World Health Organization
REGIONAL OFFICE FOR Europe

Central Asian and Eastern European Surveillance of Antimicrobial Resistance

Annual report 2017

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Abstract

This report describes resistance data gathered through the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) network from nine countries in the WHO European Region– Belarus, Bosnia and Herzegovina, Georgia, Montenegro, 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)). Guidance is provided to the reader on how to interpret the surveillance data with caution, taking into account conditions which may reduce the reliability and representativeness of the data. The aim of this report is 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

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Foreword

The awareness of antimicrobial resistance (AMR) as one of the major threats to global human and animal health continues to expand steadily, also beyond the health and agricultural sectors. This awareness is based on a growing body of evidence provided by research and surveillance from an increasing number of countries and origins around the world.

Countries of the European Union (EU) have a long tradition of collecting surveillance data on antimicrobial use and resistance, as well as health care-associated infections. After the adoption of the European strategic action plan on antibiotic resistance (2011–2020) by all 53 Member States of the WHO European Region, the WHO Regional Office for Europe, the Netherlands 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 outside the EU in setting up or strengthening national AMR surveillance.

Following the establishment of CAESAR, a number of country assessment activities were undertaken to assess the capacity of Member States to address the objectives identified in the European action plan, with a special focus on surveillance. The capacity-building needs identified during these activities are being addressed through technical trainings and workshops, study tours, exchange visits, and trouble-shooting and other twinning-type activities. Much effort has gone into strengthening national AMR reference laboratories to prepare them for their role to strengthen and maintain national laboratory networks, ensure the quality of their work, provide reference testing services and collect data centrally for surveillance purposes. Through these efforts, much improvement has been made and more countries are getting ready to produce surveillance data to shed light on their national situation, as well as to share their knowledge internationally. Currently, 19 European countries and Kosovo (in accordance with United Nations Security Council resolution 1244 (1999)) are engaged in the CAESAR network at various stages of development and participation. Nine countries and one area are now reporting data to CAESAR: Belarus, Bosnia and Herzegovina, Georgia, Montenegro, 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)).

The aim of this report is to provide guidance and inspiration to countries that are building or strengthening their national AMR 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: Lindita Molla (Albania), Perlat Kapisyzi (Albania), Silva Tafaj (Albania), Kristina Gyurjyan (Armenia), Nazifa Mursalova (Azerbaijan), Mais Sailov (Azerbaijan), Leonid Titov (Belarus), Alexander Davydov (Belarus), Julia Shyshporenok (Belarus), Amela Dedeic-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), Milena Lopicic (Montenegro), Vineta Vuksanovic (Montenegro), Iurie Pinzaru (Republic of Moldova), Radu Cojocaru (Republic of Moldova), Olga Burduniuc (Republic of Moldova), Roman S. Kozlov (Russian Federation), Marina Sukhorukova (Russian Federation), Zora Jelesic (Serbia), Deana Medic (Serbia), Andreas Kronenberg (Switzerland), Alban Ramette (Switzerland), Said Davlatov (Tajikistan), Rahmonali Nasurdinov (Tajikistan), Saranjon Bobjonova (Tajikistan), Musharafa Kilicheva (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 Yildiz (Turkey), Can H. Hekimoglu (Turkey), Gurbangul Ovliyakulova (Turkmenistan), Azat Ovezon (Turkmenistan), Irina Ganzha (Ukraine) Natalia Piven (Ukraine), Tetiana Glushkevych (Ukraine), Gulnora Abdukhalilova (Uzbekistan), 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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Finally, special thanks to the many consultants providing essential expertise to support countries and areas in strengthening their AMR surveillance systems.

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Abbreviations

AMR	antimicrobial resistance
AST	antimicrobial susceptibility testing
CAESAR	Central Asian and Eastern European Surveillance of Antimicrobial Resistance
CC	clonal complex
CLSI	Clinical and Laboratory Standards Institute
CSF	cerebrospinal fluid
E. coli	*Escherichia coli*
E. faecalis	*Enterococcus faecalis*
E. faecium	*Enterococcus faecium*
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
EQA	external quality assessment
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
K. pneumoniae	*Klebsiella pneumoniae*
MRSA	methicillin-resistant *Staphylococcus aureus*
P. aeruginosa	*Pseudomonas aeruginosa*
Susceptibility	Susceptibility of a pathogen to an antimicrobial agent
I	intermediate
I+R	intermediate or resistant
R	resistant

S	susceptible
S. aureus	*Staphylococcus aureus*
S. pneumoniae	*Streptococcus pneumoniae*
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 Netherlands National Institute for Public Health and the Environment and the European Society of Clinical Microbiology and Infectious Diseases. CAESAR aims to provide support in setting up and strengthening a national antimicrobial resistance (AMR) surveillance network to 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 in the European Union.

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[1] are members of the CAESAR network. In 2016, nine countries (Belarus, Bosnia and Herzegovina, Georgia, Montenegro, the Russian Federation, Serbia, Switzerland, the former Yugoslav Republic of Macedonia and Turkey) and Kosovo[1] have submitted data to the CAESAR database.

CAESAR collects antimicrobial susceptibility testing data from blood and cerebrospinal fluid for nine bacterial pathogens of public health and clinical importance: *Escherichia coli, Klebsiella pneumoniae, Salmonella* species, *Pseudomonas aeruginosa, Acinetobacter species, Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus faecalis* and *Enterococcus faecium*. Chapters 5 and 6 present the trends of resistance observed among these reported pathogens. Chapter 7 presents maps of the European Region, displaying the resistance proportions of a selected number of pathogen–antibiotic combinations in the CAESAR and EARS-Net countries. Annex 1 describes the pathogens under CAESAR surveillance and the main infections caused by each of the pathogens.

Georgia and Montenegro reported AMR data for the first time during this reporting period. The CAESAR data clearly show that antibiotic resistance is widespread in the European Region. While assessing the exact magnitude of resistance is still challenging in many countries, the data point out the resistance patterns present in clinical settings covered by the surveillance. High levels of carbapenem resistance in *K. pneumoniae* and high proportions of multidrug-resistant *Acinetobacter* spp. in several countries suggest the dissemination of resistant clones in the health care setting. These data provide a basis for taking action to control AMR.

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 patients eligible for blood culturing or the quality of antimicrobial 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 4, Annex 2). To further guide the interpretation of the data presented in this report, the authors and the AMR focal points introduced levels of evidence for their respective country or area. Besides guiding interpretation, the level of evidence assessment was developed to provide specific input for improving the national AMR surveillance (Chapter 4). In 2016, both Bosnia and Herzegovina and Serbia progressed from level B to level A data, by expanding their surveillance network to cover all types of hospitals and by adopting the European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodology as the national standard for antimicrobial susceptibility testing.

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

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

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. Most of the countries are still facing many challenges, and strong political support is needed to continue making progress.

One of the challenges is the limited routine antimicrobial susceptibility testing caused by the underutilization of microbiological diagnostics in clinical practice. To address this challenge the proof-of-principle AMR routine diagnostics surveillance project was established, with the objective to stimulate the collection of blood cultures from patients with suspected bloodstream infections. The proof-of-principle project can provide a first assessment of antibiotic susceptibility of the main pathogens causing community-associated and hospital-associated bloodstream infections. The first proof-of-principle project was conducted in Georgia between July 2015 and July 2016. Preliminary results were published in the 2016 CAESAR annual report.[2] This project formed the basis for the multicentre collaborative surveillance network that provided national AMR data to CAESAR for the first time, published in this report.

Chapter 8 describes the results from the CAESAR external quality assessment exercise conducted in 2016. The overall achieved results were good, and the number of countries and laboratories participating in the exercise has increased from 120 laboratories in eight countries/areas in 2013 to 254 laboratories in 18 countries/areas in 2016. Over the years, the antimicrobial 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. Accordingly, substantial progress has been achieved following the widespread implementation of up-to-date methodological guidelines. The use of the European Committee on Antimicrobial Susceptibility Testing guidelines increased from 14% in 2013 to 74% in 2016 among participating laboratories, which is reflected in their overall good performance in detecting novel resistance mechanisms.

In conclusion, the information contained in this report provides guidance, inspiration and motivation to countries that are building or strengthening their national AMR surveillance. The data in this report should be interpreted with caution as they may not fully represent the current status in countries that do not have a comprehensive surveillance system. However, the high percentages of resistance displayed and the resistance profiles reported strongly support the global call to action and emphasize the importance of good clinical practice in reducing the further development of AMR. Using surveillance data to initiate and monitor AMR control efforts in clinical settings, and increasing awareness among policy-makers and the public are essential in fighting AMR.

2 CAESAR. Annual report 2016. Copenhagen: WHO Regional Office for Europe; 2016 (http://www.euro.who.int/en/health-topics/disease-prevention/antimicrobial-resistance/publications/2016/central-asian-and-eastern-european-surveillance-of-antimicrobial-resistance.-annual-report-2016, accessed 4 October 2017).


CHAPTER
1

Introduction

Surveillance of antimicrobial resistance (AMR) is considered the backbone of both the European strategic action plan on antibiotic resistance (2011–2020) *(1)* and the Global action plan on AMR (2015) *(2)*. In 2011, when the European action plan was adopted at the 61st session of the WHO Regional Committee for Europe in Baku, Azerbaijan, many countries in the WHO European Region that are not members of the European Union (EU) did not systematically collect and share AMR data. Therefore, the WHO Regional Office for Europe, together with the Netherlands National Institute for Public Health and the Environment and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), 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.

In close collaboration with the European Centre for Disease Prevention and Control (ECDC) and using compatible methodology, CAESAR complements surveillance conducted in the EU to obtain a pan-European overview of the trends and sources of AMR. 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[1] are engaged in the CAESAR network, with a subset of these countries providing resistance data.

The CAESAR network supports setting up national AMR surveillance networks and improving laboratory quality, data management, analysis and reporting in existing surveillance networks. Country support is tailored to the phase of development and specific needs of the surveillance system. In countries with an established surveillance system, focus is on harmonizing laboratory methods and streamlining data management. In countries with antibiotic susceptibility testing being done routinely in clinical settings but not yet collecting data at the national level, the emphasis is on setting up a surveillance network and standardized data collection in parallel with harmonization of laboratory methods. In countries where bacteriological laboratory diagnostics are underutilized, the focus is on building laboratory capacity and diagnostic stewardship through proof-of-principle projects.

The efforts of the CAESAR network include (i) performing annual external quality assessment (EQA) exercises (since 2013); (ii) publishing of the CAESAR surveillance manual (2015); (iii) training courses on laboratory quality management; (iv) and training for AMR reference laboratories. The CAESAR network has supported the improvement of surveillance networks by organizing multicountry and national workshops focussing on surveillance methodology, data management, analysis and interpretation of AMR surveillance data. A pool of consultants is available to support laboratory networks making a transition to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodology and setting up laboratory quality assurance systems and to support AMR surveillance networks to set up and improve standardized (electronic) data collection, handling and storage, and data quality assurance procedures.

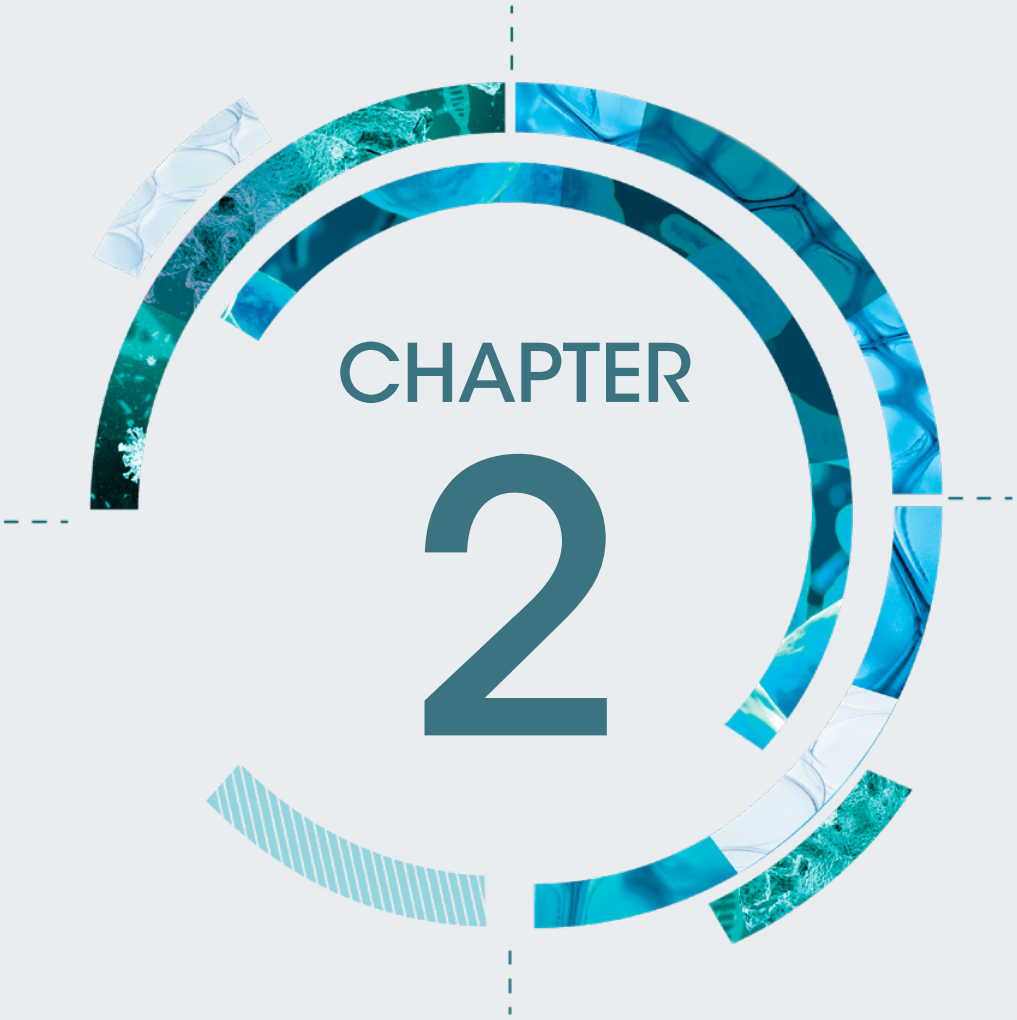
Since 2013, the CAESAR network holds annual meetings during the European Congress of Clinical Microbiology and Infectious Diseases organized by ESCMID, where all AMR focal points from CAESAR participating countries are invited to discuss AMR trends, network progress, EQA results, and specific issues and challenges related to AMR surveillance. Furthermore, since 2015, the CAESAR network has provided technical and financial support for the organization of AMR surveillance network meetings in participating countries in order to foster discussion about local surveillance data, external quality assurance results, and efforts to improve surveillance and to assess capacity-building needs.

CAESAR published its first annual report on the occasion of the first World Antibiotic Awareness Week in November 2015. The report contained AMR surveillance data from Belarus, Serbia, Switzerland, the former Yugoslav Republic of Macedonia and Turkey. The second CAESAR annual report, published during

the second World Antibiotic Awareness Week in 2016, included additional surveillance data from Bosnia and Herzegovina and the Russian Federation, as well as area-specific data from Kosovo[1]. For the first time, the report included joint maps showing data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) and the CAESAR network.

This third CAESAR annual report premieres national AMR data from Georgia and Montenegro. The other members of the CAESAR network are preparing and building the necessary capacity for AMR surveillance in order to provide data that can be shared internationally in the coming years to complete the European overview.

These efforts will also contribute to populating the WHO Global Antimicrobial Resistance Surveillance System (GLASS), in which a number of CAESAR network countries enrolled during the past year. To avoid double reporting and an additional burden on its members, the CAESAR network has agreed to provide aggregated AMR data to GLASS on behalf of those countries that are enrolled.


CHAPTER
2

Progress in CAESAR

At present, Kosovo[1] and 19 member countries are in the CAESAR network: 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.

In addition to the nine countries (Belarus, Bosnia and Herzegovina, Georgia, Montenegro, the Russian Federation, Serbia, Switzerland, the former Yugoslav Republic of Macedonia and Turkey) and Kosovo[1] currently reporting AMR data to CAESAR, all remaining countries are preparing and building the necessary capacity for AMR surveillance, which will also enable them to collect AMR data and report AMR data to CAESAR in the near future. Surveillance capacity within the CAESAR network is steadily developing and improving.

2.1 Indicators of progress in CAESAR

The AMR focal points are asked each year to fill in a short questionnaire, reporting on AMR activities being undertaken and the progress being made. The questionnaire for 2017 was divided into four main areas: (i) overall coordination; (ii) surveillance network and AMR reference laboratory; (iii) quality control; and (iv) guidelines for antimicrobial susceptibility testing (AST). Each area consisted of a set of indicators, reflecting the stepwise approach, needed to develop and strengthen AMR surveillance (Table 2.1). The results of the 2017 questionnaire are described in this chapter, as provided and approved by the AMR focal points.

2.1.1 Progress on overall AMR coordination

Addressing the threat of AMR requires political commitment. The health ministry is instrumental in providing the mandate to the institute charged with setting up a surveillance system. Support from the government is needed on legal, technical and financial aspects in order to establish a surveillance system. Through the adoption of the Global action plan on AMR *(1)* all countries have committed to develop a national action plan on AMR and incorporate surveillance activities in the national action plan. The implementation of these plans will require building this capacity through long-term investments, for instance in operational research, laboratories, human and animal health systems, competent regulatory capacities, and professional education and training, in both the human and animal health sectors. Table 2.2 shows the status of the overall coordination on AMR.

2.1.1.1 AMR focal points

Of the 19 countries participating in CAESAR, 18 countries and Kosovo[1] have appointed an AMR focal point, which is a prerequisite for participation in CAESAR (Table 2.3). The AMR focal point represents the institute, nominated by the health ministry, to play a leading role in forming an intersectoral coordinating mechanism for containing AMR.

2.1.1.2 Intersectoral coordinating mechanism

As described in the European strategic action plan on antibiotic resistance *(2)* and the Global action plan on AMR *(1)*, Member States are encouraged to: establish a sustainable, multisectoral, interdisciplinary and inclusive committee that monitors the public health risks and impact of AMR in all sectors; recommend policy options; secure overall commitment to national strategies for containing antibiotic resistance; provide technical guidance on national analysis, standards, guidelines, regulations, training and awareness; and ensure coordination where needed.

Table 2.1 Description of AMR indicators

Area	Indicators	Description
Overall AMR coordination	AMR focal point	AMR focal point appointed by health ministry
	Intersectoral 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
	AMR action plan monitoring and evaluation	Implementation of action plan is being monitored and evaluated
Surveillance network and AMR reference laboratory	Coordination of AMR surveillance	Entity appointed to coordinate AMR surveillance network
	AMR surveillance team	AMR surveillance team formed
	AMR reference laboratory nominated	AMR reference laboratory nominated
	Functional AMR reference laboratory	AMR reference laboratory assumed its functions according to a defined terms of references
	AMR surveillance	AMR surveillance established
	Periodic surveillance reports	AMR surveillance report published periodically
	AMR surveillance network meetings	Periodic AMR surveillance network meetings held
	CAESAR reporting	AMR data reported to CAESAR
	GLASS	Enrolled in GLASS
Quality control	CAESAR EQA	Participation in CAESAR EQA exercise
	Laboratory quality assurance system	Laboratory quality assurance system in place
AST guidelines	Current AST guideline	Majority of laboratories in the country use the current version of the AST guideline (EUCAST/Clinical Laboratory Standards Institute (CLSI)/other)
	Implementation of EUCAST breakpoints	Percentage of laboratories implementing EUCAST breakpoints
	Use of EUCAST disk diffusion method	Percentage of laboratories using EUCAST disk diffusion methodology
	AST committee	An AST committee has been formed

Table 2.2 Overall coordination on AMR

Country or area[a]	AMR focal point appointed by health ministry	Intersectoral coordinating mechanism to contain AMR has been set up	AMR action plan has been developed	Dedicated funds are available for AMR action plan implementation	Active implementation of AMR action plan is ongoing	Implementation of action plan is being monitored and evaluated
ALB	✓	⚙	✓	✗	✗	✗
ARM	✓	⚙	✓	⚙	⚙	✓
AZE	✓	⚙	⚙	✓	✗	✗
BLR	✓	⚙	⚙	⚙	✓	✓
BIH	✓	⚙	✗	✗	✗	✗
GEO	✓	✓	✓	⚙	✓	⚙
KAZ	✗	✗	⚙	N/A	✗	✗
KGZ	✓	✓	⚙	✗	⚙	⚙
MNE	✓	✓	✓	✓	✓	✓
MDA	✓	✓	⚙	✗	✗	✗
RUS	✓	N/A	✓	⚙	⚙	⚙
SRB	✓	⚙	⚙	✗	✗	✗
SWI	✓	✓	✓	✓	✓	✓
TJK	✓	✓	⚙	✗	✗	✗
MKD	✓	✓	✓	⚙	✓	⚙
TUR	✓	⚙	✓	⚙	✓	⚙
TKM	✓	✓	⚙	⚙	✓	⚙
UKR	✓	✓	⚙	✗	✗	✗
UZB	✓	✓	⚙	✓	⚙	✗
KOS[b]	✓	✓	⚙	⚙	⚙	⚙
No	**1**	**1**	**1**	**7**	**8**	**9**
In progress	**0**	**7**	**11**	**8**	**5**	**7**
Yes	**19**	**11**	**8**	**4**	**7**	**4**

[a] The three-letter abbreviations of countries' and areas' names come from the ISO 3166-1 alpha-3 standard of the International Organization for Standardization (ISO).

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

✓: yes; ✗: no; ⚙: in progress; N/A: not answered.

Table 2.3 AMR focal points of the CAESAR network

Country or area	AMR focal point
Albania	Lindita Molla (AMR One Health Focal Point at Institute of Public Health) and Perlat Kapisyzi (Chair, AMR Intersectoral 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	Leonid Titov (Head, Laboratory for Clinical and Experimental Microbiology, Republican Research and Practical Center for Epidemiology and Microbiology)
Bosnia and Herzegovina	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	Iurie Pinzaru (General Director, National Centre for Public Health, Ministry of Health)
Russian Federation	Roman S. Kozlov (Director, Institute of Antimicrobial Chemotherapy, Smolensk State Medical University)
Serbia	Deana Medic (Head of the Department for Pyogenic Infection, Center for Microbiology, Institute of Public Health of Vojvodina)
Switzerland	Andreas Kronenberg (Swiss Centre for Antibiotic Resistance, Institute for Infectious Diseases, University of Bern)
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, Acute Dangerous Infections Control, State Sanitary Epidemiology Service, Ministry of Health and Medical Industry)
Ukraine	Irina Ganzha (Leading Specialist, Department of Coordination with Organs of Central Power and Ministries, Public Health Department, Ministry of Health)
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 the United Nations Security Council resolution 1244 (1999).

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 crucial for overall coordination and development of 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)*.

To date, 10 countries and Kosovo[1] indicated that they have an international coordinating mechanism in place. Seven countries have indicated that they are in the process of setting up this mechanism versus six countries in the last reporting period (2015).

2.1.1.3 National action plan

The 2015 Global action plan on AMR urged Member States to have a national action plan on AMR in place by May 2017. Continuous AMR surveillance is crucial in assessing the main antibiotic resistance rates of concern and targeting adequate actions to control them and should have a prominent place in the strategic action plan to combat AMR.

Among the countries participating in CAESAR, eight countries indicated that they have an AMR action plan developed, compared to seven countries in 2015 (Table 2.2). Moreover, 10 countries and Kosovo[1] indicated that they are in the process of developing a national action plan. Four countries indicated that dedicated funds for implementation of the national action plan are available. Seven countries and Kosovo[1] are in the process of making funds available, and the remaining seven countries have no funds specifically available to implement their national action plan. Seven countries are actively implementing the national action plan, and four countries and Kosovo[1] are in the process of preparing for implementation. Four countries are monitoring and evaluating the implementation of their national action plan on AMR. Six countries and Kosovo[1] have indicated that they are in the process of setting up monitoring and evaluation of their implementation.

2.1.2 Progress on surveillance networks and AMR reference laboratories

2.1.2.1 AMR surveillance network

AMR surveillance networks enable countries (i) to describe their antibiotic resistance situation; (ii) to set priorities in infection control activities; (iii) to develop antibiotic therapy guidelines; and (iv) to perform sentinel studies. Sharing AMR data with the international community enables comparison of resistance patterns between countries, subregions and regions and participation in international activities aiming to control the spread of antibiotic resistance.

Collaboration among microbiology laboratories and inter-laboratory standardization is crucial when setting up an AMR surveillance network. Participation of laboratories in the surveillance network not only contributes to gathering resistance data but also greatly improves the quality of routine AST by offering EQA, regular teaching courses, frequent discussions within the laboratory network and during meetings, and collaboration with international networks. The AMR surveillance teams usually include staff members specialized in epidemiology, microbiology and data management and should ideally include staff with a clinical background to ensure good collaboration with the participating hospitals and the practical use of information and results.

Fifteen countries and Kosovo[1] have indicated that an institute has formally been appointed to coordinate the AMR surveillance network and 13 countries and Kosovo[1] have indicated that a surveillance coordination team has been formed (Table 2.4). Three countries indicated that they are in the process of formally appointing an institute to coordinate the AMR surveillance network, and five countries are in the process of forming an AMR surveillance team. The AMR focal points have reported that AMR surveillance teams consist of, on average, 4–10 members. Members of this team are microbiologists, epidemiologists and clinicians. Some teams also include data managers, clinical pharmacologists, laboratory technicians, molecular biologists and coordinators/administrators.

Table 2.4 AMR surveillance

Country or area[a]	Entity appointed to coordinate AMR surveillance network	AMR surveillance team formed	AMR reference laboratory nominated	AMR reference laboratory assumed its functions	AMR surveillance established	AMR surveillance report published periodically	Periodic AMR surveillance network meetings held	AMR data reported to CAESAR	Enrolled in GLASS
ALB	✓	✗	✗	✗	✗	✗	✓	✗	✗
ARM	✓	✓	✓	⚙	⚙	✗	⚙	✗	✗
AZE	✗	✓	✗	✗	✓	✗	✓	✗	✓
BLR	✓	✓	✓	✓	✓	✓	✓	✓	⚙
BIH	✓	✓	⚙	✓	⚙	✗	✓	✓	✓
GEO	✓	✓	✓	✓	⚙	✓	✓	✓	✓
KAZ	⚙	⚙	✗	✗	✗	✗	✗	✗	✗
KGZ	⚙	⚙	⚙	⚙	⚙	✗	✗	✗	⚙
MNE	✓	✓	⚙	⚙	✓	⚙	✓	✓	✗
MDA	✓	✓	✓	✓	✓	⚙	✓	✗	✗
RUS	✓	⚙	✓	✓	✓	✓	✓	✓	⚙
SRB	✓	✓	✓	✓	✓	✓	✓	✓	✗
SWI	✓	✓	✓	✓	✓	✓	✓	✓	✓
TJK	✓	✓	⚙	✗	⚙	✗	✗	✗	✗
MKD	✓	✓	✗	✓	✓	✓	✓	✓	✗
TUR	✓	✓	✓	✓	✓	⚙	✓	✓	✓
TKM	✓	⚙	✓	✓	✓	✗	✗	✗	⚙
UKR	⚙	⚙	⚙	⚙	⚙	⚙	✗	✗	✓
UZB	✓	✓	✓	✓	⚙	✗	✓	✗	✗
KOS[b]	✓	✓	✓	✓	✓	✓	✓	✓	⚙
No	1	1	4	4	2	9	5	10	9
In progress	3	5	5	4	7	4	1	0	5
Yes	16	14	11	12	11	7	14	10	6

[a] The three-letter abbreviations of countries' and areas' names come from the ISO 3166-1 alpha-3 standard.

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

✓: yes; ✗: no; ⚙: in progress.

2.1.2.2 AMR reference laboratory

The institute assigned to coordinate the AMR surveillance network often also acts as an AMR reference laboratory. In some cases a separate laboratory is nominated to fulfil this important function.

Ten countries and Kosovo[1] have nominated an AMR reference laboratory, and five countries are in the process of nomination (Table 2.4). Having a functional AMR reference laboratory is a crucial part of the surveillance network, taking the lead in introducing and maintaining standards for AST 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, 11 countries and Kosovo[1] have a fully functional AMR reference laboratory, whereas four are still in the process of establishing all required functions.

2.1.2.3 AMR surveillance and reporting

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), as well as for policy-making, monitoring interventions and presentations at scientific and professional meetings.

