World Health Organization
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Central Asian and European Surveillance of Antimicrobial Resistance

Annual report 2019

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Abstract

This report describes resistance data gathered through the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) network from 11 countries in the WHO European Region – Armenia, Belarus, Bosnia and Herzegovina, Georgia, Montenegro, North Macedonia, the Russian Federation, Serbia, Switzerland, Turkey and Ukraine – and Kosovo (in accordance with United Nations Security Council resolution 1244 (1999)). The fifth CAESAR report includes resistance data from Armenia for the first time, provides a summary of the first six years of the CAESAR external quality assessment (2013–2018) and presents the experiences of the Republic of Moldova and Tajikistan in establishing AMR surveillance systems and submitting data to CAESAR for the first time. Furthermore, the report includes a reader's guide on how to interpret the surveillance data with caution, taking into account conditions that may reduce the reliability and representativeness of the data. This report aims 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 partners remain committed to supporting countries/areas in these endeavours through the activities of the CAESAR network.

Keywords

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

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Acknowledgements

The WHO Regional Office for Europe and its partners – the Netherlands National Institute for Public Health and the Environment, and the European Society of Clinical Microbiology and Infectious Diseases – thank the antimicrobial resistance (AMR) focal point teams in countries and in Kosovo (in accordance with United Nations Security Council resolution 1244 (1999)) for providing AMR data, coordinating the CAESAR external quality assessment exercise, reporting on the progress of AMR activities and contributing to this report, and look forward to continued collaboration.

AMR focal point teams: Albana Fico (Albania), Lindita Molla (Albania), Kristina Gyurjyan (Armenia), Nune Kotsinyan (Armenia), Romella Abovyan (Armenia), Nazifa Mursalova (Azerbaijan), Leonid Titov (Belarus), Anna N. Kharkhal (Belarus), Julia A. Shyshporenok (Belarus), Valentin V. Pugach (Belarus), Amela Dedeic-Ljubovic (Bosnia and Herzegovina), Pava Dimitrijevic (Bosnia and Herzegovina; Republika Srpska), Maja Travar (Bosnia and Herzegovina; Republika Srpska), Paata Imnadze (Georgia), Lile Malania (Georgia), David Tsereteli (Georgia), Baktygul Ismailova (Kyrgyzstan), Milena Lopicic (Montenegro), Gordana Mijovic (Montenegro), Golubinka Bosevska (North Macedonia), Biljana Kakaraskoska Boceska (North Macedonia), Zaklina Cekovska (North Macedonia), Ana Kaftandzieva (North Macedonia), Nikola Panovski (North Macedonia), Olga Burduniuc (Republic of Moldova), Ecaterina Busuioc (Republic of Moldova), Vadim Rață (Republic of Moldova), Roman S. Kozlov (Russian Federation), Marina Sukhorukova (Russian Federation), Deana Medic (Serbia), Andreas Kronenberg (Switzerland), Mahmadali Tabarov (Tajikistan), Husniye Simsek (Turkey), Serap Suzuk Yıldız (Turkey), Baki Can Metin (Turkey), Can Hüseyin Hekimoğlu (Turkey), Gurbangul Ovliyakulova (Turkmenistan), Iryna Ganzha (Ukraine), Natalia Piven (Ukraine), Tatiana Glushkevych (Ukraine), Valentina Yanovskaya (Ukraine), Gulnora Abdukhalilova (Uzbekistan), Nargiza Ottamuratova (Uzbekistan), Ildar Akhmedov (Uzbekistan), Lul Raka (Kosovo (in accordance with United Nations Security Council resolution 1244 (1999))), Arsim Kurti (Kosovo (in accordance with United Nations Security Council resolution 1244 (1999))).

The WHO Regional Office for Europe would also like to acknowledge the close and fruitful collaboration with the European Centre for Disease Prevention and Control and would like to thank all European Antimicrobial Resistance Surveillance Network participating countries for providing data for the AMR maps of the European Region.

Acknowledgements are also extended to the WHO collaborating centres with a particular focus on AMR: the WHO Collaborating Centre for AMR Epidemiology and Surveillance, the Netherlands; the WHO Collaborating Centre for Capacity Building on AMR Surveillance and Research, the Russian Federation; the WHO Collaborating Centre for AMR Containment, Sweden; and the WHO Collaborating Centre for Reference and Research on AMR and Healthcare-Associated Infections, United Kingdom.

Finally, special thanks to the many consultants and experts providing essential expertise to support countries and areas in strengthening their AMR surveillance systems.

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Financial Support
CAESAR activities are funded by the National Institute for Public Health and the Environment of the Netherlands; the Ministry of Health, Welfare and Sport of the Netherlands; Germany's Federal Ministry of Health; the Norwegian Agency for Development Cooperation; the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), including the ESCMID Study Group for Antimicrobial Resistance Surveillance; and the WHO Regional Office for Europe.

Abbreviations

A. baumannii	*Acinetobacter baumannii*
AMR	antimicrobial resistance
AST	antimicrobial susceptibility testing
CAESAR	Central Asian and 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*
E. gallinarum	*Enterococcus gallinarum*
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
IACG	Ad hoc Interagency Coordination Group
ISO	International Organization for Standardization
K. oxytoca	*Klebsiella oxytoca*
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. epidermidis	*Staphylococcus epidermidis*
S. maltophilia	*Stenotrophomonas maltophilia*
S. mitis	*Streptococcus mitis*
S. pneumoniae	*Streptococcus pneumoniae*
S. salivarius	*Streptococcus salivarius*
spp.	species (for specific bacteria)
Susceptibility	susceptibility of a pathogen to an antimicrobial agent S susceptible, standard dosing regime I susceptible, increased exposure R resistant
TrACSS	Tripartite AMR country self-assessment survey
UK NEQAS	United Kingdom National External Quality Assessment Service for Microbiology
WHONET	WHO microbiology laboratory database software

Summary

In 2019, the Central Asian and Eastern European Surveillance of Antimicrobial Resistance network changed its name to the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) network. The 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 supports its network members in setting up and strengthening antimicrobial resistance (AMR) surveillance, focusing on 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*. The network currently consists of Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, North Macedonia, the Republic of Moldova, the Russian Federation, Serbia, Switzerland, Tajikistan, Turkey, Turkmenistan, Ukraine, Uzbekistan and Kosovo[1]. Eleven countries (Armenia, Belarus, Bosnia and Herzegovina, Georgia, Montenegro, North Macedonia, the Russian Federation, Serbia, Switzerland, Turkey and Ukraine) and Kosovo[1] submitted AMR data from isolates obtained in 2018 to the CAESAR database.

Chapter 2 contains 10 selected AMR maps of the WHO European Region, combining data collected by CAESAR and the European Antimicrobial Resistance Surveillance Network. Chapter 6 and 7 present country- and area-specific proportions of resistance observed for the nine pathogens under surveillance in 2018. Annex 1 provides a comprehensive overview of pathogens under CAESAR surveillance and the main infections caused by each of the pathogens.

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 settings, the presence of specific resistance patterns across clinical settings covered by the surveillance network is apparent. 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 underline the need for concerted action to combat AMR throughout the WHO European Region.

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 5, 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 against a set of predefined criteria (Chapters 6 and 7). Besides guiding interpretation, the level of evidence assessment was developed to provide specific input for improving AMR surveillance within the networks (Chapter 5). For example, in 2016 both Bosnia and Herzegovina and Serbia progressed from level B to level A data, by expanding their respective surveillance networks to cover all hospital types and by adopting the European Committee on Antimicrobial Susceptibility Testing methodology as the national standard for antimicrobial susceptibility testing.

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 contribute AMR data to regional and global networks in the near future. Chapter 3 describes the different efforts and progress made by members of the CAESAR network. Many countries are taking the necessary steps to set up or strengthen their AMR surveillance system, enabling them to get a better insight into their AMR situation.

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

However, more investment in networks, laboratories and standardization, and properly outfitted reference laboratories are needed. Recently, both the Republic of Moldova and Tajikistan have reached an important milestone in their efforts of building a national AMR surveillance network and shared data for the first time. Chapter 8 describes their experiences, challenges and process of building national AMR surveillance.

Strong political support is needed to continue making progress. One challenge that many countries face 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. Data obtained as part of this project in Armenia between 1 January 2018 and 31 October 2018 are included in Chapter 6. Currently proof-of-principle projects are ongoing in Tajikistan and Uzbekistan.

Chapter 9 describes the results from the CAESAR external quality assessment exercise conducted in 2018. Overall, the results were good, and the number of participants has increased from 120 laboratories in eight countries/areas in 2013 to 257 laboratories in 17 countries/areas in 2018. 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 due to lack of strict adherence to antimicrobial susceptibility testing guidelines. 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 90% in 2018. Overall, this increase is reflected in the good work to identify novel resistance mechanisms.

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 in place yet. 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

Frequent infections are becoming increasingly resistant to the antimicrobial medicines traditionally used to treat them, posing a fundamental threat to human and animal health and the achievement of the Sustainable Development Goals. Global recognition of the danger of antimicrobial resistance (AMR) has only grown over the last decade, and surveillance and data that inform on the magnitude of the problem are considered a cornerstone to increase this awareness and to guide effective responses.

There is an urgent need for governments to address AMR in a coordinated way. In the WHO European Region, the first steps towards a more coordinated response were formalized in September 2011, when all 53 Member States adopted the European Strategic Action Plan on Antibiotic Resistance (2011–2020) *(1)*, followed a few years later by the global action plan *(2)* on AMR, as well as the European Commission's One Health Action Plan against AMR, launched in 2017 *(3)*. Together, these plans represent the overall framework for a comprehensive AMR response in the WHO European Region, and many governments have followed suit and developed national plans of action.

The Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) network – formerly known as the Central Asian and Eastern European Surveillance of Antimicrobial Resistance network – was founded in 2012 as a collaborative effort of 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). These institutions participate directly in the activities of the network by having two or three of their experts in the CAESAR coordination group. The goal of the CAESAR network is to assist countries and areas in the WHO European Region in setting up or strengthening national AMR surveillance. The CAESAR manual *(4)* describes the objectives, methods, and organization of the CAESAR network. It details the steps required for a country or area wanting to enrol in CAESAR, as well as the tasks involved in routine data collection for AMR surveillance. The network complements the ongoing work of the European Antimicrobial Resistance Surveillance Network (EARS-Net).

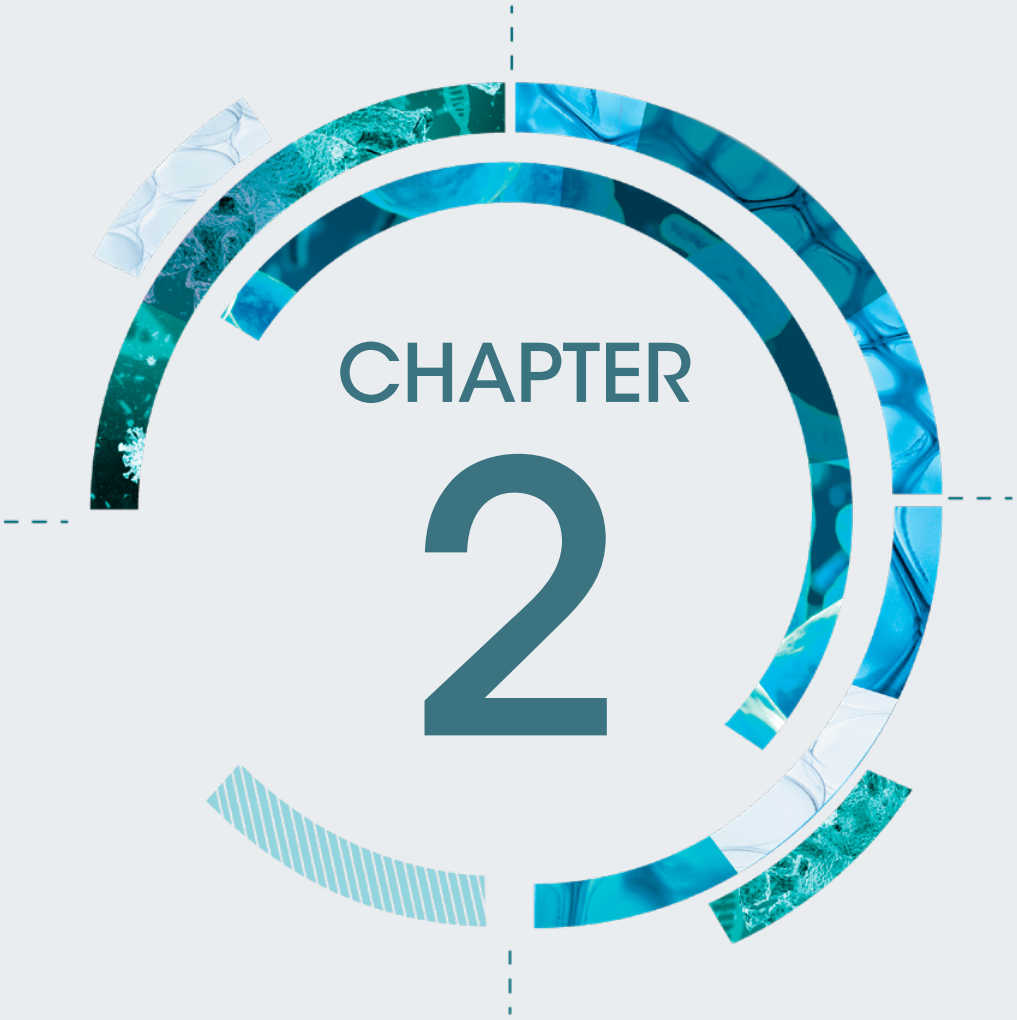
Currently, 19 countries – Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, North Macedonia, the Republic of Moldova, the Russian Federation, Serbia, Switzerland, Tajikistan, Turkey, Turkmenistan, Ukraine and Uzbekistan – and Kosovo[1] are engaged in the CAESAR network, with more than 50% of these countries and one area providing data.

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

Through these efforts, CAESAR also supports the strengthening of the WHO Global Antimicrobial Resistance Surveillance System (GLASS) and provides the latest consolidated AMR data on behalf of the countries and areas enrolled in GLASS.

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

This fifth CAESAR annual report includes, for the first time, data from Armenia, which was generated as a product of the proof-of-principle project. The Republic of Moldova and Tajikistan have made a start in this reporting period to submit AMR data to the network, which is the reason for the inclusion of a chapter dedicated to their specific journey towards establishing surveillance capacity. This report marks a milestone in the five-year history of the CAESAR annual report. Starting in 2020, surveillance data from the CAESAR network will be published together with those from EARS-Net, in a joint report with the European Centre for Disease Prevention and Control (ECDC), which is set to provide a comprehensive update of the AMR situation in the WHO European Region.


CHAPTER
2

AMR maps of the WHO European Region

2.1 Introduction

This chapter was prepared jointly with ECDC and provides an overview of AMR in the WHO European Region in 2018. In 2018, 11 countries and Kosovo[1] reported data to CAESAR, while 30 countries, including all European Union (EU) countries and two European Economic Area (EEA) countries (Iceland and Norway), reported data to EARS-Net. The figure footnotes indicate networks reporting to either EARS-Net or CAESAR. EARS-Net data are also available online at the ECDC Surveillance Atlas of Infectious Diseases website *(1)*.

CAESAR, as well as EARS-Net, is a network of AMR surveillance networks. Although both networks use comparable methods, the data presented in this chapter originate from individual national surveillance systems, in which data are generated in the process of routine diagnostics. Therefore, the data are inherently influenced by the choices made in each surveillance system and by national (and even local) practices with regard to patient sampling. As a result, the data from individual countries vary in their representativeness of the underlying population and call for a cautionary approach when comparing countries/areas with regard to resistance patterns. For example, in many CAESAR countries/areas clinicians use a restrictive patient sampling approach, favouring patients with recurrent infections or treatment failure in tertiary care centres or intensive care units. This may have contributed to the high proportions of resistance in some CAESAR countries and areas.

To guide the reader in interpreting the data for each country or area, the CAESAR network assigns levels of evidence, taking the data quality and representativeness into account; this is currently not done by EARS-Net. Countries/areas with level B data should have their proportion of resistance interpreted with caution, as improvements are needed to attain a more valid assessment of the level of prevalence of AMR in the country/area. This chapter uses a footnote in the text and a striped pattern in figures to denote countries/areas with level B data. Level A data, presented without a pattern, provide an adequate assessment of the magnitude of AMR in the country. Chapter 5 presents more information about the different levels of evidence and how they were determined for each of the CAESAR countries/areas.

2.2 Description of the maps

2.2.1 *Escherichia coli*

The most common cause of community-acquired bloodstream infections and urinary tract infections is *E. coli*. In 2018, resistance to fluoroquinolones was generally lower in northern and western parts of the WHO European Region and higher in southern and eastern parts (Fig. 2.1). In all EARS-Net countries resistance proportions ranged between 10% and 50%. Proportions exceeding 50% were found in Georgia,[2] Montenegro,[2] North Macedonia,[2] the Russian Federation[2] and Turkey. EARS-Net data have shown a significant increase in third-generation cephalosporin resistance in EU and EEA countries over the past years *(1)*. In 2018, the majority of EARS-Net countries showed resistance proportions between 10% and 25% (Fig. 2.2). Proportions between 25% and 50% were found in Bulgaria, Cyprus, Italy and Slovakia. Among CAESAR countries, resistance proportions exceeding 50% were observed in Armenia,[2]

1 All references to Kosovo should be understood as references to Kosovo in accordance with United Nations Security Council resolution 1244 (1999).
2 CAESAR country with level B data

Belarus,[2] Georgia,[2] Montenegro,[2] North Macedonia,[2] the Russian Federation[2] and Turkey, whereas the resistance proportions in Bosnia and Herzegovina and Switzerland are more comparable to that in their neighbouring EARS-Net countries (10–25%). The recent emergence of carbapenem-resistant *E. coli* is of serious concern, but overall resistant proportions are low, with only three EARS-Net countries (Bulgaria, Cyprus and Greece) and four CAESAR countries (Belarus,[2] Georgia,[2] North Macedonia[2] and Turkey) with resistance proportions of 1% or higher (Fig. 2.3).

2.2.2 *Klebsiella 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 in *K. pneumoniae* has become quite widespread in the WHO European Region. In general, countries in northern Europe report lower proportions, while countries in the southern and eastern parts of the Region report substantially higher proportions. Proportions of 50% or higher were reported in Belarus,[2] Bosnia and Herzegovina, Greece, Montenegro,[2] North Macedonia,[2] Poland, the Russian Federation,[2] Serbia and Ukraine[2] (Fig. 2.4). Carbapenem resistance is more frequently found in *K. pneumoniae* than in *E. coli*. Although proportions of resistance are low in most countries, Georgia,[2] Italy, Romania, the Russian Federation,[2] Serbia, Turkey and Ukraine[2] reported proportions between 25% and 50%, and Belarus[2] and Greece reported proportions exceeding 50% (Fig. 2.5). 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.

2.2.3 *Pseudomonas aeruginosa*

P. aeruginosa is a common cause of infection (including hospital-acquired pneumonia, bloodstream and urinary tract infections) in hospitalized patients, especially in those with compromised immune defences. It is intrinsically resistant to many antimicrobial agents and is challenging to control in health care settings. In 2018, multidrug resistance in *P. aeruginosa* was generally lower in northern Europe and higher in southern and eastern parts of the Region (Fig. 2.6). Proportions <5% were observed in the Scandinavian countries, Ireland, Luxembourg, Malta, the Netherlands and the United Kingdom, whereas proportions exceeding 50% were reported in Belarus,[2] Montenegro[2] and Serbia.

2.2.4 *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* spp. can persist in the health care environment and are difficult to eradicate once established. The proportions of multidrug-resistant *Acinetobacter* spp. vary widely within the WHO European Region, from <1% in northern European countries to >50% in many countries in southern and eastern Europe (Fig. 2.7). 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.

2.2.5 *Staphylococcus aureus*

Methicillin-resistant *Staphylococcus 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[2] have the lowest proportions (<5%) of invasive MRSA infections (Fig. 2.8). Resistance proportions exceeding 25% are found in many countries in the southern and eastern parts of the WHO European Region.

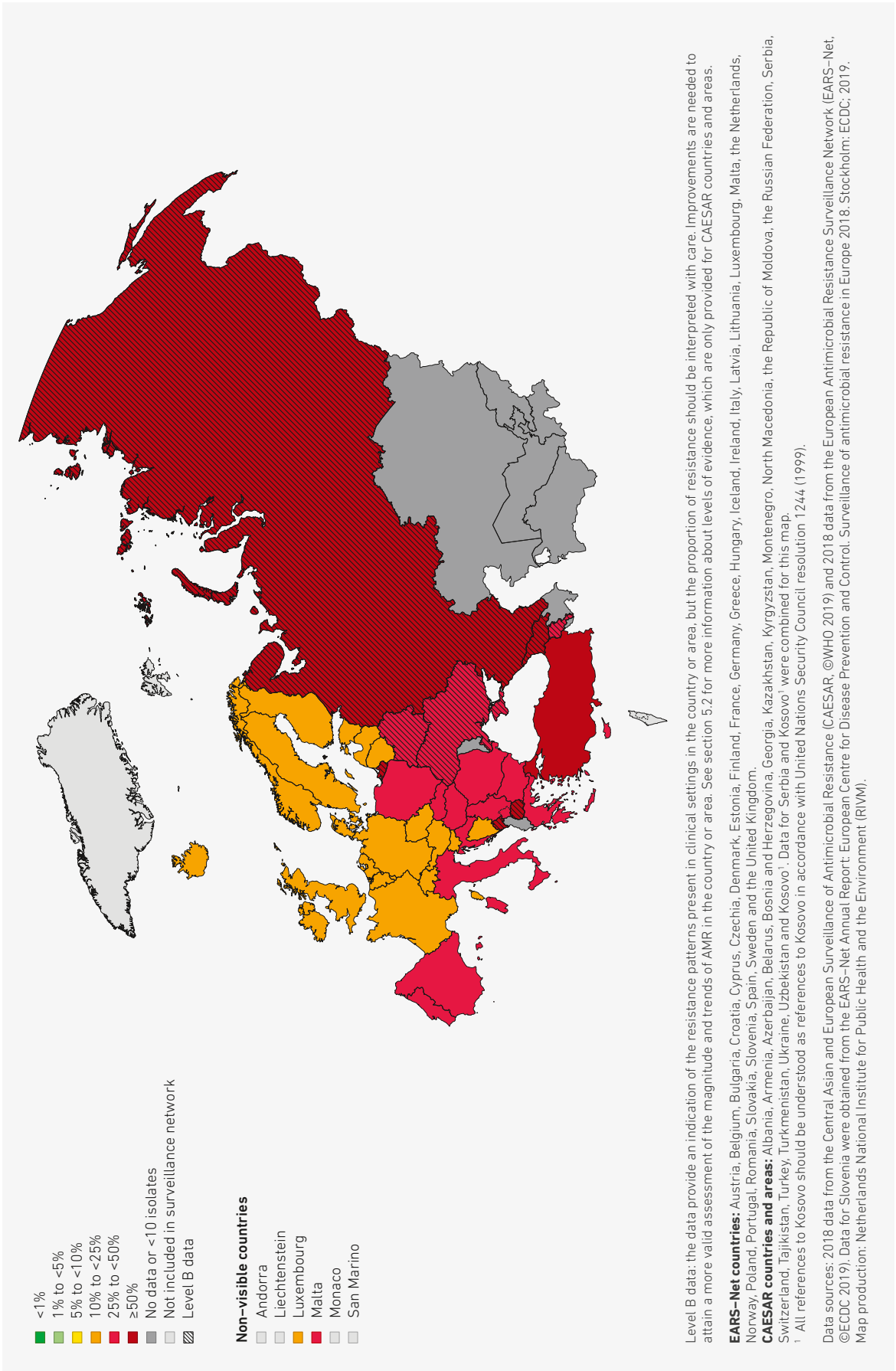
2.2.6 *Streptococcus pneumoniae*

S. pneumoniae causes a wide range of infections, from mild, self-limiting infections such as otitis media to more serious infections such as community-acquired pneumonia and meningitis, with high mortality in vulnerable patient groups. In the WHO European Region, large differences are seen in the percentage of penicillin non-wild type (Fig. 2.9). Belgium, Estonia and the Netherlands report proportions lower than 5%, whereas proportions >25% were found in Bosnia and Herzegovina, France, Romania, Serbia and Turkey.

2.2.7 *Enterococcus faecium*

E. faecium belongs to the normal bacterial microbiota of the human gastrointestinal tract. It is usually low-pathogenic but can, under certain circumstances, cause severe disease such as bloodstream infections, endocarditis and peritonitis. Resistance to vancomycin in *E. faecium* varies substantially between countries in the WHO European Region. Proportions <1% were reported by France, Iceland, Luxembourg and Slovenia, whereas proportions >50% were seen in Cyprus, North Macedonia[2] and Serbia (Fig. 2.10).

Fig. 2.1 Percentage of invasive *E coli* isolates resistant to fluoroquinolones in the European Region (EARS-Net and CAESAR), by country or area, 2018

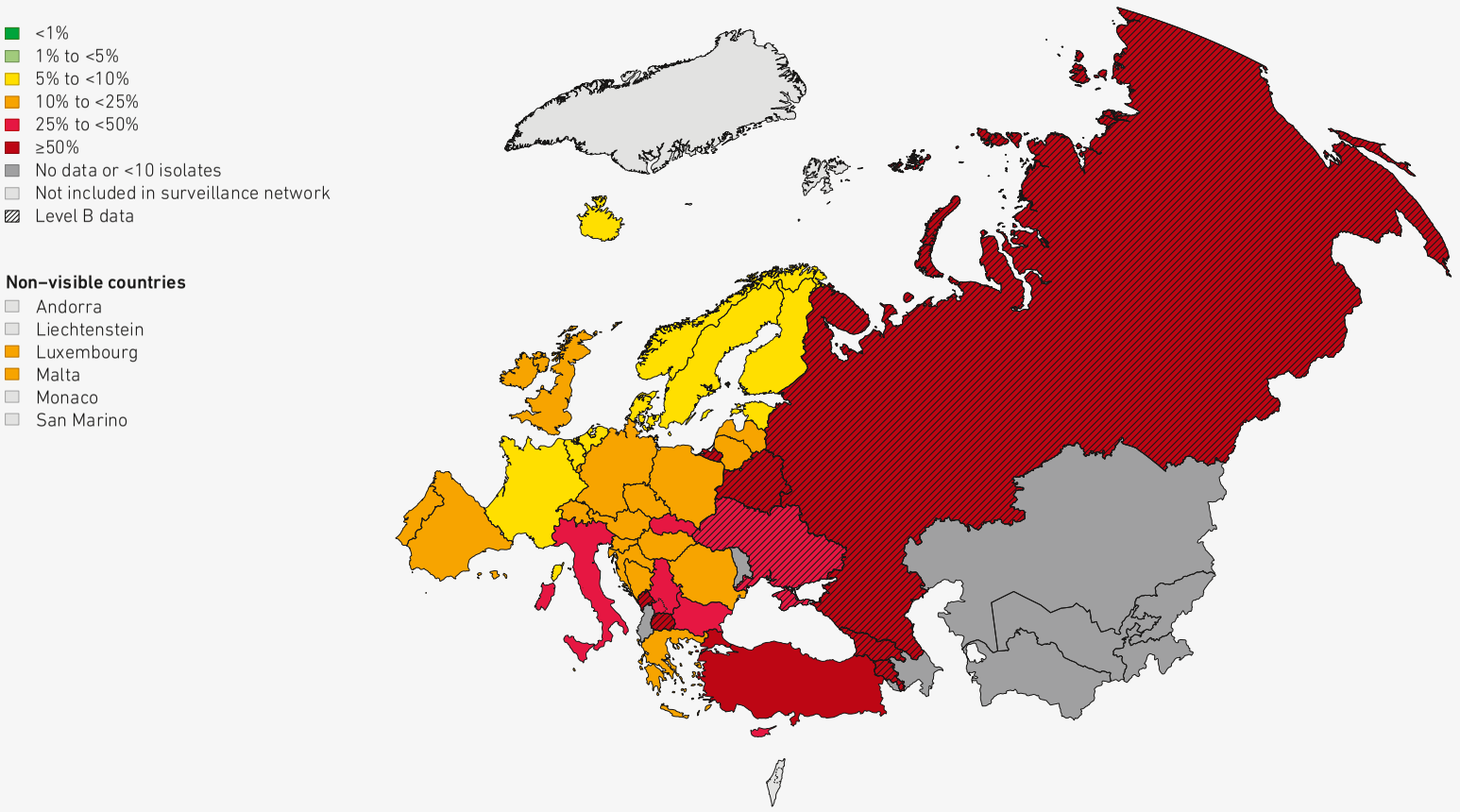


Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country or area, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of AMR in the country or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

EARS–Net countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, 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, North Macedonia, the Republic of Moldova, the Russian Federation, Serbia, Switzerland, Tajikistan, Turkey, Turkmenistan, Ukraine, Uzbekistan and Kosovo[1]. Data for Serbia and Kosovo[1] were combined for this map.
[1] All references to Kosovo should be understood as references to Kosovo in accordance with United Nations Security Council resolution 1244 (1999).

Data sources: 2018 data from the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2019) and 2018 data from the European Antimicrobial Resistance Surveillance Network (EARS–Net, ©ECDC 2019). Data for Slovenia were obtained from the EARS–Net Annual Report: European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe 2018. Stockholm: ECDC; 2019.
Map production: Netherlands National Institute for Public Health and the Environment (RIVM).

Fig. 2.2 Percentage of invasive *E. coli* isolates resistant to third-generation cephalosporins in the European Region (EARS-Net and CAESAR), by country or area, 2018



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

EARS–Net countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, 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, North Macedonia, the Republic of Moldova, the Russian Federation, Serbia, Switzerland, Tajikistan, Turkey, Turkmenistan, Ukraine, Uzbekistan and Kosovo[1]. Data for Serbia and Kosovo[1] were combined for this map.
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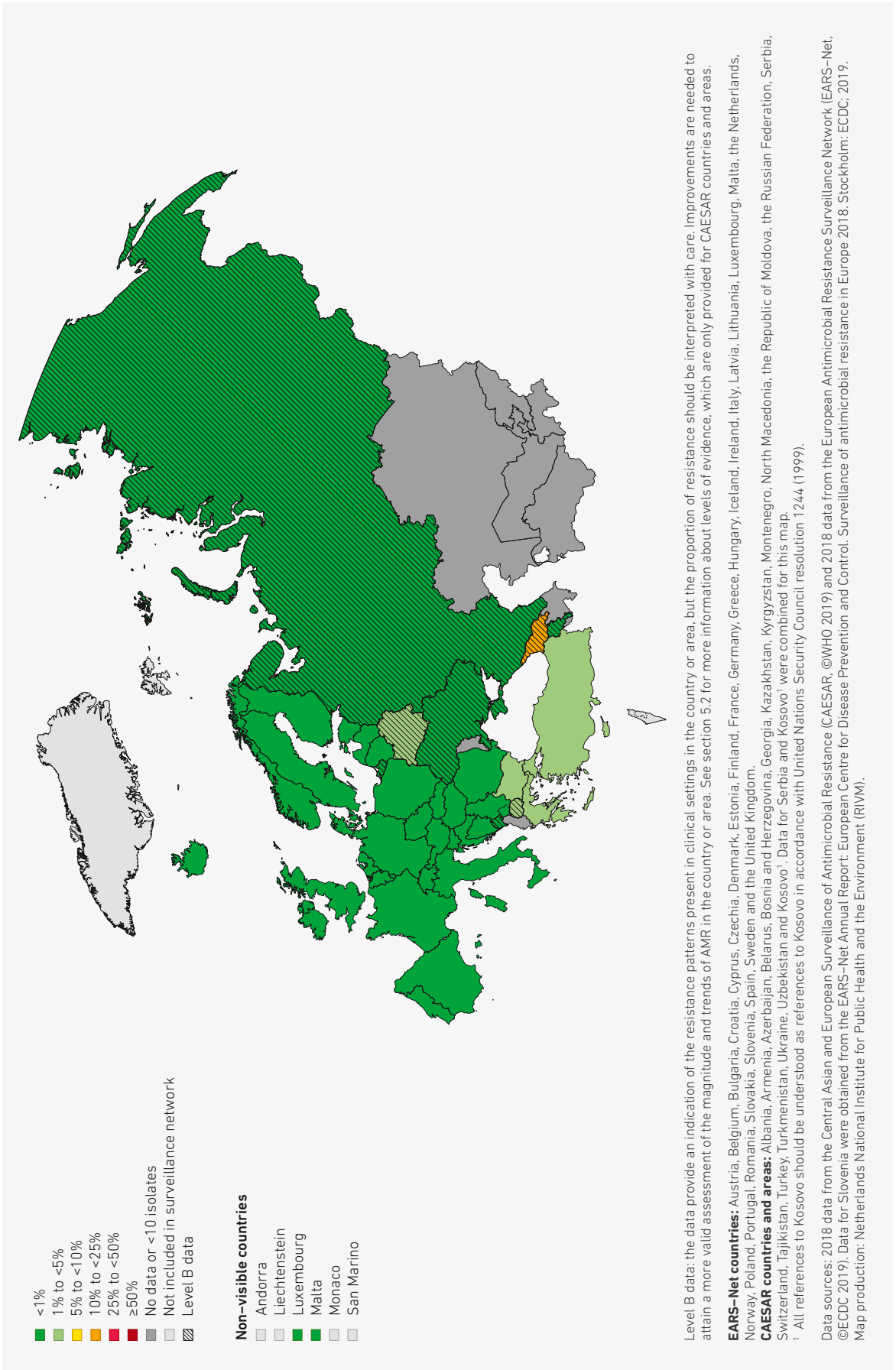
Map production: Netherlands National Institute for Public Health and the Environment (RIVM).

