimicrobial agent combinations tested and we infer derived resistance during data analysis.

Definitions

Active surveillance: surveillance based on active case-finding, testing and reporting; special efforts are made to identify all cases of disease

Bias: systematic deviation of results from the truth

Data-generating process: procedures and routes by which data reach a database – all steps from identification of patients to be sampled, via laboratory procedures to storing and selection of results for analysis

Passive surveillance: surveillance based on collecting routinely available data or notification of disease cases by health workers; no special efforts are made to identify all cases of disease

Reliability (or reproducibility): the degree to which the results of a measurement would be the same the next time the measurement was carried out

Representativeness (or generalizability): the degree to which results of surveillance are true for the population of interest

Sampling bias: systematic error resulting from the methods or procedures used to sample or select the study subjects, specimens or items or systematic differences between participants and non-participants

Target population: the group at which inference from the study is targeted; for CAESAR, patients presenting with a bloodstream infection

The WHO Regional Office for Europe

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