Ten countries and Kosovo[1] have an AMR surveillance system in place (Table 2.4). Seven countries have indicated they are developing their AMR surveillance system, in line with CAESAR methodology. This is a slight increase from 2015. Six countries and Kosovo[1] publish an AMR surveillance report periodically, which is an increase from four in 2015. Thirteen countries and Kosovo[1] hold periodic AMR surveillance network meetings, which are four more countries compared to last year. Nine countries and Kosovo[1] report AMR data to CAESAR. To date, six countries have enrolled in GLASS; four countries and Kosovo[1] are in the process of enrolling and nine countries have not yet enrolled.

2.1.3 Progress on quality control

A quality assurance system ensures reliability and reproducibility of laboratory data. Internal quality control should be a routine procedure undertaken by participating laboratories to ensure the quality of testing. It should cover all diagnostic tests and procedures including isolation, identification and AST. Internal quality control should also cover media production and equipment maintenance. Eleven countries indicated that they have a laboratory quality assurance system in place (Table 2.5). This is a significant increase from four in 2015. Five countries and Kosovo[1] indicated that they are in the process of establishing a laboratory quality system.

Besides internal quality control, regular external quality control for laboratories in the AMR surveillance network is crucial to allow for an evaluation of the quality and reliability of data provided to the AMR surveillance system. In addition, discussing EQA results provides guidance for laboratories to implement corrective action and to strive for continuous improvement. To stimulate setting up an EQA system in a country, CAESAR organizes an annual EQA scheme provided by the United Kingdom National EQA Service for Microbiology (UK NEQAS). Participating laboratories are encouraged to store the EQA isolates which can later be used to set up and improve their own internal quality control practices. Seventeen countries and Kosovo[1] are participating in the CAESAR EQA exercise (Table 2.5). The results from the EQA exercise of 2016 are presented in Chapter 8.

Table 2.5 Quality control

Country or area	Laboratory quality assurance system in place	Participation in CAESAR EQA exercise
Albania	✗	✓
Armenia	⚙	✓
Azerbaijan	✓	✓
Belarus	✓	✓
Bosnia and Herzegovina	✓	✓
Georgia	✓	✓
Kazakhstan	N/A	✗
Kyrgyzstan	⚙	✓
Montenegro	✓	✓
Republic of Moldova	✓	✓
Russian Federation	✓	✓
Serbia	✓	✓
Switzerland	✓	✗
Tajikistan	✗	✓
The former Yugoslav Republic of Macedonia	⚙	✓
Turkey	✓	✓
Turkmenistan	⚙	✓
Ukraine	✓	✓
Uzbekistan	⚙	✓
Kosovo[a]	⚙	✓
No	**3**	**2**
In progress	**6**	**0**
Yes	**11**	**18**

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

✓: yes; ✗: no; ⚙: in progress; N/A: not answered.

2.1.4 Progress on implementing AST guidelines

All laboratories participating in a 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 with the latest procedures and developments.

In recent years, many CAESAR countries have been working on updating and harmonizing the AST guidelines used nationally. CAESAR recommends countries to use either EUCAST or CLSI standards. Since EUCAST guidelines are the most widely used in the European Region and all EUCAST documents are freely downloadable in various languages *(3)*, CAESAR provides training in EUCAST methodology. In line with the EUCAST recommendation, CAESAR also advises that a group of experts within the AMR network form a AST committee or a similar working group that deals with AST methodology issues and that ensures the nationwide dissemination and adoption of the yearly updates of international standards among all members of the AMR network *(4)*.

Fifteen countries and Kosovo[1] have indicated that they use EUCAST guidelines, with versions ranging between 2015 and 2017 (Table 2.6). Of these, nine use EUCAST in combination with CLSI guidelines or different national guidelines. Azerbaijan uses only CLSI guidelines, while two countries – Kazakhstan and Turkmenistan – use only national guidelines. Countries using CLSI guidelines use versions ranging from 2004 to 2016. Five countries indicated that a AST committee has been formed. Six countries and Kosovo[1] indicated that they are in the process of setting up this committee.

Five countries and Kosovo[1] indicated that more than 50% of laboratories are implementing EUCAST breakpoints. Six countries indicated that between 10% and 50% of laboratories have implemented EUCAST breakpoints. Four countries indicated that less than 10% of laboratories have implemented this, and three countries did not provide data on this indicator. Six countries and Kosovo[1] indicated that more than 50% of laboratories use the EUCAST disk diffusion method. In four countries, the EUCAST disk diffusion method is used in 10–50% of laboratories. In five countries, this figure is less than 10%, and four countries have no data on this indicator.

2.1.5 Quality as procurement criteria

The quality of AMR data depends not only on the skills of laboratory personnel and on high-level quality management in laboratories, but also on the quality of the antimicrobial disks and media used. Unfortunately, not all manufacturers produce laboratory consumables of sufficient quality to obtain reliable test results, which can misguide treatment decisions and lead to treatment failure and can provide an incorrect presentation of the AMR situation in a country 'or area'. EUCAST has repeatedly evaluated crucial antibiotic disks for AST from nine international manufacturers, illustrating varying quality of disks both between and within manufacturers. Disks from a few of the manufacturers were consistently found to be of a high quality whereas the opposite was true for others; the EUCAST website provides the results per manufacturer *(5)*.

The work performed by EUCAST provides critical information for the purchasing of good quality laboratory consumables for AST, and stresses the need to take quality into account as one of the criteria of the tendering process, when purchasing laboratory consumables in general, and for detecting AMR in particular.

2.2 Conclusions

At the moment, nine countries and Kosovo[1] are able to provide AMR surveillance data to CAESAR. Many countries are taking the necessary steps to set up or strengthen their AMR surveillance system, enabling them to get a better insight into the AMR situation in their country and take appropriate action. This chapter has clearly shown that steady progress is being made in many countries in the CAESAR network; however, for most indicators only a slight increase in the number of countries that have implemented additional steps, or are in the process of implementation, was observed compared to 2015. This demonstrates

Table 2.6 AST guidelines as of 2017

Country or area[a]	Majority of laboratories in the country use the current version of the AST guideline (EUCAST/ CLSI/other)	Year or version of AST guideline being used	Percentage of laboratories implementing EUCAST breakpoints	Percentage of laboratories using EUCAST disk diffusion methodology	A AST committee has been formed
ALB	EUCAST	N/A	10–50	>50	⚙
ARM	EUCAST, CLSI	EUCAST version 6.0, 2016, CLSI 2004	<10	<10	✖
AZE	CLSI	2014	<10	<10	✖
BLR	EUCAST, CLSI	5.0	<10	<10	⚙
BIH	EUCAST	2016	>50	>50	⚙
GEO	EUCAST, CLSI	N/A	10–50	>50	✔
KAZ	Other	N/A	N/A	N/A	✖
KGZ	EUCAST	5.0	<10	<10	⚙
MNE	EUCAST, CLSI	2017/2016	10–50	10–50	✔
MDA	EUCAST	7.1	>50	>50	✖
RUS	EUCAST, other	7.1/2017	10–50	10–50	✔
SRB	EUCAST, CLSI	2016	>50	>50	✖
SWI	EUCAST	N/A	>50	N/A	✔
TJK	N/A	N/A	N/A	N/A	N/A
MKD	EUCAST, CLSI	2016	10–50	10–50	✔
TUR	EUCAST	2017	>50	10–50	⚙
TKM	Other	N/A	N/A	N/A	⚙
UKR	EUCAST, CLSI	2017	10–50	>50	✖
UZB	EUCAST, CLSI, other	2016	✖	<10	✖
KOS[b]	EUCAST	2016	>50	>50	⚙

[a] The three-letter abbreviations of countries' and areas' names come from the ISO 3166-1 alpha-3 standard.

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

✔: yes; ✖: no; ⚙: in progress; N/A: not answered.

that many countries are still facing a number of challenges and that the comprehensive actions needed are complex and will take time. Strong political will and support is needed to continue and maintain the progress being made. Challenges that are often observed include:

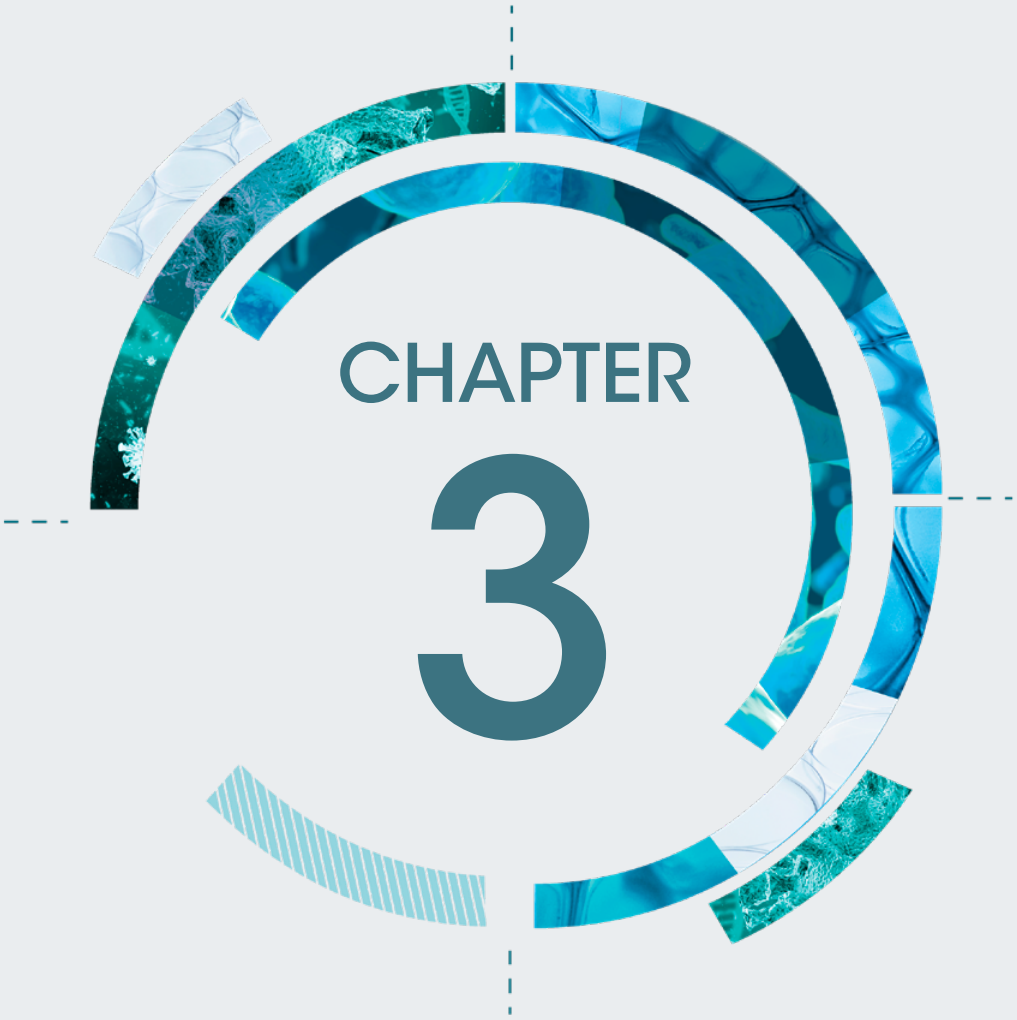
- limited human and financial resources;
- continual need to educate laboratory and hospital personnel and to stimulate better collaboration between clinicians and microbiologists;
- the need to improve sampling habits and the use of medical microbiological diagnostics in hospitals;
- the need for standard operating procedures and quality control in laboratory practice;
- the need for quality as a criteria for procurement to ensure high-quality consumables;
- the need for implementing updated guidelines on the standardization of AST, 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.

2.2.1 Support provided to countries

In the majority of countries, a situation analysis has been carried out, in collaboration with the ESCMID and the Netherlands 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 surveillance of antimicrobial consumption and resistance. Follow-up support is provided via multicountry and national AMR workshops and consultancies focusing on various technical aspects:

- national coordination, stakeholder meetings and development of national AMR action plans;
- CAESAR methods, data collection (among others, WHO microbiology laboratory database software (WHONET)) and data analysis;
- quality control, standard operating procedures, EUCAST guidelines and interpretation of AST data;
- the tasks of an AMR reference laboratory in terms of coordination of the laboratory network, quality assurance, training and confirmation of results; and
- a proof-of-principle project to promote better sampling habits, routine susceptibility testing and antibiotic stewardship.

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


CHAPTER
3

Data collection and analysis

3.1 Data collection procedures

CAESAR collects antimicrobial 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 in the Netherlands. The national AMR focal point and national data manager are responsible for collecting and verifying 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 species per year, including additional isolate and patient information for a pre-specified spectrum 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)*. In 2016, *Salmonella* species was added as a CAESAR bacterial species to further align CAESAR methodology with that of GLASS *(3)*.

CAESAR collects AST data for nine bacterial pathogens of public health and clinical importance:

- *Escherichia coli (E. coli)*
- *Klebsiella pneumoniae (K. pneumoniae)*
- *Salmonella* species
- *Pseudomonas aeruginosa (P. aeruginosa)*
- *Acinetobacter* species
- *Staphylococcus aureus (S. aureus)*
- *Streptococcus pneumoniae (S. pneumoniae)*
- *Enterococcus faecalis (E. faecalis)*
- *Enterococcus faecium (E. faecium).*

Annex 1 describes the pathogens under CAESAR surveillance and the main infections caused by each of the pathogens.

The CAESAR manual *(1)* contains a minimal panel of antimicrobial agents, recommended by EUCAST and the ESCMID Study Group for Antimicrobial Resistance Surveillance to detect resistance mechanisms. 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 distribution of patient characteristics 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. Any points for clarification about the national surveillance set-up,

laboratory methodology used and clinical practice needed to guide interpretation are discussed with the AMR focal point by email or telephone.

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, but these data are not analysed by CAESAR.

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 carbapenems is set to R. In contrast, multidrug resistance is calculated as resistance and/or intermediate resistance to at least one antibiotic in each of the antibiotic groups in the multidrug-resistant definition. Isolates with missing data on one or more of the required antibiotic groups are excluded from the analysis. The footnotes to the resistance tables in the country/area-specific chapters and the CAESAR manual specify which antibiotic combinations are used in multidrug-resistant 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 AST and promotes the use of internationally accepted guidelines (EUCAST or CLSI). If fewer than 30 AST results for a specific microorganism–antimicrobial agent combination have been submitted, the results are marked by an asterisk, indicating that they should be interpreted with caution.

Additional information regarding the analysis performed on CAESAR data can be found in the CAESAR manual *(1)*.


CHAPTER
4

Reader's guide

4.1 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 in patients presenting with a bloodstream or central nervous system infection in a country/area (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 health care-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 of average resistance patterns presented because they influence the selection of patients eligible for blood or CSF culturing or the quality of AST performed. Many different health care 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 4.2 and are discussed in detail in Annex 2.

4.2 Levels of evidence

To guide the interpretation of the data, the authors together with the national AMR focal points have come to a qualitative judgment about the level of evidence for each country/area-specific data chapter;

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

Level B The data provide an indication of resistance patterns present in clinical settings in the country/area, but the proportion 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/area.

Level C The data do not provide an adequate assessment of the magnitude and trends of AMR in the country/area. 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/area at level A is judged to provide data that allows a valid and reproducible assessment of AMR trends in the country/area. A national surveillance system that aims to provide detailed information to guide clinical policy will have different and more stringent requirements (see below).

Importantly, the results obtained at level B are not necessarily wrong, but rather less representative for the target population due to potential errors and bias in the data generation process. Nonetheless, presenting level B data has value. It allows for the critical appraisal of sources of error and bias, which is important to guide the further development of the surveillance system. As such, any suboptimal data presented in this report should be seen as a point of departure for further improvement.

Level C data are not presented in the annual report. However, the introduction of level C invites countries to start an important routine of generating and sharing data at an early stage of surveillance development. Countries with level C data are encouraged and guided to make improvements to the surveillance system until the data are judged to be level B.

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. AST methods (Were all isolates tested for each relevant antibiotic group and using current methodological standard? Was a national quality assurance system active?)
   b. AST breakpoints (Was a harmonized and up-to-date breakpoint system used?)

Table 4.1 provides an overview of the level of evidence for each country/area and the underlying assessment of the data. Detailed country- and area-specific assessments are in Chapters 5 and 6.

Table 4.1 Level of evidence and scoring of factors affecting the validity of CAESAR data 2016

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

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

4.2.1 Understanding the AMR results

Level A data provide an adequate assessment of the magnitude and trends of AMR in the country/area. These data can and should be used to create awareness about the AMR situation in the country/area and advocate for control measures to be taken where applicable. However, because the total sample of patients comprises a mix of community-acquired and health care-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 health care-associated, urosepsis versus central–line associated bloodstream infection versus pyelonephritis versus severe pneumonia) and treatment status (sample taken before/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/area. Although additional studies are needed to assess the exact magnitude and spread of these highly resistant microorganisms through the health care system, they do indicate that infection prevention and control measures are acutely needed to control the problem.

Level C data have shortcomings in many of the specified aspects assessed. In particular, antibiotic susceptibility testing is not done according to international standards. Data should not be used to inform empirical antibiotic treatment choices or AMR control policy, because due to bias, the data do not provide an adequate assessment of the AMR situation in the country/area.

Table 4.2 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 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 (active case finding)
	Bias due to laboratory procedures		
	Laboratory standards	Use of non-uniform AST methods, such as breakpoints from product inserts and out-of-date standards Sequential testing, such as testing susceptibility for carbapenems only if isolate is resistant to third-generation cephalosporins	Use national standards based on international standards for AST methodology (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 non-standard 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


CHAPTER
5

Country-specific data on AMR

5.1 Belarus

5.1.1 Surveillance set-up

All the results from routine antibiotic susceptibility testing of clinical bacteriology cultures of 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 period 1 January 2016 to 31 December 2016 were provided to CAESAR.

The AMR surveillance network comprised 16 participating laboratories in 2014, but rapidly expanded after that. In 2016, 78 laboratories participated in the network, covering about 80% of the hospitals (including multidisciplinary hospitals and national clinical research practical centres) and 80% of the Belarusian population (of 9 458 535, data from 2017 *(1)*). 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. In 2016, 30 laboratories processed blood/CSF isolates yielding organisms specified by CAESAR. The largest part of the data (about 65%) represents the laboratory of the Minsk City Centre of Hygiene and Epidemiology, which provides diagnostic support for the majority of Minsk clinics (about 20% 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 EQA exercise provided by the UK NEQAS; in 2016, nine laboratories took part in this exercise. Also since 2013, four national laboratories, including the national reference centre for AMR, take part in the WHO globally coordinated EQA 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. Recently, the Ministry of Health has prepared a special order with recommended panels for AST, aimed at harmonization of AST between laboratories in Belarus. The AMR surveillance network is currently working to prepare the implementation of this order.

Belarus has an active AMR surveillance network. Annual reports on antibiotic resistance in invasive pathogens are fed back to hospitals and hygiene and epidemiology centres. In November 2016, a workshop for representatives of all network laboratories took place. National levels of antibiotic resistance in Belarus

were discussed and laboratories shared experiences regarding data collection and interpretation, as well as technical aspects of AST.

According to national clinical guidelines, blood cultures should be taken from all patients presenting in hospitals 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 is 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. Accurate data on the number of blood cultures taken in the hospitals participating in the AMR surveillance network in Belarus are currently not available.

5.1.2 Results

Fig. 5.1 shows the distribution of microorganisms and the patient characteristics of 1 442 isolates from Belarus in 2016, by pathogen. In *E. coli*, resistance ranged from 7% for amikacin to 76% for aminopenicillins (Table 5.1). Multidrug resistance was 22% in *E. coli*. Resistance in *K. pneumoniae* ranged between 58% (amikacin) and 87% (piperacillin-tazobactam). Multidrug resistance in *K. pneumoniae* was 74%. Data on four isolates of *Salmonella* spp. were available, none of which was resistant to any of the selected agents (Table 5.2). In *P. aeruginosa*, resistance was 48% for amikacin and higher for all other selected agents (Table 5.3). Multidrug resistance was 83% in *P. aeruginosa*. However, because of the relatively low number of isolates, the results for *P. aeruginosa* should be interpreted with caution. Resistance in *Acinetobacter* spp. was 67% or higher for all agents. Multidrug resistance in *Acinetobacter* spp. was 57%. Forty-one per cent of *S. aureus* isolates were methicillin-resistant *S. aureus* (MRSA) (Table 5.4). Based on only 13 isolates of *S. pneumoniae*, 31% was resistant to penicillins (Table 5.5). Multidrug resistance in *S. pneumoniae* was 38%. Four per cent of *E. faecalis* isolates were resistant to vancomycin and 2% were non-susceptible to linezolid (Table 5.6). In *E. faecium*, 16% were resistant to vancomycin, and 2% linezolid non-susceptibility was found. Chapter 7 displays the proportions of resistance for selected pathogen–antibiotic combinations reported by Belarus in maps of the WHO European Region (Fig. 7.1–7.6).

5.1.3 Discussion

The AMR surveillance network of Belarus submitted antibiotic susceptibility testing results for 1 442 isolates from blood or CSF in 2016. The number of laboratories with eligible data for CAESAR increased from 18 to 30 in 2016. However, the majority of isolates (about 65%) still came from two laboratories serving hospitals in Minsk, reflecting low utilization of blood culture diagnostics in smaller regional hospitals and limiting the national representativeness of the data. No national guidance on the minimal set of antimicrobial agents to be tested was implemented in Belarus in 2016. Laboratories varied with regard to the antibiotic groups tested, which suggests sequential or selective testing in some laboratories. This may have led to over- or underestimation of resistance, depending on the selection and the resistance mechanism. In addition, because not all antibiotics are tested in all laboratories, the proportions of resistance may reflect different underlying patient populations and thus complicate the rank ordering of resistance proportions to antibiotics. For example, this may explain the unexpected and unlikely higher resistance of *K. pneumoniae* to piperacillin-tazobactam (87%) than to amoxicillin-clavulanic acid (84%). A mix of breakpoints was used to interpret antibiotic susceptibility test results; both CLSI 2004 and more recent (2012–2014) CLSI and EUCAST guidelines were used for interpreting disk diffusion zone values, and

CLSI or EUCAST (2012–2014) breakpoints were used for automated test results. In particular, carbapenem resistance in Enterobacteriaceae may be underestimated when older breakpoint guidelines are used.

Relatively many isolates (45%) were from patients admitted to an intensive care unit. Compared with other species, few *E. coli* (8%) and many *Acinetobacter* spp. (23%) and *K. pneumoniae* (23%) 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. Also, because not all antibiotic groups were tested in all patients the rank ordering of proportions of resistance may be unreliable.

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*. These results are in line with an increasing consumption of third-generation cephalosporins and carbapenems that was observed in recent years in Belarus. The relatively high aminopenicillin resistance in *E. faecalis* may reflect problems with species identification (inclusion of *E. faecium*, which more often is resistant to aminopenicillins), rather than resistance in *E. faecalis*. Vancomycin resistance in *E. faecium* was moderately high. The level of MRSA was higher than that of countries close to Belarus (Fig. 7.6). 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 health care 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. Furthermore, resistance levels may be influenced by sequential testing of isolates in some laboratories and may reflect different underlying patient populations, limiting the interpretation of the rank ordering of resistance proportions. The current data indicate the resistance patterns present in clinical settings in the country, but the proportion of resistance should be interpreted with care. 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 reader's guide (Table 4.1) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.1 Patient characteristics of isolates from Belarus in 2016, by pathogen

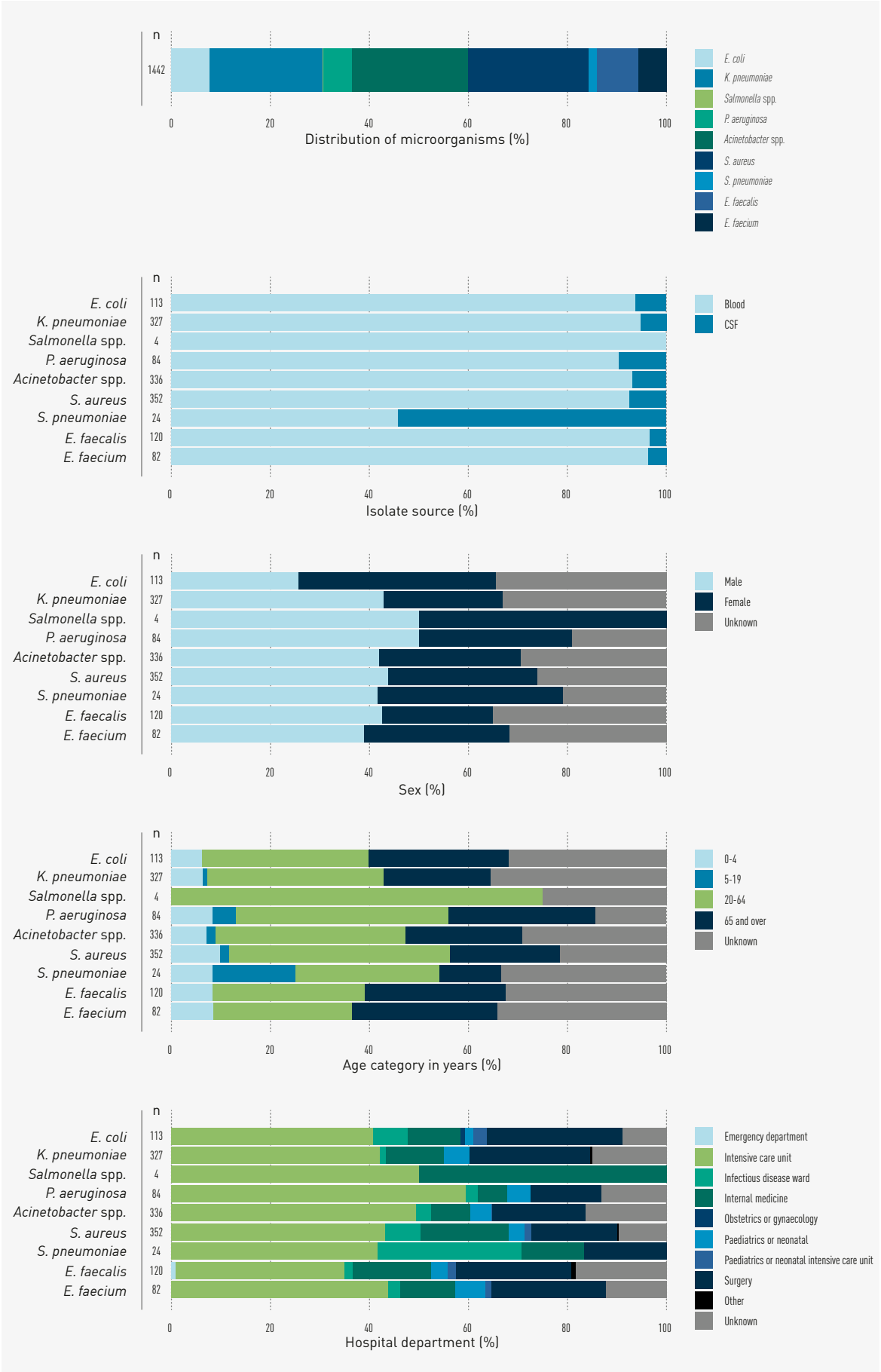


Table 5.1 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Belarus in 2016

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (R)	66	76	NA	NA
Amoxicillin-clavulanic acid (R)	54	37	167	84
Piperacillin-tazobactam (R)	54	15	189	87
Third-generation cephalosporins (R)	83	58	226	86
Third-generation cephalosporins (I+R)	83	61	226	88
Ceftazidime (R)	90	57	299	86
Ertapenem (R)	25	8*	94	83
Carbapenems (R)	106	12	321	65
Carbapenems (I+R)	106	12	321	68
Aminoglycosides (R)	81	31	275	78
Amikacin (R)	86	7	280	58
Fluoroquinolones (R)	106	47	315	82
Fluoroquinolones (I+R)	106	48	315	83
Multidrug resistance (R)	58	22	194	74

NA: not applicable.

* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.

The aminopenicillins group comprises amoxicillin and ampicillin.

The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.

The carbapenems group comprises imipenem and meropenem.

The aminoglycosides group comprises gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides. Isolates with missing data on one or more of the groups are excluded.

Table 5.2 Percentage of resistance for *Salmonella* spp. among blood and CSF isolates in Belarus in 2016

Antibiotic (group)	*Salmonella* spp.	
	N	Resistance (%)
Third-generation cephalosporins (R)	4	0*
Third-generation cephalosporins (I+R)	4	0*
Ceftazidime (R)	4	0*
Ertapenem (R)	3	0*
Carbapenems (R)	4	0*
Carbapenems (I+R)	4	0*
Fluoroquinolones (R)	4	0*
Fluoroquinolones (I+R)	4	0*

* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
The carbapenems group comprises imipenem and meropenem.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.