Fig. 2.3 Percentage of invasive *E. coli* isolates resistant to carbapenems in the European Region (EARS-Net and CAESAR), by country or area, 2018



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

EARS-Net countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, 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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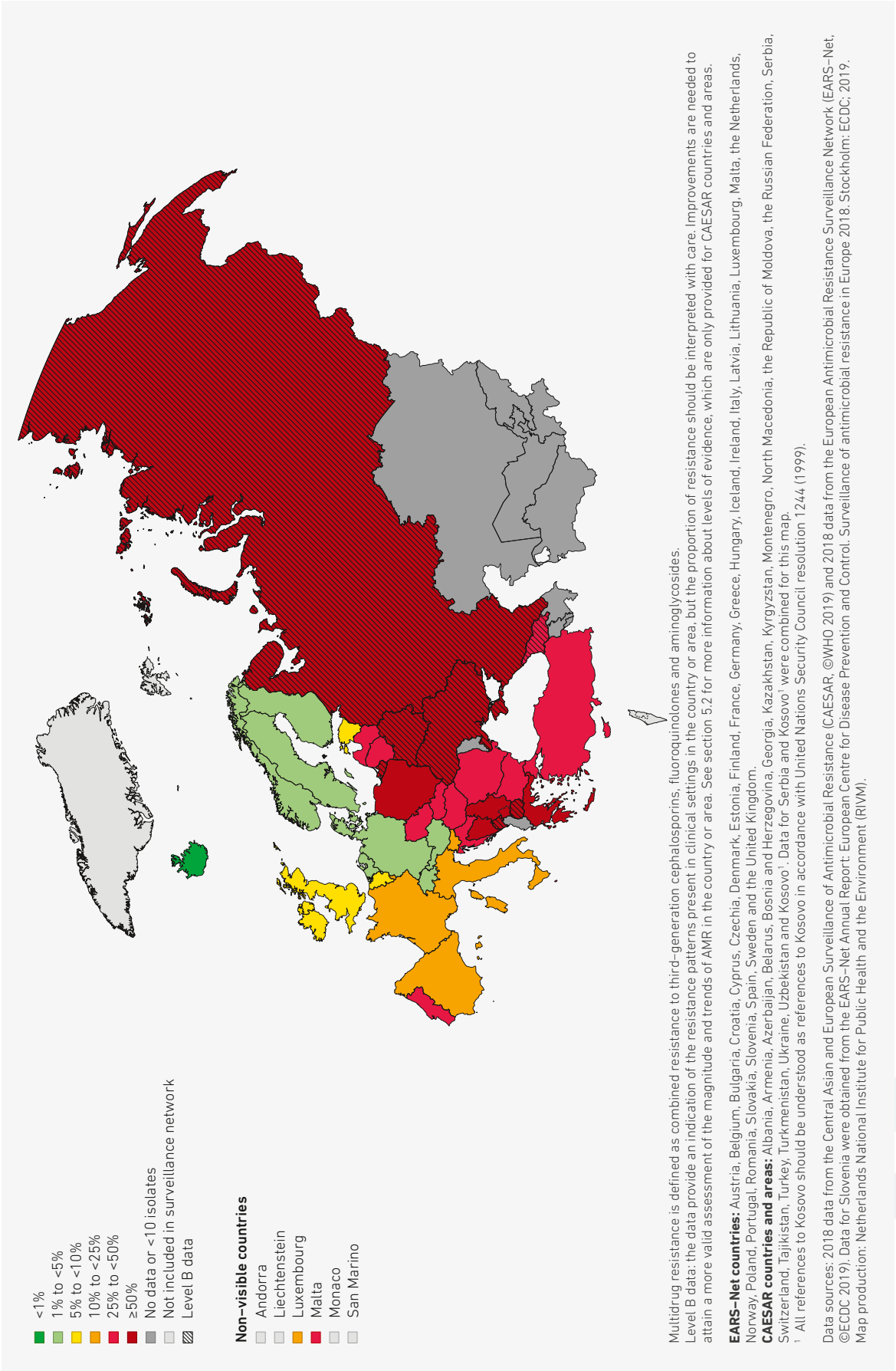
[1] All references to Kosovo should be understood as references to Kosovo in accordance with United Nations Security Council resolution 1244 (1999).

Data sources: 2018 data from the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2019) and 2018 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2019). Data for Slovenia were obtained from the EARS-Net Annual Report: European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe 2018. Stockholm: ECDC; 2019.
Map production: Netherlands National Institute for Public Health and the Environment (RIVM).

Fig. 2.4 Percentage of invasive *K. pneumoniae* isolates with multidrug resistance in the European Region (EARS-Net and CAESAR), by country or area, 2018



Multidrug resistance is defined as combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides.
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 5.2 for more information about levels of evidence, which are only provided for CAESAR countries and areas.

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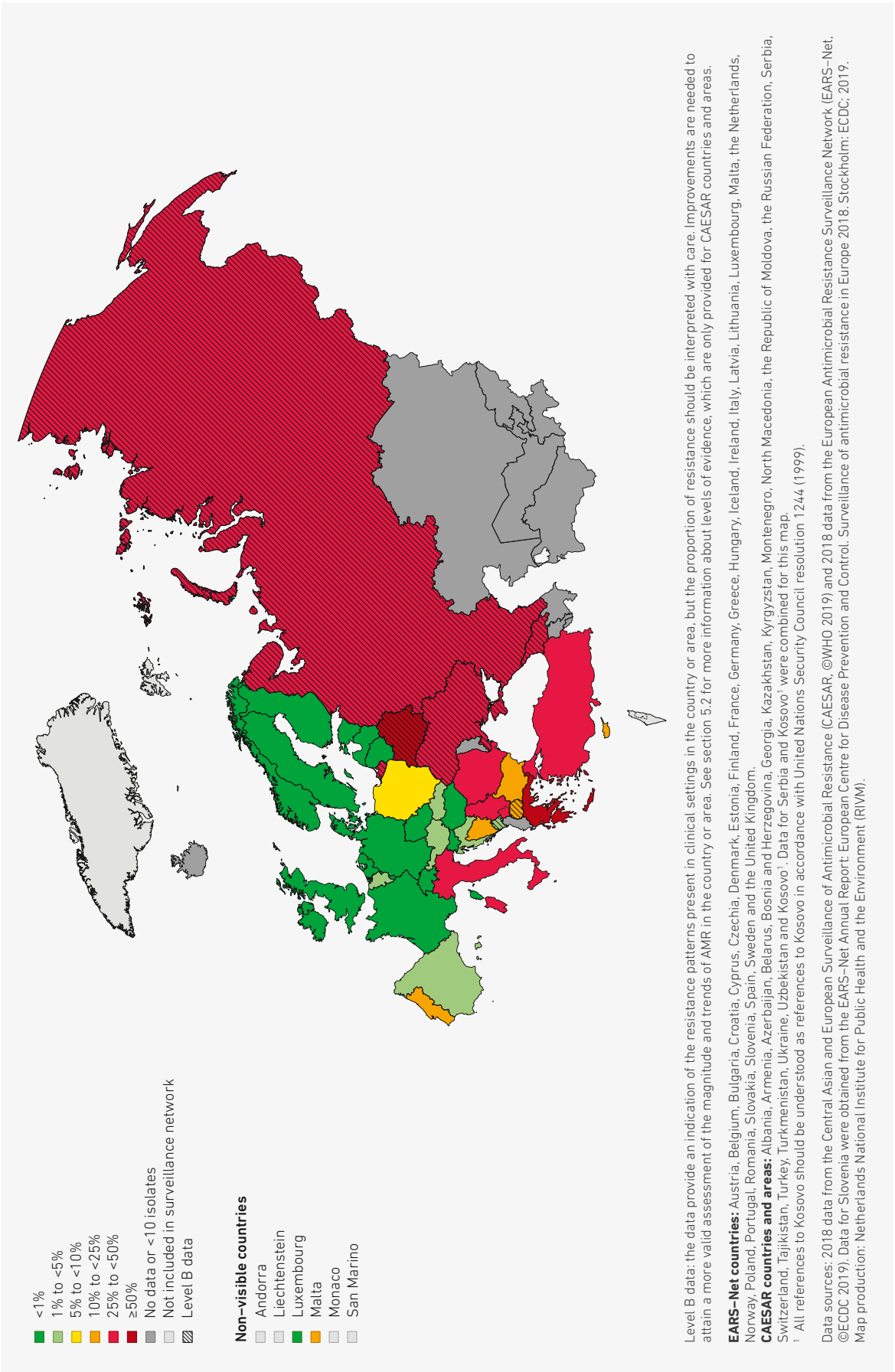
Map production: Netherlands National Institute for Public Health and the Environment (RIVM).

Fig. 2.5 Percentage of invasive *K. pneumoniae* isolates resistant to carbapenems in the European Region (EARS-Net and CAESAR), by country or area, 2018



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

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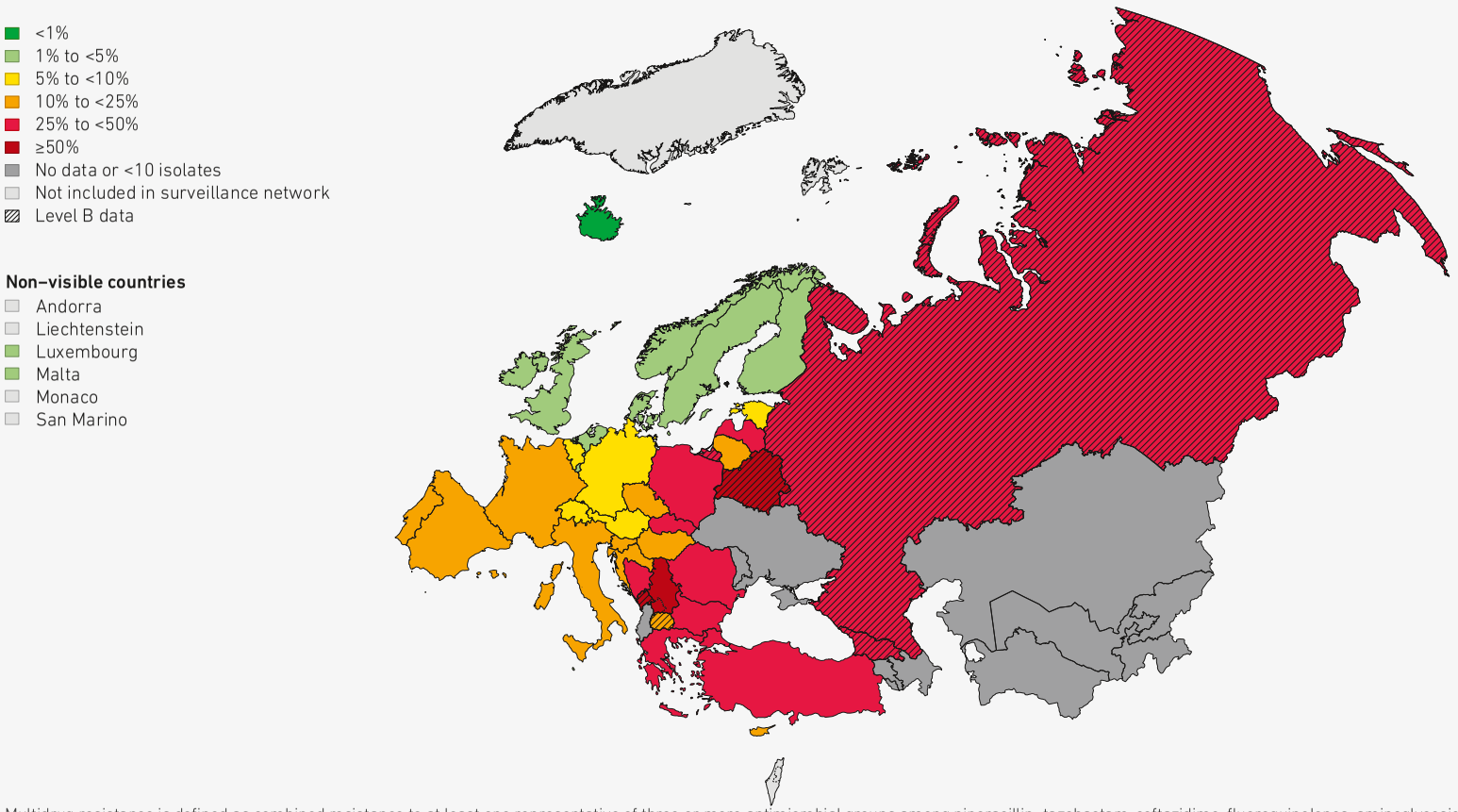
Map production: Netherlands National Institute for Public Health and the Environment (RIVM).

Fig. 2.6 Percentage of invasive *P. aeruginosa* isolates with multidrug resistance in the European Region (EARS-Net and CAESAR), by country or area, 2018



Multidrug resistance is defined as combined resistance to at least one representative of three or more antimicrobial groups among piperacillin–tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems. 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 5.2 for more information about levels of evidence, which are only provided for CAESAR countries and areas.

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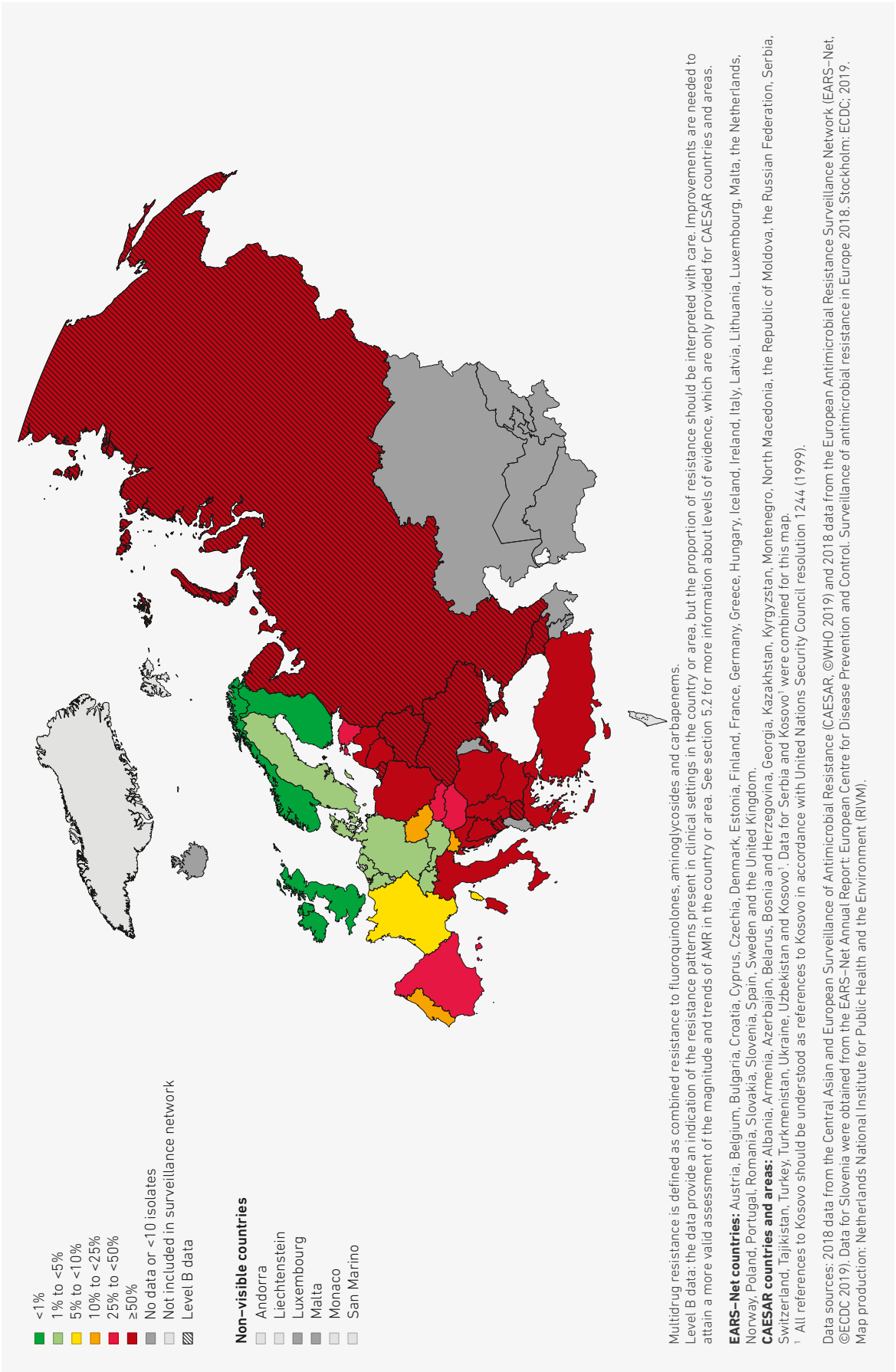
Map production: Netherlands National Institute for Public Health and the Environment (RIVM).

Fig. 2.7 Percentage of invasive *Acinetobacter* spp. isolates with multidrug resistance in the European Region (EARS-Net and CAESAR), by country or area, 2018



Multidrug resistance is defined as combined resistance to fluoroquinolones, aminoglycosides and carbapenems.
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 5.2 for more information about levels of evidence, which are only provided for CAESAR countries and areas.

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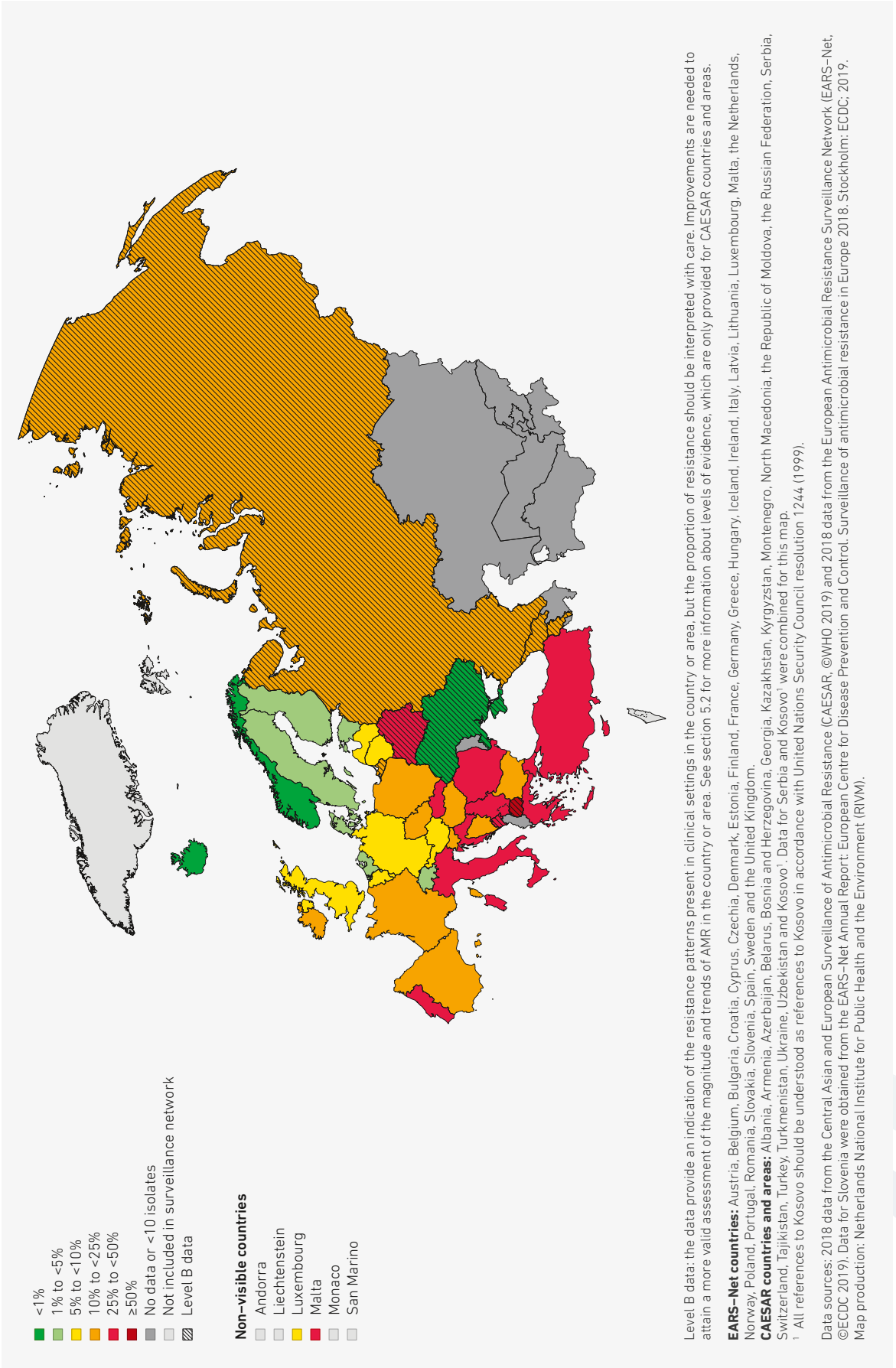
Map production: Netherlands National Institute for Public Health and the Environment (RIVM).

Fig. 2.8 Percentage of invasive *S. aureus* isolates resistant to methicillin (MRSA) in the European Region (EARS-Net and CAESAR), by country or area, 2018



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

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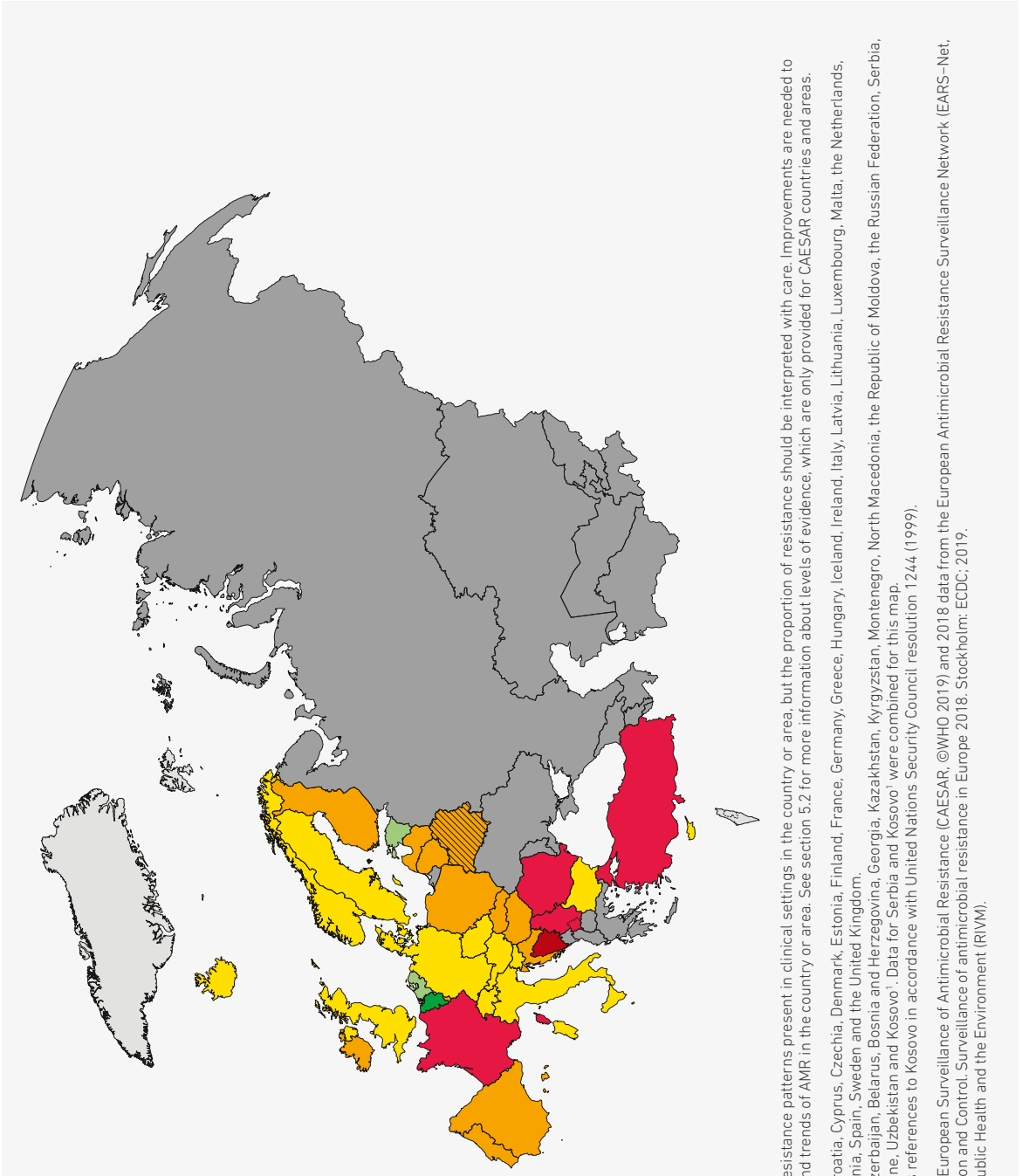
Map production: Netherlands National Institute for Public Health and the Environment (RIVM).

Fig. 2.9 Percentage of penicillin non-wild type invasive *S. pneumoniae* isolates in the European Region (EARS-Net and CAESAR), by country or area, 2018



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

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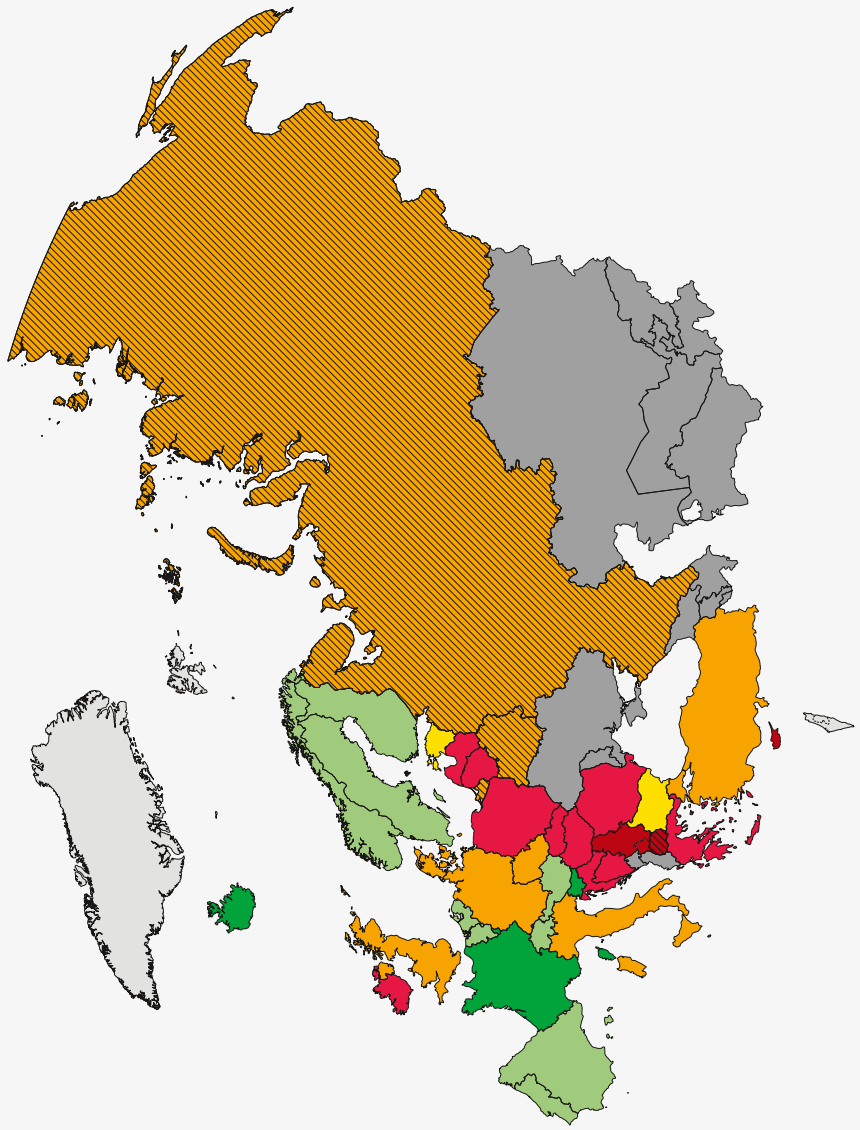
Map production: Netherlands National Institute for Public Health and the Environment (RIVM).

Fig. 2.10 *Enterococcus faecium*. **Percentage (%) of invasive isolates resistant to vancomycin in the European Region (EARS–Net and CAESAR), by country or area or area, 2018**



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

EARS–Net countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, 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, North Macedonia, the Republic of Moldova, the Russian Federation, Serbia, Switzerland, Tajikistan, Turkey, Turkmenistan, Ukraine, Uzbekistan and Kosovo[1]. Data for Serbia and Kosovo[1] were combined for this map.
[1] All references to Kosovo should be understood as references to Kosovo in accordance with United Nations Security Council resolution 1244 (1999).

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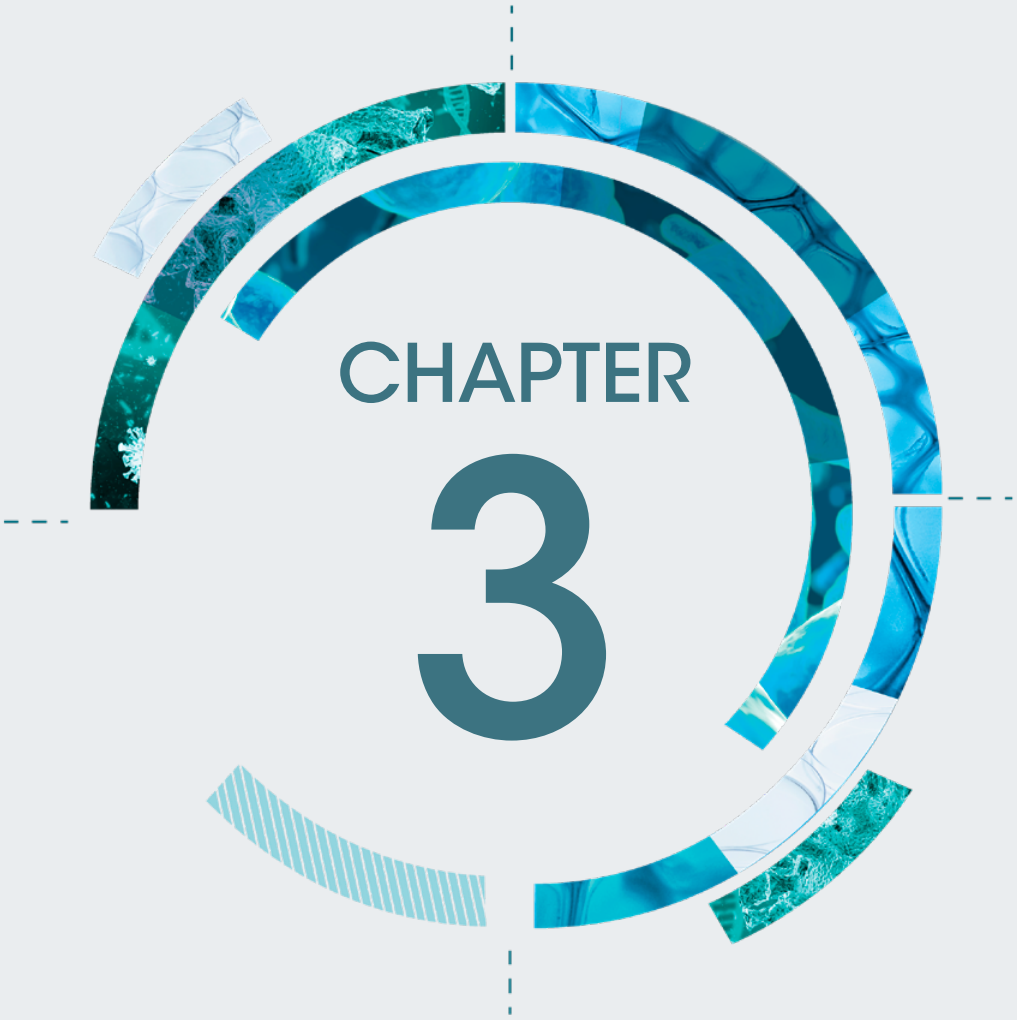
Map production: Netherlands National Institute for Public Health and the Environment (RIVM).


