World Health Organization
REGIONAL OFFICE FOR Europe

Central Asian and Eastern European Surveillance of Antimicrobial Resistance

Annual report 2018

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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 10 countries in the WHO European Region– Belarus, Bosnia and Herzegovina, Georgia, Montenegro, the Russian Federation, Serbia, Switzerland, the former Yugoslav Republic of Macedonia, Turkey and Ukraine – and Kosovo (in accordance with United Nations Security Council resolution 1244 (1999)). The fourth CAESAR report includes for the first time resistance data from Ukraine, it provides a summary of the first five years of CAESAR external quality assessment (2013-2017) and presents preliminarily results of a proof-of-principle project in Armenia. It furthermore includes a reader's guide 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 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.

Keywords

DRUG RESISTANCE, MICROBIAL
ANTI-INFECTIVE AGENTS
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Foreword

All 53 Member States of the WHO European Region adopted the European strategic action plan on antibiotic resistance in September 2011, and the Global action plan on antimicrobial resistance (AMR) was endorsed in May 2015 at the Sixty-eighth World Health Assembly. Important elements of both these plans are to: strengthen surveillance of antibiotic resistance, promote strategies for the rational use of antibiotics and strengthen surveillance of antibiotic consumption, and strengthen infection prevention and control and surveillance of antibiotic resistance in health care settings.

The Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) network originated in 2012 as a partnership between 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 with the goal to deliver on the strategic priorities of the regional and global action plan, and to create a network that would allow for the establishment and strengthening of AMR surveillance systems in the whole European Region.

Surveillance data serves as a benchmark for the antimicrobial resistance situation in participating countries and areas; sharing surveillance data enables an open dialogue about challenges, differences and communalities, and it allows to track progress and effectiveness of policy and action over time, as the surveillance systems mature.

In the early stages of the CAESAR network, 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. Capacity-building needs are then addressed through technical trainings and workshops, exchange visits, and other types of partnerships, which are tailored to the individual situation. Thus, the CAESAR network promotes coordination, planning, quality of laboratories and surveillance capacity in countries and areas where a need for that has been identified.

Significant efforts have been made to strengthen national AMR reference laboratories to prepare them for their role in strengthening and maintaining national laboratory networks, ensuring the quality of their work, providing evidence-based testing services and centralizing data collection for surveillance purposes. These efforts contribute to the WHO Global Antimicrobial Resistance Surveillance System, launched in October 2015, not only in supporting the standardization and harmonization of the ways to collect, analyse and share data on AMR at global level, but also in meeting and addressing challenges that countries in other parts of the world may face when they embark on a similar endeavour.

These efforts contribute to the growing awareness of AMR as one of the major threats to global human and animal health and to the Sustainable Development Goals. This awareness is based on a growing body of evidence provided by research and surveillance from an increasing number of countries and areas around the world.

This fourth CAESAR report includes progress updates for all 19 European countries and Kosovo (in accordance with United Nations Security Council resolution 1244 (1999)) engaged in the CAESAR network. Ten countries and one area currently report AMR data to CAESAR. Building on partnership and alliances with partners such as the European Centre for Disease Prevention and Control (ECDC) and the Global Antimicrobial Resistance Surveillance System (GLASS), we will work towards expanding the number of reporting countries, as well as improving the quality of data reported for future editions of this report.

It remains our goal to monitor the progress of AMR surveillance in the Region, to guide AMR control policies based on the evidence generated, to provide 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 colleagues in 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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Abbreviations

A. baumannii	*Acinetobacter baumannii*
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
EEA	European Economic Area
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*
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
PoP project	proof-of-principle AMR routine diagnostics surveillance project
P. aeruginosa	*Pseudomonas aeruginosa*

S. aureus	*Staphylococcus aureus*
S. pneumoniae	*Streptococcus pneumoniae*
spp.	species (for specific bacteria)
susceptibility	susceptibility of a pathogen to an antimicrobial agent I intermediate I+R intermediate or resistant R resistant S susceptible
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 an 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 provides 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, coordinated by the European Centre for Disease Prevention and Control in the European Union and European Economic Area countries.

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. Ten countries (Belarus, Bosnia and Herzegovina, Georgia, Montenegro, the Russian Federation, Serbia, Switzerland, the former Yugoslav Republic of Macedonia, Turkey and Ukraine) and Kosovo[1] submitted AMR data for 2017 to the CAESAR database. Ukraine reported AMR data for the first time during this reporting period.

CAESAR collects antimicrobial susceptibility testing data of isolates from blood and cerebrospinal fluid for nine bacterial pathogens of public health and clinical importance: *Escherichia coli*, *Klebsiella pneumoniae, Salmonella* species (spp.), *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecalis* and *Enterococcus faecium*. Chapters 5 and 6 present proportions of resistance observed among these reported pathogens in countries and one area that submitted data to CAESAR. Chapter 7 presents maps of the European Region, showing the proportions of resistance for selected pathogen–antibiotic combinations in the CAESAR and European Antimicrobial Resistance Surveillance Network countries. Annex 1 describes the pathogens under CAESAR surveillance and the main infections caused by each of the pathogens.

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 assessed the level of evidence of the data 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). For example, in 2016 both Bosnia and Herzegovina and Serbia progressed from level B to level A data, by expanding their surveillance network to cover all hospital types and by adopting the European Committee on Antimicrobial Susceptibility Testing methodology as the national standard for antimicrobial susceptibility testing.

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

In addition to the countries and area currently reporting AMR data to CAESAR, other countries are preparing and building the necessary capacity for AMR surveillance, which will enable them to report AMR data to CAESAR in the near future. Chapter 2 describes the member-specific progress being made within the CAESAR network. Many countries are taking the necessary steps to set up or strengthen their national AMR surveillance system, enabling them to get a better insight into their AMR situation. Most countries still face many challenges, and strong political support is needed to continue making progress.

One challenge 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. A successful pilot proof-of-principle project took place in Georgia between July 2015 and December 2016, which formed the basis for the multicentre collaborative surveillance network that now provides national AMR data for CAESAR. A similar proof-of-principle project started in Armenia in June 2017. Chapter 8 describes the experiences and challenges of implementing this project, as well as preliminary results.

Chapter 9 describes the results from the CAESAR external quality assessment exercise conducted in 2017. Overall, the results were good, and the number of participants has increased from 120 laboratories in eight countries/areas in 2013 to 248 laboratories in 18 countries/areas in 2017. Over these years, the antimicrobial susceptibility testing results obtained for the bacterial isolates revealed similar problems: detection of borderline susceptibility, interpretation of results of specific tests and the use of inappropriate methods. Such problems, when encountered, should not discourage: they should serve as motivation to implement the necessary measures for improvement. Accordingly, substantial progress has been achieved following the widespread implementation of up to-date methodological guidelines. The proportion of laboratories using the European Committee on Antimicrobial Susceptibility Testing guidelines increased from 14% in 2013 to 74% in 2017. Overall, this increase is reflected in the good work to identify 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 or areas that do not have a comprehensive surveillance system. However, the high percentages of resistance and the resistance profiles in this report strongly support the global call for action and emphasize the importance of good clinical practice in slowing the further development of AMR. Using surveillance data to initiate and monitor AMR control efforts in clinical settings and raising awareness among policy-makers and the public are essential in fighting AMR.


CHAPTER
1

Introduction

The rapid emergence and spread of antimicrobial resistance (AMR) is one of the biggest threats to global health, with many common infections becoming resistant to the antimicrobial medicines previously used to treat them. AMR poses a fundamental threat to human and animal health and the achievement of the Sustainable Development Goals. As currently available antimicrobial agents lose their effectiveness and the new drug development pipeline runs dry, many types of infection are becoming life threatening again and modern medicine procedures hazardous.

All 53 Member States in the WHO European Region adopted the European strategic action plan on antibiotic resistance (2011–2020) *(1)* in September 2011, and the Global action plan *(2)* on AMR was endorsed in May 2015 at the Sixty-eighth World Health Assembly. These two action plans govern WHO's work on AMR in the Region.

Surveillance of AMR is considered the cornerstone of both these action plans as an essential tool for assessing the sources of and trends in AMR, informing policies and interventions, and monitoring their impact. Countries of the European Union (EU) and the European Economic Area (EEA) have performed antibiotic resistance surveillance for almost two decades. Since 2010, the European Centre for Disease Prevention and Control (ECDC) through the European Antimicrobial Resistance Surveillance Network (EARS-Net) has coordinated this surveillance.

In 2011, when the European strategic action plan was adopted, only a few European countries outside of EARS-Net systematically collected and shared data on antibiotic resistance. 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 and areas in setting up or strengthening national AMR surveillance. Two or more experts represent each entity in the CAESAR coordination group.

In close collaboration with the ECDC and using methodology compatible to EARS-Net, CAESAR expands the surveillance conducted in the EU/EEA to obtain a pan-European overview of the trends and sources of AMR. Currently, 19 countries – 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 – and Kosovo[1] are engaged in the CAESAR network, with more than 50% of these countries and one area providing data.

The CAESAR network supports the establishment of AMR surveillance networks and helps to improve the quality of laboratory research, manage data, and analyse and report data from existing surveillance networks. Support is tailored to the development phase and specific needs of the surveillance system. In countries/areas with officially established surveillance systems, emphasis is placed on harmonizing laboratory methods and streamlining data management. In countries where antibiotic susceptibility testing is routinely performed in clinical settings but the data are not yet collected at national level, emphasis is placed on setting up a surveillance network and standardizing data collection in parallel with harmonizing laboratory methods. In countries that underutilize bacteriological laboratory diagnostics, the focus is on building laboratory capacity and diagnostic stewardship through the implementation of proof-of-principle projects.

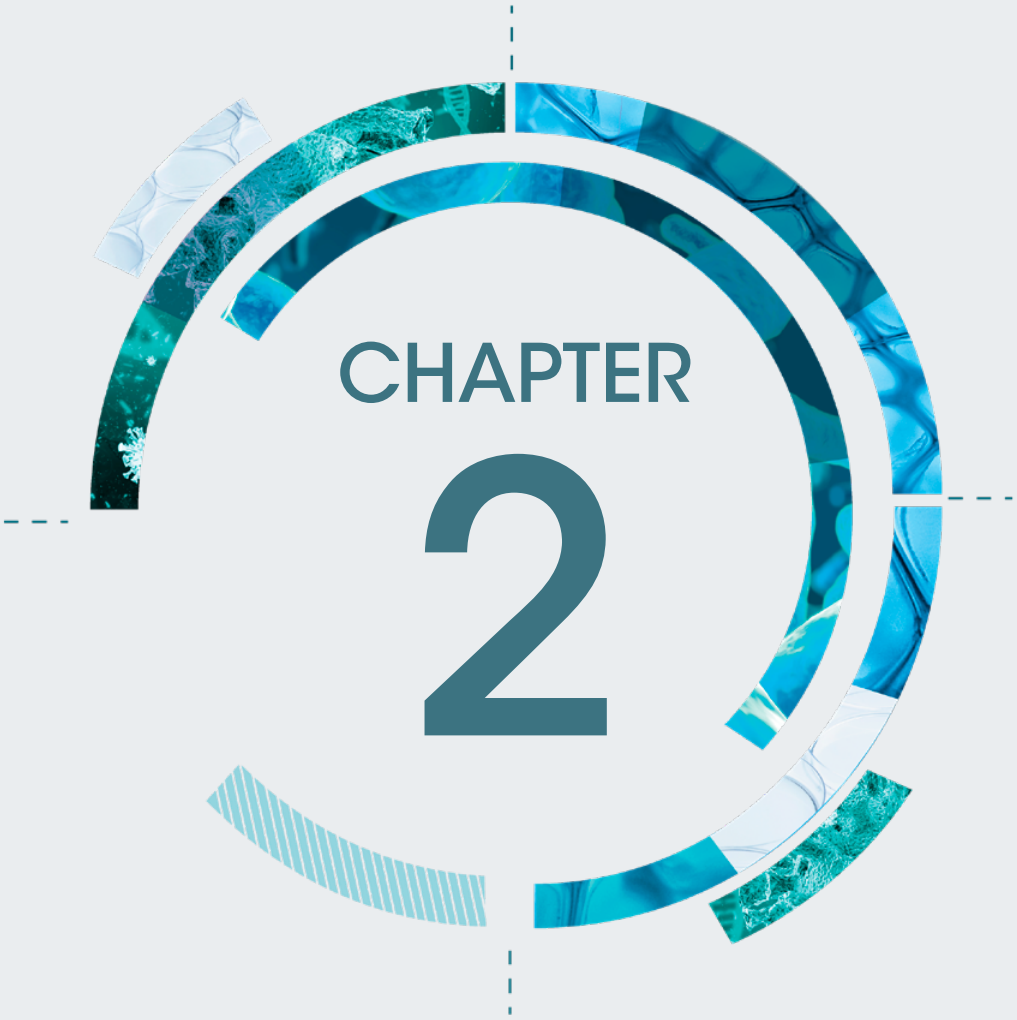
[1] All references to Kosovo should be understood as references to Kosovo in accordance with United Nations Security Council resolution 1244 (1999), and the data are presented in a separate chapter as area-specific data on AMR (Chapter 6).

The main activities of the CAESAR coordination group include (i) annual CAESAR network meetings; (ii) an annual (beginning in 2013) external quality assessment (EQA) exercises; (iii) release of the CAESAR manual (2015); (iv) training courses on laboratory quality management; (v) training of staff of AMR reference laboratories; and (vi) proof-of-principle studies. The CAESAR network has contributed to the improvement of surveillance networks by organizing multicountry and national workshops that focused on surveillance methodology, data management, and analysis and interpretation of AMR surveillance data.

Since 2013, the CAESAR network has held annual meetings, where all AMR focal points from participating CAESAR countries/areas can discuss AMR trends, network development, EQA results, and specific issues and challenges related to AMR surveillance. Since 2015, the CAESAR network has provided technical and financial assistance in organizing meetings of AMR surveillance networks. The purpose of the meetings is to discuss the data obtained by local surveillance, EQA results and efforts to improve surveillance and assess the necessary conditions for capacity building.

This fourth CAESAR annual report includes, for the first time, Ukraine as the most recent addition to CAESAR countries that provide AMR data to the network. Other members of the CAESAR network are building the necessary capacity and are preparing to provide AMR surveillance data.

These efforts will also help populate the WHO Global Antimicrobial Resistance Surveillance System (GLASS). To avoid duplication and an additional burden on network participants, by agreement with GLASS, CAESAR provides the latest consolidated AMR data on behalf of the countries and areas enrolled in GLASS.


CHAPTER
2

Progress in CAESAR

At present, Kosovo[1] and 19 countries are engaged 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.

Kosovo[1] and 10 of these countries currently report AMR data to CAESAR: Belarus, Bosnia and Herzegovina, Georgia, Montenegro, the Russian Federation, Serbia, Switzerland, the former Yugoslav Republic of Macedonia, Turkey and Ukraine.

Countries and areas in the CAESAR network are at various stages of developing their surveillance system, actively building or strengthening the necessary capacity for AMR surveillance, even those that already report data internationally. In order to stimulate progress, CAESAR encourages countries and areas that are still developing their surveillance capacity to share data once their system has reached a reasonable level of maturity. CAESAR provides an assessment of key indicators of each AMR surveillance system to guide the reader on how to interpret the data according to its validity and representativeness (Chapter 4). To help build capacity, the assessment identifies areas for improvement of the system.

The methods used in CAESAR are compatible with those used by the ECDC (through EARS-Net). This allows comparisons between countries/areas across the two networks and provides an overview of the AMR situation based on all available data for the European Region (Chapter 7). Generation of reliable and comparable data is directly linked to informed policy development and decision-making, and can be used to measure the effectiveness of AMR interventions.

2.1 Indicators of progress in CAESAR

To monitor progress, AMR focal points are asked each year to fill in a short questionnaire, reporting on the AMR activities performed and progress achieved. The questionnaire for 2018, as in previous years, is divided into four main sections: (i) overall coordination; (ii) the surveillance network and AMR reference laboratory; (iii) quality control; and (iv) guidelines for antimicrobial susceptibility testing (AST). Each section consists of a set of indicators reflecting the stepwise approach, needed to develop and strengthen national AMR surveillance (Table 2.1). The results of the 2018 questionnaire are described in this chapter, as submitted 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 developing a national action plan on AMR that incorporates surveillance activities. Implementing these plans requires capacity building through long-term investments, such as 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.

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

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 established
	AMR action plan	AMR action plan developed
	AMR action plan funds	Dedicated funds are available to implement the AMR action plan
	AMR action plan implementation	Active implementation of AMR action plan is ongoing
	AMR action plan monitoring and evaluation	Implementation of action plan is monitored and evaluated
Surveillance network and AMR reference laboratory	Coordination 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 reference
	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 assessment system in place
AST guidelines	Current AST guidelines	Majority of laboratories in the country/area use the current version of the AST guidelines (European Committee on Antimicrobial Susceptibility Testing (EUCAST)/Clinical and 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	AST committee 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 established	AMR action plan developed	Dedicated funds are available to implement AMR action plan	Active implementation of AMR action plan is ongoing	Implementation of action plan is monitored and evaluated
ALB	✓	⚙	⚙[c]	✗	✗	✗
ARM	✓	⚙	✓	⚙	⚙	✓
AZE	✓	⚙	⚙	✓	✗	✗
BLR	✓	⚙	⚙	⚙	✓	✓
BIH	✓	⚙	⚙	✗	✗	✗
GEO	✓	✓	✓	✓	✓	✓
KAZ	⚙	✗	⚙	NA	✗	✗
KGZ	✓	✓	⚙	✗	⚙	⚙
MNE	✓	✓	✓	✓	✓	✓
MDA	✓	✓	⚙	⚙	✗	✗
RUS	✓	✓	✓	⚙	⚙	⚙
SRB	✓	✓	⚙	✗	✗	✗
SWI	✓	✓	✓	✓	✓	✓
TJK	✓	✓	⚙	✗	⚙	⚙
MKD	✓	✓	✓	⚙	✓	⚙
TUR	✓	⚙	✓	⚙	✓	⚙
TKM	✓	✓	✓	⚙	✓	⚙
UKR	✓	✓	⚙	✗	✗	✗
UZB	✓	✓	⚙	✓	⚙	✗
KOS[b]	✓	✓	⚙	⚙	⚙	⚙
No	**0**	**1**	**0**	**6**	**7**	**8**
In progress	**1**	**6**	**12**	**8**	**6**	**7**
Yes	**19**	**13**	**8**	**5**	**7**	**5**

✓: yes; ✗: no; ⚙: in progress; NA: not answered.

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

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

[c] Self-reporting of data may lead to discrepancies between this report and those from previous years.

2.1.1.1 AMR focal points

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

2.1.1.2 Intersectoral coordinating mechanism

In accordance with 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 national 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.

In addition to representatives of relevant government sectors, this committee should include representatives of local professional associations, authorities and leading scientific institutions. This committee is crucial for overall coordination, development and subsequent implementation of a comprehensive national action plan on AMR, and its work could extend beyond antibiotic resistance to cover the entire field of AMR, including antiviral, antiparasitic or antifungal drugs *(2)*.

To date, 12 countries and Kosovo[1] indicated that they have an intersectoral coordinating mechanism in place. Six countries indicated that they are in the process of creating this mechanism, compared with seven countries in 2016 *(3)*.

2.1.1.3 National action plan

In accordance with the 2015 Global action plan on AMR, Member States are called upon to develop a national action plan on AMR by May 2017 *(1)*. Continuous AMR surveillance is crucial in assessing major antibiotic resistance rates of concern, targeting adequate actions to control them and assessing the impact of these actions. Surveillance should therefore have a prominent place in a national action plan to combat AMR. In addition, valid surveillance data can inform empirical treatment guidelines at local and national levels.

To date, 34 countries in the European Region have developed multisectoral national action plans, and WHO and partners continue to support the remaining countries to finalize theirs, as well as with their implementation.

Among the CAESAR network participants, eight countries indicated that they developed an AMR action plan. Moreover, 11 countries and Kosovo[1] indicated that they are in the process of developing an AMR action plan. Five countries indicated that dedicated funds to implement the national action plan are available. Seven countries and Kosovo[1] are in the process of making funds available, and the remaining countries have no funds available to implement their national action plan. Seven countries are actively implementing the national action plan, and five countries and Kosovo[1] are in the process of preparing for their implementation. Five countries are monitoring and evaluating the implementation of their national action plan on AMR. Six countries and Kosovo[1] indicated that they are in the process of setting up monitoring and evaluation of their plans.

2.1.2 Progress on surveillance networks and AMR reference laboratories

2.1.2.1 AMR surveillance network

AMR surveillance networks enable countries to (i) assess their antibiotic resistance situation; (ii) set priorities for infection prevention and control activities; and (iii) develop antibiotic therapy guidelines. Collecting and analysing AMR data according to international standards and sharing these with the international community helps to generate resistance patterns in countries, subregions and regions and to evaluate their development over time. Given the fact that AMR does not respect borders, each country/area may feel a shared responsibility to contribute data that provide an overview of the AMR situation in the European Region.

Table 2.3 AMR focal points in the CAESAR network

Country or area	AMR focal point
Albania	Albana Fico (Director of Institute of Public Health)
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, Department of Clinical Microbiology, University Clinical Centre of Republika 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	Milena Lopicic (Department of Bacteriology, Institute of Public Health)
Republic of Moldova	Olga Burduniuc (Head, AMR Reference Laboratory, National Public Health Agency, Ministry of Health, Labour and Social Protection)
Russian Federation	Roman S. Kozlov (Director, Institute of Antimicrobial Chemotherapy, Smolensk State Medical Academy)
Serbia	Deana Medic (Head, Department for Pyogenic, Respiratory and Urogenital Tract Infections with National Reference Laboratory for AMR; Institute of Public Health of Vojvodina, Center for Microbiology, Novi Sad)
Switzerland	Andreas Kronenberg (Swiss Centre for Antibiotic Resistance, Institute for Infectious Diseases, University of Bern)
Tajikistan	Mahmadali Tabarov (National Coordinator, 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 (General Directorate of Public Health of Turkey Microbiology Reference Laboratories Department, Public Health Institution of Turkey)
Turkmenistan	Gurbangul Ovliyakulova (Head, Department of Acute Dangerous Disease Surveillance, State Sanitary Epidemiology Service, Ministry of Health and Medical Industry)
Ukraine	Iryna Ganzha (Leading Specialist, Department of Coordination with Organs of Central Power and Ministries, Public Health Department, Ministry of Health)
Uzbekistan	Gulnora Abdukhalilova (Head, AMR Reference Centre, Research Institute of Epidemiology, Microbiology and Infectious Diseases)
Kosovo[a]	Lul Raka (Department of Medical Microbiology, Institute of Public Health of Kosovo[a]

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

Collaboration among microbiology laboratories and inter-laboratory standardization are crucial when setting up an AMR surveillance system. The participation of laboratories in the surveillance network not only contributes to the collection of resistance data but also improves significantly the quality of routine AST because it offers EQA, regularly conducted training courses, frequent discussions within the laboratory network and at meetings, and collaboration with international networks. The AMR surveillance teams usually include specialists in epidemiology, microbiology and data management. Ideally, the teams should include staff with a clinical background to ensure good collaboration with the participating hospitals and the practical use of information and results.

Sixteen countries and Kosovo[1] indicated that an institute was formally appointed to coordinate the AMR surveillance network, and 14 countries and Kosovo[1] reported that a surveillance coordination team was formed (Table 2.4). The AMR focal points reported that AMR surveillance teams usually include an average of 4–10 members. The team includes microbiologists, epidemiologists and clinicians. Some teams also include data managers, clinical pharmacologists, laboratory technicians, molecular biologists and coordinators/administrators.

2.1.2.2 AMR reference laboratory

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

Twelve countries nominated an AMR reference laboratory, and four countries and Kosovo[1] are in the process of nomination (Table 2.4). A fully functional AMR reference laboratory is a fundamental component of the surveillance network, taking the lead in introducing, maintaining and setting the standards for AST. Reference laboratories should have the capacity and knowledge to perform confirmatory and specialized testing. The AMR reference laboratories are fully functional in 11 countries and Kosovo[1], whereas five are still in the process of establishing all required functions.

2.1.2.3 AMR surveillance and reporting

Sharing information is one of the most important aspects of an AMR surveillance network and a crucial step in controlling resistance. It facilitates the informed decision-making and actions taken by all relevant stakeholders. AMR results should be widely disseminated to relevant professionals (such as hospital managers, heads of antibiotic or drug committees and heads of infection control committees). This will stimulate the use of the obtained data to guide routine practice (such as treatment regimes, infection prevention and control programmes, and procurement), inform policy and monitor the progress of interventions to control AMR.

Nine countries and Kosovo[1] have an AMR surveillance system in place (Table 2.4). Eight countries indicated that they are developing their AMR surveillance system, following CAESAR methodology. Eight countries and Kosovo[1] periodically publish an AMR surveillance report, compared with six countries in 2016 *(3)*. Thirteen countries and Kosovo[1] hold yearly AMR surveillance network meetings, and 10 countries and Kosovo[1] report AMR data to CAESAR. To date, six countries are enrolled in GLASS.

2.1.3 Progress on quality control

A quality assurance system ensures reliable and reproducible laboratory data. Internal quality control should be a routine procedure performed by participating laboratories to ensure quality testing. It should cover all diagnostic tests and procedures (isolation, identification and sensitivity testing), as well as media production and equipment maintenance. Twelve countries indicated that they have a national laboratory quality assessment system in place (Table 2.5), an increase from 11 in 2016 *(3)*. Five countries and Kosovo[1] reported that they are in the process of establishing a laboratory quality system.

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	✓	✓	✗[c]	✓	✓	✓	✓	✓	✓
TUR	✓	✓	✓	✓	✓	✓	✓	✓	⚙[d]
TKM	✓	⚙	✓	✓	⚙	✗	⚙	✗	✗
UKR	✓	✓	⚙	⚙	⚙	⚙	✗	✓	✓
UZB	✓	✓	✓	⚙	⚙	✗	✓	✗	✗
KOS[b]	✓	✓	⚙[d]	✓	✓	✓	✓	✓	⚙
No	1	1	3	3	2	8	3	7	9
In progress	2	4	5	5	8	3	3	1	5
Yes	17	15	12	12	10	9	14	12	6

✓: yes; ✗: no; ⚙: in progress.

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

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

[c] The laboratory at the Institute for Public Health in the former Yugoslav Republic of Macedonia is performing reference laboratory functions despite the lack of a formal nomination.

[d] Self-reporting of data may lead to discrepancies between this report and those from previous years.

Table 2.5 Quality control

Country/area	Participation in CAESAR EQA	Laboratory quality assessment system in place
Albania	✓	✗
Armenia	✓	⚙
Azerbaijan	✓	✓
Belarus	✓	✓
Bosnia and Herzegovina	✓	✓
Georgia	✓	✓
Kazakhstan	⚙	NA
Kyrgyzstan	✓	⚙
Montenegro	✓	✓
Republic of Moldova	✓	✓
Russian Federation	✓	✓
Serbia	✓	✓
Switzerland	✗	✓
Tajikistan	✓	✓
The former Yugoslav Republic of Macedonia	✓	⚙
Turkey	✓	✓
Turkmenistan	✓	⚙
Ukraine	✓	✓
Uzbekistan	✓	⚙
Kosovo[a]	✓	⚙
No	**1**	**1**
In progress	**1**	**6**
Yes	**18**	**12**

✓: yes; ✗: no; ⚙: in progress; NA: not answered.

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

In addition to internal quality control, regular external monitoring of laboratories in the AMR surveillance network is crucial to assess the quality and reliability of data entering the surveillance system. In addition, the discussion of EQA results provides guidance for laboratories to implement corrective action and strive for continuous improvement. To stimulate the establishment of an EQA system in a country/area, CAESAR offers an annual EQA scheme provided by the United Kingdom National EQA Service for Microbiology

(UK NEQAS). Participating laboratories are recommended to store the EQA isolates, which they can use later to develop their own internal quality control systems. Seventeen countries and Kosovo[1] participated in the CAESAR EQA exercise for 2017, and the results are presented in Chapter 9.

2.1.4 Progress on implementing AST guidelines

All laboratories participating in an 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 has an important task to ensure that these procedures are adequately implemented and to provide regular training courses so that network members are aware of the latest procedures and developments.

In recent years, many CAESAR members have been working on updating and harmonizing their antibiotic susceptibility guidelines. CAESAR recommends the use of EUCAST or CLSI standards. Since EUCAST guidelines are the most widely used in the European Region, all EUCAST documents translated into different languages can be downloaded from the Internet free of charge *(4)*; 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 national antibiotic committee (or a similar working group) that addresses AST methodology issues and ensures the dissemination of annually updated international standards and compliance with these standards by all members of the AMR network *(5)*.

Fifteen countries and Kosovo[1] indicated that they use EUCAST guidelines, with versions ranging from 2013 to 2018 (Table 2.6). Of these, seven use EUCAST guidelines in combination with CLSI or other national guidelines. Three countries (Azerbaijan, Georgia and Turkmenistan) use only CLSI guidelines, while Tajikistan only uses national guidelines. Countries using CLSI guidelines use versions ranging from 2004 onwards. Eight countries indicated that they formed a national antibiotic susceptibility testing committee. Five countries and Kosovo[1] reported that they are in the process of forming such a committee.

Seven countries and Kosovo[1] indicated that more than 50% of laboratories in their surveillance networks use EUCAST breakpoints. Six countries and Kosovo[1] also indicated that more than 50% of laboratories in the surveillance network use the EUCAST disk diffusion method.

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. This can lead to mistakes in treatment and treatment failure and misrepresent the AMR situation in a country or area.

EUCAST has repeatedly evaluated the disk potency of strategically important antibiotic disks for AST from nine international manufacturers; the quality of disks varied both between and within manufacturers. Disks from a few manufacturers were consistently found to be of high quality whereas the opposite was true for others. The EUCAST website presents the evaluation results *(6)*. The work performed by EUCAST provides critical information for the purchase of high-quality laboratory consumables for AST, and clearly shows that quality should be considered as one of the criteria in the tendering process, when purchasing laboratory consumables in general, and for detecting AMR in particular.

Table 2.6 AST guidelines

Country/ area[a]	AST guideline currently used by the majority of laboratories in the country/ area (EUCAST/ CLSI/other)	Year or version of AST guideline used (EUCAST/ CLSI/other)	Percentage of laboratories implementing EUCAST breakpoint	Percentage of laboratories using EUCAST disk diffusion method	An AST committee was formed
ALB	EUCAST	2013, 2016	10–50	>50	✖
ARM	EUCAST/CLSI	2016/2004	<10	<10	✖
AZE	CLSI	2014	<10	<10	✖
BIH	EUCAST	2018	>50	>50	⚙
BLR	EUCAST/CLSI	2015/NA	<10	<10	⚙
GEO	CLSI	NA	10–50	>50	✔
KAZ	EUCAST/other	NA/NA	<10	<10	✖
KGZ	EUCAST	2015	100	100	⚙
MDA	EUCAST	2017	>50	>50	✔
MKD	EUCAST/CLSI	2017/NA	>50	10–50	✔
MNE	EUCAST/CLSI	2017/2016	10–50	10–50	✔
RUS	EUCAST	2017	10–50	10–50	✔
SRB	EUCAST	2017	>50	>50	✔
SWI	EUCAST	NA	>50	NA	✔
TJK	Other	NA	NA	NA	⚙
TKM	CLSI	NA	NA	NA	⚙
TUR	EUCAST	2018	>50	10–50	✔
UKR	EUCAST/CLSI	2018/NA	10–50	>50	✖
UZB	EUCAST/CLSI/ other	2017/NA/NA	NA	<10	✖
KOS[b]	EUCAST	2016	>50	>50	⚙

✔: yes; ✖: no; ⚙: in progress; NA: not answered.

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

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

2.2 Conclusions

Currently, 10 countries and Kosovo[1] are able to provide AMR surveillance data to CAESAR; however, many countries are actively taking the necessary steps to set up or strengthen their AMR surveillance systems, enabling them to better understand the drivers of AMR in their country and take informed action. This chapter shows that many countries in the CAESAR network have made progress. Yet many countries still face a number of challenges, and the solutions are complex and comprehensive, as well as time consuming. Challenges that are often observed include:

- limited human and financial resources;
- the continuous need for training laboratory and hospital personnel and encourage better collaboration between clinicians and microbiologists;
- the need to improve sampling procedures and the use of medical microbiological diagnostics in hospitals;
- the need for standard operating procedures and quality control in laboratory practice;
- the need to include quality in the procurement criteria to ensure high-quality consumables;
- the need to implement updated guidelines on the standardization of antibiotic susceptibility testing, laboratory methods for species identification and blood culturing; and
- the need to improve laboratory information management and to set up infrastructure for centralized data collection at a national reference laboratory.

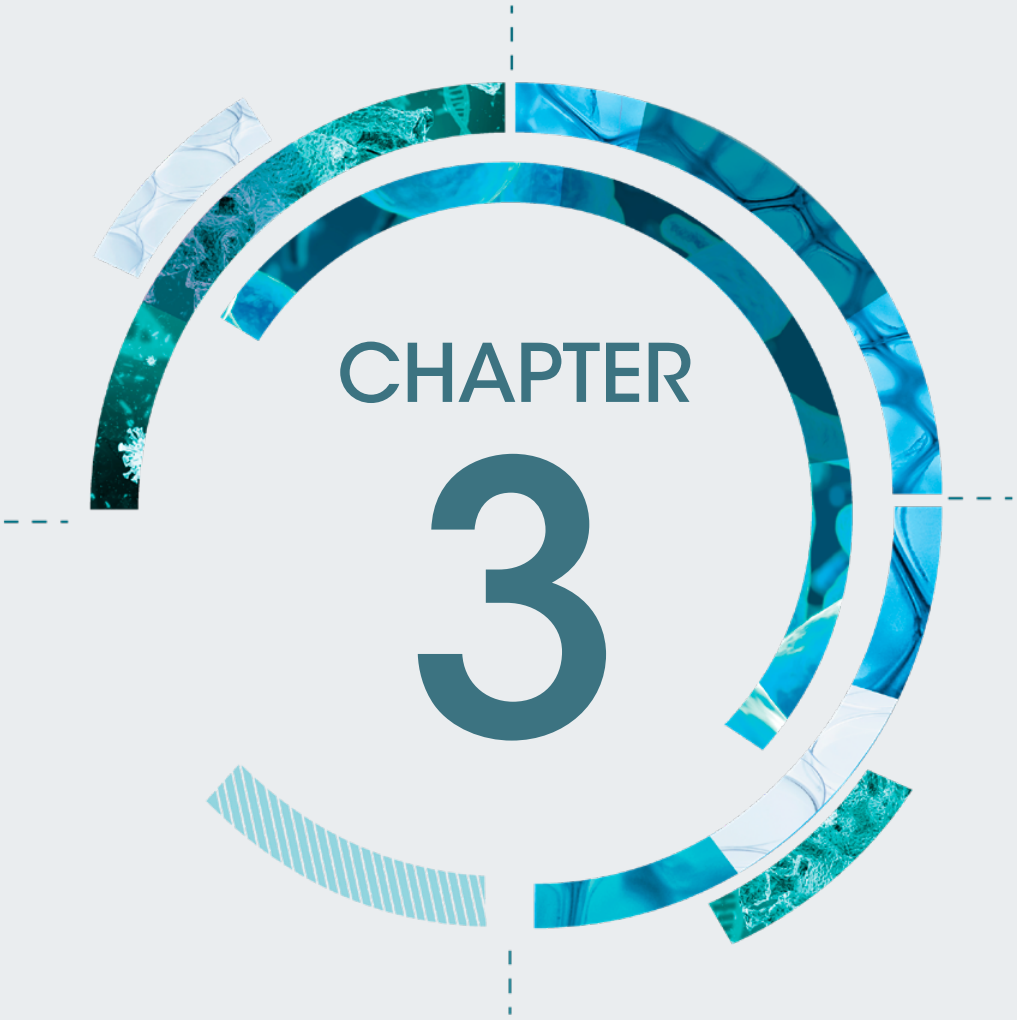
Strong political will and commitment is needed to improve on those challenge and to make further progress.

2.2.1 Support provided to countries

The WHO Regional Office for Europe, in collaboration with the ESCMID and the Netherlands National Institute for Public Health and the Environment, carried out situation analyses in the majority of countries and areas in the network. The purpose was to assess how countries and areas tackle AMR through surveillance, rational use of antimicrobials, and infection prevention and control activities. Particular attention was paid to promoting coordination, and strengthening surveillance of antimicrobial consumption and resistance. Follow-up support is provided through subregional and national AMR workshops and consultations, focusing on various technical aspects:

- coordination, stakeholder meetings and development of national AMR action plans;
- methods, data collection (among others, WHO microbiology laboratory database software (WHONET)) and data analysis for CAESAR;
- 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
- proof-of-principle projects to promote better sampling procedures, routine susceptibility testing and antibiotic stewardship.