Table 5.3 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Belarus in 2016

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	40	75	NA	NA
Ceftazidime (R)	66	80	NA	NA
Cefepime (R)	75	72	NA	NA
Carbapenems (R)	79	76	330	79
Carbapenems (I+R)	79	76	330	82
Aminoglycosides (R)	45	87	260	68
Amikacin (R)	66	48	105	67
Fluoroquinolones (R)	75	87	317	90
Multidrug resistance (R)	23	83*	252	57

NA: not applicable.
* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.
The carbapenems group comprises imipenem and meropenem.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.
For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on three or more of the groups are excluded.
For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on one or more of the groups are excluded.

Table 5.4 Percentage of resistance for *S. aureus* among blood and CSF isolates in Belarus in 2016

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)	320	41
Fluoroquinolones (R)	323	29
Norfloxacin (R)	5	20*
Vancomycin (R)	279	3
Rifampicin (R)	229	17
Linezolid (R)	239	0

* 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 oxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

Table 5.5 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Belarus in 2016

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillins (R)	13	31*
Penicillins (I+R)	13	38*
Third-generation cephalosporins (R)	18	6*
Third-generation cephalosporins (I+R)	18	17*
Fluoroquinolones (R)	15	0*
Norfloxacin (R)	0	–
Macrolides (R)	21	43*
Macrolides (I+R)	21	43*
Multidrug resistance (I+R)	13	38*

–: no data available.
* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.
Resistance to penicillins is based on penicillin or, if not available, on oxacillin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The macrolides group comprises erythromycin, clarithromycin and azithromycin.
Multidrug resistance is defined as resistance to penicillins and macrolides. Isolates with missing data on one or more of the groups are excluded.

Table 5.6 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Belarus in 2016

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (I+R)	100	47	75	97
High-level gentamicin (R)	50	56	34	68
Vancomycin (R)	114	4	76	16
Linezolid (I+R)	94	2	66	2

The aminopenicillins group comprises amoxicillin and ampicillin.

5.2 Bosnia and Herzegovina

5.2.1 Surveillance set-up

AMR surveillance activities in Bosnia and Herzegovina 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.

5.2.1.1 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 CSF for each patient, including patient information for the period 1 January to 31 December 2016. Laboratories check their data for adherence to the CAESAR protocol, microbiological consistency and plausibility and consistency with EUCAST guidelines 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.

In 2015, the AMR surveillance network in the Federation of Bosnia and Herzegovina included five out of 12 laboratories. In 2016, this number increased to six. They provide diagnostic support for three secondary care hospitals, one tertiary care hospital and two hospitals providing both secondary and tertiary care. 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 75% of the population of the Federation of Bosnia and Herzegovina (of 3 792 759, data from 2017 *(1)*). The AMR surveillance network in the Federation of Bosnia and Herzegovina is currently working to expand its network.

Antimicrobial susceptibility in the tertiary level of care is tested using automated systems. Gradient tests and disk diffusion are used as supplementary methods. 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 (UK NEQAS). Since 2016, all laboratories use EUCAST guidelines in antibiotic susceptibility testing and interpreting results.

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 2016, the number of blood cultures taken in the Federation of Bosnia and Herzegovina ranged from 2 to 20 per 1000 patient-days in the six participating hospitals.

5.2.1.2 Republika Srpska

The Commission for Control of Resistance to Antimicrobial Medicines in Republika Srpska has prepared, and currently monitors, implementation of the Program for Control of Resistance to Antimicrobial Medicines in Republika Srpska (2016–2020). The AMR focal point and data manager of Republika Srpska, who are members of the Commission, are responsible for collecting data from the University Clinical Centre of Republika Srpska. This is the largest and main hospital in Republika Srpska and it provides secondary and tertiary care. All results from the routine antibiotic susceptibility testing of clinical bacteriology cultures are collected electronically from the clinical information system. The University Clinical Centre of Republika Srpska is a referral centre for patients from Republika Srpska suspected of having sepsis or meningitis. Other microbiology laboratories in hospitals in Republika Srpska (Doboj, Prijedor, Bijeljina and Istocno Sarajevo) have less than 100–200 invasive samples per year, and are not included in the AMR surveillance network. The University Clinical Centre of Republika Srpska covers at least 85% of the population of Republika Srpska. The AMR surveillance network in Republika Srpska is currently working to expand the network to include more laboratories in CAESAR.

Confirmatory testing (phenotypical) 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 2016, were reported to CAESAR.

The antibiotic susceptibility of Gram-negative bacteria and *S. aureus*, and *Enterococcus* spp. 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. Other 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 resistances. 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 2016, 7 blood cultures per 1000 patient-days were taken in the University Clinical Centre of Republika Srpska.

5.2.2 Results

Fig. 5.2 shows the distribution of microorganisms and the patient characteristics of 899 isolates from Bosnia and Herzegovina in 2016, by pathogen. In *E. coli*, apart from aminopenicillins (71%), resistance ranged from 0% (carbapenems) to 39% (amoxicillin-clavulanic acid, Table 5.7). Multidrug resistance was 13% in *E. coli*. In *K. pneumoniae*, resistance ranged from 8% for carbapenems to 72% for aminoglycosides. Multidrug resistance in *K. pneumoniae* was 52%. Seven isolates of *Salmonella* spp. were found, none of which were resistant to any of the selected agents (Table 5.8). However, because of the relatively few isolates, the results for *Salmonella* spp. should be interpreted with caution. In *P. aeruginosa*, resistance ranged between 20% (ceftazidime) and 53% (aminoglycosides, Table 5.9). Multidrug resistance was 22% in *P. aeruginosa*. Resistance in *Acinetobacter* spp. was 87 – 96% for all antibiotics tested. Multidrug resistance in *Acinetobacter* spp. was 87%. Thirteen per cent of *S. aureus* isolates were MRSA (Table 5.10). In *S. pneumoniae*, penicillin resistance was 27% (Table 5.11). Nineteen per cent of *S. pneumoniae* isolates were multidrug resistant. However, because of the low number of isolates, the results for *S. pneumoniae* should be interpreted with caution. Vancomycin resistance was not observed in *E. faecalis* (Table 5.12). In *E. faecium*, 21% was vancomycin-resistant and 14% was non-susceptible to linezolid. Chapter 7 displays the percentages of resistance for selected pathogen–antibiotic combinations reported by Bosnia and Herzegovina in maps of the WHO European Region (Fig. 7.1–7.6).

5.2.3 Discussion

The AMR surveillance networks of Bosnia and Herzegovina submitted the antibiotic susceptibility testing results of 899 isolates from blood or CSF in 2016. The network laboratories provide good geographical coverage of Bosnia and Herzegovina, apart from the eastern part of the country. Blood cultures are generally taken before initial antibiotic treatment and come from patients admitted to a variety of hospital types and wards. *E. coli* (24%) and *S. aureus* (20%) were the main pathogens isolated. A relatively high number of *Acinetobacter* spp. isolates was seen (18%), particularly in patients admitted to intensive care units. The high levels of (multidrug) resistance in *K. pneumonia* and *Acinetobacter* spp., and vancomycin-resistant *E. faecium* suggest the dissemination of resistant clones in the health care setting. This is also reflected, for example, in the relatively high level of non-susceptibility to linezolid in *E. faecium* (14%, based on automated tests), where three out of four isolates were confirmed to be related to a nosocomial outbreak. On the other hand, the resistance levels in *E. coli* and *S. aureus* were only moderately high. The

distribution of pathogens and the variation in resistance levels between species suggest that the data represent a mix of community-acquired and health care-associated infections.

The data from Bosnia and Herzegovina are assessed as level A, which is an improvement from 2015 where data were as level B. The significant amount of high-quality antibiotic susceptibility testing data from a geographically representative network including samples from a variety of patients – health care-associated as well as community-acquired infections – adequately assesses the trends of AMR in the country. Including more data from regional hospitals (especially in the eastern part of the country) and increasing the diagnostic utilization of blood cultures will lead to more valid assessment of the magnitude of AMR. The reader's guide (Table 4.1) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.2 Patient characteristics of isolates from Bosnia and Herzegovina in 2016, by pathogen

Table 5.7 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Bosnia and Herzegovina in 2016

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (R)	213	71	NA	NA
Amoxicillin-clavulanic acid (R)	199	39	103	59
Piperacillin-tazobactam (R)	84	7	87	11
Third-generation cephalosporins (R)	215	23	149	70
Third-generation cephalosporins (I+R)	215	23	149	72
Ceftazidime (R)	205	19	149	66
Ertapenem (R)	13	8*	37	0
Carbapenems (R)	191	0	150	8
Carbapenems (I+R)	191	2	150	11
Aminoglycosides (R)	207	23	148	72
Amikacin (R)	171	9	137	58
Fluoroquinolones (R)	215	28	149	56
Fluoroquinolones (I+R)	215	29	149	56
Multidrug resistance (R)	199	13	142	52

NA: not applicable.

* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.

The aminopenicillins group comprises amoxicillin and ampicillin.

The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.

The carbapenems group comprises imipenem and meropenem.

The aminoglycosides group comprises gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides. Isolates with missing data on one or more of the groups are excluded.

Table 5.8 Percentage of resistance for *Salmonella* spp. among blood and CSF isolates in Bosnia and Herzegovina in 2016

Antibiotic (group)	*Salmonella* spp.	
	N	Resistance (%)
Third-generation cephalosporins (R)	7	0*
Third-generation cephalosporins (I+R)	7	0*
Ceftazidime (R)	6	0*
Ertapenem (R)	2	0*
Carbapenems (R)	3	0*
Carbapenems (I+R)	3	0*
Fluoroquinolones (R)	7	0*
Fluoroquinolones (I+R)	7	0*

* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
The carbapenems group comprises imipenem and meropenem.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.

Table 5.9 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Bosnia and Herzegovina in 2016

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	55	22	NA	NA
Ceftazidime (R)	44	20	NA	NA
Cefepime (R)	48	23	NA	NA
Carbapenems (R)	61	23	158	91
Carbapenems (I+R)	61	30	158	91
Aminoglycosides (R)	59	53	157	96
Amikacin (R)	56	34	148	87
Fluoroquinolones (R)	58	40	158	95
Multidrug resistance (R)	37	22	157	87

NA: not applicable.
The carbapenems group comprises imipenem and meropenem.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.
For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on three or more of the groups are excluded.
For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on one or more of the groups are excluded.

Table 5.10 Percentage of resistance for *S. aureus* among blood and CSF isolates in Bosnia and Herzegovina in 2016

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)	180	13
Fluoroquinolones (R)	179	12
Norfloxacin (R)	33	24
Vancomycin (R)	180	0
Rifampicin (R)	131	3
Linezolid (R)	116	0

MRSA is calculated as resistance to cefoxitin or, if not available, oxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

Table 5.11 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Bosnia and Herzegovina in 2016

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillins (R)	22	27*
Penicillins (I+R)	22	27*
Third-generation cephalosporins (R)	22	14*
Third-generation cephalosporins (I+R)	22	14*
Fluoroquinolones (R)	19	0*
Norfloxacin (R)	10	0*
Macrolides (R)	21	24*
Macrolides (I+R)	21	29*
Multidrug resistance (I+R)	21	19*

* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.
Resistance to penicillins is based on penicillin or, if not available, on oxacillin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The macrolides group comprises erythromycin, clarithromycin, and azithromycin.
Multidrug resistance is defined as resistance to penicillins and macrolides. Isolates with missing data on one or more of the groups are excluded.

Table 5.12 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Bosnia and Herzegovina in 2016

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (I+R)	57	4	38	84
High-level gentamicin (R)	58	57	38	95
Vancomycin (R)	57	0	38	21
Linezolid (I+R)	30	0	29	14*

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

5.3 Georgia

5.3.1 Surveillance set-up

The proof-of-principle AMR surveillance project established the basis for national AMR surveillance in Georgia *(2,3)*. As a result of the proof-of-principle project, the Richard Lugar Center for Public Health Research of the National Center for Disease Control and Public Health of Georgia developed a routine for standardized collection of AST results from the network laboratories. 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. Four hospitals that participated in the proof-of-principle project (three general hospitals in Tbilisi and one referral hospital in Telavi) submitted antibiotic susceptibility testing results to CAESAR for all first isolates yielding organisms (specified by CAESAR), for the period 1 January to 31 December 2016. Together these four hospitals cover about 15% of the population in Georgia (of 3 972 532, data from 2017 *(1)*).

As per proof-of-principle protocol, 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).

Blood cultures were processed at the hospital's bacteriology laboratory. Two hospitals did not have bacteriology laboratory capabilities, and blood cultures were transported to the national AMR reference laboratory at Lugar Center or Telavi Laboratory support station, for full processing, directly following the blood collection. Antibiotic susceptibility was tested by disk diffusion according to EUCAST standards. All positive blood culture isolates were sent to the Lugar Center for quality assurance and confirmatory antibiotic susceptibility testing. The data presented in this chapter were generated by the Lugar Center reference laboratory that retested all isolates.

Due to the activities of the proof-of-principle project, the rate of blood sampling increased from an average of 1.8 to 5.8 per 1000 patient-days in the participating hospitals. Blood culturing practice and EUCAST methodology have since been adopted as routine practice in the hospitals that participated in the proof-of-principle project. The surveillance network is currently being expanded.

5.3.2 Results

Fig. 5.3 shows the distribution of microorganisms and the patient characteristics of 70 isolates from the Georgia in 2016, by pathogen. In nine *E. coli* isolates, resistance ranged from 0% for amikacin, carbapenems and ertapenem to 100% for aminopenicillins (Table 5.13). Multidrug resistance was 56% in *E. coli*. Resistance in *K. pneumoniae* ranged from 9% for carbapenems to 97% for third-generation cephalosporins. Multidrug resistance in *K. pneumoniae* was 31%. Data were not available for *Salmonella* spp. from blood or CSF. Resistance in *P. aeruginosa* (six isolates) ranged from 33% (piperacillin-tazobactam and ceftazidime) to 83% (carbapenems, Table 5.14). Multidrug resistance was 40% in *P. aeruginosa*. In *Acinetobacter* spp., resistance ranged from 0% (fluoroquinolones, one isolate) to 100% (amikacin, six isolates). Multidrug resistance in *Acinetobacter* spp. (based on one isolate) was 0%. Eleven per cent of nine *S. aureus* isolates were MRSA (Table 5.15). Two *S. pneumoniae* isolates were found, none of which was resistant to any of the selected agents (Table 5.16). In two isolates of *E. faecalis*, vancomycin resistance was not observed but 50% was non-susceptible to linezolid (Table 5.17). No data were available for *E. faecium* in 2016. Chapter 7 displays the percentages of resistance for selected pathogen–antibiotic combinations reported by Georgia in maps of the WHO European Region (Fig. 7.1–7.6).

5.3.3 Discussion

This is the first year that Georgia reported AMR data to CAESAR. The Georgian AMR surveillance network submitted antibiotic susceptibility testing results for 70 isolates from blood in 2016. In the majority of patients that had a blood culture taken, the infection was characterized as nosocomial, precluding the generalization of results to patients with community-acquired infections. In addition, a large proportion of blood samples was taken from children in the age of 0-4 years old, particularly neonates admitted to the neonatal intensive care unit. The three largest participating hospitals are located in the city of Tbilisi; therefore, the geographical representativeness of the data for the country of Georgia is limited. Although the utilization of blood culture diagnostics significantly improved during the proof-of-principle project, and the results provide an important first systematic insight into AMR in Georgia, the absolute number of isolates per species was still low. Besides bias towards higher resistance caused by selective sampling of nosocomial infections, few isolates make the observed percentages 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 Georgia, especially patients with community-acquired infections. The proof-of-principle project has contributed to strengthening of laboratory capacity and to the introduction of bacteriological diagnostics in routine medical care, thereby forming a basis for a national AMR surveillance network and participation in CAESAR. Further strengthening and expansion of the surveillance system in the coming years is crucial for continued reporting of AMR data to CAESAR. 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.

The patient population sampled had high levels of resistance to third-generation cephalosporins, aminoglycosides and fluoroquinolones in *E. coli* and *K. pneumoniae*. Carbapenem resistance was not observed in *E. coli* from blood or CSF in 2016, but three *K. pneumoniae* isolates (9%) were carbapenem resistant. The high levels of resistance in *P. aeruginosa* and *Acinetobacter* spp. (although based on a low number of isolates) are concerning and may reflect the dissemination of resistant clones in the health care setting. The level of MRSA, on the other hand, was relatively low compared to countries close to Georgia (Fig. 7.6), although careful interpretation is required because of the small number of isolates (n=9). Too few antibiotic susceptibility testing results for *S. pneumoniae* and *E. faecalis* were available to allow interpretation.

The data from Georgia are assessed as level B. The overrepresentation of nosocomial infections (selective sampling), underrepresentation of regional areas and the 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 percentages of resistance should be interpreted with care. Increasing diagnostic utilization of blood cultures and sampling of community-acquired infections, and including regional hospitals in AMR surveillance, will lead to more valid assessment of AMR in the country. The reader's guide (Table 4.1) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.3 Patient characteristics of isolates from Georgia in 2016, by pathogen

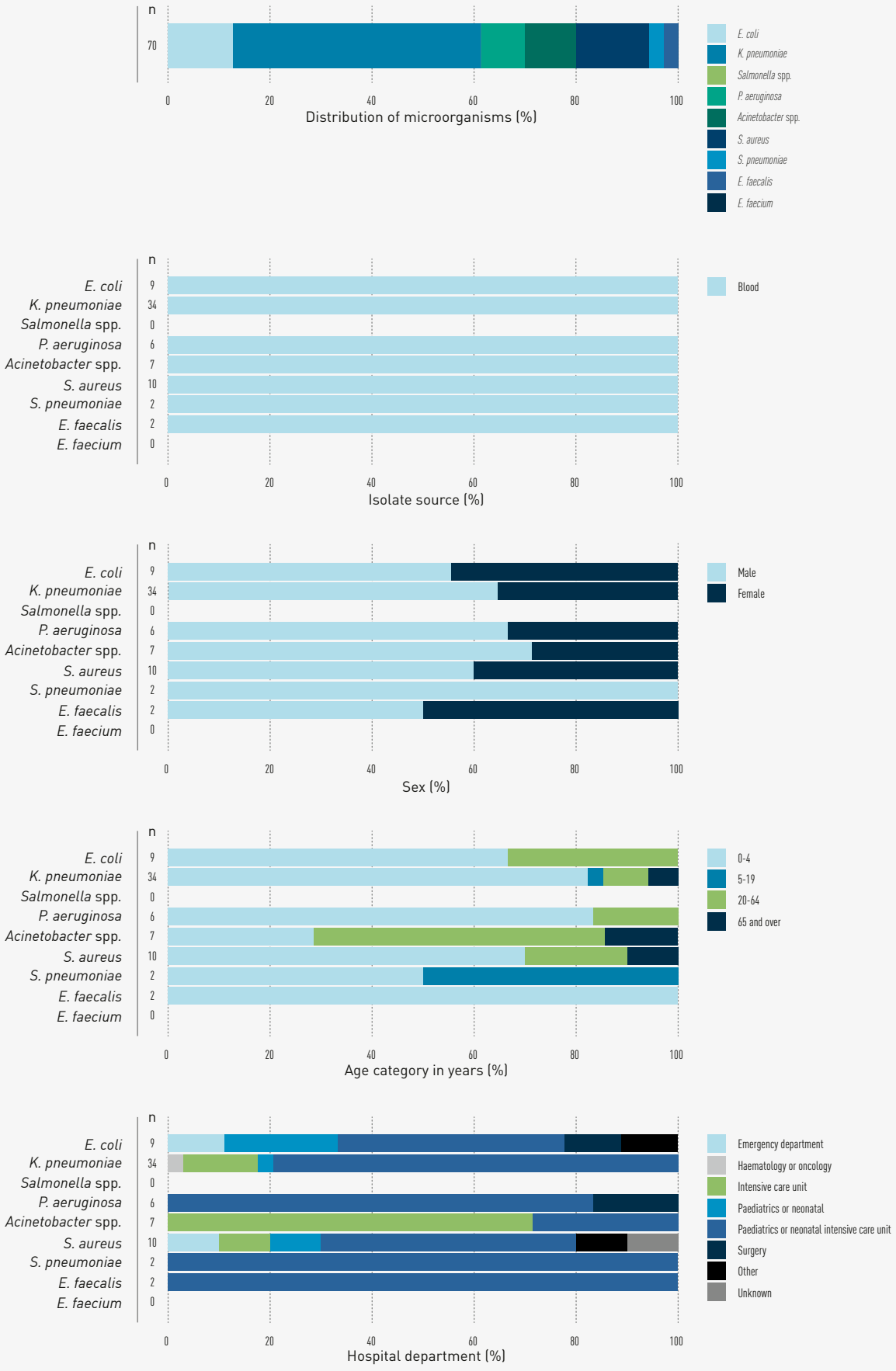


Table 5.13 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood isolates in Georgia in 2016

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (R)	7	100*	NA	NA
Amoxicillin-clavulanic acid (R)	9	44*	32	87
Piperacillin-tazobactam (R)	9	22*	32	78
Third-generation cephalosporins (R)	9	67*	33	97
Third-generation cephalosporins (I+R)	9	67*	33	97
Ceftazidime (R)	9	67*	32	97
Ertapenem (R)	8	0*	28*	14*
Carbapenems (R)	9	0*	33	9
Carbapenems (I+R)	9	0*	33	21
Aminoglycosides (R)	9	78*	33	70
Amikacin (R)	4	0*	12	58*
Fluoroquinolones (R)	9	67*	29	34*
Fluoroquinolones (I+R)	9	67*	29	48*
Multidrug resistance (R)	9	56*	29	31*

NA: not applicable.

* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.

The aminopenicillins group comprises amoxicillin and ampicillin.

The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.

The carbapenems group comprises imipenem and meropenem.

The aminoglycosides group comprises gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides. Isolates with missing data on one or more of the groups are excluded.

Table 5.14 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood isolates in Georgia in 2016

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	6	33*	NA	NA
Ceftazidime (R)	6	33*	NA	NA
Cefepime (R)	0	–	NA	NA
Carbapenems (R)	6	83*	7	71*
Carbapenems (I+R)	6	83*	7	71*
Aminoglycosides (R)	6	50*	7	71*
Amikacin (R)	3	67*	6	100*
Fluoroquinolones (R)	5	40*	1	0*
Multidrug resistance (R)	5	40*	1	0*

NA: not applicable.

–: no data available.

* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.

The carbapenems group comprises imipenem and meropenem.

The aminoglycosides group comprises gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin and levofloxacin.

For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on three or more of the groups are excluded.

For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on one or more of the groups are excluded.

Table 5.15 Percentage of resistance for *S. aureus* among blood isolates in Georgia in 2016

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)	9	11*
Fluoroquinolones (R)	6	33*
Norfloxacin (R)	0	–
Vancomycin (R)	10	0*
Rifampicin (R)	10	10*
Linezolid (R)	10	0*

–: no data available.

* 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, oxacillin.

The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

Table 5.16 Percentage of resistance for *S. pneumoniae* among blood isolates in Georgia in 2016

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillins (R)	2	0*
Penicillins (I+R)	2	0*
Third-generation cephalosporins (R)	2	0*
Third-generation cephalosporins (I+R)	2	0*
Fluoroquinolones (R)	2	0*
Norfloxacin (R)	2	0*
Macrolides (R)	2	0*
Macrolides (I+R)	2	0*
Multidrug resistance (I+R)	2	0*

* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.
Resistance to penicillins is based on penicillin or, if not available, on oxacillin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The macrolides group comprises erythromycin, clarithromycin, and azithromycin.
Multidrug resistance is defined as resistance to penicillins and macrolides. Isolates with missing data on one or more of the groups are excluded.

Table 5.17 Percentage of resistance for *E. faecalis* and *E. faecium* among blood isolates in Georgia in 2016

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (I+R)	0	–	0	–
High-level gentamicin (R)	0	–	0	–
Vancomycin (R)	2	0*	0	–
Linezolid (I+R)	2	50*	0	–

–: no data available.
* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.
The aminopenicillins group comprises amoxicillin and ampicillin.

5.4 Montenegro

5.4.1 Surveillance set-up

All eight public microbiological laboratories that examine hospital samples in Montenegro are included in the AMR surveillance network. Antibiotic susceptibility testing data for blood and CSF samples are sent in paper form from these laboratories to the central laboratory at the Institute of Public Health in Podgorica where data are entered into a database. Upon receipt, the data are checked with regard to quality and consistency. Errors are corrected in direct communication with the laboratory, where applicable. All strains suspected of carbapenemase production are confirmed by gradient strip test and Carba NP test before incorporating the result into the final data set. These confirmatory tests are performed at the Centre for Medical Microbiology of the Institute of Public Health in Podgorica. A subset of AST results containing all first isolates from blood and CSF cultures yielding organisms specified by CAESAR for the period 1 January 2016 to 31 December 2016 were provided to CAESAR. According to these specifications, data were available from five laboratories in 2016.

The AMR surveillance system of Montenegro covers 100% of the population (of 626 250, data from 2017 *(1)*). The seven public microbiological laboratories are organizationally part of the primary health care system but provide diagnostic services for one specialized hospital and seven general hospitals in Montenegro. The central laboratory of the Institute of Public Health provides diagnostic services to the Clinical Centre of Montenegro in Podgorica. Blood culturing is done using a manual system, and antibiotic susceptibility is tested using the disk diffusion method in the four peripheral laboratories. The central laboratory of the Institute of Public Health in Podgorica uses an automated blood culturing system, and disk diffusion and an automated system for AST. All laboratories perform gradient tests according to EUCAST guidelines. All laboratories participate in international external quality control programmes (UK NEQAS) and perform internal quality control on a regular basis. The majority of AST (in all laboratories but one peripheral laboratory) in 2016 was performed according to CLSI guidelines. However, there is consensus among laboratories about switching step by step from CLSI to EUCAST. The National AST committee was established two years ago and organizes annual meetings.

According to national clinical bacteriology guidelines by the Ministry of Health in Montenegro, blood cultures are taken from all patients with suspected bloodstream infections (sepsis) presenting in hospital and CSF cultures are taken from patients suspected of having meningitis. However, adherence to these guidelines is suboptimal and blood culture diagnostics are underutilized due to several reasons. The clinical bacteriology guideline has not been translated into practical recommendations for clinicians about when to take blood cultures. Furthermore, financial constraints negatively impact the procurement and continuous availability of high-quality equipment and materials for taking and processing blood cultures. Because the laboratories and microbiologists are not physically in the hospitals, there is also a lack of direct communication between microbiologists and clinicians and a logistical barrier to taking blood cultures. In 2016, in the five laboratories with eligible data, 3137 blood cultures were processed. The number of blood cultures taken ranged from 1 to 14 per 1000 patient-days in the hospitals that are diagnostically supported by these laboratories.

5.4.2 Results

Fig. 5.4 shows the distribution of microorganisms and the patient characteristics of 143 isolates from Montenegro in 2016, by pathogen. In *E. coli*, resistance ranged from 0% for carbapenems to 100% for aminopenicillins (Table 5.18). Multidrug resistance was 6% in *E. coli*. Resistance in *K. pneumoniae* ranged from 4% (carbapenems) to 89% (third-generation cephalosporins). Multidrug resistance in *K. pneumoniae* was 63%. One isolate of *Salmonella* spp. was found, which was susceptible to all selected agents (Table 5.19). Resistance in five *P. aeruginosa* isolates ranged from 40% to 80% (Table 5.20). Multidrug resistance was 60% in *P. aeruginosa*. In *Acinetobacter* spp. (13 isolates), resistance was between 85% and 92%. Multidrug resistance in *Acinetobacter* spp. was 85%. Thirty-four per cent of *S. aureus* isolates were MRSA (Table 5.21).

Based on only seven *S. pneumoniae* isolates, resistance to penicillins was 43%. Multidrug resistance was 20% in *S. pneumoniae* (Table 5.22). Based on less than 15 isolates each, vancomycin resistance was not observed in *E. faecalis* and *E. faecium* (Table 5.23). Chapter 7 displays the percentages of resistance for selected pathogen–antibiotic combinations reported by Montenegro in maps of the WHO European Region (Fig. 7.1–7.6).

5.4.3 Discussion

This is the first year that Montenegro reported AMR data to CAESAR. Laboratories in Montenegro submitted antibiotic susceptibility testing results for 143 isolates from blood or CSF in 2016. The five laboratories that submitted data provide good geographical coverage. However, most isolates (96%) were processed at the central laboratory of the Institute of Public Health in the capital city *Podgorica*, which provides diagnostic support for the main referral hospital in the country. The low overall number of isolates reflects the low utilization of blood culture diagnostics in general. Blood cultures will generally be taken in patients with antibiotic treatment failure or recurrent infections. Besides bias towards higher resistance caused by this selective sampling, a low number of isolates makes the observed percentages 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 Montenegro, especially patients with community-acquired infections.