CHAPTER
3

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, North Macedonia, the Republic of Moldova, the Russian Federation, Serbia, Switzerland, Tajikistan, Turkey, Turkmenistan, Ukraine and Uzbekistan.

Among these, 11 countries (Armenia[3], Belarus, Bosnia and Herzegovina, Georgia, Montenegro, North Macedonia, the Russian Federation, Serbia, Switzerland, Turkey and Ukraine) and one area (Kosovo[1]) are providing AMR data to the CAESAR database. Moreover, this report includes an account of the experience of two additional countries (the Republic of Moldova and Tajikistan) whose efforts at establishing and strengthening their national surveillance systems have culminated in their ability to share, for the first time, resistance data with the CAESAR network.

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. 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 5).

The methods used in CAESAR are compatible with those used by the ECDC (through EARS-Net). This approach 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 2). The generation of reliable and comparable information is directly linked to informed policy development and decision-making and can be used to measure the effectiveness of AMR interventions.

3.1 Indicators of progress in CAESAR

A specified set of indicators has been selected to monitor progress (Table 3.1). These indicators refer to four main components of AMR activities: (i) overall coordination; (ii) the surveillance network and AMR reference laboratory; (iii) quality control; and (iv) guidelines for antimicrobial susceptibility testing (AST). In order to avoid the additional burden of double reporting, information regarding overall coordination was extracted from the Tripartite AMR country self-assessment survey (TrACSS), a global exercise of monitoring country progress on AMR *(1)*. Bosnia and Herzegovina did not submit a national response to TrACSS but separately by entity. Responses received from the two entities – the Federation of Bosnia and Herzegovina and Republika Srpska – that were in agreement are reported accordingly; otherwise the results are reported either as missing or not available. The AMR focal point from Kosovo[1] filled out a similar questionnaire to that administered during TrACCS. For the remaining three components, instead, the AMR focal points from each country/area were asked to fill in a short ad hoc questionnaire. This chapter describes the results of the 2019 questionnaire, with final approval from the AMR focal points.

3.1.1 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

1 All references to Kosovo should be understood as references to Kosovo in accordance with United Nations Security Council resolution 1244 (1999).
3 In this report, Armenia provided data through the proof-of-principle AMR routine diagnostics surveillance project.

Table 3.1 Description of AMR indicators

Area	Indicators	Description
Overall AMR coordination	AMR focal point	AMR focal point appointed by health ministry
	Multisector and One Health collaboration/coordination	Based on the One Health approach, a multisector coordinating mechanism to contain AMR established
	AMR action plan	AMR action plan developed
	AMR action plan funding sources	Dedicated funds 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	AMR action plan has relevant sectors involved with a defined monitoring and evaluation process in place
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 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 (EUCAST/CLSI/ other)
	Implementation of EUCAST breakpoints	Percentage of laboratories implementing EUCAST breakpoint
	Use of EUCAST disk diffusion method	Percentage of laboratories using EUCAST disk diffusion methodology
	AST committee	AST committee formed

CLSI: Clinical Laboratory Standards Institute; EQA: external quality assessment; EUCAST: European Committee on Antimicrobial Susceptibility Testing.

the government is needed on legal, technical and financial aspects to establish a surveillance system. Through the adoption of the global action plan on AMR *(2)*, 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 3.2 shows the status of the overall coordination on AMR.

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 20 members of CAESAR, 18 countries and Kosovo[1] have appointed an AMR focal point (Table 3.3) and one country is in the process of appointing one.

Multisector and One Health coordination/collaboration mechanism

In accordance with the European Strategic Action Plan on Antibiotic Resistance *(3)* and the global action plan on AMR *(2)*, 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; recommends policy options; secures overall commitment to national strategies for containing antibiotic resistance; provides technical guidance on national analysis, standards, guidelines, regulations, training and awareness; and ensures coordination when 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 and antifungal drugs *(3)*.

To date, 18 countries and Kosovo[1] reported having a multisector and One Health coordination/collaboration mechanism compared with 12 countries and Kosovo[1] in 2017 *(4)*. Moreover, six countries indicated that they were in the process of setting up this mechanism in 2017 *(4)*.

National action plan

Following the global action plan on AMR, Member States were called upon to develop a national action plan on AMR by May 2017 *(2)*. Continuous AMR surveillance is crucial in assessing significant 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 the national action plan to combat AMR. Also, valid surveillance data can inform empirical treatment guidelines at the local and national levels.

According to the results from the 2018–2019 Global Monitoring of Country Progress on Antimicrobial Resistance, 39 countries in the WHO European Region have developed multisectoral national action plans *(5)*, while WHO and partners continue to support the remaining countries to finalize theirs, as well as with their implementation.

Among the CAESAR network participants, 15 countries and Kosovo[1] indicated that they have an AMR action plan developed. Moreover, three countries reported being in the process of developing a national action plan. Finally, two countries indicated that the national AMR action plan has funding sources identified, that the implementation of the plan is ongoing, and that it is being monitored and evaluated.

3.1.2 Progress on surveillance networks and AMR reference laboratories

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

Table 3.2 Overall coordination on AMR[a]

Country or area[b]	AMR focal point appointed by health ministry	Multisector and One Health collaboration/ coordination	AMR action plan developed	Dedicated funds available to implement the AMR action plan	Active implementation of AMR action plan is ongoing	Implementation of AMR action plan is monitored and evaluated
ALB	✓	✓	⚙	✗	✗	✗
ARM	✓	✓	✓	✗	✗	✗
AZE	✓	✓	⚙	✗	✗	✗
BLR	✓	✓	✓	✗	✗	✗
BIH	✓	NA	NA	NA	NA	NA
GEO	✓	✓	✓	✓	✓	✓
KAZ	⚙	✓	✓	✗	✗	✗
KGZ	✓	✓	⚙	✗	✗	✗
MNE	✓	✓	✓	✗	✗	✗
MKD	✓	✓	✓	✗	✗	✗
MDA	✓	✓	✓	✗	✗	✗
RUS	✓	✓	✓	✗	✗	✗
SRB	✓	✓	✓	✗	✗	✗
SWI	✓	✓	✓	✓	✓	✓
TJK	✓	✓	✓	✗	✗	✗
TUR	✓	✓	✓	✗	✗	✗
TKM	✓	✓	✓	✗	✗	✗
UKR	✓	✓	✓	✗	✗	✗
UZB	✓	✓	✓	✗	✗	✗
KOS[c]	✓	✓	✓	✗	✗	✗
No	**0**	**0**	**0**	**17**	**17**	**17**
In progress	**1**	**0**	**3**	**0**	**0**	**0**
Yes	**19**	**19**	**16**	**2**	**2**	**2**

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

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

[b] 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).

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

Table 3.3 AMR focal points of the CAESAR network

Country or area	AMR focal point
Albania	Albana Fico (Director, 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 nomination pending, National Center on Public Health Development, Ministry of Health
Kyrgyzstan	Baktygul Ismailova (Chief Specialist, Public Health Department, Ministry of Health)
Montenegro	Milena Lopicic (Department of Bacteriology, Institute of Public Health)
North Macedonia	Golubinka Bosevska (Head, Laboratory for Virology and Molecular Diagnostics, 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)
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 Center, 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).

and analysing AMR data according to international standards and sharing these with the international community helps to give insight about 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. Collaboration among microbiology laboratories and inter-laboratory standardization are crucial when setting up an AMR surveillance system. Laboratory participation 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.

Seventeen 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 3.4). The AMR focal points reported that AMR surveillance teams usually range between 4 and 10 members. The team includes microbiologists, epidemiologists and clinicians. Some teams also include data managers, clinical pharmacologists, laboratory technicians, molecular biologists and coordinators/administrators.

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 critical role. 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 12 countries and Kosovo[1], whereas two countries are still in the process of establishing all required functions.

AMR surveillance and reporting

Sharing information is one of the most important aspects of any 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 appropriate professionals (such as hospital managers, heads of antibiotic or drug committees, and heads of infection control committees). This will stimulate the use of 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.

Fourteen countries and Kosovo[1] have an AMR surveillance system in place, whereas four countries indicated that they are in the process of establishing their AMR surveillance system. Eight countries and Kosovo[1] periodically publish an AMR surveillance report – the same number as in 2017 *(4)*. Fourteen countries and Kosovo[1] hold yearly AMR surveillance network meetings. Finally, to date, only five countries are enrolled in GLASS (Table 3.4).

3.1.3 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. Fifteen countries and Kosovo[1] indicated that they have a quality assurance system in place for assessing laboratory procedures (Table 3.5), an increase from 12 in 2017 *(4)*. Three countries reported that they are in the process of establishing a national laboratory quality system.

Table 3.4 AMR surveillance[a]

Country or area[b]	Institute 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	✓	✓	✓	✓	✓	✓	NA	✓	⚙
BIH	✗	✗	✗	✗	⚙	✗	✓	✓	✓
GEO	✓	✓	✓	✓	✓	✓	✓	✓	✓
KAZ	✓	✓	✓	✓	⚙	✗	⚙	✗	✗
KGZ	✗	✓	✗	✗	⚙	✗	✓	✗	✗
MNE	✓	✓	✓	⚙	✓	✗	✓	✓	✗
MKD	✓	✓	✗	✗	✓	✓	✓	✓	✓
MDA	✓	✓	✓	✓	✓	⚙	✓	⚙	✗
RUS	✓	⚙	✓	✓	✓	✓	✓	✓	✓
SRB	✓	✓	✓	✓	✓	✓	✓	✓	✗
SWI	✓	✓	✓	✓	✓	✓	✗	✓	✓
TJK	✓	✓	✓	✓	✓	✗	✓	⚙	✗
TUR	✓	✓	✓	✓	✓	✓	✓	✓	⚙
TKM	✓	⚙	✓	✓	✓	✗	⚙	✗	✗
UKR	✓	✓	⚙	✓	✓	✓	✓	✓	✗
UZB	✓	✓	✓	✓	✓	✗	✓	✗	✗
KOS[c]	✓	✓	⚙	✓	✓	✓	✓	✓	⚙
No	2	3	5	5	1	10	1	6	12
In progress	0	2	2	2	4	1	3	2	3
Yes	18	15	13	13	15	9	15	12	5

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

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

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

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

Table 3.5 Quality control

Country/area	Participation in CAESAR EQA	Laboratory quality assessment system in place
Albania	✓	✗
Armenia	✓	⚙
Azerbaijan	✓	✓
Belarus	✓	✓
Bosnia and Herzegovina	✓	✓
Georgia	✓	⚙
Kazakhstan	⚙	✓
Kyrgyzstan	✓	✓
Montenegro	✓	✓
North Macedonia	✓	NA
Republic of Moldova	✓	✓
Russian Federation	✓	✓
Serbia	✓	✓
Switzerland	✗	✓
Tajikistan	✓	✓
Turkey	✓	✓
Turkmenistan	✓	⚙
Ukraine	✓	✓
Uzbekistan	✓	✓
Kosovo[a]	✓	✓
No	**1**	**1**
In progress	**1**	**3**
Yes	**18**	**15**

✓: 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. Besides, 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 2018 even though only 16 countries and Kosovo[1] sent in results. Chapter 9 presents a summary of the EQA exercise.

3.1.4 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 *(6)*. Moreover, CAESAR provides training on the EUCAST methodology. In line with the EUCAST recommendation, CAESAR also advises that a group of experts within the AMR network form a national antimicrobial susceptibility testing 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 *(7)*.

Eighteen countries and Kosovo[1] indicated that they use EUCAST guidelines, with the version ranging from 2016 to 2019 (Table 3.6). Of these, 13 countries use EUCAST guidelines in combination with CLSI or other national guidelines. Five countries and Kosovo[1] use EUCAST guidelines exclusively, while no country uses only CLSI guidelines. Eight countries and Kosovo[1] indicated that they formed an antibiotic susceptibility testing committee. Six countries reported that they are in the process of forming such a committee.

3.1.5 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 misrepresentation of the AMR situation in a country or area.

EUCAST has repeatedly evaluated the quality of antimicrobial disks of strategically important antibiotic disks for AST from nine international manufacturers. The results of these evaluations have been published on the EUCAST website *(8)* and as a scientific article *(9)*. 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 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 3.6 AST guidelines

Country/ area[a]	EUCAST		CLSI		Other			An AST committee was formed
	Percentage of laboratories	Year or version	Percentage of laboratories	Year or version	Type	Percentage of laboratories	Year or version	
ALB	>50	2018	<10	2017	–	–	–	✖
ARM	10–50	2019	10–50	3.0	–	–	–	✖
AZE	<10	NA	>50	NA	–	–	–	✖
BLR	10–50	2019	>50	NA	–	–	–	⚙
BIH	>50	2019	10–50	2017	–	–	–	⚙
GEO	>50	2019	10–50	2016	–	–	–	✔
KAZ	<10	2018	–	–	–	–	–	⚙
KGZ	>50	2018	–	–	–	–	–	✖
MNE	>50	2019	10–50	2016	–	–	–	✔
MKD	>50	2019	–	–	–	–	–	✔
MDA	>50	2019	10–50	2019	–	–	–	✔
RUS	>50	2018/ 2016	<10	NA	Old national guideline	10–50	2004	✔
SRB	>50	2018	–	–	–	–	–	✔
SWI	>50	NA	<10	NA	–	–	–	✔
TJK	<10	2017	–	–	National guideline	>50	2004	⚙
TUR	>50	2019	<10	NA	–	–	–	✔
TKM	–	–	<10	NA	NA	10–50	NA	⚙
UKR	10–50	2019	–	–	National guidance, Ministry of Health Order no. 167	10–50	NA	⚙
UZB	10–50	2019	–	–	–	–	–	✖
KOS[b]	>50	NA	–	–	–	–	–	✔

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

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

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

3.2 Conclusions

Currently, 11 countries and Kosovo[1] can provide AMR surveillance data to CAESAR, compared with only five countries in 2012 *(10)*. However many countries are actively taking the necessary steps to set up or strengthen their AMR surveillance system, enabling them to get a better understanding of the drivers of AMR in their country and take informed action. This chapter shows that members in the CAESAR network have made progress. Yet some countries still face considerable challenges, and the solutions are complex, as well as resource- and time-consuming. Problems that are often observed include:

- limited human and financial resources;
- the continuous need for training laboratory and hospital personnel and encouraging 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 are needed to address those challenges and to make further progress.

3.2.1 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
4

Data collection and analysis

4.1 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 isolates from blood and cerebrospinal fluid (CSF), 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 CAESAR international data manager, based at the National Institute for Public Health and the Environment in the Netherlands. 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. They should provide 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 (as described in the CAESAR manual *(1)*), which is compatible with the EARS-Net format *(2)*.

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

- *E. coli*
- *K. pneumoniae*
- *Salmonella* spp.
- *P. aeruginosa*
- *Acinetobacter* spp.
- *S. aureus*
- *S. pneumoniae*
- *E. faecalis*
- *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 to be tested and reported, recommended by EUCAST and the ESCMID Study Group for Antimicrobial Resistance Surveillance to detect resistance mechanisms. 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 required nor analysed by CAESAR.

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 reported antimicrobial agents, 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.

In addition to AMR data, the AMR focal point and data manager in each country or area are asked to provide information on the set-up of the surveillance system and laboratory procedures. This information is used to guide the reader in interpretation of the data from the different countries/areas. More information on data interpretation is available in Chapter 5 and Annex 2.

4.2 Analysis

Before analysis, AMR data are de-duplicated if needed, i.e. only the first isolate per patient per microorganism is included in the analyses. Antimicrobial susceptibility results are presented as the proportion of isolates of a specific microorganism that are (i) resistant (R) or (ii) susceptible, increased exposure or resistant (I+R) to a specific antimicrobial agent: for example, the number of *E. coli* isolates resistant to ceftazidime is divided by the total number of *E. coli* isolates in which susceptibility to this antibiotic was tested. The results are rounded off to the nearest whole percentage.

In some cases, the resistance proportions are calculated by combining the results for antibiotics that represent a group or class of antibiotics. The outcome is then based on the most resistant result. For example, both imipenem and meropenem represent the class of carbapenems and are therefore analysed as a group. If *E. coli* susceptibility to imipenem is I and susceptibility to meropenem is R, the susceptibility to imipenem/meropenem is set to R.

In contrast, multidrug resistance is calculated as R to at least one antibiotic in each of the antibiotic groups in the multidrug resistance definition (with the exception of *S. pneumoniae* where multidrug resistance is calculated as combined I+R to penicillin and R to macrolides). The table notes in the country/area-specific data 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 of multidrug resistance.

The I and 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, the corresponding reported proportions of I and R isolates 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)*.

For penicillin susceptibility in *S. pneumoniae*, the proportions of I and R isolates are presented as a combined category "%(I+R)". This is because some laboratories only report the result of the 1 µg oxacillin screening disk. When the oxacillin zone diameter is ≥20 mm, the isolate can reliably be reported susceptible to all beta-lactam antibiotics including penicillins, regardless of the clinical indication (including meningitis). When the zone diameter is <20 mm, penicillin cannot be used to treat meningitis patients. When the clinical indication is meningitis, penicillin should be reported R. However, for indications other than meningitis, a zone diameter <20 mm requires the penicillin minimum inhibitory concentration (MIC) to be determined and interpreted according to the clinical breakpoints established for infections other than meningitis. When oxacillin is reported R but a penicillin MIC is not available in the data, correct categorization cannot be achieved; the isolate may either be I or R in case of an indication other than meningitis. Therefore, for *S. pneumoniae*, the proportions of I and R isolates are not presented separately for penicillin or for multidrug resistance (which also includes penicillin). This means that the reported proportion I+R should be interpreted as the proportion that is resistant in case of meningitis. For non-meningitis indications, the percentage I+R should be interpreted as the percentage non-wild type. For this report, the term penicillin non-wild-type refers to *S. pneumoniae* isolates reported by the local laboratories as I or R to penicillin, assuming MICs to penicillin above those of the wild-type, i.e. >0.06 mg/L. For laboratories using EUCAST, this approach correctly defines all penicillin non-wild-type (i.e. I/R) *S. pneumoniae* isolates. For laboratories using the CLSI methodology, isolates within the S category for benzylpenicillin might be non-wild-type

since the penicillin susceptibility breakpoint for non-meningitis cases is set as ≤2 mg/L. Due to this limitation, the actual percentage of penicillin non-wild-type *S. pneumoniae* might be higher than reported.


CHAPTER
5

Reader's guide

5.1 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 5.1 and are discussed in detail in Annex 2.

5.2 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.

Table 5.1 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

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.

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 5.2 provides an overview of the level of evidence for each country/area and the underlying assessment of the data from 2018.

Table 5.2 Level of evidence and scoring of factors affecting the validity of CAESAR data, 2018

		Armenia	Belarus	Bosnia and Herzegovina	Georgia	Montenegro	North Macedonia	Russian Federation	Serbia	Switzerland	Turkey	Ukraine	Kosovo[a]
Level of evidence		B	B	A	B	B	B	B	A	A	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).

5.3 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
6

Country-specific data on AMR

6.1 Armenia

Data presented are for the period 1 January–31 October 2018, derived from a proof-of-principle AMR routine diagnostics surveillance project, which included four laboratories supporting tertiary hospitals by design.

6.1.1 Surveillance set-up and data quality assessment

Table 6.1 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from Armenia in 2018. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.1 Level of evidence and scoring of factors affecting the validity of CAESAR data from Armenia in 2018

Level of evidence: B			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+/–	• The surveillance network comprises 11 (21% of) laboratories of which four submitted data. • Most laboratories are located in or close to the capital. • The estimated coverage of the total population (2 979 000)[a] is not available.
	Hospital types	+/–	• The network comprises tertiary (80%) and secondary (20%) care hospitals.
Sampling procedures	Selection of patients	–	• Clinical guidelines to define cases eligible for sampling are in place. • Underutilization and selective usage of blood and CSF culture diagnostics are indicated by: - the small number of samples taken per 1000 patient days: mean 2, range 1–3 in the four hospitals providing denominator data; - the small total number of isolates; and - the large proportion of isolates from intensive care units (45%). *Patient characteristics of isolates from Armenia are available in Fig. 6.1.*
	Sample size	–	• The total number of isolates is 44. • Fewer than 30 isolates are available for all pathogens.
Laboratory procedures	AST methods	+	• The national standard for AST is EUCAST. • The main method for AST is disk diffusion (all laboratories). • Not all isolates are tested for each relevant antibiotic. • Confirmatory testing of all isolates is performed at the reference laboratory (both identification and AST). • Internal quality control is regularly performed in all laboratories. • All laboratories participated in the EQA in 2018.
	AST breakpoints	+	• EUCAST breakpoints are used in 10 out of 11 laboratories (90%).

[a] Estimated population mid-2017, United Nations *(1)*.

6.1.2 Results

Fig. 6.1 shows the distribution of CAESAR microorganisms and the characteristics of patients (broken down by pathogen) of blood isolates in Armenia in 2018. Resistance percentages for these isolates are presented in Tables 6.2–6.6.

Fig. 6.1 Patient characteristics of isolates in Armenia in 2018, by pathogen

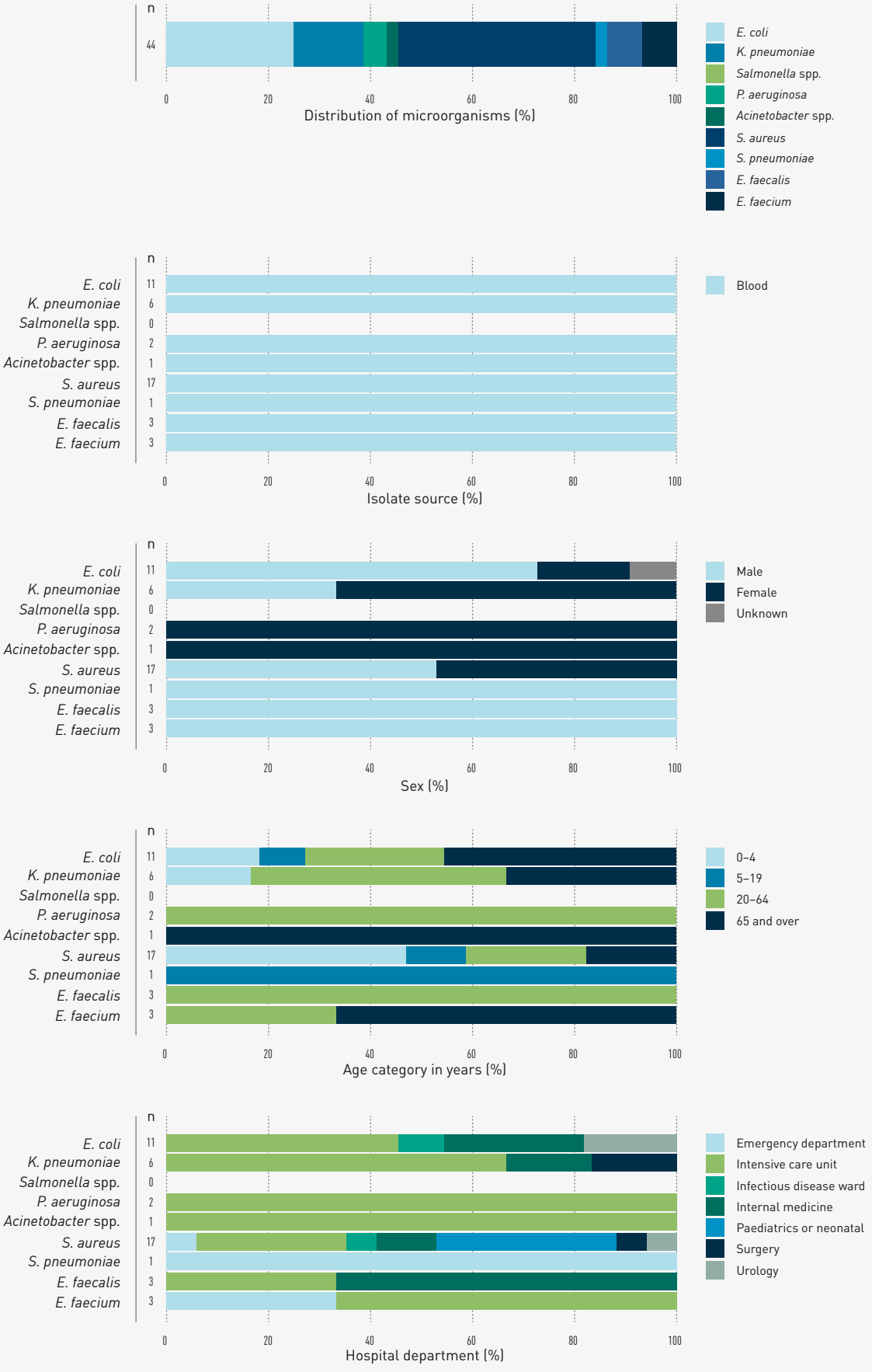


Table 6.2 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Armenia in 2018

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	11	91*	0*	NA	NA	NA
Amoxicillin-clavulanic acid	11	73*	0*	6	100*	0*
Piperacillin-tazobactam	11	9*	9*	6	50*	50*
Cefotaxime/ceftriaxone	11	55*	0*	6	100*	0*
Ceftazidime	11	45*	9*	6	100*	0*
Ertapenem	11	0*	0*	6	0*	17*
Imipenem/meropenem	11	0*	36*	6	0*	100*
Gentamicin/tobramycin	11	36*	9*	6	67*	0*
Amikacin	11	0*	0*	6	0*	0*
Ciprofloxacin/levofloxacin/ofloxacin	11	36*	0*	6	100*	0*
Multidrug resistance[a]	11	27*	NA	6	67*	NA

NA = not applicable.

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

[a] Multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin, levofloxacin and/or ofloxacin), third-generation cephalosporins (cefotaxime, ceftriaxone and/or ceftazidime) and aminoglycosides (gentamicin and/or tobramycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.3 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Armenia in 2018

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	2	0*	0*	NA	NA	NA
Ceftazidime	2	0*	0*	NA	NA	NA
Cefepime	2	0*	0*	NA	NA	NA
Imipenem/meropenem	2	0*	0*	1	0*	0*
Gentamicin/tobramycin	2	0*	0*	1	0*	0*
Amikacin	2	0*	0*	1	0*	0*
Ciprofloxacin/levofloxacin	2	0*	0*	1	100*	0*
Multidrug resistance[a]	2	0*	NA	1	0*	NA

NA = not applicable.

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

[a] For *P. aeruginosa*, multidrug resistance is defined as combined resistance to at least one representative of three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem).

For *Acinetobacter* spp., multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.4 Resistance levels for *S. aureus* among blood and CSF isolates in Armenia in 2018

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	17	24*	NA
Ciprofloxacin/levofloxacin/ofloxacin	17	0*	0*
Vancomycin	16	0*	0*
Rifampicin	17	0*	0*
Linezolid	17	0*	NA

NA = not applicable.

* A small number of isolates was 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.

Table 6.5 Resistance levels for *S. pneumoniae* among blood and CSF isolates in Armenia in 2018

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%(I+R)
Penicillin[a]	1	NA	NA	0*
Cefotaxime/ceftriaxone	0	–	–	NA
Levofloxacin/moxifloxacin	1	0*	0*	NA
Erythromycin/clarithromycin/azithromycin	1	0*	0*	NA
Multidrug resistance[b]	1	NA	NA	0*

NA = not applicable.

– = no data available.

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

[a] The percentage I+R to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage I+R should be interpreted as the percentage R. For non-meningitis indications, the percentage I+R should be interpreted as the percentage of penicillin non-wild type. For this report, the term penicillin non-wild type refers to *S. pneumoniae* isolates reported by the local laboratories as I or R to penicillin, assuming MICs to penicillin above those of the wild-type, i.e. >0.06 mg/L. The analysis is based on the qualitative susceptibility categories S, I and R as quantitative susceptibility information was missing for a large proportion of the data. For laboratories using EUCAST, this approach correctly defines all penicillin non-wild type (i.e. I/R) *S. pneumoniae* isolates. However, for laboratories using the CLSI methodology, isolates within the S category for benzylpenicillin might be non-wild type since the penicillin susceptibility breakpoint for non-meningitis cases is set as ≤ 2 mg/L. Due to this limitation, the actual percentage of penicillin non-wild type *S. pneumoniae* might be higher than reported in this table.

[b] Multidrug resistance is defined as combined penicillin non-wild type and resistance (R) to macrolides (erythromycin, clarithromycin and/or azithromycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.6 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in Armenia in 2018

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	3	0*	0*	3	67*	0*
High-level gentamicin	3	33*	0*	3	0*	0*
Vancomycin	3	0*	0*	3	0*	0*
Linezolid	3	0*	0*	3	0*	0*

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

6.1.3 Conclusion

Data from Armenia are assessed as level B based on the following strength and limitations regarding data quality and representativeness.

The strength is:

- AST results are reliable and comparable, as all results were confirmed at the reference laboratory.

The limitations are:

- the representativeness of results is limited by overrepresentation of severely ill patients and children under 1 year of age, in tertiary hospitals in the capital; and
- the small number of isolates make observed resistance percentages more sensitive to random variation (e.g. due to nosocomial outbreaks).

As a result of limitations in the data quality, the reported percentages of resistance should be interpreted with caution and are not necessarily generalizable to any one patient presenting with invasive infection in Armenia, especially patients with community-acquired infections.

Nevertheless, in the patient population sampled, a high level of resistance to third-generation cephalosporins (cefotaxime/ceftriaxone and ceftazidime) was seen in *E. coli* (Table 6.2). The proportion of MRSA was similar to that in neighbouring countries (Table 6.4, Fig. 2.8). Too few antibiotic susceptibility test results for *K. pneumoniae* (Table 6.2), *Salmonella* spp. (no isolates), *P. aeruginosa*, *Acinetobacter* spp. (Table 6.3), *S. pneumoniae* (Table 6.5), *E. faecalis* and *E. faecium* (Table 6.6) were available to allow interpretation.

6.2 Belarus

6.2.1 Surveillance set-up and data quality assessment

Table 6.7 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from Belarus in 2018. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.7 Level of evidence and scoring of factors affecting the validity of CAESAR data from Belarus in 2018

Level of evidence: B			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+	• The surveillance network comprises 118 laboratories (>90% of hospitals) of which 41 submitted data. • Laboratories are geographically spread within Belarus; some regions are underrepresented. • The estimated coverage of the total population (9 498 000)[a] is >90%.
	Hospital types	+	The network comprises tertiary (21%) and secondary (79%) care hospitals.
Sampling procedures	Selection of patients	–	• National clinical guidelines to define cases eligible for sampling are in place. • Underutilization and selective usage of blood and CSF culture diagnostics are indicated by: - the small number of samples taken per 1000 patient days, although exact data are not available; - the relatively large proportion (61%) of isolates that come from the capital (20% of population); - the large proportion of isolates from intensive care units (58%); - the large proportion of nosocomial pathogens (32% *K. pneumoniae*, 22% *Acinetobacter* spp.) and the small proportion of *E. coli* (8%); and - the generally high resistance percentages. *Patient characteristics of isolates from Belarus are available in Fig. 6.2.*
	Sample size	+	• The total number of isolates is 1848. • At least 30 isolates are available for all pathogens except for *Salmonella* spp.
Laboratory procedures	AST methods	+/–	• The national standard for AST is CLSI guidelines 2004, but 25% of laboratories (>80% of tests) use more recent CLSI or EUCAST guidelines (2009–2014). • The main methods for AST are semi-automated systems (29 laboratories) and disk diffusion (89 laboratories). • Not all isolates are tested for each relevant antibiotic. • Confirmatory testing of exceptional phenotypes or highly resistant microorganisms is recommended to be performed, locally or at the reference laboratory. • Internal quality control is regularly performed in all laboratories. • Twelve laboratories participated in the CAESAR EQA in 2018.
	AST breakpoints	+/–	• CLSI 2004 breakpoints are used in 75% of laboratories (<20% of tests). • More recent CLSI breakpoints (2012–2014) or EUCAST breakpoints are used in 25% of laboratories (>80% of tests).