Further support and collaboration between members and partners within the CAESAR network are fundamental to continue the process of building a network of AMR surveillance systems throughout the European Region.


CHAPTER
3

Data collection and analysis

3.1 Data collection procedures

Based on a request for data sent to the AMR focal point in each participating country or area, CAESAR collects antimicrobial susceptibility test results of invasive isolates and basic patient information from participating AMR surveillance networks. The data are initially processed by the data manager in each country or area and sent electronically to the National Institute for Public Health and the Environment in the Netherlands to the CAESAR international data manager. The AMR focal point and data manager in each country or area are responsible for collecting and verifying data from the laboratories in their 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. They should also provide additional information on the isolate and patient for a pre-defined list of bacterial species and antimicrobial agents. Data are collected and exported in the CAESAR data format *(1)*, which is compatible with the EARS-Net format *(2)*. To further align CAESAR methodology with that of GLASS *(3)*, in 2016 *Salmonella* spp. was added as bacterial species under CAESAR surveillance.

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

- *Escherichia coli (E. coli)*
- *Klebsiella pneumoniae* (*K. pneumoniae*)
- *Salmonella* spp.
- *Pseudomonas aeruginosa* (*P. aeruginosa*)
- *Acinetobacter* spp.
- *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 these 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, they are analysed and the results are reported back to the AMR focal point using 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 of the data are discussed by email or telephone with the AMR focal point. In addition to the bacterial species listed in the CAESAR manual, countries/areas are encouraged to include pathogen–antibiotic combinations in their surveillance system that are of local 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 or resistant (I+R) to a specific antimicrobial agent: for example, the number of *E. coli* isolates resistant to ciprofloxacin is divided by the total number of *E. coli* isolates in which susceptibility to this antibiotic was tested. The resistance proportions are rounded off to the nearest whole percentage and are usually calculated by combining the results for the antibiotics representing the group or class, basing the outcome on the most resistant result. For example, if *E. coli* susceptibility to imipenem is I and susceptibility to meropenem is R, then the susceptibility to imipenem/meropenem 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. The table notes in the country/area-specific chapters specify which antibiotic combinations are used to analyse multidrug resistance. Isolates with missing data on one or more of the required antibiotic groups are excluded from the analysis.

The R and I+R interpretations are based on the clinical breakpoint criteria used by local laboratories. CAESAR encourages participants to adopt network-wide standards for AST and promotes the use of internationally accepted guidelines (EUCAST or CLSI). If fewer than 30 AST results for a specific pathogen–antibiotic combination were submitted, then the table data are marked with an asterisk, indicating that they should be interpreted with caution. Additional information regarding the analysis performed on CAESAR data is available in the CAESAR manual *(1)*.


CHAPTER
4

Reader's guide

4.1 Data validity

This report presents the AMR surveillance data that were collected and analysed in order 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, it provides the average susceptibility pattern of bacteria in patients presenting with a bloodstream or central nervous system infection in a country/area (target population). The sample for inclusion in a surveillance system should consist of different types of patients (such as children or intensive care unit or neurosurgery patients) with various types of infection (such as community-acquired and health care-associated bloodstream infection), 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 participating in the surveillance programme; the selection of patients for obtaining blood cultures; the transportation and processing of samples in the laboratory; the methods used for AST; and the aggregation and analysis of the data. In some countries/areas, limiting conditions outside the direct control of the 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 steps of the data generation and analysis process, requiring commitment and professional training at each level to ensure high-quality data. Several sources of error and bias in AMR surveillance data are presented in Table 4.1 and are discussed in detail in Annex 2.

4.2 Levels of evidence

To guide the interpretation of the data presented in this report, the authors together with the AMR focal points proposed a qualitative assessment of the level of evidence presented in each chapter with country/area-specific data.

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 basis for data collection requires targeted improvements to allow a valid assessment of the AMR situation.

The assessment of the level of evidence concerns the specific goals of CAESAR as a regional surveillance network, which aims to be transparent about the quality and representativeness of the data collected and presented. Countries/areas that are still developing their surveillance capacity are encouraged to share data once their system has reached a reasonable level of maturity.

For CAESAR reporting, a yearly assessment for each country or area is made, to guide interpretation of the data presented in the report. To arrive at the level of evidence, several aspects of the AMR surveillance system that could negatively affect the validity of the data are assessed against a set of criteria.

Table 4.1 Sources of error and bias in AMR surveillance data

Type of error/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 Continued training of laboratory staff Set up quality assurance 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 prior to treatment initiation (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 or area-specific standards based on international standards for AST methodology (such as EUCAST) Test susceptibility to all indicator antimicrobials (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	Train laboratory staff Implement laboratory quality assurance systems Perform confirmatory testing of highly resistant microorganisms Procure high-quality and quality-controlled materials
	Bias from data aggregation and analysis procedures		
		Include repeat isolates from individual patients Use of varying expert rules: different rules for deriving resistance used in each laboratory	Collect raw data Use standardized data aggregation and analysis methods

1. **Surveillance system**
   a. geographic coverage (Are all major geographic regions represented?)
   b. selection of surveillance sites (Are all major hospital types represented?)

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

3. **Laboratory procedures:**
   a. AST methods (Are all isolates tested for each relevant antibiotic group and using current methodological standards? Is a network-wide quality assurance system active?)
   b. AST breakpoints (Is a harmonized and up-to-date breakpoint system used?)

Table 4.2 provides an overview of the level of evidence for each country/area and the underlying assessment of the data from 2017.

Table 4.2 Level of evidence and scoring of factors affecting the validity of CAESAR data, 2017

		Belarus	Bosnia and Herzegovina	Georgia	Montenegro	Russian Federation	Serbia	Switzerland	The former Yugoslav Republic of Macedonia	Turkey	Ukraine	Kosovo[a]
Level of evidence		B	A	B	B	B	A	A	B	A	B	B
Surveillance system	Geographic 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).

4.3 Understanding the AMR results

Level A data allow for the valid and reproducible assessment of AMR trends in the country/area. The data can be used to raise awareness about AMR and to support the adoption of AMR control policies. However, the resistance proportions as included in the CAESAR report should not be used as the sole source for informing empirical treatment choices, as the total sample of patients comprises a mix of community-

acquired and health care-associated infections in different types of patients. 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 blood stream infection versus severe pneumonia) and treatment status (before and after empirical antibiotic treatment).

Level B data are not necessarily wrong but rather less representative for the target population due to systematic errors or biases in the data generation process. Nevertheless, presenting level B data allows for the critical evaluation of sources of error and bias, which should be seen as a starting point to further improve and develop the surveillance system. The magnitude of resistance presented is biased and thus precludes the use of data for guiding empirical antibiotic treatment choices. However, the data indicate the presence of multidrug-resistant microorganisms or exceptional antimicrobial resistant phenotypes of public health importance (e.g. carbapenem-resistant Enterobacteriaceae) in clinical settings in the country/area. Although further research is needed to assess the extent of the problem and the spread of these microorganisms in the health care system, the data indicate that infection prevention and control measures are acutely needed to control the problem.

Level C data should not be used to inform empirical antibiotic treatment choices or AMR control policy. The data do not provide an adequate assessment of the AMR situation in the country/area due to substantial errors in AST. However, the surveillance system has shown the capacity to collect routine AST data from a network of laboratories. The current basis for data collection requires targeted improvements to allow a valid assessment of the AMR situation. Level C data are not presented in the annual report. A country or area with level C data is encouraged and guided to make improvements to the surveillance system until the data are assessed to be level B.


CHAPTER
5

Country-specific data on AMR

5.1 Belarus

5.1.1 Surveillance set-up

In Belarus, results from routine antibiotic susceptibility testing of clinical bacteriology cultures of all microorganisms and specimen types are collected from clinical microbiology laboratories using the WHONET software and sent by email quarterly. Data are collected by the team from the national reference centre for AMR, which is the Laboratory for Clinical and Experimental Microbiology of the Republican Research and Practical Center for Epidemiology and Microbiology in Minsk. The data are processed, and their quality and consistency are checked. Data with errors are sent back to the laboratory, where they are corrected if possible. Confirmatory testing of highly resistant microorganisms and unexpected phenotypes is recommended. However, it is not always possible due to problems in isolate selection, storage and transferral to the national reference centre for AMR, the centre's high workload and other logistical reasons. A subset of antibiotic susceptibility test results, containing all first isolates from blood and CSF cultures per patient yielding organisms specified by CAESAR for the period 1 January 2017 to 31 December 2017, was submitted to CAESAR.

The AMR surveillance network comprised 16 participating laboratories in 2014, but rapidly expanded after that. In 2017, 114 laboratories participated in the network, providing services to more than 90% of hospitals (including multidisciplinary hospitals and national clinical research centres) and covering more than 90% of the population of Belarus (of 9 452 113, data from 2018 *(1)*). Participating laboratories are geographically spread out, but some large urban centres and regions are underrepresented because they use software incompatible with WHONET. In 2017, 51 laboratories processed blood/CSF isolates yielding organisms specified by CAESAR. The majority of data (about 55%) came from the laboratory of the Minsk City Centre of Hygiene and Epidemiology, which provides diagnostic support to most of the clinics in Minsk (about 20% of the population of Belarus).

Antimicrobial susceptibility is mostly tested using the disk diffusion method and automated systems. Some laboratories use gradient tests for selected combinations of microorganisms and antimicrobial agents or to confirm the results. All laboratories use quality management systems and are audited regularly by ISO and the International Electrotechnical Commission (IEC) (using the ISO/IEC 17025:2005 standard). Since 2013, eight laboratories from all regions of Belarus have participated in the international CAESAR EQA exercise developed by UK NEQAS; in 2017, 13 laboratories took part. Also since 2013, four national laboratories, including the national reference centre for AMR, have participated in the WHO-coordinated EQA programme for the WHO Global Invasive Bacterial Vaccine Preventable Diseases Laboratory Network.

Laboratories should follow national guidelines on bacteriological methods published in 2009. For antibiotic susceptibility testing methods and interpretation, Belarus 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 updated information from the manufacturer. To harmonize the implementation of AST in laboratories in Belarus, the Ministry of Health issued a special order with recommended antibiotic panels for AST. The AMR surveillance network is currently preparing the implementation of this order.

Belarus has an active AMR surveillance network. Annual reports on antibiotic resistance in invasive pathogens are sent to hospitals and hygiene and epidemiology centres. In November 2017, a workshop was held for representatives of all network laboratories. National levels of antibiotic resistance in Belarus were discussed, and laboratories shared their experience on data collection and interpretation, as well as on the technical aspects of AST.

According to national clinical guidelines, blood cultures should be obtained from all hospitalized patients with suspected bloodstream infection (bacteraemia, sepsis, endocarditis), and CSF cultures for patients with suspected meningitis. For all hospitalized patients with pneumonia, sputum culture is mandatory, but a blood culture is taken only if the patient is hospitalized in an intensive care unit or has serious 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). Bacteriology cultures and antibiotic susceptibility testing are financed by the national budget. The reason for the small number of positive cultures may be due to logistic issues and lack of funding, laboratory equipment and reagents (blood culture instruments and blood culture bottles). This is especially felt at regional level, where laboratories are not equipped with automated blood culture systems. Accurate data on the number of blood cultures obtained in 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 characteristics of patients (broken down by pathogen) of 1720 isolates obtained in Belarus in 2017. In *E. coli*, resistance ranged from 9% for imipenem/meropenem to 70% for amoxicillin/ampicillin (Table 5.1). Multidrug resistance was 24% in *E. coli*. In *K. pneumoniae*, resistance was 59% for amikacin and higher for all other selected agents. Multidrug resistance in *K. pneumoniae* was 74%. Based on 13 isolates of *Salmonella* spp., no resistance to any of the selected agents was observed (Table 5.2). In *P. aeruginosa*, resistance ranged between 44% (piperacillin-tazobactam) and 78% (imipenem/meropenem) (Table 5.3). Multidrug resistance was 48% in *P. aeruginosa*. However, because of the relatively small number of isolates, the results for multidrug-resistant *P. aeruginosa* should be interpreted with caution. Resistance in *Acinetobacter* spp. was 72% or higher for all studied agents. Multidrug resistance in *Acinetobacter* spp. was 62%. Forty-one percent of *S. aureus* isolates were methicillin-resistant *S. aureus* (MRSA) (Table 5.4). Based on only 17 isolates of *S. pneumoniae*, 29% were non-susceptible to penicillin (Table 5.5). Multidrug resistance in *S. pneumoniae* was 24%. Two per cent of *E. faecalis* isolates were resistant to vancomycin, and 2% were non-susceptible to linezolid (Table 5.6). In *E. faecium*, 17% were resistant to vancomycin, and 3% were non-susceptible to linezolid. In Chapter 7, maps of the WHO European Region show the proportions of resistance for selected pathogen–antibiotic combinations reported by Belarus (Fig. 7.1–7.6).

5.1.3 Discussion

The AMR surveillance network of Belarus submitted antibiotic susceptibility testing results for 1720 isolates from blood or CSF in 2017. The number of laboratories with data that met the requirements of CAESAR increased from 30 in 2016 to 51 in 2017. However, the majority of isolates (about 55%) still came from one laboratory serving hospitals in Minsk, reflecting the underutilization of blood culture diagnostics in smaller regional hospitals and limiting the national representativeness of the data. In 2017, national recommendations for the minimal set of antimicrobial agents to be tested were not implemented in Belarus. Laboratories differed with regard to the antibiotic groups tested, which suggests the use of sequential or selective testing by some of them. This may have led to over- or underestimation of resistance to specific antibiotics, depending on sampling and the mechanism of resistance. In addition, because not all antibiotics were tested in all laboratories, the proportions of resistance may reflect different underlying patient populations and thus complicate the ranking of resistance proportions to antibiotics. 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 to interpret disk diffusion zone diameters, and CLSI or EUCAST (2012–2014) breakpoints were used to interpret the results of automated AST systems. In particular, carbapenem resistance in Enterobacteriaceae may be underestimated when older breakpoint guidelines are used.

Many isolates (55%) were obtained from patients admitted to an intensive care unit. Compared with other species, few *E. coli* (9%) and many *K. pneumoniae* (29%) and *Acinetobacter* spp. (21%) were isolated. In general, high percentages of resistance were found for all pathogens. The combination of factors such as an overrepresentation of intensive care unit patients, a skewed distribution of pathogens and high percentages of resistance indicates selective sampling of patients. This could include, likely, severely ill patients with a history of hospitalization and antibiotic treatment, patients who failed to respond to empirical antimicrobial treatment, or patients from departments with high selective pressure of antimicrobials and a high risk of transmission of highly resistant microorganisms. The suspicion of selective sampling is in accordance with low utilization of blood culture diagnostics by clinicians, limited to severely ill patients admitted to intensive care units 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 ranking of proportions of resistance may be unreliable.

Nevertheless, the data suggest that in Enterobacteriaceae, resistance to third-generation cephalosporins (cefotaxime/ceftriaxone and ceftazidime), 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 the increased use of third-generation cephalosporins and carbapenems observed in recent years in Belarus. 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 proportion of MRSA was higher than that in neighbouring countries (Fig. 7.6). Too few antibiotic susceptibility testing results for *S. pneumoniae* were available to allow interpretation. The relatively high aminopenicillin resistance in *E. faecalis* may reflect problems with species identification (inclusion of *E. faecium*, which is more often resistant to aminopenicillins), rather than resistance in *E. faecalis*. Vancomycin resistance in *E. faecium* was moderately high.

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. 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, which limits the interpretation of the ranking 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 the utilization of blood culture diagnostics will lead to a more valid assessment of AMR in the country. The reader's guide (Table 4.2) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.1 Patient characteristics of isolates in Belarus in 2017, by pathogen

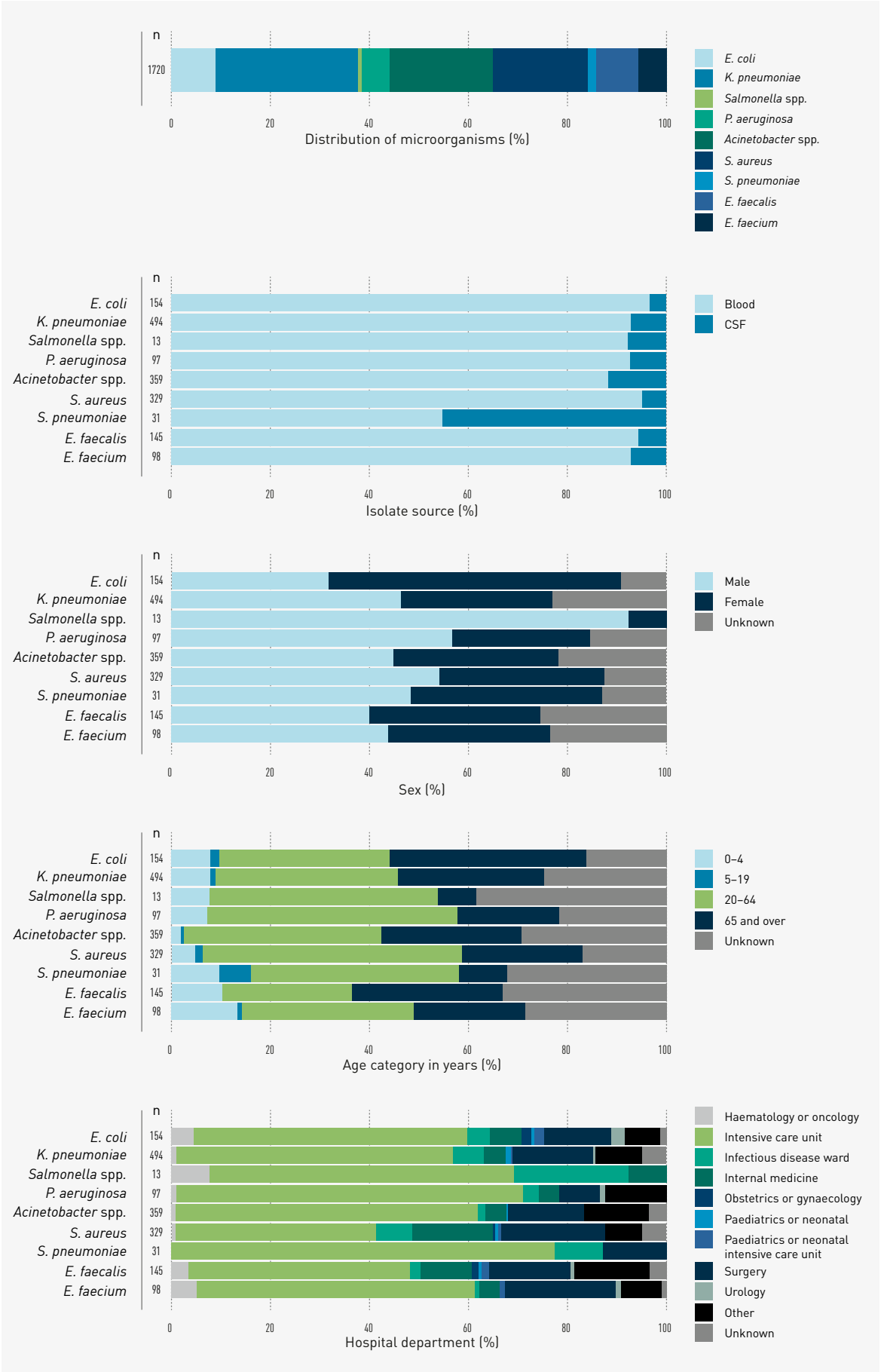


Table 5.1 Percentages of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Belarus, 2017

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (R)[a]	71	70	NA	NA
Amoxicillin-clavulanic acid (R)	58	26	176	86
Piperacillin-tazobactam (R)	76	14	234	83
Cefotaxime/ceftriaxone (R)[b]	130	50	364	86
Cefotaxime/ceftriaxone (I+R)[b]	130	50	364	88
Ceftazidime (R)	93	46	311	86
Ertapenem (R)	14	0*	34	50
Imipenem/meropenem (R)[c]	150	9	464	73
Imipenem/meropenem (I+R)[c]	150	11	464	75
Gentamicin/tobramycin (R)[d]	81	26	286	76
Amikacin (R)	61	11	241	59
Ciprofloxacin/levofloxacin/ofloxacin (R)[e]	145	45	471	85
Ciprofloxacin/levofloxacin/ofloxacin (I+R)[e]	145	46	471	86
Multidrug resistance (R)[f]	79	24	266	74

NA: not applicable.

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

[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[c] Imipenem and meropenem are indicators for the group of carbapenems.

[d] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[e] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

[f] Multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin/ofloxacin, cefotaxime/ceftriaxone/ceftazidime and gentamicin/tobramycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.2 Percentages of resistance for *Salmonella* spp. among blood and CSF isolates in Belarus, 2017

Antibiotic (group)	*Salmonella* spp.	
	N	Resistance (%)
Cefotaxime/ceftriaxone (R)[a]	12	0*
Cefotaxime/ceftriaxone (I+R)[a]	12	0*
Ceftazidime (R)	7	0*
Ertapenem (R)	0	–
Imipenem/meropenem (R)[b]	11	0*
Imipenem/meropenem (I+R)[b]	11	0*
Ciprofloxacin/levofloxacin (R)[c]	13	0*
Ciprofloxacin/levofloxacin (I+R)[c]	13	31*

–: no data available.

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

[a] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[b] Imipenem and meropenem are indicators for the group of carbapenems.

[c] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.

Table 5.3 Percentages of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Belarus, 2017

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	50	44	NA	NA
Ceftazidime (R)	75	65	NA	NA
Cefepime (R)	87	67	NA	NA
Imipenem/meropenem (R)[a]	93	78	349	87
Imipenem/meropenem (I+R)[a]	93	81	349	92
Gentamicin/tobramycin (R)[b]	53	62	206	73
Amikacin (R)	62	53	72	72
Ciprofloxacin/levofloxacin (R)[c]	94	76	348	94
Multidrug resistance (R)[d]	29	48*	196	62

NA: not applicable.

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

[a] Imipenem and meropenem are indicators for the group of carbapenems.

[b] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[c] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.

[d] For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. For *Acinetobacter* spp., multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. Isolates with missing data on one or more of the groups were excluded in the calculation of multidrug resistance.

Table 5.4 Percentages of resistance for *S. aureus* among blood and CSF isolates in Belarus, 2017

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)[a]	299	41
Ciprofloxacin/levofloxacin/ofloxacin (R)[b]	309	31
Vancomycin (R)	240	0
Rifampicin (R)	229	18
Linezolid (R)	289	0

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

[b] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

Table 5.5 Percentages of resistance for *S. pneumoniae* among blood and CSF isolates in Belarus, 2017

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillin (I+R)[a]	17	29*
Cefotaxime/ceftriaxone (R)[b]	20	15*
Cefotaxime/ceftriaxone (I+R)[b]	20	25*
Levofloxacin/moxifloxacin (R)[c]	30	0
Erythromycin/clarithromycin/azithromycin (R)[d]	27	22*
Erythromycin/clarithromycin/azithromycin (I+R)[d]	27	30*
Multidrug resistance (I+R)[e]	17	24*

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

[a] Non-susceptibility to penicillin is based on penicillin or, if not available, on oxacillin.

[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[c] Levofloxacin and moxifloxacin are indicators for the group of fluoroquinolones.

[d] Erythromycin, clarithromycin and azithromycin are indicators for the group of macrolides.

[e] Multidrug resistance is defined as non-susceptibility to penicillin and erythromycin/clarithromycin/azithromycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.6 Percentages of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Belarus, 2017

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (I+R)[a]	122	32	83	93
High-level gentamicin (R)	113	66	76	75
Vancomycin (R)	142	2	96	17
Linezolid (I+R)	126	2	89	3

[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

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 the other in Republika Srpska. The surveillance set-up for each network in Bosnia and Herzegovina is described separately.

5.2.1.1 Federation of Bosnia and Herzegovina

In the Federation of Bosnia and Herzegovina, the AMR focal point and the data manager are responsible for collecting data from participating laboratories. Before submitting the data, laboratories check the data for compliance with the CAESAR protocol, microbiological consistency and reliability and compliance with EUCAST guidelines. Each laboratory sends data electronically in Excel-based data entry forms prepared in advance by the data manager according to the CAESAR protocols. The data manager and AMR focal point approve the data before sending it to CAESAR. Antibiotic susceptibility testing results of all first isolates from blood and CSF cultures per patient yielding organisms specified by CAESAR for the period 1 January 2017 to 31 December 2017 were submitted to CAESAR.

In 2017, six of 12 laboratories in the Federation of Bosnia and Herzegovina were part of the AMR surveillance network. They provide diagnostic support to three secondary care hospitals, one tertiary care hospital and two hospitals providing both secondary and tertiary care. The laboratories are geographically spread out and demographically representative, including urban and rural areas. Six other laboratories process very few samples (<50 per year) and are not included in the network. AMR surveillance in the Federation of Bosnia and Herzegovina covers about 75% of the population of the Federation of Bosnia and Herzegovina (which comprises about two thirds of the total population of Bosnia and Herzegovina (of 3 503 554, data from 2018 *(1)*).

In three laboratories, antimicrobial susceptibility is tested using automated systems. Gradient tests and disk diffusion are used as supplementary methods. In three other laboratories, only providing services for secondary care, disk diffusion is the main method for AST. Since 2016, all laboratories have used EUCAST guidelines in antibiotic susceptibility testing and interpreting results. If highly resistant microorganisms or exceptional phenotypes are found, strains are usually sent to the clinical microbiology laboratory at the university hospital in Sarajevo for confirmation. This is the functional reference laboratory in the Federation of Bosnia and Herzegovina. The Federal Ministry of Health has not yet nominated a reference laboratory yet. All laboratories use an internal quality management system and participate in international external quality control programmes (UK NEQAS).

According to clinical guidelines, blood samples are collected from all patients presenting with signs of a bloodstream infection (sepsis) and CSF from patients with suspected meningitis. In 2017, the number of blood cultures obtained in the Federation of Bosnia and Herzegovina ranged from three to 20 per 1000 patient days in six participating hospitals.

5.2.1.2 Republika Srpska

The Commission for Control of Resistance to Antimicrobial Medicines in Republika Srpska has developed, 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, who are members of the Commission, are responsible for collecting data.

All results from routine antibiotic susceptibility testing of clinical bacteriology cultures are collected electronically from the clinical information system. Confirmatory testing (phenotypical) of highly resistant microorganisms is done before including the results 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 2017 to 31 December 2017, was reported to CAESAR.

The majority of data (95%) represents patients from the University Clinical Centre of Republika Srpska in Banja Luka. As the largest and main hospital in Republika Srpska, it provides secondary and tertiary care and covers at least 85% of the population of Republika Srpska. Since 2017, the AMR surveillance network has included regional laboratories serving general hospitals in Prijedor, Bijeljina and Istočno Sarajevo.

In all laboratories in Republika Srpska, most of the antibiotic susceptibility testing of Gram-negative bacteria, *S. aureus*, *S. pneumoniae* and *Enterococcus* spp. is performed using automated systems. If highly resistant microorganisms or exceptional phenotypes are found, the results are confirmed by gradient tests or disk diffusion. All laboratories use quality management systems, with internal and external international (UK NEQAS) quality control programmes. Laboratories should follow guidelines on bacteriological methods. Republika Srpska has adopted EUCAST methods as the standard for conducting and interpreting the results of antibiotic susceptibility testing.

According to clinical guidelines, blood cultures are obtained from all patients with suspected bloodstream infections (sepsis), and CSF cultures from patients with suspected meningitis. The costs of bacteriology cultures are reimbursed through the universal health insurance scheme. In 2017, sampling rates in the four participating hospitals were estimated at 2–9 blood cultures per 1000 patient days.

5.2.2 Results

Fig. 5.2 shows the distribution of microorganisms and the characteristics of patients (broken down by pathogen) of 828 isolates obtained in Bosnia and Herzegovina in 2017. In *E. coli*, apart from amoxicillin/ampicillin (73%), resistance ranged from 1% (imipenem/meropenem) to 42% (amoxicillin-clavulanic acid, Table 5.7). Multidrug resistance was 13% in *E. coli*. In *K. pneumoniae*, resistance ranged from 11% for imipenem/meropenem to 77% for amoxicillin-clavulanic acid. Multidrug resistance in *K. pneumoniae* was 43%. Six isolates of *Salmonella* spp. were found, one of which (17%) was resistant to ciprofloxacin/levofloxacin (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 19% (ceftazidime) and 46% (ciprofloxacin/levofloxacin, Table 5.9). Multidrug resistance was 33% in *P. aeruginosa*. Resistance in *Acinetobacter* spp. was 87–96% for all antibiotics tested. Multidrug resistance in *Acinetobacter* spp. was 93%. Twenty-six per cent of *S. aureus* isolates were methicillin-resistant (MRSA, Table 5.10). In *S. pneumoniae*, non-susceptibility to penicillin was 42% (Table 5.11). Thirty-three per cent of *S. pneumoniae* isolates were multidrug resistant. Vancomycin resistance in *E. faecalis* was 1% (Table 5.12). In *E. faecium*, 35% was vancomycin-resistant and 8% was non-susceptible to linezolid. In Chapter 7, maps of the WHO European Region show the proportions of resistance for selected pathogen–antibiotic combinations reported by Bosnia and Herzegovina (Fig. 7.1–7.6).

5.2.3 Discussion

The AMR surveillance networks of Bosnia and Herzegovina submitted the antibiotic susceptibility testing results of 828 isolates from blood or CSF in 2017. The network laboratories provide good geographical coverage of Bosnia and Herzegovina, although few isolates were available from the eastern part of the country. Blood samples were generally taken before initial antibiotic treatment and came from patients admitted to a variety of hospital types and departments.

The main pathogens isolated were *E. coli* (23%) and *S. aureus* (19%). In *E. coli*, two isolates were found resistant to carbapenems (imipenem/meropenem), which were both confirmed to be carbapenemase-producers by phenotypic methods. Importantly, observed resistance percentages for ertapenem were lower than for imipenem/meropenem in both *E. coli* and *K. pneumoniae*, which is unusual and likely explained by testing only a subset of isolates for ertapenem. A relatively high proportion of *Acinetobacter* spp. isolates was seen (15%), particularly in patients admitted to intensive care units. The high levels of (multidrug) resistance in *K. pneumoniae* and *Acinetobacter* spp., and vancomycin-resistant *E. faecium*

suggest the dissemination of resistant clones in the health care setting. Furthermore, although based on a relatively small number of isolates, resistance levels in *S. pneumoniae* were rather high and concerning. On the other hand, the resistance levels in *E. coli*, *P. aeruginosa* and *S. aureus* were only moderately high. The relatively high levels of resistance to gentamicin (high level) and non-susceptibility to linezolid in *E. faecium* were most likely due to methodological issues in automated testing, which the laboratories will address. The distribution of pathogens and hospital departments, and the variation in resistance levels between species suggest that the data represent a mix of community-acquired and health care-associated infections.

Data from Bosnia and Herzegovina are assessed as level A. 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) by increasing the utilization of blood culture diagnostics will lead to a more valid assessment of the magnitude of AMR. The reader's guide (Table 4.2) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.2 Patient characteristics of isolates in Bosnia and Herzegovina in 2017, by pathogen

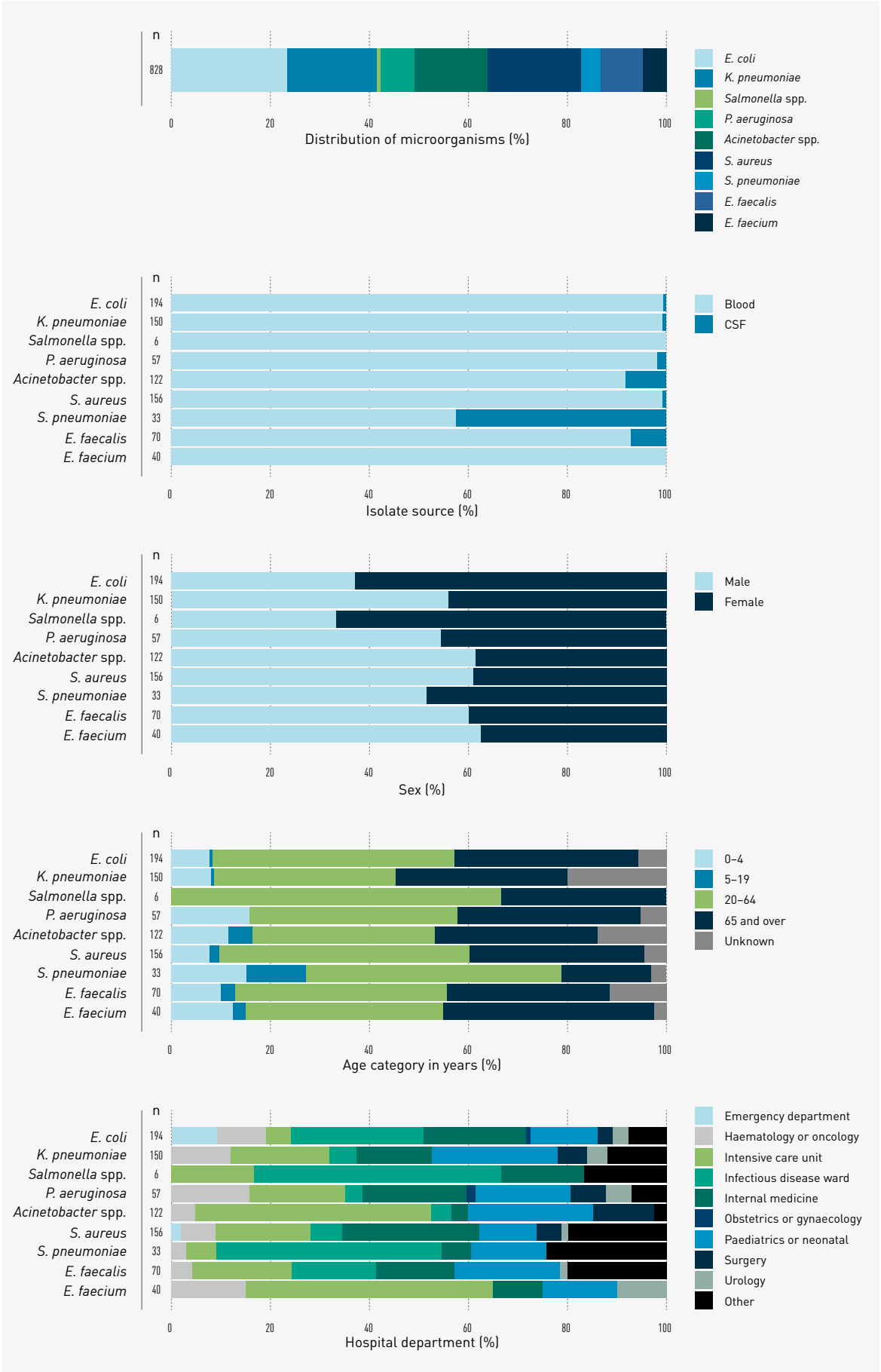


Table 5.7 Percentages of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Bosnia and Herzegovina, 2017

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (R)[a]	158	73	NA	NA
Amoxicillin-clavulanic acid (R)	190	42	148	77
Piperacillin-tazobactam (R)	179	6	138	33
Cefotaxime/ceftriaxone (R)[b]	194	25	150	61
Cefotaxime/ceftriaxone (I+R)[b]	194	25	150	63
Ceftazidime (R)	193	19	148	58
Ertapenem (R)	77	0	74	7
Imipenem/meropenem (R)[c]	183	1	145	11
Imipenem/meropenem (I+R)[c]	183	2	145	16
Gentamicin/tobramycin (R)[d]	189	25	148	64
Amikacin (R)	179	10	142	23
Ciprofloxacin/levofloxacin/ofloxacin (R)[e]	188	27	145	54
Ciprofloxacin/levofloxacin/ofloxacin (I+R)[e]	188	28	145	54
Multidrug resistance (R)[f]	186	13	143	43

NA: not applicable.

[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[c] Imipenem and meropenem are indicators for the group of carbapenems.

[d] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[e] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

[f] Multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin/ofloxacin, cefotaxime/ceftriaxone/ceftazidime and gentamicin/tobramycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.8 Percentages of resistance for *Salmonella* spp. among blood and CSF isolates in Bosnia and Herzegovina, 2017

Antibiotic (group)	*Salmonella* spp.	
	N	Resistance (%)
Cefotaxime/ceftriaxone (R)[a]	6	0*
Cefotaxime/ceftriaxone (I+R)[a]	6	0*
Ceftazidime (R)	6	0*
Ertapenem (R)	1	0*
Imipenem/meropenem (R)[b]	6	0*
Imipenem/meropenem (I+R)[b]	6	0*
Ciprofloxacin/levofloxacin (R)[c]	6	17*
Ciprofloxacin/levofloxacin (I+R)[c]	6	17*

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

[a] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[b] Imipenem and meropenem are indicators for the group of carbapenems.