Nevertheless, the patient population sampled had very high levels of resistance to third-generation cephalosporins and aminoglycosides in *E. coli* and *K. pneumoniae*. Carbapenem resistance was not observed in *E. coli* from blood or CSF in 2016, but one *K. pneumoniae* isolate (4%) was confirmed to be carbapenem resistant. The level of MRSA was similar to countries close to Montenegro (Fig. 7.6). Too few antibiotic susceptibility testing results for *Salmonella* spp., *P. aeruginosa*, *S. pneumoniae* and *E. faecalis* were available to allow interpretation. The high level of resistance in *Acinetobacter* spp. (although based on a limited number of isolates tested) is concerning and may reflect the dissemination of resistant clones in the health care setting.

The data from Montenegro are assessed as level B. The selective sampling of patients with treatment failure or recurrent infections, the underrepresentation of blood culture results from general hospitals, and an overall relative 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. The data indicate the resistance patterns present in clinical settings in the country, but the percentages of resistance should be interpreted with care. Increasing diagnostic utilization of blood cultures, especially in regional hospitals, will lead to more valid assessment of AMR in the country. The reader's guide (Table 4.1) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.4 Patient characteristic of isolates from Montenegro in 2016, by pathogen

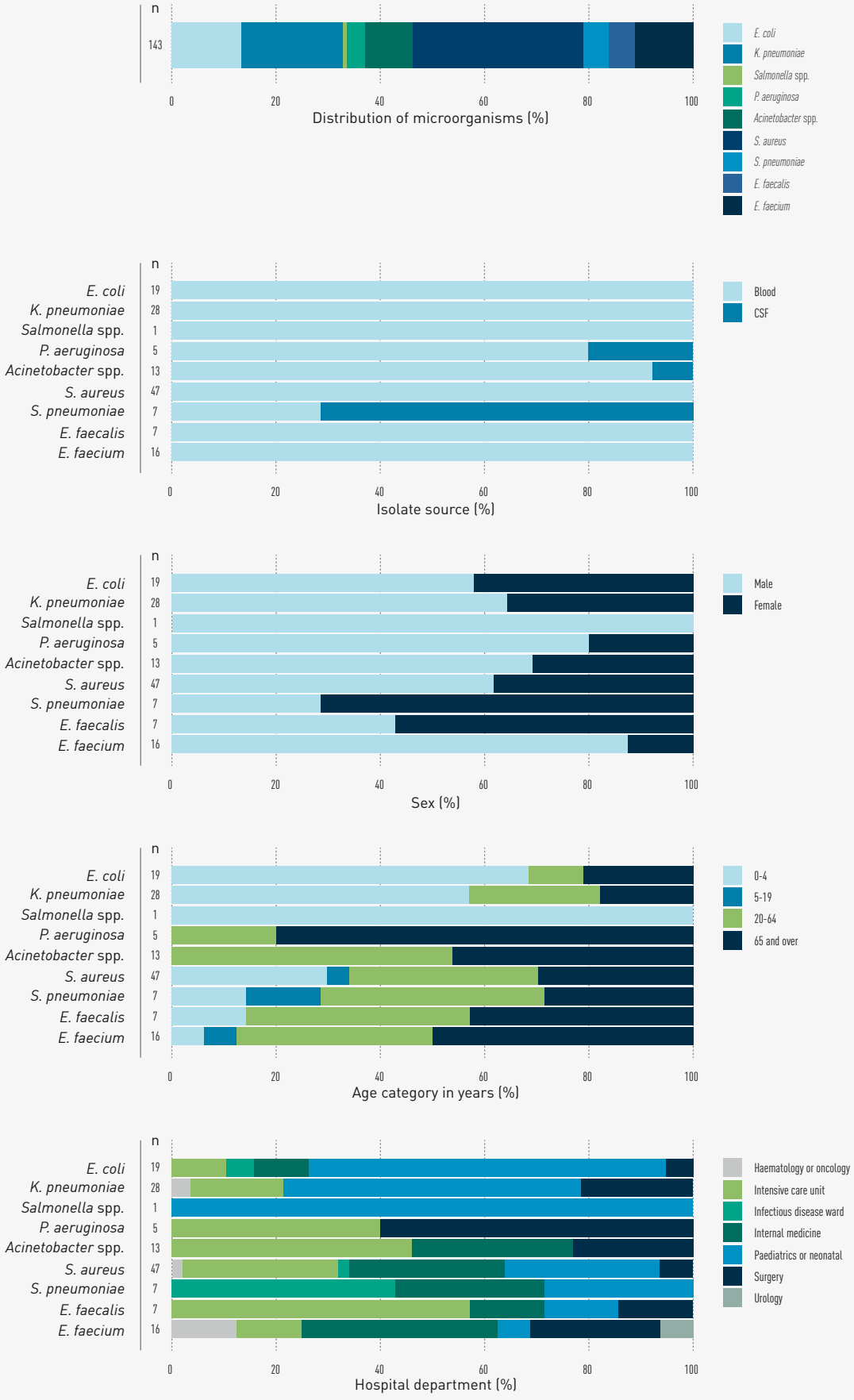


Table 5.18 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Montenegro in 2016

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (R)	17	100*	NA	NA
Amoxicillin-clavulanic acid (R)	18	56*	27	85*
Piperacillin-tazobactam (R)	17	12*	27	63*
Third-generation cephalosporins (R)	18	83*	27	89*
Third-generation cephalosporins (I+R)	18	83*	27	89*
Ceftazidime (R)	19	63*	26	85*
Ertapenem (R)	16	0*	16	0*
Carbapenems (R)	19	0*	27	4*
Carbapenems (I+R)	19	0*	27	4*
Aminoglycosides (R)	19	74*	28	82*
Amikacin (R)	19	11*	27	22*
Fluoroquinolones (R)	19	16*	27	63*
Fluoroquinolones (I+R)	19	16*	27	78*
Multidrug resistance (R)	18	6*	27	63*

NA: not applicable.

* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.

The aminopenicillins group comprises amoxicillin and ampicillin.

The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.

The carbapenems group comprises imipenem and meropenem.

The aminoglycosides group comprises gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides. Isolates with missing data on one or more of the groups are excluded.

Table 5.19 Percentage of resistance for *Salmonella* spp. among blood and CSF isolates in Montenegro in 2016

Antibiotic (group)	*Salmonella* spp.	
	N	Resistance (%)
Third-generation cephalosporins (R)	1	0*
Third-generation cephalosporins (I+R)	1	0*
Ceftazidime (R)	1	0*
Ertapenem (R)	1	0*
Carbapenems (R)	1	0*
Carbapenems (I+R)	1	0*
Fluoroquinolones (R)	1	0*
Fluoroquinolones (I+R)	1	0*

* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
The carbapenems group comprises imipenem and meropenem.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.

Table 5.20 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Montenegro in 2016

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	5	40*	NA	NA
Ceftazidime (R)	5	40*	NA	NA
Cefepime (R)	5	40*	NA	NA
Carbapenems (R)	5	80*	13	92*
Carbapenems (I+R)	5	80*	13	92*
Aminoglycosides (R)	5	60*	13	85*
Amikacin (R)	5	40*	13	85*
Fluoroquinolones (R)	5	60*	13	85*
Multidrug resistance (R)	5	60*	13	85*

NA: not applicable.
* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.
The carbapenems group comprises imipenem and meropenem.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.
For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on three or more of the groups are excluded.
For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on one or more of the groups are excluded.

Table 5.21 Percentage of resistance for *S. aureus* among blood and CSF isolates in Montenegro in 2016

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)	47	34
Fluoroquinolones (R)	45	20
Norfloxacin (R)	2	0*
Vancomycin (R)	40	0
Rifampicin (R)	38	24
Linezolid (R)	38	0

* 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, oxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

Table 5.22 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Montenegro in 2016

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillins (R)	7	43*
Penicillins (I+R)	7	43*
Third-generation cephalosporins (R)	5	0*
Third-generation cephalosporins (I+R)	5	0*
Fluoroquinolones (R)	6	0*
Norfloxacin (R)	1	0*
Macrolides (R)	5	20*
Macrolides (I+R)	5	20*
Multidrug resistance (I+R)	5	20*

* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.
Resistance to penicillins is based on penicillin or, if not available, on oxacillin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The macrolides group comprises erythromycin, clarithromycin, and azithromycin.
Multidrug resistance is defined as resistance to penicillins and macrolides. Isolates with missing data on one or more of the groups are excluded.

Table 5.23 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Montenegro in 2016

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (I+R)	7	86*	16	6*
High-level gentamicin (R)	7	71*	14	50*
Vancomycin (R)	6	0*	14	0*
Linezolid (I+R)	5	0*	15	0*

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

5.5 Russian Federation

5.5.1 Surveillance set-up

Antibiotic susceptibility testing results from the Russian Federation are obtained from an annual national surveillance study on AMR of bacterial pathogens causing infections among hospitalized patients. Clinical bacterial isolates are collected from 44 laboratories, each serving one tertiary care or specialized hospital, in 26 cities. Each laboratory is requested to submit a maximum of 150 consecutive, non-duplicate isolates annually (one isolate of each species per patient or case of infection), from relevant clinical specimens including but not limited to blood. 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 re-identified at the species level by means of matrix-assisted laser desorption and ionization–time of flight mass spectrometry. Antibiotic susceptibility is tested 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 period 1 January to 31 December 2016 was provided to CAESAR. Extensive data from the national AMR surveillance network in the Russian Federation are currently available through the interactive web platform *(4)*.

In 2016, data from 26 laboratories were eligible to be provided to CAESAR. These laboratories are geographically spread throughout the Russian Federation, 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.

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 based on EUCAST, and expansion of the network to include locally generated data from additional laboratories. The national guidance on antibiotic susceptibility testing methods and breakpoints has been updated according to EUCAST. The reference laboratory is using EUCAST methodology. The majority of laboratories in the surveillance network have implemented the new national guidelines (based on EUCAST methodology and clinical breakpoints) for disk diffusion methods, but not for automated testing due to lack of EUCAST-based panels on the market in 2016–2017.

5.5.2 Results

Fig. 5.5 shows the distribution of microorganisms and the patient characteristics of 454 isolates from the Russian Federation in 2016, by pathogen. In *E. coli*, resistance ranged from 2% for carbapenems to 93% for aminopenicillins (Table 5.24). Multidrug resistance was 51% in *E. coli*. In *K. pneumoniae*, resistance ranged from 12% (carbapenems) to 91% (third-generation cephalosporins). Multidrug resistance in *K. pneumoniae* was 85%. No data on *Salmonella* spp. were available. Resistance in *P. aeruginosa* ranged from 21% (amikacin) to 58% (fluoroquinolones, Table 5.25). Multidrug resistance was 51% in *P. aeruginosa*.

In *Acinetobacter* spp., resistance was 74% for carbapenems and higher for all other selected agents. Multidrug resistance in *Acinetobacter* spp. was 60%. Twenty-tree per cent of *S. aureus* isolates were MRSA (Table 5.26). No data on *S. pneumoniae* were available. In *E. faecalis* as well as *E. faecium*, vancomycin resistance was not observed (Table 5.27). Chapter 7 displays the proportions of resistance for selected pathogen–antibiotic combinations reported by the Russian Federation in maps of the WHO European Region (Fig. 7.1–7.6).

5.5.3 Discussion

The AMR surveillance network of the Russian Federation submitted antibiotic susceptibility testing results for 454 isolates from blood or CSF in 2016. The laboratories in the network are distributed throughout the western part of the Russian Federation and provide diagnostic support mainly for 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. 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, the low number of 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.

Enterobacteriaceae had high resistance to fluoroquinolones and third-generation cephalosporins. Resistance to carbapenems was 12% in *K. pneumoniae* and 2% in *E. coli*. 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. 7.6). The high percentages of multidrug resistance in *P. aeruginosa* and *Acinetobacter* spp. are concerning and may reflect dissemination of resistant clones in the health care setting.

The data from the Russian Federation are assessed as level B. The generalizability of the results is limited by the overrepresentation of nosocomial infections in 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 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. Improving the use of blood culture diagnostics and further 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 reader's guide (Table 4.1) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.5 Patient characteristics of isolates from the Russian Federation in 2016, by pathogen

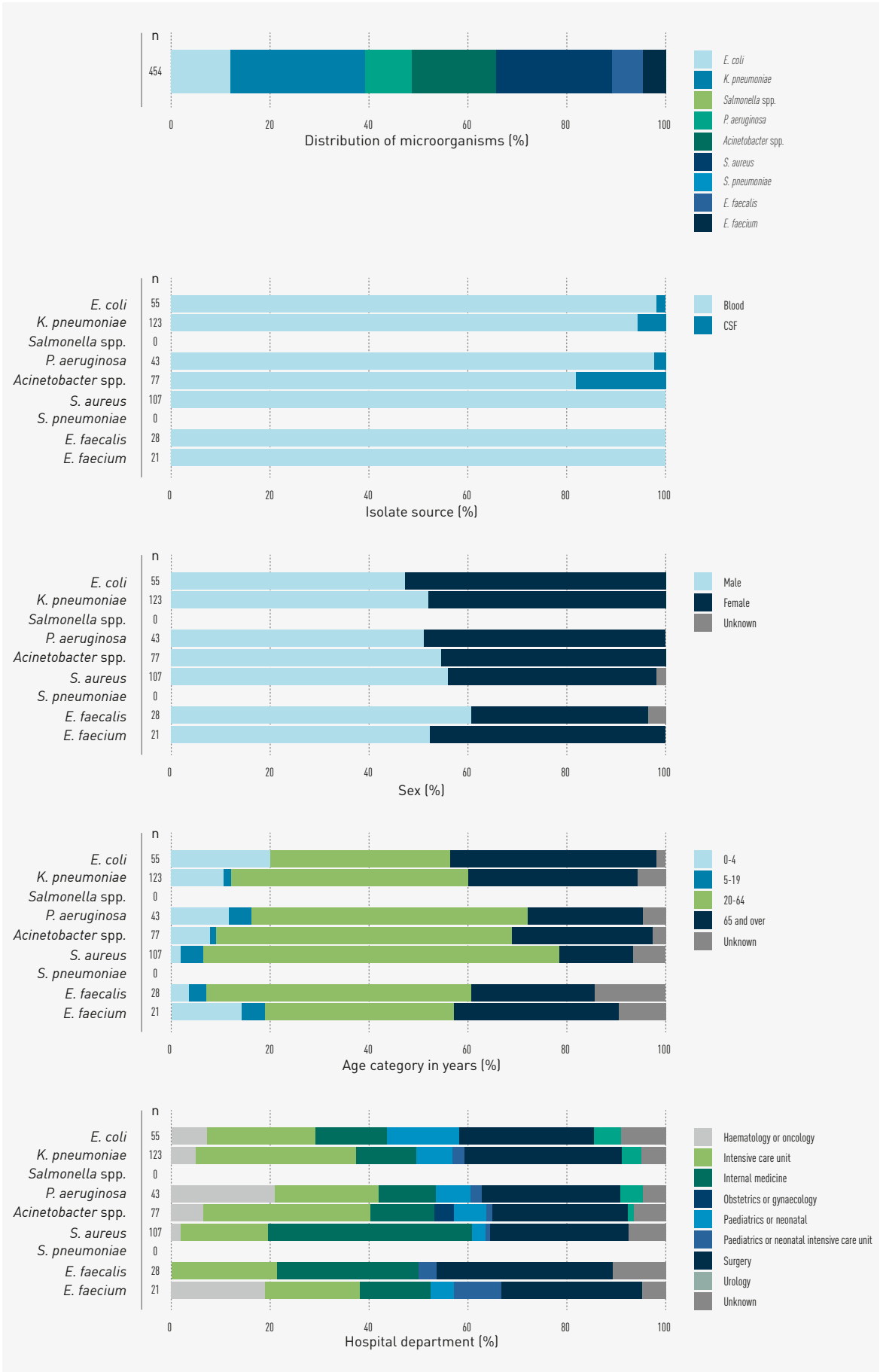


Table 5.24 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in the Russian Federation in 2016

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (R)	55	93	NA	NA
Amoxicillin-clavulanic acid (R)	32	72	75	89
Piperacillin-tazobactam (R)	32	19	75	65
Third-generation cephalosporins (R)	55	84	123	91
Third-generation cephalosporins (I+R)	55	84	123	91
Ceftazidime (R)	55	73	123	89
Ertapenem (R)	55	13	123	43
Carbapenems (R)	55	2	123	12
Carbapenems (I+R)	55	7	123	25
Aminoglycosides (R)	55	56	123	89
Amikacin (R)	55	9	123	21
Fluoroquinolones (R)	55	75	123	89
Fluoroquinolones (I+R)	55	80	123	90
Multidrug resistance (R)	55	51	123	85

NA: not applicable.
The aminopenicillins group comprises amoxicillin and ampicillin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
The carbapenems group comprises imipenem and meropenem.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.
Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides. Isolates with missing data on one or more of the groups are excluded.

Table 5.25 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in the Russian Federation in 2016

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	43	49	NA	NA
Ceftazidime (R)	43	47	NA	NA
Cefepime (R)	43	42	NA	NA
Carbapenems (R)	43	49	77	74
Carbapenems (I+R)	43	63	77	75
Aminoglycosides (R)	43	56	77	75
Amikacin (R)	43	21	77	86
Fluoroquinolones (R)	43	58	77	94
Multidrug resistance (R)	43	51	77	60

NA: not applicable.

The carbapenems group comprises imipenem and meropenem.

The aminoglycosides group comprises gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin and levofloxacin.

For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on three or more of the groups are excluded.

For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on one or more of the groups are excluded.

Table 5.26 Percentage of resistance for *S. aureus* among blood and CSF isolates in the Russian Federation in 2016

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)	107	23
Fluoroquinolones (R)	107	32
Norfloxacin (R)	0	–
Vancomycin (R)	107	0
Rifampicin (R)	107	2
Linezolid (R)	107	0

–: no data available.

MRSA is calculated as resistance to cefoxitin or, if not available, oxacillin.

The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

Table 5.27 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in the Russian Federation in 2016

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (I+R)	28	0*	21	95*
High-level gentamicin (R)	28	61*	21	71*
Vancomycin (R)	28	0*	21	0*
Linezolid (I+R)	28	0*	21	0*

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

5.6 Serbia

5.6.1 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 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, the AMR surveillance network in Serbia comprised 14 laboratories. In 2016, this number increased to 22 participating laboratories. The laboratories provide diagnostic support for 26 hospitals: about 50% of the general hospitals and 50% of the academic and top clinical hospitals, including the largest clinical centres in the country. They are geographically dispersed and cover about 75% of the population (of 8 776 940, data from 2017 *(1)*).

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 AST guidelines. Approximately 95% of the antibiotic susceptibility tests in 2016 were performed according to EUCAST guidelines. Since January 2017, all network laboratories are using EUCAST guidelines for AST. Several laboratories are accredited according to ISO/IEC 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, provided by UK NEQAS) EQA exercise. There is no regular national EQA programme. In 2009, the Ministry of Health nominated 25 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.

Serbia has an active AMR surveillance network that is in the process of expanding to also include regional laboratories providing service for smaller general hospitals. Furthermore, they organized a national network meeting in November 2016. National levels of AMR and sources of bias and error in these data were discussed, as were the measures that need to be taken to improve the data quality and representativeness.

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.

5.6.2 Results

Fig. 5.6 shows the distribution of microorganisms and the patient characteristics of 2176 isolates from Serbia in 2016, by pathogen. In *E. coli*, resistance ranged from 1% for carbapenems to 72% for aminopenicillins (Table 5.28). Multidrug resistance was 22% in *E. coli*. In *K. pneumoniae*, resistance was 35% for carbapenems and higher for all other selected agents. Multidrug resistance in *K. pneumoniae* was 63%. In 13 isolates of *Salmonella* spp., resistance was observed for third-generation cephalosporins (8%) and fluoroquinolones (9%, Table 5.29). In *P. aeruginosa*, resistance ranged between 34% (piperacillin-tazobactam) and 56% (aminoglycosides, Table 5.30). Multidrug resistance was 48% in *P. aeruginosa*. Resistance in *Acinetobacter* spp. was 91% for amikacin and higher for all other selected antibiotics. Multidrug resistance in *Acinetobacter* spp. was 92%. Twenty-seven per cent of *S. aureus* isolates were MRSA (Table 5.31). In *S. pneumoniae*, resistance was found for penicillins (26%) and macrolides (31%, Table 5.32). Twenty-eight per cent of *S. pneumoniae* isolates were multidrug resistant. Vancomycin resistance was 9% in *E. faecalis* and 35% in

E. faecium (Table 5.33). Chapter 7 displays the proportions of resistance for selected pathogen–antibiotic combinations reported by Serbia in maps of the WHO European Region (Fig. 7.1–7.6).

5.6.3 Discussion

The AMR surveillance network submitted antibiotic susceptibility testing results for 2176 isolates from blood or CSF in Serbia in 2016. The network laboratories provide good geographical coverage. With the expansion of the network from 14 to 22 laboratories, smaller regional hospitals are well represented. However, the relatively large number of isolates from patients admitted to intensive care units, the relatively low number of *E. coli* and the generally high percentages of resistance, suggest that the results disproportionally reflect nosocomial infections in severely ill patients, following initial antibiotic treatment, 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, in the specific patient population sampled, high levels of resistance were seen in *K. pneumoniae*. In *E. coli*, moderately high resistance was found for third-generation cephalosporins, aminoglycosides and fluoroquinolones. Two *E. coli* isolates were carbapenem-resistant based on automated testing and the results were not confirmed. The level of MRSA was similar to countries close to Serbia (Fig. 7.6). 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 health care setting.

The data from Serbia are assessed as level A, which is an improvement from 2015 where data were assessed as level B. The large quantity of good quality antibiotic susceptibility testing data from a geographically representative network adequately assesses the trends of AMR in the country. However, although the network comprises a variety of different hospital types, the data suggest disproportionate sampling of nosocomial infections in more severely ill and pretreated patients, and this case mix should be taken into account when interpreting the data. The reader's guide (Table 4.1) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.6 Patient characteristics of isolates from Serbia in 2016, by pathogen

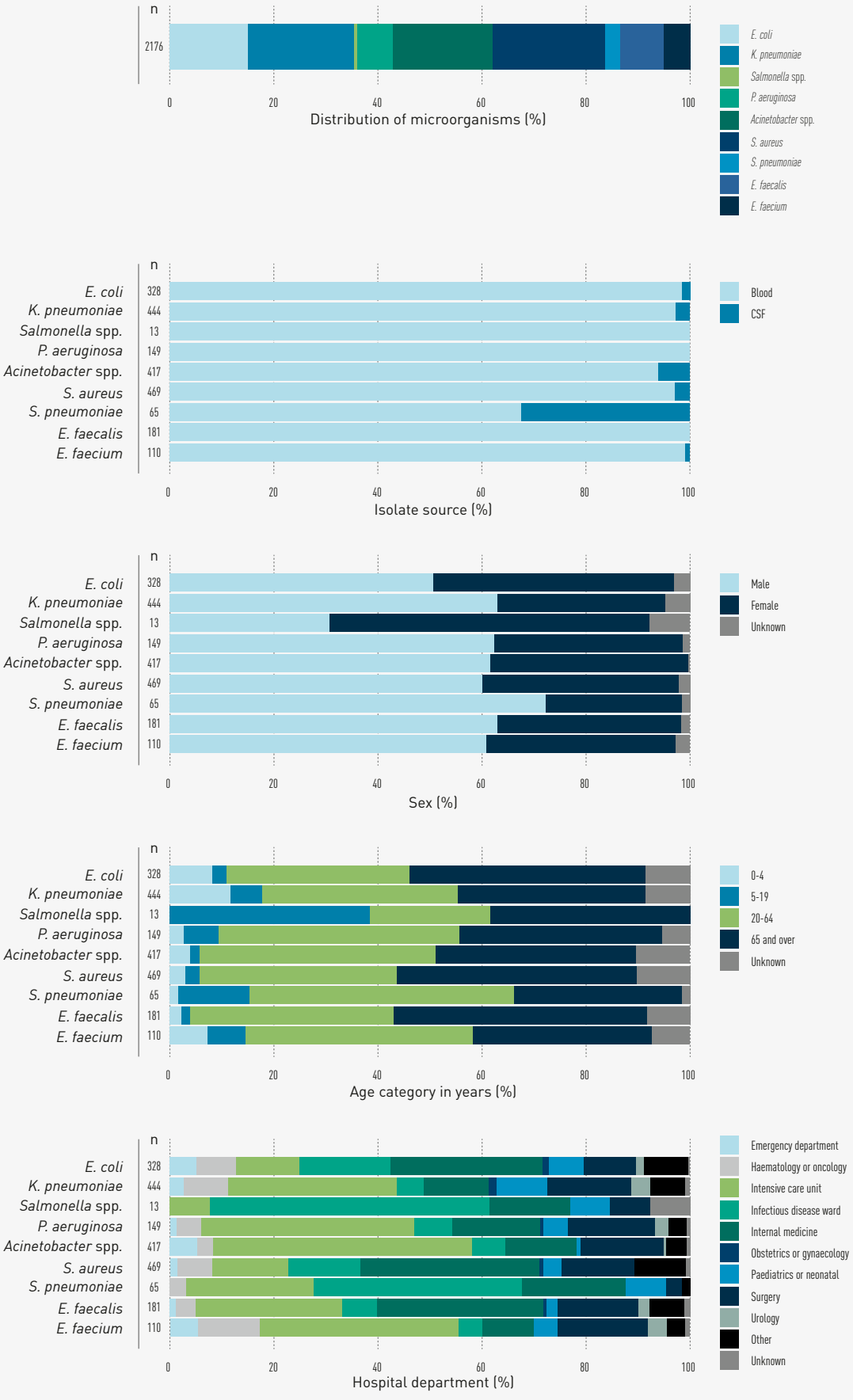


Table 5.28 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Serbia in 2016

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (R)	320	72	NA	NA
Amoxicillin-clavulanic acid (R)	243	52	389	93
Piperacillin-tazobactam (R)	314	19	427	83
Third-generation cephalosporins (R)	323	35	435	90
Third-generation cephalosporins (I+R)	323	35	435	90
Ceftazidime (R)	229	30	332	87
Ertapenem (R)	294	3	370	49
Carbapenems (R)	325	1	443	35
Carbapenems (I+R)	325	2	443	40
Aminoglycosides (R)	290	33	434	81
Amikacin (R)	325	10	438	50
Fluoroquinolones (R)	313	45	427	74
Fluoroquinolones (I+R)	313	46	427	74
Multidrug resistance (R)	271	22	408	63

NA: not applicable.
The aminopenicillins group comprises amoxicillin and ampicillin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
The carbapenems group comprises imipenem and meropenem.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.
Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides. Isolates with missing data on one or more of the groups are excluded.

Table 5.29 Percentage of resistance for *Salmonella* spp. among blood and CSF isolates in Serbia in 2016

Antibiotic (group)	*Salmonella* spp.	
	N	Resistance (%)
Third-generation cephalosporins (R)	13	8*
Third-generation cephalosporins (I+R)	13	8*
Ceftazidime (R)	5	0*
Ertapenem (R)	4	0*
Carbapenems (R)	5	0*
Carbapenems (I+R)	5	0*
Fluoroquinolones (R)	11	9*
Fluoroquinolones (I+R)	11	9*

* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
The carbapenems group comprises imipenem and meropenem.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.

Table 5.30 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Serbia in 2016

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	143	34	NA	NA
Ceftazidime (R)	143	48	NA	NA
Cefepime (R)	148	45	NA	NA
Carbapenems (R)	148	43	417	97
Carbapenems (I+R)	148	47	417	97
Aminoglycosides (R)	141	56	391	94
Amikacin (R)	147	38	388	91
Fluoroquinolones (R)	146	53	389	97
Multidrug resistance (R)	126	48	385	92

NA: not applicable.
The carbapenems group comprises imipenem and meropenem.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.
For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on three or more of the groups are excluded.
For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on one or more of the groups are excluded.

Table 5.31 Percentage of resistance for *S. aureus* among blood and CSF isolates in Serbia in 2016

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)	463	27
Fluoroquinolones (R)	404	20
Norfloxacin (R)	272	14
Vancomycin (R)	448	0
Rifampicin (R)	406	17
Linezolid (R)	428	0

MRSA is calculated as resistance to cefoxitin or, if not available, oxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

Table 5.32 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Serbia in 2016

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillins (R)	61	26
Penicillins (I+R)	61	43
Third-generation cephalosporins (R)	65	0
Third-generation cephalosporins (I+R)	65	5
Fluoroquinolones (R)	55	0
Norfloxacin (R)	32	0
Macrolides (R)	58	31
Macrolides (I+R)	58	31
Multidrug resistance (I+R)	54	28

Resistance to penicillins is based on penicillin or, if not available, on oxacillin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The macrolides group comprises erythromycin, clarithromycin, and azithromycin.
Multidrug resistance is defined as resistance to penicillins and macrolides. Isolates with missing data on one or more of the groups are excluded.