[a] Estimated population mid-2017, United Nations *(1)*.

6.2.2 Results

Fig. 6.2 shows the distribution of CAESAR microorganisms and the characteristics of patients (broken down by pathogen) of blood and CSF isolates in Belarus in 2018. Resistance percentages for these isolates are presented in Tables 6.8–6.13.

Fig. 6.2 Patient characteristics of isolates in Belarus in 2018, by pathogen

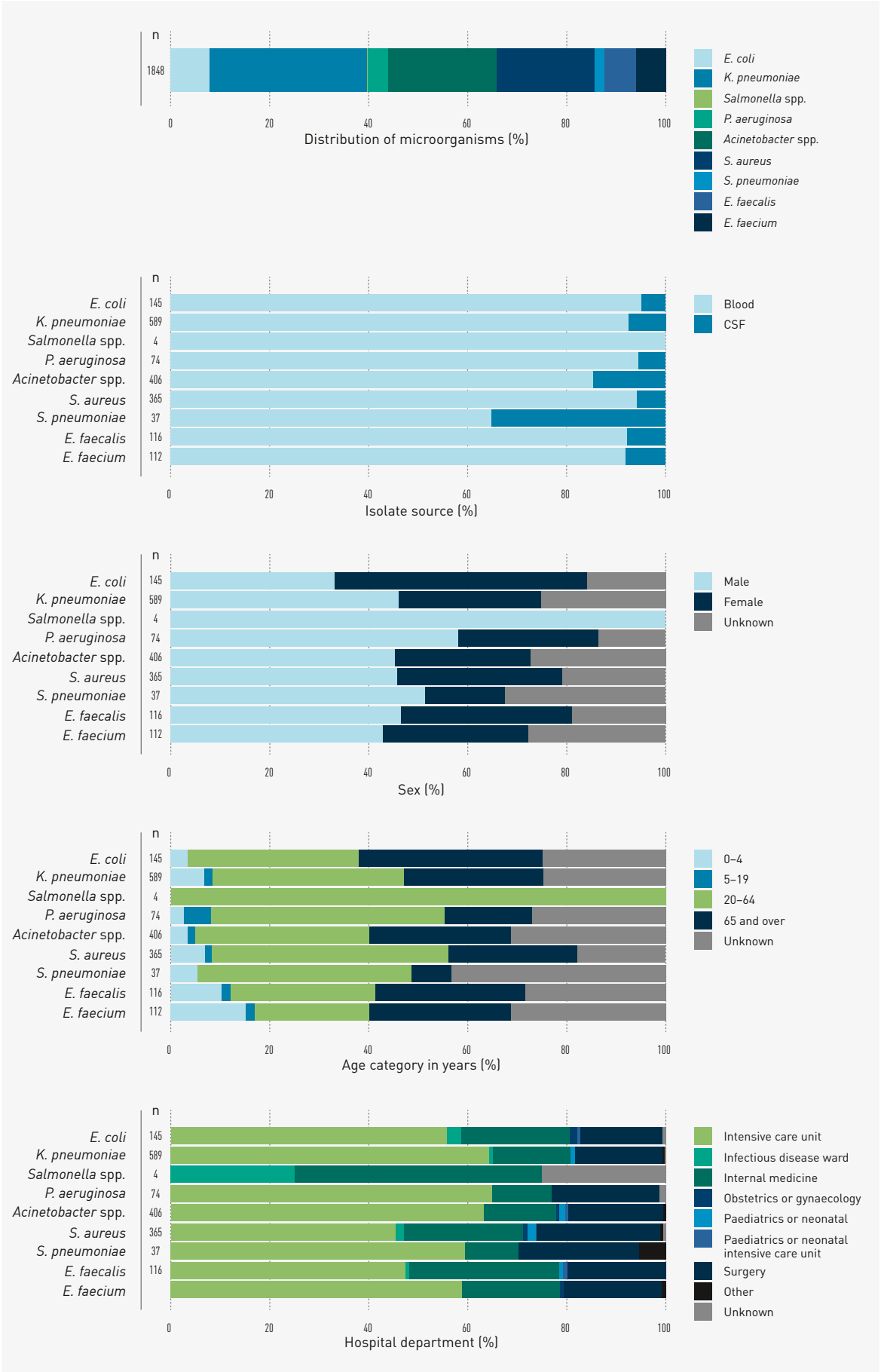


Table 6.8 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Belarus in 2018

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	39	69	3	NA	NA	NA
Amoxicillin-clavulanic acid	29	21*	21*	92	78	0
Piperacillin-tazobactam	51	24	6	156	72	3
Cefotaxime/ceftriaxone	120	52	3	448	86	1
Ceftazidime	53	43	9	189	81	3
Ertapenem	19	0*	0*	44	64	2
Imipenem/meropenem	136	3	4	563	76	2
Gentamicin/tobramycin	56	30	2	184	74	3
Amikacin	50	10	4	233	63	1
Ciprofloxacin/levofloxacin/ofloxacin	140	45	1	568	85	2
Multidrug resistance[a]	55	22	NA	168	72	NA

NA = not applicable.

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

[a] Multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin, levofloxacin and/or ofloxacin), third-generation cephalosporins (cefotaxime, ceftriaxone and/or ceftazidime) and aminoglycosides (gentamicin and/or tobramycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.9 Resistance levels for *Salmonella* spp. among blood and CSF isolates in Belarus in 2018

Antibiotic (group)	*Salmonella* spp.		
	N	%R	%I
Cefotaxime/ceftriaxone	4	25*	25*
Ceftazidime	1	100*	0*
Ertapenem	0	–	–
Imipenem/meropenem	3	0*	0*
Ciprofloxacin/levofloxacin	3	33*	0*

– = no data available.

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

Table 6.10 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Belarus in 2018

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	20	50*	0*	NA	NA	NA
Ceftazidime	49	65	6	NA	NA	NA
Cefepime	69	62	3	NA	NA	NA
Imipenem/meropenem	69	68	6	393	94	2
Gentamicin/tobramycin	29	66*	3*	141	69	6
Amikacin	50	48	4	102	79	8
Ciprofloxacin/levofloxacin	72	68	1	396	93	4
Multidrug resistance[a]	14	50*	NA	130	68	NA

NA = not applicable.

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

[a] For *P. aeruginosa*, multidrug resistance is defined as combined resistance to at least one representative of three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on three or more of the groups are excluded from the analysis of multidrug resistance.

For *Acinetobacter* spp., multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.11 Resistance levels for *S. aureus* among blood and CSF isolates in Belarus in 2018

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	331	37	NA
Ciprofloxacin/levofloxacin/ofloxacin	353	29	3
Vancomycin	292	0	0
Rifampicin	266	14	1
Linezolid	322	0	NA

NA = not applicable.

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

Table 6.12 Resistance levels for *S. pneumoniae* among blood and CSF isolates in Belarus in 2018

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%(I+R)
Penicillin[a]	23	NA	NA	17*
Cefotaxime/ceftriaxone	26	4*	15*	NA
Levofloxacin/moxifloxacin	36	0	0	NA
Erythromycin/clarithromycin/azithromycin	34	26	6	NA
Multidrug resistance[b]	22	NA	NA	14*

NA = not applicable.

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

[a] The percentage I+R to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage I+R should be interpreted as the percentage R. For non-meningitis indications, the percentage I+R should be interpreted as the percentage of penicillin non-wild type. For this report, the term penicillin non-wild type refers to *S. pneumoniae* isolates reported by the local laboratories as I or R to penicillin, assuming MICs to penicillin above those of the wild-type, i.e. >0.06 mg/L. The analysis is based on the qualitative susceptibility categories S, I and R as quantitative susceptibility information was missing for a large proportion of the data. For laboratories using EUCAST, this approach correctly defines all penicillin non-wild type (i.e. I/R) *S. pneumoniae* isolates. However, for laboratories using the CLSI methodology, isolates within the S category for benzylpenicillin might be non-wild type since the penicillin susceptibility breakpoint for non-meningitis cases is set as ≤ 2 mg/L. Due to this limitation, the actual percentage of penicillin non-wild type *S. pneumoniae* might be higher than reported in this table.

[b] Multidrug resistance is defined as combined penicillin non-wild type and resistance (R) to macrolides (erythromycin, clarithromycin and/or azithromycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.13 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in Belarus in 2018

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	78	21	0	86	97	0
High-level gentamicin	73	66	0	74	76	0
Vancomycin	111	4	0	110	17	0
Linezolid	102	3	1	98	2	0

6.2.3 Conclusion

Data from Belarus are assessed as level B based on the following strengths and limitations regarding data quality and representativeness.

The strengths are:

- the network has good geographical and population coverage and includes various types of hospitals
- the number of isolates is large.

The limitations are:

- the representativeness of results is limited by overrepresentation of severely ill patients with hospital-acquired infections in the capital; and
- the comparability of results is limited by the absence of harmonized AST guidelines and breakpoints, and the variation in the proportion of isolates tested for each relevant antibiotic.

As a result of limitations in the data quality, the reported percentages of resistance should be interpreted with caution and are not necessarily generalizable to any one patient presenting with invasive infection in Belarus, especially patients with community-acquired infections.

Nevertheless, in the patient population sampled, resistance to third-generation cephalosporins (cefotaxime/ceftriaxone and ceftazidime), aminoglycosides (gentamicin/tobramycin) and fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin) was high in *E. coli*, and very high in *K. pneumoniae* (Table 6.8). In *K. pneumoniae* in addition, very high levels of resistance to carbapenems (imipenem/meropenem) were observed. The high levels of resistance in *P. aeruginosa* and *Acinetobacter* spp. (Table 6.10) are concerning and likely reflect the spread of resistant clones in the health care setting. The proportion of MRSA was higher than that in neighbouring countries (Table 6.11, Fig. 2.8). Moderate resistance levels were observed in *S. pneumoniae* (Table 6.12). In *E. faecium*, resistance to vancomycin was moderately high (Table 6.13).

6.3 Bosnia and Herzegovina

6.3.1 Surveillance set-up and data quality assessment

AMR surveillance activities in Bosnia and Herzegovina are conducted by two networks; one in the Federation of Bosnia and Herzegovina, and one in Republika Srpska. The Brčko district is not represented in AMR surveillance. Table 6.14 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from Bosnia and Herzegovina in 2018. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.14 Level of evidence and scoring of factors affecting the validity of CAESAR data from Bosnia and Herzegovina in 2018

Level of evidence: A			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+	• The two surveillance networks comprise 12 laboratories: - six (50% of) laboratories in the Federation of Bosnia and Herzegovina, all of which submitted data; and - six (86% of) laboratories in the Republika Srpska, all of which submitted data. • Laboratories are geographically spread within Bosnia and Herzegovina. • The estimated coverage of the population is 75% in the Federation of Bosnia and Herzegovina and 85% in Republika Srpska.
	Hospital types	+	• The network in the Federation of Bosnia and Herzegovina comprises tertiary (17%), secondary (50%) and mixed tertiary and secondary (33%) care hospitals. • The network in Republika Srpska comprises tertiary (50%) and secondary (50%) care hospitals.
Sampling procedures	Selection of patients	+/–	• National clinical guidelines to define cases eligible for sampling are in place. • Underutilization and selective usage of blood and CSF culture diagnostics (especially in regional hospitals) are indicated by: - the small number of samples taken per 1000 patient days: mean 7, range 3–16 in the seven hospitals providing denominator data; and - in Republika Srpska 83% of data are from the main tertiary care centre in Banja Luka (University Clinical Centre). *Patient characteristics of isolates from Bosnia and Herzegovina are available in Fig. 6.3.*
	Sample size	+	• The total number of isolates is 1092. • At least 30 isolates are available for all pathogens except for *Salmonella* spp.
Laboratory procedures	AST methods	+	• The national standard for AST is EUCAST. • The methods for AST are: - a combination of a semi-automated system and disk diffusion (three laboratories) and disk diffusion only (three laboratories) in the Federation of Bosnia and Herzegovina; and - a semi-automated system (University Clinical Centre) and disk diffusion (five laboratories) in Republika Srpska. • Not all isolates are tested for each relevant antibiotic. • Confirmatory testing of exceptional phenotypes or highly resistant microorganisms is performed at the expert laboratory (Federation of Bosnia and Herzegovina) or locally (Republika Srpska). • Quality management systems are in place in all laboratories. • Ten out of 12 laboratories participated in the CAESAR EQA in 2018.
	AST breakpoints	+	• EUCAST breakpoints are used in eight out of 12 laboratories (67%).

6.3.2 Results

Fig. 6.3 shows the distribution of CAESAR microorganisms and the characteristics of patients (broken down by pathogen) of blood and CSF isolates in Bosnia and Herzegovina in 2018. Resistance percentages for these isolates are presented in Tables 6.15–6.20.

Fig. 6.3 Patient characteristics of isolates in Bosnia and Herzegovina in 2018, by pathogen

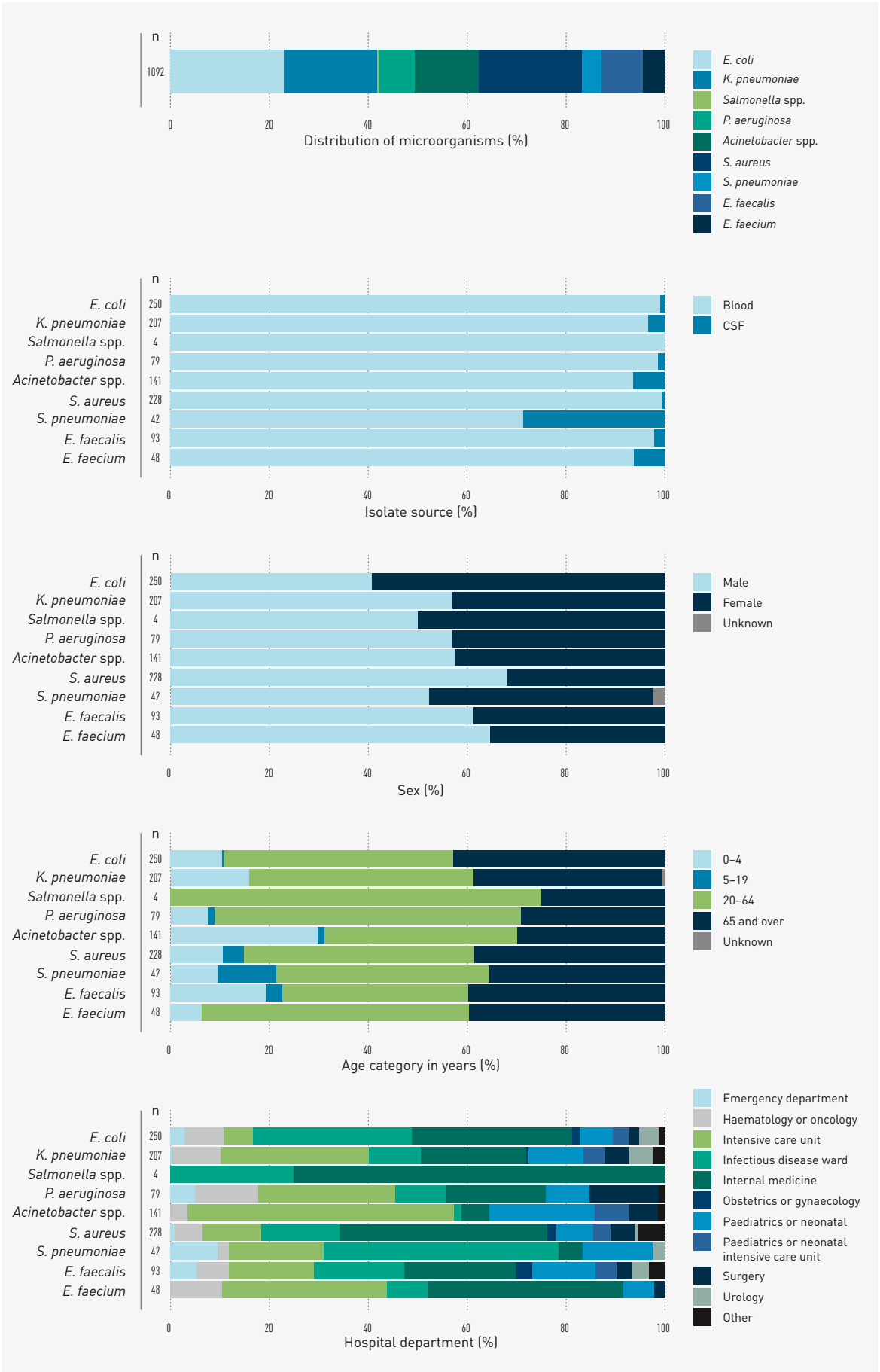


Table 6.15 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Bosnia and Herzegovina in 2018

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	250	69	0	NA	NA	NA
Amoxicillin-clavulanic acid	250	28	1	207	83	0
Piperacillin-tazobactam	247	6	0	206	46	1
Cefotaxime/ceftriaxone	250	20	0	207	71	0
Ceftazidime	250	17	2	207	69	0
Ertapenem	172	0	0	135	19	1
Imipenem/meropenem	249	0	0	207	18	3
Gentamicin/tobramycin	250	17	2	207	69	0
Amikacin	249	6	0	207	12	5
Ciprofloxacin/levofloxacin/ofloxacin	248	24	0	207	59	0
Multidrug resistance[a]	248	10	NA	207	55	NA

NA = not applicable.

[a] Multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin, levofloxacin and/or ofloxacin), third-generation cephalosporins (cefotaxime, ceftriaxone and/or ceftazidime) and aminoglycosides (gentamicin and/or tobramycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.16 Resistance levels for *Salmonella* spp. among blood and CSF isolates in Bosnia and Herzegovina in 2018

Antibiotic (group)	*Salmonella* spp.		
	N	%R	%I
Cefotaxime/ceftriaxone	4	0*	0*
Ceftazidime	4	0*	0*
Ertapenem	3	0*	0*
Imipenem/meropenem	4	0*	0*
Ciprofloxacin/levofloxacin	4	0*	0*

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

Table 6.17 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Bosnia and Herzegovina in 2018

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	79	24	1	NA	NA	NA
Ceftazidime	79	30	1	NA	NA	NA
Cefepime	79	24	3	NA	NA	NA
Imipenem/meropenem	79	30	4	141	93	1
Gentamicin/tobramycin	79	41	0	141	99	0
Amikacin	79	22	4	140	92	0
Ciprofloxacin/levofloxacin	79	43	0	141	99	0
Multidrug resistance[a]	79	33	NA	141	93	NA

NA = not applicable.

[a] For *P. aeruginosa*, multidrug resistance is defined as combined resistance to at least one representative of three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on three or more of the groups are excluded from the analysis of multidrug resistance.

For *Acinetobacter* spp., multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.18 Resistance levels for *S. aureus* among blood and CSF isolates in Bosnia and Herzegovina in 2018

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	228	16	NA
Ciprofloxacin/levofloxacin/ofloxacin	228	9	0
Vancomycin	223	0	0
Rifampicin	132	2	0
Linezolid	210	0	NA

NA = not applicable.

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

Table 6.19 Resistance levels for *S. pneumoniae* among blood and CSF isolates in Bosnia and Herzegovina in 2018

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%(I+R)
Penicillin[a]	42	NA	NA	52
Cefotaxime/ceftriaxone	42	2	7	NA
Levofloxacin/moxifloxacin	42	0	0	NA
Erythromycin/clarithromycin/azithromycin	42	36	0	NA
Multidrug resistance[b]	42	NA	NA	29

NA = not applicable.

[a] The percentage I+R to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage I+R should be interpreted as the percentage R. For non-meningitis indications, the percentage I+R should be interpreted as the percentage of penicillin non-wild type. For this report, the term penicillin non-wild type refers to *S. pneumoniae* isolates reported by the local laboratories as I or R to penicillin, assuming MICs to penicillin above those of the wild-type, i.e. >0.06 mg/L. The analysis is based on the qualitative susceptibility categories S, I and R as quantitative susceptibility information was missing for a large proportion of the data. For laboratories using EUCAST, this approach correctly defines all penicillin non-wild type (i.e. I/R) *S. pneumoniae* isolates. However, for laboratories using the CLSI methodology, isolates within the S category for benzylpenicillin might be non-wild type since the penicillin susceptibility breakpoint for non-meningitis cases is set as ≤ 2 mg/L. Due to this limitation, the actual percentage of penicillin non-wild type *S. pneumoniae* might be higher than reported in this table.

[b] Multidrug resistance is defined as combined penicillin non-wild type and resistance (R) to macrolides (erythromycin, clarithromycin and/or azithromycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.20 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in Bosnia and Herzegovina in 2018

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	93	0	0	47	100	0
High-level gentamicin	92	37	0	48	96	0
Vancomycin	92	0	0	48	38	0
Linezolid	87	0	0	45	0	0

6.3.3 Conclusion

Data from Bosnia and Herzegovina are assessed as level A based on the following strengths and limitation regarding data quality and representativeness.

The strengths are:

- the network has good geographical and population coverage and includes various types of hospitals;
- the data represent a mix of health care-associated and community-acquired infections in patients from various types of hospital departments; and
- AST results seem reliable and comparable.

The limitation is:

- the representativeness of results is limited by underrepresentation of patients from regional hospitals, especially from the eastern part of the country.

The significant amount of high-quality antibiotic susceptibility test data from a geographically representative network including samples from a variety of patients adequately assesses the trends of AMR in the country, although the magnitude of resistance should be interpreted with caution.

In *K. pneumoniae* (Table 6.15) and *Acinetobacter* spp. (Table 6.17), very high levels of (multidrug) resistance were observed. In addition, in *E. faecium* resistance to vancomycin was high (Table 6.20). These findings 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 (Table 6.19). On the other hand, the resistance levels in *E. coli* (Table 6.15), *P. aeruginosa* (Table 6.17) and *S. aureus* (Table 6.18) were only moderately high.

6.4 Georgia

6.4.1 Surveillance set-up and data quality assessment

Table 6.21 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from Georgia in 2018. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.21 Level of evidence and scoring of factors affecting the validity of CAESAR data from Georgia in 2018

Level of evidence: B			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+	• The surveillance network comprises 17 laboratories (50% of hospitals) of which 13 submitted data. • Most laboratories are located in or close to the capital. • The estimated coverage of the total population (3 728 000)[a] is 60%.
	Hospital types	+	• The network comprises tertiary (66%), secondary (22%) and primary (11%) care hospitals.
Sampling procedures	Selection of patients	–	• National clinical guidelines to define cases eligible for sampling are in place. • Underutilization and selective usage of blood and CSF culture diagnostics (especially in regional hospitals) are indicated by: - the small number of samples taken per 1000 patient days: mean 11, range 4–66 in the nine hospitals providing denominator data; and - the large proportion of isolates from intensive care units (65%). *Patient characteristics of isolates from Georgia are available in Fig. 6.4.*
	Sample size	–	• The total number of isolates is 292. • Fewer than 30 isolates are available for some pathogens.
Laboratory procedures	AST methods	+/–	• There is no national standard for AST. • The main methods for AST are disk diffusion (most laboratories) and a combination of a semi-automated system and disk diffusion. • Not all isolates are tested for each relevant antibiotic. • Confirmatory testing of most exceptional phenotypes is performed at the reference laboratory. • Internal quality control is regularly performed in 60% of laboratories. • All laboratories participated in the CAESAR EQA in 2018.
	AST breakpoints	+/–	• EUCAST breakpoints are used in 12 out of 17 laboratories (70%).

[a] Estimated population mid-2017, United Nations *(1)*.

6.4.2 Results

Fig. 6.4 shows the distribution of CAESAR microorganisms and the characteristics of patients (broken down by pathogen) of blood and CSF isolates in Georgia in 2018. Resistance percentages for these isolates are presented in Tables 6.22–6.27.

Fig. 6.4 Patient characteristics of isolates in Georgia in 2018, by pathogen

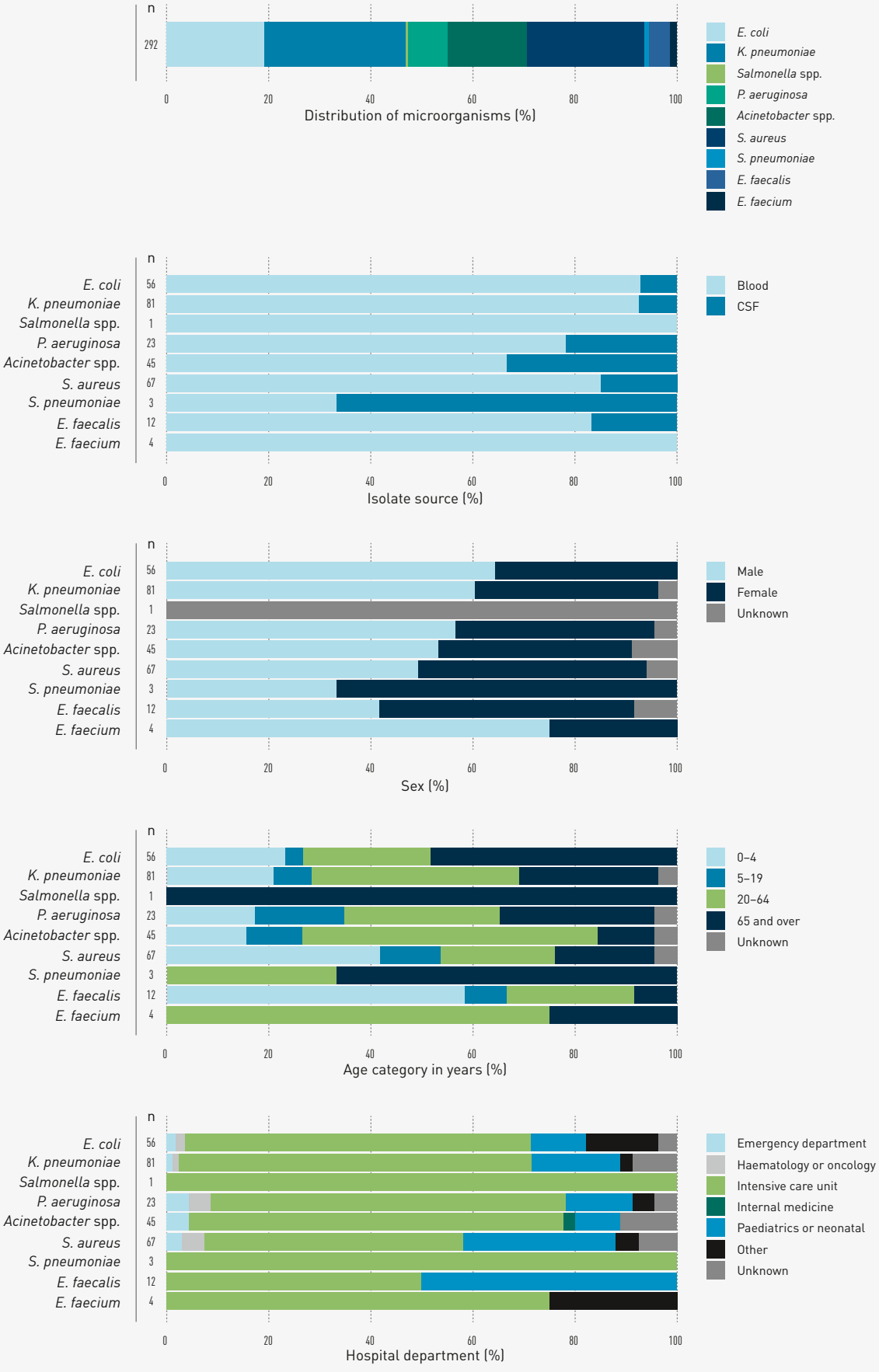


Table 6.22 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Georgia in 2018

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	18	83*	0*	NA	NA	NA
Amoxicillin-clavulanic acid	46	52	2	66	83	3
Piperacillin-tazobactam	45	22	7	75	51	9
Cefotaxime/ceftriaxone	56	55	2	81	88	1
Ceftazidime	54	50	4	77	78	4
Ertapenem	4	50*	0*	13	62*	0*
Imipenem/meropenem	56	11	2	81	28	5
Gentamicin/tobramycin	24	46*	4*	74	49	11
Amikacin	22	27*	9*	74	39	11
Ciprofloxacin/levofloxacin/ofloxacin	55	51	2	81	56	2
Multidrug resistance[a]	24	38*	NA	74	35	NA

NA = not applicable.

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

[a] Multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin, levofloxacin and/or ofloxacin), third-generation cephalosporins (cefotaxime, ceftriaxone and/or ceftazidime) and aminoglycosides (gentamicin and/or tobramycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.23 Resistance levels for *Salmonella* spp. among blood and CSF isolates in Georgia in 2018

Antibiotic (group)	*Salmonella* spp.		
	N	%R	%I
Cefotaxime/ceftriaxone	1	0*	0*
Ceftazidime	1	0*	0*
Ertapenem	0	–	–
Imipenem/meropenem	1	0*	0*
Ciprofloxacin/levofloxacin	1	0*	0*

– = no data available.

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

Table 6.24 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Georgia in 2018

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	20	35*	5*	NA	NA	NA
Ceftazidime	23	70*	4*	NA	NA	NA
Cefepime	21	62*	14*	NA	NA	NA
Imipenem/meropenem	23	43*	4*	45	89	0
Gentamicin/tobramycin	22	55*	9*	45	78	2
Amikacin	21	52*	5*	43	79	0
Ciprofloxacin/levofloxacin	23	48*	4*	45	98	0
Multidrug resistance[a]	20	45*	NA	45	71	NA

NA = not applicable.

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

[a] For *P. aeruginosa*, multidrug resistance is defined as combined resistance to at least one representative of three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on three or more of the groups are excluded from the analysis of multidrug resistance.

For *Acinetobacter* spp., multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.25 Resistance levels for *S. aureus* among blood and CSF isolates in Georgia in 2018

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	53	15	NA
Ciprofloxacin/levofloxacin/ofloxacin	67	33	0
Vancomycin	12	0*	0*
Rifampicin	37	14	14
Linezolid	39	3	NA

NA = not applicable.

* A small number of isolates was 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.

Table 6.26 Resistance levels for *S. pneumoniae* among blood and CSF isolates in Georgia in 2018

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%(I+R)
Penicillin[a]	3	NA	NA	0*
Cefotaxime/ceftriaxone	0	–	–	NA
Levofloxacin/moxifloxacin	3	0*	0*	NA
Erythromycin/clarithromycin/azithromycin	3	0*	0*	NA
Multidrug resistance[b]	3	NA	NA	0*

NA = not applicable.

– = no data available.

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

[a] The percentage I+R to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage I+R should be interpreted as the percentage R. For non-meningitis indications, the percentage I+R should be interpreted as the percentage of penicillin non-wild type. For this report, the term penicillin non-wild type refers to *S. pneumoniae* isolates reported by the local laboratories as I or R to penicillin, assuming MICs to penicillin above those of the wild-type, i.e. >0.06 mg/L. The analysis is based on the qualitative susceptibility categories S, I and R as quantitative susceptibility information was missing for a large proportion of the data. For laboratories using EUCAST, this approach correctly defines all penicillin non-wild type (i.e. I/R) *S. pneumoniae* isolates. However, for laboratories using the CLSI methodology, isolates within the S category for benzylpenicillin might be non-wild type since the penicillin susceptibility breakpoint for non-meningitis cases is set as ≤ 2 mg/L. Due to this limitation, the actual percentage of penicillin non-wild type *S. pneumoniae* might be higher than reported in this table.

[b] Multidrug resistance is defined as combined penicillin non-wild type and resistance (R) to macrolides (erythromycin, clarithromycin and/or azithromycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.27 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in Georgia in 2018

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	10	50*	0*	4	75*	0*
High-level gentamicin	5	80*	0*	4	75*	0*
Vancomycin	12	17*	0*	4	0*	0*
Linezolid	8	13*	0*	3	0*	0*

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

6.4.3 Conclusion

Data from Georgia are assessed as level B based on the following strengths and limitations regarding data quality and representativeness.

The strengths are:

- the network includes various types of hospitals
- AST results seem reliable.

The limitations are:

- the representativeness of results is limited by overrepresentation of severely ill patients with hospital-acquired infections in the capital;
- the small number of isolates make observed resistance percentages more sensitive to random variation (e.g. due to nosocomial outbreaks); and
- the comparability of results is limited by the absence of harmonized AST guidelines.