[c] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.

Table 5.9 Percentages of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Bosnia and Herzegovina, 2017

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	57	23	NA	NA
Ceftazidime (R)	57	19	NA	NA
Cefepime (R)	47	30	NA	NA
Imipenem/meropenem (R)[a]	57	23	122	95
Imipenem/meropenem (I+R)[a]	57	28	122	95
Gentamicin/tobramycin (R)[b]	57	44	122	95
Amikacin (R)	57	39	120	87
Ciprofloxacin/levofloxacin (R)[c]	57	46	121	96
Multidrug resistance (R)[d]	57	33	121	93

NA: not applicable.

[a] Imipenem and meropenem are indicators for the group of carbapenems.

[b] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[c] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.

[d] For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. For *Acinetobacter* spp., multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. Isolates with missing data on one or more of the groups were excluded in the calculation of multidrug resistance.

Table 5.10 Percentages of resistance for *S. aureus* among blood and CSF isolates in Bosnia and Herzegovina, 2017

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)[a]	156	26
Ciprofloxacin/levofloxacin/ofloxacin (R)[b]	131	18
Vancomycin (R)	156	0
Rifampicin (R)	119	3
Linezolid (R)	154	0

[a] MRSA is calculated as resistance to cefoxitin or, if not available, oxacillin.
[b] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

Table 5.11 Percentages of resistance for *S. pneumoniae* among blood and CSF isolates in Bosnia and Herzegovina, 2017

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillin (I+R)[a]	33	42
Cefotaxime/ceftriaxone (R)[b]	20	10*
Cefotaxime/ceftriaxone (I+R)[b]	20	20*
Levofloxacin/moxifloxacin (R)[c]	26	12*
Erythromycin/clarithromycin/azithromycin (R)[d]	30	37
Erythromycin/clarithromycin/azithromycin (I+R)[d]	30	37
Multidrug resistance (I+R)[e]	30	33

* A small number of isolates were tested (N < 30), and the percentage resistance should be interpreted with caution.
[a] Non-susceptibility to penicillin is based on penicillin or, if not available, on oxacillin.
[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.
[c] Levofloxacin and moxifloxacin are indicators for the group of fluoroquinolones.
[d] Erythromycin, clarithromycin and azithromycin are indicators for the group of macrolides.
[e] Multidrug resistance is defined as non-susceptibility to penicillin and erythromycin/clarithromycin/azithromycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.12 Percentages of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Bosnia and Herzegovina, 2017

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (I+R)[a]	70	3	40	100
High-level gentamicin (R)	69	59	40	97
Vancomycin (R)	70	1	40	35
Linezolid (I+R)	68	0	40	8

[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

5.3 Georgia

5.3.1 Surveillance set-up

A proof-of-principle AMR routine diagnostics surveillance project (PoP project) took place in Georgia between 1 July 2015 and 31 December 2016. Four hospitals participated, supported by three laboratories. The project established the basis for national AMR surveillance in the country *(2, 3)*, with the Richard Lugar Center for Public Health Research of the National Center for Disease Control and Public Health of Georgia as the AMR reference centre. In this role, the Lugar Center provides technical support and receives isolates from hospitals throughout Georgia for confirmatory testing and further characterization of strains. The project also resulted in the Lugar Center developing a routine for standardized collection of AST results from network laboratories.

In 2017, the network expanded to 20 laboratories that are geographically spread throughout the country. The laboratories provide services to approximately 150 of 300 (50%) hospitals in Georgia, most of which (80%) are multidisciplinary general hospitals. Together these hospitals cover about 60% of the population in Georgia (of 3 907 131, data from 2018 *(1)*). In 2017, results from routine antibiotic susceptibility testing of clinical bacteriology cultures of blood, CSF and faeces samples yielding pathogens eligible for CAESAR/GLASS reporting, were collected from the laboratories on paper-based isolate record forms. The data were entered into an electronic database by the national AMR surveillance team at the Lugar Center. A subset of antibiotic susceptibility testing results, containing all isolates from blood and CSF cultures per patient yielding organisms specified by CAESAR for the period 1 January 2017 to 31 December 2017, was submitted to CAESAR. According to these specifications, data were available from six laboratories in 2017.

The three laboratories that participated in the proof-of-principle project have adopted standardized routine blood culturing practices and EUCAST methodology for antibiotic susceptibility testing (using the disk diffusion method). Of the remaining laboratories in the network, approximately 60% use EUCAST guidelines; 40% use CLSI guidelines, but most of them are planning to switch to EUCAST in 2018/2019. Some use the disk diffusion method; others have automated systems operating with consumables and software that comply with EUCAST methodology. The Lugar Center performs confirmatory testing of exceptional phenotypes using phenotypic and genotypic methods. Enrolled in the EQA programme offered by UK NEQAS since 2016, the Lugar Center provided EQA exercises and mentoring on EUCAST methodology to 14 country laboratories in 2017.

Georgia has an active AMR surveillance network, which has organized workshops on CAESAR participation and data collection. In November 2017, meetings, symposiums and lectures took place in three different (central and regional) locations in Georgia. The national AMR surveillance team is currently working on further expanding the network, as well as on collecting local data electronically.

Utilization of routine blood culture diagnostics in Georgia is low due to a lack of funds and a perception by clinicians of a lack of clinical utility. Sampling is generally restricted to patients in intensive care units after initial antibiotic treatment. As part of the proof-of-principle project, clinicians were instructed to recruit patients through active case finding from hospital departments admitting patients with suspected bloodstream infections from the community (e.g. emergency department) and from departments where patients were at risk of developing hospital-acquired bloodstream infections (e.g. intensive care units, urology or surgical departments). As a result, the rate of blood sampling increased from an average of 1.8 to 5.8 per 1000 patient days between 1 July 2015 and 31 December 2016 in the four participating hospitals. Data on blood sampling rates are not yet available for hospitals that joined the AMR surveillance network after the proof-of-principle project. The AMR surveillance team has shared proof-of-principle project protocols with those hospitals and is working with them to implement standardized sampling methodology.

5.3.2 Results

Fig. 5.3 shows the distribution of microorganisms and the characteristics of patients (broken down by pathogen) of 201 isolates obtained in Georgia in 2017. In *E. coli*, resistance ranged from 0% (imipenem/

meropenem) to 37% (cefotaxime/ceftriaxone and ciprofloxacin/levofloxacin/ofloxacin, Table 5.13). Multidrug resistance was 16% in *E. coli*. Resistance in *K. pneumoniae* ranged from 47% for imipenem/meropenem to 92% for amoxicillin-clavulanic acid. Multidrug resistance in *K. pneumoniae* was 40%. Data were not available for *Salmonella* spp. from blood or CSF. Resistance in *P. aeruginosa* (16 isolates) ranged from 38% (amikacin) to 67% (cefepime, Table 5.14). Multidrug resistance was 42% in *P. aeruginosa*. In *Acinetobacter* spp., resistance ranged between 68% (gentamicin/tobramycin) to 88% (ciprofloxacin/levofloxacin). Multidrug resistance in *Acinetobacter* spp. was 58%. Eleven per cent of nine *S. aureus* isolates were methicillin-resistant (MRSA, Table 5.15). In *S. pneumoniae*, one of two isolates (50%) was non-susceptible to penicillin, and multidrug resistance was not observed (Table 5.16). In *E. faecalis*, vancomycin resistance was not observed, but two of seven tested isolates (29%) were non-susceptible to linezolid (Table 5.17). In three *E. faecium* isolates, vancomycin resistance was not observed. One isolate was tested for linezolid and found non-susceptible. In Chapter 7, maps of the WHO European Region show the proportions of resistance for selected pathogen–antibiotic combinations reported by Georgia (Fig. 7.1–7.6).

5.3.3 Discussion

The Georgian AMR surveillance network submitted antibiotic susceptibility testing results for 201 isolates from blood and CSF in 2017, which is an important improvement compared with the 70 isolates submitted in 2016. After the proof-of-principle project in 2015/2016, the national AMR surveillance team at the National Center for Disease Control and Public Health has made great efforts to expand the surveillance network that now comprises 20 laboratories providing services for 150 hospitals in all regions of Georgia. However, only six laboratories (14 hospitals), all from the capital Tbilisi, could provide data eligible for CAESAR in 2017. This reflects the underutilization of blood culture diagnostics by clinicians in Georgia, especially in regional hospitals. During the proof-of-principle project, the majority of samples obtained in routine clinical practice were characterized as coming from nosocomial infections. Besides bias towards higher resistance caused by selective sampling of nosocomial infections, the small number of isolates made the observed percentages of resistance more sensitive to random variation, such as from nosocomial outbreaks. Therefore, 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 patient population sampled had high levels of resistance to all selected agents in *K. pneumoniae*, *P. aeruginosa* and *Acinetobacter* spp. The high levels of resistance are concerning and may reflect the dissemination of resistant clones in the health care setting. On the other hand, resistance in *E. coli* was only moderately high, and the proportion of MRSA was relatively low compared to that in neighbouring countries (Fig. 7.6). Too few antibiotic susceptibility testing results for *S. pneumoniae* and *E. faecium* were available to allow interpretation. Importantly, observed resistance for ertapenem was lower than non-susceptibility to imipenem/meropenem in both *E. coli* and *K. pneumoniae*, which is unusual and likely explained by testing only a subset of isolates for ertapenem. Linezolid non-susceptibility was observed in *S. aureus* (n=1), *E. faecalis* (n=2) and *E. faecium* (n=1), which is most likely due to methodological issues in automated testing. The reference laboratory did not receive these isolates for confirmation.

Data from Georgia are assessed as level B. The overrepresentation of nosocomial infections (selective sampling) and the overall small number of isolates (underutilization of blood culture diagnostics) constrain the representativeness of the results. The antibiotic susceptibility testing results seem to be reliable. However, the comparability of results is limited by the absence of harmonized breakpoint guidelines. The data indicate the resistance patterns present in clinical settings in the country, but the percentages of resistance should be interpreted with care. Increasing the utilization of blood culture diagnostics (especially in regional hospitals), sampling of patients with community-acquired infections, and harmonization of antibiotic susceptibility testing methods and breakpoints will lead to more valid assessment of AMR in the country. The reader's guide (Table 4.2) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.3 Patient characteristics of isolates in Georgia in 2017, by pathogen

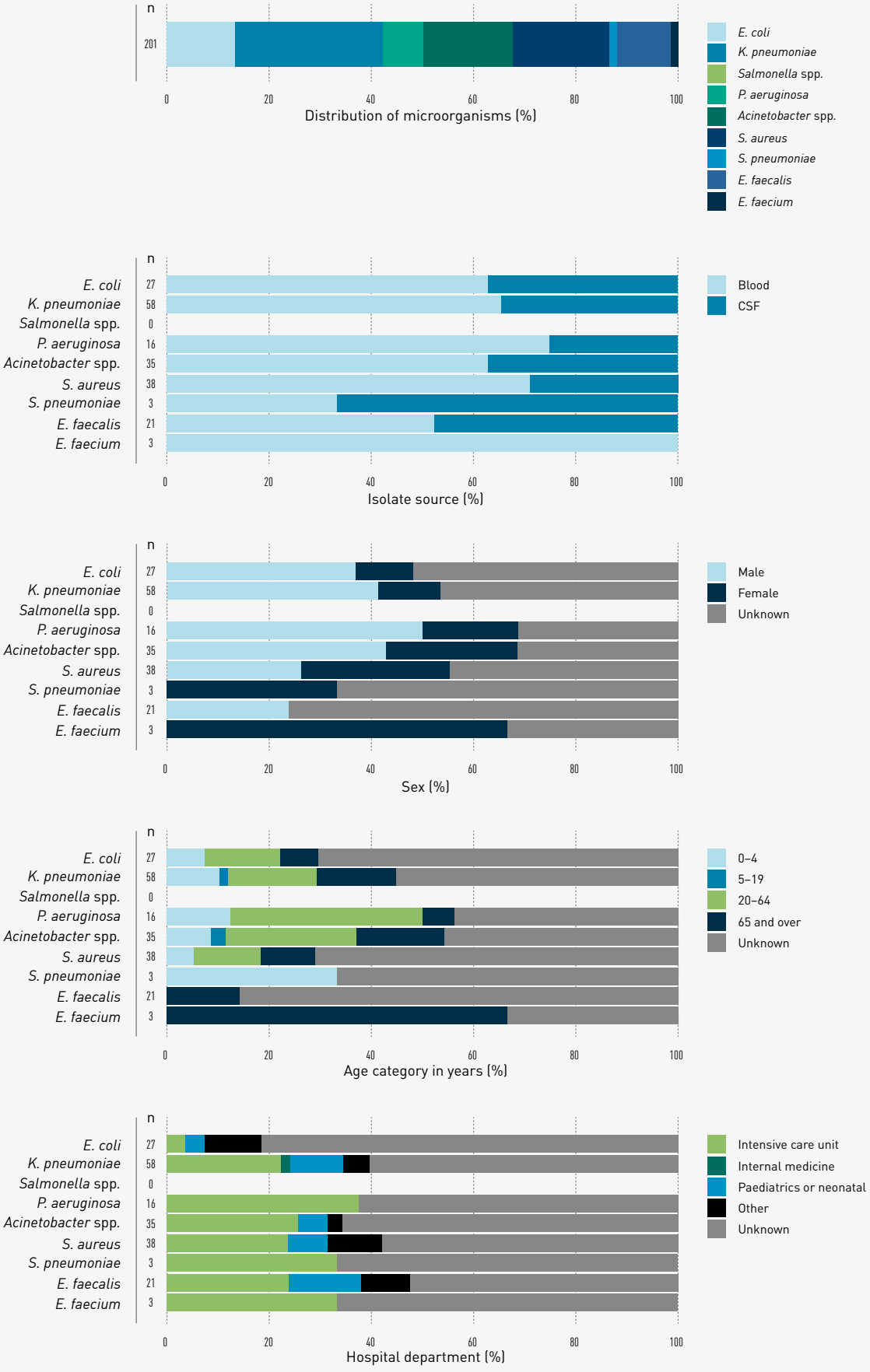


Table 5.13 Percentages of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Georgia, 2017

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (R)[a]	6	100*	NA	NA
Amoxicillin-clavulanic acid (R)	8	50*	38	92
Piperacillin-tazobactam (R)	26	4*	49	49
Cefotaxime/ceftriaxone (R)[b]	27	37*	56	87
Cefotaxime/ceftriaxone (I+R)[b]	27	37*	56	89
Ceftazidime (R)	26	35*	56	89
Ertapenem (R)	7	0*	16	50*
Imipenem/meropenem (R)[c]	27	0*	57	47
Imipenem/meropenem (I+R)[c]	27	4*	57	56
Gentamicin/tobramycin (R)[d]	25	32*	52	65
Amikacin (R)	26	8*	54	56
Ciprofloxacin/levofloxacin/ofloxacin (R)[e]	27	37*	56	59
Ciprofloxacin/levofloxacin/ofloxacin (I+R)[e]	27	37*	56	64
Multidrug resistance (R)[f]	25	16*	50	40

NA: not applicable.

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

[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[c] Imipenem and meropenem are indicators for the group of carbapenems.

[d] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[e] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

[f] Multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin/ofloxacin, cefotaxime/ceftriaxone/ceftazidime and gentamicin/tobramycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.14 Percentages of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Georgia, 2017

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	15	40*	NA	NA
Ceftazidime (R)	15	53*	NA	NA
Cefepime (R)	15	67*	NA	NA
Imipenem/meropenem (R)[a]	16	56*	34	85
Imipenem/meropenem (I+R)[a]	16	62*	34	88
Gentamicin/tobramycin (R)[b]	14	50*	34	68
Amikacin (R)	13	38*	27	70*
Ciprofloxacin/levofloxacin (R)[c]	16	56*	34	88
Multidrug resistance (R)[d]	12	42*	33	58

NA: not applicable.

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

[a] Imipenem and meropenem are indicators for the group of carbapenems.

[b] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[c] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.

[d] For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. For *Acinetobacter* spp., multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. Isolates with missing data on one or more of the groups were excluded in the calculation of multidrug resistance.

Table 5.15 Percentages of resistance for *S. aureus* among blood and CSF isolates in Georgia, 2017

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)[a]	35	11
Ciprofloxacin/levofloxacin/ofloxacin (R)[b]	37	14
Vancomycin (R)	25	0*
Rifampicin (R)	24	0*
Linezolid (R)	25	4*

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

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

[b] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

Table 5.16 Percentages of resistance for *S. pneumoniae* among blood and CSF isolates in Georgia, 2017

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillin (I+R)[a]	2	50*
Cefotaxime/ceftriaxone (R)[b]	3	33*
Cefotaxime/ceftriaxone (I+R)[b]	3	33*
Levofloxacin/moxifloxacin (R)[c]	3	0*
Erythromycin/clarithromycin/azithromycin (R)[d]	3	0*
Erythromycin/clarithromycin/azithromycin (I+R)[d]	3	0*
Multidrug resistance (I+R)[e]	2	0*

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

[a] Non-susceptibility to penicillin is based on penicillin or, if not available, on oxacillin.

[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[c] Levofloxacin and moxifloxacin are indicators for the group of fluoroquinolones.

[d] Erythromycin, clarithromycin and azithromycin are indicators for the group of macrolides.

[e] Multidrug resistance is defined as non-susceptibility to penicillin and erythromycin/clarithromycin/azithromycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.17 Percentages of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Georgia, 2017

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (I+R)[a]	20	55*	3	67*
High-level gentamicin (R)	18	44*	3	100*
Vancomycin (R)	21	0*	3	0*
Linezolid (I+R)	7	29*	1	100*

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

[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

5.4 Montenegro

5.4.1 Surveillance set-up

All eight public microbiology laboratories that process hospital samples in Montenegro are included in the AMR surveillance network. Using paper forms, the laboratories send antibiotic susceptibility testing data for blood and CSF samples 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. 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 2017 to 31 December 2017, was submitted to CAESAR. According to these specifications, data were available from four laboratories in 2017.

The AMR surveillance system of Montenegro covers the entire population (of 629 219, data from 2018 *(1)*). The eight laboratories are part of the primary health care system but provide diagnostic services to one specialized hospital (the Clinical Centre of Montenegro) and seven general hospitals in Montenegro. The central laboratory of the Institute of Public Health also provides diagnostic services to the Clinical Centre of Montenegro in Podgorica.

Blood cultures are performed using a manual system, and antibiotic susceptibility is tested using the disk diffusion method in the peripheral laboratories. The central laboratory of the Institute of Public Health in Podgorica uses an automated blood culture system, and disk diffusion and an automated system for AST. In 2017, the majority of AST (in all but one peripheral laboratory) was performed according to CLSI guidelines, but in 2018 many laboratories switched to EUCAST guidelines. All strains suspected of carbapenemase production are confirmed by phenotypic methods at the Centre for Medical Microbiology of the Institute of Public Health in Podgorica. All laboratories participate in the CAESAR external quality control programme provided by UK NEQAS and perform internal quality control on a regular basis. Established in 2015, the national AST committee organizes annual meetings.

According to national clinical bacteriology guidelines by the Ministry of Health in Montenegro, blood samples are obtained from all patients with suspected bloodstream infections (sepsis) presenting in hospital and CSF cultures from patients with suspected meningitis. However, adherence to these guidelines is suboptimal, and utilization of blood culture diagnostics is low due to several reasons. The clinical bacteriology guideline does not include practical recommendations for clinicians about when to take blood samples. Furthermore, financial constraints limit the procurement and continuous availability of high-quality equipment and materials for collecting and processing blood samples. Laboratories are not located in hospitals, causing a lack of direct communication between microbiologists and clinicians and a logistical barrier to taking blood samples. In 2017, the number of blood samples ranged from 0 to 15 per 1000 patient days in the eight hospitals supported by the laboratories in the network.

5.4.2 Results

Fig. 5.4 shows the distribution of microorganisms and the characteristics of patients (broken down by pathogen) of 133 blood and CSF isolates obtained in Montenegro in 2017. In *E. coli*, resistance ranged from 0% (imipenem/meropenem, amikacin) to 89% (amoxicillin/ampicillin, Table 5.18). Multidrug resistance was 5% in *E. coli*. Resistance in *K. pneumoniae* ranged from 14% for imipenem/meropenem to 97% for cefotaxime/ceftriaxone. Multidrug resistance in *K. pneumoniae* was 59%. One isolate of *Salmonella* spp. was found, which was susceptible to all selected agents (Table 5.19). Resistance in 14 *P. aeruginosa* isolates ranged from 7% (amikacin) to 57% (gentamicin/tobramycin, Table 5.20). Multidrug resistance was 38% in *P. aeruginosa*. In *Acinetobacter* spp. (10 isolates), resistance was 90–100% for all selected agents. Multidrug resistance in *Acinetobacter* spp. was 78%. Twenty-three per cent of *S. aureus* isolates were methicillin-resistant (MRSA, Table 5.21). Based on only four *S. pneumoniae* isolates, non-susceptibility to penicillin, as well as multidrug resistance, was 25% (Table 5.22). In 12 *E. faecalis* isolates, vancomycin resistance

was not observed, but in *E. faecium*, two of six isolates (33%) were vancomycin-resistant (Table 5.23). In Chapter 7, maps of the WHO European Region show the proportions of resistance for selected pathogen–antibiotic combinations reported by Montenegro (Fig. 7.1–7.6).

5.4.3 Discussion

Laboratories in Montenegro submitted antibiotic susceptibility testing results for 133 isolates from blood or CSF in 2017. The four laboratories that submitted data provide good geographical coverage. However, most isolates (94%) were processed at the central laboratory of the Institute of Public Health in the capital, Podgorica, which provides diagnostic support to the main referral hospital in the country. The overall small number of isolates reflects the underutilization of blood culture diagnostics in general. Blood cultures were generally taken in patients with antibiotic treatment failure or recurrent infections. Besides bias towards higher resistance caused by this selective sampling, the small number of isolates made 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 (cefotaxime/ceftriaxone and ceftazidime) and aminoglycosides (gentamicin/tobramycin) in *E. coli* and *K. pneumoniae*. Carbapenem (imipenem/meropenem) resistance was not observed in *E. coli* from blood or CSF in 2017, but four *K. pneumoniae* isolates (14%) were confirmed as carbapenem resistant. The proportion of MRSA was similar to that in neighbouring countries (Fig. 7.6). Too few antibiotic susceptibility testing results for *Salmonella* spp., *P. aeruginosa*, *S. pneumoniae*, *E. faecalis* and *E. faecium* were available to allow interpretation. The high levels 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.

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 a relatively small overall number of isolates (underutilization 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 the utilization of blood culture diagnostics, especially in regional hospitals, will lead to more valid assessment of AMR in the country. The reader's guide (Table 4.2) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.4 Patient characteristics of isolates in Montenegro in 2017, by pathogen

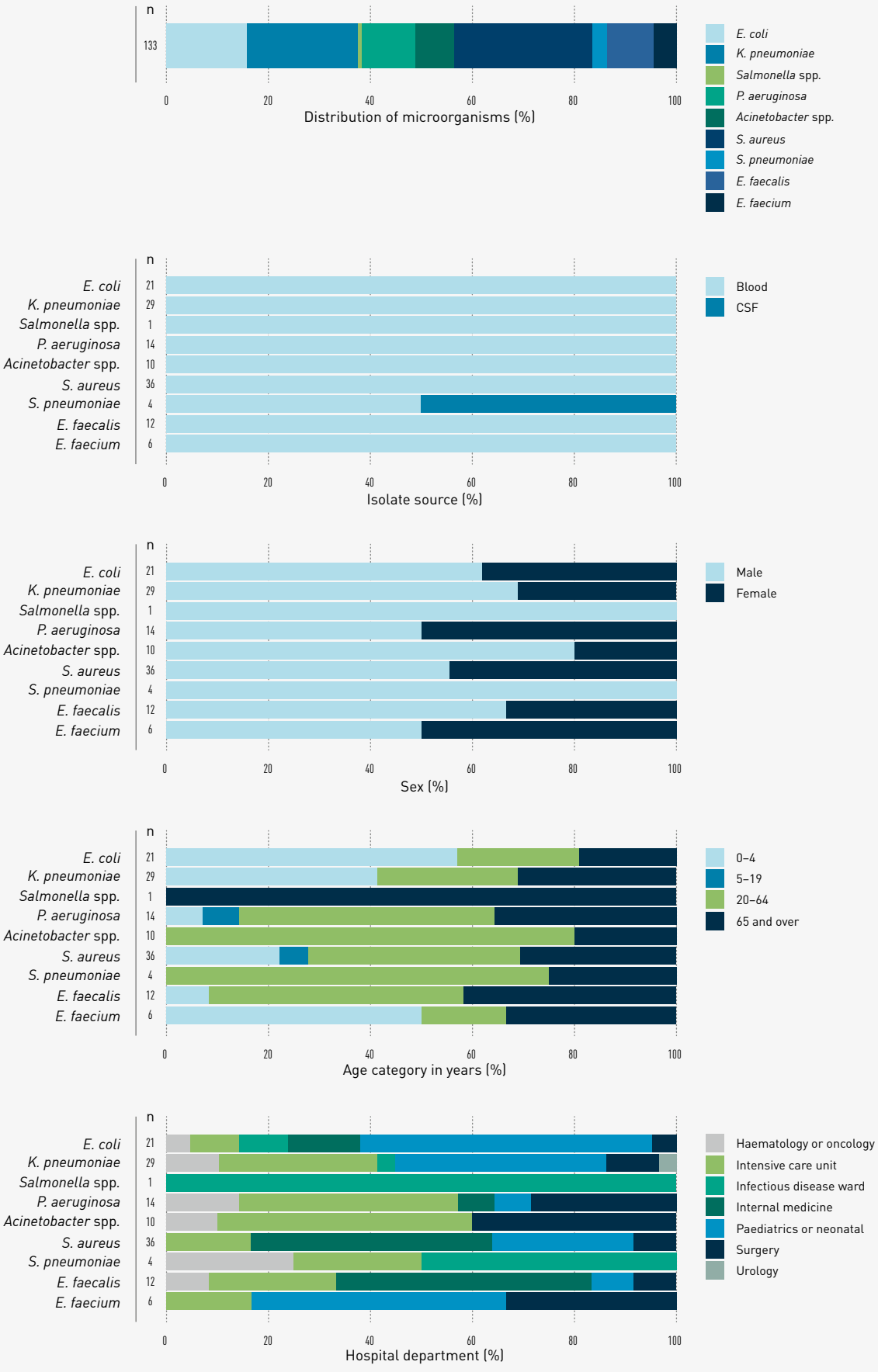


Table 5.18 Percentages of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Montenegro, 2017

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (R)[a]	18	89*	NA	NA
Amoxicillin-clavulanic acid (R)	20	65*	29	86*
Piperacillin-tazobactam (R)	19	21*	26	81*
Cefotaxime/ceftriaxone (R)[b]	20	70*	29	97*
Cefotaxime/ceftriaxone (I+R)[b]	20	70*	29	97*
Ceftazidime (R)	20	65*	28	96*
Ertapenem (R)	12	0*	8	25*
Imipenem/meropenem (R)[c]	20	0*	29	14*
Imipenem/meropenem (I+R)[c]	20	0*	29	14*
Gentamicin/tobramycin (R)[d]	20	45*	29	97*
Amikacin (R)	20	0*	29	41*
Ciprofloxacin/levofloxacin/ofloxacin (R)[e]	20	25*	29	59*
Ciprofloxacin/levofloxacin/ofloxacin (I+R)[e]	20	45*	29	62*
Multidrug resistance (R)[f]	19	5*	29	59*

NA: not applicable.

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

[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[c] Imipenem and meropenem are indicators for the group of carbapenems.

[d] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[e] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

[f] Multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin/ofloxacin, cefotaxime/ceftriaxone/ceftazidime and gentamicin/tobramycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.19 Percentages of resistance for *Salmonella* spp. among blood and CSF isolates in Montenegro, 2017

Antibiotic (group)	*Salmonella* spp.	
	N	Resistance (%)
Cefotaxime/ceftriaxone (R)[a]	1	0*
Cefotaxime/ceftriaxone (I+R)[a]	1	0*
Ceftazidime (R)	1	0*
Ertapenem (R)	0	–
Imipenem/meropenem (R)[b]	1	0*
Imipenem/meropenem (I+R)[b]	1	0*
Ciprofloxacin/levofloxacin (R)[c]	1	0*
Ciprofloxacin/levofloxacin (I+R)[c]	1	0*

–: no data available.

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

[a] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[b] Imipenem and meropenem are indicators for the group of carbapenems.

[c] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.

Table 5.20 Percentages of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Montenegro, 2017

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	14	21*	NA	NA
Ceftazidime (R)	13	38*	NA	NA
Cefepime (R)	11	55*	NA	NA
Imipenem/meropenem (R)[a]	14	36*	10	90*
Imipenem/meropenem (I+R)[a]	14	36*	10	90*
Gentamicin/tobramycin (R)[b]	14	57*	10	90*
Amikacin (R)	14	7*	10	100*
Ciprofloxacin/levofloxacin (R)[c]	14	50*	9	100*
Multidrug resistance (R)[d]	13	38*	9	78*

NA: not applicable.

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

[a] Imipenem and meropenem are indicators for the group of carbapenems.

[b] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[c] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.

[d] For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. For *Acinetobacter* spp., multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. Isolates with missing data on one or more of the groups were excluded in the calculation of multidrug resistance.

Table 5.21 Percentages of resistance for *S. aureus* among blood and CSF isolates in Montenegro, 2017

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)[a]	35	23
Ciprofloxacin/levofloxacin/ofloxacin (R)[b]	36	8
Vancomycin (R)	13	0*
Rifampicin (R)	17	0*
Linezolid (R)	25	0*

* A small number of isolates were tested (N < 30), and the percentage resistance should be interpreted with caution.
[a] MRSA is calculated as resistance to cefoxitin or, if not available, oxacillin.
[b] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

Table 5.22 Percentages of resistance for *S. pneumoniae* among blood and CSF isolates in Montenegro, 2017

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillin (I+R)[a]	4	25*
Cefotaxime/ceftriaxone (R)[b]	4	25*
Cefotaxime/ceftriaxone (I+R)[b]	4	25*
Levofloxacin/moxifloxacin (R)[c]	3	0*
Erythromycin/clarithromycin/azithromycin (R)[d]	4	50*
Erythromycin/clarithromycin/azithromycin (I+R)[d]	4	75*
Multidrug resistance (I+R)[e]	4	25*

* A small number of isolates were tested (N < 30), and the percentage resistance should be interpreted with caution.
[a] Non-susceptibility to penicillin is based on penicillin or, if not available, on oxacillin.
[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.
[c] Levofloxacin and moxifloxacin are indicators for the group of fluoroquinolones.
[d] Erythromycin, clarithromycin and azithromycin are indicators for the group of macrolides.
[e] Multidrug resistance is defined as non-susceptibility to penicillin and erythromycin/clarithromycin/azithromycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.23 Percentages of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Montenegro, 2017

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (I+R)[a]	11	9*	6	67*
High-level gentamicin (R)	11	55*	6	67*
Vancomycin (R)	12	0*	6	33*
Linezolid (I+R)	10	0*	3	0*

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

[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

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, most of which serve 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 not included in the surveillance system. 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 department and the type of specimen. According to CAESAR specifications, data from 37 laboratories were available for CAESAR in 2017. These laboratories are geographically spread out in the Russian Federation and serve mainly large city hospitals that provide tertiary care.

All isolates submitted to the laboratory of the Institute of Antimicrobial Chemotherapy that meet the criteria of the surveillance 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 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 2017 to 31 December 2017, was submitted to CAESAR. Extensive data from the national AMR surveillance network in the Russian Federation are available through an interactive web platform *(4)*.

The Russian Federation has an active AMR surveillance network, which has recently expanded to include local data from additional laboratories. Furthermore, the national guideline on antibiotic susceptibility testing methods and breakpoints has been updated according to EUCAST. The reference laboratory uses 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 a lack of EUCAST-based panels on the market in 2016–2017.

According to current practices, blood cultures are obtained from patients with severe infections and suspected sepsis. Most often these are patients with hospital-acquired infections and patients whose initial or empirical treatment was ineffective. 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. In nine network hospitals that provided denominator data, sampling rates ranged between 0 and 50 per 1000 patient days in 2017.

5.5.2 Results

Fig. 5.5 shows the distribution of microorganisms and the characteristics of patients (broken down by pathogen) of 419 blood and CSF isolates obtained in the Russian Federation in 2017. In *E. coli*, resistance ranged from 0% (imipenem/meropenem and amikacin) to 87% (amoxicillin/ampicillin, Table 5.24). Multidrug resistance was 37% in *E. coli*. In *K. pneumoniae*, resistance ranged from 21% for imipenem/meropenem to 91% for cefotaxime/ceftriaxone. Multidrug resistance in *K. pneumoniae* was 76%. No data on *Salmonella* spp. were available. Resistance in *P. aeruginosa* ranged from 22% (amikacin) to 64%

(piperacillin-tazobactam and ciprofloxacin/levofloxacin, Table 5.25). Multidrug resistance was 62% in *P. aeruginosa*. In *Acinetobacter* spp., resistance was 90% for gentamicin/tobramycin and higher for all other selected agents. Multidrug resistance in *Acinetobacter* spp. was 84%. Sixteen per cent of *S. aureus* isolates were methicillin-resistant (MRSA, Table 5.26). In *S. pneumoniae*, 28% of isolates were non-susceptible to penicillin (Table 5.27). Multidrug resistance in *S. pneumoniae* was 22%. In *E. faecalis*, as well as *E. faecium*, vancomycin resistance was not observed (Table 5.28). In Chapter 7, maps of the WHO European Region show the proportions of resistance for selected pathogen–antibiotic combinations reported by the Russian Federation (Fig. 7.1–7.6).

5.5.3 Discussion

The AMR surveillance network of the Russian Federation submitted antibiotic susceptibility testing results for 419 isolates from blood or CSF in 2017. The laboratories in the network are geographically spread out in the western part of the Russian Federation and mainly provide diagnostic support to tertiary care facilities. The small overall number of blood isolates (about 5% of the total number of isolates collected) reflects the underutilization of blood culture diagnostics by clinicians. Restrictive sampling among severely ill or unsuccessfully treated patients is also reflected in the high proportion of samples from patients in intensive care units (60%). Samples are not generally taken from patients with community-acquired infections, which may explain the relatively small number of *E. coli* and *S. pneumoniae* isolates. The reported percentages of resistance disproportionately represent nosocomial infections. Besides reflecting selective sampling, the small number of isolates made 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 an invasive infection in the Russian Federation, especially patients with community-acquired infections.

In the patient population sampled, high levels of resistance to third-generation cephalosporins (cefotaxime/ceftriaxone and ceftazidime) and fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin) were observed in both *E. coli* and *K. pneumoniae*. Resistance to carbapenems (imipenem/meropenem) was not observed in *E. coli* from blood or CSF in 2017, but was 21% in *K. pneumoniae*. The proportion of MRSA was moderate and similar to that in 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.