Table 5.33 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Serbia in 2016

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (I+R)	181	4	110	94
High-level gentamicin (R)	169	63	101	91
Vancomycin (R)	181	9	110	35
Linezolid (I+R)	180	0	108	0

The aminopenicillins group comprises amoxicillin and ampicillin.

5.7 Switzerland

5.7.1 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. 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 period 1 January to 31 December 2016.

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; in 2016 about 90% of laboratories used EUCAST. 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 approved by the Swiss Agency for Therapeutic Products (Swissmedic) and are participating in at least one national or international external quality assurance programme. Switzerland therefore decided not to participate in the CAESAR EQA 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.

5.7.2 Results

Fig. 5.7 shows the distribution of microorganisms and the patient characteristics of 9503 isolates from Switzerland, by pathogen. In *E. coli*, resistance ranged from 0% for carbapenems and ertapenem to 46% for aminopenicillins (Table 5.34). Multidrug resistance was 3% in *E. coli*. Resistance in *K. pneumoniae* was 1% for carbapenems and was highest for amoxicillin-clavulanic acid (13%). Multidrug resistance in *K. pneumoniae* was 3%. In *Salmonella* spp., resistance was highest for fluoroquinolones (7%, Table 5.35). Resistance in *P. aeruginosa* ranged between 2% (aminoglycosides and amikacin) and 10% (piperacillin-tazobactam, Table 5.36). Four per cent of *P. aeruginosa* isolates were multidrug resistant. The percentages of resistance in *Acinetobacter* spp. ranged from 7% for carbapenems to 15% for aminoglycosides. Multidrug resistance in *Acinetobacter* spp. was 7%. Four per cent of *S. aureus* isolates were MRSA (Table 5.37). In *S. pneumoniae*, resistance to penicillins was 3% (Table 5.38). Three per cent of *S. pneumoniae* isolates were multidrug resistant. Vancomycin resistance was 0% in *E. faecalis* and 2% in *E. faecium* (Table 5.39). In *E. faecalis*, 1% of the isolates were non-susceptible to linezolid. Chapter 7 displays the proportions of resistance for selected pathogen–antibiotic combinations reported by Switzerland in maps of the WHO European Region (Fig. 7.1–7.6).

5.7.3 Discussion

The AMR surveillance network submitted antibiotic susceptibility testing results for 9503 isolates from blood or CSF in Switzerland in 2016. *E. coli* was the main pathogen isolated (50%), followed by *S. aureus* (17%) and *K. pneumoniae* (10%). About 6% 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. For all

pathogens, the percentages of resistance are comparable with those in countries close to Switzerland and comparable with those in 2015 *(5)*.

Although carbapenemase-producing Enterobacteriaceae are still rare in Switzerland, an increase from 69 isolates (including non-invasive strains) in 2013 to 121 isolates in 2015 was observed in the Swiss national AMR surveillance. Important regional trends were found and molecular data indicate a high diversity of different carbapenemases, with OXA-48, KPC- and NDM-type carbapenemases being the most prevalent in Switzerland *(6)*. These observations led to the decision to declare carbapenemase-producing Enterobacteriaceae as a notifiable disease, starting on 1 January 2016.

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 reader's guide (Table 4.1) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.7 Patient characteristics of isolates from Switzerland in 2016, by pathogen

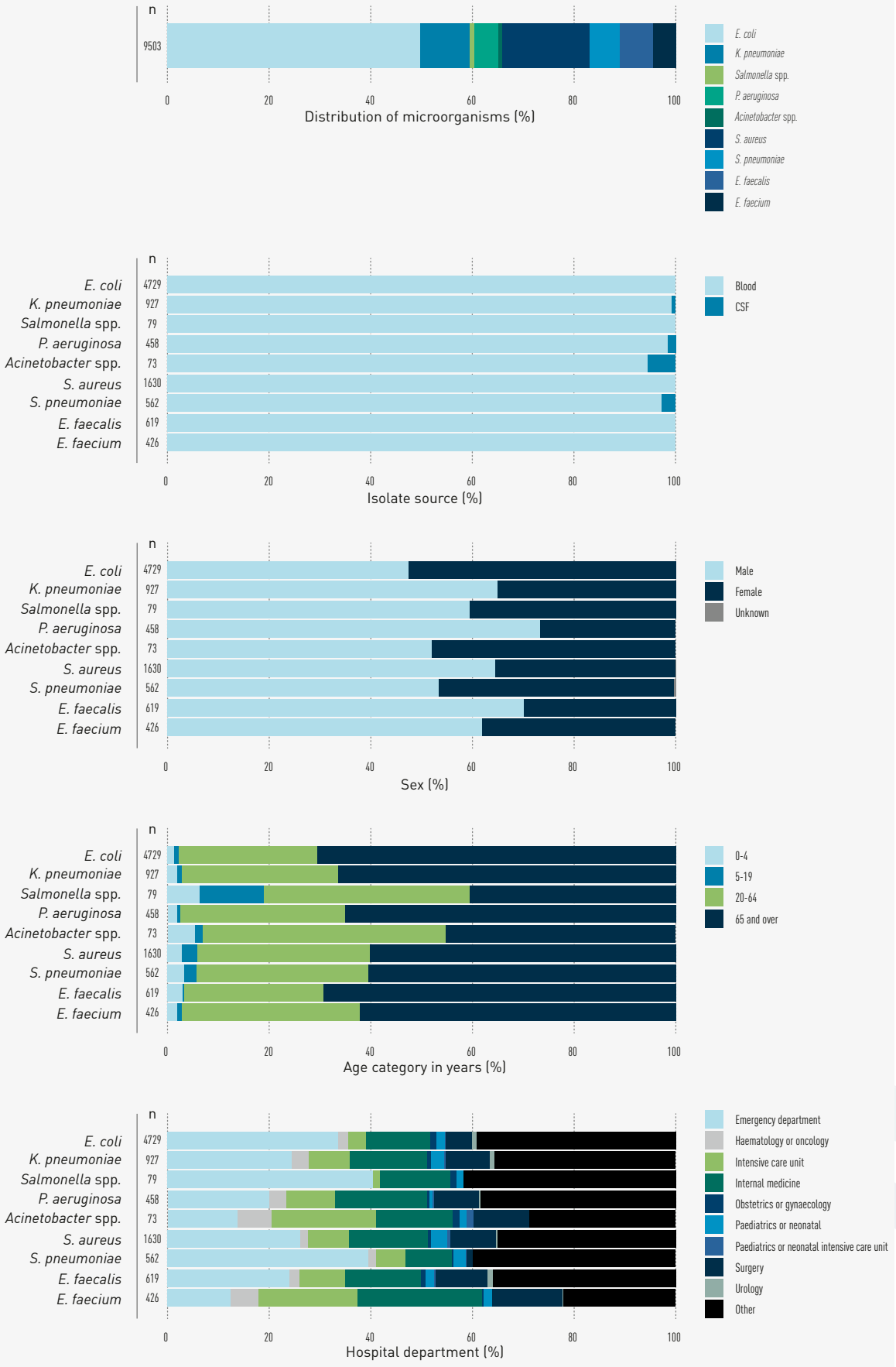


Table 5.34 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Switzerland in 2016

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (R)	4346	46	NA	NA
Amoxicillin-clavulanic acid (R)	4665	21	917	13
Piperacillin-tazobactam (R)	4521	5	879	7
Third-generation cephalosporins (R)	4700	9	921	6
Third-generation cephalosporins (I+R)	4700	9	921	7
Ceftazidime (R)	4684	7	906	6
Ertapenem (R)	2985	0	547	1
Carbapenems (R)	4723	0	926	1
Carbapenems (I+R)	4723	0	926	1
Aminoglycosides (R)	4665	9	911	5
Amikacin (R)	3005	2	578	2
Fluoroquinolones (R)	4686	16	920	6
Fluoroquinolones (I+R)	4686	17	920	9
Multidrug resistance (R)	4626	3	906	3

NA: not applicable.
The aminopenicillins group comprises amoxicillin and ampicillin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
The carbapenems group comprises imipenem and meropenem.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.
Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides. Isolates with missing data on one or more of the groups are excluded.

Table 5.35 Percentage of resistance for *Salmonella* spp. among blood and CSF isolates in Switzerland in 2016

Antibiotic (group)	*Salmonella* spp.	
	N	Resistance (%)
Third-generation cephalosporins (R)	78	1
Third-generation cephalosporins (I+R)	78	1
Ceftazidime (R)	70	1
Ertapenem (R)	45	0
Carbapenems (R)	70	0
Carbapenems (I+R)	70	0
Fluoroquinolones (R)	70	7
Fluoroquinolones (I+R)	70	7

The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
The carbapenems group comprises imipenem and meropenem.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.

Table 5.36 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Switzerland in 2016

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	440	10	NA	NA
Ceftazidime (R)	441	7	NA	NA
Cefepime (R)	438	3	NA	NA
Carbapenems (R)	452	8	73	7
Carbapenems (I+R)	452	11	73	7
Aminoglycosides (R)	457	2	73	15
Amikacin (R)	400	2	61	8
Fluoroquinolones (R)	455	7	73	14
Multidrug resistance (R)	423	4	73	7

NA: not applicable.
The carbapenems group comprises imipenem and meropenem.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.
For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on three or more of the groups are excluded.
For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on one or more of the groups are excluded.

Table 5.37 Percentage of resistance for *S. aureus* among blood and CSF isolates in Switzerland in 2016

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)	1621	4
Fluoroquinolones (R)	1564	7
Norfloxacin (R)	242	10
Vancomycin (R)	1320	0
Rifampicin (R)	1528	0
Linezolid (R)	531	0

MRSA is calculated as resistance to cefoxitin or, if not available, oxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

Table 5.38 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Switzerland in 2016

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillins (R)	548	3
Penicillins (I+R)	548	6
Third-generation cephalosporins (R)	400	0
Third-generation cephalosporins (I+R)	400	0
Fluoroquinolones (R)	428	2
Norfloxacin (R)	11	0*
Macrolides (R)	543	8
Macrolides (I+R)	543	9
Multidrug resistance (I+R)	530	3

* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.
Resistance to penicillins is based on penicillin or, if not available, on oxacillin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The macrolides group comprises erythromycin, clarithromycin, and azithromycin.
Multidrug resistance is defined as resistance to penicillins and macrolides. Isolates with missing data on one or more of the groups are excluded.

Table 5.39 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Switzerland in 2016

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (I+R)	566	1	354	81
High-level gentamicin (R)	200	12	121	36
Vancomycin (R)	553	0	374	2
Linezolid (I+R)	366	1	224	0

The aminopenicillins group comprises amoxicillin and ampicillin.

5.8 The former Yugoslav Republic of Macedonia

5.8.1 Surveillance set-up

All results from the routine antibiotic susceptibility testing of clinical bacteriology cultures were collected on paper monthly from 14 microbiology laboratories (out of 19 providing blood culture diagnostic services) 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 (which only collects data on resistant species, from all specimen types and from all 30 public and private laboratories in the country). 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 period 1 January to 31 December 2016 were provided to CAESAR. In 2016, 11 laboratories in the network provided data that were eligible for CAESAR.

In 2014, six laboratories participated in national surveillance, but this number increased to 14 in 2016. These provide diagnostic support for almost all hospitals, including academic, clinical and general 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 and cover about 100% of the population (of 2 083 308, data from 2017 *(1)*). 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. Some laboratories use gradient tests for minimum inhibitory concentrations to confirm highly resistant microorganisms or exceptional phenotypes. Sixteen microbiological laboratories took part in the international CAESAR EQA exercise provided by the UK NEQAS in 2016.

Laboratories are required to follow national guidelines on bacteriological methods for testing special resistances. For methods and interpretation of antibiotic susceptibility testing, most laboratories still use the CLSI standards 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. 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; however, the number of blood cultures from hospitals is low due to lack of funds.

5.8.2 Results

Fig. 5.8 shows the distribution of microorganisms and the patient characteristics of 269 isolates from the former Yugoslav Republic of Macedonia in 2016, by pathogen. In *E. coli*, resistance ranged from 0% for carbapenems and ertapenem to 93% for aminopenicillins (Table 5.40). Multidrug resistance was 46% in *E. coli*. Resistance in *K. pneumoniae* was 13% for carbapenems and higher for all other agents. Multidrug resistance in *K. pneumoniae* was 58%. Data were not available for *Salmonella* spp. from blood or CSF. Resistance in *P. aeruginosa* ranged between 20% (amikacin) and 41% (carbapenems, Table 5.41). Multidrug resistance was 17% in *P. aeruginosa*. In *Acinetobacter* spp., resistance was 78% for amikacin and higher for all other agents. Multidrug resistance in *Acinetobacter* spp. was 74%. Forty-eight per cent of *S. aureus* isolates were MRSA (Table 5.42). Based on only 11 *S. pneumoniae* isolates, resistance to penicillins was

27% (Table 5.43). Multidrug resistance was 30% in *S. pneumoniae*. Vancomycin resistance was 0% in *E. faecalis* and 53% in *E. faecium* (Table 5.44). Chapter 7 displays the percentages of resistance for selected pathogen–antibiotic combinations reported by the former Yugoslav Republic of Macedonia in maps of the WHO European Region (Fig. 7.1–7.6).

5.8.3 Discussion

CAESAR laboratories in the former Yugoslav Republic of Macedonia submitted antibiotic susceptibility testing results for 269 isolates from blood or CSF in 2016. The 11 laboratories with eligible data provide good geographical coverage, except for the eastern part of the country. However, most isolates (about 66%) 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, the low number of isolates makes the observed percentages 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 was not observed in *E. coli* from blood or CSF in 2016, but 3 *K. pneumoniae* isolates (13%) were carbapenem resistant. One was KPC-positive; one was negatively tested for carbapenemase genes, and one was not further investigated. The level of MRSA was similar to countries close to the former Yugoslav Republic of Macedonia (Fig. 7.6). Too few antibiotic susceptibility testing results for *P. aeruginosa*, *S. pneumoniae* and *E. faecium* were available to allow interpretation. The high levels of resistance in *Acinetobacter* spp. are concerning and may reflect the dissemination of resistant clones in the health care setting.

The data from the former Yugoslav Republic of Macedonia are assessed as level B. The overrepresentation of more severely ill and pretreated patients receiving tertiary care (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 percentages 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 to more valid assessment of AMR in the country. The reader's guide (Table 4.1) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.8 Patient characteristics of isolates from the former Yugoslav Republic of Macedonia in 2016, by pathogen

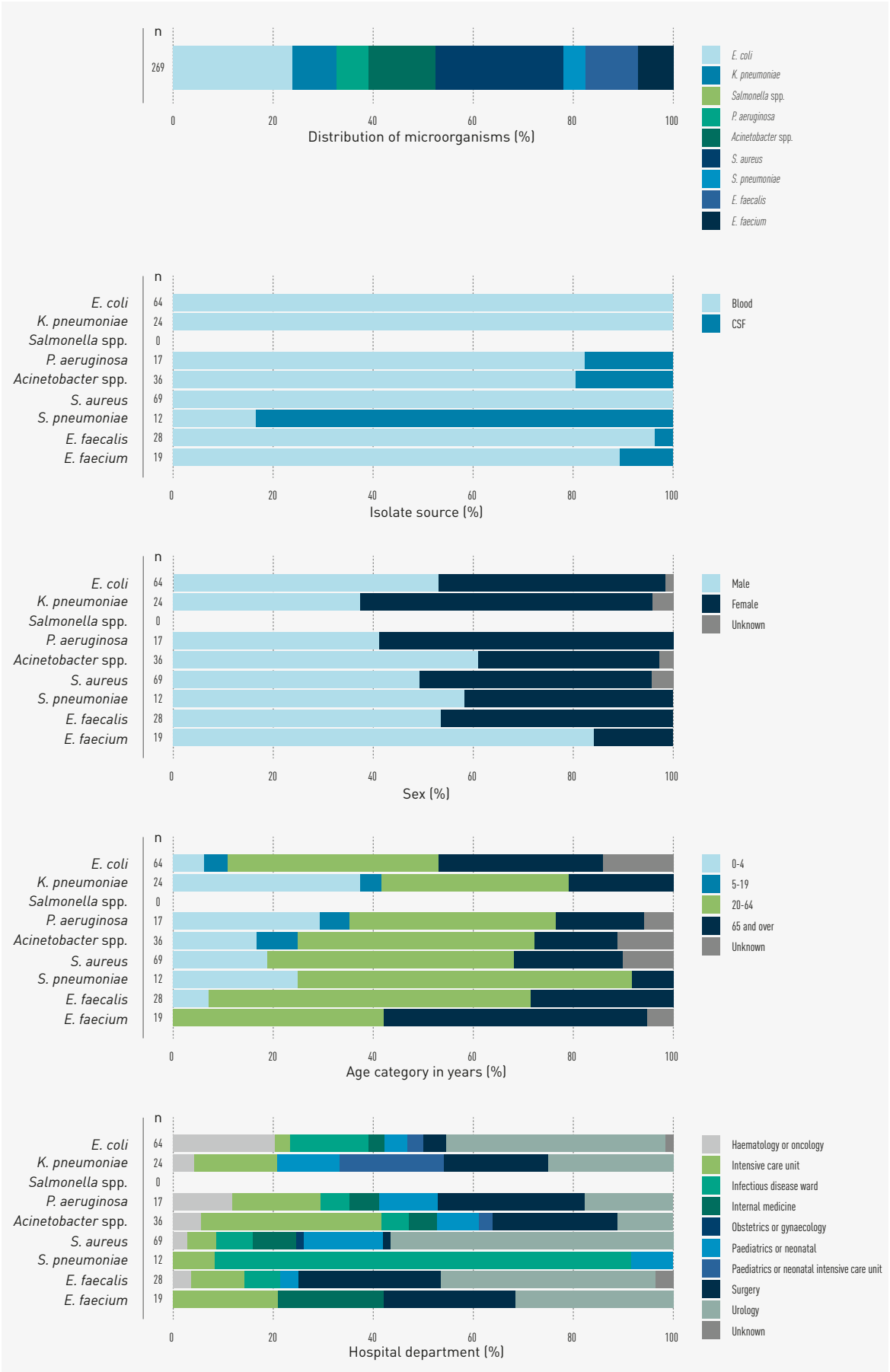


Table 5.40 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in the former Yugoslav Republic of Macedonia in 2016

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (R)	42	93	NA	NA
Amoxicillin-clavulanic acid (R)	36	69	20	80*
Piperacillin-tazobactam (R)	4	50*	18	50*
Third-generation cephalosporins (R)	40	67	19	100*
Third-generation cephalosporins (I+R)	40	72	19	100*
Ceftazidime (R)	59	73	24	92*
Ertapenem (R)	18	0*	4	25*
Carbapenems (R)	64	0	24	13*
Carbapenems (I+R)	64	0	24	17*
Aminoglycosides (R)	64	61	24	96*
Amikacin (R)	56	5	24	17*
Fluoroquinolones (R)	63	78	24	62*
Fluoroquinolones (I+R)	63	78	24	67*
Multidrug resistance (R)	39	46	19	58*

NA: not applicable.

* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.

The aminopenicillins group comprises amoxicillin and ampicillin.

The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.

The carbapenems group comprises imipenem and meropenem.

The aminoglycosides group comprises gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides. Isolates with missing data on one or more of the groups are excluded.

Table 5.41 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in the former Yugoslav Republic of Macedonia in 2016

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	15	33*	NA	NA
Ceftazidime (R)	6	33*	NA	NA
Cefepime (R)	15	27*	NA	NA
Carbapenems (R)	17	41*	36	81
Carbapenems (I+R)	17	41*	36	81
Aminoglycosides (R)	17	29*	35	83
Amikacin (R)	15	20*	18	78*
Fluoroquinolones (R)	17	35*	36	92
Multidrug resistance (R)	6	17*	35	74

NA: not applicable.

* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.

The carbapenems group comprises imipenem and meropenem.

The aminoglycosides group comprises gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin and levofloxacin.

For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on three or more of the groups are excluded.

For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on one or more of the groups are excluded.

Table 5.42 Percentage of resistance for *S. aureus* among blood and CSF isolates in the former Yugoslav Republic of Macedonia in 2016

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)	69	48
Fluoroquinolones (R)	69	12
Norfloxacin (R)	8	38*
Vancomycin (R)	67	0
Rifampicin (R)	64	5
Linezolid (R)	67	0

* 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, oxacillin.

The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

Table 5.43 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in the former Yugoslav Republic of Macedonia in 2016

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillins (R)	11	27*
Penicillins (I+R)	11	27*
Third-generation cephalosporins (R)	12	0*
Third-generation cephalosporins (I+R)	12	8*
Fluoroquinolones (R)	12	0*
Norfloxacin (R)	2	0*
Macrolides (R)	11	36*
Macrolides (I+R)	11	45*
Multidrug resistance (I+R)	10	30*

* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.
Resistance to penicillins is based on penicillin or, if not available, on oxacillin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The macrolides group comprises erythromycin, clarithromycin, and azithromycin.
Multidrug resistance is defined as resistance to penicillins and macrolides. Isolates with missing data on one or more of the groups are excluded.

Table 5.44 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in the former Yugoslav Republic of Macedonia in 2016

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (I+R)	21	29*	14	93*
High-level gentamicin (R)	20	75*	14	93*
Vancomycin (R)	25	0*	17	53*
Linezolid (I+R)	27	0*	19	5*

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

5.9 Turkey

5.9.1 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 BacLink 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 period 1 January to 31 December 2016, with the exception of *Salmonella*.

The 105 laboratories participating in the network were selected from different geographical regions of the country to reflect the distribution of the population. In 2016, data from 67 laboratories were included: 35 clinical microbiology laboratories of university hospitals, 30 clinical microbiology laboratories of state hospitals and two clinical microbiology laboratories of private hospitals. These hospitals cover about 39% of the hospital beds in Turkey and about 22% of the population (of 80 417 526, data from 2017 *(1)*).

Antimicrobial susceptibility is mostly tested using automated systems (62 of 67 laboratories in 2016). Of these 62, 23 laboratories used a combination of automated systems and disk diffusion methods. In 2016, five laboratories used only disk diffusion methods. 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 EQA (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, EUCAST guidelines were implemented in 67 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 taken in university hospitals and state hospitals are reimbursed through the National Health Insurance Fund. In 69 network laboratories that provided denominator data, a total of 435 233 blood cultures were processed in 2016, yielding sampling rates ranging between 0 and 7.2 per 1000 patient-days in the hospitals for which they provide service.

5.9.2 Results

Fig. 5.9 shows the distribution of microorganisms and the patient characteristics of 16 494 isolates from Turkey in 2016, by pathogen. In *E. coli*, resistance ranged from 1% for amikacin to 79% for aminopenicillins (Table 5.45). Multidrug resistance in *E. coli* was 18%. Resistance in *K. pneumoniae* was 22% for amikacin and higher for all other antibiotic groups. Multidrug resistance was 35% in *K. pneumoniae*. No data on *Salmonella* spp. were available. In *P. aeruginosa*, resistance ranged from 13% (amikacin) to 37% (carbapenems, Table 5.46). Multidrug resistance in *P. aeruginosa* was 28%. Resistance in *Acinetobacter* spp. was 68% for amikacin and higher for all other selected agents. Multidrug resistance was 76% in *Acinetobacter* spp. Twenty-three per cent of *S. aureus* were MRSA (Table 5.47). In *S. pneumoniae*, resistance ranged from 5% (fluoroquinolones) to 39% (macrolides, Table 5.48). Multidrug resistance was 30% in *S. pneumoniae*. The percentage of resistance to penicillin in S. pneumoniae isolates was calculated according to non-meningitis breakpoints for 2016 isolates, leading to a wide range of isolates falling into the intermediate category which was absent in the previous years' reports. Prior to 2016, meningitis breakpoints were used. One per

cent of *E. faecalis* isolates were resistant to vancomycin (Table 5.49). In *E. faecium*, vancomycin resistance was 15%, and 1% was non-susceptible to linezolid. Chapter 7 displays the proportions of resistance for selected pathogen–antibiotic combinations reported by Turkey in maps of the WHO European Region (Fig. 7.1–7.6).

5.9.3 Discussion

The AMR surveillance network of Turkey submitted antibiotic susceptibility testing results for 16 494 isolates from blood or CSF in 2016. The large number of isolates and the distribution of pathogens, with *E. coli* being the most common pathogen isolated (24%) suggest that the data represent a mix of community-acquired and health care-associated infections. However, the relatively large proportion of isolates coming from patients admitted to intensive care units (22%) and the relatively large proportions of *K. pneumoniae*, *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 take blood cultures from patients admitted to an intensive care unit more often compared with patients in the emergency department.

E. coli and *K. pneumoniae* had high resistance to third-generation cephalosporins and fluoroquinolones. Carbapenem resistance in 2016 was comparable to that in 2015 for both *E. coli* and *K. pneumoniae*. About half of the carbapenem-resistant *E. coli* isolates were only resistant to imipenem, based on automated test values that were not confirmed with an alternative test method. 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 health care setting. *Salmonella* spp. were not included in AMR surveillance in Turkey in 2016. These data will be available from 2017 onwards. The level of MRSA was similar to countries close to Turkey (Fig. 7.6). The relatively low number of *S. pneumoniae* isolates and their moderate to 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.

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 health care-associated infections are overrepresented in the data, and this case mix should be taken into account when interpreting the data. The reader's guide (Table 4.1) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.9 Patient characteristic of isolates from Turkey in 2016, by pathogen

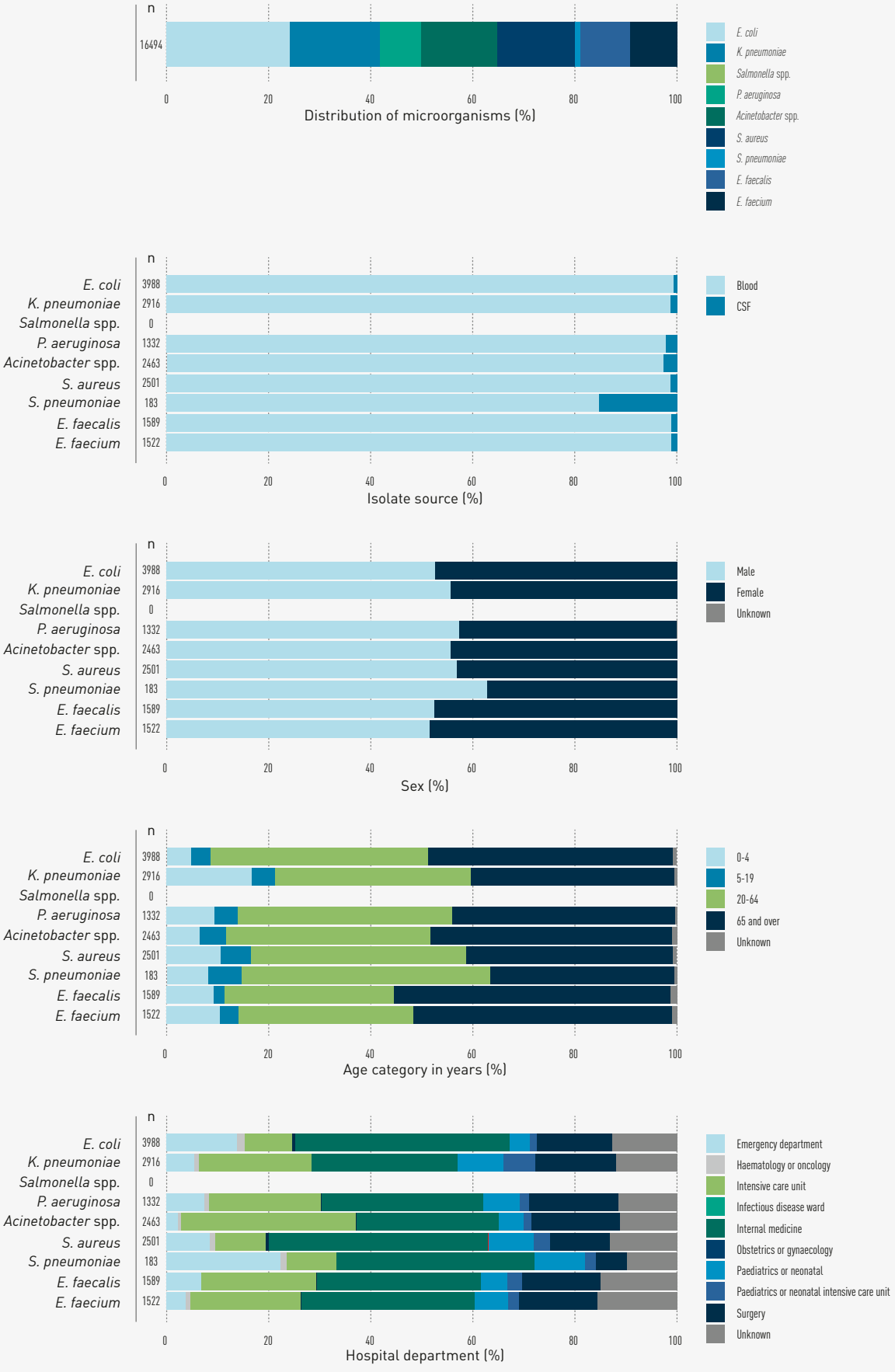


Table 5.45 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Turkey in 2016

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (R)	2887	79	NA	NA
Amoxicillin-clavulanic acid (R)	2571	63	1908	77
Piperacillin-tazobactam (R)	3333	23	2460	59
Third-generation cephalosporins (R)	3546	51	2589	68
Third-generation cephalosporins (I+R)	3546	52	2589	68
Ceftazidime (R)	3349	44	2568	71
Ertapenem (R)	3198	7	2463	46
Carbapenems (R)	3865	3	2837	30
Carbapenems (I+R)	3865	5	2837	41
Aminoglycosides (R)	3679	27	2712	48
Amikacin (R)	3781	1	2820	22
Fluoroquinolones (R)	3670	50	2770	55
Fluoroquinolones (I+R)	3670	55	2770	64
Multidrug resistance (R)	3111	18	2361	35

NA: not applicable.
The aminopenicillins group comprises amoxicillin and ampicillin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
The carbapenems group comprises imipenem and meropenem.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.
Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides. Isolates with missing data on one or more of the groups are excluded.