As a result of limitations in the data quality, 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.

Nevertheless, the patient population sampled had high levels of resistance to all selected agents in *E. coli*, *K. pneumoniae* (Table 6.22), *P. aeruginosa* and *Acinetobacter* spp. (Table 6.24). These high levels of resistance are concerning and may reflect the dissemination of resistant clones in the health care setting. On the other hand, the proportion of MRSA was moderate and similar to that in neighbouring countries (Table 6.25, Fig. 2.8). Too few antibiotic susceptibility test results for *Salmonella* spp. (Table 6.23), *S. pneumoniae* (Table 6.26), *E. faecalis* and *E. faecium* (Table 6.27) were available to allow interpretation.

6.5 Montenegro

6.5.1 Surveillance set-up and data quality assessment

Table 6.28 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from Montenegro in 2018. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.28 Level of evidence and scoring of factors affecting the validity of CAESAR data from Montenegro in 2018

Level of evidence: B			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+	• The surveillance network comprises eight (100% of) laboratories of which five submitted data. • Laboratories are geographically spread within Montenegro. • The estimated coverage of the total population (622 000)[a] is 100%.
	Hospital types	+	• The network comprises tertiary (13%) and secondary (87%) care hospitals.
Sampling procedures	Selection of patients	–	• National clinical guidelines to define cases eligible for sampling are in place. • Underutilization and selective usage of blood and CSF culture diagnostics (especially in regional hospitals) are indicated by: - the small number of samples taken per 1000 patient days: mean 9, range 1–16 in the eight hospitals providing denominator data; - the large proportion (90%) of data that come from the main tertiary care centre in the capital; and - the generally high resistance percentages. *Patient characteristics of isolates from Montenegro are available in Fig. 6.5.*
	Sample size	–	• The total number of isolates is 136. • Fewer than 30 isolates are available for all pathogens except for *S. aureus*.
Laboratory procedures	AST methods	+	• The national standard for AST is EUCAST. • The main methods for AST are an automated system (reference laboratory) and disk diffusion (regional laboratories). • Not all isolates are tested for each relevant antibiotic. • Confirmatory testing of all strains suspected of carbapenemase production is performed by phenotypic methods at the reference laboratory. • Internal quality control is regularly performed in all laboratories. • All laboratories participated in the CAESAR EQA 2018.
	AST breakpoints	+	• EUCAST breakpoints are used in six out of eight laboratories (75%).

[a] Estimated population mid-2017, United Nations *(1)*.

6.5.2 Results

Fig. 6.5 shows the distribution of CAESAR microorganisms and the characteristics of patients (broken down by pathogen) of blood and CSF isolates in Montenegro in 2018. Resistance percentages for these isolates are presented in Tables 6.29–6.34.

Fig. 6.5 Patient characteristics of isolates in Montenegro in 2018, by pathogen

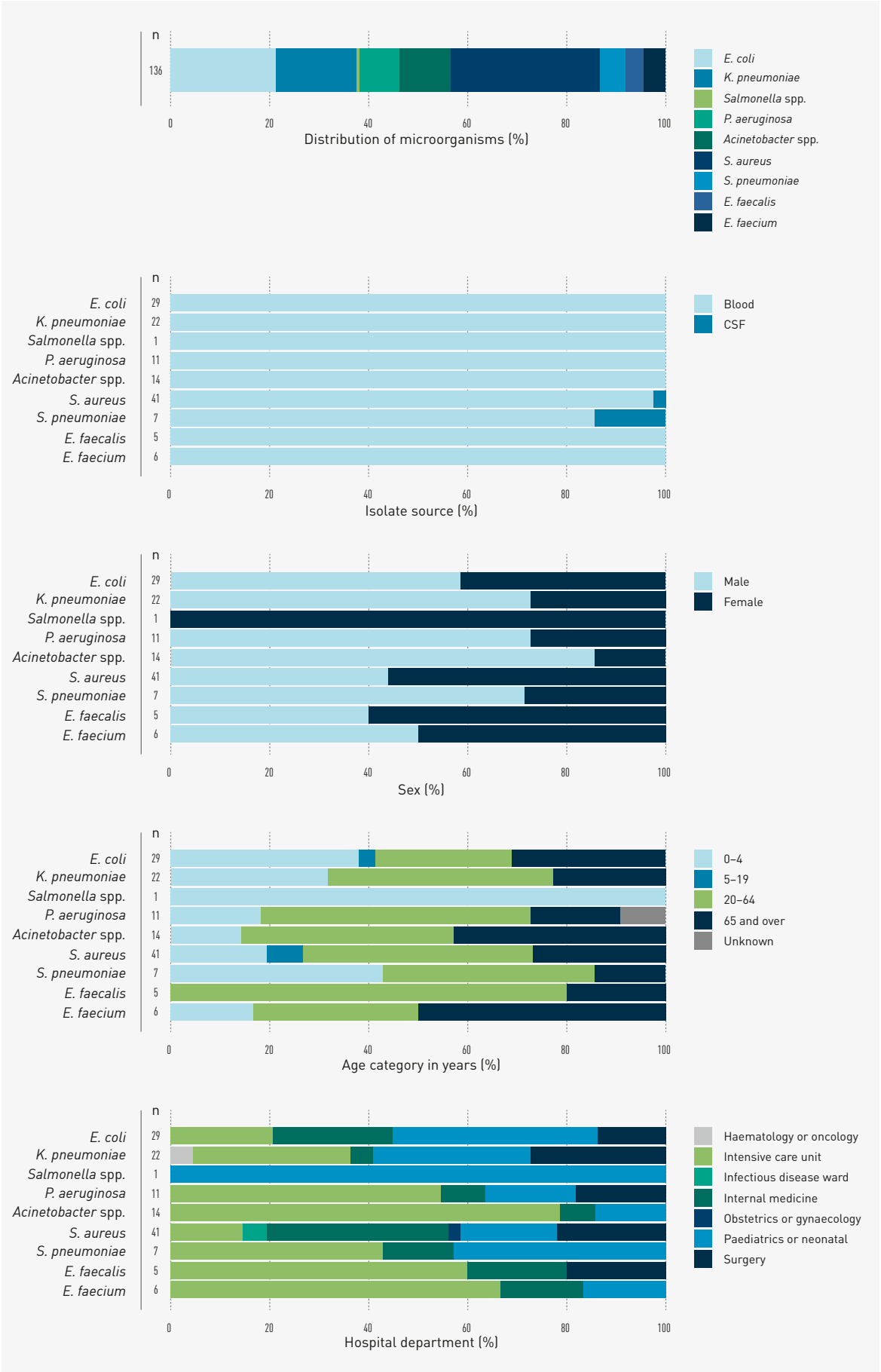


Table 6.29 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Montenegro in 2018

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	29	83*	0*	NA	NA	NA
Amoxicillin-clavulanic acid	29	55*	0*	22	91*	0*
Piperacillin-tazobactam	25	8*	20*	20	55*	15*
Cefotaxime/ceftriaxone	29	62*	0*	22	95*	0*
Ceftazidime	26	58*	0*	22	91*	5*
Ertapenem	26	8*	0*	10	10*	10*
Imipenem/meropenem	29	0*	0*	22	5*	0*
Gentamicin/tobramycin	29	52*	0*	22	91*	0*
Amikacin	28	4*	4*	22	5*	18*
Ciprofloxacin/levofloxacin/ofloxacin	29	55*	3*	22	64*	0*
Multidrug resistance[a]	29	38*	NA	22	59*	NA

NA = not applicable.

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

[a] Multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin, levofloxacin and/or ofloxacin), third-generation cephalosporins (cefotaxime, ceftriaxone and/or ceftazidime) and aminoglycosides (gentamicin and/or tobramycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.30 Resistance levels for *Salmonella* spp. among blood and CSF isolates in Montenegro in 2018

Antibiotic (group)	*Salmonella* spp.		
	N	%R	%I
Cefotaxime/ceftriaxone	1	0*	0*
Ceftazidime	0	–	–
Ertapenem	1	0*	0*
Imipenem/meropenem	1	0*	0*
Ciprofloxacin/levofloxacin	1	100*	0*

– = no data available.

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

Table 6.31 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Montenegro in 2018

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	11	73*	0*	NA	NA	NA
Ceftazidime	10	50*	0*	NA	NA	NA
Cefepime	10	60*	0*	NA	NA	NA
Imipenem/meropenem	11	64*	27*	14	86*	0*
Gentamicin/tobramycin	11	82*	0*	14	86*	0*
Amikacin	11	36*	9*	14	86*	0*
Ciprofloxacin/levofloxacin	11	91*	0*	14	86*	0*
Multidrug resistance[a]	10	90*	NA	14	86*	NA

NA = not applicable.

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

[a] For *P. aeruginosa*, multidrug resistance is defined as combined resistance to at least one representative of three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on three or more of the groups are excluded from the analysis of multidrug resistance.

For *Acinetobacter* spp., multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.32 Resistance levels for *S. aureus* among blood and CSF isolates in Montenegro in 2018

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	41	29	NA
Ciprofloxacin/levofloxacin/ofloxacin	41	17	0
Vancomycin	37	0	0
Rifampicin	29	14*	83*
Linezolid	31	0	NA

NA = not applicable.

* A small number of isolates was 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.

Table 6.33 Resistance levels for *S. pneumoniae* among blood and CSF isolates in Montenegro in 2018

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%(I+R)
Penicillin[a]	6	NA	NA	50*
Cefotaxime/ceftriaxone	6	0*	0*	NA
Levofloxacin/moxifloxacin	7	0*	0*	NA
Erythromycin/clarithromycin/azithromycin	7	29*	0*	NA
Multidrug resistance[b]	6	NA	NA	33*

NA = not applicable.

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

[a] The percentage I+R to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage I+R should be interpreted as the percentage R. For non-meningitis indications, the percentage I+R should be interpreted as the percentage of penicillin non-wild type. For this report, the term penicillin non-wild type refers to *S. pneumoniae* isolates reported by the local laboratories as I or R to penicillin, assuming MICs to penicillin above those of the wild-type, i.e. >0.06 mg/L. The analysis is based on the qualitative susceptibility categories S, I and R as quantitative susceptibility information was missing for a large proportion of the data. For laboratories using EUCAST, this approach correctly defines all penicillin non-wild type (i.e. I/R) *S. pneumoniae* isolates. However, for laboratories using the CLSI methodology, isolates within the S category for benzylpenicillin might be non-wild type since the penicillin susceptibility breakpoint for non-meningitis cases is set as ≤ 2 mg/L. Due to this limitation, the actual percentage of penicillin non-wild type *S. pneumoniae* might be higher than reported in this table.

[b] Multidrug resistance is defined as combined penicillin non-wild type and resistance (R) to macrolides (erythromycin, clarithromycin and/or azithromycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.34 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in Montenegro in 2018

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	5	0*	0*	6	100*	0*
High-level gentamicin	5	60*	0*	6	67*	0*
Vancomycin	5	0*	0*	6	50*	0*
Linezolid	5	0*	0*	6	0*	0*

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

6.5.3 Conclusion

Data from Montenegro are assessed as level B based on the following strengths and limitations regarding data quality and representativeness.

The strengths are:

- the network has good geographical and population coverage and includes various types of hospitals
- AST results seem reliable and comparable.

The limitations are:

- the representativeness of results is limited by overrepresentation of patients with treatment failure or recurrent infection in a single tertiary care hospital in the capital; and
- the small number of isolates make observed resistance percentages more sensitive to random variation (e.g. due to nosocomial outbreaks).

As a result of limitations in the data quality, 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, in the patient population sampled, resistance to third-generation cephalosporins (cefotaxime/ceftriaxone and ceftazidime), aminoglycosides (gentamicin/tobramycin) and fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin) were high in *E. coli* and *K. pneumoniae* (Table 6.29). The proportion of *K. pneumoniae* resistant to carbapenems (imipenem/meropenem) was lower than in neighbouring countries (Fig. 2.5). The high levels of resistance in *P. aeruginosa* and *Acinetobacter* spp. (although based on a small number of isolates) are concerning and may reflect the expansion of resistant clones in the health care setting (Table 6.31). The proportion of MRSA was similar to that in neighbouring countries (Table 6.32, Fig. 2.8). Too few isolates were available for *Salmonella* spp. (Table 6.30), *S. pneumoniae* (Table 6.33), *E. faecalis* and *E. faecium* (Table 6.34) to allow interpretation.

6.6 North Macedonia

6.6.1 Surveillance set-up and data quality assessment

Table 6.35 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from North Macedonia in 2018. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.35 Level of evidence and scoring of factors affecting the validity of CAESAR data from North Macedonia in 2018

Level of evidence: B			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+	• The surveillance network comprises 18 (100% of) laboratories providing blood and CSF culture diagnostics of which 11 submitted data. • Laboratories are geographically spread within North Macedonia. • The estimated coverage of the total population (2 075 000)[a] is 100%.
	Hospital types	+	• The network comprises tertiary (55%) and secondary (45%) care hospitals.
Sampling procedures	Selection of patients	–	• National clinical guidelines to define cases eligible for sampling are in place. • Underutilization and selective usage of blood and CSF culture diagnostics (especially in regional hospitals) are indicated by: - the small number of samples taken per 1000 patient days: mean 9, range 0–40 in the 32 hospitals providing denominator data; - the relatively large proportion (60%) of data that come from the main tertiary care hospital in the capital; and - generally high resistance percentages. *Patient characteristics of isolates from North Macedonia are available in Fig. 6.6.*
	Sample size	–	• The total number of isolates is 264. • Fewer than 30 isolates are available for some pathogens.
Laboratory procedures	AST methods	+	• The national standard for AST is EUCAST. • The main method for AST is a combination of semi-automated systems and disk diffusion. • Not all isolates are tested for each relevant antibiotic. • Confirmatory and additional testing for some strains is performed in two out of 18 laboratories (11%). • Internal quality control is regularly performed in 44% of laboratories. • Seventeen out of 18 laboratories participated in the CAESAR EQA in 2018.
	AST breakpoints	+	• EUCAST breakpoints are used in 17 out of 18 laboratories (94%).

[a] Estimated population mid-2017, United Nations *(1)*.

6.6.2 Results

Fig. 6.6 shows the distribution of CAESAR microorganisms and the characteristics of patients (broken down by pathogen) of blood and CSF isolates in North Macedonia in 2018. Resistance percentages for these isolates are presented in Tables 6.36–6.40.

Fig. 6.6 Patient characteristics of isolates in North Macedonia in 2018, by pathogen

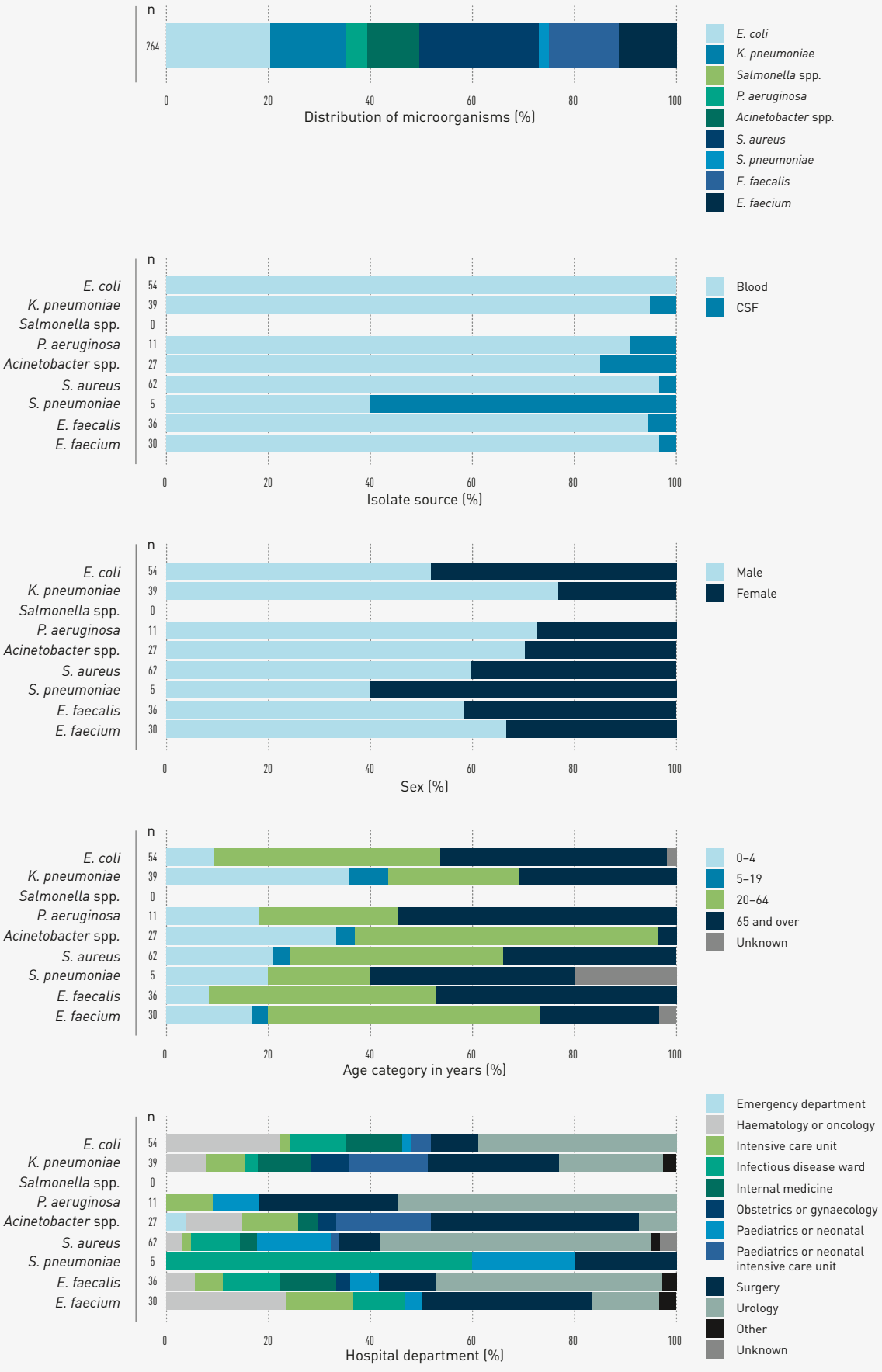


Table 6.36 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in North Macedonia in 2018

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	53	96	0	NA	NA	NA
Amoxicillin-clavulanic acid	48	75	0	37	95	0
Piperacillin-tazobactam	52	38	4	36	94	0
Cefotaxime/ceftriaxone	53	79	0	37	95	0
Ceftazidime	49	63	16	39	92	0
Ertapenem	31	3	0	23	30*	9*
Imipenem/meropenem	54	4	0	39	21	8
Gentamicin/tobramycin	53	51	2	38	89	0
Amikacin	51	6	35	37	5	22
Ciprofloxacin/levofloxacin/ofloxacin	54	74	2	39	87	0
Multidrug resistance[a]	52	40	NA	38	79	NA

NA = not applicable.

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

[a] Multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin, levofloxacin and/or ofloxacin), third-generation cephalosporins (cefotaxime, ceftriaxone and/or ceftazidime) and aminoglycosides (gentamicin and/or tobramycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.37 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in North Macedonia in 2018

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	10	0*	0*	NA	NA	NA
Ceftazidime	11	36*	0*	NA	NA	NA
Cefepime	7	29*	0*	NA	NA	NA
Imipenem/meropenem	11	9*	9*	27	78*	4*
Gentamicin/tobramycin	11	36*	0*	27	89*	0*
Amikacin	11	0*	27*	25	68*	16*
Ciprofloxacin/levofloxacin	11	27*	0*	27	96*	0*
Multidrug resistance[a]	10	20*	NA	27	74*	NA

NA = not applicable.

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

[a] For *P. aeruginosa*, multidrug resistance is defined as combined resistance to at least one representative of three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on three or more of the groups are excluded from the analysis of multidrug resistance.

For *Acinetobacter* spp., multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.38 Resistance levels for *S. aureus* among blood and CSF isolates in North Macedonia in 2018

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	61	54	NA
Ciprofloxacin/levofloxacin/ofloxacin	62	16	0
Vancomycin	56	0	0
Rifampicin	58	7	0
Linezolid	59	0	NA

NA = not applicable.

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

Table 6.39 Resistance levels for *S. pneumoniae* among blood and CSF isolates in North Macedonia in 2018

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%(I+R)
Penicillin[a]	5	NA	NA	60*
Cefotaxime/ceftriaxone	3	0*	67*	NA
Levofloxacin/moxifloxacin	4	0*	0*	NA
Erythromycin/clarithromycin/azithromycin	5	60*	0*	NA
Multidrug resistance[b]	5	NA	NA	60*

NA = not applicable.

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

[a] The percentage I+R to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage I+R should be interpreted as the percentage R. For non-meningitis indications, the percentage I+R should be interpreted as the percentage of penicillin non-wild type. For this report, the term penicillin non-wild type refers to *S. pneumoniae* isolates reported by the local laboratories as I or R to penicillin, assuming MICs to penicillin above those of the wild-type, i.e. >0.06 mg/L. The analysis is based on the qualitative susceptibility categories S, I and R as quantitative susceptibility information was missing for a large proportion of the data. For laboratories using EUCAST, this approach correctly defines all penicillin non-wild type (i.e. I/R) *S. pneumoniae* isolates. However, for laboratories using the CLSI methodology, isolates within the S category for benzylpenicillin might be non-wild type since the penicillin susceptibility breakpoint for non-meningitis cases is set as ≤ 2 mg/L. Due to this limitation, the actual percentage of penicillin non-wild type *S. pneumoniae* might be higher than reported in this table.

[b] Multidrug resistance is defined as combined penicillin non-wild type and resistance (R) to macrolides (erythromycin, clarithromycin and/or azithromycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.40 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in North Macedonia in 2018

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	34	12	6	30	93	7
High-level gentamicin	30	77	0	27	67*	0*
Vancomycin	36	3	0	30	57	0
Linezolid	32	0	0	30	0	0

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

6.6.3 Conclusion

Data from North Macedonia are assessed as level B based on the following strengths and limitations regarding data quality and representativeness.

The strengths are

- the network has good geographical and population coverage and includes various types of hospitals;
- the data represent a mix of health care associated and community-acquired infections in patients from various types of hospital departments; and
- AST results seem reliable and comparable.

The limitations are:

- the representativeness of results is limited by overrepresentation of patients with treatment failure or recurrent infection; and
- the small number of isolates make resistance proportions more sensitive to random variation (e.g. due to nosocomial outbreaks).

As a result of limitations in the data quality, the reported percentages of resistance should be interpreted with caution and are not necessarily generalizable to any one patient presenting with invasive infection in North 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* (Table 6.36). Resistance in *P. aeruginosa*, although based on a small number of isolates, was moderately high (Table 6.37). The proportion of MRSA was concerning and higher than that in most neighbouring countries (Table 6.38, Fig. 2.8). The high levels of resistance in *Acinetobacter* spp. (Table 6.37) and *E. faecium* (Table 6.40) are concerning and may reflect the dissemination of resistant clones in the health care setting. Too few antibiotic susceptibility testing results for *Salmonella* spp. (no isolates) and *S. pneumoniae* (Table 6.39) were available to allow interpretation.

6.7 Russian Federation

6.7.1. Surveillance set-up and data quality assessment

Table 6.41 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from the Russian Federation in 2018. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.41 Level of evidence and scoring of factors affecting the validity of CAESAR data from the Russian Federation in 2018

Level of evidence: B			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+	• The surveillance network comprises 46 (1% of) laboratories of which 30 submitted data. • Laboratories are geographically spread within the western part of the Russian Federation. • The estimated coverage of the total population (143 507 000)[a] is not available.
	Hospital types	–	• The network comprises tertiary (96%) and secondary (4%) care hospitals.
Sampling procedures	Selection of patients	–	• National clinical guidelines to define cases eligible for sampling are being implemented. • Underutilization and selective usage of blood and CSF culture diagnostics in some hospitals are indicated by: - the small number of samples taken per 1000 patient days in some hospitals: mean 16, range 1–86 in the 17 hospitals providing denominator data; - the large proportion of isolates from intensive care units (66%); and - the relatively large proportion of nosocomial pathogens (15% *Acinetobacter* spp., 32% *K. pneumoniae*), small proportion of *E. coli* (15%) and no isolates of *S. pneumoniae*. *Patient characteristics of isolates from the Russian Federation are available in Fig. 6.7.*
	Sample size	+/–	• The total number of isolates is 536. • Fewer than 30 isolates are available for some pathogens.
Laboratory procedures	AST methods	+	• The national standard for AST is based on EUCAST methodology. • For all submitted isolates, species identification and AST were performed at the national reference laboratory, using EUCAST guidelines. • The method for AST at the reference laboratory is broth microdilution. • Confirmatory testing and additional characterization of exceptional phenotypes is performed at the reference laboratory. • Internal quality control is regularly performed in all laboratories. • Thirty-three laboratories participated in the CAESAR EQA in 2018.
	AST breakpoints	+	• EUCAST breakpoints are used at the reference laboratory. • EUCAST breakpoints are used in most laboratories for disk diffusion, but only partly in automated testing.

[a] Estimated population mid-2013, United Nations *(1)*.

6.7.2 Results

Fig. 6.7 shows the distribution of CAESAR microorganisms and the characteristics of patients (broken down by pathogen) of blood and CSF isolates in the Russian Federation in 2018. Resistance percentages for these isolates are presented in Tables 6.42–6.45.

Fig. 6.7 Patient characteristics of isolates in the Russian Federation in 2018, by pathogen

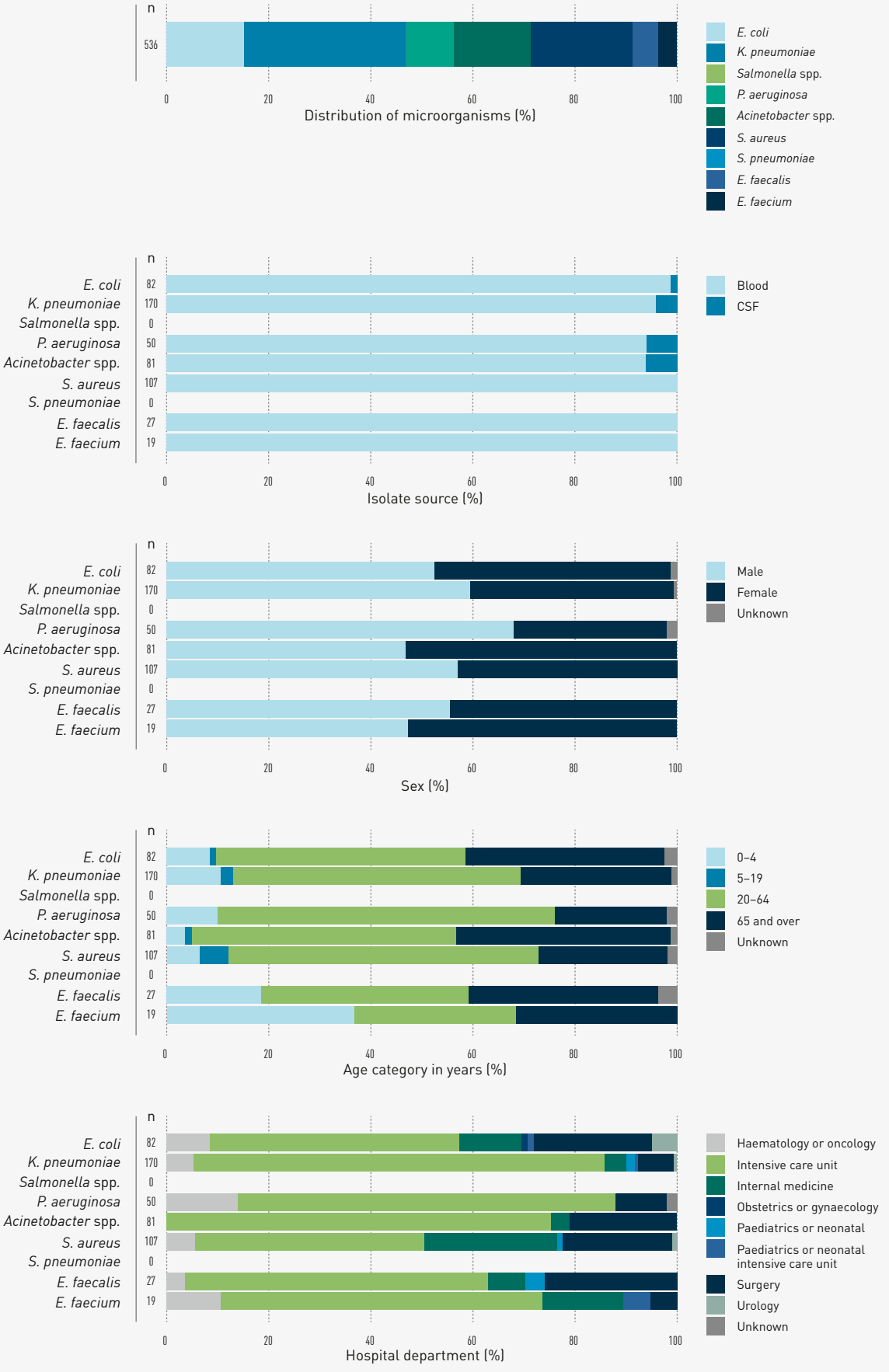


Table 6.42 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in the Russian Federation in 2018

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	82	88	0	NA	NA	NA
Amoxicillin-clavulanic acid	82	73	0	170	91	0
Piperacillin-tazobactam	82	16	2	170	79	4
Cefotaxime/ceftriaxone	82	66	0	170	84	4
Ceftazidime	82	39	23	170	79	3
Ertapenem	82	1	0	170	69	0
Imipenem/meropenem	82	0	0	170	31	25
Gentamicin/tobramycin	82	32	1	170	84	1
Amikacin	82	0	2	170	54	4
Ciprofloxacin/levofloxacin/ofloxacin	82	62	2	170	87	1
Multidrug resistance[a]	82	23	NA	170	75	NA

NA = not applicable.

[a] Multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin, levofloxacin and/or ofloxacin), third-generation cephalosporins (cefotaxime, ceftriaxone and/or ceftazidime) and aminoglycosides (gentamicin and/or tobramycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.43 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in the Russian Federation in 2018

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	49	41	0	NA	NA	NA
Ceftazidime	49	39	0	NA	NA	NA
Cefepime	50	32	0	NA	NA	NA
Imipenem/meropenem	49	53	4	81	79	11
Gentamicin/tobramycin	49	37	0	81	89	0
Amikacin	49	24	10	81	89	1
Ciprofloxacin/levofloxacin	49	43	0	81	98	0
Multidrug resistance[a]	49	41	NA	81	70	NA

NA = not applicable.

[a] For *P. aeruginosa*, multidrug resistance is defined as combined resistance to at least one representative of three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on three or more of the groups are excluded from the analysis of multidrug resistance.

For *Acinetobacter* spp., multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.44 Resistance levels for *S. aureus* among blood and CSF isolates in the Russian Federation in 2018

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	107	14	NA
Ciprofloxacin/levofloxacin/ofloxacin	107	17	0
Vancomycin	107	0	0
Rifampicin	107	2	0
Linezolid	107	0	NA

NA = not applicable.

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

Table 6.45 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in the Russian Federation in 2018

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	27	0*	0*	19	100*	0*
High-level gentamicin	27	41*	0*	19	89*	0*
Vancomycin	27	0*	0*	19	11*	0*
Linezolid	27	0*	0*	19	0*	0*

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

6.7.3 Conclusion

Data from the Russian Federation are assessed as level B based on the following strengths and limitations regarding data quality and representativeness.

The strengths are:

- the network has good geographical coverage of the western part of the country
- AST results are reliable and comparable, as all isolates were (re)tested at the reference laboratory.

The limitations are:

- the representativeness of results is limited by overrepresentation of severely ill and pretreated patients with hospital-acquired infections in tertiary care hospitals; and
- the small number of isolates make observed resistance percentages more sensitive to random variation, such as due to nosocomial outbreaks.

As a result of limitations in the data quality, 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 Russian Federation, especially patients with community-acquired infections.

Nevertheless, in the patient population sampled, resistance to third-generation cephalosporins (cefotaxime/ceftriaxone and ceftazidime), aminoglycosides (gentamicin/tobramycin) and fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin) was high in *E. coli*, and very high in *K. pneumoniae* (Table 6.42). In *K. pneumoniae* in addition, high levels of resistance to carbapenems (imipenem/meropenem) were observed. Resistance in *P. aeruginosa* was moderate to high, especially for carbapenems (imipenem/meropenem, Table 6.43). The high percentages of resistance in *Acinetobacter* spp. are concerning and may reflect dissemination of resistant clones in the health care setting (Table 6.43). The proportion of MRSA was moderate and similar to that in surrounding countries (Table 6.44, Fig. 2.8). In *E. faecium*, vancomycin resistance was moderately low (although based on a small number of isolates, Table 6.45). There were no isolates of *Salmonella* spp. and *S. pneumoniae*.