Data from the Russian Federation are assessed as level B. The data represent various geographic regions in the country. However, the generalizability of the results is limited by the overrepresentation of nosocomial infections in more severely ill and pretreated patients (selective sampling), the absence of general hospitals in the surveillance system and a small total number of isolates (underutilization of blood culture diagnostics). The antibiotic susceptibility testing results are considered reliable and comparable, because all isolates were (re)tested at the national AMR reference laboratory using standardized and quality controlled methods. The data indicate the resistance patterns present in clinical settings in the country, but the proportion of resistance should be interpreted with care. Expanding the network to include a variety of different hospital types and increasing the utilization of blood culture diagnostics, also in patients with community-acquired infections, will lead to more valid assessment of the magnitude of AMR in the country. The reader's guide (Table 4.2) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.5 Patient characteristics of isolates in the Russian Federation in 2017, by pathogen

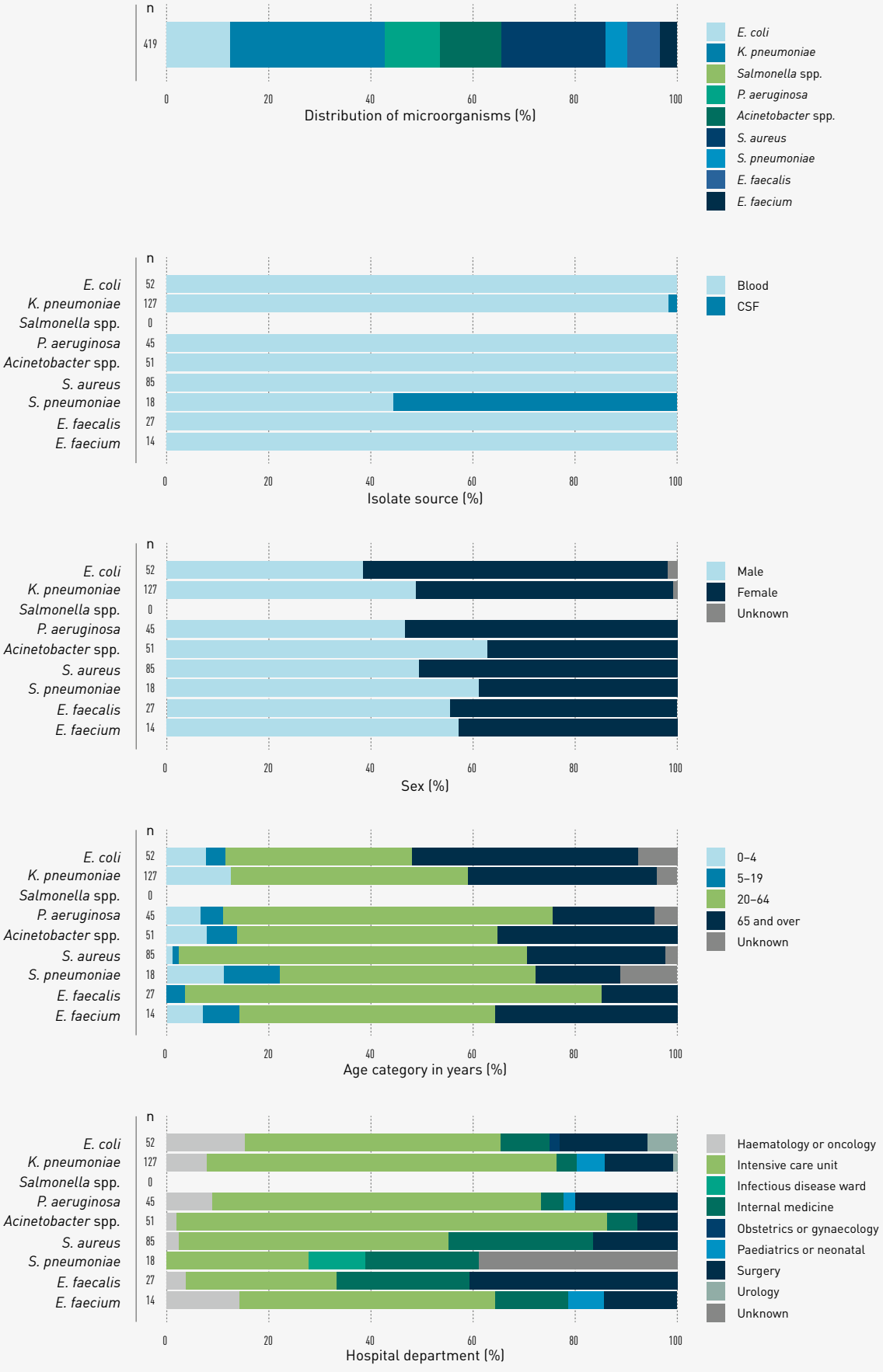


Table 5.24 Percentages of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in the Russian Federation, 2017

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (R)[a]	52	87	NA	NA
Amoxicillin-clavulanic acid (R)	52	27	127	80
Piperacillin-tazobactam (R)	52	17	127	65
Cefotaxime/ceftriaxone (R)[b]	52	73	127	91
Cefotaxime/ceftriaxone (I+R)[b]	52	73	127	91
Ceftazidime (R)	52	56	127	81
Ertapenem (R)	52	2	127	40
Imipenem/meropenem (R)[c]	52	0	127	21
Imipenem/meropenem (I+R)[c]	52	0	127	28
Gentamicin/tobramycin (R)[d]	52	42	127	81
Amikacin (R)	52	0	125	29
Ciprofloxacin/levofloxacin/ofloxacin (R)[e]	52	60	125	80
Ciprofloxacin/levofloxacin/ofloxacin (I+R)[e]	52	63	125	86
Multidrug resistance (R)[f]	52	37	125	76

NA: not applicable.

[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[c] Imipenem and meropenem are indicators for the group of carbapenems.

[d] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[e] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

[f] Multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin/ofloxacin, cefotaxime/ceftriaxone/ceftazidime and gentamicin/tobramycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.25 Percentages of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in the Russian Federation, 2017

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	45	64	NA	NA
Ceftazidime (R)	45	58	NA	NA
Cefepime (R)	45	42	NA	NA
Imipenem/meropenem (R)[a]	45	51	51	92
Imipenem/meropenem (I+R)[a]	45	64	51	94
Gentamicin/tobramycin (R)[b]	45	60	51	90
Amikacin (R)	45	22	51	94
Ciprofloxacin/levofloxacin (R)[c]	45	64	51	94
Multidrug resistance (R)[d]	45	62	51	84

NA: not applicable.

[a] Imipenem and meropenem are indicators for the group of carbapenems.

[b] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[c] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.

[d] For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. For *Acinetobacter* spp., multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. Isolates with missing data on one or more of the groups were excluded in the calculation of multidrug resistance.

Table 5.26 Percentages of resistance for *S. aureus* among blood and CSF isolates in the Russian Federation, 2017

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)[a]	85	16
Ciprofloxacin/levofloxacin/ofloxacin (R)[b]	85	22
Vancomycin (R)	85	0
Rifampicin (R)	85	2
Linezolid (R)	85	0

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

[b] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

Table 5.27 Percentages of resistance for *S. pneumoniae* among blood and CSF isolates in the Russian Federation, 2017

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillin (I+R)[a]	18	28*
Cefotaxime/ceftriaxone (R)[b]	18	0*
Cefotaxime/ceftriaxone (I+R)[b]	18	22*
Levofloxacin/moxifloxacin (R)[c]	18	0*
Erythromycin/clarithromycin/azithromycin (R)[d]	18	22*
Erythromycin/clarithromycin/azithromycin (I+R)[d]	18	22*
Multidrug resistance (I+R)[e]	18	22*

* A small number of isolates were tested (N < 30), and the percentage resistance should be interpreted with caution.
[a] Non-susceptibility to penicillin is based on penicillin or, if not available, on oxacillin.
[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.
[c] Levofloxacin and moxifloxacin are indicators for the group of fluoroquinolones.
[d] Erythromycin, clarithromycin and azithromycin are indicators for the group of macrolides.
[e] Multidrug resistance is defined as non-susceptibility to penicillin and erythromycin/clarithromycin/azithromycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.28 Percentages of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in the Russian Federation, 2017

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (I+R)[a]	27	0*	14	86*
High-level gentamicin (R)	27	56*	14	79*
Vancomycin (R)	27	0*	14	0*
Linezolid (I+R)	27	0*	14	0*

* A small number of isolates were tested (N < 30), and the percentage resistance should be interpreted with caution.
[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

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. The national reference laboratory for AMR – the Center for Microbiology of the Institute for Public Health of Vojvodina in Novi Sad – collects the data. As data come in, their quality and consistency are checked. If errors are detected, the data are sent back to the laboratory and corrected, where applicable. After that, the data are uploaded into the national WHONET database.

In 2014, the AMR surveillance network in Serbia comprised 14 laboratories. In 2016, the number of participating laboratories increased to 22. The laboratories provide diagnostic support to 26 hospitals, representing about 50% of all general hospitals and 50% of academic hospitals, including the largest clinical centres in the country. They are geographically spread out and cover about 75% of the population (of 8 762 027, data from 2018 *(1)*).

Antimicrobial susceptibility is most often tested using the disk diffusion method; some laboratories use a combination of an automated system and disk diffusion, and if necessary according to AST guidelines, gradient tests are used. The national AST committee translated the EUCAST clinical breakpoint table into Serbian and implemented this as a national guideline on methods for testing antimicrobial susceptibility *(5)*. Since January 2017, all network laboratories use EUCAST guidelines for AST. Several laboratories are accredited according to the ISO/IEC 17025:2005 standard, and others are according to ISO 9001 and ISO 14 001 standards. All laboratories have internal quality control systems and participate in the national and international (CAESAR, provided by UK NEQAS) EQA exercises. There is no regular national EQA programme. In 2008, the Ministry of Health appointed the national AMR reference laboratory, but funding is insufficient, additional staff could not be allocated and the sending of reports and bacterial strains to reference laboratories is not regulated, but done voluntarily.

Serbia has an active AMR surveillance network and organizes annual national network meetings where CAESAR AMR and EQA results are presented, and AST guidelines and recommendations are discussed among clinical microbiologists. In 2018, the network further expanded with two additional laboratories.

Blood cultures are obtained from all patients with suspected bloodstream infections (sepsis), and CSF cultures from patients with suspected meningitis. The costs of bacteriology cultures are reimbursed through the National Health Insurance Fund. In 2017, the number of blood cultures ranged from 0 to 82 per 1000 patient days in the 22 hospitals supported by the laboratories in the network.

5.6.2 Results

Fig. 5.6 shows the distribution of microorganisms and the characteristics of patients (broken down by pathogen) of 2339 blood and CSF isolates obtained in Serbia in 2017. In *E. coli*, resistance ranged from 1% for imipenem/meropenem to 63% for amoxicillin/ampicillin (Table 5.29). Multidrug resistance was 21% in *E. coli*. In *K. pneumoniae*, resistance was 35% for imipenem/meropenem and higher for all other selected agents. Multidrug resistance in *K. pneumoniae* was 64%. In 13 isolates of *Salmonella* spp., resistance was observed for ciprofloxacin/levofloxacin (8%, Table 5.30). In *P. aeruginosa*, resistance ranged between 37% (amikacin) and 60% (gentamicin/tobramycin, Table 5.31). Multidrug resistance was 51% in *P. aeruginosa*. Resistance in *Acinetobacter* spp. was 94–96% for all selected antibiotics. Multidrug resistance in *Acinetobacter* spp. was 92%. Twenty-six per cent of *S. aureus* isolates were methicillin-resistant (MRSA, Table 5.32). In *S. pneumoniae*, non-susceptibility to penicillin was 38%, and 23% of isolates were multidrug resistant (Table 5.33). In *E. faecalis*, vancomycin resistance was 10% and 1% was non-susceptible to linezolid (Table 5.34). In *E. faecium*, 46% of isolates were vancomycin-resistant. In Chapter 7, maps of the

WHO European Region show the proportions of resistance for selected pathogen–antibiotic combinations reported by Serbia (Fig. 7.1–7.6).

5.6.3 Discussion

The AMR surveillance network submitted antibiotic susceptibility testing results for 2339 isolates from blood or CSF in Serbia in 2017. The network provides good geographical coverage and comprises tertiary care facilities, as well as smaller regional hospitals. However, the relatively large number of isolates from patients admitted to intensive care units (21%), the relatively high proportions of *Acinetobacter* spp. (18%) and *K. pneumoniae* (18%) 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, including carbapenem (imipenem/meropenem) resistance, were seen in *K. pneumoniae*. In *E. coli*, moderately high resistance was found for third-generation cephalosporins (cefotaxime/ceftriaxone and ceftazidime), aminoglycosides (gentamicin/tobramycin) and fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin). Four *E. coli* isolates were carbapenem-resistant (two based on automated testing and two based on disk diffusion), but carbapenemase production was not assessed. The proportion of MRSA was similar to that in neighbouring countries (Fig. 7.6). The levels of resistance in *S. pneumoniae* to penicillin and macrolides (erythromycin/clarithromycin/azithromycin) were high. The high percentages of resistance in *P. aeruginosa*, *Acinetobacter* spp. and *E. faecium* are concerning and may reflect the dissemination of resistant clones in the health care setting.

Data from Serbia 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, 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 4.2) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.6 Patient characteristics of isolates in Serbia in 2017, by pathogen

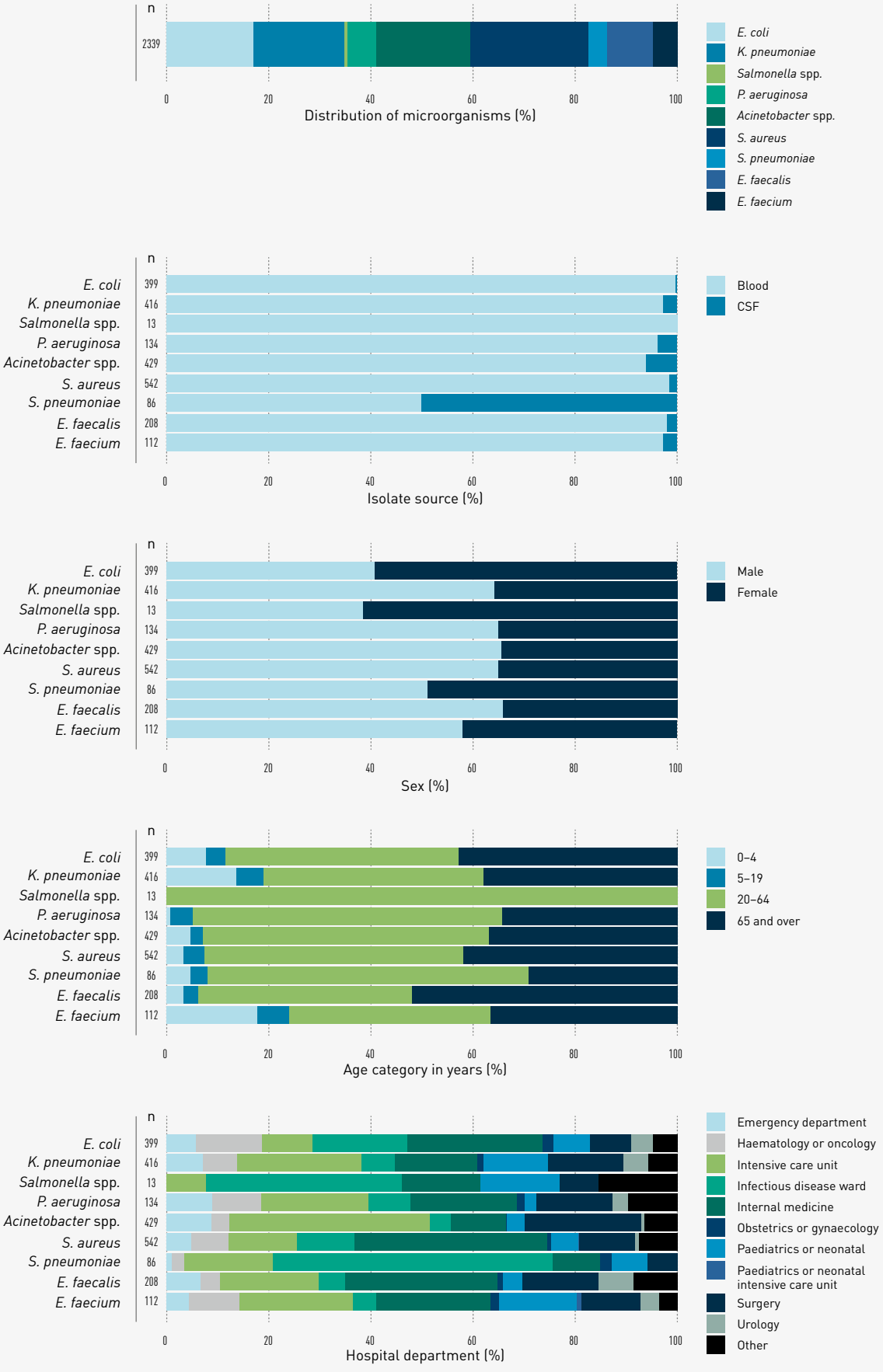


Table 5.29 Percentages of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Serbia, 2017

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (R)[a]	365	63	NA	NA
Amoxicillin-clavulanic acid (R)	291	39	323	90
Piperacillin-tazobactam (R)	374	16	378	72
Cefotaxime/ceftriaxone (R)[b]	395	29	406	84
Cefotaxime/ceftriaxone (I+R)[b]	395	30	406	85
Ceftazidime (R)	350	25	347	82
Ertapenem (R)	344	1	304	44
Imipenem/meropenem (R)[c]	399	1	416	35
Imipenem/meropenem (I+R)[c]	399	1	416	39
Gentamicin/tobramycin (R)[d]	382	35	393	76
Amikacin (R)	392	9	392	43
Ciprofloxacin/levofloxacin/ofloxacin (R)[e]	394	40	407	76
Ciprofloxacin/levofloxacin/ofloxacin (I+R)[e]	394	44	407	78
Multidrug resistance (R)[f]	377	21	384	64

NA: not applicable.

[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[c] Imipenem and meropenem are indicators for the group of carbapenems.

[d] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[e] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

[f] Multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin/ofloxacin, cefotaxime/ceftriaxone/ceftazidime and gentamicin/tobramycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.30 Percentages of resistance for *Salmonella* spp. among blood and CSF isolates in Serbia, 2017

Antibiotic (group)	*Salmonella* spp.	
	N	Resistance (%)
Cefotaxime/ceftriaxone (R)[a]	13	0*
Cefotaxime/ceftriaxone (I+R)[a]	13	0*
Ceftazidime (R)	12	0*
Ertapenem (R)	8	0*
Imipenem/meropenem (R)[b]	10	0*
Imipenem/meropenem (I+R)[b]	10	0*
Ciprofloxacin/levofloxacin (R)[c]	13	8*
Ciprofloxacin/levofloxacin (I+R)[c]	13	31*

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

[a] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[b] Imipenem and meropenem are indicators for the group of carbapenems.

[c] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.

Table 5.31 Percentages of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Serbia, 2017

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	125	44	NA	NA
Ceftazidime (R)	130	55	NA	NA
Cefepime (R)	132	51	NA	NA
Imipenem/meropenem (R)[a]	133	49	429	95
Imipenem/meropenem (I+R)[a]	133	52	429	96
Gentamicin/tobramycin (R)[b]	132	60	429	94
Amikacin (R)	130	37	385	94
Ciprofloxacin/levofloxacin (R)[c]	134	57	428	96
Multidrug resistance (R)[d]	121	51	428	92

NA: not applicable.

[a] Imipenem and meropenem are indicators for the group of carbapenems.

[b] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[c] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.

[d] For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. For *Acinetobacter* spp., multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. Isolates with missing data on one or more of the groups were excluded in the calculation of multidrug resistance.

Table 5.32 Percentages of resistance for *S. aureus* among blood and CSF isolates in Serbia, 2017

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)[a]	541	26
Ciprofloxacin/levofloxacin/ofloxacin (R)[b]	522	22
Vancomycin (R)	524	0
Rifampicin (R)	462	15
Linezolid (R)	517	0

[a] MRSA is calculated as resistance to cefoxitin or, if not available, oxacillin.
[b] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

Table 5.33 Percentages of resistance for *S. pneumoniae* among blood and CSF isolates in Serbia, 2017

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillin (I+R)[a]	86	38
Cefotaxime/ceftriaxone (R)[b]	78	1
Cefotaxime/ceftriaxone (I+R)[b]	78	10
Levofloxacin/moxifloxacin (R)[c]	77	5
Erythromycin/clarithromycin/azithromycin (R)[d]	79	27
Erythromycin/clarithromycin/azithromycin (I+R)[d]	79	27
Multidrug resistance (I+R)[e]	79	23

[a] Non-susceptibility to penicillin is based on penicillin or, if not available, on oxacillin.
[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.
[c] Levofloxacin and moxifloxacin are indicators for the group of fluoroquinolones.
[d] Erythromycin, clarithromycin and azithromycin are indicators for the group of macrolides.
[e] Multidrug resistance is defined as non-susceptibility to penicillin and erythromycin/clarithromycin/azithromycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.34 Percentages of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Serbia, 2017

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (I+R)[a]	208	8	111	92
High-level gentamicin (R)	195	71	109	90
Vancomycin (R)	199	10	109	46
Linezolid (I+R)	207	1	112	0

[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

5.7 Switzerland

5.7.1 Surveillance set-up

The Swiss Centre for Antibiotic Resistance was established in 2004 in the framework of a national research programme. It is run by the Institute for Infectious Diseases, University of Bern and funded by the Swiss Federal Office of Public Health and the University of Bern. Twenty-three 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. 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 2017 to 31 December 2017, was submitted to CAESAR.

In 2017, the AMR network in Switzerland expanded with three additional laboratories, and further expansions are planned for 2018. The 23 participating laboratories provide services to about 80% of hospitalized patients and one third of ambulatory practitioners. The laboratories are geographically spread out across all regions and include university and general hospital laboratories, as well as private laboratories.

There are no national antibiotic susceptibility testing guidelines, but the Swiss Society for Microbiology (SSM) provides recommendations for specific adaptations due to new international guidelines or new technical developments. Most laboratories changed from CLSI to EUCAST guidelines between 2011 and 2013; in 2017, about 90% of laboratories used EUCAST guidelines. Most laboratories use automated systems; unusual antibiotic susceptibility testing results are confirmed locally. Collection and confirmatory testing of isolates are not centralized; however, microorganisms with new or difficult to detect resistance mechanisms may be sent to the National Reference Centre for the Early Detection and Monitoring of Antibiotic Resistance (NARA) for further analysis. Since 2016, carbapenemase-producing Enterobacteriaceae have to be sent to one of seven predefined Swiss expert laboratories for confirmation and further analysis. 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 participate in at least one national or international EQA programme. Switzerland therefore decided not to participate in the CAESAR EQA exercise.

Switzerland has an active AMR surveillance network. The steering committee, which meets at least twice yearly, makes all strategic decisions. It includes representatives of all university laboratories, two private laboratories, the Federal Office of Public Health, the NARA, the SSM, the Swiss Society for Infectious Diseases (SSI), the National Center for Infection Control (swissnoso), and one representative of veterinary medicine. Data on the most important resistance trends are published monthly by the Federal Office of Public Health; more detailed analyses that include veterinary data are published every second year in November. In addition, data are regularly presented at national conferences of the SSI and SSM.

Blood cultures are obtained from all patients with suspected bloodstream infections presenting in hospital, and CSF cultures from patients with suspected meningitis. The costs of bacteriology cultures are reimbursed through the universal health insurance scheme.

5.7.2 Results

Fig. 5.7 shows the distribution of microorganisms and the characteristics of patients (broken down by pathogen) of 11 003 blood and CSF isolates obtained in Switzerland in 2017. In *E. coli*, resistance ranged from 0% for imipenem/meropenem and ertapenem to 49% for amoxicillin/ampicillin (Table 5.35). Multidrug resistance was 3% in *E. coli*. Resistance in *K. pneumoniae* ranged from 0% (imipenem/meropenem and ertapenem) to 13% (amoxicillin-clavulanic acid). Multidrug resistance in *K. pneumoniae* was 3%. In *Salmonella* spp., resistance was highest for ciprofloxacin/levofloxacin (16%, Table 5.36). Resistance in *P. aeruginosa* ranged between 1% (amikacin) and 9% (piperacillin-tazobactam, Table 5.37). Multidrug resistance in *P. aeruginosa* was 4%. In *Acinetobacter* spp. resistance ranged from 10% for imipenem/meropenem to 16%

for gentamicin/tobramycin. Multidrug resistance in *Acinetobacter* spp. was 9%. Four per cent of *S. aureus* isolates were methicillin-resistant (MRSA, Table 5.38). In *S. pneumoniae*, non-susceptibility to penicillin was 6% (Table 5.39). Three per cent of *S. pneumoniae* isolates were multidrug resistant. Vancomycin resistance was 0% in *E. faecalis* and 2% in *E. faecium* (Table 5.40). In Chapter 7, maps of the WHO European Region show the proportions of resistance for selected pathogen–antibiotic combinations reported by Switzerland (Fig. 7.1–7.6).

5.7.3 Discussion

The AMR surveillance network submitted antibiotic susceptibility testing results for 11 003 isolates from blood or CSF in Switzerland in 2017. The main pathogen isolated was *E. coli* (49%), followed by *S. aureus* (18%). About 5% of isolates were from patients admitted to intensive care units whereas 33% comprised patients in emergency departments, indicating that the data provide a good representation of nosocomial, as well as community-acquired infections. 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 were comparable with those in countries close to Switzerland and comparable with the results in 2016 *(6)*.

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; OXA-48, KPC- and NDM-type carbapenemases were the most prevalent in Switzerland *(7)*. These observations led to the decision to declare carbapenemase-producing Enterobacteriaceae as a notifiable disease on 1 January 2016. In 2016, 142 carbapenemase-producing Enterobacteriaceae isolates were observed; this number decreased to 114 in 2017.

Data from Switzerland are assessed as level A. The data presented are 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 4.2) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.7 Patient characteristics of isolates in Switzerland in 2017, by pathogen

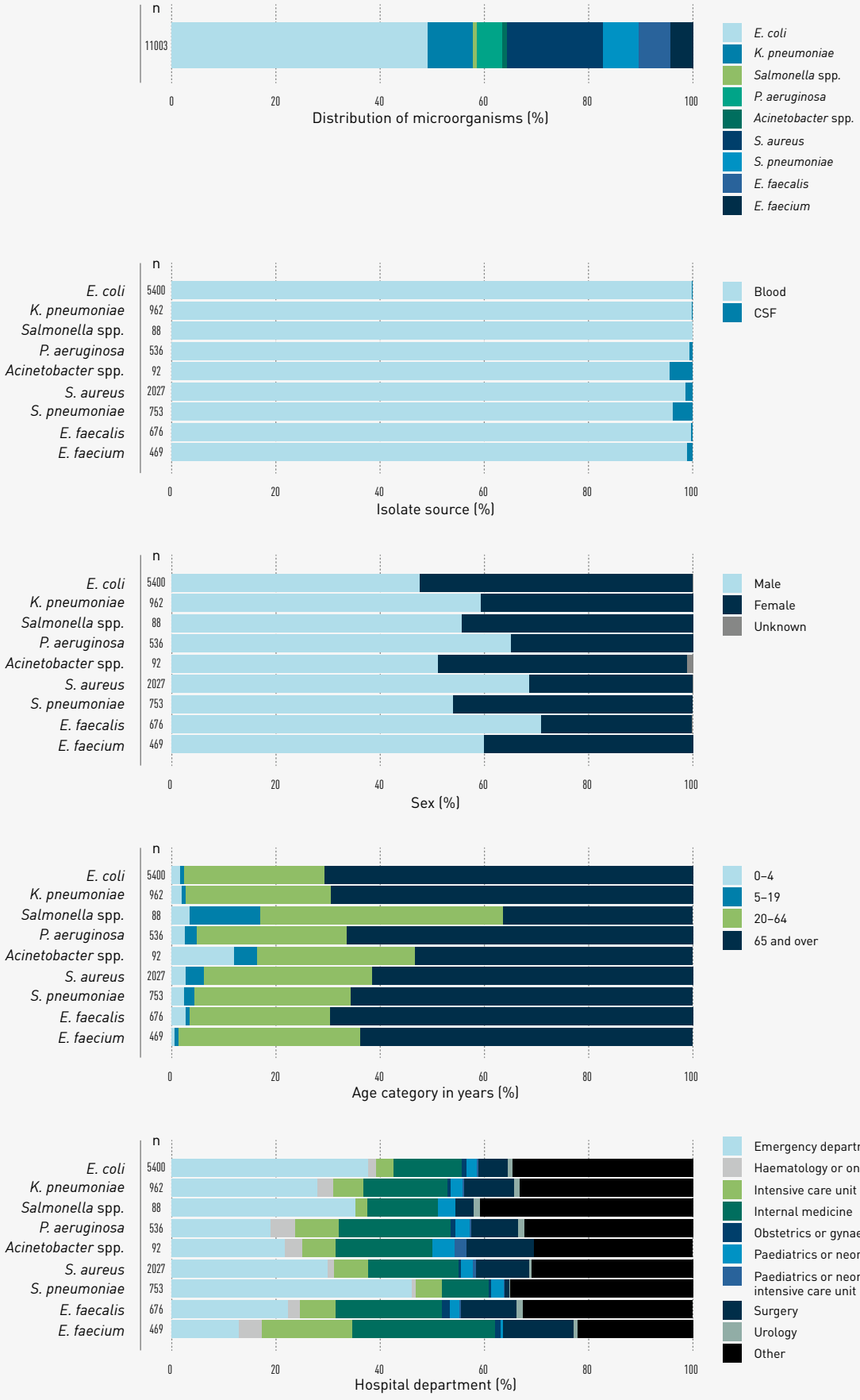


Table 5.35 Percentages of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Switzerland, 2017

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (R)[a]	5394	49	NA	NA
Amoxicillin-clavulanic acid (R)	5390	23	960	13
Piperacillin-tazobactam (R)	5372	4	959	5
Cefotaxime/ceftriaxone (R)[b]	5375	9	960	6
Cefotaxime/ceftriaxone (I+R)[b]	5375	9	960	7
Ceftazidime (R)	5372	7	947	6
Ertapenem (R)	4060	0	714	0
Imipenem/meropenem (R)[c]	5378	0	959	0
Imipenem/meropenem (I+R)[c]	5378	0	959	0
Gentamicin/tobramycin (R)[d]	5388	8	961	5
Amikacin (R)	3968	2	730	1
Ciprofloxacin/levofloxacin/ofloxacin (R)[e]	5397	17	961	8
Ciprofloxacin/levofloxacin/ofloxacin (I+R)[e]	5397	19	961	11
Multidrug resistance (R)[f]	5385	3	959	3

NA: not applicable.

[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[c] Imipenem and meropenem are indicators for the group of carbapenems.

[d] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[e] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

[f] Multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin/ofloxacin, cefotaxime/ceftriaxone/ceftazidime and gentamicin/tobramycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.36 Percentages of resistance for *Salmonella* spp. among blood and CSF isolates in Switzerland, 2017

Antibiotic (group)	*Salmonella* spp.	
	N	Resistance (%)
Cefotaxime/ceftriaxone (R)[a]	88	1
Cefotaxime/ceftriaxone (I+R)[a]	88	1
Ceftazidime (R)	65	2
Ertapenem (R)	54	0
Imipenem/meropenem (R)[b]	68	0
Imipenem/meropenem (I+R)[b]	68	0
Ciprofloxacin/levofloxacin (R)[c]	83	16
Ciprofloxacin/levofloxacin (I+R)[c]	83	17

[a] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.
[b] Imipenem and meropenem are indicators for the group of carbapenems.
[c] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.

Table 5.37 Percentages of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Switzerland, 2017

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	536	9	NA	NA
Ceftazidime (R)	510	8	NA	NA
Cefepime (R)	516	5	NA	NA
Imipenem/meropenem (R)[a]	533	8	91	10
Imipenem/meropenem (I+R)[a]	533	11	91	14
Gentamicin/tobramycin (R)[b]	535	3	89	16
Amikacin (R)	503	1	77	13
Ciprofloxacin/levofloxacin (R)[c]	535	8	91	14
Multidrug resistance (R)[d]	508	4	89	9

NA: not applicable.
[a] Imipenem and meropenem are indicators for the group of carbapenems.
[b] Gentamicin and tobramycin are indicators for the group of aminoglycosides.
[c] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.
[d] For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. For *Acinetobacter* spp., multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. Isolates with missing data on one or more of the groups were excluded in the calculation of multidrug resistance.

Table 5.38 Percentages of resistance for *S. aureus* among blood and CSF isolates in Switzerland, 2017

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)[a]	1983	4
Ciprofloxacin/levofloxacin/ofloxacin (R)[b]	2006	7
Vancomycin (R)	1854	0
Rifampicin (R)	1983	0
Linezolid (R)	909	0

[a] MRSA is calculated as resistance to cefoxitin or, if not available, oxacillin.
[b] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

Table 5.39 Percentages of resistance for *S. pneumoniae* among blood and CSF isolates in Switzerland, 2017

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillin (I+R)[a]	723	6
Cefotaxime/ceftriaxone (R)[b]	498	0
Cefotaxime/ceftriaxone (I+R)[b]	498	0
Levofloxacin/moxifloxacin (R)[c]	525	1
Erythromycin/clarithromycin/azithromycin (R)[d]	650	9
Erythromycin/clarithromycin/azithromycin (I+R)[d]	650	9
Multidrug resistance (I+R)[e]	621	3

[a] Non-susceptibility to penicillin is based on penicillin or, if not available, on oxacillin.
[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.
[c] Levofloxacin and moxifloxacin are indicators for the group of fluoroquinolones.
[d] Erythromycin, clarithromycin and azithromycin are indicators for the group of macrolides.
[e] Multidrug resistance is defined as non-susceptibility to penicillin and erythromycin/clarithromycin/azithromycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.40 Percentages of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Switzerland, 2017

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (I+R)[a]	674	1	462	80
High-level gentamicin (R)	273	11	186	28
Vancomycin (R)	676	0	465	2
Linezolid (I+R)	460	0	292	0

[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

5.8 The former Yugoslav Republic of Macedonia

5.8.1 Surveillance set-up

Results from routine antibiotic susceptibility testing of clinical bacteriology blood and CSF cultures are collected on paper monthly from all microbiological laboratories in the former Yugoslav Republic of Macedonia providing blood and CSF culture diagnostic services (19 out of 30 active public and private microbiological laboratories in 2017). The CAESAR national data team collects 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. After receiving the data, their quality and consistency are checked by the CAESAR data manager. If errors are detected, the data are sent back to the laboratory 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 2017 to 31 December 2017, was submitted to CAESAR. According to CAESAR specifications, data from 10 laboratories (eight public and two private) were available for CAESAR in 2017.

The 19 laboratories participating in CAESAR provide diagnostic support to almost all hospitals, including the University Clinical Center in Skopje (consisting of several specialized tertiary care university clinics), as well as general hospitals. The laboratories are geographically spread out in the capital, Skopje, and the south-western, western, central and eastern parts of the country and cover almost the entire population (of 2 085 051, data from 2018 *(1)*). Almost half the population lives and uses health services in Skopje. The capital is well covered with public and private microbiology laboratories that report data to CAESAR. Patients from other hospitals in the country are referred to the University Clinical Center in Skopje.

Antimicrobial susceptibility is routinely tested using disk diffusion methods and automated systems. Some laboratories use gradient tests for minimum inhibitory concentrations (MIC) to confirm highly resistant microorganisms. Sometimes, laboratories are requested to send the strain to the laboratory of the Institute for Public Health or the Institute of Microbiology and Parasitology at the Medical Faculty of Skopje for confirmation or additional investigation. In 2013, EUCAST guidelines were adopted as the national standard for bacteriological methods for testing antimicrobial susceptibility. EUCAST documents were translated and distributed to all laboratories, and workshops for implementation were held. Since 2016, annual EUCAST updates have been distributed to laboratories in January. As a result, 26 of 30 laboratories (87%) used EUCAST in 2017. One laboratory providing blood and CSF culture diagnostics is accredited according to ISO 17 025 standards. Nineteen (of 30) microbiology laboratories participated in the international CAESAR EQA exercise provided by UK NEQAS in 2017.

According to national clinical guidelines, blood cultures should be obtained from all patients with suspected bloodstream infections (sepsis), and CSF cultures from patients with suspected meningitis presenting in a hospital. In 2017, blood sampling rates ranged from 0 to 37 per 1000 patient days in 37 hospitals and clinics in the former Yugoslav Republic of Macedonia.

5.8.2 Results

Fig. 5.8 shows the distribution of microorganisms and the characteristics of patients (broken down by pathogen) of 255 blood and CSF isolates obtained in the former Yugoslav Republic of Macedonia in 2017. In *E. coli*, resistance ranged from 0% for imipenem/meropenem to 83% for amoxicillin/ampicillin (Table 5.41). Multidrug resistance was 39% in *E. coli*. Resistance in *K. pneumoniae* was 17% for imipenem/meropenem and higher for all other agents. Multidrug resistance in *K. pneumoniae* was 70%. Data were not available for *Salmonella* spp. from blood or CSF. Resistance in *P. aeruginosa* ranged between 13% (amikacin) and 47% (ciprofloxacin/levofloxacin, Table 5.42). Multidrug resistance was 24% in *P. aeruginosa*. In *Acinetobacter* spp., resistance was 62% for amikacin and higher for all other agents. Multidrug resistance

in *Acinetobacter* spp. was 75%. Fifty-three per cent of *S. aureus* isolates were methicillin-resistant (MRSA, Table 5.43). Based on only six *S. pneumoniae* isolates, non-susceptibility to penicillin, as well as multidrug resistance, was 83% (Table 5.44). Vancomycin resistance was not observed in *E. faecalis*, but was 52% in *E. faecium* (Table 5.45). In Chapter 7, maps of the WHO European Region show the proportions of resistance for selected pathogen–antibiotic combinations reported by the former Yugoslav Republic of Macedonia (Fig. 7.1–7.6).