Table 5.46 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Turkey in 2016

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	1203	31	NA	NA
Ceftazidime (R)	1286	24	NA	NA
Cefepime (R)	1168	30	NA	NA
Carbapenems (R)	1281	37	2373	92
Carbapenems (I+R)	1281	48	2373	93
Aminoglycosides (R)	1305	27	2408	78
Amikacin (R)	1285	13	2287	68
Fluoroquinolones (R)	1252	35	2324	92
Multidrug resistance (R)	1090	28	2266	76

NA: not applicable.

The carbapenems group comprises imipenem and meropenem.

The aminoglycosides group comprises gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin and levofloxacin.

For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on three or more of the groups are excluded.

For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on one or more of the groups are excluded.

Table 5.47 Percentage of resistance for *S. aureus* among blood and CSF isolates in Turkey in 2016

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)	1887	23
Fluoroquinolones (R)	2195	13
Norfloxacin (R)	0	–
Vancomycin (R)	2465	0
Rifampicin (R)	4	100*
Linezolid (R)	2360	0

–: no data available.

* 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, oxacillin.

The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

Table 5.48 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Turkey in 2016

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillins (R)	174	16
Penicillins (I+R)	174	47
Third-generation cephalosporins (R)	113	7
Third-generation cephalosporins (I+R)	113	29
Fluoroquinolones (R)	130	5
Norfloxacin (R)	0	–
Macrolides (R)	163	39
Macrolides (I+R)	163	42
Multidrug resistance (I+R)	155	30

–: no data available.
Resistance to penicillins is based on penicillin or, if not available, on oxacillin.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
The fluoroquinolones group comprises levofloxacin and moxifloxacin.
The macrolides group comprises erythromycin, clarithromycin, and azithromycin.
Multidrug resistance is defined as resistance to penicillins and macrolides. Isolates with missing data on one or more of the groups are excluded.

Table 5.49 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Turkey in 2016

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (I+R)	1437	6	1392	91
High-level gentamicin (R)	767	60	851	65
Vancomycin (R)	1518	1	1467	15
Linezolid (I+R)	1425	0	1368	1

The aminopenicillins group comprises amoxicillin and ampicillin.


CHAPTER
6

Area-specific data on AMR

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

6.1.1 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 period 1 January to 31 December 2016. The dataset comprises only patients from the University Clinical Center of Kosovo with laboratory tests conducted at the Institute of Public Health of Kosovo, 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 120–2100 beds. The participating laboratories are geographically spread throughout Kosovo[1] and cover about 90% of the population (of 1 816 200, data from 2016 *(1)*).

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 an accreditation institute, but they all took part in the CAESAR international external quality control programme in 2016 (provided by UK NEQAS).

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 hospitals. Blood cultures are usually taken from neonates, whereas among older children and adults the utilization of blood culture diagnostics is very low. CSF cultures are taken from patients suspected of having meningitis. Kosovo[1] has not established a health insurance system yet. At the University Clinical Center of Kosovo, the tertiary care hospital (2100 beds) that receives microbiological diagnostic support from the Institute of Public Health of Kosovo, 2347 blood samples were taken in 2016, yielding a sampling rate of 5.1 samples per 1000 patient-days. The number of blood cultures in regional hospitals is low due to lack of funding and insufficient awareness among clinicians.

6.1.2 Results

Fig. 6.1 shows the distribution of microorganisms and the patient characteristics of 157 isolates from Kosovo[1] in 2016, by pathogen. In 18 *E. coli* isolates, resistance ranged from 0% (piperacillin-tazobactam, carbapenems and ertapenem) to 78% for aminopenicillins (Table 6.1). Multidrug resistance was 22% in *E. coli*. Resistance in *K. pneumoniae*, resistance ranged from 0% for carbapenems and ertapenem to 86% for aminoglycosides and third-generation cephalosporins. Multidrug resistance in *K. pneumoniae* was 10%. Two isolates of *Salmonella* spp. were found, one of which (50%) was resistant to fluoroquinolones only (Table 6.2). Based on only eight *P. aeruginosa* isolates, resistance was lowest for fluoroquinolones and piperacillin-tazobactam (13%), and highest for aminoglycosides (62%, Table 6.3). Multidrug resistance was 25% in *P. aeruginosa*. Resistance in *Acinetobacter* spp. was 95% for all agents. Multidrug resistance in *Acinetobacter* spp. was 95%, as well. Twenty-three per cent of 13 *S. aureus* isolates were MRSA (Table 6.4). In seven isolates of *S. pneumoniae*, resistance was 29% or higher except for fluoroquinolones, norfloxacin and third-generation cephalosporins (0%, Table 6.5). Multidrug resistance was 29% in *S. pneumoniae*. Both in *E. faecalis* and *E. faecium* (13 isolates each), resistance to vancomycin was 15% and linezolid non-susceptibility was not observed (Table 6.6). Chapter 7 displays the percentage of resistance for selected pathogen–antibiotic combinations reported by Kosovo[1] in maps of the WHO European Region (Fig. 7.1–7.6).

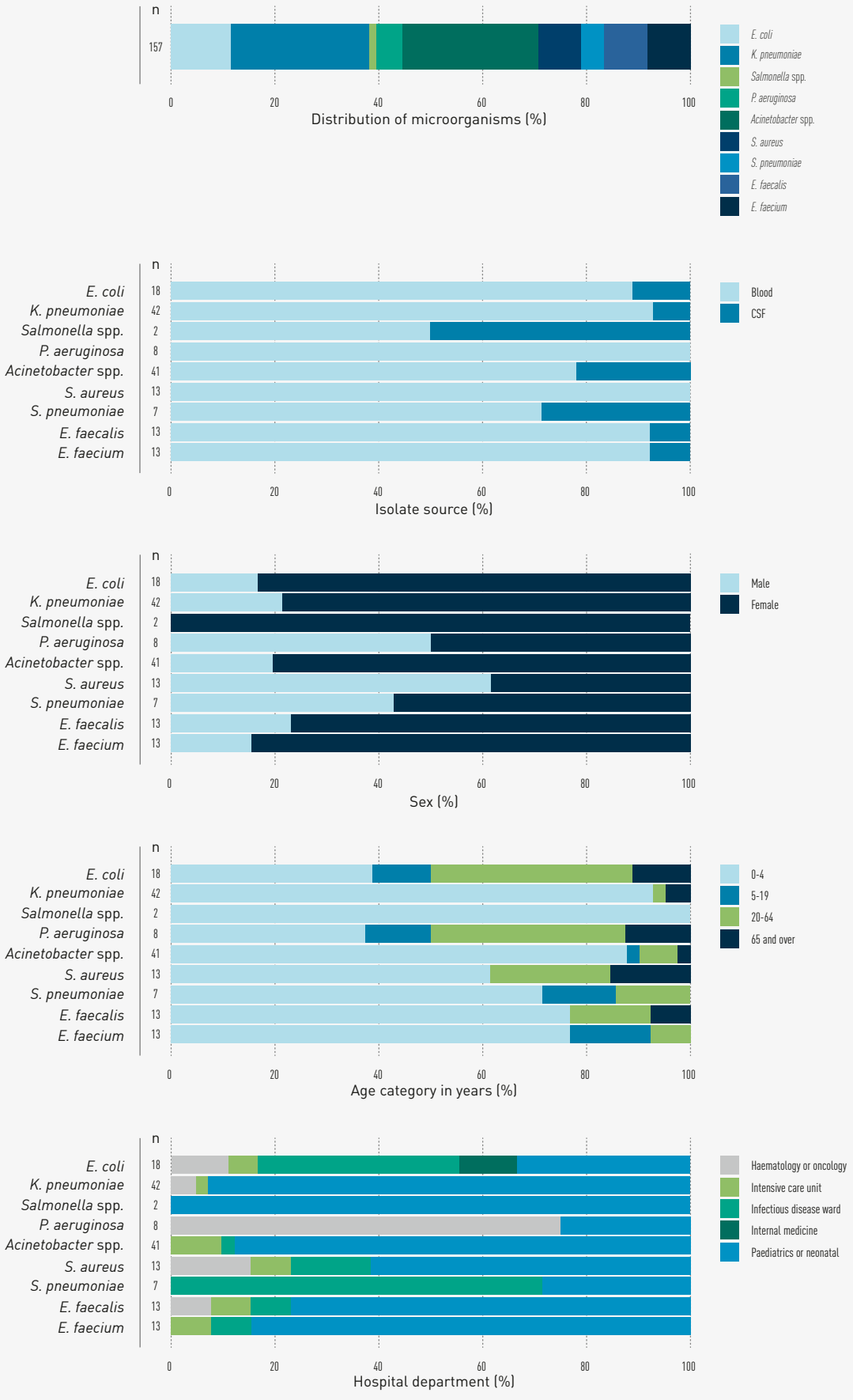
6.1.3 Discussion

The AMR surveillance network of Kosovo[1] submitted antibiotic susceptibility testing results for 157 isolates from blood or CSF in 2016. 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%) 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 absence of data from general hospitals 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 percentages 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 observed in blood and CSF in 2016. The level of MRSA was similar to that of nearby countries (Fig. 7.6). Vancomycin resistance was 15% (two isolates) in both *E. faecium* and *E. faecalis*. Too few antibiotic susceptibility testing results for *Salmonella* spp., *P. aeruginosa*, and *S. pneumoniae* were available to allow interpretation. The high levels of resistance in *Acinetobacter* spp. are concerning and may reflect the dissemination of resistant clones in the health care 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. 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 reader's guide (Table 4.1) provides additional information on interpreting the data and how the level of evidence was determined. Kosovo[1] has an active AMR surveillance network that has been working on implementing harmonized antibiotic susceptibility testing methods and breakpoints. Furthermore, the network is working on collecting data from regional laboratories electronically, to be able to expand the coverage of AMR surveillance and make the observed results more representative for the area of Kosovo.[1]

Fig. 6.1 Patient characteristic of isolates from Kosovo[a], in 2016, by pathogen



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

Table 6.1 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Kosovo[a] in 2016

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (R)	18	78*	NA	NA
Amoxicillin-clavulanic acid (R)	0	–	0	–
Piperacillin-tazobactam (R)	18	0*	42	5
Third-generation cephalosporins (R)	18	61*	42	86
Third-generation cephalosporins (I+R)	18	61*	42	86
Ceftazidime (R)	18	61*	42	50
Ertapenem (R)	18	0*	42	0
Carbapenems (R)	18	0*	42	0
Carbapenems (I+R)	18	0*	42	0
Aminoglycosides (R)	18	44*	42	86
Amikacin (R)	18	6*	42	74
Fluoroquinolones (R)	18	33*	42	10
Fluoroquinolones (I+R)	18	39*	42	24
Multidrug resistance (R)	18	22*	42	10

NA: not applicable.

–: no data available.

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

* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.

The aminopenicillins group comprises amoxicillin and ampicillin.

The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.

The carbapenems group comprises imipenem and meropenem.

The aminoglycosides group comprises gentamicin and tobramycin.

The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

Multidrug resistance is defined as resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides. Isolates with missing data on one or more of the groups are excluded.

Table 6.2 Percentage of resistance for *Salmonella* spp. among blood and CSF isolates in Kosovo[a] in 2016

Antibiotic (group)	*Salmonella* spp.	
	N	Resistance (%)
Third-generation cephalosporins (R)	2	0*
Third-generation cephalosporins (I+R)	2	0*
Ceftazidime (R)	2	0*
Ertapenem (R)	2	0*
Carbapenems (R)	2	0*
Carbapenems (I+R)	2	0*
Fluoroquinolones (R)	2	50*
Fluoroquinolones (I+R)	2	50*

[a] In accordance with United Nations Security Council resolution 1244 (1999).
* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.
The third-generation cephalosporins group comprises cefotaxime and ceftriaxone.
The carbapenems group comprises imipenem and meropenem.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.

Table 6.3 Percentage of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Kosovo[a] in 2016

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	8	13*	NA	NA
Ceftazidime (R)	8	25*	NA	NA
Cefepime (R)	8	25*	NA	NA
Carbapenems (R)	8	25*	41	95
Carbapenems (I+R)	8	25*	41	95
Aminoglycosides (R)	8	62*	41	95
Amikacin (R)	8	25*	41	95
Fluoroquinolones (R)	8	13*	41	95
Multidrug resistance (R)	8	25*	41	95

NA: not applicable.
[a] In accordance with United Nations Security Council resolution 1244 (1999).
* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.
The carbapenems group comprises imipenem and meropenem.
The aminoglycosides group comprises gentamicin and tobramycin.
The fluoroquinolones group comprises ciprofloxacin and levofloxacin.
For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on three or more of the groups are excluded.
For *Acinetobacter* spp., multidrug resistance is defined as resistance to fluoroquinolones, aminoglycosides and carbapenems. Isolates with missing data on one or more of the groups are excluded.

Table 6.4 Percentage of resistance for *S. aureus* among blood and CSF isolates in Kosovo[a] in 2016

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)	13	23*
Fluoroquinolones (R)	13	8*
Norfloxacin (R)	0	–
Vancomycin (R)	13	0*
Rifampicin (R)	13	8*
Linezolid (R)	13	0*

–: no data available.
[a] In accordance with United Nations Security Council resolution 1244 (1999).
* 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, oxacillin.
The fluoroquinolones group comprises ciprofloxacin, ofloxacin and levofloxacin.

Table 6.5 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Kosovo[a] in 2016

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillins (R)	7	29*
Penicillins (I+R)	7	43*
Third-generation cephalosporins (R)	7	0*
Third-generation cephalosporins (I+R)	7	0*
Fluoroquinolones (R)	7	0*
Norfloxacin (R)	7	0*
Macrolides (R)	7	29*
Macrolides (I+R)	7	29*
Multidrug resistance (I+R)	7	29*

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

Table 6.6 Percentage of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Kosovo[a] in 2016

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Aminopenicillins (I+R)	13	15*	13	85*
High-level gentamicin (R)	13	46*	13	38*
Vancomycin (R)	13	15*	13	15*
Linezolid (I+R)	13	0*	13	0*

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

* Few isolates were tested (N < 30), and the percentage of resistance should be interpreted with caution.

The aminopenicillins group comprises amoxicillin and ampicillin.


CHAPTER
7

AMR maps of the WHO European Region

7.1 Introduction

This chapter presents the 2016 AMR data from the CAESAR countries and areas together with the 2016 data from EARS-Net provided by the ECDC. For 2016, 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 AMR in the country. Level A data, presented without shading, provide an adequate assessment of the magnitude of AMR in the country. Chapter 4 presents more information about the different levels of evidence. More details on EARS-Net are available on its website *(1)*. The latest EARS-Net data from 2016 are in the ECDC Surveillance Atlas of Infectious Diseases *(2)*. This chapter was prepared in collaboration with the ECDC to provide an overview of AMR in the European Region.

7.2 Description of the maps

7.2.1 *E. coli*

E. coli is the most frequent cause of bloodstream infections and urinary tract infections from community origin. EARS-Net data have shown a significant increase in third-generation cephalosporin resistance in EU and European Economic Area countries *(2)*. In 2016, the majority of EARS-Net countries showed resistance proportions between 10% and 25%. Proportions of more than 25% were found in Bulgaria, Cyprus, Italy and Slovakia. Among the CAESAR countries and areas, Belarus, Montenegro, the Russian Federation, the former Yugoslav Republic of Macedonia, Turkey and Kosovo[1] reported resistance proportions exceeding 50%, whereas the resistance proportion in Serbia is more comparable to its neighbouring EARS-Net countries (25–50%), as are the resistance proportions in Bosnia and Herzegovina and Switzerland (10–25%) (Fig. 7.1). The recent emergence of carbapenem resistant *E. coli* is of serious concern, but overall resistant proportions are low, with only one EARS-Net country (Romania) and four of the CAESAR countries (Belarus, the Russian Federation, Serbia and Turkey) reporting carbapenem-resistant isolates (Fig. 7.2).

7.2.2 *K. 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 proportions are reported from northern European countries and much higher proportions from the southern, and eastern parts

of the European Region, even exceeding 50% in Belarus, Bosnia and Herzegovina, Montenegro, Poland, Romania, the Russian Federation, Serbia, Slovakia and the former Yugoslav Republic of Macedonia (Fig. 7.3). Compared to *E. coli*, carbapenem resistance is more frequently found in *K. pneumoniae*. Though low proportions of resistance are seen in most countries, proportions between 25% and 50% are reported by Italy, Romania, Serbia and Turkey, and proportions exceeding 50% reported by Belarus and Greece (Fig 7.4). These high proportions of multidrug resistance and carbapenem resistance in many countries are concerning, may reflect the dissemination of resistant clones in the health care settings and indicate the serious limitation in treatment options for patients with (invasive) infections with *K. pneumoniae* in these countries.

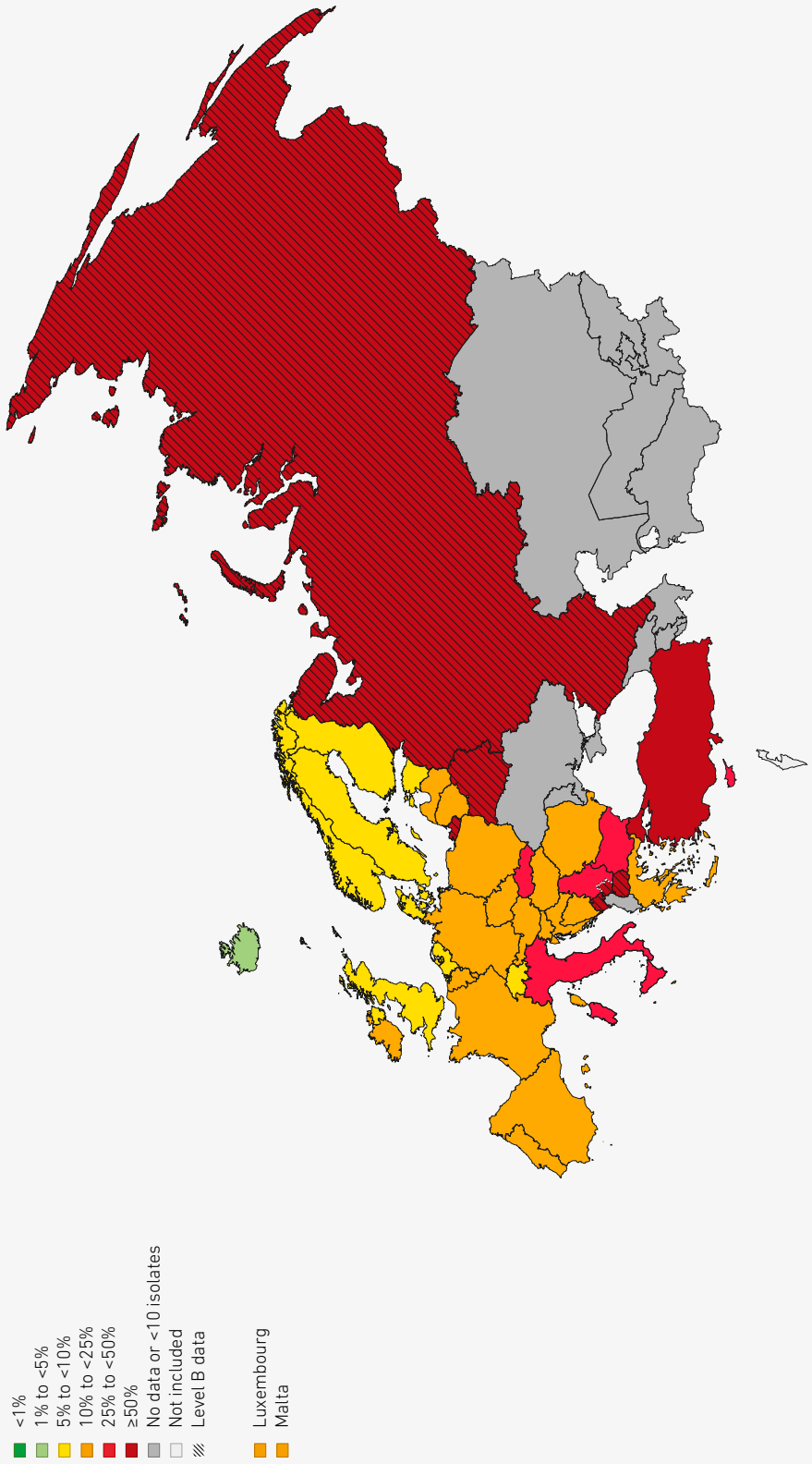
7.2.3 *Acinetobacter* spp.

Acinetobacter spp. mainly cause health care-associated infections, such as (ventilator-associated) pneumonia, (central-line associated) bloodstream infections and postoperative wound infections. Multidrug-resistant *Acinetobacter* spp. often cause hospital outbreaks if appropriate prevention and control measures are not implemented. Acinetobacter species can persist in the health care environment and are difficult to eradicate once established. The presence of multidrug-resistant *Acinetobacter* spp. varies widely within the European Region, with proportions <1% in northern European countries to proportions exceeding 50% in many countries in southern and eastern Europe (Fig 7.5). These high proportions of multidrug-resistance are concerning, may reflect the dissemination of resistant clones in the health care settings and indicate the serious limitation in treatment options for patients with (invasive) infections with *Acinetobacter* spp. in these countries.

7.2.4 *S. aureus*

MRSA is one of the most frequent causes of antibiotic-resistant health care-associated infections worldwide. In addition, increasing levels of community-associated MRSA are being reported from many parts of the world, including Europe. *S. aureus* mainly cause skin, soft tissue, bone infections, and bloodstream infections. *S. aureus* is the most common cause of postoperative wound infections. The Scandinavian countries, Estonia, Latvia, the Netherlands and Switzerland have the lowest proportions of MRSA (< 5%). Resistance proportions of more than 25% are found in many of the countries in the southern and eastern parts of the European Region (Fig. 7.6).

Figure 7.1. Third-generation cephalosporin-resistant *E. coli* in the European Region (EARS-Net and CAESAR), 2016

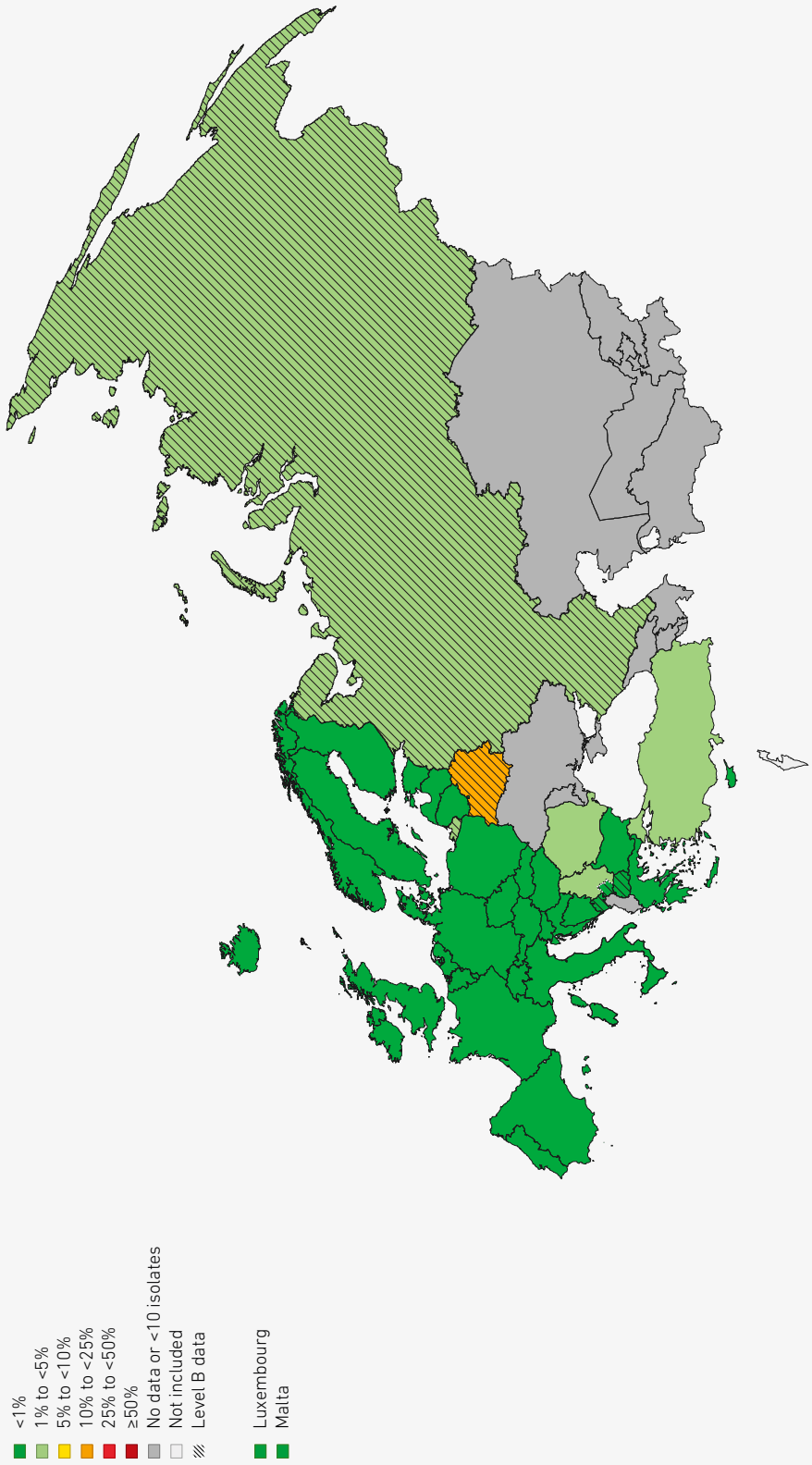


Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country or area, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of AMR in the country or area. For more information about levels of evidence, see section 4.2 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, the 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, 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))

Data sources: 2016 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2017) and 2016 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2017).