6.8 Serbia

6.8.1 Surveillance set-up and data quality assessment

Table 6.46 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from Serbia in 2018. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.46 Level of evidence and scoring of factors affecting the validity of CAESAR data from Serbia in 2018

Level of evidence: A			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+	• The surveillance network comprises 24 (78% of) laboratories, all of which submitted data. • Laboratories are geographically spread within Serbia. • The estimated coverage of the total population (7 021 000)[a] is 78%.
	Hospital types	+	• The network comprises tertiary (37%) and secondary (63%) care hospitals.
Sampling procedures	Selection of patients	+/–	• Clinical guidelines to define cases eligible for sampling are not in place. • Underutilization and selective usage of blood and CSF culture diagnostics in some hospitals are indicated by: - the small number of samples taken per 1000 patient days in some hospitals: mean 17, range 1–85 in the 24 hospitals providing denominator data; and - the relatively large proportion of nosocomial pathogens (19% *Acinetobacter* spp., 18% *K. pneumoniae*, 17% *Enterococcus* spp.). *Patient characteristics of isolates from Serbia are available in Fig. 6.8.*
	Sample size	+	• The total number of isolates is 2764. • At least 30 isolates are available for all pathogens except for *Salmonella* spp.
Laboratory procedures	AST methods	+	• The national standard for AST is EUCAST. • The main methods for AST are disk diffusion (most laboratories) and a combination of a semi-automated system and disk diffusion. • Not all isolates are tested for each relevant antibiotic. • Confirmatory testing of highly resistant microorganisms is performed at the reference laboratory on a voluntary basis. • Quality management systems are in place in all laboratories. • All laboratories participated in the CAESAR EQA in 2018.
	AST breakpoints	+	• EUCAST breakpoints are used in all laboratories.

[a] Annual average population in 2017, based on results of 2011 population census, United Nations *(1)*.

6.8.2 Results

Fig. 6.8 shows the distribution of CAESAR microorganisms and the characteristics of patients (broken down by pathogen) of blood and CSF isolates in Serbia in 2018. Resistance percentages for these isolates are presented in Tables 6.47–6.52.

Fig. 6.8 Patient characteristics of isolates in Serbia in 2018, by pathogen

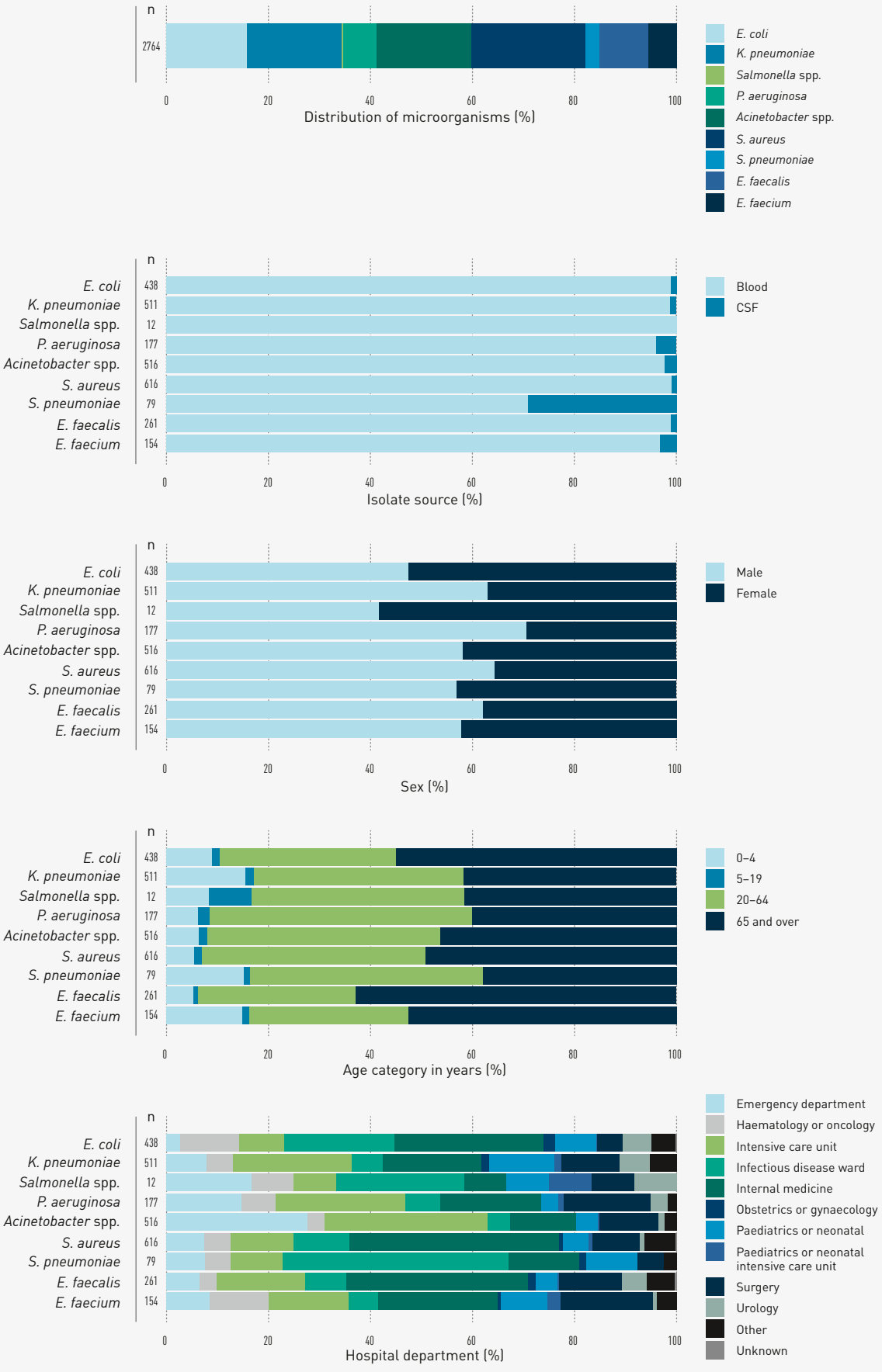


Table 6.47 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Serbia in 2018

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	416	67	0	NA	NA	NA
Amoxicillin-clavulanic acid	289	33	0	326	84	0
Piperacillin-tazobactam	425	9	2	455	77	3
Cefotaxime/ceftriaxone	431	28	0	478	85	1
Ceftazidime	420	21	5	436	83	1
Ertapenem	404	2	0	399	53	0
Imipenem/meropenem	437	1	0	511	36	5
Gentamicin/tobramycin	432	28	5	502	70	4
Amikacin	431	5	12	499	37	17
Ciprofloxacin/levofloxacin/ofloxacin	436	39	4	509	73	6
Multidrug resistance[a]	429	17	NA	500	59	NA

NA = not applicable.

[a] Multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin, levofloxacin and/or ofloxacin), third-generation cephalosporins (cefotaxime, ceftriaxone and/or ceftazidime) and aminoglycosides (gentamicin and/or tobramycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.48 Resistance levels for *Salmonella* spp. among blood and CSF isolates in Serbia in 2018

Antibiotic (group)	*Salmonella* spp.		
	N	%R	%I
Cefotaxime/ceftriaxone	11	0*	0*
Ceftazidime	10	0*	0*
Ertapenem	11	0*	0*
Imipenem/meropenem	11	0*	0*
Ciprofloxacin/levofloxacin	12	0*	0*

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

Table 6.49 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Serbia in 2018

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	176	52	0	NA	NA	NA
Ceftazidime	176	57	0	NA	NA	NA
Cefepime	169	55	0	NA	NA	NA
Imipenem/meropenem	177	56	2	516	96	0
Gentamicin/tobramycin	177	59	0	516	93	0
Amikacin	177	40	12	443	91	2
Ciprofloxacin/levofloxacin	177	59	0	515	97	2
Multidrug resistance[a]	175	56	NA	515	92	NA

NA = not applicable.

[a] For *P. aeruginosa*, multidrug resistance is defined as combined resistance to at least one representative of three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on three or more of the groups are excluded from the analysis of multidrug resistance.

For *Acinetobacter* spp., multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.50 Resistance levels for *S. aureus* among blood and CSF isolates in Serbia in 2018

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	612	29	NA
Ciprofloxacin/levofloxacin/ofloxacin	616	23	0
Vancomycin	588	0	0
Rifampicin	530	15	2
Linezolid	594	0	NA

NA = not applicable.

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

Table 6.51 Resistance levels for *S. pneumoniae* among blood and CSF isolates in Serbia in 2018

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%(I+R)
Penicillin[a]	77	NA	NA	32
Cefotaxime/ceftriaxone	76	0	14	NA
Levofloxacin/moxifloxacin	78	1	0	NA
Erythromycin/clarithromycin/azithromycin	74	27	0	NA
Multidrug resistance[b]	72	NA	NA	22

NA = not applicable.

[a] The percentage I+R to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage I+R should be interpreted as the percentage R. For non-meningitis indications, the percentage I+R should be interpreted as the percentage of penicillin non-wild type. For this report, the term penicillin non-wild type refers to *S. pneumoniae* isolates reported by the local laboratories as I or R to penicillin, assuming MICs to penicillin above those of the wild-type, i.e. >0.06 mg/L. The analysis is based on the qualitative susceptibility categories S, I and R as quantitative susceptibility information was missing for a large proportion of the data. For laboratories using EUCAST, this approach correctly defines all penicillin non-wild type (i.e. I/R) *S. pneumoniae* isolates. However, for laboratories using the CLSI methodology, isolates within the S category for benzylpenicillin might be non-wild type since the penicillin susceptibility breakpoint for non-meningitis cases is set as ≤ 2 mg/L. Due to this limitation, the actual percentage of penicillin non-wild type *S. pneumoniae* might be higher than reported in this table.

[b] Multidrug resistance is defined as combined penicillin non-wild type and resistance (R) to macrolides (erythromycin, clarithromycin and/or azithromycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.52 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in Serbia in 2018

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	261	5	0	154	90	1
High-level gentamicin	255	65	0	147	84	0
Vancomycin	261	5	0	154	54	0
Linezolid	255	0	0	153	1	0

6.8.3 Conclusion

Data from Serbia are assessed as level A based on the following strengths and limitations regarding data quality and representativeness.

The strengths are:

- the network has good geographical and population coverage and includes various types of hospitals
- the number of isolates is large
- AST results seem reliable and comparable.

The limitation is:

- the representativeness of results is limited by overrepresentation of patients with hospital-acquired infections.

The significant amount of high-quality antibiotic susceptibility test data from a geographically representative network including samples from a variety of patients adequately assesses the trends of AMR in the country. However, the magnitude of resistance should be interpreted with caution as the data suggest disproportionate sampling of nosocomial infections in severely ill and pretreated patients.

Moderately high resistance was found for third-generation cephalosporins (cefotaxime/ceftriaxone and ceftazidime), aminoglycosides (gentamicin/tobramycin) and fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin) in *E. coli* (Table 6.47). High levels of resistance, including carbapenem (imipenem/meropenem) resistance, were seen in *K. pneumoniae* (Table 6.47). The proportion of MRSA was similar to that in neighbouring countries (Table 6.50, Fig. 2.8). In *S. pneumoniae*, high levels of resistance were found for penicillin and macrolides (erythromycin/clarithromycin/azithromycin, Table 6.51). The high percentages of resistance in *P. aeruginosa*, *Acinetobacter* spp. (Table 6.49) and *E. faecium* (Table 6.52) are concerning and may reflect the dissemination of resistant clones in the health care setting.

6.9 Switzerland

6.9.1 Surveillance set-up and data quality assessment

Table 6.53 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from Switzerland in 2018. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.53 Level of evidence and scoring of factors affecting the validity of CAESAR data from Switzerland in 2018

Level of evidence: A			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+	• The surveillance network comprises 29 laboratories, all of which submitted data. • Laboratories are geographically spread within Switzerland. • The estimated coverage of the total population (8 420 000)[a] is 87% of hospitalized patients and >30% of ambulatory practitioners' patients.
	Hospital types	+	• The network comprises tertiary (5%), secondary (12%) and primary (83%) care hospitals.
Sampling procedures	Selection of patients	+	• Clinical guidelines to define cases eligible for sampling are in place. • There are no indications for underutilization and selective usage of blood and CSF culture diagnostics. *Patient characteristics of isolates from Switzerland are available in Fig. 6.9.*
	Sample size	+	• The total number of isolates is 11 518. • At least 30 isolates are available for all pathogens.
Laboratory procedures	AST methods	+	• There is no national standard for AST. • The main method for AST is a semi-automated system (most laboratories). • Not all isolates are tested for each relevant antibiotic. • Confirmatory testing of exceptional phenotypes is performed locally or at an expert laboratory. • Quality management systems are in place in all laboratories. • All laboratories participate in at least one national or international EQA programme (not the CAESAR EQA).
	AST breakpoints	+	• EUCAST breakpoints are used in 28 out of 29 laboratories (97%).

[a] Estimated population 1 January 2017, United Nations *(1)*.

6.9.2 Results

Fig. 6.9 shows the distribution of CAESAR microorganisms and the characteristics of patients (broken down by pathogen) of blood and CSF isolates in Switzerland in 2018. Resistance percentages for these isolates are presented in Tables 6.54–6.59.

Fig. 6.9 Patient characteristics of isolates in Switzerland in 2018, by pathogen

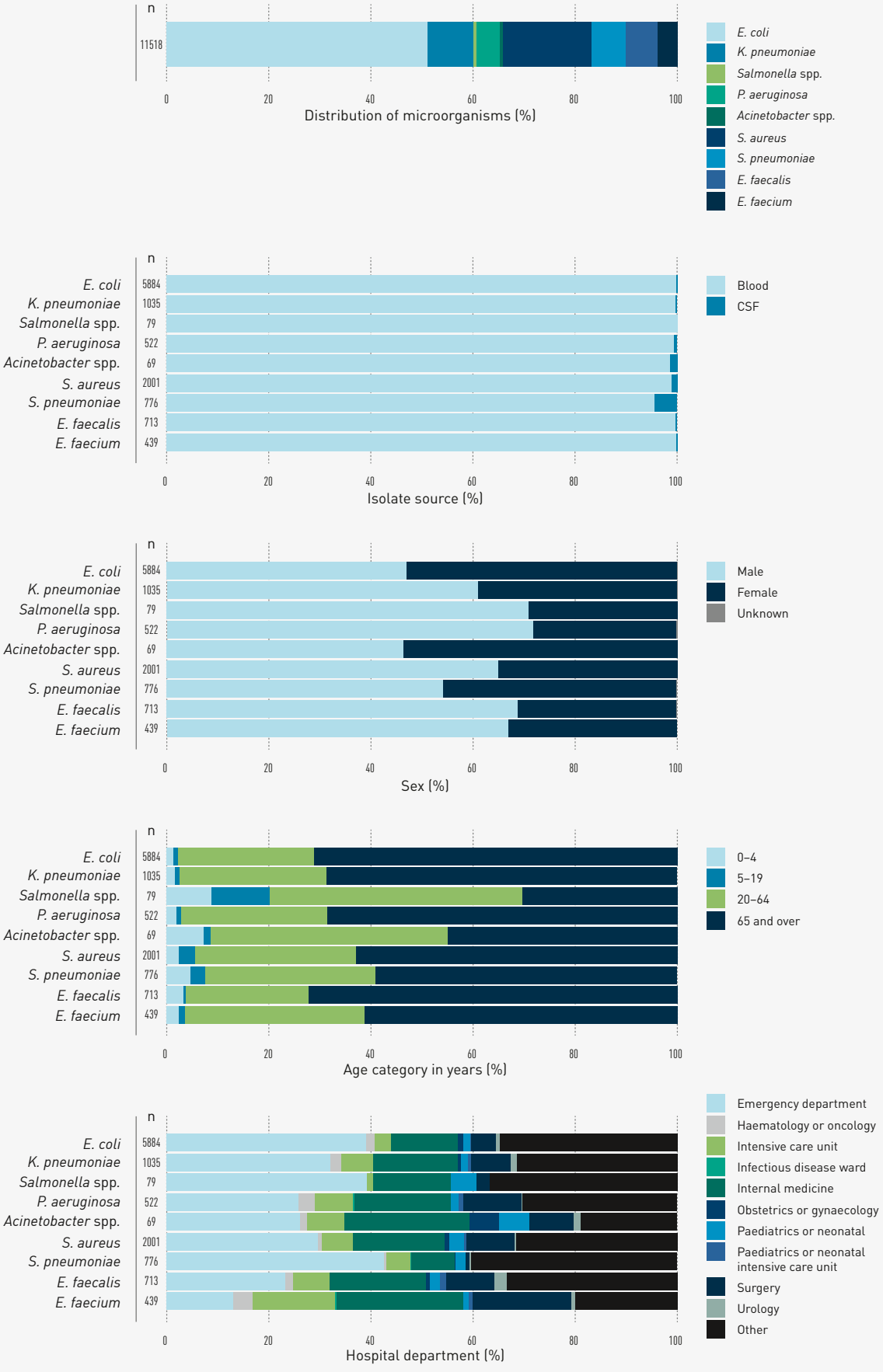


Table 6.54 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Switzerland in 2018

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	5581	49	1	NA	NA	NA
Amoxicillin-clavulanic acid	5869	24	5	1033	12	3
Piperacillin-tazobactam	5648	5	3	986	7	6
Cefotaxime/ceftriaxone	5856	10	0	1031	9	0
Ceftazidime	5772	7	3	1021	8	1
Ertapenem	3993	0	0	709	2	0
Imipenem/meropenem	5860	0	0	1033	1	0
Gentamicin/tobramycin	5851	9	0	1033	6	0
Amikacin	4289	2	1	760	1	1
Ciprofloxacin/levofloxacin/ofloxacin	5880	18	2	1033	11	2
Multidrug resistance[a]	5848	3	NA	1030	4	NA

NA = not applicable.

[a] Multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin, levofloxacin and/or ofloxacin), third-generation cephalosporins (cefotaxime, ceftriaxone and/or ceftazidime) and aminoglycosides (gentamicin and/or tobramycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.55 Resistance levels for *Salmonella* spp. among blood and CSF isolates in Switzerland in 2018

Antibiotic (group)	*Salmonella* spp.		
	N	%R	%I
Cefotaxime/ceftriaxone	79	0	0
Ceftazidime	67	0	0
Ertapenem	46	0	0
Imipenem/meropenem	54	0	0
Ciprofloxacin/levofloxacin	74	14	3

Table 6.56 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Switzerland in 2018

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	510	12	0	NA	NA	NA
Ceftazidime	490	9	0	NA	NA	NA
Cefepime	501	9	1	NA	NA	NA
Imipenem/meropenem	522	9	3	69	3	1
Gentamicin/tobramycin	522	4	0	65	5	0
Amikacin	486	2	2	60	5	2
Ciprofloxacin/levofloxacin	519	11	0	69	3	0
Multidrug resistance[a]	478	7	NA	65	3	NA

NA = not applicable.

[a] For *P. aeruginosa*, multidrug resistance is defined as combined resistance to at least one representative of three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on three or more of the groups are excluded from the analysis of multidrug resistance.

For *Acinetobacter* spp., multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.57 Resistance levels for *S. aureus* among blood and CSF isolates in Switzerland in 2018

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	1689	5	NA
Ciprofloxacin/levofloxacin/ofloxacin	1999	6	1
Vancomycin	1776	0	0
Rifampicin	1937	1	0
Linezolid	842	0	NA

NA = not applicable.

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

Table 6.58 Resistance levels for *S. pneumoniae* among blood and CSF isolates in Switzerland in 2018

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%(I+R)
Penicillin[a]	732	NA	NA	6
Cefotaxime/ceftriaxone	511	0	1	NA
Levofloxacin/moxifloxacin	554	0	0	NA
Erythromycin/clarithromycin/azithromycin	628	10	0	NA
Multidrug resistance[b]	588	NA	NA	4

NA = not applicable.

[a] The percentage I+R to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage I+R should be interpreted as the percentage R. For non-meningitis indications, the percentage I+R should be interpreted as the percentage of penicillin non-wild type. For this report, the term penicillin non-wild type refers to *S. pneumoniae* isolates reported by the local laboratories as I or R to penicillin, assuming MICs to penicillin above those of the wild-type, i.e. >0.06 mg/L. The analysis is based on the qualitative susceptibility categories S, I and R as quantitative susceptibility information was missing for a large proportion of the data. For laboratories using EUCAST, this approach correctly defines all penicillin non-wild type (i.e. I/R) *S. pneumoniae* isolates. However, for laboratories using the CLSI methodology, isolates within the S category for benzylpenicillin might be non-wild type since the penicillin susceptibility breakpoint for non-meningitis cases is set as ≤ 2 mg/L. Due to this limitation, the actual percentage of penicillin non-wild type *S. pneumoniae* might be higher than reported in this table.

[b] Multidrug resistance is defined as combined penicillin non-wild type and resistance (R) to macrolides (erythromycin, clarithromycin and/or azithromycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.59 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in Switzerland in 2018

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	672	0	0	369	78	1
High-level gentamicin	276	5	0	179	33	0
Vancomycin	709	0	0	438	3	0
Linezolid	456	1	0	254	0	0

6.9.3 Conclusion

Data from Switzerland are assessed as level A based on the following strengths regarding data quality and representativeness.

The strengths are:

- the network has good geographical and population coverage and includes various types of hospitals;
- the data represent a mix of health care-associated and community-acquired infections in patients from various types of hospital departments, with no indications for selective sampling of patients;
- the number of isolates is large; and
- AST results seem reliable and comparable.

The significant amount of high-quality antibiotic susceptibility test data from a geographically representative network including samples from a variety of patients adequately assesses the trends and magnitude of AMR in the country.

Resistance levels for most pathogen–antibiotic combinations were low to moderate and comparable with those in countries close to Switzerland (Chapter 2). In *E. coli* and *K. pneumoniae*, resistance to third-generation cephalosporins (cefotaxime/ceftriaxone and ceftazidime) was moderately low, and resistance to carbapenems (imipenem/meropenem) was low (Table 6.54). MRSA was observed less frequently than in neighbouring countries (Table 6.57, Fig. 2.8).

6.10 Turkey

6.10.1 Surveillance set-up and data quality assessment

Table 6.60 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from Turkey in 2018. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.60 Level of evidence and scoring of factors affecting the validity of CAESAR data from Turkey in 2018

Level of evidence: A			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+	• The surveillance network comprises 120 laboratories (15% of laboratories with surveillance capacity) of which 67 submitted data. • Laboratories are geographically spread within Turkey. • The estimated coverage of the total population (80 313 000)[a] is 28%.
	Hospital types	+	• The network comprises tertiary (76%) and secondary (24%) care hospitals.
Sampling procedures	Selection of patients	+/–	• National clinical guidelines to define cases eligible for sampling are in place. • Underutilization and selective usage of blood and CSF culture diagnostics in some hospitals are indicated by: - the small number of samples taken per 1000 patient days in some hospitals: mean 36, range 4–110; and - the relatively large proportion of nosocomial pathogens (13% *Acinetobacter* spp., 19% *K. pneumoniae*, 17% *Enterococcus* spp.). *Patient characteristics of isolates from Turkey are available in Fig. 6.10.*
	Sample size	+	• The total number of isolates is 20 660. • At least 30 isolates are available for all pathogens except for *Salmonella* spp.
Laboratory procedures	AST methods	+	• The national standard for AST is EUCAST. • The main methods for AST are a semi-automated system (47 out of 67 laboratories that submitted data), a combination of a semi-automated system and disk diffusion (12 laboratories) and a combination of disk diffusion and gradient strip tests (eight laboratories). • Not all isolates are tested for each relevant antibiotic. • Confirmatory testing of exceptional phenotypes is performed at the reference laboratory. • Internal quality control is regularly performed in all laboratories. • Fifty-three laboratories that submitted data participated in the CAESAR EQA in 2018.
	AST breakpoints	+	• EUCAST breakpoints are used in all laboratories.

[a] Estimated population mid-2017, United Nations *(1)*.

6.10.2 Results

Fig. 6.10 shows the distribution of CAESAR microorganisms and the characteristics of patients (broken down by pathogen) of blood and CSF isolates in Turkey in 2018. Resistance percentages for these isolates are presented in Tables 6.61–6.66.

Fig. 6.10 Patient characteristics of isolates in Turkey in 2018, by pathogen

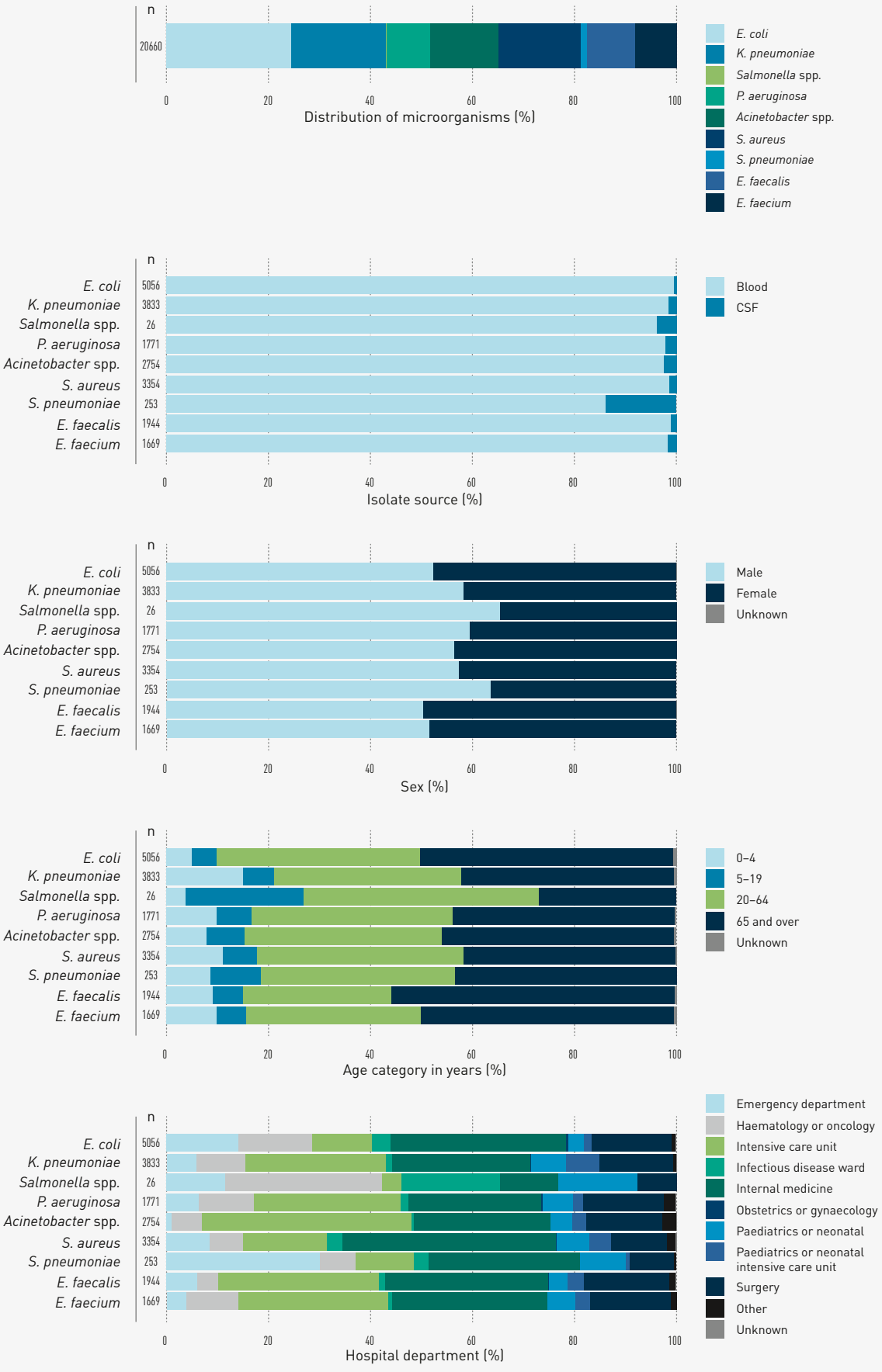


Table 6.61 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Turkey in 2018

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	4154	77	0	NA	NA	NA
Amoxicillin-clavulanic acid	3973	62	0	2872	76	0
Piperacillin-tazobactam	4564	21	4	3492	60	7
Cefotaxime/ceftriaxone	4721	52	1	3542	71	1
Ceftazidime	4474	43	8	3413	69	3
Ertapenem	4433	7	0	3329	50	0
Imipenem/meropenem	4759	3	2	3641	34	7
Gentamicin/tobramycin	4785	24	2	3632	46	2
Amikacin	4795	2	5	3669	23	5
Ciprofloxacin/levofloxacin/ofloxacin	4606	52	7	3557	63	6
Multidrug resistance[a]	4477	18	NA	3442	40	NA

NA = not applicable.

[a] Multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin, levofloxacin and/or ofloxacin), third-generation cephalosporins (cefotaxime, ceftriaxone and/or ceftazidime) and aminoglycosides (gentamicin and/or tobramycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.62 Resistance levels for *Salmonella* spp. among blood and CSF isolates in Turkey in 2018

Antibiotic (group)	*Salmonella* spp.		
	N	%R	%I
Cefotaxime/ceftriaxone	23	0*	0*
Ceftazidime	19	0*	0*
Ertapenem	13	0*	0*
Imipenem/meropenem	17	0*	0*
Ciprofloxacin/levofloxacin	4	25*	0*

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

Table 6.63 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Turkey in 2018

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	1646	34	0	NA	NA	NA
Ceftazidime	1700	27	0	NA	NA	NA
Cefepime	1641	28	0	NA	NA	NA
Imipenem/meropenem	1682	38	3	2643	92	0
Gentamicin/tobramycin	1730	19	0	2704	79	0
Amikacin	1690	12	5	2619	69	4
Ciprofloxacin/levofloxacin	1674	33	0	2575	94	2
Multidrug resistance[a]	1451	28	NA	2526	79	NA

NA = not applicable.

[a] For *P. aeruginosa*, multidrug resistance is defined as combined resistance to at least one representative of three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on three or more of the groups are excluded from the analysis of multidrug resistance.

For *Acinetobacter* spp., multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.64 Resistance levels for *S. aureus* among blood and CSF isolates in Turkey in 2018

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	3316	30	NA
Ciprofloxacin/levofloxacin/ofloxacin	3005	14	0
Vancomycin	3008	0	0
Rifampicin	296	24	5
Linezolid	3239	0	NA

NA = not applicable.

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

Table 6.65 Resistance levels for *S. pneumoniae* among blood and CSF isolates in Turkey in 2018

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%(I+R)
Penicillin[a]	243	NA	NA	44
Cefotaxime/ceftriaxone	184	5	15	NA
Levofloxacin/moxifloxacin	229	7	0	NA
Erythromycin/clarithromycin/azithromycin	217	37	0	NA
Multidrug resistance[b]	211	NA	NA	28

NA = not applicable.

[a] The percentage I+R to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage I+R should be interpreted as the percentage R. For non-meningitis indications, the percentage I+R should be interpreted as the percentage of penicillin non-wild type. For this report, the term penicillin non-wild type refers to *S. pneumoniae* isolates reported by the local laboratories as I or R to penicillin, assuming MICs to penicillin above those of the wild-type, i.e. >0.06 mg/L. The analysis is based on the qualitative susceptibility categories S, I and R as quantitative susceptibility information was missing for a large proportion of the data. For laboratories using EUCAST, this approach correctly defines all penicillin non-wild type (i.e. I/R) *S. pneumoniae* isolates. However, for laboratories using the CLSI methodology, isolates within the S category for benzylpenicillin might be non-wild type since the penicillin susceptibility breakpoint for non-meningitis cases is set as ≤ 2 mg/L. Due to this limitation, the actual percentage of penicillin non-wild type *S. pneumoniae* might be higher than reported in this table.

[b] Multidrug resistance is defined as combined penicillin non-wild type and resistance (R) to macrolides (erythromycin, clarithromycin and/or azithromycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.66 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in Turkey in 2018

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	1866	4	1	1580	86	4
High-level gentamicin	1337	37	0	1208	55	0
Vancomycin	1815	1	0	1570	14	0
Linezolid	1851	0	0	1598	0	0

6.10.3 Conclusion

Data from Turkey are assessed as level A based on the following strengths and limitation regarding data quality and representativeness.