5.8.3 Discussion

CAESAR laboratories in the former Yugoslav Republic of Macedonia submitted antibiotic susceptibility testing results for 255 isolates from blood or CSF in 2017. The 10 laboratories with eligible data provide good geographical coverage, except for the eastern part of the country. The majority of isolates were *E. coli* (30%) and *S. aureus* (20%), suggesting a mix of hospital-acquired and community-acquired infections was sampled. However, a large part of isolates (about 56%) were processed at the Institute of Microbiology and Parasitology at the Medical Faculty of Skopje, which provides diagnostic support to the main tertiary care hospital in the country. The overrepresentation 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 overall small number of isolates of CAESAR pathogens reflects the underutilization of blood culture diagnostics in general, which is thought to result from financial constraints. Besides bias towards higher resistance caused by selective sampling, the small number of isolates made 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.

Nevertheless, the patient population sampled had very high levels of resistance to third-generation cephalosporins (cefotaxime/ceftriaxone and ceftazidime), aminoglycosides (gentamicin/tobramycin) and fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin) in *E. coli* and *K. pneumoniae*. Carbapenem (imipenem/meropenem) resistance was not observed in *E. coli* from blood or CSF in 2017. In *K. pneumoniae*, four isolates (17%) were carbapenem resistant, all of which were confirmed to be carbapenemase-producers by phenotypic methods. Importantly, the observed resistance percentage for ertapenem (0%) was lower than for imipenem/meropenem in *K. pneumoniae*, which is unusual and likely explained by testing only a subset of (imipenem/meropenem susceptible) isolates for ertapenem. The proportion of MRSA was concerning and higher than that in most neighbouring countries (Fig. 7.6). Too few antibiotic susceptibility testing results for *P. aeruginosa* and *S. pneumoniae* were available to allow interpretation. The high levels of resistance in *Acinetobacter* spp. and *E. faecium* are concerning and may reflect the dissemination of resistant clones in the health care setting.

Data from the former Yugoslav Republic of Macedonia are assessed as level B. The species distribution suggests that the data represent a mix of hospital-associated and community-acquired infections. However, the overrepresentation of more severely ill and pretreated patients receiving tertiary care (selective sampling) and an overall small number of isolates (underutilization 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. Increasing the utilization of blood culture diagnostics, especially in regional hospitals, will lead to more valid assessment of AMR in the country. The reader's guide (Table 4.2) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.8 Patient characteristics of isolates in the former Yugoslav Republic of Macedonia in 2017, by pathogen

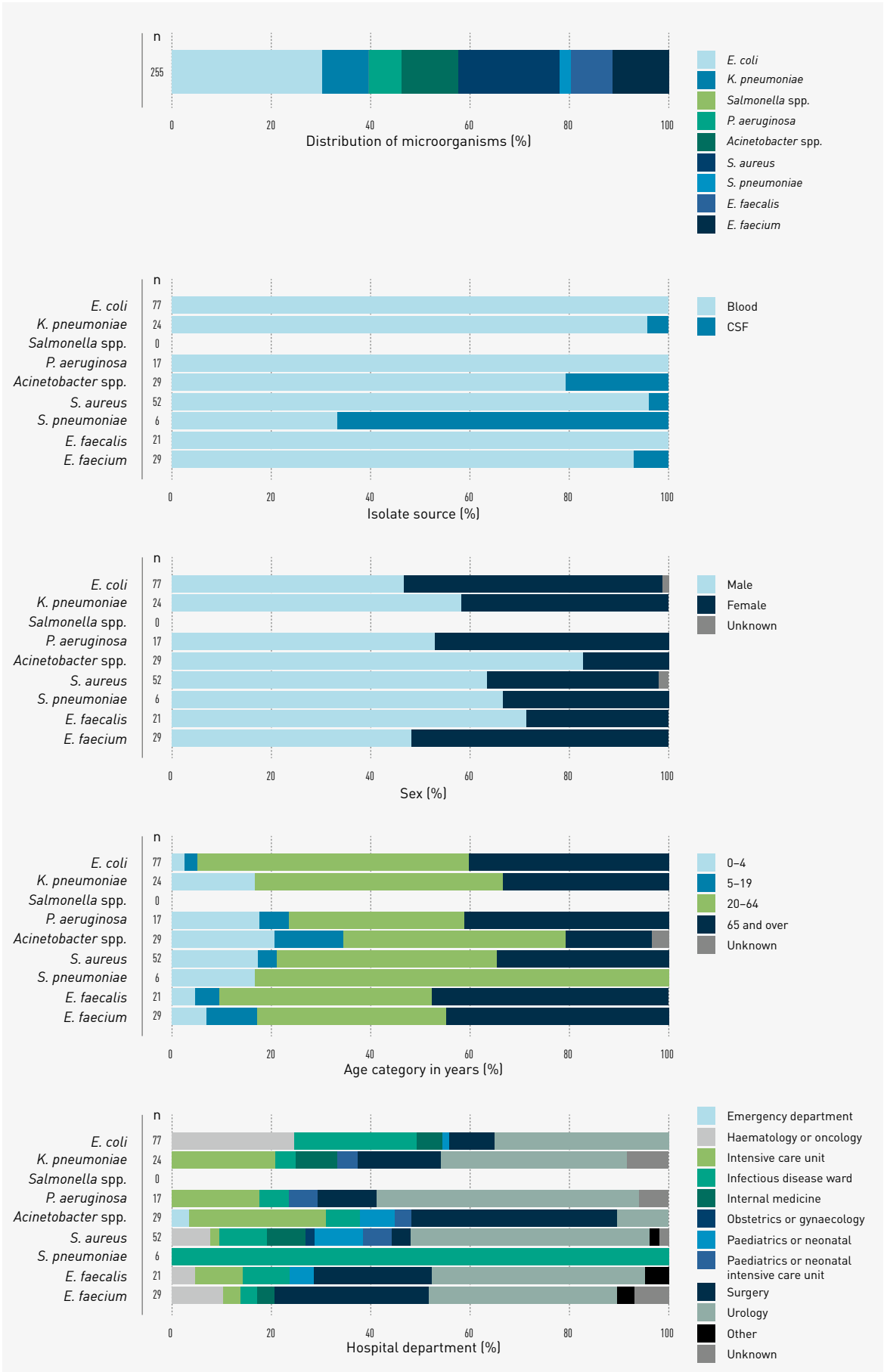


Table 5.41 Percentages of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in the former Yugoslav Republic of Macedonia, 2017

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (R)[a]	35	83	NA	NA
Amoxicillin-clavulanic acid (R)	68	60	20	80*
Piperacillin-tazobactam (R)	74	27	19	58*
Cefotaxime/ceftriaxone (R)[b]	71	73	21	81*
Cefotaxime/ceftriaxone (I+R)[b]	71	75	21	81*
Ceftazidime (R)	60	60	21	76*
Ertapenem (R)	24	0*	5	0*
Imipenem/meropenem (R)[c]	77	0	23	17*
Imipenem/meropenem (I+R)[c]	77	0	23	26*
Gentamicin/tobramycin (R)[d]	76	50	23	78*
Amikacin (R)	60	12	22	32*
Ciprofloxacin/levofloxacin/ofloxacin (R)[e]	77	62	23	70*
Ciprofloxacin/levofloxacin/ofloxacin (I+R)[e]	77	62	23	70*
Multidrug resistance (R)[f]	75	39	23	70*

NA: not applicable.

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

[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[c] Imipenem and meropenem are indicators for the group of carbapenems.

[d] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[e] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

[f] Multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin/ofloxacin, cefotaxime/ceftriaxone/ceftazidime and gentamicin/tobramycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.42 Percentages of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in the former Yugoslav Republic of Macedonia, 2017

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	17	35*	NA	NA
Ceftazidime (R)	17	24*	NA	NA
Cefepime (R)	15	33*	NA	NA
Imipenem/meropenem (R)[a]	17	29*	28	82*
Imipenem/meropenem (I+R)[a]	17	29*	28	86*
Gentamicin/tobramycin (R)[b]	17	29*	28	82*
Amikacin (R)	15	13*	21	62*
Ciprofloxacin/levofloxacin (R)[c]	17	47*	29	79*
Multidrug resistance (R)[d]	17	24*	28	75*

NA: not applicable.

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

[a] Imipenem and meropenem are indicators for the group of carbapenems.

[b] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[c] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.

[d] For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. For *Acinetobacter* spp., multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. Isolates with missing data on one or more of the groups were excluded in the calculation of multidrug resistance.

Table 5.43 Percentages of resistance for *S. aureus* among blood and CSF isolates in the former Yugoslav Republic of Macedonia, 2017

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)[a]	49	53
Ciprofloxacin/levofloxacin/ofloxacin (R)[b]	48	21
Vancomycin (R)	41	0
Rifampicin (R)	31	3
Linezolid (R)	46	0

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

[b] Ciprofloxacin, ofloxacin and levofloxacin are indicators for the group of fluoroquinolones

Table 5.44 Percentages of resistance for *S. pneumoniae* among blood and CSF isolates in the former Yugoslav Republic of Macedonia, 2017

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillin (I+R)[a]	6	83*
Cefotaxime/ceftriaxone (R)[b]	4	75*
Cefotaxime/ceftriaxone (I+R)[b]	4	75*
Levofloxacin/moxifloxacin (R)[c]	6	0*
Erythromycin/clarithromycin/azithromycin (R)[d]	6	83*
Erythromycin/clarithromycin/azithromycin (I+R)[d]	6	83*
Multidrug resistance (I+R)[e]	6	83*

* A small number of isolates were tested (N < 30), and the percentage resistance should be interpreted with caution.
[a] Non-susceptibility to penicillin is based on penicillin or, if not available, on oxacillin.
[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.
[c] Levofloxacin and moxifloxacin are indicators for the group of fluoroquinolones.
[d] Erythromycin, clarithromycin and azithromycin are indicators for the group of macrolides.
[e] Multidrug resistance is defined as non-susceptibility to penicillin and erythromycin/clarithromycin/azithromycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.45 Percentages of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in the former Yugoslav Republic of Macedonia, 2017

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (I+R)[a]	20	20*	27	85*
High-level gentamicin (R)	14	64*	16	87*
Vancomycin (R)	21	0*	29	52*
Linezolid (I+R)	21	0*	29	0*

* A small number of isolates were tested (N < 30), and the percentage resistance should be interpreted with caution.
[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

5.9 Turkey

5.9.1 Surveillance set-up

The Turkish national AMR surveillance system was established in 2011. The national reference laboratory at the General Management of Public Health of Turkey of the Ministry of Health in Ankara collects national data on AMR. Antibiotic susceptibility testing results from blood and CSF culture isolates are collected in three-month intervals from participating laboratories, using Excel-based standardized data entry forms. After receiving the data, their quality and consistency are checked. If errors are detected, the data are sent back to the laboratory and corrected, where applicable. Then, the data are converted into the CAESAR data format using the BacLink utility in WHONET. 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 2017 to 31 December 2017, was submitted to CAESAR.

The 120 laboratories participating in the network were selected from different geographical regions of the country to reflect the distribution of the population. In 2017, CAESAR-eligible data from 70 clinical microbiology laboratories were submitted to CAESAR: 31 serving university hospitals and 39 serving public hospitals. These hospitals account for 38% of the total bed capacity in Turkey and cover about 28% of the population (of 81 916 871, data from 2018 *(1)*).

In 2017, most (47 of 70) laboratories tested for antimicrobial susceptibility using automated systems. Of these 47, 23 laboratories used a combination of automated systems and disk diffusion methods. Since 2017, all laboratories have been using EUCAST guidelines for AST, which are updated annually. If unusual resistance is detected, isolates are sent to the national reference centre for confirmation. All laboratories have implemented internal quality control. Network laboratories have participated in the annual national EQA programme provided by the General Management of Public Health of Turkey and in the international (UK NEQAS) EQA exercise since 2011.

Turkey has an active AMR surveillance network. In 2017, AMR surveillance data were presented at a national microbiology and infectious disease congress. National AMR surveillance standard operating procedures have been revised and distributed to participating laboratories. A national AMR surveillance web page was created to publish all annual reports of the national AMR surveillance system and CAESAR *(8)*.

According to national clinical guidelines, blood cultures are obtained from all patients with suspected bloodstream infections presenting in hospital, and CSF cultures from patients with suspected meningitis. The costs of bacteriology cultures taken in university hospitals and state hospitals are reimbursed through the National Health Insurance Fund. Accurate data on sampling rates in Turkish hospitals are not available due to the absence of standardized blood sampling methods. The Turkish Society of Clinical Microbiology has prepared blood sampling guidelines and training modules that are being implemented in hospitals.

5.9.2 Results

Fig. 5.9 shows the distribution of microorganisms and the characteristics of patients (broken down by pathogen) of 18 722 blood and CSF isolates obtained in Turkey in 2017. In *E. coli*, resistance ranged from 2% for amikacin to 78% for amoxicillin/ampicillin (Table 5.46). Multidrug resistance in *E. coli* was 19%. Resistance in *K. pneumoniae* was 19% for amikacin and higher for all other selected agents. Multidrug resistance was 39% in *K. pneumoniae*. In only 21 isolates of *Salmonella* spp., resistance was not observed for any of the agents tested (Table 5.47). In *P. aeruginosa*, resistance ranged from 19% (amikacin) to 37% (piperacillin-tazobactam and imipenem/meropenem, Table 5.48). Multidrug resistance in *P. aeruginosa* was 32%. Resistance in *Acinetobacter* spp. was 71% for amikacin and higher for all other selected agents. Multidrug resistance was 78% in *Acinetobacter* spp. Twenty-six per cent of *S. aureus* were methicillin-resistant (MRSA, Table 5.49). In *S. pneumoniae*, non-susceptibility to penicillin was 46% (Table 5.50). Multidrug resistance was 30% in *S. pneumoniae*. One percent of *E. faecalis* isolates were resistant to

vancomycin (Table 5.51). In *E. faecium*, vancomycin resistance was 13%, and 1% was non-susceptible to linezolid. In Chapter 7, maps of the WHO European Region show the proportions of resistance for selected pathogen–antibiotic combinations reported by Turkey (Fig. 7.1–7.6).

5.9.3 Discussion

The AMR surveillance network in Turkey submitted antibiotic susceptibility testing results for 18 722 isolates from blood or CSF in 2017. The large number of isolates and the distribution of pathogens, with *E. coli* 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 from patients admitted to intensive care units (29%) 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.

High levels of resistance of *E. coli* and *K. pneumoniae* to third-generation cephalosporins (cefotaxime/ceftriaxone and ceftazidime) and fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin) were observed. Resistance to carbapenems (imipenem/meropenem) in 2017 was comparable to that in previous years for both *E. coli* and *K. pneumoniae*. In about half of the carbapenem-resistant *E. coli* isolates, resistance was 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. The proportion of MRSA was similar to that in neighbouring countries (Fig. 7.6). The relatively small number of *S. pneumoniae* isolates and their moderate to high percentages of resistance may indicate infrequent use of routine blood cultures in severe pneumonia cases and selective sampling of treatment failures. Resistance in *P. aeruginosa* in general was moderately high, as was vancomycin resistance in *E. faecium*.

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 4.2) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.9 Patient characteristics of isolates in Turkey in 2017, by pathogen

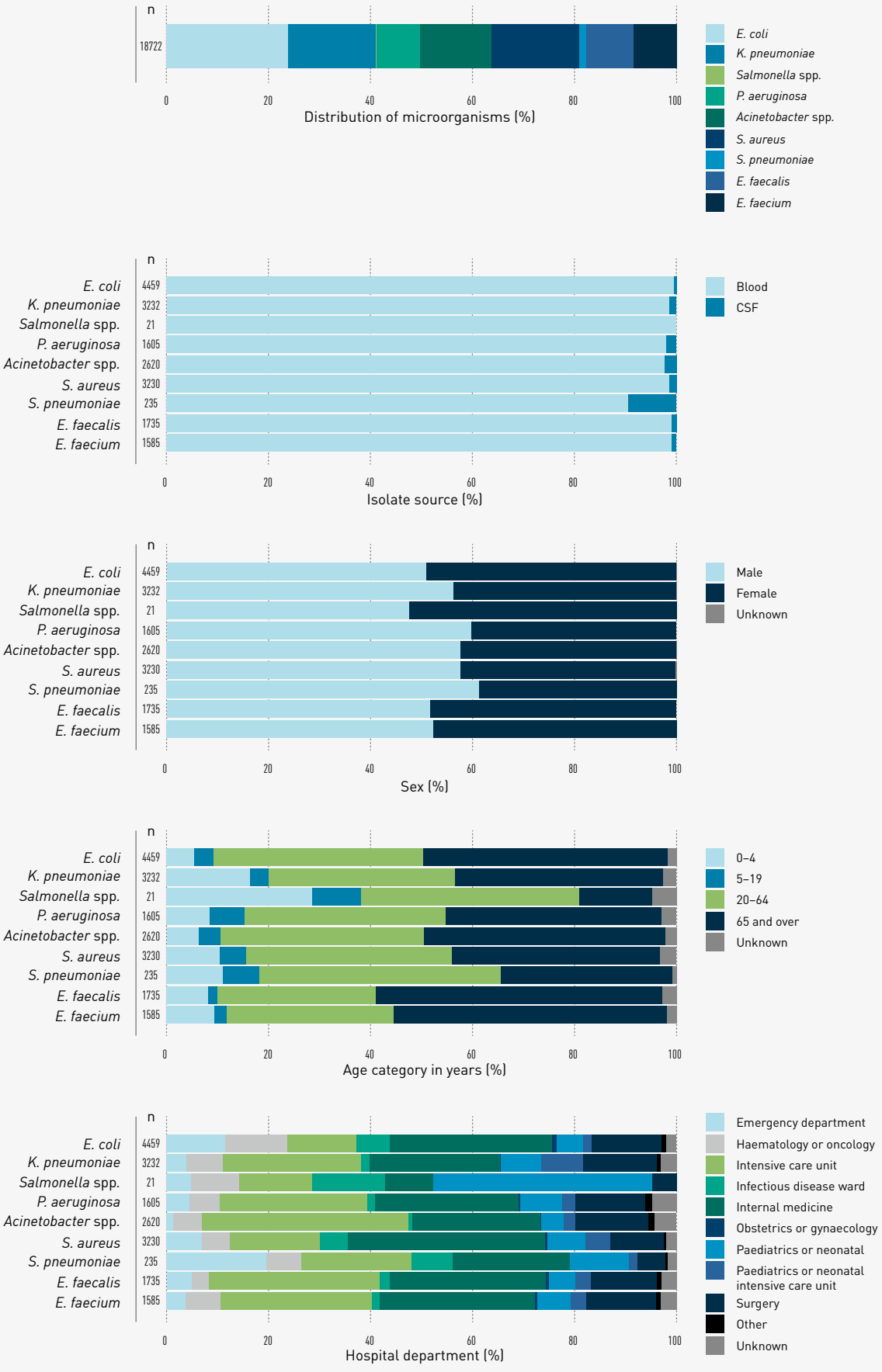


Table 5.46 Percentages of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Turkey, 2017

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (R)[a]	3652	78	NA	NA
Amoxicillin-clavulanic acid (R)	3110	59	1980	72
Piperacillin-tazobactam (R)	4022	22	2998	58
Cefotaxime/ceftriaxone (R)[b]	4059	52	2880	71
Cefotaxime/ceftriaxone (I+R)[b]	4059	53	2880	72
Ceftazidime (R)	3701	44	2803	69
Ertapenem (R)	3818	6	2815	43
Imipenem/meropenem (R)[c]	4321	3	3165	32
Imipenem/meropenem (I+R)[c]	4321	4	3165	38
Gentamicin/tobramycin (R)[d]	4083	27	2991	45
Amikacin (R)	4218	2	3060	19
Ciprofloxacin/levofloxacin/ofloxacin (R)[e]	4022	52	3009	61
Ciprofloxacin/levofloxacin/ofloxacin (I+R)[e]	4022	60	3009	66
Multidrug resistance (R)[f]	3755	19	2821	39

NA: not applicable.

[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[c] Imipenem and meropenem are indicators for the group of carbapenems.

[d] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[e] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

[f] Multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin/ofloxacin, cefotaxime/ceftriaxone/ceftazidime and gentamicin/tobramycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.47 Percentages of resistance for *Salmonella* spp. among blood and CSF isolates in Turkey, 2017

Antibiotic (group)	*Salmonella* spp.	
	N	Resistance (%)
Cefotaxime/ceftriaxone (R)[a]	19	0*
Cefotaxime/ceftriaxone (I+R)[a]	19	0*
Ceftazidime (R)	10	0*
Ertapenem (R)	7	0*
Imipenem/meropenem (R)[b]	10	0*
Imipenem/meropenem (I+R)[b]	10	0*
Ciprofloxacin/levofloxacin (R)[c]	0	–
Ciprofloxacin/levofloxacin (I+R)[c]	0	–

–: no data available.

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

[a] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[b] Imipenem and meropenem are indicators for the group of carbapenems.

[c] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.

Table 5.48 Percentages of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Turkey, 2017

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	1491	37	NA	NA
Ceftazidime (R)	1481	30	NA	NA
Cefepime (R)	1541	34	NA	NA
Imipenem/meropenem (R)[a]	1552	37	2540	91
Imipenem/meropenem (I+R)[a]	1552	44	2540	92
Gentamicin/tobramycin (R)[b]	1519	27	2558	78
Amikacin (R)	1540	19	2481	71
Ciprofloxacin/levofloxacin (R)[c]	1525	36	2505	93
Multidrug resistance (R)[d]	1279	32	2421	78

NA: not applicable.

[a] Imipenem and meropenem are indicators for the group of carbapenems.

[b] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[c] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.

[d] For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. For *Acinetobacter* spp., multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. Isolates with missing data on one or more of the groups were excluded in the calculation of multidrug resistance.

Table 5.49 Percentages of resistance for *S. aureus* among blood and CSF isolates in Turkey, 2017

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)[a]	3147	26
Ciprofloxacin/levofloxacin/ofloxacin (R)[b]	3028	14
Vancomycin (R)	3190	0
Rifampicin (R)	209	44
Linezolid (R)	3224	0

[a] MRSA is calculated as resistance to cefoxitin or, if not available, oxacillin.
[b] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

Table 5.50 Percentages of resistance for *S. pneumoniae* among blood and CSF isolates in Turkey, 2017

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillin (I+R)[a]	213	46
Cefotaxime/ceftriaxone (R)[b]	161	6
Cefotaxime/ceftriaxone (I+R)[b]	161	24
Levofloxacin/moxifloxacin (R)[c]	193	7
Erythromycin/clarithromycin/azithromycin (R)[d]	205	40
Erythromycin/clarithromycin/azithromycin (I+R)[d]	205	40
Multidrug resistance (I+R)[e]	186	30

[a] Non-susceptibility to penicillin is based on penicillin or, if not available, on oxacillin.
[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.
[c] Levofloxacin and moxifloxacin are indicators for the group of fluoroquinolones.
[d] Erythromycin, clarithromycin and azithromycin are indicators for the group of macrolides.
[e] Multidrug resistance is defined as non-susceptibility to penicillin and erythromycin/clarithromycin/azithromycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.51 Percentages of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Turkey, 2017

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (I+R)[a]	1587	4	1424	89
High-level gentamicin (R)	1125	38	1060	52
Vancomycin (R)	1720	1	1551	13
Linezolid (I+R)	1690	0	1563	1

[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

5.10 Ukraine

5.10.1 Surveillance set-up

The microbiological reference laboratory of the Public Health Center of the Ministry of Health of Ukraine in Kyiv annually collects the results of antibiotic susceptibility testing. Results from routine antibiotic susceptibility testing of isolates from blood, CSF, urine and surgical wound cultures yielding organisms specified by CAESAR are collected from microbiology laboratories in the national network of Ukraine, using electronic (Excel-based) isolate record forms. The results are analysed and summarized in a newsletter, which is sent to regions. 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 2017 to 31 December 2017, was available for four laboratories and was submitted to CAESAR.

The AMR surveillance network in Ukraine comprises five laboratories: the microbiological reference laboratory of the Public Health Center in Kyiv, providing services at national level, and four diagnostic laboratories, each of which provides services for one multidisciplinary clinical hospital (tertiary care). Two laboratories are located in Kyiv (one providing services at city level, the other at national level). One laboratory (located in Chmelnitski, the western part of the country) provides services at regional level, and the other (located in Dnipropetrovsk, the south-eastern part of the country) provides services at city level.

Laboratories of large multidisciplinary hospitals (included in surveillance) are equipped with automated AST systems, with software updated annually according to EUCAST. In other laboratories (one of which included in surveillance), antimicrobial susceptibility is mainly performed by disk diffusion methods according to national recommendations (2007). Gradient tests are rarely used, due to the high costs. Highly resistant organisms or unusual phenotypes are sent to the reference laboratory to confirm results. All laboratories have a quality management system. Preparations are in progress for the accreditation of diagnostic laboratories in accordance with ISO 15 189. Since 2016, all five laboratories have been involved in the international (CAESAR) EQA exercise provided by UK NEQAS. Samples obtained under the CAESAR EQA are retained and used within the national system for EQA for diagnostic laboratories that are not part of the CAESAR national network.

Ukraine has an active AMR surveillance network. EUCAST guidelines were translated, with implementation planned for 2018. In 2017, with the support of the WHO Regional Office for Europe, laboratory training was conducted for laboratories (potential future participants of the CAESAR network). Each participant received copies of translated EUCAST documents.

According to national clinical recommendations, blood cultures should be obtained from all hospitalized patients with suspected bloodstream infection (sepsis), and CSF samples from patients with suspected meningitis. Costs for bacteriological diagnostics are financed through local budgets. The Ministry of Health provides funding for national-level laboratories.

5.10.2 Results

Fig. 5.10 shows the distribution of microorganisms and the characteristics of patients (broken down by pathogen) of 155 blood and CSF isolates obtained in Ukraine in 2017. In 11 *E. coli* isolates, resistance ranged from 0% for imipenem/meropenem to 82% for amoxicillin/ampicillin (Table 5.52). Multidrug resistance was 30% in *E. coli*. In *K. pneumoniae*, resistance was 28% for imipenem/meropenem and higher for all other selected agents. Multidrug resistance in *K. pneumoniae* was 40%. Four isolates of *Salmonella* spp. were found, one of which was non-susceptible to ciprofloxacin/levofloxacin only (Table 5.53). In nine isolates of *P. aeruginosa*, resistance ranged between 57% and 100% for all selected agents (Table 5.54). Multidrug resistance was 100% in *P. aeruginosa*. Resistance in *Acinetobacter* spp. was 40% (imipenem/meropenem) or higher. Multidrug resistance in *Acinetobacter* spp. was 50%. In 19 *S. aureus* isolates, methicillin resistance

(MRSA) was not observed (Table 5.55). Six isolates of *S. pneumoniae* were found, one of which was resistant to erythromycin/clarithromycin/azithromycin only (Table 5.56). Vancomycin resistance was not observed in *E. faecalis* (Table 5.57). In *E. faecium*, two isolates (17%) were vancomycin-resistant, and one (8%) was non-susceptible to linezolid. In Chapter 7, maps of the WHO European Region show the proportions of resistance for selected pathogen–antibiotic combinations reported by Ukraine (Fig. 7.1–7.6).

5.10.3 Discussion

This is the first year that Ukraine reported AMR data to CAESAR. The AMR surveillance network submitted antibiotic susceptibility testing results for 155 isolates from blood or CSF in Ukraine in 2017. The four laboratories that submitted data are located in three different regions of the country. However, the laboratories provide service for tertiary care facilities, and smaller regional hospitals are underrepresented. The overrepresentation of tertiary care centres suggests that data represent mainly referred patients after initial antibiotic treatment. Besides bias towards higher resistance caused by selective sampling of referred, pretreated patients with nosocomial infections, the absolute number of isolates was low, which made the observed resistance percentages more sensitive to random variation, such as from nosocomial outbreaks. Furthermore, a mix of breakpoint guidelines was used to interpret antibiotic susceptibility test results; national guidelines from 2007 were used to interpret disk diffusion zone diameters (one laboratory) and up-to-date EUCAST guidelines were used to interpret the results of automated AST systems (three laboratories). In particular, carbapenem resistance in Enterobacteriaceae may be underestimated when older breakpoint guidelines are used. In conclusion, the reported percentages of resistance should be interpreted with caution and are not necessarily generalizable to any one patient presenting with invasive infection in Ukraine, especially patients with community-acquired infections.

Nevertheless, in the specific patient population sampled, high levels of resistance to all selected agents were seen in *K. pneumoniae*, *Acinetobacter* spp. and *E. faecium*. These high levels of resistance are concerning and may reflect the dissemination of resistant clones in the health care setting. On the other hand, MRSA was not observed in 2017 in blood or CSF isolates (although errors in AST cannot be ruled out) which indicates a lower incidence of MRSA than in the neighbouring countries (Fig 7.6). Too few antibiotic susceptibility testing results for *E. coli*, *P. aeruginosa*, *S. pneumoniae* and *E. faecium* were available to allow interpretation.

Data from Ukraine are assessed as level B. The representativeness of the results is limited by the inclusion of laboratories providing diagnostic support to a specific patient population (tertiary care, referred patients), overrepresentation of more severely ill and pretreated patients (selective sampling) and a small total number of isolates (underutilization of blood culture diagnostics). The antibiotic susceptibility testing results seem to be reliable for laboratories using automated systems with EUCAST-compatible software (three of four laboratories), but the use of older national breakpoint guidelines by one laboratory limits the validity and comparability of the results. The data indicate the resistance patterns present in clinical settings in the country, but the percentages of resistance should be interpreted with care. Including data from general hospitals, increasing the utilization of blood culture diagnostics and harmonization of antibiotic susceptibility testing according to up-to-date international guidelines will lead to more valid assessment of the magnitude of AMR. The reader's guide (Table 4.2) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 5.10 Patient characteristics of isolates in Ukraine in 2017, by pathogen

Table 5.52 Percentages of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Ukraine, 2017

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (R)[a]	11	82*	NA	NA
Amoxicillin-clavulanic acid (R)	0	–	21	81*
Piperacillin-tazobactam (R)	9	33*	17	82*
Cefotaxime/ceftriaxone (R)[b]	11	36*	29	59*
Cefotaxime/ceftriaxone (I+R)[b]	11	36*	29	62*
Ceftazidime (R)	11	36*	28	61*
Ertapenem (R)	8	0*	22	45*
Imipenem/meropenem (R)[c]	11	0*	29	28*
Imipenem/meropenem (I+R)[c]	11	0*	29	31*
Gentamicin/tobramycin (R)[d]	10	30*	25	56*
Amikacin (R)	10	20*	27	37*
Ciprofloxacin/levofloxacin/ofloxacin (R)[e]	11	45*	29	69*
Ciprofloxacin/levofloxacin/ofloxacin (I+R)[e]	11	45*	29	72*
Multidrug resistance (R)[f]	10	30*	25	40*

NA: not applicable.

–: no data available.

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

[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[c] Imipenem and meropenem are indicators for the group of carbapenems.

[d] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[e] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

[f] Multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin/ofloxacin, cefotaxime/ceftriaxone/ceftazidime and gentamicin/tobramycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.53 Percentages of resistance for *Salmonella* spp. among blood and CSF isolates in Ukraine, 2017

Antibiotic (group)	*Salmonella* spp.	
	N	Resistance (%)
Cefotaxime/ceftriaxone (R)[a]	4	0*
Cefotaxime/ceftriaxone (I+R)[a]	4	0*
Ceftazidime (R)	4	0*
Ertapenem (R)	1	0*
Imipenem/meropenem (R)[b]	3	0*
Imipenem/meropenem (I+R)[b]	3	0*
Ciprofloxacin/levofloxacin (R)[c]	4	0*
Ciprofloxacin/levofloxacin (I+R)[c]	4	25*

* A small number of isolates were tested (N < 30), and the percentage resistance should be interpreted with caution.
[a] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.
[b] Imipenem and meropenem are indicators for the group of carbapenems.
[c] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.

Table 5.54 Percentages of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Ukraine, 2017

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	7	57*	NA	NA
Ceftazidime (R)	8	87*	NA	NA
Cefepime (R)	8	87*	NA	NA
Imipenem/meropenem (R)[a]	9	78*	30	40
Imipenem/meropenem (I+R)[a]	9	78*	30	47
Gentamicin/tobramycin (R)[b]	7	100*	18	50*
Amikacin (R)	8	75*	27	59*
Ciprofloxacin/levofloxacin (R)[c]	8	75*	25	80*
Multidrug resistance (R)[d]	7	100*	18	50*

NA: not applicable.
* A small number of isolates were tested (N < 30), and the percentage resistance should be interpreted with caution.
[a] Imipenem and meropenem are indicators for the group of carbapenems.
[b] Gentamicin and tobramycin are indicators for the group of aminoglycosides.
[c] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.
[d] For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. For *Acinetobacter* spp., multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. Isolates with missing data on one or more of the groups were excluded in the calculation of multidrug resistance.

Table 5.55 Percentages of resistance for *S. aureus* among blood and CSF isolates in Ukraine, 2017

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)[a]	19	0*
Ciprofloxacin/levofloxacin/ofloxacin (R)[b]	20	0*
Vancomycin (R)	13	0*
Rifampicin (R)	16	0*
Linezolid (R)	16	0*

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

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

[b] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

Table 5.56 Percentages of resistance for *S. pneumoniae* among blood and CSF isolates in Ukraine, 2017

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillin (I+R)[a]	6	0*
Cefotaxime/ceftriaxone (R)[b]	6	0*
Cefotaxime/ceftriaxone (I+R)[b]	6	0*
Levofloxacin/moxifloxacin (R)[c]	6	0*
Erythromycin/clarithromycin/azithromycin (R)[d]	6	17*
Erythromycin/clarithromycin/azithromycin (I+R)[d]	6	17*
Multidrug resistance (I+R)[e]	6	0*

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

[a] Non-susceptibility to penicillin is based on penicillin or, if not available, on oxacillin.

[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[c] Levofloxacin and moxifloxacin are indicators for the group of fluoroquinolones.

[d] Erythromycin, clarithromycin and azithromycin are indicators for the group of macrolides.

[e] Multidrug resistance is defined as non-susceptibility to penicillin and erythromycin/clarithromycin/azithromycin. Isolates with missing data on one or more of the groups were excluded.

Table 5.57 Percentages of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Ukraine, 2017

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (I+R)[a]	18	17*	12	100*
High-level gentamicin (R)	18	44*	12	75*
Vancomycin (R)	27	0*	12	17*
Linezolid (I+R)	31	0	12	8*

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

[a] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.


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 are collected monthly, electronically at the Institute of Public Health of Kosovo[1] and on paper at the six microbiology laboratories at the six regional institutes of public health. The AMR surveillance network managed by the Institute of Public Health of Kosovo[1] collects the data. As data come in, their quality and consistency are checked. If errors are detected, the data are sent back to the laboratory and corrected, where applicable. Confirmatory testing of highly resistant microorganisms is required before the results are included in the final dataset; the Institute of Public Health of Kosovo[1] performs these tests. 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 2017 to 31 December 2017, was submitted to CAESAR.

The dataset comprises only patients from the University Clinical Center of Kosovo[1] with laboratory tests conducted at the Institute of Public Health of Kosovo[1] since data from regional laboratories are sparse due to low utilization of blood culture diagnostics, and 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 1 808 720, data from 2018 *(1)*). The University Clinical Center is the only tertiary health care facility in Kosovo[1] that also offers general hospital services to the capital city and neighbouring municipalities (34% of the population).

The Institute of Public Health of Kosovo[1] tests antimicrobial susceptibility using automated systems and disk diffusion methods; regional laboratories only use disk diffusion methods. If highly resistant microorganisms or exceptional phenotypes are found, the Institute of Public Health of Kosovo[1] confirms the results. Laboratories (for clinical microbiology) in Kosovo[1] are not yet accredited by an accreditation institute, but all seven laboratories took part in the CAESAR international external quality control exercise in 2017 (provided by UK NEQAS).

Laboratories should follow guidelines on methods for AST, including exceptional phenotypes. 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 samples are not taken from all patients with suspected bloodstream infections (sepsis) presenting in hospitals. Blood cultures are usually obtained from newborns, but the utilization of blood culture diagnostics among older children and adults is very low. CSF cultures are obtained from patients with suspected meningitis. Kosovo[1] has not yet established a health insurance system. At the University Clinical Center of Kosovo[1], the tertiary care hospital (2100 beds), 2698 blood samples were taken in 2017, yielding

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

a sampling rate of six samples per 1000 patient days. The number of blood cultures in regional hospitals is small due to a lack of funding and insufficient awareness among clinicians.

Kosovo[1] has an active AMR surveillance network that has been working on implementing harmonized antibiotic susceptibility testing methods and breakpoints. The network is also working on collecting data electronically from regional laboratories to expand the coverage of AMR surveillance.