Figure 7.2. Carbapenem-resistant *E.coli* in the European Region (EARS-Net and CAESAR), 2016

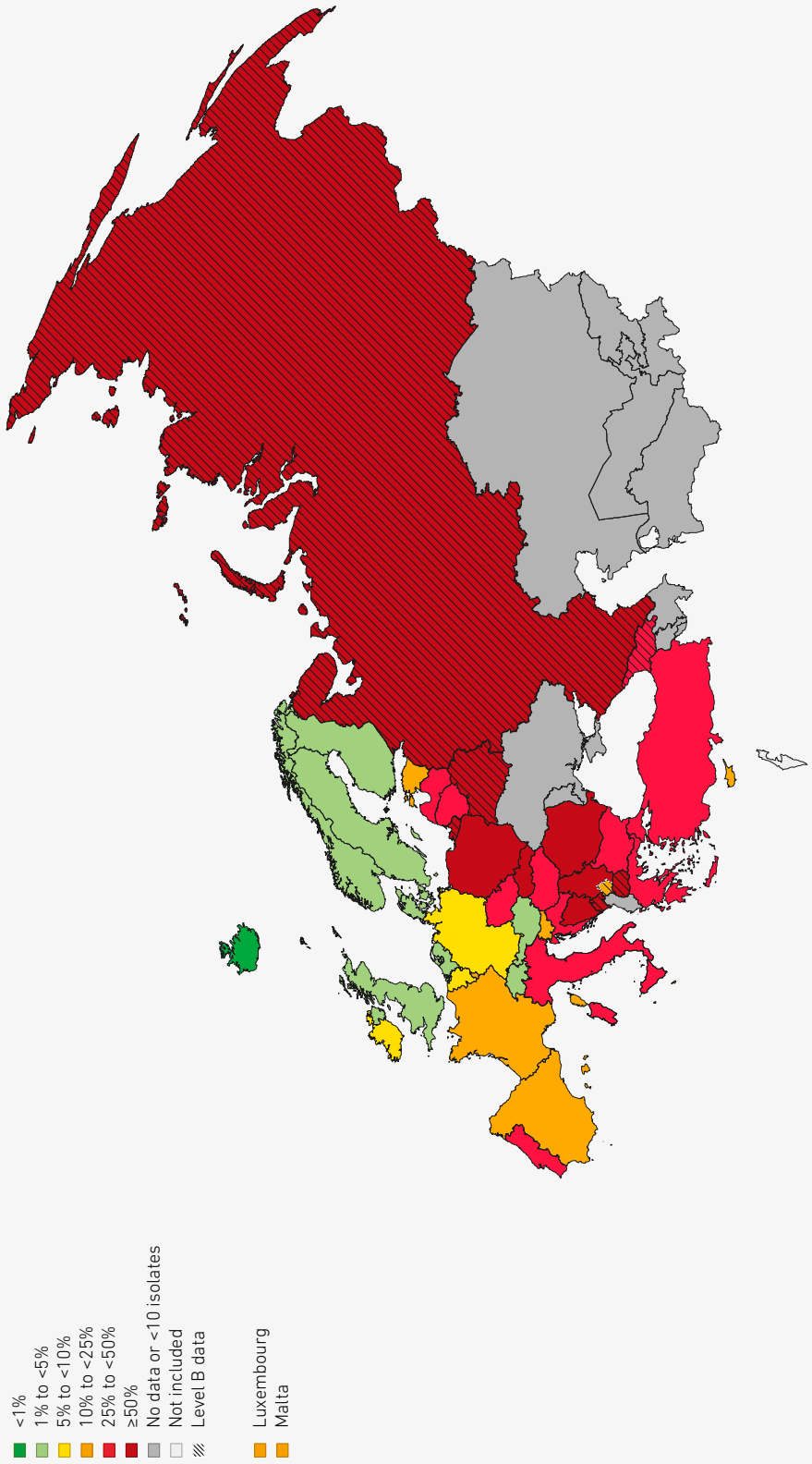


Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country or area, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of AMR in the country or area. For more information about levels of evidence, see section 4.2 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, the 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, 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))

Data sources: 2016 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2017) and 2016 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2017).

Figure 7.3. Multidrug-resistant (combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides) *K. pneumoniae* in the European Region (EARS-Net and CAESAR), 2016

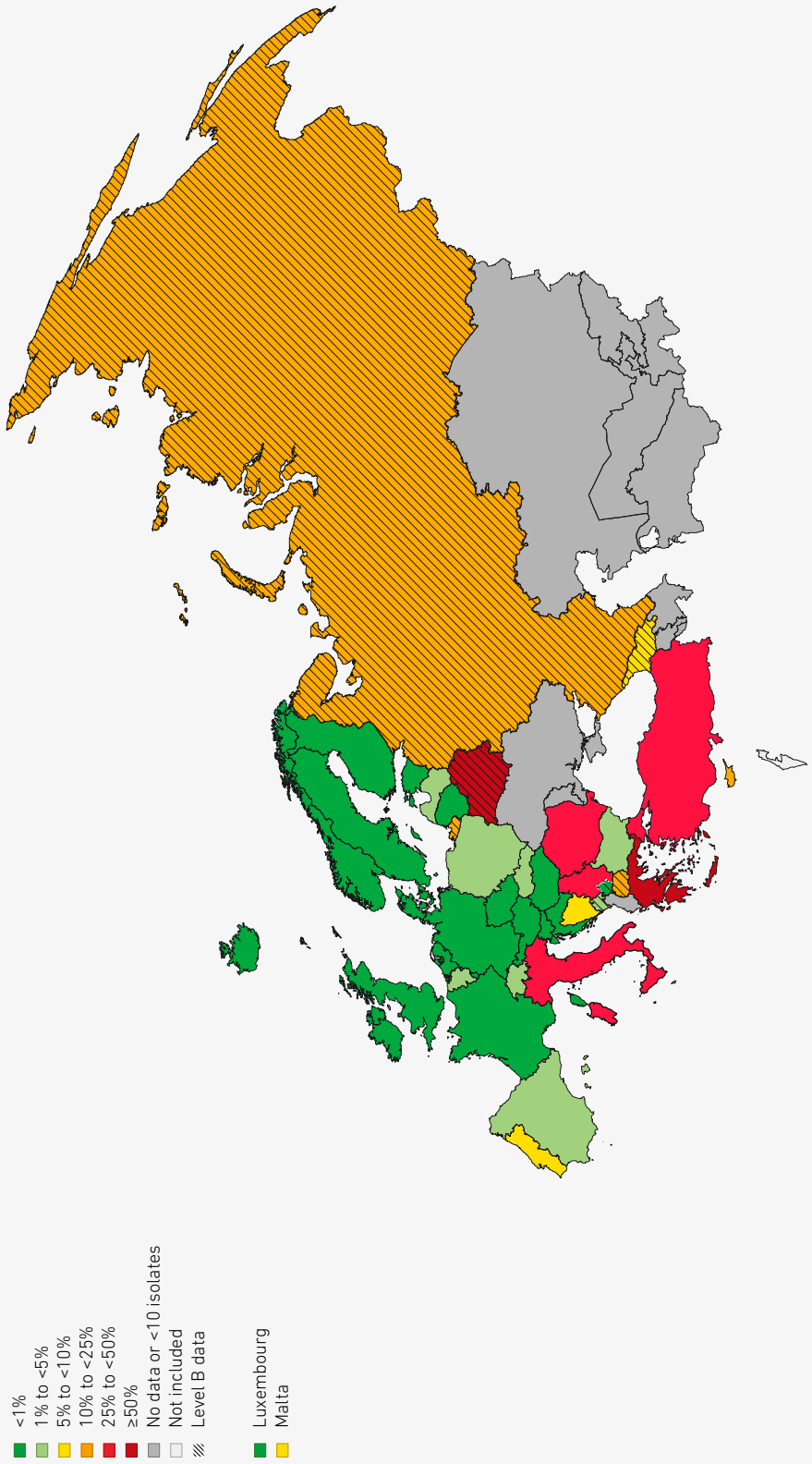


Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country or area, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of AMR in the country or area. For more information about levels of evidence, see section 4.2 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, the 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, 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))

Data sources: 2016 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2017) and 2016 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2017).

Figure 7.4. Carbapenem-resistant *K. pneumoniae* in the European Region (EARS-Net and CAESAR), 2016

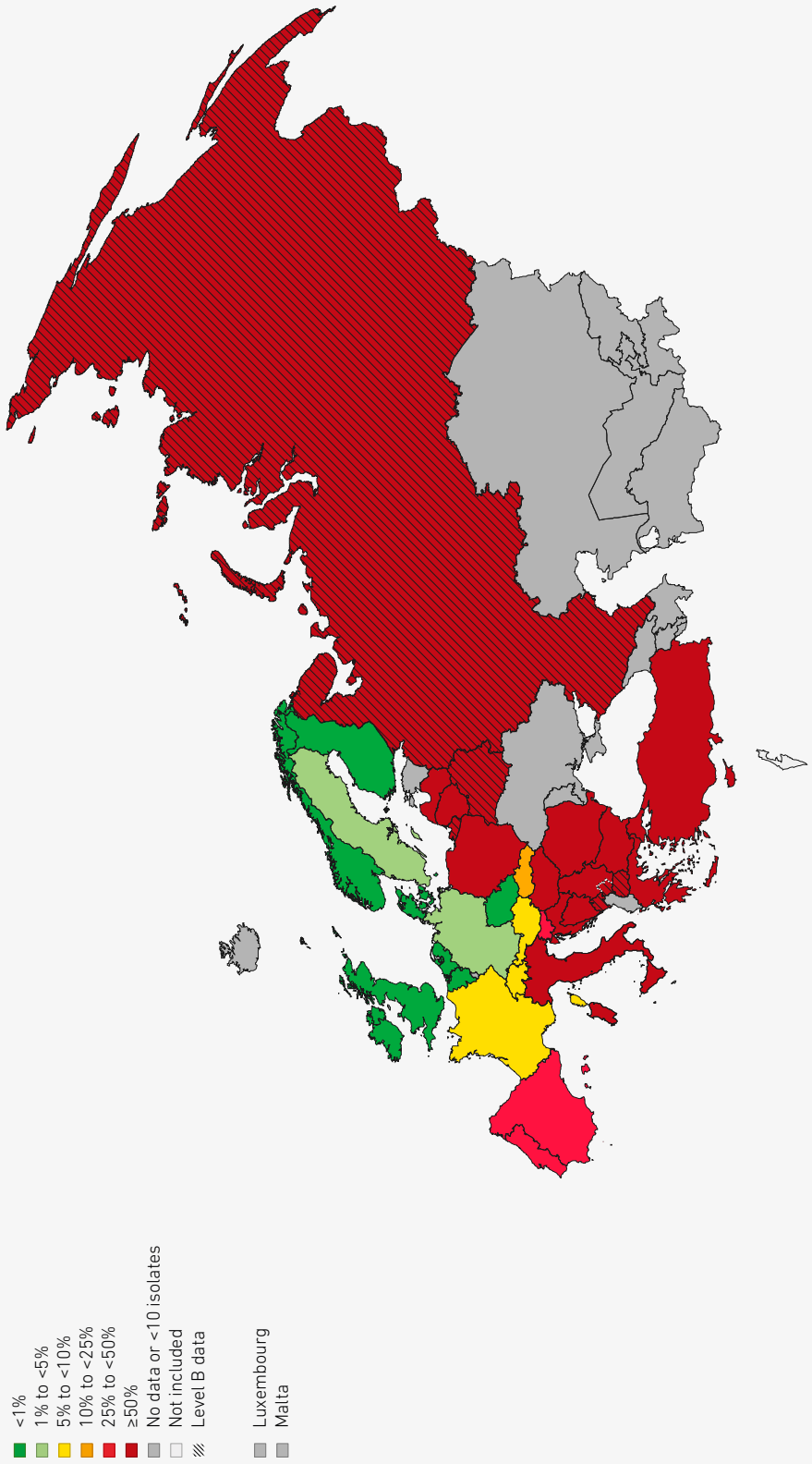


Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country or area, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of AMR in the country or area. For more information about levels of evidence, see section 4.2 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, the 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, 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))

Data sources: 2016 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2017) and 2016 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2017).

Figure 7.5. Multidrug-resistant (combined resistance to fluoroquinolones, aminoglycosides and carbapenems) *Acinetobacter* spp. in the European Region (EARS-Net and CAESAR), 2016

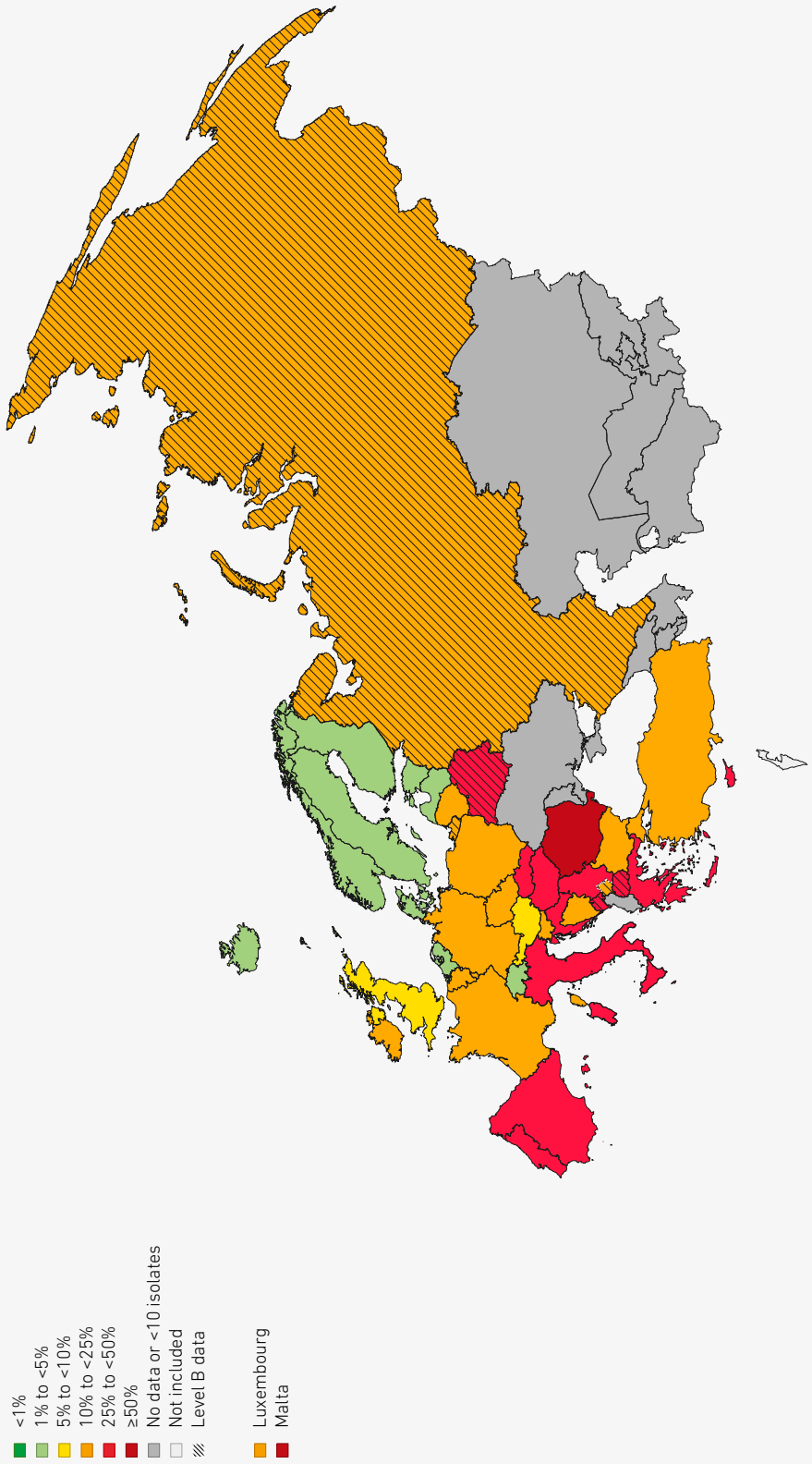


Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country or area, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of AMR in the country or area. For more information about levels of evidence, see section 4.2 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, the 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, 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))

Data sources: 2016 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2017) and 2016 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2017).

Figure 7.6. MRSA in the European Region (EARS-Net and CAESAR), 2016



Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country or area, 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 or area. For more information about levels of evidence, see section 4.2 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, the 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, 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))

Data sources: 2016 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2017) and 2016 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2017).


CHAPTER
8

CAESAR EQA

8.1 Introduction

The objective of the CAESAR EQA programme is to assess the quality of the AST practices in participating laboratories by distributing the same well-characterized isolates to all laboratories in the network. All laboratories examine the challenge isolates and report their results within the defined time frame. The EQA results are used to assess capacity-building needs in countries. The EQA is a joint exercise with EARS-Net that is hosted at ECDC. The UK NEQAS, based at Public Health England National Infection Service in Colindale, London (United Kingdom) 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 EQA coordinator. All participating laboratories receive reports from the UK NEQAS highlighting the performance of each individual laboratory in comparison to all other laboratories in the CAESAR network thereby enabling the independent assessment of performance and the identification of problems in laboratory procedures. The EQA of CAESAR countries is co-financed by ESCMID.

This chapter describes the results from the CAESAR EQA exercise conducted in 2016.

8.2 CAESAR EQA in 2016

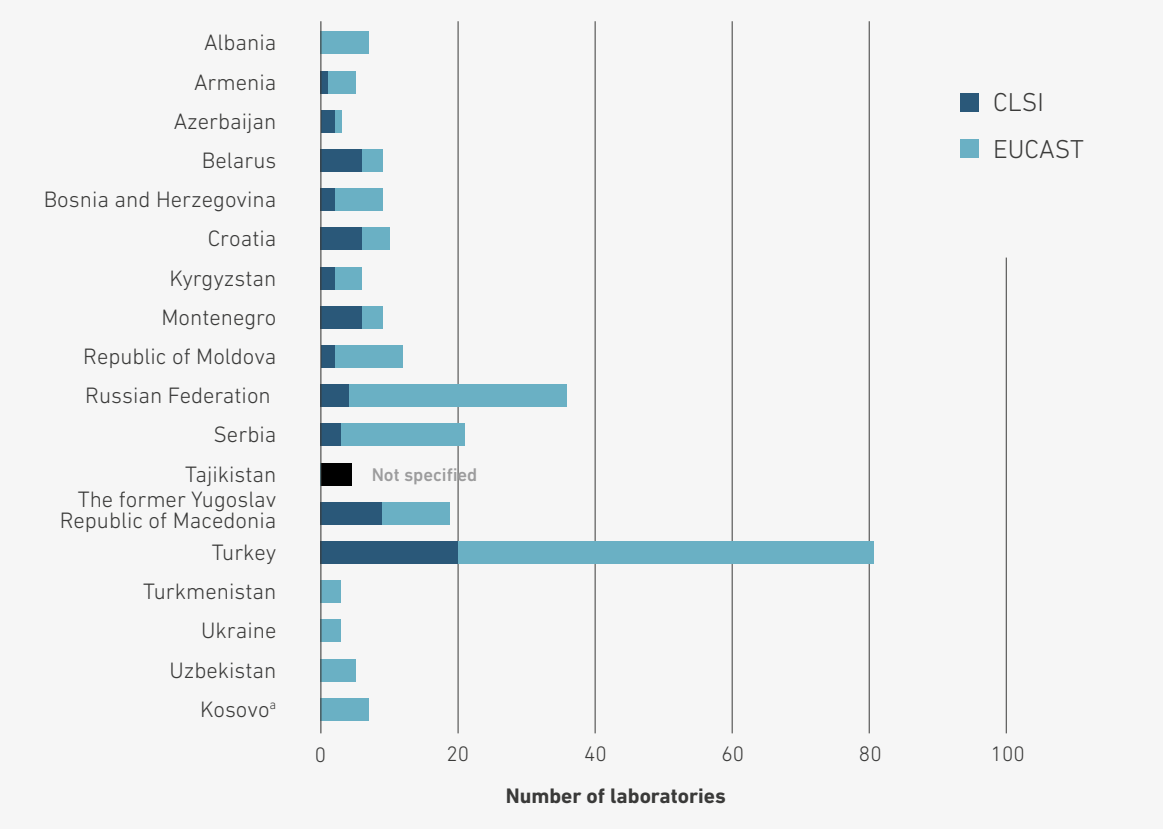
A panel of six lyophilized isolates were prepared and found fully compliant in quality control testing by the UK NEQAS, and the results were confirmed in two expert reference laboratories. The panel included the following strains: *E. coli* (specimen 3682), *K. pneumoniae* (specimen 3683), *P. aeruginosa* (specimen 3684), *S. aureus* (specimen 3685), *A. baumannii* complex (specimen 3686) and *S. pneumoniae* (specimen 3687). The EQA panels were dispatched on 12 September 2016 to all participants in 18 countries or areas participating in the CAESAR network. Participants were requested to return results within four weeks. Results were returned from 18 countries and areas by 254 of 272 participants (93%): 7 of 9 laboratories from Albania, 5 of 5 from Armenia, 3 of 3 from Azerbaijan, 9 of 9 from Belarus, 9 of 9 from Bosnia and Herzegovina, 10 of 11 from Georgia, 6 of 6 from Kyrgyzstan, 9 of 10 from Montenegro, 12 of 12 from the Republic of Moldova, 40 of 41 from the Russian Federation, 21 of 22 from Serbia, 4 of 5 from Tajikistan, 19 of 21 from the former Yugoslav Republic of Macedonia, 81 of 90 from Turkey, 3 of 3 from Turkmenistan, 3 of 3 from Ukraine, 6 of 6 from Uzbekistan and 7 of 7 from Kosovo[1].

8.2.1 Methods and guidelines used

Fig. 8.1 presents a breakdown of the methods and guidelines used by participants examining the EQA specimens. Almost all participants followed international guidelines: CLSI (26%) and EUCAST (74%), with just one participant in Uzbekistan that followed the British Society for Antimicrobial Chemotherapy guidelines (not shown in the figure). In most of the countries and areas (71%), both guidelines were stated to be in use among the participating laboratories, whereas in four countries and areas, Albania, Turkmenistan, Ukraine and Kosovo[1], all participating laboratories homogeneously used the EUCAST guideline.

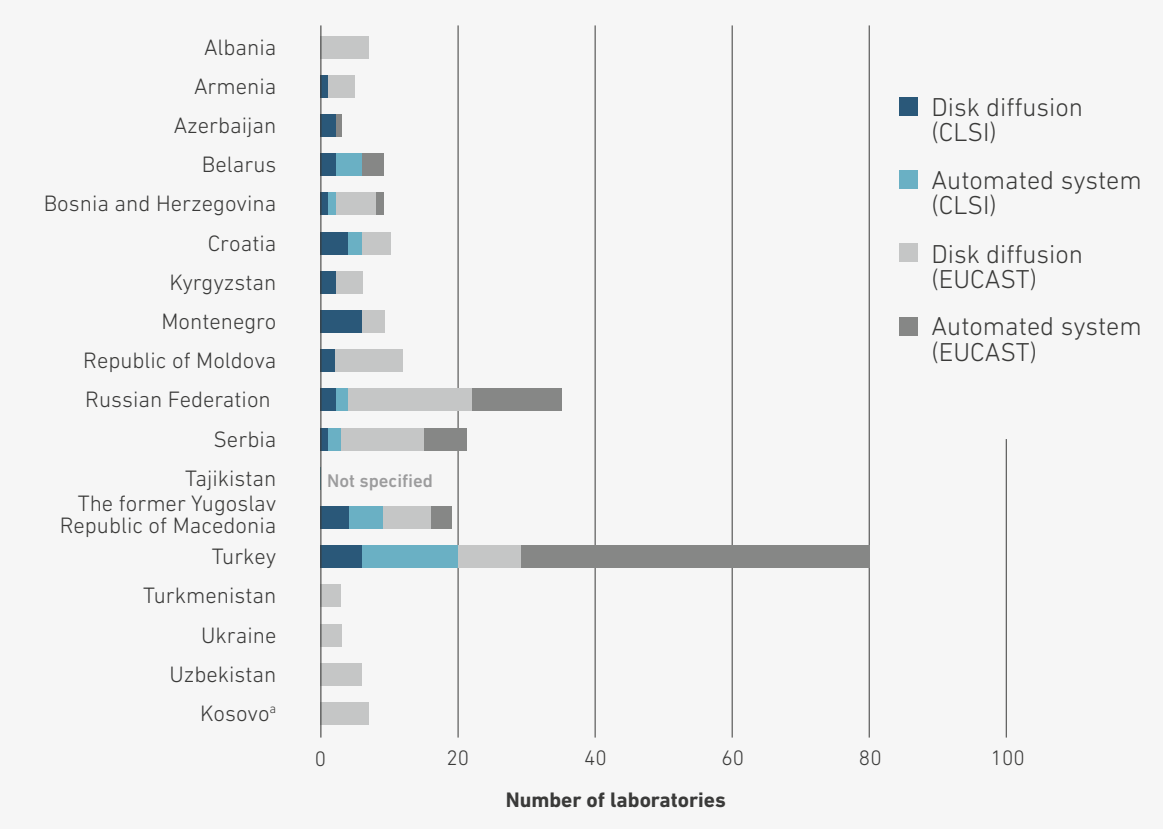
Among participants which specified the susceptibility testing method used for the survey strains (n = 245), the breakdown of the methods used revealed that 55% of the laboratories used disk diffusion susceptibility testing methods and 44% used an automated instrument; of the remaining participants, two performed minimum inhibitory concentration testing using gradient strip tests and eight participants did not specify any method (Fig. 8.2).

Fig. 8.1 Number of laboratories and type of guideline used per country or area



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

Fig. 8.2 Number of laboratories and type of susceptibility testing method per country or area



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

8.2.2 Antimicrobial susceptibility results

Participants' results were collated, analysed and presented in individual laboratory reports, which were subsequently uploaded onto the secure UK NEQAS website. The reports display the individual laboratory's results and the overall results for all CAESAR network laboratories that have participated in the exercise so that laboratories can make suitable comparisons. Participants can access their reports at any time, as well as download a printed copy.

EQA is a valuable tool in the quality assurance of AST and indicates the validity of comparing collated data between laboratories for the purpose of resistance surveillance. In general, performance was very good and consistent with that seen in previous EQA surveys among participants in the European Region in both EARS-Net and the CAESAR network. Problems, where experienced, were mostly related to borderline susceptibility, testing of beta-lactam/beta-lactamase inhibitor combinations (notably testing of piperacillin-tazobactam) and novel resistance mechanisms (e.g. methicillin resistance in *S. aureus* mediated by *mecC* gene). The specimens distributed and their important antimicrobial susceptibility features are outlined in Table 8.1. The different isolates are described in more detail on the next pages, and the results by country or area are given in Tables 8.2–8.7.

Table 8.1 Specimens distributed in the CAESAR EQA survey in 2016 and their important antimicrobial susceptibility features

Specimen number	Organism	Correct identification among participating laboratories (*n* = 254) (%)	Important antimicrobial susceptibility features of the strain
3682	*E. coli*	99	Acquired AmpC beta-lactamase enzyme (BIL-1) Reduced susceptibility to ertapenem
3683	*K. pneumoniae*	91	Both OXA-1 and SHV-1 enzymes Resistant to beta-lactam agents including inhibitor combinations, colistin (by EUCAST methodology) and quinolones Intermediately resistant to amikacin (by EUCAST methodology)
3684	*P. aeruginosa*	100	Resistant to carbapenems, likely to be mediated by porin loss/efflux as no known carbapenemase enzyme is present Resistant and intermediate to piperacillin-tazobactam by EUCAST and CLSI breakpoints, respectively.
3685	*S. aureus*	98	*mecC* gene Resistant to beta-lactam agents and susceptible to all other antibiotics
3686	*A. baumannii* complex	91	Resistant to gentamicin and ciprofloxacin Susceptible to amikacin, colistin, imipenem, meropenem and tobramycin
3687	*S. pneumoniae*	98	Wild type for penicillin (minimum inhibitory concentration = 0.015 mg/L)

The susceptibility of the pathogens isolated against the antimicrobial agents tested was defined as susceptible (S), intermediate (I) or resistant (R).

Specimen 3682 was an *E. coli* that harboured an acquired AmpC ß-lactamase enzyme (BIL-1) conferring resistance to all reference ß-lactam agents except imipenem and meropenem (Table 8.1). All but two participants correctly identified the isolate; the two misidentifications were noted as *K. pneumoniae* and *Acinetobacter* spp. Among reasons that may have caused these misidentifications, contamination and mislabelling of cultures should be considered since the survey also contained these two species.