The strengths are:

- the network has good geographical coverage and includes various types of hospitals
- the data represent a mix of health care-associated and community-acquired infections
- the number of isolates is large
- AST results seem reliable and comparable.

The limitation is:

- the representativeness of results is limited by overrepresentation of severely ill patients with hospital-acquired infections in tertiary care hospitals.

The significant amount of high-quality antibiotic susceptibility test data from a geographically representative network including samples from a variety of patients adequately assesses the trends of AMR in the country. However, the magnitude of resistance should be interpreted with caution as the data suggest disproportionate sampling of nosocomial infections in severely ill and pretreated patients.

In *E. coli* and *K. pneumoniae*, high levels of resistance to third-generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime) and fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin) were observed (Table 6.61). In *K. pneumoniae* in addition, high levels of resistance to carbapenems (imipenem/meropenem) were observed. The high levels of resistance in *Acinetobacter* spp. (Table 6.63) are concerning and likely reflect the dissemination of resistant clones in the health care setting. The proportion of MRSA was similar to that in neighbouring countries (Table 6.64, Fig. 2.8). In *S. pneumoniae*, high levels of resistance were found for penicillin and macrolides (erythromycin/clarithromycin/azithromycin (Table 6.65). Resistance in *P. aeruginosa* was moderately high in general (Table 6.63), as was vancomycin resistance in *E. faecium* (Table 6.66).

6.11 Ukraine

6.11.1 Surveillance set-up and data quality assessment

Table 6.67 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from Ukraine in 2018. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.67 Level of evidence and scoring of factors affecting the validity of CAESAR data from Ukraine in 2018

Level of evidence: B			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+/–	• The surveillance network comprises five (0.6% of) laboratories of which four submitted data. • Laboratories are located in three different regions of Ukraine. • The estimated coverage of the total population (42 316000)[a] is 0.45%.
	Hospital types	–	• The network comprises tertiary care hospitals.
Sampling procedures	Selection of patients	–	• National clinical guidelines to define cases eligible for sampling are in place. • Underutilization and selective usage of blood and CSF culture diagnostics (especially in regional hospitals) are indicated by: - the small number of samples per 1000 patient days: mean 8, range 3–12 in the three hospitals providing denominator data; - the large proportion of isolates from intensive care units (41%); - the relatively large proportion of nosocomial pathogens (19% *Acinetobacter* spp., 25% *K. pneumoniae*); and - generally high resistance percentages. *Patient characteristics of isolates from Ukraine are available in Fig. 6.11.*
	Sample size	–	• The total number of isolates is 155. • Fewer than 30 isolates are available for all pathogens except for *K. pneumoniae*.
Laboratory procedures	AST methods	+	• The national standard for AST is EUCAST. • The main methods for AST are a combination of a semi-automated system and disk diffusion (four laboratories) and disk diffusion only (one laboratory). • Not all isolates are tested for each relevant antibiotic. • Confirmatory testing of exceptional phenotypes or highly resistant microorganisms is performed by some laboratories and at the reference laboratory. • Quality management systems are in place in all laboratories. • All laboratories participated in the CAESAR EQA in 2018.
	AST breakpoints	+	• EUCAST breakpoints are used in all laboratories.

[a] Estimated population mid-2017, United Nations *(1)*.

6.11.2 Results

Fig. 6.11 shows the distribution of CAESAR microorganisms and the characteristics of patients (broken down by pathogen) of blood and CSF isolates in Ukraine in 2018. Resistance percentages for these isolates are presented in Tables 6.68–6.72.

Fig. 6.11 Patient characteristics of isolates in Ukraine in 2018, by pathogen

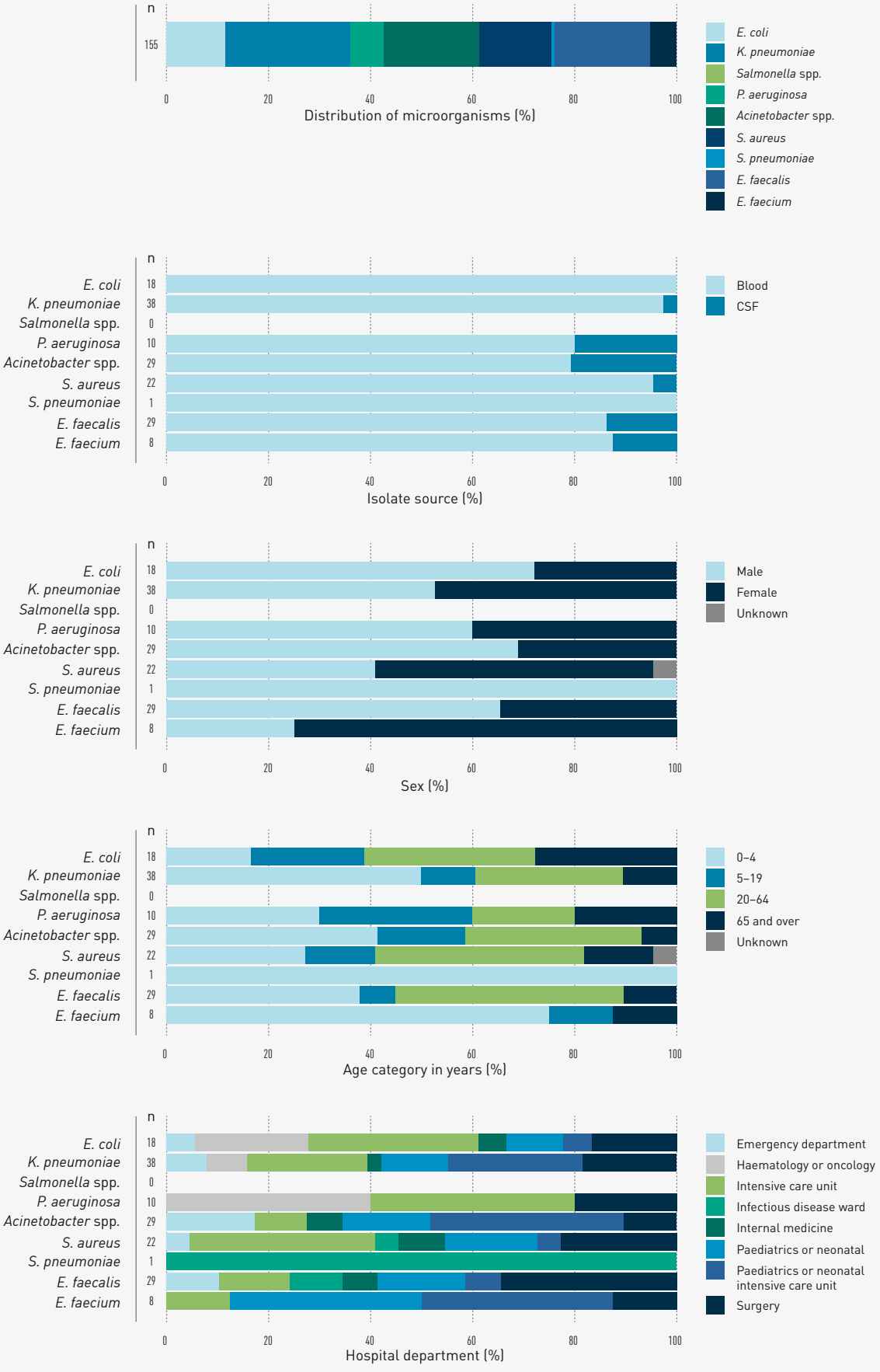


Table 6.68 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Ukraine in 2018

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	12	58*	0*	NA	NA	NA
Amoxicillin-clavulanic acid	13	54*	0*	31	87	0
Piperacillin-tazobactam	11	36*	0*	30	67	10
Cefotaxime/ceftriaxone	15	33*	0*	35	77	3
Ceftazidime	16	44*	0*	32	87	0
Ertapenem	11	0*	0*	27	59*	0*
Imipenem/meropenem	18	0*	0*	37	43	3
Gentamicin/tobramycin	18	22*	0*	35	66	6
Amikacin	17	18*	0*	37	51	11
Ciprofloxacin/levofloxacin/ofloxacin	18	44*	0*	38	79	0
Multidrug resistance[a]	18	17*	NA	34	59	NA

NA = not applicable.

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

[a] Multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin, levofloxacin and/or ofloxacin), third-generation cephalosporins (cefotaxime, ceftriaxone and/or ceftazidime) and aminoglycosides (gentamicin and/or tobramycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.69 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Ukraine in 2018

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	9	89*	0*	NA	NA	NA
Ceftazidime	10	70*	0*	NA	NA	NA
Cefepime	10	80*	0*	NA	NA	NA
Imipenem/meropenem	10	100*	0*	28	75*	11*
Gentamicin/tobramycin	9	67*	0*	27	81*	0*
Amikacin	8	62*	0*	26	81*	8*
Ciprofloxacin/levofloxacin	9	67*	0*	29	86*	0*
Multidrug resistance[a]	9	78*	NA	26	65*	NA

NA = not applicable.

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

[a] For *P. aeruginosa*, multidrug resistance is defined as combined resistance to at least one representative of three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on three or more of the groups are excluded from the analysis of multidrug resistance.

For *Acinetobacter* spp., multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.70 Resistance levels for *S. aureus* among blood and CSF isolates in Ukraine in 2018

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	20	0*	NA
Ciprofloxacin/levofloxacin/ofloxacin	22	5*	0*
Vancomycin	18	0*	0*
Rifampicin	15	0*	0*
Linezolid	20	0*	NA

NA = not applicable.

* A small number of isolates was 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.

Table 6.71 Resistance levels for *S. pneumoniae* among blood and CSF isolates in Ukraine in 2018

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%(I+R)
Penicillin[a]	1	NA	NA	100*
Cefotaxime/ceftriaxone	1	100*	0*	NA
Levofloxacin/moxifloxacin	1	0*	0*	NA
Erythromycin/clarithromycin/azithromycin	1	100*	0*	NA
Multidrug resistance[b]	1	NA	NA	100*

NA = not applicable.

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

[a] The percentage I+R to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage I+R should be interpreted as the percentage R. For non-meningitis indications, the percentage I+R should be interpreted as the percentage of penicillin non-wild type. For this report, the term penicillin non-wild type refers to *S. pneumoniae* isolates reported by the local laboratories as I or R to penicillin, assuming MICs to penicillin above those of the wild-type, i.e. >0.06 mg/L. The analysis is based on the qualitative susceptibility categories S, I and R as quantitative susceptibility information was missing for a large proportion of the data. For laboratories using EUCAST, this approach correctly defines all penicillin non-wild type (i.e. I/R) *S. pneumoniae* isolates. However, for laboratories using the CLSI methodology, isolates within the S category for benzylpenicillin might be non-wild type since the penicillin susceptibility breakpoint for non-meningitis cases is set as ≤ 2 mg/L. Due to this limitation, the actual percentage of penicillin non-wild type *S. pneumoniae* might be higher than reported in this table.

[b] Multidrug resistance is defined as combined penicillin non-wild type and resistance (R) to macrolides (erythromycin, clarithromycin and/or azithromycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 6.72 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in Ukraine in 2018

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	22	14*	0*	8	100*	0*
High-level gentamicin	19	63*	0*	8	62*	0*
Vancomycin	24	4*	0*	8	0*	0*
Linezolid	26	0*	4*	8	0*	0*

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

6.11.3 Conclusion

Data from Ukraine are assessed as level B based on the following strengths and limitations regarding data quality and representativeness.

The strengths are:

- the network has coverage in three different regions of the country
- AST results seem reliable and comparable.

The limitations are:

- the representativeness of results is limited by overrepresentation of severely ill and pretreated patients with nosocomial infections in tertiary care hospitals; and
- the small number of isolates make observed resistance percentages more sensitive to random variation (e.g. due to nosocomial outbreaks).

As a result of limitations in the data quality, 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 patient population sampled, high levels of resistance to all selected agents were seen in *K. pneumoniae* (Table 6.68) and *Acinetobacter* spp. (Table 6.69). These high levels of resistance are concerning and may reflect the dissemination of resistant clones in the health care setting. In *E. coli*, although based on a small number of isolates, moderate resistance levels were found for most agents (Table 6.68). MRSA was not observed in 2018 in blood or CSF isolates, although errors in AST cannot be ruled out (Table 6.70, Fig. 2.8). Too few antibiotic susceptibility testing results for *Salmonella* spp. (no isolates), *P. aeruginosa* (Table 6.58), *S. pneumoniae* (Table 6.71) and *E. faecium* (Table 6.72) were available to allow interpretation.


CHAPTER
7

Area-specific data on AMR

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

7.1.1 Surveillance set-up and data quality assessment

Table 7.1 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from Kosovo[1] in 2018. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 7.1 Level of evidence and scoring of factors affecting the validity of CAESAR data from Kosovo[a] in 2018

Level of evidence: B			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+/–	• The surveillance network comprises seven laboratories (90% of hospitals) of which one submitted data. • Laboratories are geographically spread within Kosovo[a]. • The estimated coverage of the total population (1 800 000)[b] is 90%.
	Hospital types	–	• The network comprises tertiary (14%) and secondary (86%) care hospitals (data are available from only one tertiary care hospital).
Sampling procedures	Selection of patients	–	• Clinical guidelines to define cases eligible for sampling are not in place. • Underutilization and selective usage of blood and CSF culture diagnostics (particularly in adults, children other than neonates and in regional hospitals) are indicated by: - the small number of samples taken per 1000 patient days: 5; - the large proportion of isolates from neonatal/paediatric intensive care units (73%); - the large proportion of nosocomial pathogens (34% *Acinetobacter* spp., 32% *K. pneumoniae*) and small proportion of *E. coli* (6%); and - generally high resistance percentages. *Patient characteristics of isolates from Kosovo[a] are available in Fig. 7.1.*
	Sample size	–	• The total number of isolates is 207. • Fewer than 30 isolates are available for most pathogens.
Laboratory procedures	AST methods	+	• The unified standard for AST in the network is EUCAST. • The main methods for AST are a combination of a semi-automated system and disk diffusion (one laboratory) and disk diffusion only (regional laboratories). • Not all isolates are tested for each relevant antibiotic. • Confirmatory testing of exceptional phenotypes or highly resistant microorganisms is performed at the expert laboratory. • Internal quality control is regularly performed in all laboratories. • All laboratories participated in the CAESAR EQA in 2018.
	AST breakpoints	+	• EUCAST breakpoints are used in all laboratories.

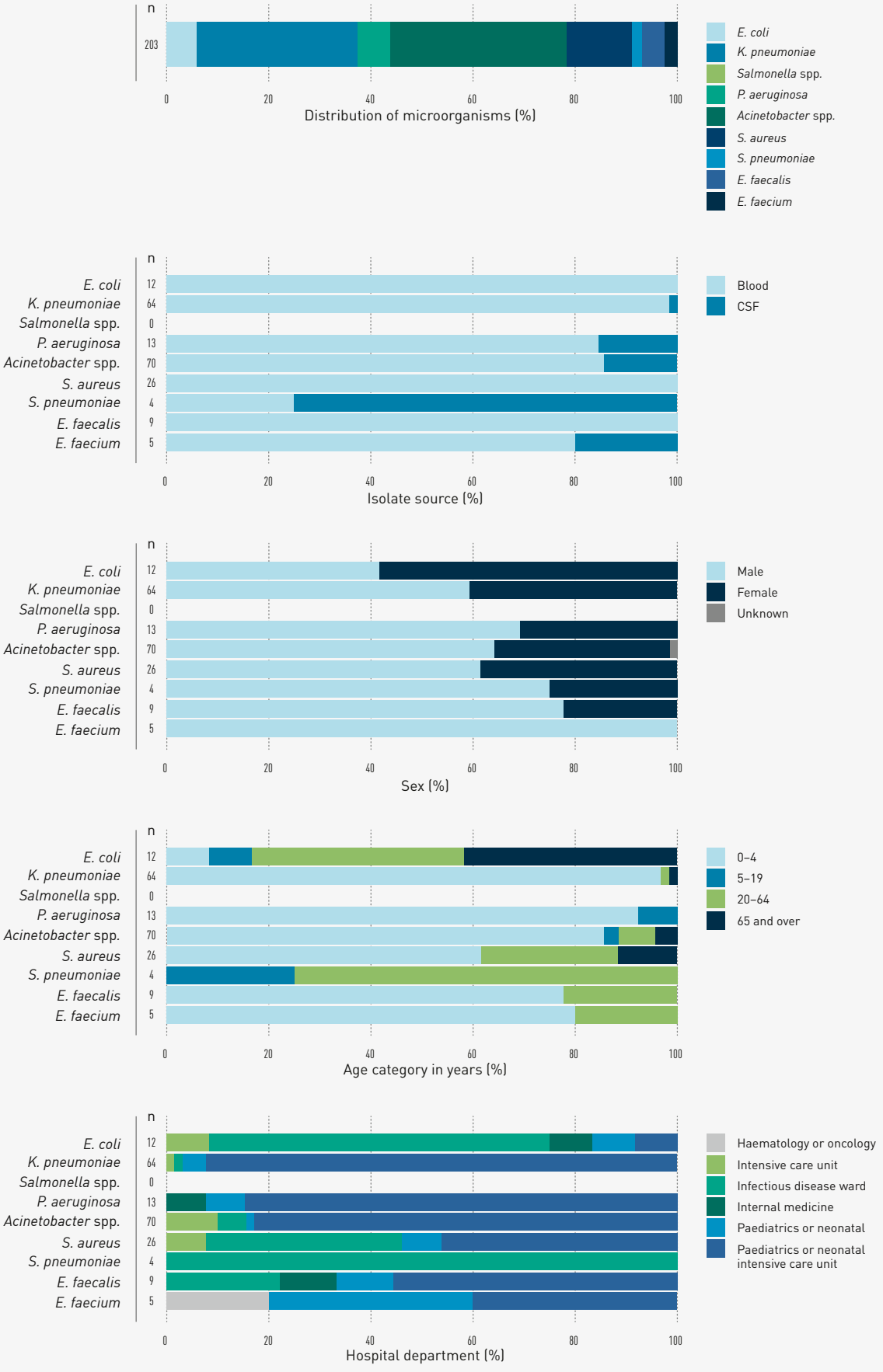
[a] In accordance with United Nations Security Council resolution 1244 (1999).
[b] Sergy Koryak, WHO Country Office in Serbia, personal communication, 26 August 2019.

7.1.2 Results

Fig. 7.1 shows the distribution of CAESAR microorganisms and the characteristics of patients (broken down by pathogen) of blood and CSF isolates in Kosovo[1] in 2018. Resistance percentages for these isolates are presented in Tables 7.2–7.6.

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

Fig. 7.1 Patient characteristics of isolates in Kosovo[a] in 2018, by pathogen



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

Table 7.2 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Kosovo[a] in 2018

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	12	92*	0*	NA	NA	NA
Amoxicillin-clavulanic acid	12	58*	0*	64	36	0
Piperacillin-tazobactam	12	33*	0*	64	9	5
Cefotaxime/ceftriaxone	12	58*	0*	64	97	0
Ceftazidime	12	50*	0*	64	8	9
Ertapenem	12	0*	0*	64	2	0
Imipenem/meropenem	12	0*	0*	64	2	0
Gentamicin/tobramycin	12	58*	0*	64	95	0
Amikacin	12	0*	42*	64	91	3
Ciprofloxacin/levofloxacin/ofloxacin	12	58*	17*	64	6	0
Multidrug resistance[b]	12	58*	NA	64	6	NA

NA = not applicable.

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

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

[b] Multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin, levofloxacin and/or ofloxacin), third-generation cephalosporins (cefotaxime, ceftriaxone and/or ceftazidime) and aminoglycosides (gentamicin and/or tobramycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 7.3 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Kosovo[a] in 2018

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	13	46*	0*	NA	NA	NA
Ceftazidime	13	23*	0*	NA	NA	NA
Cefepime	13	38*	0*	NA	NA	NA
Imipenem/meropenem	13	77*	0*	70	89	0
Gentamicin/tobramycin	13	69*	0*	70	90	0
Amikacin	13	46*	23*	70	89	0
Ciprofloxacin/levofloxacin	13	54*	0*	70	87	0
Multidrug resistance[b]	13	62*	NA	70	87	NA

NA = not applicable.

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

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

[b] For *P. aeruginosa*, multidrug resistance is defined as combined resistance to at least one representative of three or more antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on three or more of the groups are excluded from the analysis of multidrug resistance.

For *Acinetobacter* spp., multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (ciprofloxacin and/or levofloxacin), aminoglycosides (gentamicin and/or tobramycin) and carbapenems (imipenem and/or meropenem). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 7.4 Resistance levels for *S. aureus* among blood and CSF isolates in Kosovo[a] in 2018

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[b]	26	58*	NA
Ciprofloxacin/levofloxacin/ofloxacin	26	0*	0*
Vancomycin	26	0*	0*
Rifampicin	26	0*	0*
Linezolid	26	0*	NA

NA = not applicable.

* A small number of isolates was 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.

Table 7.5 Resistance levels for *S. pneumoniae* among blood and CSF isolates in Kosovo[a] in 2018

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%(I+R)
Penicillin[b]	4	NA	NA	50*
Cefotaxime/ceftriaxone	4	0*	0*	NA
Levofloxacin/moxifloxacin	4	0*	0*	NA
Erythromycin/clarithromycin/azithromycin	4	50*	0*	NA
Multidrug resistance[c]	4	NA	NA	50*

NA = not applicable.

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

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

[b] The percentage I+R to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage I+R should be interpreted as the percentage R. For non-meningitis indications, the percentage I+R should be interpreted as the percentage of penicillin non-wild type. For this report, the term penicillin non-wild type refers to *S. pneumoniae* isolates reported by the local laboratories as I or R to penicillin, assuming MICs to penicillin above those of the wild-type, i.e. >0.06 mg/L. The analysis is based on the qualitative susceptibility categories S, I and R as quantitative susceptibility information was missing for a large proportion of the data. For laboratories using EUCAST, this approach correctly defines all penicillin non-wild type (i.e. I/R) *S. pneumoniae* isolates. However, for laboratories using the CLSI methodology, isolates within the S category for benzylpenicillin might be non-wild type since the penicillin susceptibility breakpoint for non-meningitis cases is set as ≤ 2 mg/L. Due to this limitation, the actual percentage of penicillin non-wild type *S. pneumoniae* might be higher than reported in this table.

[c] Multidrug resistance is defined as combined penicillin non-wild type and resistance (R) to macrolides (erythromycin, clarithromycin and/or azithromycin). Isolates with missing data on one or more of the groups are excluded from the analysis of multidrug resistance.

Table 7.6 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in Kosovo[a] in 2018

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	9	0*	0*	5	100*	0*
High-level gentamicin	9	67*	0*	5	100*	0*
Vancomycin	9	0*	0*	5	80*	0*
Linezolid	9	0*	0*	5	0*	0*

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

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

7.1.3 Conclusion

Data from Kosovo[1] are assessed as level B based on the following strengths and limitations regarding data quality and representativeness.

The strengths are:

- the network has good geographical and population coverage and includes various types of hospitals (although data are available for one tertiary care hospital only); and
- AST results seem reliable and comparable.

The limitations are:

- the representativeness of results is limited by overrepresentation of severely ill and pretreated patients and neonates, in a single tertiary care hospital in Pristina; and
- the small number of isolates make observed resistance percentages more sensitive to random variation (e.g. due to nosocomial outbreaks).

As a result of limitations in the data quality, 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 adults and patients with community-acquired infections.

Nevertheless, in the patient population sampled, resistance to third-generation cephalosporins (cefotaxime/ceftriaxone) and aminoglycosides (gentamicin/tobramycin) were high in *E.coli* (although based on a small number of isolates) and very high in *K. pneumoniae* (Table 7.2). However, the proportion of *K. pneumoniae* resistant to carbapenems (imipenem/meropenem) was lower than in neighbouring countries (Fig. 2.5). 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 (Table 7.3). The proportion of MRSA was concerning and higher than in most countries close to Kosovo[1] (Table 7.4, Fig. 2.8). Too few antibiotic susceptibility test results for *Salmonella* spp. (no isolates), *S. pneumoniae* (Table 7.5), *E. faecalis* and *E. faecium* (Table 7.6) were available to allow interpretation.


CHAPTER
8

Establishing AMR surveillance

This chapter highlights the progress made in the Republic of Moldova and Tajikistan towards establishing national AMR surveillance. For the first time, both countries responded to the CAESAR network data call in 2019. While the data submitted does not yet meet the requirements for inclusion in this report, the countries have made important steps towards setting up a national AMR surveillance network that deserve to be highlighted and acknowledged. This chapter includes a brief discussion of health system characteristics, which potentially play a role in establishing routine microbiological diagnostics and laboratory-based surveillance in the two countries, and provides an overview of the critical steps taken and challenges met along the way.

8.1 Republic of Moldova

8.1.1 Health and population context

The Republic of Moldova has a double disease burden as rates of both communicable and noncommunicable diseases have steadily increased in the last decades. The main causes of years of life lost due to premature death in the country in 2017 were ischaemic heart disease, cerebrovascular disease and cirrhosis of the liver *(1)*. The critical challenges in communicable disease control in the Republic of Moldova are tuberculosis and HIV/AIDS *(2)*.

Health expenditure per person has more than tripled since the year 2000 when it was estimated to be US$ 123 per capita. However, total health expenditure in absolute terms (US$ purchasing power parity) is still very low relative to other countries of the European Region, and this significantly limits the volume of the package of services provided and their quality. The share of public expenditure as a percentage of gross domestic product is also much lower in the Republic of Moldova compared with other countries in the WHO European Region, while the share of private spending is quite high. This situation places a particularly high burden on the poorest in the population, who are often at risk of catastrophic health care costs.

The number of both doctors and mid-level health personnel is low, particularly for general practitioners: in 2017, the Republic of Moldova had 49 family doctors per 100 000 population *(3)* compared with an average of 92 per 100 000 population in the 28 EU countries *(4)*. Additional country information is in Table 8.1.

The benefits package under the micro-health insurance scheme is the same for all insured people in the Republic of Moldova, and all have access to the same package of primary care benefits irrespective of insurance status. However, there are considerable imbalances in insurance coverage, which inevitably lead to inequity in access to services. As in many places throughout the Region, benefits packages do not cover microbiological diagnostic tests for everyone, and their costs often surpass that of conventional antibiotic treatment regimens, i.e. those commonly used to treat organisms under AMR surveillance.

8.1.2 Status of AMR surveillance

The process that led to the establishment of a national AMR surveillance network in the Republic of Moldova involved some key steps, both in terms of stakeholder participation and administrative procedures – with the former playing an instrumental role in advancing the latter. Indeed, all relevant stakeholders devoted

Table 8.1 Selected indicators of the Republic of Moldova

Indicator	Value
Population[a]	2 681 734
Life expectancy at birth (years)[b]	72.3
Under-five mortality rate (deaths per 1000 live births)[b]	16
Total health expenditure per capita(purchasing power parity US$)[b]	514
World Bank income group[c]	Lower-middle income
Gross national income per capita (US$)[b]	2240
Individuals using the Internet (%)[d]	76

[a] National Bureau of Statistics of the Republic of Moldova *(5)*.
[b] WHO Regional Office for Europe *(6)*.
[c] World Bank *(7)*.
[d] World Bank Open Data [online database]. Washington (DC): World Bank; 2019 (https://data.worldbank. org/, accessed 4 November 2019) *(8)*.

great efforts to harmonizing laboratory standards and surveillance methodology, and to advocating the benefits of taking part in a national surveillance network. Moreover, a joint workshop was organized at the onset to bring together all the different experts concerned – microbiologists, epidemiologists, clinicians and regulators – and ad hoc training on EUCAST methodology was provided to microbiologists. In parallel to these activities, the Ministry of Health, Labour and Social Protection together with the AMR coordinator initiated the development of a national framework, culminating in a ministerial order and the official designation of responsible agencies, including an AMR focal point, reference laboratory and national coordinator. Formalizing the network governance early on was a key success factor in shaping further development of the network. Government approval of the draft national programme on preventing and combating AMR in 2019 will create favourable conditions to further strengthen the surveillance system and other AMR prevention and control initiatives.

Currently, the network comprises 12 public laboratories: 10 public health laboratories and two clinical laboratories. Each of the public health laboratories serves several primary district hospitals, which means that samples require transportation from districts to one of the 10 laboratories. The clinical laboratories serve two secondary and tertiary hospitals. Network participation is voluntary and, in principle, is open to both public and private laboratories. With flexible costs, private laboratories are often able to provide microbiological services to public hospitals at a more competitive market price. Currently, this contributes to less than optimal availability of AMR data at laboratory level. At the same time, there is no explicit referral system for both blood samples and reference testing between different levels of hospitals – local, district and national.

8.1.3 Challenges

One main challenge, familiar to many countries in the Region, is the small number of blood cultures taken. The Republic of Moldova has therefore expressed an interest to participate in a proof-of-principle AMR routine diagnostics surveillance project (PoP project) *(9)* to promote the utility of microbiological diagnostics such as cultures and AST in the diagnostic work-up of suspected blood stream infection. Ultimately the PoP project is meant to encourage more frequent and systematic use of blood culture diagnostic services, thus improving quality of patient care and surveillance for AMR. While the data management and reporting system appears to be adequate at the national reference laboratory level, the

data received from peripheral network laboratories still require further improvements. Besides, capacity building at all levels in data management is needed. Few laboratories have systematically implemented laboratory software to enter and store results, while paper-based data collection is still commonly used.

Procurement remains challenging, notably that of laboratory consumables. Despite adopting a centralized procurement approach for all public health laboratories, in recent years substandard materials such as antimicrobial discs are often purchased, as a result of budgetary constraints and lack of stringent quality criteria. Hospital laboratories, despite being responsible for their own procurement of such consumables and materials, encounter similar quality challenges with the products they buy.

Finally, budget constraints and the limited availability of human resources remain significant obstacles for a more comprehensive implementation of AMR surveillance. In this sense, it would be desirable that dedicated public funds be made available to ensure that the functions of reference laboratory and surveillance network can be properly fulfilled.

8.1.4 Next steps

Currently, the national AMR surveillance network only includes public health laboratories. Future plans include to actively involve more private laboratories in the surveillance network, by inviting interested parties to national network meetings, sharing information and presenting the benefits of being part of the network, such as the possibility of participating in the EQA.

On-the-job training at laboratories and participation in the CAESAR EQA are among the most praised advantages of being part of the national AMR network. A national EQA is carried out twice a year, but it only includes a small number of microorganisms. A desirable measure to overcome the challenges of budget constraints and limited availability of human resources is to invite laboratories that want to be part of the network to start participating in the costs of activities and contributing with their resources.

8.2 Tajikistan

8.2.1 Health and population context

Tajikistan has a high burden of infectious diseases compared with other countries in central Asia. The main causes of years of life lost due to premature death in Tajikistan in 2017 were lower respiratory infections, neonatal disorders and ischemic heart disease *(10)*. Of the 25 most important causes of disease burden, as measured by disability-adjusted life years, diarrheal diseases showed the largest decrease, falling by 75% from 1990 to 2010. Additional country information is in Table 8.2.

Although the Government of Tajikistan supports general health expenditure at the levels of oblasts, regional administrative divisions and local authorities, the most important sources of health financing in the country are formal and informal out-of-pocket payments and external resources.

Most public expenditure is still spent on inpatient care, although the share of resources devoted to primary health care has been increasing in recent years *(11)*. Compared with other countries of the WHO European Region, absolute expenditure per capita is by far the lowest, while the share of public expenditure as a percentage of total health expenditure is also one of the lowest. A basic benefit package was adopted in 2007, but it has so far only been extended to a limited number of pilot districts.

The basic benefits package (2014–2016) does not include blood cultures for diagnosis of antimicrobial growth and susceptibility *(11)*. Moreover, there is no assessment of the costs involved in using EUCAST methodology for AST at national level. The State Sanitary Epidemiological Surveillance Service (SSESS) is in charge of releasing health statistics on communicable diseases. However, it currently needs more

Table 8.2 Selected indicators of Tajikistan

Indicator	Value
Population[a]	9 321 000
Life expectancy at birth (years)[b]	69.7
Under-five mortality rate (deaths per 1000 live births)[b]	45
Total health expenditure per capita(purchasing power parity US$)[b]	185
World Bank income group[c]	Low income
Gross national income per capita (US$)[b]	1280
Individuals using the Internet (%)[c]	22

[a] Population Division, United Nations Department of Economic and Social Affairs *(12)*.
[b] WHO Regional Office for Europe *(6)*.
[c] World Bank *(7)*.

technical capacity and resources. For example, its extensive network of more than 100 laboratories is understaffed and lacks basic equipment to perform most of its assigned duties. Furthermore, public health services are fragmented into several vertical structures and programmes, each with its own system for data collection.