6.1.2 Results

Fig. 6.1 shows the distribution of microorganisms and the characteristics of patients (broken down by pathogen) of 189 blood and CSF isolates obtained in Kosovo[1] in 2017. In 19 *E. coli* isolates, resistance ranged from 0% (ertapenem, imipenem/meropenem and amikacin) to 79% (amoxicillin/ampicillin, Table 6.1). Multidrug resistance was 26% in *E. coli*. Resistance in *K. pneumoniae* ranged from 0% for ertapenem and imipenem/meropenem to 100% for amoxicillin-clavulanic acid. Multidrug resistance in *K. pneumoniae* was 8%. One isolate of *Salmonella* spp. was found, in which resistance to the selected agents was not observed (Table 6.2). In 19 *P. aeruginosa* isolates, resistance was lowest for ceftazidime (32%), and highest for imipenem/meropenem (74%, Table 6.3). Multidrug resistance was 53% in *P. aeruginosa*. Resistance in *Acinetobacter* spp. was 89% or higher for all agents. Multidrug resistance in *Acinetobacter* spp. was 89%. Fifty-eight per cent of 19 *S. aureus* isolates were methicillin-resistant (MRSA, Table 6.4). In four isolates of *S. pneumoniae*, non-susceptibility to penicillin, as well as multidrug resistance, was 25% (Table 6.5). Vancomycin resistance was 9% in 11 *E. faecalis* isolates and 25% in 8 *E. faecium* isolates (Table 6.6). In Chapter 7, maps of the WHO European Region show the proportions of resistance for selected pathogen–antibiotic combinations reported by Kosovo[1] (Fig. 7.1–7.6).

6.1.3 Discussion

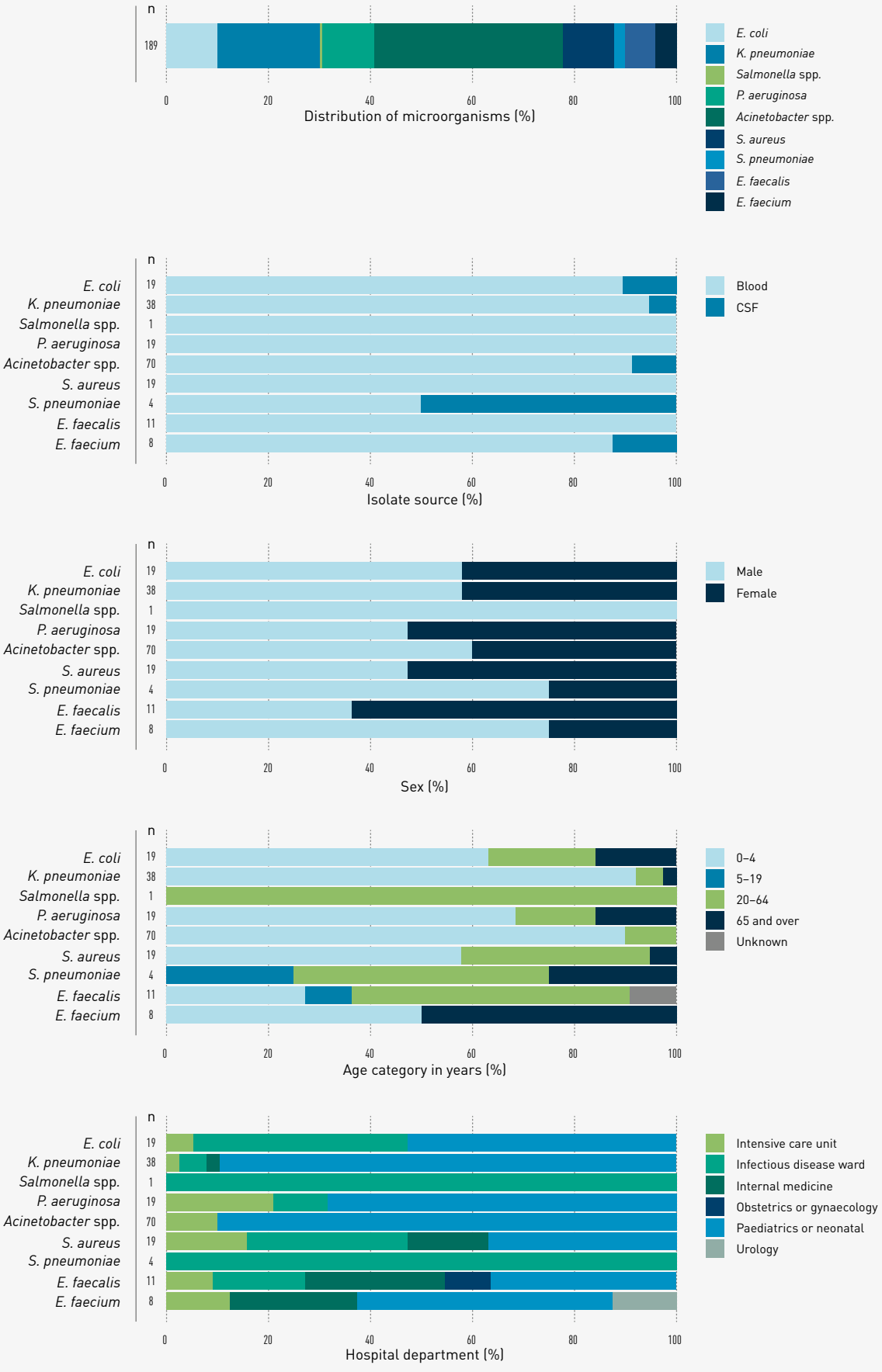
The AMR surveillance network of Kosovo[1] submitted antibiotic susceptibility testing results for 189 isolates from blood or CSF in 2017. Although the network comprises seven public laboratories, this report only includes results from isolates processed at the Institute of Public Health of Kosovo[1], which provides microbiological diagnostic support to the main tertiary care hospital. Importantly, the majority of isolates (75%) were from children aged 0–4 years, reflecting the high utilization of blood culture diagnostics in the neonatal department. The small number of isolates from older children and adults reflects the underutilization of blood culture diagnostics in other departments, which is thought to be due to low perceived benefits by clinicians. The small 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 empiric antibiotic treatment preceding referral. In addition, the small numbers of isolates made 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 in Kosovo[1], especially patients with community-acquired infections.

Nevertheless, in the patient population sampled, high levels of resistance to third-generation cephalosporins (cefotaxime/ceftriaxone) and aminoglycosides (gentamicin/tobramycin) were seen in *E. coli* and very high levels in *K. pneumoniae* were observed. However, resistance to carbapenems (ertapenem, imipenem/meropenem) was not detected in *K. pneumoniae* or *E. coli* in blood and CSF in 2017. The proportion of MRSA was concerning and higher than that in most countries close to Kosovo[1] (Fig. 7.6). Too few antibiotic susceptibility testing results for *Salmonella* spp., *S. pneumoniae*, *E. faecalis* and *E. faecium* were available to allow interpretation. The high levels of resistance in *P. aeruginosa* and *Acinetobacter* spp. are concerning and may reflect the dissemination of resistant clones in the health care setting.

Data from Kosovo[1] are assessed as level B. The representativeness of the results is limited by the inclusion of only one laboratory providing diagnostic support to a specific patient population (tertiary care, neonatal

patients), overrepresentation of more severely ill and pretreated patients (selective sampling) and an overall small number of isolates (underutilization 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 proportions of resistance should be interpreted with care. Including data from regional hospitals and increasing the utilization of blood culture diagnostics, especially from the adult population, will lead to a more valid assessment of the magnitude of AMR. The reader's guide (Table 4.2) provides additional information on interpreting the data and how the level of evidence was determined.

Fig. 6.1 Patient characteristics of isolates in Kosovo[a] in 2017, by pathogen



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

Table 6.1 Percentages of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Kosovo[a], 2017

Antibiotic (group)	*E. coli*		*K. pneumoniae*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (R)[b]	19	79*	NA	NA
Amoxicillin-clavulanic acid (R)	19	58*	38	100
Piperacillin-tazobactam (R)	19	26*	38	55
Cefotaxime/ceftriaxone (R)[c]	19	47*	38	97
Cefotaxime/ceftriaxone (I+R)[c]	19	47*	38	97
Ceftazidime (R)	19	32*	38	66
Ertapenem (R)	19	0*	38	0
Imipenem/meropenem (R)[d]	19	0*	38	0
Imipenem/meropenem (I+R)[d]	19	0*	38	0
Gentamicin/tobramycin (R)[e]	19	47*	38	97
Amikacin (R)	19	0*	38	87
Ciprofloxacin/levofloxacin/ofloxacin (R)[f]	19	26*	38	8
Ciprofloxacin/levofloxacin/ofloxacin (I+R)[f]	19	26*	38	8
Multidrug resistance (R)[g]	19	26*	38	8

NA: not applicable.

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

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

[b] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.

[c] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[d] Imipenem and meropenem are indicators for the group of carbapenems.

[e] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[f] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

[g] Multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin/ofloxacin, cefotaxime/ceftriaxone/ceftazidime, and gentamicin/tobramycin. Isolates with missing data on one or more of the groups were excluded.

Table 6.2 Percentages of resistance for *Salmonella* spp. among blood and CSF isolates in Kosovo[a], 2017

Antibiotic (group)	*Salmonella* spp.	
	N	Resistance (%)
Cefotaxime/ceftriaxone (R)[b]	1	0*
Cefotaxime/ceftriaxone (I+R)[b]	1	0*
Ceftazidime (R)	1	0*
Ertapenem (R)	1	0*
Imipenem/meropenem (R)[c]	1	0*
Imipenem/meropenem (I+R)[c]	1	0*
Ciprofloxacin/levofloxacin (R)[d]	1	0*
Ciprofloxacin/levofloxacin (I+R)[d]	1	0*

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

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

[b] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[c] Imipenem and meropenem are indicators for the group of carbapenems.

[d] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.

Table 6.3 Percentages of resistance for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Kosovo[a], 2017

Antibiotic (group)	*P. aeruginosa*		*Acinetobacter* spp.	
	N	Resistance (%)	N	Resistance (%)
Piperacillin-tazobactam (R)	19	42*	NA	NA
Ceftazidime (R)	19	32*	NA	NA
Cefepime (R)	19	42*	NA	NA
Imipenem/meropenem (R)[b]	19	74*	70	89
Imipenem/meropenem (I+R)[b]	19	74*	70	89
Gentamicin/tobramycin (R)[c]	19	47*	70	93
Amikacin (R)	19	42*	70	90
Ciprofloxacin/levofloxacin (R)[d]	19	42*	70	89
Multidrug resistance (R)[e]	19	53*	70	89

NA: not applicable.

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

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

[b] Imipenem and meropenem are indicators for the group of carbapenems.

[c] Gentamicin and tobramycin are indicators for the group of aminoglycosides.

[d] Ciprofloxacin and levofloxacin are indicators for the group of fluoroquinolones.

[e] For *P. aeruginosa*, multidrug resistance is defined as resistance to three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. For *Acinetobacter* spp., multidrug resistance is defined as resistance to ciprofloxacin/levofloxacin, gentamicin/tobramycin and imipenem/meropenem. Isolates with missing data on one or more of the groups were excluded in the calculation of multidrug resistance.

Table 6.4 Percentages of resistance for *S. aureus* among blood and CSF isolates in Kosovo[a], 2017

Antibiotic (group)	*S. aureus*	
	N	Resistance (%)
MRSA (R)[b]	19	58*
Ciprofloxacin/levofloxacin/ofloxacin (R)[c]	19	16*
Vancomycin (R)	19	0*
Rifampicin (R)	19	16*
Linezolid (R)	18	0*

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

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

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

[c] Ciprofloxacin, levofloxacin and ofloxacin are indicators for the group of fluoroquinolones.

Table 6.5 Percentages of resistance for *S. pneumoniae* among blood and CSF isolates in Kosovo[a], 2017

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillin (I+R)[b]	4	25*
Cefotaxime/ceftriaxone (R)[c]	4	0*
Cefotaxime/ceftriaxone (I+R)[c]	4	0*
Levofloxacin/moxifloxacin (R)[d]	4	25*
Erythromycin/clarithromycin/azithromycin (R)[e]	4	25*
Erythromycin/clarithromycin/azithromycin (I+R)[e]	4	25*
Multidrug resistance (I+R)[f]	4	25*

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

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

[b] Non-susceptibility to penicillin is based on penicillin or, if not available, on oxacillin.

[c] Cefotaxime and ceftriaxone are indicators for the group of third-generation cephalosporins.

[d] Levofloxacin and moxifloxacin are indicators for the group of fluoroquinolones.

[e] Erythromycin, clarithromycin and azithromycin are indicators for the group of macrolides.

[f] Multidrug resistance is defined as non-susceptibility to penicillin and erythromycin/clarithromycin/azithromycin. Isolates with missing data on one or more of the groups were excluded.

Table 6.6 Percentages of resistance for *E. faecalis* and *E. faecium* among blood and CSF isolates in Kosovo[a], 2017

Antibiotic (group)	*E. faecalis*		*E. faecium*	
	N	Resistance (%)	N	Resistance (%)
Amoxicillin/ampicillin (I+R)[b]	11	18*	8	100*
High-level gentamicin (R)	11	64*	8	87*
Vancomycin (R)	11	9*	8	25*
Linezolid (I+R)	11	0*	8	0*

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

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

[b] Amoxicillin and ampicillin are indicators for the group of aminopenicillins.


CHAPTER
7

AMR maps of the WHO European Region

7.1 Introduction

This chapter presents the AMR data for 2017 from the countries and areas in the CAESAR network together with the data from EARS-Net provided by the ECDC. In 2017, 30 countries, including all EU countries and two EEA countries (Iceland and Norway), reported their data to EARS-Net. The CAESAR network and EARS-Net use the same methods; this allows comparisons between countries across the two networks and provides an overview of the AMR situation based on all available data for the European Region. Several countries in the CAESAR network are not yet able to report level A or level B data, but they are actively setting up and strengthening their national AMR surveillance systems, which will add colour to the maps in the future. The footnotes 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.

Map legends 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 data, whereas EARS-Net does not make this distinction. On the maps, countries/areas with level B data are shaded, indicating that the proportion of resistance should be interpreted with caution, and improvements are needed to attain a more valid assessment of the level of prevalence of AMR in the country/area. 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 2017 are accessible through the ECDC Surveillance Atlas of Infectious Diseases *(2)*. This chapter was prepared jointly with the ECDC to provide an overview of AMR in the European Region.

7.2 Description of the maps

7.2.1 *E. coli*

The most common cause of community-acquired bloodstream infections and urinary tract infections is *E. coli*. EARS-Net data have shown a significant increase in third-generation cephalosporin resistance in EU and EEA countries *(2)*. In 2017, the majority of EARS-Net countries showed resistance proportions between 10% and 25%. Proportions exceeding 25% were found in Bulgaria, Cyprus, Italy and Slovakia. Among the CAESAR countries and areas, resistance proportions exceeding 50% were observed in Montenegro, the Russian Federation, the former Yugoslav Republic of Macedonia and Turkey, whereas the resistance proportion in Serbia is more comparable to that in its neighbouring EARS-Net countries (25–50%), as are the resistance proportions in Bosnia and Herzegovina (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 two EARS-Net countries (Cyprus and Greece) and four CAESAR countries (Belarus, Bosnia and Herzegovina, Serbia and Turkey) with resistance proportions of 1% or higher (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 is easily transmitted between patients, leading to nosocomial outbreaks. Multidrug resistance has become quite widespread in the European Region. In general, countries in northern Europe report lower proportions, while countries in the southern and eastern parts of the European Region report substantially higher proportions. Proportions of 50% or higher were reported in Belarus, Bulgaria, Montenegro, Poland, Romania, the Russian Federation, Serbia, Slovakia and the former Yugoslav Republic of Macedonia (Fig. 7.3). Carbapenem resistance is more frequently found in *K. pneumoniae* than in *E. coli*. Although in most countries, proportions of resistance are low, Georgia, Italy, Serbia, Turkey and Ukraine reported proportions between 25% and 50%, and Belarus and Greece reported proportions exceeding 50% (Fig 7.4). These high proportions of multidrug resistance and carbapenem resistance are concerning, may reflect the dissemination of resistant clones in the health care setting, and indicate the serious limitations in treatment options for patients with (invasive) infections caused by *K. pneumoniae* in these countries.

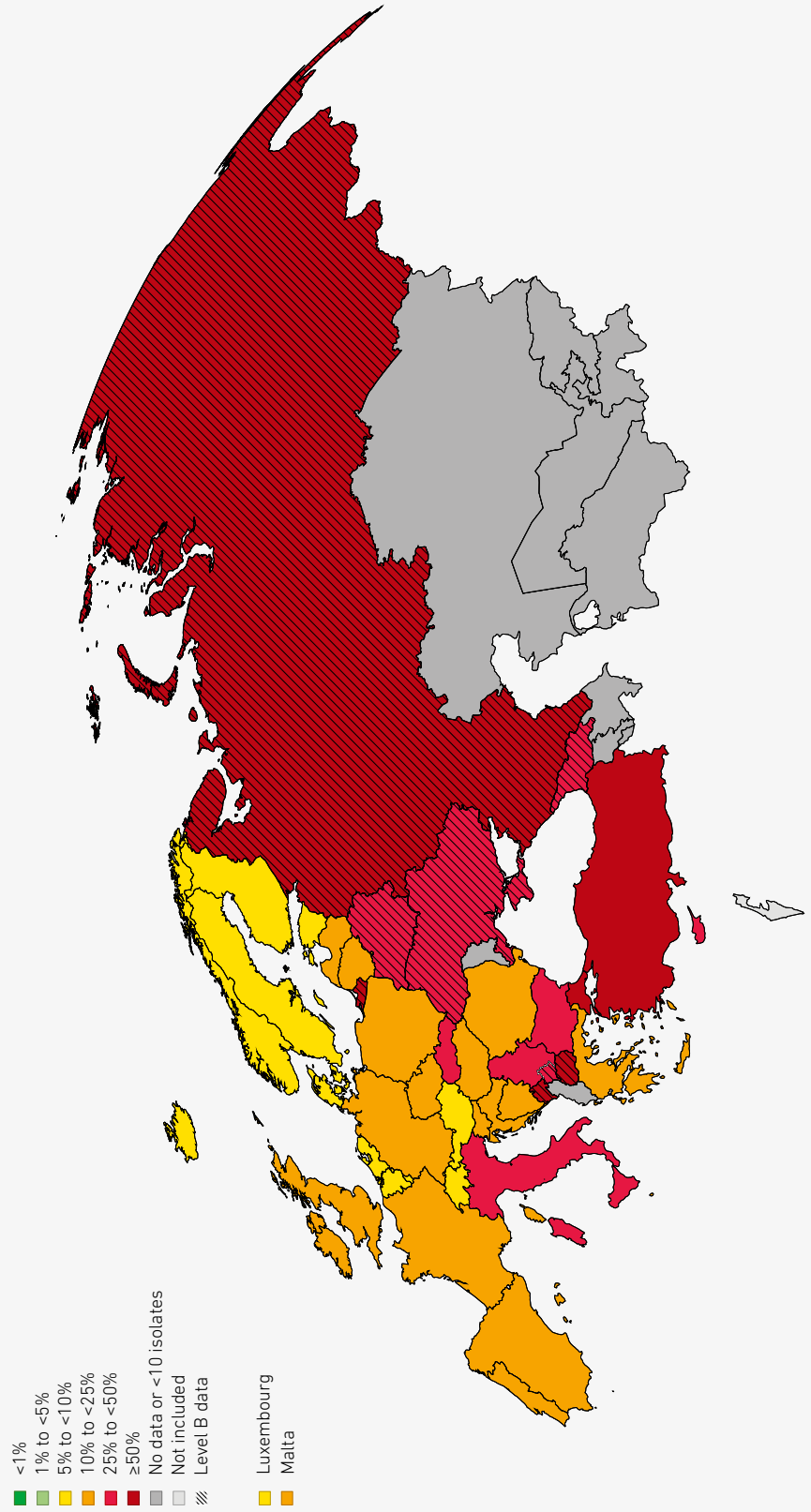
7.2.3 *Acinetobacter* spp.

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 proportions of multidrug-resistant *Acinetobacter* spp. varies widely within the European Region, from <1% in northern European countries to >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 setting and indicate the serious limitations in treatment options for patients with (invasive) infections caused by *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, many parts of the world, including Europe, are reporting increasing levels of community-associated MRSA. *S. aureus* mainly causes infections of the skin, soft tissue and bone, and bloodstream infections. It is the most common cause of postoperative wound infections. The Scandinavian countries, Estonia, the Netherlands, Switzerland and Ukraine have the lowest proportions (<5%) of invasive MRSA infections. Resistance proportions exceeding 25% are found in many countries in the southern and eastern parts of the European Region (Fig. 7.6).

Fig. 7.1 Third-generation cephalosporin-resistant *E. coli* in the European Region (EARS-Net and CAESAR), 2017

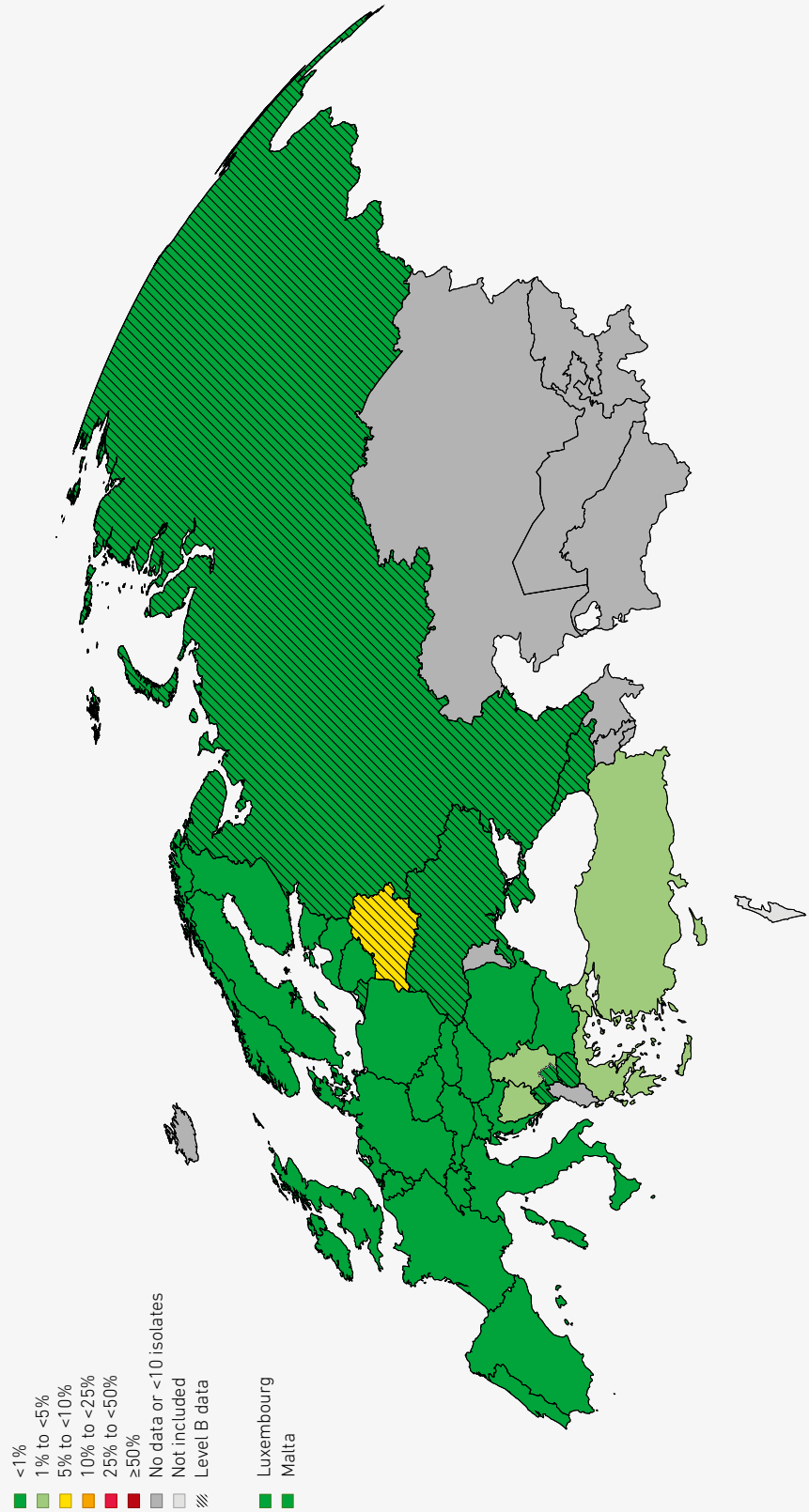


Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country or area, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of AMR in the country or area. See section 4.2 for more information about levels of evidence, which 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 and the 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: 2017 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2018) and 2017 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2018).

Fig. 7.2 Carbapenem-resistant *E. coli* in the European Region (EARS-Net and CAESAR), 2017



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. See section 4.2 for more information about levels of evidence, which 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 and the 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: 2017 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2018) and 2017 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2018).

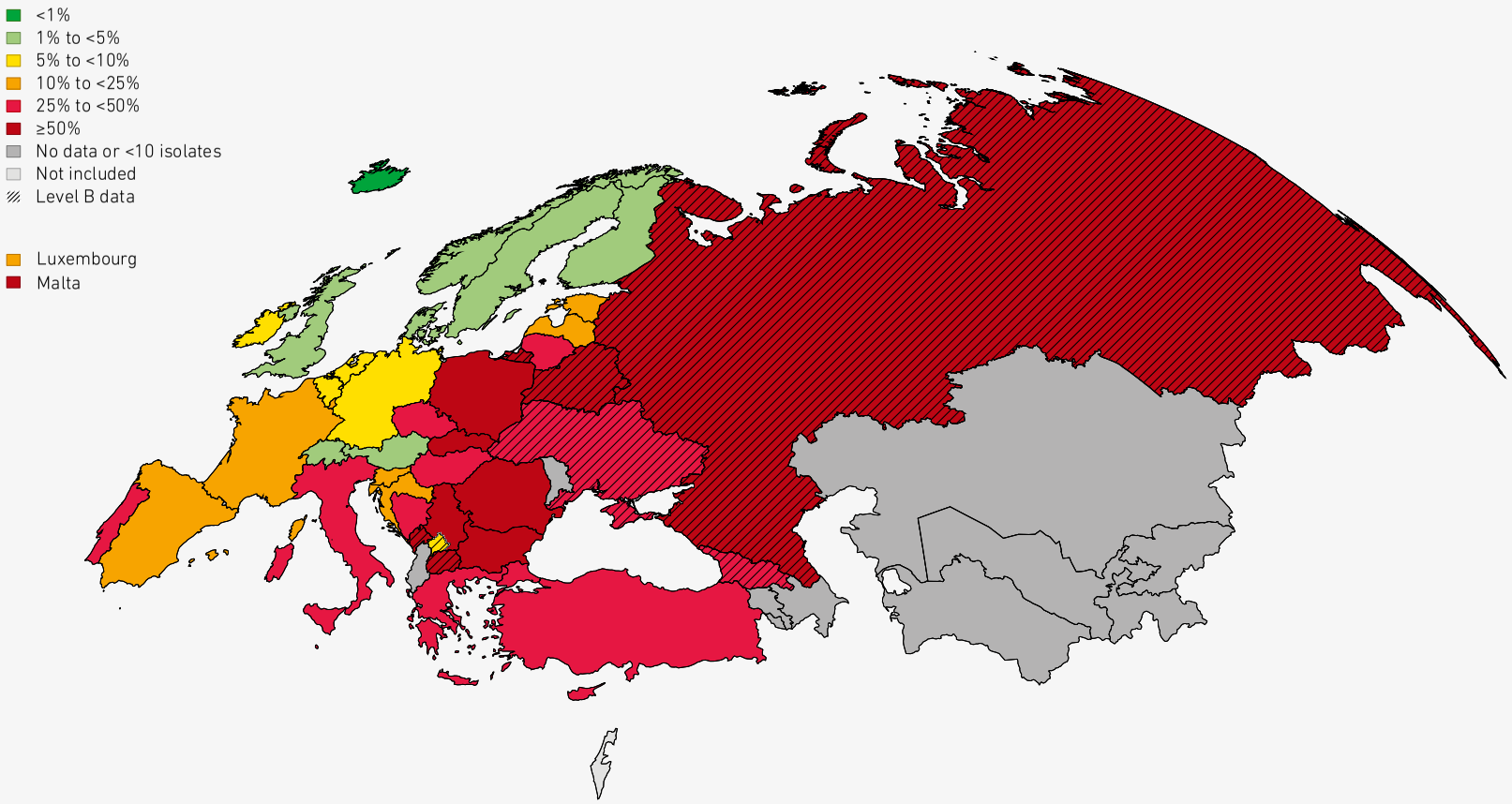


Fig. 7.3 Multidrug-resistant (combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides) *K. pneumoniae* in the European Region (EARS-Net and CAESAR), 2017

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. See section 4.2 for more information about levels of evidence, which are only provided for CAESAR countries and areas.

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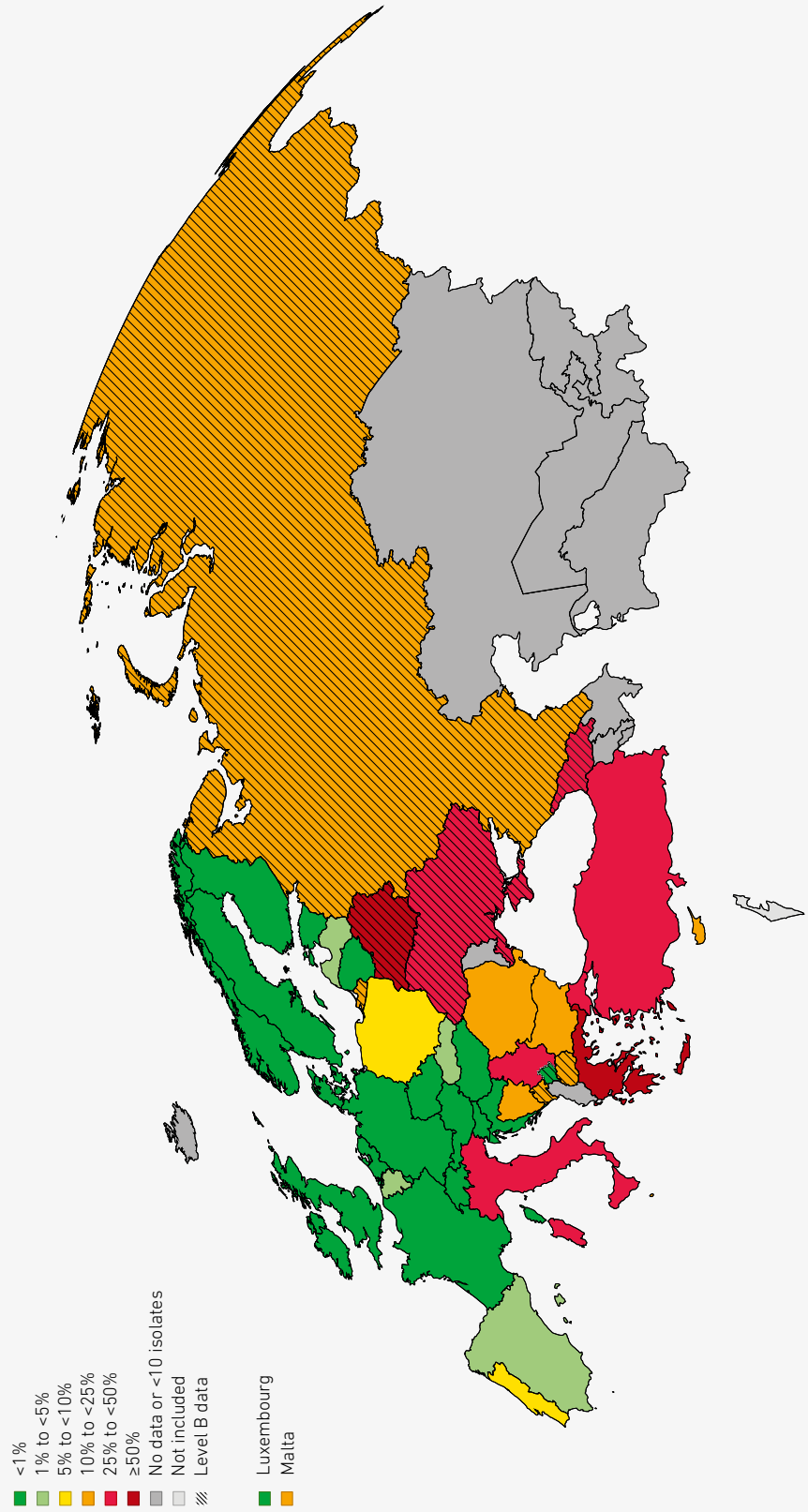
Data sources: 2017 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2018) and 2017 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2018).

Fig. 7.4 Carbapenem-resistant *K. pneumoniae* in the European Region (EARS-Net and CAESAR), 2017

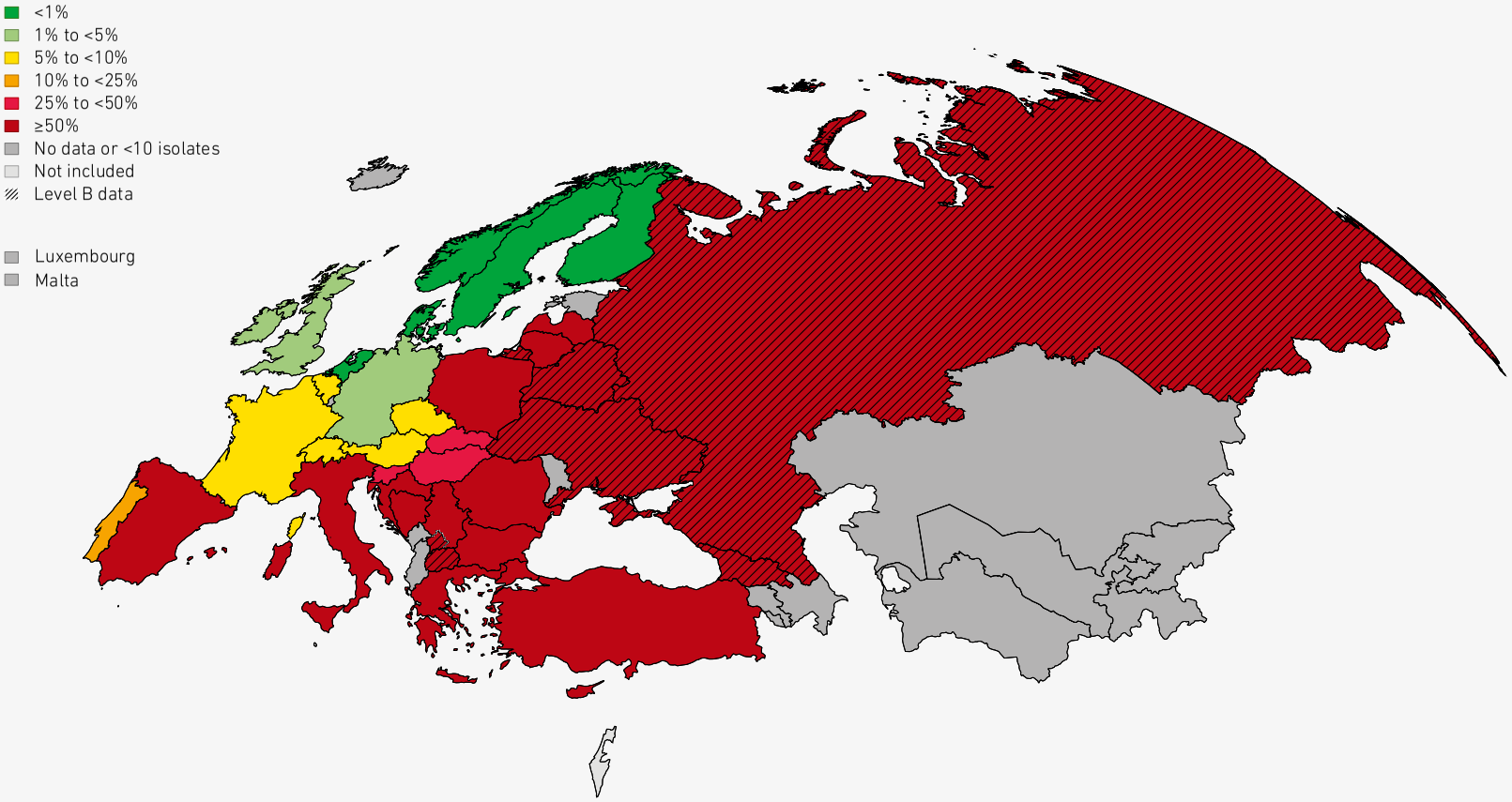


Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country or area, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of AMR in the country or area. See section 4.2 for more information about levels of evidence, which 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 and the 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: 2017 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2018) and 2017 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2018).