Table 8.2 *E. coli* (specimen 3682): 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 (7)	Armenia (5)	Azerbaijan (3)	Belarus (9)	Bosnia and Herzegovina (9)	Georgia (10)	Kyrgyzstan (6)	Montenegro (9)	Republic of Moldova (12)	Russian Federation (40)	Serbia (21)	Tajikistan (4)	The former Yugoslav Republic of Macedonia (19)	Turkey (81)	Turkmenistan (3)	Ukraine (3)	Uzbekistan (6)	Kosovo[a] (7)
Identification			100	100	100	100	100	100	100	100	100	100	100	75	100	100	100	100	100	86
Amikacin	2–4	S/S	71	100	100	89	100	80	100	100	100	97	95	25	100	98	50	100	83	86
Amoxicillin	≥128	R/R	100	100	100	88	100	100	75	100	92	94	100	100	100	90	100	100	100	100
Amoxicillin-clavulanic acid	≥128(64)[b]	R/R	100	100	100	100	100	100	100	89	100	100	100	–	100	100	100	100	100	100
Ampicillin	≥128	R/R	100	100	100	100	100	100	100	100	92	100	100	100	100	100	100	100	80	100
Cefotaxime	≥128	R/R	100	100	100	100	100	40	100	89	92	89	100	0	100	97	–	100	67	100
Ceftazidime	≥128	R/R	100	100	67	100	100	100	100	100	92	100	100	–	100	99	–	100	100	100
Ceftriaxone	≥128	R/R	100	100	100	100	100	60	100	89	83	100	100	50	100	99	33	100	100	100
Ciprofloxacin	0.03	S/S	71	100	100	89	100	100	83	100	100	100	100	100	100	99	100	100	80	100
Colistin	≤0.25	S/–	–	100	–	86	100	100	–	0	0	100	100	–	100	100	–	100	100	100
Ertapenem	4	R/R	100	–	–	0	0	44	50	33	0	27	26	–	30	32	–	0	0	75
Gentamicin	0.5–2	S/S	100	100	67	89	100	90	60	100	100	97	95	0	100	96	100	100	83	86
Imipenem	0.5	S/S	57	100	67	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Levofloxacin	–	S/S[c]	100	100	100	100	100	100	100	100	100	96	100	100	100	100	100	100	100	100
Meropenem	0.12–0.25	S/S	43	100	100	89	89	100	100	100	91	96	100	–	95	100	100	100	83	100
Ofloxacin	–	S/Sc	100	100	100	89	100	100	100	100	100	93	100	–	100	100	100	100	80	100
Piperacillin-tazobactam	≥128	R/R	71	0	100	33	63	10	100	0	11	48	38	–	24	49	–	0	–	33
Tobramycin	1	S/S	100	60	100	89	100	89	100	86	92	81	100	100	94	83	100	100	100	67

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

[b] Reference results for amoxicillin-clavulanic acid minimal inhibitory concentrations relate to tests with a fixed concentration of 2 mg/L clavulanic acid. Minimal inhibitory concentrations in parenthesis relate to tests with a 2:1 ratio of amoxicillin:clavulanic acid.

[c] Results based on participants' consensus, because no reference laboratory results are available.

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

Excluding ertapenem and piperacillin-tazobactam, good consensus was observed for all antimicrobial agents (Table 8.2). The minimal inhibitory concentration of ertapenem as determined by the reference laboratory was 4 mg/L which corresponds to the resistant category in both CLSI and EUCAST. However,

among participants returning results for ertapenem (*n* = 182), 65.4% indicated the strain as susceptible to ertapenem, 4.9% as intermediate and only 29.7% correctly as resistant, showing that ertapenem non-susceptibility, which is not uncommon among AmpC beta-lactamase producing *E. coli* isolates, may be missed. It is important to note that erroneous susceptible results to ertapenem were more frequent among participants using automated systems than those using a disk diffusion or minimal inhibitory concentration method.

Another antimicrobial causing low performance was noted as piperacillin-tazobactam. Even though the isolate had a high piperacillin-tazobactam minimal inhibitory concentration (i.e. ≥128 mg/L), which corresponds to the resistant category by both CLSI and EUCAST, participants who tested piperacillin-tazobactam susceptibility (*n* = 200) reported variable results (41.5% susceptible, 18% intermediate and 40.5% resistant). Participants using automated systems or minimal inhibitory concentration methods were more likely to report reduced susceptibility (intermediate or resistant) than those using disk diffusion methodology.

Specimen 3683 was a *K. pneumoniae* which produces both OXA-1 and SHV-1 enzymes, expressing resistance to many beta-lactam agents including inhibitor combinations, colistin (by EUCAST methods) and quinolones (Table 8.3). The participants demonstrated the lowest overall performance for this strain when correct identification rate at the genus level was considered. Correct identification at the species level was reported by 231 (91%) participants, whereas eight and three participants identified the isolate as *K. oxytoca* and *Klebsiella* spp., respectively. False identification at the genus level was observed in 12 participants (*E. coli*; *n* = 6, *Enterobacter aerogenes*; *n* = 3, *Enterobacter cloacae*; *n* = 1, *Enterobacter* spp.; *n* = 1, *Streptococcus pyogenes*; *n* = 1).

Table 8.3 *K. pneumoniae* (specimen 3683): 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 (7)	Armenia (5)	Azerbaijan (3)	Belarus (9)	Bosnia and Herzegovina (9)	Georgia (10)	Kyrgyzstan (6)	Montenegro (9)	Republic of Moldova (12)	Russian Federation (40)	Serbia (21)	Tajikistan (4)	The former Yugoslav Republic of Macedonia (19)	Turkey (81)	Turkmenistan (3)	Ukraine (3)	Uzbekistan (6)	Kosovo[a] (7)
Identification			100	0	100	100	100	70	100	100	100	98	95	0	100	95	33	100	67	57
Amikacin	16	I/S	60	60	67	22	44	80	83	89	92	47	52	50	56	63	50	100	67	43
Amoxicillin	>32	R/R	100	100	100	100	100	100	100	100	100	93	100	100	100	100	100	100	100	100
Amoxicillin-clavulanic acid	>64–>128[b]	R/R	100	100	100	100	100	88	100	100	91	94	100	–	100	100	100	100	100	100
Ampicillin	>32–>64	R/R	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	80	100
Cefotaxime	2–4	I-R/I-R	71	0	67	100	67	0	0	56	42	78	83	–	88	71	0	100	33	43
Ceftazidime	1	S/S	57	100	67	56	100	90	100	89	58	38	81	100	53	68	100	100	50	100
Ceftriaxone	1	S/S	100	100	67	56	100	100	100	89	83	33	90	75	56	625	100	100	67	100
Ciprofloxacin	>4–>8	R/R	71	100	100	100	100	100	100	89	100	100	100	50	100	100	100	100	100	100
Colistin	32	R/–	–	0	–	100	100	78	–	100	100	87	94	–	90	75	–	100	–	100
Ertapenem	2–4	R/R	83	–	–	56	86	56	100	100	100	93	90	–	75	92	–	100	100	100
Gentamicin	>16–>32	R/R	86	60	100	100	100	100	100	100	75	100	100	100	100	100	50	100	100	100
Imipenem	0.5–1	S/S	29	100	67	78	100	70	83	100	100	79	91	100	90	79	100	100	83	86
Levofloxacin	–	R/Rc	71	60	100	100	88	100	67	100	64	96	100	100	94	97	67	100	100	100
Meropenem	0.5	S/S	71	100	100	56	89	80	40	78	18	74	95	–	68	68	100	100	0	80
Ofloxacin	–	R/R[c]	100	100	33	78	67	100	100	89	64	100	100	100	100	100	100	100	83	100
Piperacillin-tazobactam	>64	R/R	100	0	100	100	88	90	100	89	89	95	100	–	83	100	–	100	–	100
Tobramycin	>16–>32	R/R	100	100	100	100	100	100	100	100	92	100	100	–	100	100	100	100	100	100

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

[b] Reference results for amoxicillin-clavulanic acid minimal inhibitory concentrations relate to tests with a fixed concentration of 2 mg/L clavulanic acid.

[c] Results based on participants' consensus, because no reference laboratory results are available.

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

Consensus was poor regarding the results of susceptibility testing of third-generation cephalosporins (cefotaxime, ceftriaxone and ceftazidime). For example, 176 participants reported variable results for cefotaxime (36.9% susceptible, 19.9% intermediate and 43.2% resistant). For cefotaxime, where the intended result was intermediate or resistant, participants using disk diffusion methodology were more likely to report susceptible results than participants using an automated system or MIC methodology.

This strain expressed intermediate resistance to amikacin (minimal inhibitory concentration 16 mg/L) by EUCAST breakpoints, but was susceptible by CLSI criteria. The 240 participants reporting amikacin susceptibility reported variable results (23.3% susceptible, 37.1% intermediate and 39.6% resistant). Participants using CLSI methodology were more likely to report amikacin as susceptible or intermediate than participants using EUCAST methodology.

The organism was susceptible to both imipenem and meropenem by EUCAST and CLSI breakpoints. Participants' results for these two agents were similar. Although there was good overall concordance for these agents, participants using EUCAST methodology were more likely to report imipenem and meropenem as susceptible or intermediate than participants using CLSI methodology. Participants using disk diffusion or minimal inhibitory concentration methods were more likely to report imipenem and xmeropenem as susceptible than participants using automated methods.

Specimen 3684 contained a strain of *P. aeruginosa* resistant to ciprofloxacin, gentamicin, tobramycin, carbapenems and piperacillin-tazobactam (Table 8.4). A good concordance of results was obtained for all agents except ceftazidime and piperacillin-tazobactam. The carbapenem resistance in this isolate is likely to be mediated by porin loss/efflux as no known carbapenemase enzyme is present.

Table 8.4 *P. aeruginosa* (specimen 3684): 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) determined by the reference laboratory	Intended interpretation	Percentage of laboratories giving the correct result																	
		EUCAST/ CLSI	Albania (7)	Armenia (5)	Azerbaijan (3)	Belarus (9)	Bosnia and Herzegovina (9)	Georgia (10)	Kyrgyzstan (6)	Montenegro (9)	Republic of Moldova (12)	Russian Federation (40)	Serbia (21)	Tajikistan (4)	The former Yugoslav Republic of Macedonia (19)	Turkey (81)	Turkmenistan (3)	Ukraine (3)	Uzbekistan (6)	Kosovo[a] (7)
Identification			100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	83	100
Amikacin	4	S/S	100	100	100	100	100	90	100	100	100	91	91	100	100	99	67	100	83	86
Ceftazidime	8	S/S	0	100	67	0	22	60	67	22	25	35	33	0	33	47	100	0	50	57
Ciprofloxacin	32	R/R	100	100	100	100	100	100	100	100	92	100	100	50	100	100	100	100	83	100
Colistin	2	S/S	0	100	–	100	100	89	–	100	100	100	100	–	92	100	–	100	–	100
Gentamicin	≥128	R/R	100	100	100	100	100	100	100	100	100	100	100	100	100	99	100	100	83	100
Imipenem	32	R/R	100	100	100	100	100	100	100	100	92	97	100	–	95	100	67	100	67	100
Levofloxacin	–	R/R[b]	100	100	100	100	100	100	100	100	100	100	100	100	94	100	100	100	100	100
Meropenem	32	R/R	100	100	100	100	100	100	100	100	100	97	100	–	100	100	100	100	83	100
Piperacillin-tazobactam	64	R/I	100	0	100	78	44	40	100	0	67	64	91	–	65	76	–	100	–	50
Tobramycin	≥128	R/R	100	80	100	100	100	100	100	100	100	100	100	–	100	100	100	100	100	100

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

[b] Results based on participants' consensus, because no reference laboratory results are available.

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

Ceftazidime was susceptible by both EUCAST and CLSI breakpoints (minimal inhibitory concentration = 8 mg/L); however, the participants reported variable results (39.2% susceptible, 14.1% intermediate and 46.7% resistant). Participants using CLSI methodology were more likely to report ceftazidime as resistant or intermediate than participants using EUCAST methodology.

The organism was resistant and intermediate to piperacillin-tazobactam by EUCAST and CLSI breakpoints, respectively. Although concordance for this combination was good overall, participants using EUCAST methodology were more likely to report piperacillin-tazobactam as resistant than participants using CLSI methodology. In line with differences in breakpoints, participants following EUCAST guidelines were more likely to report intermediate or resistant than those following CLSI guidelines. Participants using disk diffusion methodology were also more likely to report this isolate susceptible than those using an automated method.

The participants demonstrated the best performance for this organism in regard to correct identification; only one laboratory among 254 failed to identify the strain at the species level yielding a correct identification rate of >99%.

Specimen 3685 was an MRSA containing the *mecC* gene which is responsible for methicillin resistance (Table 8.5). Accordingly, the strain was resistant to beta-lactam agents and susceptible to all other antibiotics examined. A good concordance was achieved with all agents tested except cefoxitin and oxacillin. The organism was resistant to cefoxitin by EUCAST and CLSI breakpoints and resistant to oxacillin by CLSI breakpoints. For cefoxitin, participants reported the following results: 38.4% susceptible, 0.5% intermediate and 61.1% resistant. There was no overall difference in results obtained using EUCAST methods compared with CLSI methods. The poor performance in detecting methicillin resistance due to acquisition of the *mecC* gene revealed the need for improving the laboratory methods to better identify this novel resistance mechanism. All but four laboratories correctly identified the strain, of which three identified the strain as *S. epidermidis* highlighting the need to review the laboratory procedures for the reliable differentiation of *S. aureus* from coagulase-negative staphylococci. The remaining one laboratory identified the strain as *A. baumannii*.

Table 8.5 *S. aereus* (specimen 3685): 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) determined by the reference laboratory	Intended interpretation EUCAST/ CLSI	Percentage of laboratories giving the correct result																	
			Albania (7)	Armenia (5)	Azerbaijan (3)	Belarus (9)	Bosnia and Herzegovina (9)	Georgia (10)	Kyrgyzstan (6)	Montenegro (9)	Republic of Moldova (12)	Russian Federation (40)	Serbia (21)	Tajikistan (4)	The former Yugoslav Republic of Macedonia (19)	Turkey (81)	Turkmenistan (3)	Ukraine (3)	Uzbekistan (6)	Kosovo[a] (7)
Identification			100	80	100	100	100	100	100	100	100	98	100	50	100	100	100	100	100	100
Cefoxitin	16	R/R	100	0	0	50	22	40	83	67	83	55	81	–	79	58	–	100	0	83
Ciprofloxacin	0.25	S/S	86	100	67	89	100	100	100	100	92	94	95	100	79	96	67	100	83	100
Clindamycin	<0.12	S/S	100	80	100	78	100	100	83	100	100	85	100	–	79	91	67	100	100	57
Erythromycin	<0.25	S/S	86	100	67	100	100	100	83	100	100	94	100	100	95	91	100	100	83	86
Fusidic acid	<0.12	S/–	100	100	100	88	100	100	–	100	100	95	100	100	88	100	–	100	–	100
Gentamicin	0.5	S/S	86	100	100	89	100	100	40	89	67	91	95	75	95	62	67	100	100	86
Oxacillin	–	–/R	–	0	100	56	14	0	–	100	40	67	88	–	86	51	–	100	67	57
Penicillin	>0.5	R/R	75	100	100	88	89	70	100	100	100	93	100	–	100	99	33	100	100	100
Rifampicin	<0.008	S/S	50	100	100	89	100	100	100	80	100	71	76	–	75	84	100	100	100	100
Teicoplanin	0.5	S/S	–	–	–	88	100	100	–	100	100	100	100	–	100	100	–	100	–	100
Tetracycline	0.25	S/S	86	100	100	89	100	100	100	100	83	100	100	100	89	99	100	100	100	86
Vancomycin	1	S/S	–	100	100	89	100	100	–	100	100	96	100	50	93	99	–	100	0	75

[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 3686 was an *A. baumannii* complex strain susceptible to amikacin, colistin, imipenem, meropenem and tobramycin but resistant to ciprofloxacin and gentamicin (Table 8.6). A good consensus of results was achieved among the participants with all of the antimicrobial agents tested except for doripenem. The performance of the participating laboratories in regard to identifying the strain was reasonably high; 91% of the participants correctly identified the strain at the species level and an additional 7% at the genus level. A few laboratories (n = 6) demonstrated misidentifications (*Klebsiella* spp., n = 2; *E. coli*; n = 1, *P. aeruginosa*, n = 1; *S. aureus*, n = 1; *Streptococcus* spp., n = 1) mainly suggesting problems in processing of the specimens rather than lack of laboratory capacity.

Table 8.6 *A. baumannii* complex (specimen 3686): 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) determined by the reference laboratory	Intended interpretation	Percentage of laboratories giving the correct result																	
		EUCAST/ CLSI	Albania (7)	Armenia (5)	Azerbaijan (3)	Belarus (9)	Bosnia and Herzegovina (9)	Georgia (10)	Kyrgyzstan (6)	Montenegro (9)	Republic of Moldova (12)	Russian Federation (40)	Serbia (21)	Tajikistan (4)	The former Yugoslav Republic of Macedonia (19)	Turkey (81)	Turkmenistan (3)	Ukraine (3)	Uzbekistan (6)	Kosovo[a] (7)
Identification			100	100	67	100	89	90	100	78	100	98	91	0	79	96	100	100	67	71
Amikacin	4–8	S/S	100	100	67	100	100	60	100	89	83	75	81	50	87	68	50	100	83	71
Ciprofloxacin	32–≥128	R/R	100	100	100	100	100	100	100	100	100	100	100	50	100	100	100	100	100	100
Colistin	0.5–1	S/S	–	100	–	89	100	100	–	100	100	100	100	–	100	99	–	100	–	100
Doripenem	–	R/Rb	33	–	–	83	0	–	–	100	–	44	71	–	0	36	33	0	–	100
Gentamicin	≥128	R/R	100	60	100	89	100	100	60	100	67	100	95	100	100	99	33	100	83	100
Imipenem	1–2	S/S	17	100	67	100	88	90	100	100	83	84	100	100	100	93	100	100	100	86
Meropenem	2	S/S	17	60	100	75	88	80	0	89	18	69	95	–	79	95	0	100	17	20
Tobramycin	2	S/S	100	100	100	89	100	56	80	43	92	83	82	–	94	89	50	100	100	67

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

[b] Results based on participants' consensus, because no reference laboratory results are available.

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

Specimen 3687 was a strain of *S. pneumoniae* which was resistant to erythromycin and clindamycin, but susceptible to all other agents examined (Table 8.7). A good consensus of results was achieved with all of the agents tested with no significant issues arising. Satisfactory performance was obtained for the identification, and 248 of 254 (98%) participants correctly identified the strain as *S. pneumoniae*.

Table 8.7 *S. pneumoniae* (specimen 3687): 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) determined by the reference laboratory	Intended interpretation	Percentage of laboratories giving the correct result																	
		EUCAST/ CLSI	Albania (7)	Armenia (5)	Azerbaijan (3)	Belarus (9)	Bosnia and Herzegovina (9)	Georgia (10)	Kyrgyzstan (6)	Montenegro (9)	Republic of Moldova (12)	Russian Federation (40)	Serbia (21)	Tajikistan (4)	The former Yugoslav Republic of Macedonia (19)	Turkey (81)	Turkmenistan (3)	Ukraine (3)	Uzbekistan (6)	Kosovo[a] (7)
Identification			100	100	100	100	100	100	100	100	100	100	100	0	100	100	100	100	83	100
Cefotaxime	≤0.015	S/S	100	100	50	100	100	100	100	100	100	96	100	–	93	100	–	100	83	100
Cefotaxime (meningitis)	–	S/S	100	100	100	100	100	100	100	100	100	96	100	–	92	100	–	100	100	100
Cefotaxime (pneumonia)	–	S/S	100	100	100	100	100	100	100	100	100	100	100	–	92	100	–	100	100	100
Ceftriaxone	0.03	S/S	100	100	50	100	100	100	100	100	100	96	100	100	100	100	100	100	83	100
Ceftriaxone (meningitis)	–	S/S	100	100	100	100	100	100	100	100	100	96	100	–	100	97	–	100	100	100
Ceftriaxone (pneumonia)	–	S/S	100	100	100	100	100	100	100	100	100	100	100	–	100	100	–	100	100	100
Clindamycin	–	R/Rb	100	100	100	89	89	78	100	100	92	88	100	0	100	90	100	100	100	100
Erythromycin	>2	R/R	100	100	100	100	100	80	100	100	92	97	100	0	94	92	100	100	60	100
Levofloxacin	1	S/S	83	100	67	100	100	100	100	100	100	97	100	–	100	99	100	100	100	100
Moxifloxacin	≤0.12	S/S	83	100	–	100	100	100	50	100	100	93	100	–	94	100	100	100	83	100
Norfloxacin	–	S/Sb	100	100	–	100	100	100	100	100	100	100	100	–	100	100	–	100	100	100
Oxacillin	–	S/S	100	60	67	100	100	100	100	100	100	100	95	67	92	87	100	100	60	71
Penicillin	0.015	S/S	100	100	0	100	100	100	–	100	100	86	100	0	86	94	–	100	100	83
Penicillin (meningitis)	–	S/S	100	100	–	100	100	100	–	100	50	78	100	–	85	90	–	100	100	100
Penicillin (pneumonia)	–	S/S	100	100	–	100	100	100	–	100	100	91	100	–	85	95	–	100	100	100

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

[b] Results based on participants' consensus, because no reference laboratory results are available.

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


CHAPTER
9

Concluding remarks

The third CAESAR annual report reflects the continuing progress of CAESAR as a mobilizer, a network, an initiator and an innovator. Through CAESAR activities, decision-makers are engaged to acknowledge the importance of surveillance and to provide the legislative support needed to make it an integral part of the national health system. Countries assign the role of national AMR reference laboratory to the institution that is best placed to serve the national surveillance system, together with the public health institute, and provide support to the laboratory network. The national reference laboratory is supported to fulfil its central role through training, trouble-shooting and twinning activities. EQA is provided and the importance of national external and internal quality assessments is stressed.

The CAESAR network includes experienced professionals, as well as those recently assigned to new roles and responsibilities, and creates opportunities to meet and learn from each other during national and international meetings and workshops. In countries where treatment is mostly empirical without the benefit of diagnostic support, proof-of-principle studies are initiated to stimulate routine sampling to support treatment decisions, to improve the capacity of the laboratories, to increase communication between microbiologists and clinicians, and to lay the foundation for local and national surveillance. The transition from paper-based to electronic recording is promoted and supported through data management and analysis training.

Acknowledging differences in the quality of the reported data, assessed following clear criteria, is an important innovation of the CAESAR network. Not only does it remind the reader to be cautious when interpreting the data, it also lowers the threshold for sharing data while providing motivation to improve the system guided by the criteria used to assess data quality.

Of course, the entire process is not nearly as smooth or linear as presented here, and each country has its own challenges and unique context. Nonetheless, in essence, these are the programme elements of the CAESAR network that work towards sustained local, national, regional and global surveillance.

The results presented in this report illustrate that the overall approach is working. Since the last CAESAR report published in 2016, several accomplishments have taken place.

- More national AMR reference laboratories are in place.
- Two more countries provided national data to the CAESAR network.
- The data quality from two countries, Bosnia and Herzegovina and Serbia, improved from level B to level A.
- One pathogen was added to those under surveillance.
- Participation in the EQA has increased and the results have improved.
- More countries have started or are preparing a proof-of-principle study.

Though considered by many as small steps, these are all big achievements, brought about by dedicated professionals and colleagues in- and outside the countries.

In the coming years, CAESAR will continue to respond to the needs of countries and to adapt to new situations by learning from its successes and mistakes. The surveillance infrastructure being built through CAESAR activities will enable countries to incorporate additional specimens and pathogen–antibiotic

combinations as relevant, as well as pave the way for full participation in GLASS. For those countries/areas that are generating national AMR data through their surveillance networks, the data give important indications for the presence of highly resistant microorganisms of public health importance in clinical settings participating in the country. For example, the high levels of carbapenem resistance in *K. pneumoniae* and high proportions of multidrug-resistant *Acinetobacter* spp. in several countries indicate the need for improved infection prevention and control measures in these clinical settings. It is encouraged that the national focal points and other stakeholders use these data to advocate for the implementation of local and national policies that will make these improvements possible.

With the control of AMR continuing to be 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 health care settings and the community.

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ANNEX
1

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)*.

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.

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;
- are commonly seen as urinary and respiratory tract infections and, among neonates, bloodstream infections;
- are a common cause of gram-negative bloodstream infections; and
- can spread readily between patients, leading to nosocomial outbreaks, which 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.

Pseudomonas aeruginosa

P. aeruginosa:

- is a non-fermentative gram-negative bacterium that is ubiquitous in aquatic environments in nature;
- 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;
- commonly causes hospital-acquired pneumonia (including ventilator-associated pneumonia) and bloodstream and urinary tract infections;
- is difficult to control in hospitals and institutional environments, because of its ubiquity, enormous versatility and intrinsic tolerance to many detergents, disinfectants and antimicrobial compounds;
- causes bacterial complication among people with cystic fibrosis, leading to chronic colonization and intermittent exacerbation of the condition with, for example, bronchiolitis and acute respiratory distress syndrome; and
- is common in burn units, where eradicating colonizing strains with classic infection control procedures is almost impossible.

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). 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;
- are not considered ubiquitous in nature, in contrast to many species of the *Acinetobacter* genus; and
- have low carrying rates on the skin and in the faeces.

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.

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 one of the most important human pathogens;

- can cause a variety of infections – most notably skin, soft tissue, bone and bloodstream infections –and is also the most common cause of postoperative wound infections; and

- produces toxic factors (some strains) 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 health care 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.

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;

- causes other common, mild, self-limiting infections such as acute otitis media but also extends to cases of invasive disease with high mortality such as meningitis; and

- is associated with the highest case-fatality rate among the bacterial causes of meningitis, and is the most likely infection to leave survivors with permanent residual symptoms.

It caused about 826 000 deaths (582 000–926 000) among children 1–59 months old. The clinical burden of pneumococcal infection is concentrated among the oldest and youngest sections of the population. For HIV-negative children, pneumococcal infection corresponds to 11% of all deaths in this age group *(4)*.

It is 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.

Enterococcus faecium and *Enterococcus faecalis*

Enterococci:

- belong to the normal bacterial microbiota of the gastrointestinal tract of both humans and other animals, are usually low-pathogenic but can cause invasive disease under certain circumstances;

- can act as true pathogens and not only as opportunistic commensals, as high-risk clones were recently recognized;

- can cause a variety of infections, including endocarditis, bloodstream and urinary tract infections, and are associated with peritonitis and intra-abdominal abscesses;

- contribute to increasing mortality as well as additional hospital stay;

- emerge as important nosocomial pathogens, as documented in epidemiological data collected over the last two decades and 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*, with the latter clones isolated from farm animals; and

- are highly tenacious and thus easily disseminate in the hospital setting and infections caused by resistant strains are difficult to treat.

E. faecalis and *E. faecium* cause the vast majority of clinical enterococci infections in humans. 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.

Salmonella

Salmonella:

- is a major cause of foodborne illness throughout the world;

- is a zoonotic pathogen and can thus be found in the intestines of many food-producing animals such as poultry and pigs, and infection is usually acquired by consumption of contaminated water or food of animal origin such as undercooked meat, poultry, eggs and milk;

- can also contaminate the surface of fruits and vegetables through contact with human or animal faeces, which can lead to foodborne outbreaks; and

- mostly causes gastroenteritis, while some strains, particularly *Salmonella enterica* serotypes Typhi and Paratyphi, are more invasive and typically cause enteric fever – a more serious infection that poses problems for treatment due to antibiotic-resistant strains in many parts of the world.

CAESAR focuses on nontyphoidal Salmonella, because these are the main diarrhoeal pathogens transmitted via the food chain. In many countries, the incidence of nontyphoidal Salmonella infections has increased markedly in recent years, for reasons that are unclear. One estimate suggests that there are around 94 million cases, resulting in 155 000 deaths, of nontyphoidal Salmonella gastroenteritis each year. The majority of the disease burden, according to this study, is in the WHO South-East Asian Region and the WHO Western Pacific Region *(5)*.

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ANNEX
2

Sources of errors and bias in AMR 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 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 to a certain extent. 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 12 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 expected amount of deviation from reality due to 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 deviation.

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 plated out when testing antibiotic susceptibility using disk diffusion will vary every time. Random variation in the concentration of the inoculum will result in either larger or smaller inhibition zones. Depending on the specific breakpoints, this may affect the categorization into susceptible/intermediate/resistant. When combining all results, this could lead to over- or underestimating a resistance proportion. In general, this deviation will be a mix of over- or underestimation, and the deviations will cancel each other out when results are combined. Again, sample size will reduce the effect of random over- and underestimations. The amount of measurement variation 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 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 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 are 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 or sepsis should be sampled. Including only special patient categories (such as 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 and therefore more likely to be infected with a resistant pathogen. The use of microbiological diagnostics is subject to financial and logistical constraints outside the control of a 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 laboratory capacity is limited or results are not communicated timely enough to influence clinical decision-making. Furthermore, sampling of patients may occur after antimicrobial therapy has already been started or following self-treatment in settings where over-the-counter sales of antibiotics is common, resulting in an underrepresentation of infections that respond to first-line antibiotics.

The timing of sample collection may also influence the resistance proportions found. Ad hoc or convenience sampling for a limited time period, especially during outbreaks, will bias results. Any influence of outbreaks of antibiotic-resistant bacteria or seasonal variation can be overcome by sampling throughout the year.

Bias from laboratory procedures – measurement error

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

Correctly identifying species is 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 there are clear indications of problems with species identification. For example, a high proportion 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 accurate 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 their 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 or different versions of standards may be problematic.

Importantly, susceptibility to all indicated antimicrobial agents should be tested for each isolate included in surveillance. Differential or sequential testing, 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 includes only the first isolate per microorganism per person per year in analyses, 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 makes comparison between laboratories or countries problematic. To prevent varying application of expert rules from biasing the results and to standardize the interpretation, CAESAR collects antibiotic susceptibility testing results as tested.

Recommended reading

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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 selecting 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, all patients presenting with a bloodstream infection

The WHO Regional Office for Europe

The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

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