Fig. 7.5 Multidrug-resistant (combined resistance to fluoroquinolones, aminoglycosides and carbapenems) *Acinetobacter* spp. in the European Region (EARS-Net and CAESAR), 2017



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. See section 4.2 for more information about levels of evidence, which 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 and the United Kingdom.
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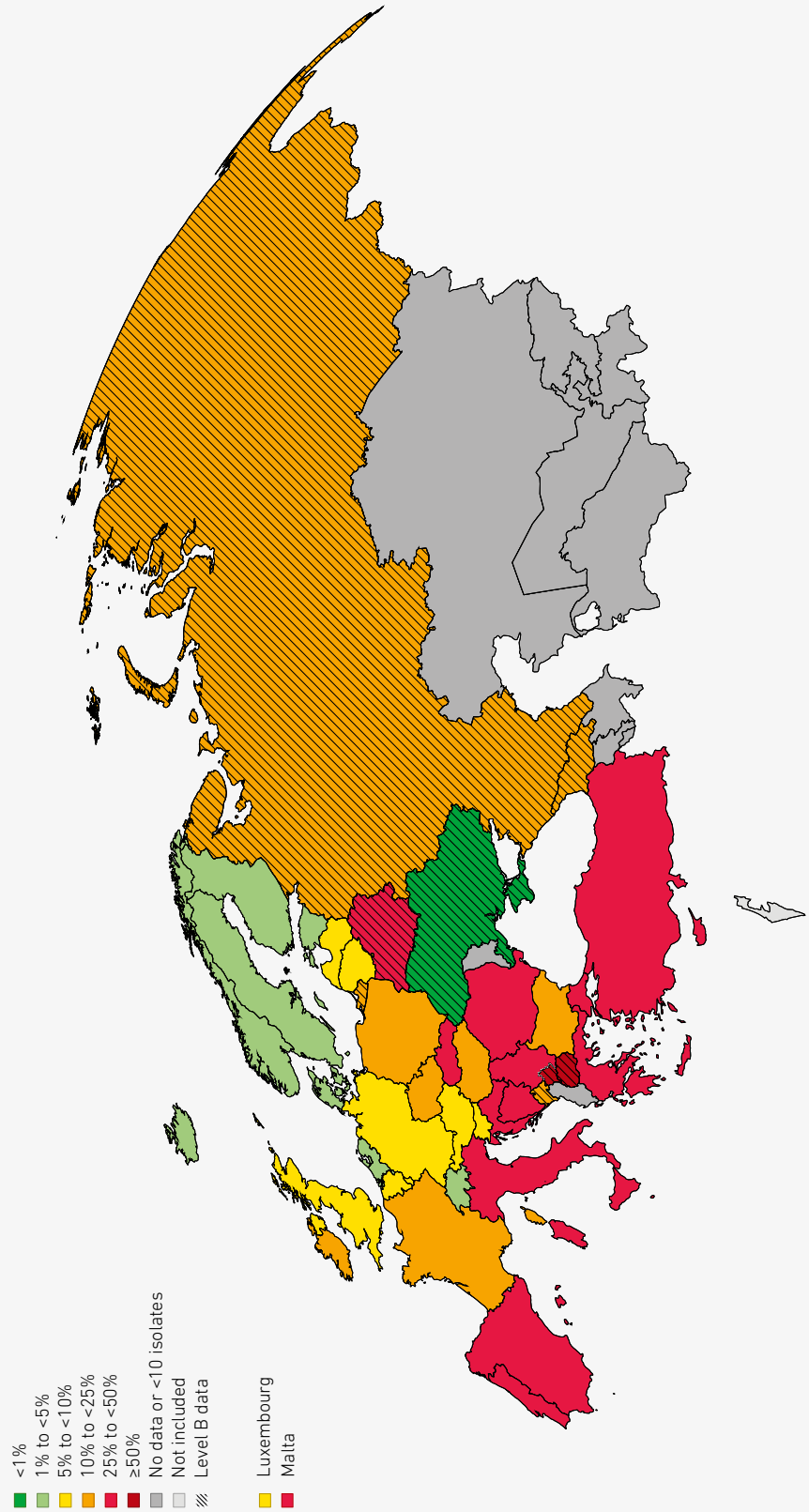
Data sources: 2017 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2018) and 2017 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2018).

Fig. 7.6 MRSA in the European Region (EARS-Net and CAESAR), 2017



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. See section 4.2 for more information about levels of evidence, which 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 and the 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: 2017 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2018) and 2017 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2018).


CHAPTER
8

PoP project in Armenia

8.1 Background

One of the main limiting factors to functional AMR surveillance in the WHO European Region and beyond is the underutilization of bacteriological diagnostics in routine clinical practice. Laboratory-based surveillance requires samples that are taken and processed. This is necessary for high-quality clinical care, guiding appropriate antibacterial treatment, the development of institutional antibiograms, and surveillance data that are valid and indicative of the AMR situation in a country or area.

The purpose of the PoP project is to contribute to improving clinical care for patients admitted with suspected bloodstream infections, in accordance with evidence-based medicine. The PoP project thereby provides an opportunity to investigate antibiotic susceptibility patterns for the most common pathogens causing community-acquired and hospital-acquired bloodstream infections *(1)*.

In addition, the PoP project's main goals *(1)* are to:

- demonstrate to clinicians the value of clinical microbiology as part of the diagnostic work-up of patients with suspected bloodstream infections and to improve the clinical work-up and timely feedback of laboratory results to prescribers of antimicrobial drugs, thus allowing for optimization of antimicrobial therapy; and

- establish and support a surveillance network as a starting point for a functional national sentinel laboratory-based surveillance system for AMR.

The PoP project was first successfully piloted in Georgia in 2015–2016 *(2)*, and AMR surveillance data from Georgia have been presented in the CAESAR annual report since 2017 *(3)*. The Pop project protocol is available online *(1)*.

8.2 Methods

Implementation of the PoP project in Armenia started in 2017 with four hospitals in the capital city, Yerevan, participating. Two are general hospitals: Armenia Republican Medical Center (729 beds) and the Medical University Clinic – Heratsi Hospital Complex No. 1 (206 beds). The others are paediatric hospitals: Arabkir Medical Center and Institute of Child and Adolescent Health (260 beds) and the Medical University Clinic – Muratsan Hospital Complex (258 beds). Data collection started on 1 June 2017 and continues until the end of October 2018. The Ministry of Health and its National Center for Disease Control and Prevention (NCDC) are coordinating the project; the multidisciplinary project team consists of epidemiologists, clinicians, data mangers and microbiologists, as well as support personnel.

At the start of the project, microbiologists from participating laboratories received training in blood culturing procedures and techniques, as well as antibiotic susceptibility testing following EUCAST methods. Microbiologists and clinicians received training on the principles of antimicrobial stewardship and a multidisciplinary approach to the management of infection. All blood culture materials and laboratory consumables for species identification, antibiotic susceptibility testing and confirmatory testing for up to 2000 tests were provided free of charge by the Netherlands National Institute for Public Health and the Environment.

At each study site, a local team, comprising a clinician, an epidemiologist and a bacteriologist, is responsible for conducting the study. Clinicians were instructed to recruit patients through active case finding, from hospital departments admitting patients with suspected bloodstream infection from the community (such as emergency departments), and wards where patients are at risk of developing hospital-acquired bloodstream infections (such as intensive care units and departments of urology or surgery). As the project progressed, other wards with cases of suspected bloodstream infections were included.

Patients meeting the criteria for systemic inflammatory response syndrome and with a clinical suspicion of a systemic infection are eligible for blood culturing. For each patient included, the project team completes a clinical data form and, for each positive blood culture, a laboratory results form. The process of communication and feedback of results between the microbiologist (laboratory) and clinician are registered on a feedback form, which includes information on the action taken by the clinician upon receiving the laboratory results (escalation, de-escalation or modification of antibiotic therapy). The project team collects data forms at weekly evaluation meetings and enters the data into an electronic database at the NCDC.

Blood cultures are processed at each of the participating hospital's in-house bacteriology laboratory. Bacteriologists are advised to actively report preliminary results (gram stain of a positive blood culture) and final reports (species identification and antibiotic susceptibility testing) back to the clinician as soon as these are available, to allow clinicians to adjust the (empirical) antibiotic therapy. Consecutively, all positive blood culture isolates are sent to the NCDC National Reference Laboratory for quality assurance and confirmatory antibiotic susceptibility testing.

Blood culturing is performed using a manual blood culture system according to standard operating procedures described in the PoP protocol. Culture bottles are checked daily for growth. If no growth is seen, blind subcultures are made at 24 hours, 48 hours and 7 days. Antibiotic susceptibility is tested by disk diffusion according to EUCAST standards. The tested pathogen–antibiotic combinations are based on the recommendations in the CAESAR manual *(4)*, including indicator antibiotics for the main antibiotic groups, plus some empirical treatment options not in the CAESAR manual.

The ultimate goal is to ensure the sustainability of the methodology and procedures defined in the PoP protocol, and to continue building national sentinel laboratory-based surveillance capacity after the PoP project ends. Efforts are made throughout the project implementation to engage in regular dialogue with hospital staff and decision-makers about the sustainability of the project and to address barriers to sustainable implementation.

8.3 Preliminary findings

Up until August 2018, blood samples were collected from 1788 patients with suspected bloodstream infection (Table 8.1). Demographic characteristics of patients from whom blood cultures were taken are in Table 8.2. The overall blood culture sampling rate was 3.8 per 1000 patient-days.

The overall positivity rate of blood cultures was 5%. The blood culture sampling rate was higher in both paediatric hospitals compared with general hospitals (6.4 vs 1.4 per 1000 patient-days), but the positivity rate was lower (2.9% vs 14.6%).

Table 8.3 shows the pathogens identified by the national reference laboratory. Of the 1788 blood cultures, 90 were positive: 26 cultures with Gram-negative bacteria (29%), 63 cultures with Gram-positive bacteria (70%) and one with a fungus (1%). The most common bacterium identified was *S. aureus* (33.3%). For a few isolates, discrepancies were found between results from the hospitals' in-house laboratories and the reference laboratory. This provided an opportunity, however, to evaluate and improve local laboratory procedures.

Table 8.1 Number of patients who had a blood culture taken per hospital

Hospital	N
Armenia Republican Medical Center	194
Medical University Clinic – Heratsi Hospital Complex No. 1	127
Arabkir Medical Center and Institute of Child and Adolescent Health	772
Medical University Clinic – Muratsan Hospital Complex	695
Total	**1788**

8.4 Discussion

8.4.1 Progress made

By the project's mid-term evaluation in March 2018, several of the PoP project's goals and objectives *(1)* had already been reached. Clinicians and microbiologists indicated that they acquired knowledge and a better understanding of AST and treatment of bloodstream infections. In addition, the project has contributed to strengthening laboratory capacity, the use of new techniques, and stricter adherence to protocols and EUCAST guidelines. Hospital microbiologists feel more engaged within their network of peers, and supported by microbiologists at the reference laboratory. This, together with the practice of parallel testing of all isolates at the reference laboratory, has contributed to an increased trust in the quality of the AST.

The project has laid the basis for national AMR surveillance, including a system for sending samples to the national reference laboratory and electronic data collection. Armenia expects to contribute AMR surveillance data to the CAESAR network in the near future.

8.4.2 Challenges

Unfortunately, the number of blood cultures taken per 1000 patient-days in general hospitals has remained relatively low throughout the project. This most likely has limited the expected increase in experience and knowledge of AMR for both microbiologists and clinicians. Also, information on local and national AMR patterns from the PoP project is thus far limited.

One explanation for the small number of positive blood cultures could be that patients with infectious conditions may seek treatment at home rather than at the hospital. In Armenia, hospital care is not free of charge for adults, and antibiotics were available over-the-counter until March 2018. Because of these factors, patients with bacterial diseases who were admitted to hospital were often previously exposed to antibiotics prior to admission, which decreased the chance of identifying a pathogen in a blood culture *(5)*.

In both paediatric hospitals, the number of blood cultures taken per 1000 patient-days was significantly higher than that in general hospitals, but the proportion of blood cultures growing a pathogen was relatively low. As in adults, the positivity rate of paediatric blood cultures increases with the volume taken *(6)*, and the blood volume taken in children is generally lower than in adults. In contrast to adult hospital care, hospital admission in Armenia is free of charge for children; thus, a large proportion of children admitted to the hospital may have had mild (for example, viral) infections. In addition, in one of the paediatric

Table 8.2 Characteristics of patients who had a blood culture taken

Characteristics	Armenia Republican Medical Center		Medical University Clinic – Heratsi Hospital Complex No. 1		Arabkir Medical Center and Institute of Child and Adolescent Health		Medical University Clinic – Muratsan Hospital Complex	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	53	19	56	20	4	5	2	10
Age group	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
0–1 month	–	–	3	2.4	179	23.2	642	92.4
1 month–4 years	1	0.5	–	–	344	44.6	16	2.3
5–19 years	4	2.1	1	0.8	247	32.0	10	1.4
20–64 years	132	68.0	66	52.0	2	0.3	21	3.0
65 and above	57	29.4	56	44.1	–	–	4	0.6
Unknown	–	–	1	0.8	–	–	2	0.3
Gender								
Male	104	53.6	79	62.2	449	58.2	379	54.5
Female	90	46.4	48	37.8	323	41.8	315	45.3
Unknown	–	–	–	–	–	–	1	0.1
Department								
Intensive care unit (ICU)	96	49.5	51	40.2	4	0.5	6	0.9
Neonatal/Paediatric ICU	–	–	–	–	101	13.1	46	6.6
Emergency department	1	0.5	–	–	182	23.6	–	–
Neonatal/Paediatric	–	–	3	2.4	31	4.0	598	86.0
Haematology/Oncology	–	–	2	1.6	–	–	24	3.5
Infectious disease ward	–	–	–	–	140	18.1	–	–
Urology	20	10.3	11	8.7	8	1.0	1	0.1
Obstetrics/Gynaecology	1	0.5	–	–	–	–	–	–
Internal medicine	27	13.9	8	6.3	28	3.6	1	0.1
Other	43	22.2	45	35.4	274	35.5	15	2.2
Unknown	6	3.1	7	5.5	4	0.5	4	0.6
Patient on antibiotics at time of blood draw								
No	76	39.2	40	31.5	617	79.9	404	58.1
Yes	112	57.7	79	62.2	152	19.7	284	40.9
Unknown	6	3.1	8	6.3	3	0.4	7	1.0
Type of infection								
Community acquired	79	40.7	65	51.2	638	82.6	106	15.3
Nosocomial	109	56.2	55	43.3	131	17.0	585	84.2
Unknown	6	3.1	7	5.5	3	0.4	4	0.6

SD: standard deviation.

Table 8.3 Distribution of identified pathogens

Bacterial species	N	Percentage
E. coli	14	15.6
K. pneumoniae	6	6.7
P. aeruginosa	3	3.3
Acinetobacter spp.	1	1.1
S. aureus	30	33.3
S. pneumoniae	–	–
E. faecalis	4	4.4
E. faecium	2	2.2
Coagulase-negative *Staphylococcus* spp.	18	20.0
Other	12	13.4
Total	**90**	**–**

hospitals, it was routine practice to take a blood culture from every transferred neonate, regardless of symptomatology, which also influenced the percentage of positive blood cultures.

8.5 Next steps

By the time this report was prepared the PoP project was going to conclude by 31 October 2018. Project data will be analyzed and reported as a next step.

Ensuring the sustainability of the project after October 2018 will be a challenge. Continued financing and the involvement of managers are needed at all levels (government, reference laboratory, individual laboratories and hospitals).

Because of the project, hospital administrators and clinicians are more aware of the lack of knowledge on antimicrobial stewardship, and additional training was organized during the mid-term evaluation. However, there is a need for further training and possible expansion of the medical education curriculum.

Parallel to the implementation of the PoP project, the Ministry of Health of Armenia is making important progress on its AMR policy. The PoP project may have contributed by raising awareness, providing standardized guidance and acting as a catalyst. First, the Ministry of Health is planning to implement PoP methodology in all hospitals in Armenia. However, these hospitals lack laboratory consumables of a sufficient quality, and training of clinicians and microbiologists is needed. Second, the Ministry of Health plans to assess the possibility of implementing WHONET (software for standardized AST data collection) by performing laboratory assessments throughout the country. Third, since March 2018, regulations have been in place to prohibit the sale of antibiotics without a doctor's prescription. Over time, these actions will hopefully result in widely used routine bacteriological diagnostics that will provide a more reliable overview of the antibiotic resistance levels in Armenia.

Box 1 shows the results of a qualitative evaluation of the PoP project in Armenia.

Box 1. Qualitative evaluation of the PoP project in Armenia

Successful implementation of the PoP project depends on various factors, including support from hospital management, and national and local teams, as well as the capacity of professionals to take on the stated responsibilities and perform the required tasks. Therefore the mid-term review of the PoP project in Armenia was used to form a better understanding of how these target groups are influenced to perform specified behaviours (or not), which is essential in understanding how the PoP project is implemented and how it can be improved. The evaluation also aimed to identify the project benefits and the expected barriers to sustainability and scale-up, as perceived and experienced by the target groups.

Four focus group discussions were held, one with each of the following target groups: clinicians, nurses, microbiologists and epidemiologists. Interviews were conducted with clinicians and hospital managers. All the interviews and focus groups discussions were recorded and transcribed, and subsequently analysed following standard models for qualitative data analysis.

The qualitative evaluation resulted in several findings.

- **All target groups believed that the hospitals have benefitted greatly from being part of the PoP project.** Informants explained that the project introduced new approaches and standards, which improved hospital practices in blood sampling, AST and rational use of antibiotics, laboratory capacities and treatment outcomes. Respondents felt that the project reduced financial costs due to shortened hospital stays, caused fewer complications in patients, and led to more targeted antibiotic procurement. Many of these developments have improved the status and reputation of the hospital.
- **All target groups believed that the project had greatly improved the inter-relationships between everyone involved.** Informants reported that a major benefit of the project was the improved working relationships, in particular between clinicians and the other professions. Standardization of routines and practices, according to international standards, created a common frame of reference and increased trust in the process for all involved.
- **While all target groups were very willing to continue implementing the PoP methodology beyond the project, they were also concerned about how to secure the financial resources to do so.** All target groups repeatedly mentioned limited resources as a main barrier to sustainability. Procurement of laboratory materials is expensive due to a lack of competition in the market, which may lead to hospitals cutting costs by compromising on the quantity and quality of the materials.
- **Most target groups expressed a concern about the current lack of discussion and decision-making on how to ensure sustainability.** Hospital managers were aware of the financial challenges of sustaining the PoP methodology, but have not yet sufficiently discussed this internally. There were no clear solutions or suggestions on how to address the funding challenges after the project ends, but some informants referred decision-making on financial support to the Ministry of Health.
- **Target groups perceived a lack of evidence and clear progress indicators of the PoP project to be the main obstacles for initiating discussions on sustainability.** It was mentioned that in order for hospital managers to start discussing project continuation and sustainability, clear evidence on the project's benefits and progress was needed. This is currently not available, but is expected to be provided by the end-of-project evaluation. A suggestion to develop an advocacy tool or a set of progress indicators would help frame discussions of sustainability at the start of the project.
- **Target groups were concerned about how the project could be scaled-up and integrated into the wider capacity building of national AMR surveillance.** Scaling up the project to national level was seen as an important step, as it would provide high-quality service delivery by having standard operating procedures, a national centralized procurement, a distribution system of quality laboratory materials and harmonization of data across hospitals.

These findings suggest that discussions on project continuity and sustainability need to take place from the start of the project. Developing a clear set of progress and/or target indicators adapted to each project site could aide these discussions. Further discussions on deferred responsibility and accountability may be beneficial. Moreover, procurement of materials remains a matter of concern and should be addressed to ensure sustainability and quality of care. It is essential that the progress made is not compromised and that the PoP methodology is followed as much as possible.

A more detailed account of the evaluation will be available as part of the final PoP project report for Armenia.

Notes: these findings should be interpreted in light of the design and delivery of the evaluation. All data are based on the perspectives and experiences of the target groups and are therefore subjective and contextualized. However, most of the benefits and challenges identified are expected to apply to many of the CAESAR network countries.


CHAPTER
9

CAESAR EQA

9.1 Introduction

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.

The annual EQA for the laboratories in the CAESAR network is coordinated by UK NEQAS, based at the Public Health England National Infection Service in Colindale, London (United Kingdom). The CAESAR EQA aligns with the EARS-Net EQA, which is organized annually by the ECDC.

UK NEQAS prepares the specimens and performs quality control testing, organizes logistics and arranges the shipment to the countries and areas in collaboration with the AMR focal points and EQA coordinator. Each laboratory then examines the same well-characterized specimens, and reports back their results within the defined time frame. The results are assessed if the data collected by participating laboratories from all countries/areas are valid and can be pooled and analysed collectively.

All participating laboratories receive reports from UK NEQAS highlighting the performance of each individual laboratory in comparison to all other laboratories in the CAESAR EQA network and to the participating laboratories in the national network, thereby enabling the independent assessment of performance and the identification of problem areas.

The main objectives of the CAESAR EQA are to assess:

- the accuracy of the AST results reported by the participating laboratories
- the laboratory performance for identification accuracy of the survey strains
- the comparability between laboratories and countries/areas.

Furthermore, it serves as an educational tool by allowing laboratories to perform self-assessment using the extensive and individual report prepared by UK NEQAS for each participating laboratory. Critical appraisal of the EQA report should be an essential component of the quality management system. To reduce or eliminate failures, each failure in the EQA report should be addressed and thoroughly investigated, the factors responsible for the mistake should be identified and corrective actions should be taken.

For countries not currently submitting data to CAESAR, participation in the CAESAR EQA serves as a capacity-building exercise that enables formation of an early version of a national network, which with time transforms into a national surveillance network.

This chapter describes the results from the CAESAR EQA exercise conducted in 2017 and provides a summary of the first five years of CAESAR EQA (2013–2017).

9.2 CAESAR EQA in 2017

A panel of six lyophilised isolates was prepared and found fully compliant in quality control testing by UK NEQAS, and the results were confirmed in two expert reference laboratories. The panel included the following strains: *S. pneumoniae* (specimen 4323), *S. aureus* (specimen 4324), *E. faecium* (specimen 4325), *E. coli* (specimen 4326), *K. pneumoniae* (specimen 4327) and *A. baumannii* complex (specimen 4328). The

EQA panels were dispatched on 11 September 2017 to all participating laboratories in 18 countries or areas participating in the CAESAR network. Participating laboratories were requested to return results within four weeks. Results were returned from 16 countries/areas by 248 of 290 (86%) participating laboratories: 10 of 11 laboratories from Albania, 11 of 11 from Armenia, 3 of 3 from Azerbaijan, 13 of 13 from Belarus, 10 of 10 from Bosnia and Herzegovina, 6 of 6 from Kyrgyzstan, 7 of 8 from Montenegro, 12 of 12 from the Republic of Moldova, 22 of 22 from Serbia, 33 of 47 from the Russian Federation, 19 of 21 from the former Yugoslav Republic of Macedonia, 81 of 87 from Turkey, 3 of 3 from Turkmenistan, 5 of 5 from Ukraine, 6 of 6 from Uzbekistan and 7 of 7 from Kosovo[1]. Network laboratories in Georgia (*n* = 13) and Tajikistan (*n* = 5) could not take part in 2017 EQA exercise due to delay in delivery of the EQA samples. The intended results for the survey were announced on 12 January 2018.

9.2.1 Methods and guidelines used

Fig. 9.1 presents a breakdown of the methods and guidelines used by participating laboratories examining the EQA specimens. International guidelines were followed in all participating laboratories: CLSI (13%) and EUCAST (87%). Homogenous adherence to one guideline was observed in eight countries and areas. All participating laboratories in Albania, Armenia, Serbia, Turkmenistan, Ukraine, Uzbekistan and Kosovo[1] used the EUCAST guideline, whereas all participating laboratories in Azerbaijan used the CLSI guideline.

Among participating laboratories that specified the susceptibility testing method used for the survey strains (*n* = 248), the breakdown of the methods used revealed that 63.3% (*n* = 157) of the laboratories used the disk diffusion susceptibility testing method and 35.9% (*n* = 89) used an automated instrument; the remaining two laboratories performed MIC testing using gradient strip tests (Fig. 9.2).

9.2.2 Antimicrobial susceptibility results

Participating laboratories' 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 laboratories, which give laboratories the opportunity to make suitable comparisons. Participating laboratories can access their reports at any time, as well as download a printed copy.

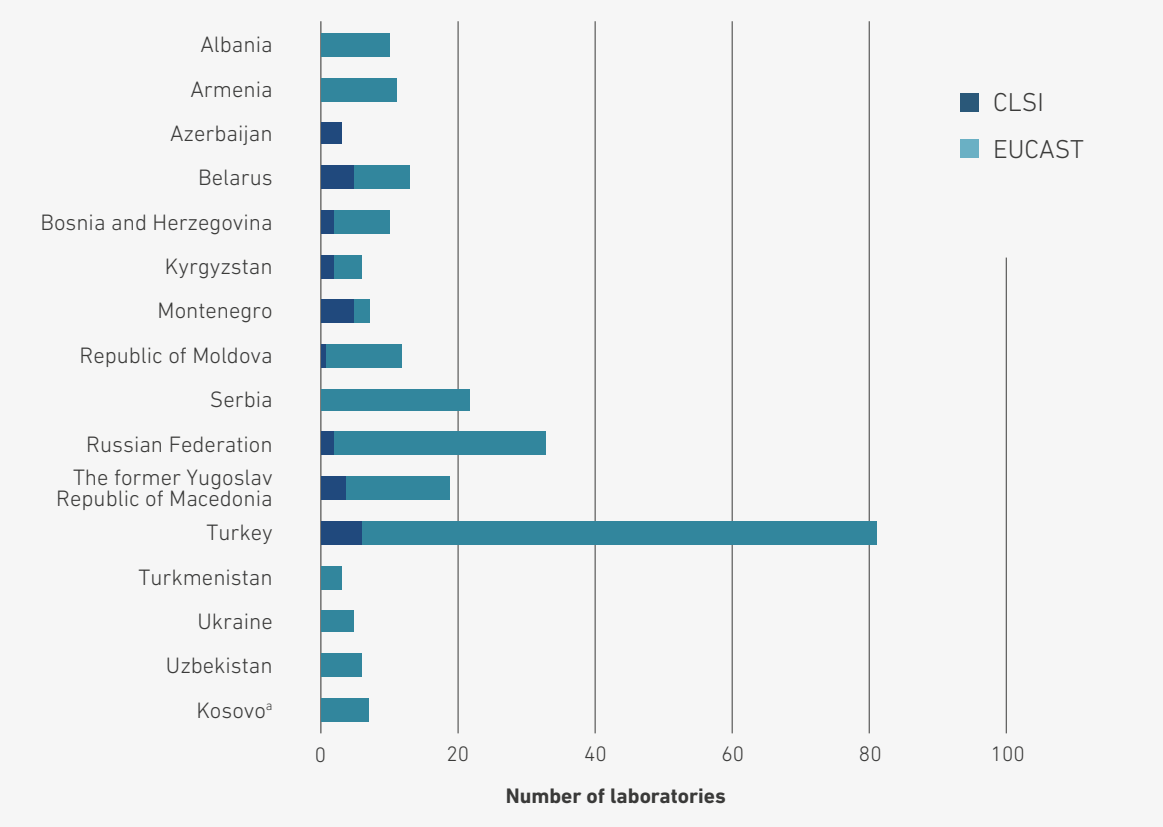
In general, performance was very good and consistent with that seen in previous EQA surveys among participating laboratories in the European Region. Problems were mostly related to borderline susceptibility, testing of beta-lactam/beta-lactamase inhibitor combinations (notably testing of piperacillin-tazobactam) and novel resistance mechanisms (e.g. low-level colistin resistance mediated by *mec-1* gene). The specimens distributed and their important antimicrobial susceptibility features are outlined in Table 9.1. The different isolates are described in more detail on the next pages, and the results by country or area are given in Tables 9.2–9.7. The susceptibility of the challenge strains isolated against the antimicrobial agents tested was defined as susceptible (S), intermediate (I) or resistant (R).

Specimen 4323 contained a strain of *S. pneumoniae* with intermediate level of resistance to penicillin (MIC = 0.25 mg/L). The strain was resistant to erythromycin and was susceptible to clindamycin.

For the results of penicillin susceptibility a poor consensus was observed. In the context of meningitis, 92.4% of the participating laboratories correctly reported penicillin as resistant. This is especially important since the use of benzylpenicillin should be avoided for penicillin intermediate or resistant strains (strains with benzylpenicillin MIC ≥ 0.06 mg/L) in meningitis cases. In the context of pneumonia, however, 38.9% of the participating laboratories correctly reported penicillin as susceptible.

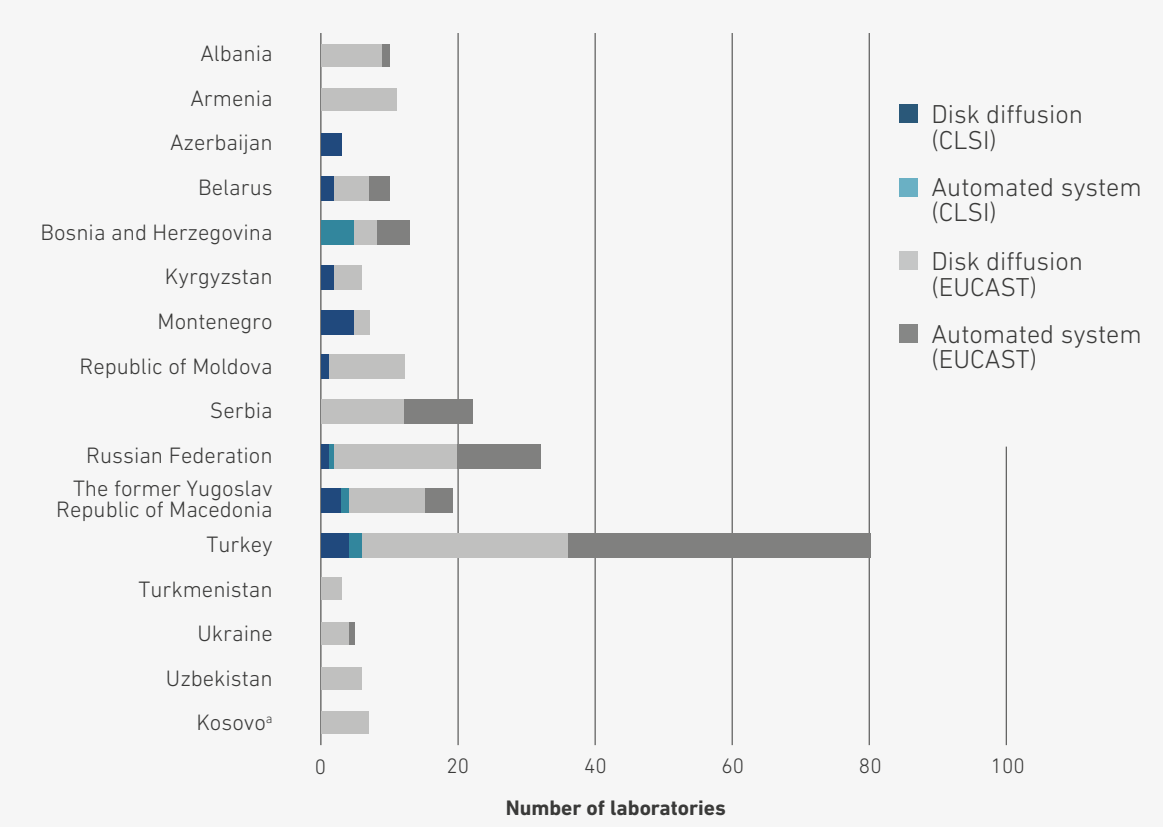
[1] All references to Kosovo should be understood as references to Kosovo in accordance with United Nations Security Council resolution 1244 (1999).

Fig. 9.1 Number of laboratories and type of guideline used per country or area



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

Fig. 9.2 Number of laboratories and type of susceptibility testing method per country or area



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

Table 9.1 Specimens distributed in the CAESAR EQA survey in 2017, evaluation of laboratory performance for identification and important antimicrobial susceptibility features of the strains

Specimen number	Organism	Correct identification among participating laboratories (*n* = 248)		Failures in identification at species level	Important antimicrobial susceptibility features of the strain
		%	*n*		
4323	*S. pneumoniae*	99	247	No result provided (*n* = 1)	Intermediate level of resistance to penicillin
4324	*S. aureus*	100	248	–	MRSA, resistant to linezolid, tetracycline and clindamycin but not to erythromycin
4325	*E. faecium*	88	219	*E. faecalis* (*n* = 21) *Enterococcus* spp. (*n* = 6) *Streptococcus* spp. (*n* = 1) *E. coli* (*n* = 1)	Amoxicillin and ampicillin resistant, vancomycin and teicoplanin susceptible, positive for high-level gentamicin resistance
4326	*E. coli*	99	246	*E. faecium* (*n* = 1) *K. pneumoniae* (*n* = 1)	*mcr-1* gene positive, colistin, fluoroquinolones and amoxicillin-clavulanic acid resistant
4327	*K. pneumoniae*	98	242	*Klebsiella oxytoca* (*n* = 2) *Klebsiella* spp. (*n* = 1) *E. coli* (*n* = 1) *Enterobacter aerogenes* (*n* = 1) *Pseudomonas* spp. (*n* = 1)	OXA-1 and SHV-1 genes positive, intermediate/ resistant phenotype to cefotaxime but susceptible to ceftriaxone and ceftazidime, resistant to ertapenem but susceptible to imipenem and meropenem, susceptible/ intermediate to amikacin but resistant to gentamicin and tobramycin, resistant to colistin
4328	*A. baumannii* complex	96	239	*Acinetobacter* spp. (*n* = 9)	GES-12 carbapenemase-producing isolate, susceptible to colistin only

There was a good consensus achieved for ceftriaxone (91.9%) and cefotaxime (91.4%) susceptibility testing and a good concordance of results was achieved for all of the other agents tested.

Among 248 participating laboratories 247 correctly identified the strain as *S. pneumoniae* suggesting optimal laboratory capacity to revive and process this strain, which requires incubation at 5% carbon dioxide.

Table 9.2 *S. pneumoniae* (specimen 4323): MIC and intended results reported by the reference laboratories and the percentage of laboratories giving the correct result per country or area

Agent	MIC range (mg/L), reference laboratory	Intended interpretation	Percentage of laboratories giving the correct result															
		EUCAST/ CLSI	Albania (10)	Armenia (11)	Azerbaijan (3)	Belarus (13)	Bosnia and Herzegovina (10)	Kyrgyzstan (6)	Montenegro (7)	Republic of Moldova (12)	Serbia (22)	Russian Federation (33)	The former Yugoslav Republic of Macedonia (19)	Turkey (81)	Turkmenistan (3)	Ukraine (5)	Uzbekistan (6)	Kosovo[a] (7)
Identification			100	100	100	100	100	100	100	100	100	100	100	99	100	100	100	100
Cefotaxime	0.12–0.25	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Cefotaxime (meningitis)	–	S/S	–	0	–	92	100	100	–	90	100	81	91	–	–	100	–	80
Cefotaxime (pneumonia)	–	S/S	86	0	–	92	100	100	–	100	100	93	100	–	–	100	67	80
Ceftriaxone	0.25–0.5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Ceftriaxone (meningitis)	–	S/S	–	0	–	92	100	100	–	90	100	84	90	–	–	100	–	80
Ceftriaxone (pneumonia)	–	S/S	88	0	–	92	100	100	–	100	100	92	100	–	–	100	67	80
Clindamycin	–	S/S[b]	70	90	–	100	100	80	100	100	95	88	100	92	0	100	–	86
Erythromycin	4–8	R/R	67	90	67	85	89	100	86	83	96	91	100	91	100	100	100	86
Levofloxacin	1	S/S	78	100	100	100	100	100	–	100	96	100	94	99	100	80	80	75
Moxifloxacin	0.12	S/S	100	100	–	100	100	–	–	100	100	100	94	–	100	80	100	–
Norfloxacin	–	S/S[b]	67	–	–	–	100	–	–	100	100	–	91	–	–	80	50	–
Oxacillin	–	R/R	100	100	100	80	100	80	100	90	100	89	91	86	0	100	100	71
Penicillin	0.25	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Penicillin (meningitis)	–	R/R	100	100	–	91	100	–	–	78	96	100	93	88	–	100	100	75
Penicillin (pneumonia)	–	S/S	–	13	–	46	29	–	–	71	64	36	29	30	–	25	33	75

[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 4324 contained an MRSA strain that was resistant to beta-lactam agents, clindamycin, linezolid and tetracycline. A substantial part of the participating laboratories (16%) failed to detect cefoxitin resistance in this strain, which is the key indicator to call this strain an MRSA. Similarly, less than half (46%) of the participating laboratories correctly detected linezolid resistance. Failure in detecting resistance to linezolid was more evident among laboratories using the disk diffusion method. Among laboratories returning results for vancomycin susceptibility (n = 188), three laboratories reported vancomycin disk

diffusion test results even though vancomycin susceptibility should only be tested with a MIC method for *S. aureus*. Laboratories using disk diffusion as the routine method for AST should employ a MIC method (e.g. vancomycin gradient strip tests) for testing vancomycin susceptibility of *S. aureus* isolates.

All participating laboratories correctly identified this strain as *S. aureus*.

Specimen 4325 contained a strain of *E. faecium* that was resistant to amoxicillin/ampicillin and expressed high-level gentamicin resistance but was susceptible to vancomycin and teicoplanin.

High-level gentamicin resistance (MIC >512 mg/L) was correctly detected by 88.0% of participating laboratories. For the other agents a good consensus was observed (range of concordance in providing the correct result: 93.5–97.9%).

Table 9.3 *S. aureus* (specimen 4324): MIC and intended results reported by the reference laboratories and the percentage of laboratories giving the correct result per country or area

Agent	MIC range (mg/L), reference laboratory	Intended interpretation	Percentage of laboratories giving the correct result															
		EUCAST/ CLSI	Albania (10)	Armenia (11)	Azerbaijan (3)	Belarus (13)	Bosnia and Herzegovina (10)	Kyrgyzstan (6)	Montenegro (7)	Republic of Moldova (12)	Serbia (22)	Russian Federation (33)	The former Yugoslav Republic of Macedonia (19)	Turkey (81)	Turkmenistan (3)	Ukraine (5)	Uzbekistan (6)	Kosovo[a] (7)
Identification			100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Cefoxitin	16	R/R	100	100	50	100	90	80	86	82	100	96	95	97	0	100	100	80
Ciprofloxacin	0.5	S/S	90	100	67	82	89	100	100	92	100	97	94	99	33	100	67	100
Clindamycin	>4	R/R	100	100	–	100	100	100	100	100	100	97	100	99	0	100	–	100
Erythromycin	0.5	S/S	100	100	67	100	100	100	100	100	100	88	90	93	100	100	80	86
Fusidic acid	≤0.12	S/–	100	100	–	90	100	–	100	100	100	100	100	100	–	100	–	100
Gentamicin	0.5	S/S	80	100	67	100	90	83	100	100	100	97	89	94	100	100	100	100
Linezolid	16	R/R	67	56	–	58	50	33	25	56	55	36	75	41	–	0	0	–
Oxacillin	–	R/R	–	88	100	100	100	–	–	89	100	95	100	98	–	100	–	100
Penicillin	>0.5	R/R	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	83
Rifampicin	≤0.008	S/S	83	100	100	85	75	–	100	83	90	65	100	98	100	80	100	–
Teicoplanin	0.5	S/S	–	83	–	92	100	–	–	67	100	–	100	100	–	100	67	–
Tetracycline	>8	R/R	100	100	100	100	100	100	100	100	100	100	100	100	0	100	80	100
Vancomycin	1	S/S	20	71	–	92	100	–	–	71	100	100	100	100	–	100	67	100

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

Correct identification at the species level was achieved by 219 (88%) of the participating laboratories, and numerous misidentifications were observed (*E. faecalis*, *n* = 21; *Enterococcus* spp., *n* = 6, *Streptococcus* spp., *n* = 1; *E. coli*, *n* = 1). Accept for one (i.e. *E. coli*) all other misidentifications were highly suggestive of the lack of laboratory capacity to correctly identify *Enterococcus* spp. at the species level. Further analysis of the results revealed that the same laboratory that reported this strain as *E. coli*, identified the test strain of *E. coli* (number 4326) as *E. faecium*, demonstrating a good example of specimen mix-up during laboratory testing, which could lead to erroneous patient results if it occurs during actual testing of clinical specimens.

Specimen 4326 contained an *E. coli* strain possessing the *mcr-1* gene, exhibiting resistance to amoxicillin, amoxicillin-clavulanic acid, colistin and quinolones.

Most participating laboratories did not achieve the intended result for amoxicillin-clavulanic acid: 40.4% correctly identified amoxicillin-clavulanic acid resistance. The reference MIC for this strain was 32 mg/L, tested with a fixed clavulanic acid concentration of 2 mg/L, which is resistant by EUCAST and CLSI breakpoints of >8 mg/L and ≥32 mg/L, respectively. Laboratories using EUCAST methodology were more likely to achieve the intended result than laboratories using CLSI methodology (43% vs. 19%), potentially due to the strain's MIC being close to the (higher) CLSI breakpoint. Laboratories following EUCAST methodology were more likely to achieve the intended result if they used disk diffusion, rather than an automated method (49% vs. 35%).

There was a poor consensus of reported results for colistin testing, with an intended result of resistant (reference MIC = 4 mg/L, EUCAST breakpoint >2 mg/L). This strain was reported as resistant by 43.1% of participating laboratories. There is no CLSI colistin breakpoint for *E. coli*, and EUCAST recommends the use of a MIC method to determine colistin susceptibility. However 28 out of 133 (21.1%) laboratories that reported using EUCAST methodology stated that they used disk diffusion method.

Table 9.4 *E. faecium* (specimen 4325): MIC and intended results reported by the reference laboratories and the percentage of laboratories giving the correct result per country or area

Agent	MIC range (mg/L), reference laboratory	Intended interpretation	Percentage of laboratories giving the correct result															
		EUCAST/ CLSI	Albania (10)	Armenia (11)	Azerbaijan (3)	Belarus (13)	Bosnia and Herzegovina (10)	Kyrgyzstan (6)	Montenegro (7)	Republic of Moldova (12)	Serbia (22)	Russian Federation (33)	The former Yugoslav Republic of Macedonia (19)	Turkey (81)	Turkmenistan (3)	Ukraine (5)	Uzbekistan (6)	Kosovo[a] (7)
Identification			80	91	0	92	90	67	43	100	100	91	95	96	100	100	17	57
Amoxicillin	32	R/R	100	100	–	100	100	75	–	80	100	–	100	–	100	100	100	57
Ampicillin	32–64	R/R	100	100	100	100	100	100	86	92	100	100	100	100	100	100	80	57
Gentamicin (high-level resistance)	>512	Positive	100	100	–	85	100	–	–	–	91	68	62	97	–	100	67	–
Teicoplanin	1	S/S	56	100	–	100	100	–	–	100	100	–	100	99	–	100	100	–
Vancomycin	1	S/S	70	100	100	100	100	100	100	100	100	97	100	99	100	100	100	100

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

Table 9.5 *E. coli* (specimen 4326): MIC and intended results reported by the reference laboratories and the percentage of laboratories giving the correct result per country or area

Agent	MIC range (mg/L), reference laboratory	Intended interpretation	Percentage of laboratories giving the correct result															
		EUCAST/ CLSI	Albania (10)	Armenia (11)	Azerbaijan (3)	Belarus (13)	Bosnia and Herzegovina (10)	Kyrgyzstan (6)	Montenegro (7)	Republic of Moldova (12)	Serbia (22)	Russian Federation (33)	The former Yugoslav Republic of Macedonia (19)	Turkey (81)	Turkmenistan (3)	Ukraine (5)	Uzbekistan (6)	Kosovo[a] (7)
Identification			100	100	67	92	100	100	100	100	100	100	100	100	100	100	100	100
Amikacin	2–4	S/S	80	100	100	100	100	100	100	92	100	97	95	100	100	100	83	86
Amoxicillin	>32	R/R	80	100	–	100	100	67	–	100	100	–	100	94	100	100	100	100
Amoxicillin-clavulanic acid	32[b]	R/R	78	100	–	36	0	0	17	92	23	13	33	43	0	80	67	43
Ampicillin	>32	R/R	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Cefotaxime	0.5	S/S	90	91	67	67	100	100	100	100	100	93	100	100	0	100	33	100
Ceftazidime	0.5–1	S/S	89	100	67	67	90	100	100	100	100	94	95	99	100	100	100	100
Ceftriaxone	0.25	S/S	80	100	–	75	100	100	100	92	100	96	100	99	100	100	100	100
Ciprofloxacin	>4	R/R	90	100	100	100	100	83	100	100	100	100	94	100	100	100	100	100
Colistin	4	R/R	–	–	–	11	50	–	–	–	33	–	–	41	–	0	–	–
Ertapenem	0.03	S/S	67	100	–	100	100	100	100	89	100	96	100	100	100	100	67	100
Gentamicin	1	S/S	100	100	67	92	100	100	100	100	100	97	90	100	100	100	100	83
Imipenem	0.12	S/S	57	9	–	100	100	100	100	100	100	100	100	100	100	100	100	100
Levofloxacin	–	R/R[c]	13	100	–	100	100	83	100	100	100	100	100	98	100	100	83	100
Meropenem	0.03	S/S	78	100	–	100	100	100	86	73	100	100	95	100	100	100	83	100
Ofloxacin	–	R/R[c]	83	100	100	100	–	80	100	100	100	–	100	–	100	100	100	100
Piperacillin-tazobactam	8	S/S	78	100	–	92	89	–	86	64	96	77	89	91	–	80	83	57
Tobramycin	0.5	S/S	100	91	100	100	100	100	75	75	100	88	94	95	100	100	100	83

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

[b] Reference results for amoxicillin-clavulanic acid MICs 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.

Specimen 4327 was a strain of *K. pneumoniae* possessing both OXA-1 and SHV-1 enzymes and thereby expressing dissociated resistance to 3rd generation cephalosporins, with an intermediate/resistant phenotype to cefotaxime and susceptible to ceftazidime/ceftriaxone. The strain also expressed dissociated resistance to carbapenems, being resistant to ertapenem and susceptible to imipenem and meropenem.

The strain was resistant to ciprofloxacin, colistin, beta-lactam/beta-lactamase inhibitor combinations, gentamicin and tobramycin, but susceptible/intermediate to amikacin (MIC = 16 mg/L) by CLSI/EUCAST breakpoints, respectively. A poor consensus was achieved for the intended result, with 36.6% of laboratories reporting a result of intermediate or susceptible.

Among participating laboratories, 69.0%, 65.5% and 67.7% provided the correct responses for cefotaxime, ceftazidime and ceftriaxone, respectively.

Reduced susceptibility (intermediate/resistant) to ertapenem was detected by 95.0% of participating laboratories. However, 79.7% and 70.8% of laboratories reported the intended result of susceptible for imipenem and meropenem, respectively. No differences were seen for these agents between laboratories following different guidelines or using different methods.

Colistin resistance was correctly identified by 85.0% of participating laboratories. Similar to the *E. coli* strain (specimen no. 4326), 26 out of 134 (19.4%) laboratories that reported using EUCAST methodology stated that they used the disk diffusion method, and it is unclear what criteria they used to categorize the susceptibility result.

A few laboratories (*n* = 6) had issues with (i) misidentification, or (ii) failing to perform identification at the species level (*Klebsiella oxytoca*, *n* = 2; *Klebsiella* spp., *n* = 1; *E. coli*; *n* = 1, *Enterobacter aerogenes*, *n* = 1; *Pseudomonas* spp., *n* = 1), suggesting a lack of laboratory capacity to perform identification at the species level and also suboptimal methodology resulting in misidentifications.

Specimen 4328 was a strain of *A. baumannii* complex, which was susceptible to colistin, but resistant to other classes of agents tested. Two reference laboratories independently determined the colistin MIC as either 0.5 - 1 g/L, which is susceptible according to both CLSI and EUCAST. Colistin susceptibility was reported by a total of 160 laboratories, and all used a MIC method for susceptibility testing of colistin. Among these, three laboratories reported resistant results, and one laboratory reported intermediate result. A good concordance of results was achieved for all other agents tested (range of concordance in providing the correct result: 87.7-100%).

Satisfactory performance was obtained for the identification; 239 out of 248 (96.4%) participating laboratories correctly identified the strain as *A. baumannii* complex, and 9 out of 248 (3.6%) provided an identification result as *Acinetobacter* spp.

9.3 Summary of the first five years of CAESAR EQA (2013–2017)

The CAESAR EQA programme in collaboration with UK NEQAS started in 2013, following the same methodology that makes it possible to assess progress over time.

Many of the countries now submitting data to CAESAR started by participating in the yearly EQA exercise, which formed the core of the national network in which the national AMR reference laboratory usually undertakes the role of a local coordinator that receives the samples from UK NEQAS and delivers them to participating laboratories in the local network.

On the other hand, for countries that are already submitting data to CAESAR, the yearly EQA survey serves more as an educational activity in which laboratories receive carefully selected challenge strains, which usually include recently emerged resistance mechanisms (e.g. *S. aureus* with *mecC* (specimen no. 3685, 2016 or *E. coli* with *mcr-1* (specimen no. 4326, 2017)). The laboratories usually prepare stock cultures from these well-characterized strains and use them in their future quality control studies.

Table 9.6 *K. pneumoniae* (specimen 4327): MIC and intended results reported by the reference laboratories and the percentage of laboratories giving the correct result per country or area

Agent	MIC range (mg/L), reference laboratory	Intended interpretation	Percentage of laboratories giving the correct result															
		EUCAST/ CLSI	Albania (10)	Armenia (11)	Azerbaijan (3)	Belarus (13)	Bosnia and Herzegovina (10)	Kyrgyzstan (6)	Montenegro (7)	Republic of Moldova (12)	Serbia (22)	Russian Federation (33)	The former Yugoslav Republic of Macedonia (19)	Turkey (81)	Turkmenistan (3)	Ukraine (5)	Uzbekistan (6)	Kosovo[a] (7)
Identification			100	100	67	100	100	100	86	100	100	94	100	99	100	100	100	86
Amikacin	16	I/S	0	0	0	18	30	0	29	8	23	18	42	34	100	0	17	0
Amoxicillin	>32	R/R	100	100	–	100	100	100	–	100	100	–	100	–	100	100	100	100
Amoxicillin-clavulanic acid	>64–>128[b]	R/R	100	100	–	100	100	100	100	100	100	97	100	100	100	100	67	86
Ampicillin	>32–>64	R/R	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Cefotaxime	2–4	I–R/I–R	30	18	33	69	78	33	100	75	84	72	94	–	100	80	100	43
Ceftazidime	1	S/S	100	27	–	54	80	80	57	83	96	42	56	67	0	80	67	100
Ceftriaxone	1	S/S	100	82	67	73	89	100	43	67	90	44	47	63	33	80	67	86
Ciprofloxacin	>4–>8	R/R	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Colistin	32	R/–	–	100	–	100	100	–	–	–	89	–	–	80	–	100	–	–
Ertapenem	2–4	R/R	67	100	–	60	100	100	100	78	100	89	80	92	100	100	83	50
Gentamicin	>16–>32	R/R	100	100	100	100	100	100	100	83	100	100	100	99	33	100	83	100
Imipenem	0.5–1	S/S	67	9	–	62	78	100	100	92	100	85	100	74	100	60	83	100
Levofloxacin	–	R/R[c]	100	100	50	100	100	100	–	92	100	96	100	96	100	100	83	100
Meropenem	0.5	S/S	56	91	–	69	80	20	86	36	100	72	79	66	–	80	17	100
Ofloxacin	–	R/R[c]	100	100	–	100	–	80	57	92	100	–	100	–	100	100	100	100
Piperacillin-tazobactam	>64	R/R	100	100	–	100	100	–	86	91	100	100	100	97	–	100	100	86
Tobramycin	>16–>32	R/R	100	100	100	100	100	100	100	92	100	95	100	100	100	100	83	100

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

[b] Reference results for amoxicillin-clavulanic acid MICs 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.

Table 9.7 *A. baumannii* complex (specimen 4328): MIC and intended results reported by the reference laboratories and the percentage of laboratories giving the correct result per country or area

Agent	MIC range (mg/L) determined by the reference laboratory	Intended interpretation	Percentage of laboratories giving the correct result															
		EUCAST/ CLSI	Albania (10)	Armenia (11)	Azerbaijan (3)	Belarus (13)	Bosnia and Herzegovina (10)	Kyrgyzstan (6)	Montenegro (7)	Republic of Moldova (12)	Serbia (22)	Russian Federation (33)	The former Yugoslav Republic of Macedonia (19)	Turkey (81)	Turkmenistan (3)	Ukraine (5)	Uzbekistan (6)	Kosovo[a] (7)
Identification			100	100	100	100	100	100	100	100	86	97	84	99	100	100	100	86
Amikacin	≥128	R/R	90	100	100	100	89	100	71	92	100	100	100	95	0	100	100	100
Ciprofloxacin	64–≥128	R/R	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Colistin	0.5–1	S/S	40	100	–	100	100	–	–	–	100	–	100	97	–	100	–	–
Doripenem	–	R/R[b]	–	–	–	–	–	–	–	–	100	–	–	–	0	100	100	–
Gentamicin	32–64	R/R	100	100	33	77	80	100	100	67	100	97	100	99	100	100	33	100
Imipenem	32–64	R/R	100	100	–	100	100	100	100	92	100	100	100	100	33	100	83	100
Levofloxacin	–	R/R[b]	100	100	–	100	100	100	75	91	100	96	100	100	100	100	100	100
Meropenem	64–≥128	R/R	100	100	–	100	100	100	100	73	100	100	100	100	0	100	67	100
Tobramycin	32	R/R	100	100	100	67	86	100	75	83	100	88	77	97	0	100	17	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.

9.3.1 Expansion of the CAESAR EQA network

Between 2013 and 2017, the number of participating laboratories in the CAESAR EQA network steadily increased and reached 290 participating laboratories in 18 countries or areas (Table 9.8). The CAESAR EQA started in 2013 with 128 participating laboratories from eight countries or areas (Belarus, Georgia, Kyrgyzstan, Montenegro, Serbia, the former Yugoslav Republic of Macedonia, Turkey and Kosovo[1]. In 2014, the number of participating laboratories increased to 184 with the inclusion of four countries (Albania, Azerbaijan, Bosnia and Herzegovina and the Russian Federation). In 2015, the number of participating laboratories increased to 252 with the Republic of Moldova, Tajikistan and Turkmenistan joining the network. In 2016, three more countries (Armenia, Ukraine and Uzbekistan) enrolled in the exercise, and the number of participating laboratories increased to 272. In 2017, even though no new countries joined the EQA network, the number of participating laboratories increased to 290.

9.3.2 Strains distributed and laboratory performance for correct identification

In general, participating laboratories performed satisfactorily in regards to identification of the specimens at the species level. Less than 40% of laboratories use conventional methods for identification, which in

some instances reflects as a failure to provide identification at the species level, e.g. for *Acinetobacter* spp. and *Enterococcus* spp. Given the importance of these pathogens for their role in human infections, and different susceptibility features inherently exhibited by different species within the genus, the laboratories should put more efforts into correct identification at the species level. The EQA strains distributed and the percentage of correct identification among the participating laboratories is summarized in Table 9.9. So far, only organisms whose antimicrobial susceptibility results are collected by CAESAR have been sent to laboratories. A strain of each *E. coli*, *K. pneumoniae*, *S. aureus* and *S. pneumoniae* were distributed in all five surveys conducted so far.

Greater care is needed when processing the isolates, since some identification errors indicate a mix up of samples with either other EQA samples or with other specimens in the laboratory, or contamination. These errors indicate a potential for mistakes with clinical samples.

9.3.3 Trends in AST guidelines

Starting from the very beginning, CAESAR aimed to collect reliable and comparable surveillance data on AMR and promoted strict adherence to international guidelines on AST. In 2013, when the first CAESAR EQA exercise was conducted, 88% of the participating laboratories indicated CLSI as their AST guideline and 12% indicated EUCAST. However, a strong shift towards the EUCAST methodology has taken place which, as of 2017, was used as the guideline in 87% of the CAESAR EQA participating laboratories in 18 countries or areas (Fig. 9.3). The fact that all EUCAST documents can be freely accessed and the translation of EUCAST documents into local languages such as Russian and Turkish may have contributed to the uptake of the EUCAST methodology in those settings.

9.3.4 Laboratory performance for AST

Generally, discrepancies were more common when the isolate had borderline susceptibility, or when the laboratories failed to strictly follow AST guidelines. A recent example of the latter is the problems observed in reporting of colistin susceptibility results for specimen number 4326 (*E. coli*, colistin MIC = 4 mg/L) and 4327 (*K. pneumoniae*, colistin MIC = 32 mg/L) that were distributed as part of the 2017 EQA exercise. Both strains were resistant to colistin, but the percentage of laboratories reporting the strains correctly as resistant to colistin was 43.1% for *E. coli* and 85% for *K. pneumoniae*. Despite the clear recommendation from EUCAST to use only broth microdilution method for the determination of colistin susceptibility in *Enterobacteriaceae*, some of the participating laboratories that followed EUCAST methodology (26 out of 134 (19.4%) for the *E. coli* isolate and 28 out of 133 (21.1%) for the *K. pneumoniae* isolate), reported colistin susceptibility using the disk diffusion method. This result is inconsistent, as there are no clinical breakpoints for colistin that could guide interpretation of disk diffusion test results, if indeed EUCAST breakpoint tables had been followed.

Similar to the problems observed in susceptibility testing of colistin for *Enterobacteriaceae*, problems associated with poor adherence to guidelines were also observed for susceptibility testing of vancomycin for *S. aureus* and susceptibility testing of penicillin for *S. pneumoniae*. For these organism–antimicrobial combinations, disk diffusion method cannot be used, and a method to determine the MIC of the antimicrobial is needed. For laboratories using disk diffusion method for routine AST, gradient strip tests can be used to determine the MIC of vancomycin for *S. aureus* and penicillin for *S. pneumoniae*.

However, it should be noted that broth microdilution is so far the only valid method for AST of colistin and that disk diffusion and the currently available gradient tests should not be used. The gradient strips underestimate the colistin MIC values and undercall resistance.

Repeating problems have also been observed with reporting of *S. pneumoniae* susceptibility results for benzylpenicillin, which are dependent on the site of infection. Different clinical breakpoints for different

Table 9.8 Countries or areas participating in the CAESAR EQA and expansion of the network, 2013–2017

Country or area	Year (no. of returned results/total no. of laboratories)				
	2013	2014	2015	2016	2017
Belarus	8/8	6/8	8/8	9/9	13/13
Georgia	1/1	5/9	10/10	10/11	0/13[b]
Kyrgyzstan	3/3	5/5	5/5	6/6	6/6
Montenegro	1/1	6/7	8/9	9/10	7/8
Serbia	14/14	14/14	14/14	21/22	22/22
The former Yugoslav Republic of Macedonia	15/16	13/17	16/17	19/21	19/21
Turkey	72/78	68/77	98/106	81/90	81/87
Kosovo[a]	6/7	7/7	7/7	7/7	7/7
Albania	–	2/2	6/7	7/9	10/11
Azerbaijan	–	3/3	3/3	3/3	3/3
Bosnia and Herzegovina	–	4/4	7/7	9/9	10/10
Russian Federation	–	26/31	31/39	40/41	33/47
Republic of Moldova	–	–	12/12	12/12	12/12
Tajikistan	–	–	1/5	4/5	0/5[b]
Turkmenistan	–	–	3/3	3/3	3/3
Armenia	–	–	–	5/5	11/11
Ukraine	–	–	–	3/3	5/5
Uzbekistan	–	–	–	6/6	6/6
Network total	120/128 (94%)	159/184 (86%)	229/252 (91%)	254/272 (93%)	248/290 (91%)[c]

[a] In accordance with United Nations Security Council resolution 1244 (1999).
[b] Network laboratories in Georgia and Tajikistan could not take part in the 2017 EQA exercise due to delay in delivery of the EQA samples.
[c] The percentage of laboratories returning results was calculated only for laboratories that received the EQA samples (n = 272).

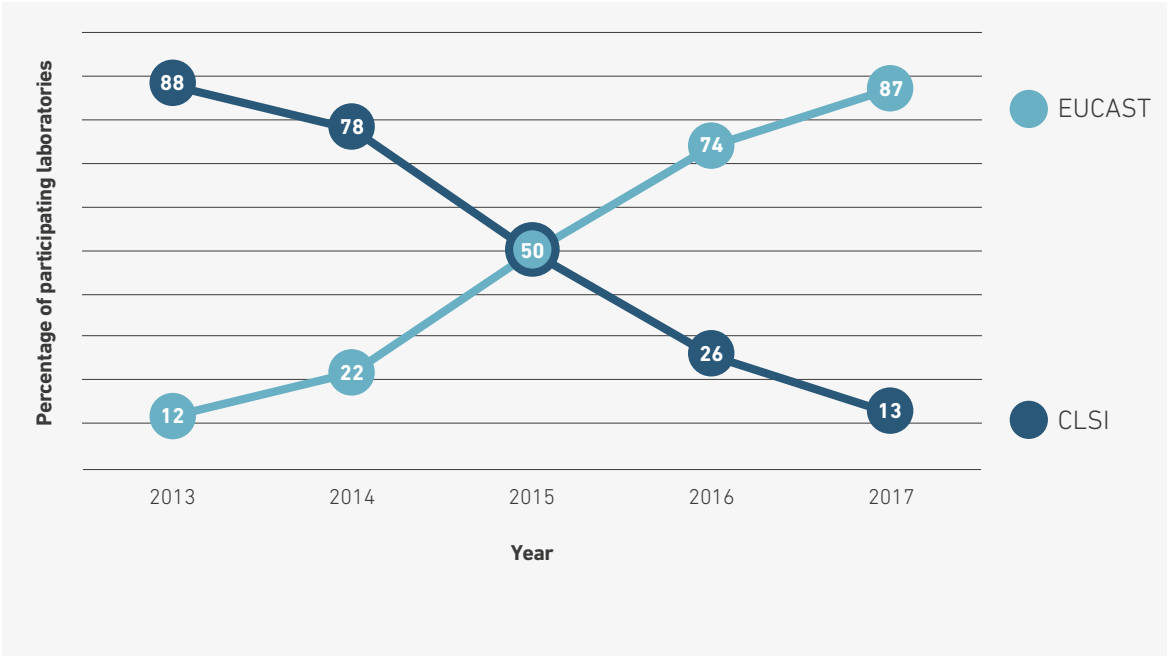
infection types (such as meningitis and other than meningitis) should be taken into account when interpreting the results.

Each laboratory must examine and document reasons for performance errors to inform corrective action. The materials used and the methods followed should be checked. More importantly, the staff performing the tests should be adequately trained and proven to be competent.

Table 9.9 Specimens distributed as part of the CAESAR EQA and the percentage of correct identification at the species level among participating laboratories, 2013–2017

Organism	Year									
	2013		2014		2015		2016		2017	
	Specimen no.	%	Specimen no.	%	Specimen no.	%	Specimen no.	%	Specimen no.	%
E. coli	1951	100	2496	100	3092	94	3682	99	4326	99
K. pneumoniae	1952	97	2497	92	3089	99	3683	91	4327	98
P. aeruginosa	1956	100	–	–	3093	99	3684	100	–	–
A. baumannii complex	1950	87	2501	98	–		3686	91	4328	96
S. aureus	1953	100	2498	99	3090	99	3685	98	4324	100
S. pneumoniae	1954	99	2499	99	3091	100	3687	98	4323	99
E. faecium	–	–	2500	87	–	–	–	–	4325	88
E. faecalis	–	–	–	–	3088	98	–	–	–	–

Fig. 9.3 Trends in AST guidelines used by CAESAR EQA participating laboratories, 2013–2017



9.3.5 Future perspectives and the need for improvement

The CAESAR EQA network showed a remarkable growth in the number of participating laboratories between 2013 and 2017, now including 290 laboratories in 18 countries and areas. Building functioning quality assurance systems in the network laboratories should be the next priority going forward.

Even though EQA is a very useful exercise, it is only a minor component of a comprehensive quality assurance system. Components such as clinically relevant testing strategies, testing of reference strains for internal (routine) quality control, training, technical competency, organism–AST result verification, supervisor review of results, standardization and documentation are of great importance to provide a strong quality assurance system for AST.

The most important limitations of CAESAR EQA may be considered as follows:

- the number of specimens distributed is small (six specimens per year)
- specimens do not reflect routine isolates
- laboratories may not treat specimens as routine.

Much of the network`s focus should be directed to strengthening the capacities of national reference laboratories on AMR so that they may build the required competency to organize national EQA surveys with shorter turnaround time, which are truly tailored to the needs of their respective systems.


CHAPTER
10

Concluding remarks

The fourth edition of the CAESAR annual report illustrates an ever-growing and evolving network. Building the foundation for AMR surveillance is at the heart of the network, which now includes data from 10 countries and one area, and provides a benchmark for the quality of reported data. Chapter 8 on the preliminary results from the proof-of-principle project in Armenia provides an excellent example of how CAESAR supports diagnostic stewardship in the European Region. EQA participation continues to increase; going forward, the emphasis will not only be on growth but on enabling participating laboratories to evolve, improve, and maintain the good work that has been started. The importance of well-equipped and well-staffed reference laboratories to support surveillance networks cannot be overrated. The international community calls for more and better data to feed the ever-growing body of evidence on the effects of AMR on humans, animals, the environment and the economy; policy-makers need access to surveillance data to design, implement and measure effective policies to control AMR in their constituencies. Therefore AMR surveillance truly is the cornerstone of an effective response to AMR, and investments in staff, equipment and quality consumables are needed to keep them functional and useful.

The CAESAR network therefore advocates with national decision-makers to realize the role and full potential of their respective networks and to continuously work on improving them. It is important for network members to remain connected, which is why CAESAR has supported national CAESAR network meetings since 2015 as a platform to discuss methodologies, data, EQA results and training needs.

The WHO Regional Office for Europe and ECDC jointly organized the Meeting of the Antimicrobial Resistance, Antimicrobial Consumption and Healthcare-Associated Infections Surveillance Networks in June 2018 at the UN City in Copenhagen, Denmark, marking the first time all surveillance networks hosted by the Regional Office[2] were together under one roof. This first joint meeting was the logical consequence of good collaboration and alignment of methodologies from the start, as illustrated by the joint EARS-Net/CAESAR AMR maps of the WHO European Region that have been featured in the CAESAR annual reports since 2016. These maps are now an integral part of the publication, and the CAESAR network continues to strive towards joint European reporting of AMR surveillance data.

This reporting period includes several key achievements.

- Eleven countries and one area have an AMR reference laboratory in place.
- Ten countries and one area provide data to the CAESAR network.
- Participation in the EQA has again expanded with 248 laboratories from 16 countries/areas, and overall results continue to improve.
- Two central Asian countries are preparing to implement a proof-of-principle project, while one additional country concluded a project in October 2018.

Developments are not limited to the WHO European Region. Experience gained from CAESAR has greatly contributed to the development of GLASS, to which more and more CAESAR members are signing up. WHO and ECDC are aware of the importance of avoiding double reporting and any additional burden to Member States. Therefore, CAESAR coordinates closely with ECDC and GLASS to share data that has been submitted according to high professional standards and through agreed mechanisms. Launched

[2] Surveillance networks hosted by ECDC are EARS-Net, the European Surveillance of Antimicrobial Consumption Network and the Healthcare-Associated Infections Surveillance Network. Surveillance networks hosted by the Regional Office are CAESAR and the WHO Antimicrobial Medicines Consumption Network.

in 2016, the CAESAR module in GLASS is open to GLASS national focal points from CAESAR countries and to the Regional Office The second GLASS report is forthcoming and will provide important insight from around the world.

With AMR remaining high on the political agenda, discussions of the CAESAR coordination group on the network's future directions were very active and innovative this year. Key topics included, among others, new and innovative ways of performing EQA, and the need to provide diagnostic stewardship support in settings that want to participate in the CAESAR network but have very limited samples available.

Finally, it is important to remember that the CAESAR network builds on the dedication and work of many individuals who connect to collectively improve surveillance in the European Region. They all strive to improve their overview of local resistance patterns and contribute to a more complete picture of AMR surveillance in the European Region. Through its activities, the CAESAR network will continue to support countries and areas in all steps of AMR surveillance, including the incorporation of additional specimens and pathogen–antibiotic combinations, as they prepare for full participation in GLASS.

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 and areas 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)*.

E. coli

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

- is the most frequent cause of both community-acquired and 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 direct contact with animals, through consumption of contaminated food or person-to-person contact.

K. pneumoniae

Like *E. coli*, bacteria of the species *K. pneumoniae* are frequent colonizers of the gut in humans, particularly in individuals 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 medical care;
- are usually 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 occur 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.

P. 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 cause of infection in hospitalized patients with localised 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;
- may chronically colonize patients with cystic fibrosis, causing severe intermittent exacerbation of the condition with, for example, bronchiolitis and acute respiratory distress syndrome; and
- is commonly found in burn units where it is almost impossible to eradicate colonizing strains with classic infection control procedures.

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, 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 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 receipt of broad-spectrum antimicrobial agents, especially third-generation cephalosporins, fluoroquinolones and carbapenems.

S. aureus

S. aureus:

- is a gram-positive bacterium that can be part of the normal flora 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.

S. pneumoniae

S. pneumoniae:

- is the leading cause worldwide of community-acquired pneumonia, which is among the main causes of death of children under 5 years of age;

- 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.

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

It is commonly found in 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 day-care centres.

E. faecium and *E. 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 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 enterococcal 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 treatment of human infections caused by penicillin-resistant *E. faecium*.

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
- often 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 reality. Every measurement includes a risk of deviating from the true value 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 selecting patients for sampling (such as sampling bias), when processing samples in the laboratory (such as measurement error) or when aggregating data for analysis (such as including follow-up isolates).

Random error will always occur, and investigators can reduce the amount of error to a certain extent. In contrast, investigators can significantly reduce systematic error by careful consideration of certain aspects of 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, suppose that in a certain hospital a weekly average of 11 blood cultures is obtained. 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 may result in a different number each week, such as 9, 13, 10 and 12 during the first, second, third and fourth week, respectively. The observed weekly number of blood cultures varies by chance. Random variation may result in either over- or underestimating a resistance proportion. The expected deviation from the true value due to random error or, in other words, the statistical precision of a measurement, depends on sample size. The smaller the sample size, the greater the potential deviation is from the true value; the larger the sample size, the less deviation.

Measurement variation

Random error also occurs whenever measurements are taken and results from slight variations in how measurement procedures are applied across measurements. For example, the concentration of an inoculum that is plated out when testing antibiotic susceptibility using disk diffusion will vary each 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 of the antibiotic as 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, a larger sample size will reduce the effect of random over- and underestimations. When using automated measuring systems for AST, the measurement variation is generally small and acceptable. If testing is performed manually, the error depends on the experience and qualification of the laboratory technician and the thoroughness of the measurements. Standardizing procedures, training laboratory staff and ensuring quality will minimize random measurement variation.

Systematic error

Bias from sampling procedures – selecting participating sites

In order to obtain a representative assessment of AMR in a country or area, the selection of participating laboratories in the surveillance system of a country or area 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 specific 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 severely ill patients, patients among whom treatment is problematic or patients for whom there is high suspicion of resistant infections. That is, the decision on whether to obtain a blood sample is made taking into account clinical predictions. 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 blood stream infection, sepsis or meningitis should be sampled. Including only specific 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. This is 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 not followed, when poor-quality laboratory materials are used (such as old 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. 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 misclassified as *E. faecalis*.

A laboratory quality management system and regular application of internal quality assurance procedures allow the timely detection and correction of systematic error in laboratory procedures. 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 the findings are correct or a result of laboratory error. This double-checking of results

is important because finding 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 should be done according to well developed and scientifically validated standards. Both EUCAST and CLSI provide comprehensive methodological standards for routine antibiotic susceptibility testing, confirmatory testing and interpreting the results. Laboratory methods and interpretive criteria (clinical breakpoints) may differ between standards and change over time. This may lead to inconsistent results in 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 when resistance to third-generation cephalosporins is found, 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. Repeat blood cultures are more likely obtained from patients with infections caused by resistant microorganisms compared with patients with infections caused by susceptible pathogens. If repeat isolates from the same patient are included when calculating the proportion of resistance, this 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, which is the convention when conducting surveillance.

In practice, when interpreting antibiotic susceptibility testing results, expert rules are often used to report 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 surveillance systems may use different expert rules, making it difficult to compare data obtained in different laboratories or countries. To prevent the use of different expert rules from biasing the results and to standardize the interpretation of results, CAESAR collects all the results obtained by testing the sensitivity to each of the antibiotics.

Recommended reading

Cornaglia G, Hryniewicz W, Jarlier V, Kahlmeter G, Mittermayer H, Stratchounski L, et al. European recommendations for antimicrobial resistance surveillance. Clin Microbiol Infect. 2004;10(4):349–83.

Hindler JF, Stelling J. Analysis and presentation of cumulative antibiograms: a new consensus guideline from the Clinical and Laboratory Standards Institute. Clin Infect Dis. 2007;44(6):867–73.

Rempel OR, Laupland KB. Surveillance for antimicrobial resistant organisms: potential sources and magnitude of bias. Epidemiol Infect. 2009;137(12):1665–73.

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 true value

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 or meningitis

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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