8.2.2 Status of AMR surveillance

During 2018, Tajikistan achieved a significant milestone in setting up a national AMR surveillance network: the 2018–2022 National Action Plan to Tackle Antimicrobial Resistance was developed and approved. One of the primary objectives of the Plan is to "strengthen the knowledge and evidence base through surveillance and research" *(13)*. A central component for achieving this objective is the development of an extended national AMR surveillance network.

Currently, Tajikistan has 101 bacteriological laboratories of which 63 work under the SSESS and 38 as part of state hospitals. Following the breakdown of the Soviet Union and civil war, financing and supply of the national laboratory system greatly suffered from substantial reductions in public spending, directly affecting AMR surveillance activities. Today, many laboratories are still not able to perform AST, and reporting to the surveillance network is still too irregular. Most SSESS laboratories are in poor condition, but some laboratories located in hospitals have been able to invest in improved facilities, equipment and supplies. Guidelines and standard operation procedures for AST and interpretation of the results have often not been updated for decades.

Only six of the 101 bacteriological laboratories in Tajikistan are currently implementing EUCAST standards and methodology. Of these six laboratories, five are located in Dushanbe and one in Khorugh. Overall, one of the main challenges is the quality of the consumables available in many laboratories and the substandard procedures adopted.

In 2018, according to the National Action Plan to Tackle Antimicrobial Resistance, the National Reference Laboratory has been identified as the leading reference laboratory, responsible for establishing a sentinel AMR surveillance system with technical support from WHO. The overall coordinating role of all AMR-related issues has been assigned to the Service of State Supervision of Health Care and Social Protection of the Population.

Since the surveillance network was established, yearly meetings have been held among different stakeholders – including epidemiologists, infectious diseases physicians and laboratory professionals – to discuss Tajikistan's participation in the CAESAR network and in all related activities for surveillance and laboratory training. These meetings have represented an essential opportunity for sharing data on AMR and for interacting with counterparts from the scientific community. In December 2017, 30 laboratory professionals attended the first AMR laboratory course, which introduced EUCAST methods and guidelines.

Moreover, through the technical support provided by WHO and international partners and collaborating centres, three rounds of training have been conducted in 2018–2019. These trainings were geared towards the introduction of routine microbiological diagnostics, the establishment of an AMR sentinel surveillance mechanisms in the country, the presentation of EUCAST standards and the PoP project. The participants of these three rounds of training included 12 laboratory professionals from the National Reference Laboratory and four selected hospitals located in Dushanbe.

8.2.3 Challenges

Tajikistan still faces several challenges while organizing and strengthening its AMR surveillance network. It is crucial to gather wider and continuous political support that can sustain the expansion of the surveillance network and the financing of quality laboratory supplies.

A major challenge is related to the lack of qualified personnel, which limits the capacity of the network to increase its geographical scope and range of activities. In particular, the scarcity of trained staff limits the capacity for increasing the number of laboratories and hospitals in the surveillance network and the number of clinical samples processed. Much work still needs to be done to generate regular communication and solid trust between laboratory staff and clinicians regarding the quality of routine microbiological diagnostics.

The abovementioned challenge with procuring laboratory materials contributes to restricting more systematic and widespread testing. This challenge is both financial – insufficient resources available – and structural – limited number of suppliers due to the relative small size of the local market and to the entry barriers for foreign producers.

Finally, in this initial stage, Tajikistan should consider revising national regulatory guidelines to adapt protocols, guidelines and standard operating procedures for microbiological diagnostics, following the latest recommendations.

8.2.4 Next steps

The plan for the coming years includes several measures aimed at strengthening the existing capacity within the surveillance network while taking relevant actions towards increasing the size and breadth of the network. First of all, it is necessary to establish a national laboratory committee to coordinate AMR surveillance network functions. In addition, it is crucial to review the channels for procuring laboratory materials and financing mechanisms. Given that the lack of a unique format for data collection is hampering the exchange of information within the national network, one of the next steps should also include the development and adaptation of a single format for data collection. Finally, communication with the network can be enhanced by building up a system for regular reporting to regional levels.

To address the limited capacity for bacteriology cultures and AST, Tajikistan has planned to conduct a PoP project. The primary purpose of the PoP project is to highlight the need for standard diagnostics and AST and, more in general, to strengthen surveillance of AMR. Moreover, the PoP project aims at emphasizing the importance of close communication and collaboration between clinicians and microbiologists. Preparatory work for the implementation of the PoP project in Tajikistan started in May 2019. The first

step included workshops and training delivered to microbiologists working at hospitals identified as study sites for the PoP project. Then, the National Bioethics Committee adapted and approved the PoP protocol and, following a ministerial order from the Ministry of Health and Social Protection of the Population, a coordination group was established. Finally, with technical support from WHO, more ad-hoc training was organized, the relevant materials procured and documents translated. In particular, the PoP protocol was translated into Russian, and working papers were printed and distributed to health staff. Different training sessions have been organized, specifically targeting nurses (on the right technique for blood collection) and doctors (on the patients' recruitment criteria under the PoP project). Implementation of the PoP project was officially launched in June 2019 with the inclusion of four hospitals located in Dushanbe: one paediatric, one infectious disease and two general hospitals. So far more than 600 patients have been enrolled of which 159 had a positive blood sample identified.


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 and performs quality control on the samples, organizes logistics and arranges the shipment to the countries and areas in collaboration with the AMR focal points and EQA coordinators. Each participating laboratory then examines the same well-characterized specimens, and reports back their results within the defined time frame. The results are assessed and, if the data collected by participating laboratories from all countries/areas are valid, 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 exercise 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; and
- the comparability between laboratories and countries/areas in terms of identification and AST accuracy.

Many of the countries and areas now submitting data to CAESAR started by participating in the yearly EQA exercise, which formed the core of the network in which the 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/areas 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 such as *S. aureus* with *mecC* (specimen 3685, 2016) or *E. coli* with *mcr-1* (specimen 4326, 2017 and specimen 4928, 2018). The laboratories usually prepare stock cultures from these well-characterized strains and use them in their future quality control studies.

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 failure 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 2018 and provides a summary of the six exercises performed hitherto (2013–2018).

9.2 CAESAR EQA in 2018

A panel of six lyophilized 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: *E. faecium* (specimen 4926), *K. pneumoniae* (specimen 4927), *E. coli* (specimen 4928), *S. aureus* (specimen 4929), *P. aeruginosa* (specimen 4930), and *S. pneumoniae* (specimen 4931). The EQA panels were dispatched on 10 September 2018 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 17 countries/areas by 257 of 287 (90%) participating laboratories: 10 of 10 laboratories from Albania, 11 of 11 from Armenia, 12 of 13 from Belarus, 10 of 10 from Bosnia and Herzegovina, 17 of 17 from Georgia, 6 of 6 from Kyrgyzstan, 8 of 8 from Montenegro, 17 of 18 from North Macedonia, 14 of 14 from the Republic of Moldova, 33 of 53 from the Russian Federation, 24 of 24 from Serbia, 6 of 7 from Tajikistan, 67 of 71 from Turkey, 4 of 4 from Turkmenistan, 5 of 5 from Ukraine, 6 of 6 from Uzbekistan and 7 of 7 from Kosovo[1]. Laboratories in Azerbaijan (n = 3) could not take part in the 2018 EQA exercise due to delay in delivery of the EQA samples.

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 (10%) and EUCAST (90%). Homogenous adherence to one guideline was observed in 10 countries and areas. All participating laboratories in Albania, Kyrgyzstan, North Macedonia, the Republic of Moldova, Serbia, Tajikistan, Ukraine, Uzbekistan and Kosovo[1] used the EUCAST guideline, whereas all participating laboratories in Turkmenistan used the CLSI guideline.

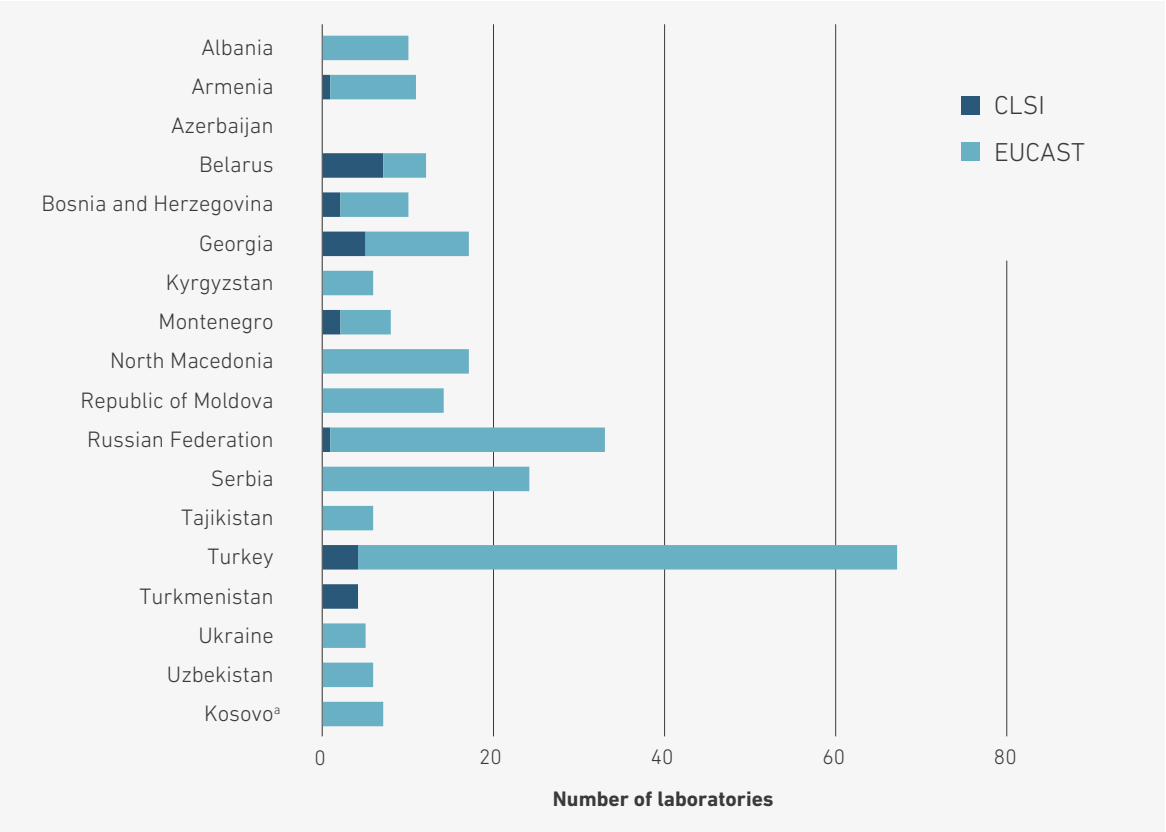
Among participating laboratories that specified the susceptibility testing method used for the survey strains (n = 257), the breakdown of the methods used revealed that 58% (n = 150) of the laboratories used a disk diffusion susceptibility testing method and 42% (n = 107) used a semi-automated AST instrument (Fig. 9.2).

9.2.2 Antimicrobial susceptibility results

Participating laboratories' results were collated, analysed and presented in individual laboratory reports, which were available on 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. Laboratories can access their reports at any time, as well as download a printable copy. Due to issues in electronic submission of results, five laboratories in Tajikistan could not submit their data online using the UK NEQAS results entry platform; however, the data were made available to the CAESAR coordination group were analysed and are included in this chapter.

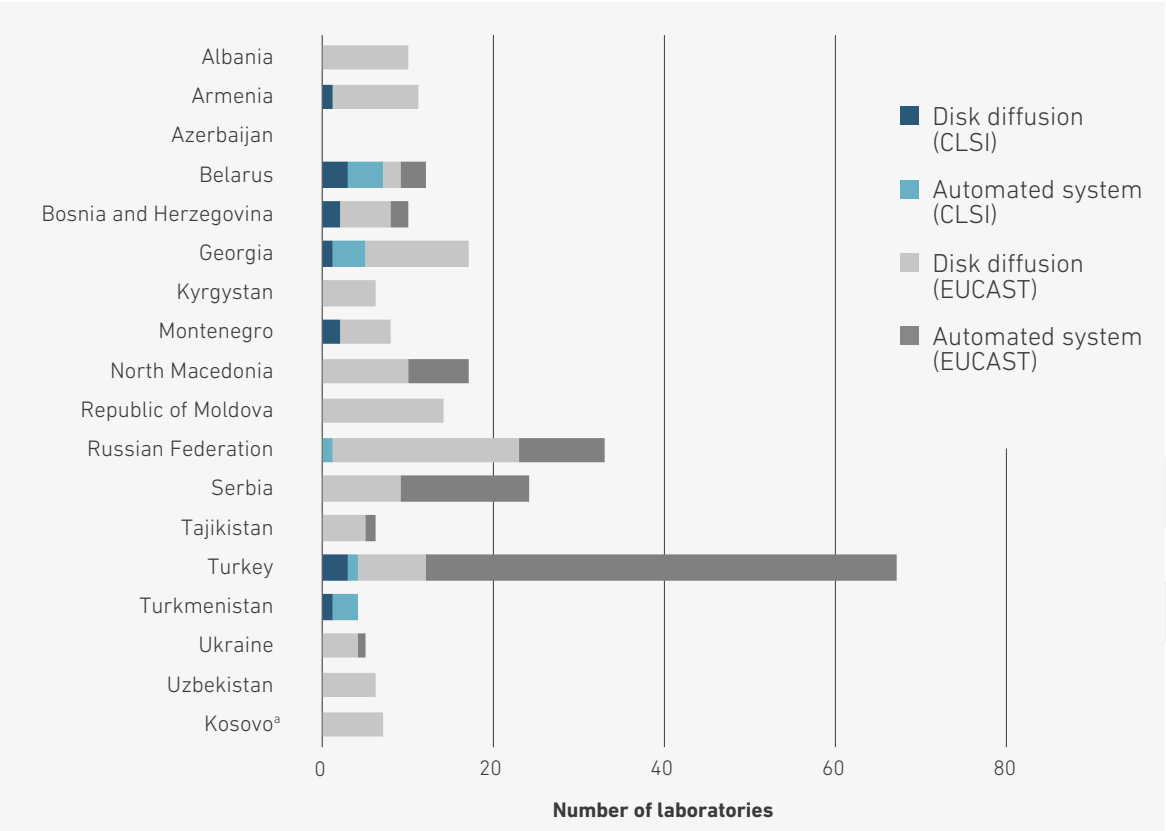
1 All references to Kosovo should be understood as references to Kosovo in accordance with United Nations Security Council resolution 1244 (1999).

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).

In general, performance was very good and consistent with that seen in previous EQA surveys among laboratories in the European Region. The major problems encountered are:

- borderline susceptibility to third-generation cephalosporins and carbapenems in *K. pneumoniae* (specimen 4927) and to ceftazidime in *P. aeruginosa* (specimen 4930));
- determination of susceptibility to beta-lactam agents in *S. pneumoniae* (specimen 4931);
- determination of susceptibility to beta-lactam/beta-lactamase inhibitor combinations (notably susceptibility to amoxicillin-clavulanic acid in *E. coli* (specimen 4928) and piperacillin-tazobactam in *P. aeruginosa* (specimen 4930)); and
- determination of high-level aminoglycoside resistance in *E. faecium* (specimen 4926); and novel resistance mechanisms (e.g. low-level colistin resistance mediated by *mec-1* gene in *E. coli* (specimen 4928)).

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, standard dosing regimen (S), susceptible, increased exposure (I) or resistant (R).

Specimen 4926 contained a strain of *E. faecium* that was resistant to amoxicillin, ampicillin, teicoplanin and vancomycin but did not express high-level gentamicin resistance.

A very high concordance was achieved for amoxicillin, ampicillin, teicoplanin and vancomycin, but not for high-level gentamicin resistance (MIC >512 mg/L). Even though the strain had a gentamicin MIC of 32 mg/L (i.e. susceptible to high-level gentamicin), 89 (34.6%) of the participating laboratories reported the strain as resistant to high-level gentamicin. The correct result was reported by 120 (46.7%) of the laboratories and 48 (18.7%) laboratories did not report any result for this agent, indicating a lack of laboratory capacity.

Correct identification at the species level was achieved by 233 (91%) of the participating laboratories, and numerous laboratories failed to provide correct identification (*E. faecalis*, *n* = 10; *E. gallinarum*, *n* = 1; *Streptococcus* spp., *n* = 4; and *S. epidermidis*, *n* = 1) or correct identification at the species level (*Enterococcus* spp., *n* = 6). The misidentifications are highly suggestive of a lack of laboratory capacity to correctly identify *Enterococcus* spp. at the species level, especially for laboratories using conventional methods for identification. Two laboratories did not provide a result for this strain, either because the laboratories failed to grow the strain in the laboratory or because a satisfactory identification could not be achieved.

Specimen 4927 was a strain of *K. pneumoniae* producing the OXA-48 enzyme. The strain was susceptible to aminoglycosides, fluoroquinolones and colistin, S/I to third-generation cephalosporins, I/R to carbapenems and R to amoxicillin, ampicillin and beta-lactam/beta-lactamase inhibitor combinations.

MICs close to susceptibility breakpoints resulted in poor concordance for third-generation cephalosporins; cefotaxime (MIC = 2 mg/L), ceftriaxone (MIC = 1 mg/L) and ceftazidime (MIC = 1 mg/L), as well as for carbapenems; imipenem (MIC = 4 mg/L) and meropenem (MIC = 4 mg/L).

The strain had a MIC of 4 mg/L for both imipenem and meropenem, which fall into the I category with EUCAST and into the R category with CLSI clinical breakpoints. Among laboratories that provided results for these two agents, 42.3% and 48.0% reported correct results for imipenem, and 39.2% and 31.8% for meropenem following the EUCAST and CLSI clinical breakpoints, respectively.

Correct identification at the species level was achieved by 247 (96%) of the participating laboratories, and only a few misidentifications were observed: *K. oxytoca*, *n* = 1; and *P. aeruginosa*, *n* = 2. Additionally, four

Table 9.1 Specimens distributed in the CAESAR EQA survey in 2018, evaluation of laboratory performance for identification and important antimicrobial susceptibility features of the strains

Specimen number	Organism	Correct identification among participating laboratories (*n* = 257)		Failures in identification at species level	Important antimicrobial susceptibility features of the strain
		%	*n*		
4926	*E. faecium*	91	233	*E. faecalis* (*n* = 10) *Enterococcus* spp. (*n* = 6) *E. gallinarum* (*n* = 1) *Streptococcus* spp. (*n* = 4) *Staphylococcus epidermidis* (*n* = 1) No result provided (*n* = 2)	Resistant to amoxicillin, ampicillin, teicoplanin and vancomycin but negative for high-level gentamicin resistance
4927	*K. pneumoniae*	96	247	*Klebsiella oxytoca* (*n* = 1) *Klebsiella* spp. (*n* = 4) *Enterobacterales* spp. (*n* = 1) *P. aeruginosa* (*n* = 2) No result provided (*n* = 2)	OXA-48 carbapenemase producing strain
4928	*E. coli*	97	249	*Enterobacterales* spp. (*n* = 1) *P. aeruginosa* (*n* = 1) *E. faecalis* (*n* = 1) *Enterococcus* spp. (*n* = 1) No result provided (*n* = 4)	*mcr-1* gene positive (colistin MIC = 4 mg/L). Amoxicillin-clavulanic acid MIC on the susceptible breakpoint (8 mg/L)
4929	*S. aureus*	97	248	*S. epidermidis* (*n* = 2) Coagulase-negative *Staphylococcus spp.* (*n* = 1) *Streptococcus* spp. (*n* = 2) No result provided (*n* = 4)	Methicillin resistant (MRSA)
4930	*P. aeruginosa*	95	244	*Pseudomonas* spp. (*n* = 6) *Acinetobacter baumannii* (*n* = 1) *Stenotrophomonas maltophilia* (*n* = 1) *Proteus* spp. (*n* = 2) No result provided (*n* = 3)	Resistant to carbapenems and fluoroquinolones
4931	*S. pneumoniae*	94	241	*Streptococcus mitis* (*n* = 2) *Streptococcus salivarius* (*n* = 4) *Streptococcus* spp. (*n* = 1) Viridans *Streptococcus* (*n* = 1) *S. epidermidis* (*n* = 2) *Klebsiella* spp. (*n* = 2) No result provided (*n* = 4)	Reduced susceptibility to cefotaxime and ceftriaxone. Susceptible to fluoroquinolones but resistant to clindamycin, erythromycin and penicillin.

laboratories reported *Klebsiella* spp.; one laboratory reported *Enterobacterales* spp. and two laboratories did not provide an identification result for this strain suggesting a lack of laboratory capacity to perform identification at the species level and also suboptimal methodology resulting in misidentifications.

Specimen 4928 contained an *E. coli* strain carrying the *mcr-1* gene, exhibiting resistance to amoxicillin, ampicillin, fluoroquinolones and colistin.

The intended result for amoxicillin-clavulanic acid was susceptible (MIC = 8 mg/L) with both EUCAST and CLSI breakpoints, but on the susceptible breakpoint. The intended result for amoxicillin-clavulanic acid was only achieved by 51.7% of laboratories.

Table 9.2 *E. faecium* (specimen 4926): 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)	Belarus (12)	Bosnia and Herzegovina (10)	Georgia (17)	Kyrgyzstan (6)	Montenegro (8)	North Macedonia (17)	Republic of Moldova (14)	Russian Federation (33)	Serbia (24)	Tajikistan (6)	Turkey (67)	Turkmenistan (4)	Ukraine (5)	Uzbekistan (6)	Kosovo[a] (7)
Identification	–	–	60	100	100	90	94	67	88	100	100	94	100	17	97	100	100	100	43
Amoxicillin	–	R/R	100	100	100	100	100	100	100	100	100	100	100	–	–	100	100	100	100
Ampicillin	>8	R/R	100	100	100	100	100	100	100	100	100	100	100	75	100	100	100	100	100
Gentamicin (high-level resistance)	32	Negative/ Negative	75	100	20	67	7	–	83	50	71	59	61	67	51	–	100	83	100
Teicoplanin	>32	R/R	75	100	100	89	100	–	–	93	100	–	100	–	100	–	100	100	–
Vancomycin	>32	R/R	89	100	100	100	100	100	100	94	100	97	100	–	100	100	100	100	100

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

Interestingly, two laboratories that stated that they followed EUCAST guidelines reported I for amoxicillin-clavulanic acid. However, there is no I category for amoxicillin-clavulanic acid in the 2018 EUCAST clinical breakpoint tables and these two laboratories may need to review and update their methodology.

There was a poor consensus of reported results for colistin, with an intended result of resistant (reference MIC = 4 mg/L, EUCAST breakpoint >2 mg/L). This strain was reported as resistant by 40.9% of laboratories. CLSI has no colistin clinical breakpoints for *E. coli*, and EUCAST's recommendation for colistin susceptibility testing is colistin MIC determination with broth microdilution method only. A substantial portion of the laboratories using EUCAST methodology (105 out of 229, 45.9%) failed to provide a result for colistin susceptibility, a clear indication of how colistin susceptibility testing continues to be a challenge for routine clinical microbiology laboratories. However, among laboratories that reported results for colistin susceptibility using EUCAST methodology (*n* = 124), 15 laboratories (12.1%) stated that they used disk diffusion method.

Correct identification at the species level was achieved by 249 (97%) of the laboratories, and only a few misidentifications were observed: *P. aeruginosa*, *n* = 1; *E. faecalis*, *n* = 1; and *Enterococcus* spp., *n* = 1. Additionally, one laboratory reported the strain as *Enterobacterales* spp. and four laboratories did not provide an identification result for this strain.

Specimen 4929 contained an MRSA strain that was resistant to beta-lactam agents, erythromycin, clindamycin, fluoroquinolones, gentamicin and rifampicin.

Overall concordance for the detection of methicillin resistance was very high; 225 out of 227 laboratories (99.1%) that provided results for cefoxitin correctly reported the strain as resistant to cefoxitin. Among the remaining laboratories (*n* = 30), oxacillin MIC results were provided by 17 laboratories, all correctly reporting the strain as resistant to oxacillin. Thirteen laboratories (5.0%) did not provide a result on methicillin resistance (cefoxitin and/or oxacillin susceptibility).

Table 9.3 *K. pneumoniae* (specimen 4927): 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)	Belarus (12)	Bosnia and Herzegovina (10)	Georgia (17)	Kyrgyzstan (6)	Montenegro (8)	North Macedonia (17)	Republic of Moldova (14)	Russian Federation (33)	Serbia (24)	Tajikistan (6)	Turkey (67)	Turkmenistan (4)	Ukraine (5)	Uzbekistan (6)	Kosovo[a] (7)
Identification	–	–	100	100	100	90	100	100	100	100	100	97	100	33	99	100	100	100	86
Amikacin	0.5–2	S/S	100	100	100	100	100	67	100	100	100	100	100	67	99	100	100	83	100
Amoxicillin	≥128	R/R	100	100	–	100	92	100	100	93	100	–	100	–	–	–	100	100	100
Amoxicillin-clavulanic acid[b]	≥128	R/R	100	100	100	100	100	100	100	100	100	96	100	–	100	100	100	100	86
Ampicillin	≥128	R/R	100	100	100	100	100	100	100	100	100	100	96	33	100	100	100	100	86
Cefotaxime	2	I/I	0	40	9	20	0	0	75	14	14	29	50	–	–	0	80	83	29
Ceftazidime	1	S/S	50	46	36	90	94	0	100	94	14	64	100	–	67	0	80	17	71
Ceftriaxone	1	S/S	50	82	27	56	94	50	50	79	50	33	91	83	61	0	20	33	100
Ciprofloxacin	0.03	S/S	88	100	100	90	82	100	100	100	93	93	100	83	98	100	100	83	100
Colistin	≤0.25	S/–	–	71	100	100	–	–	–	92	–	–	95	–	98	–	100	83	–
Ertapenem	8–64	R/R	83	100	89	100	100	0	86	91	21	100	100	–	100	50	100	0	–
Gentamicin	0.25–0.5	S/S	100	100	100	100	100	67	100	100	100	90	100	83	99	100	100	100	100
Imipenem	4	I/R	25	9	73	40	12	50	50	59	29	38	57	–	52	33	40	33	43
Levofloxacin[c]	–	S/S	100	100	100	100	100	100	100	100	100	92	100	–	97	100	100	100	100
Meropenem	4	I/R	38	9	55	30	6	33	57	29	14	24	61	–	54	50	80	0	40
Ofloxacin[c]	–	S/S	83	100	100	–	100	100	100	100	93	–	100	–	–	0	100	83	100
Piperacillin-tazobactam	≥128	R/R	100	100	100	100	100	100	100	100	100	100	100	–	100	100	100	100	100
Tobramycin	0.25	S/S	100	100	100	100	100	100	100	100	100	85	100	–	–	100	100	100	100

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

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

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

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

Approximately 94% of laboratories (*n* = 257) correctly detected methicillin resistance in this strain, which is a clear improvement as compared with last year's results for the detection of methicillin resistance in another *S. aureus* strain (specimen 4324) where 16% of participating laboratories failed to detect cefoxitin resistance.

Table 9.4 *E. coli* (specimen 4928): 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)	Belarus (12)	Bosnia and Herzegovina (10)	Georgia (17)	Kyrgyzstan (6)	Montenegro (8)	North Macedonia (17)	Republic of Moldova (14)	Russian Federation (33)	Serbia (24)	Tajikistan (6)	Turkey (67)	Turkmenistan (4)	Ukraine (5)	Uzbekistan (6)	Kosovo[a] (7)
Identification	–	–	90	100	100	100	100	100	88	100	100	94	100	33	100	100	100	100	100
Amikacin	≤4	S/S	71	100	100	100	100	67	100	100	100	97	100	50	99	100	100	100	100
Amoxicillin	>32	R/R	100	100	–	100	–	100	100	100	100	–	100	–	–	100	100	100	100
Amoxicillin-clavulanic acid[b]	8	S/S	50	0	83	80	71	50	50	75	14	79	73	–	37	0	0	0	86
Ampicillin	>32	R/R	100	91	92	100	100	100	100	100	100	100	100	75	100	100	100	100	100
Cefotaxime	≤0.5	S/S	100	100	75	90	100	100	100	100	100	86	100	–	–	–	100	67	100
Ceftazidime	≤0.5	S/S	75	91	80	90	100	33	88	100	86	93	100	–	97	100	100	67	100
Ceftriaxone	0.12	S/S	75	100	91	100	88	100	100	100	100	82	100	83	98	100	100	67	100
Ciprofloxacin	>2	R/R	88	100	100	90	100	100	100	100	100	97	100	67	100	100	100	83	100
Colistin	4	R/–	–	100	14	33	–	–	–	50	–	–	32	–	43	–	50	0	–
Ertapenem	≤0.12	S/S	100	100	100	87	100	100	71	100	71	92	100	–	97	50	100	33	60
Gentamicin	≤0.5	S/S	71	100	92	90	88	67	100	100	100	87	100	83	99	100	100	100	100
Imipenem	≤0.5	S/S	75	55	100	100	94	50	100	100	79	97	100	–	100	0	80	33	100
Levofloxacin[c]	–	R/R	100	100	100	100	100	100	88	100	100	100	100	–	94	100	100	67	–
Meropenem	≤0.12	S/S	88	100	100	100	100	83	100	100	43	97	100	–	100	100	100	67	60
Ofloxacin[c]	–	R/R	100	100	100	–	100	100	100	100	100	–	100	–	–	–	100	83	100
Piperacillin-tazobactam	4	S/S	100	100	100	90	100	67	75	100	79	71	100	–	94	100	100	17	83
Tobramycin	≤2	S/S	88	100	100	100	100	100	100	100	100	83	100	–	–	100	100	83	60

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

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

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

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

Among laboratories returning results for vancomycin susceptibility (n = 200), two reported vancomycin disk diffusion test results even though vancomycin susceptibility for *S. aureus* should only be tested with a MIC method. Laboratories using disk diffusion as the routine method for AST should consider having

an additional MIC method (e.g. vancomycin gradient strip tests) for testing vancomycin susceptibility of *S. aureus* isolates.

Correct identification at the species level was achieved by 248 (97%) of the laboratories, and only a few misidentifications were observed: *S. epidermidis*, *n* = 2; coagulase-negative *Staphylococcus* spp., *n* = 1; and *Streptococcus* spp., *n* = 2. Four laboratories did not provide an identification result for this strain.

Specimen 4930 was a strain of *P. aeruginosa*, which was susceptible to aminoglycosides, ceftazidime, piperacillin-tazobactam and colistin. The strain was resistant to imipenem, meropenem, ciprofloxacin and levofloxacin.

An excellent concordance was achieved for amikacin, imipenem, meropenem, ciprofloxacin and levofloxacin among the participating laboratories and the concordance for tobramycin and gentamicin was

Table 9.5 *S. aureus* (specimen 4929): 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)	Belarus (12)	Bosnia and Herzegovina (10)	Georgia (17)	Kyrgyzstan (6)	Montenegro (8)	North Macedonia (17)	Republic of Moldova (14)	Russian Federation (33)	Serbia (24)	Tajikistan (6)	Turkey (67)	Turkmenistan (4)	Ukraine (5)	Uzbekistan (6)	Kosovo[a] (7)
Identification	–	–	80	100	100	100	100	100	100	100	100	94	100	50	99	100	100	100	86
Cefoxitin	>64	R/R	88	100	100	100	100	100	100	100	100	100	100	–	100	–	100	83	100
Ciprofloxacin	≥128	R/R	100	100	100	100	100	100	100	100	100	100	100	50	99	100	100	67	100
Clindamycin	≥128	R/R	100	100	91	100	100	100	100	100	100	100	100	–	100	100	100	67	100
Erythromycin	≥128	R/R	100	100	100	100	100	100	100	100	100	100	100	50	98	100	100	67	100
Fusidic acid	0.06–0.12	S/–	–	86	100	100	–	–	100	100	100	–	100	–	100	–	100	83	100
Gentamicin	64	R/R	75	100	100	100	88	100	88	100	71	97	100	67	96	100	100	83	100
Linezolid	1–2	S/S	–	100	100	88	100	100	100	100	100	100	100	–	97	100	100	83	–
Oxacillin	–	R/R	–	100	100	100	–	–	100	100	–	–	100	–	100	100	100	80	100
Penicillin	>64	R/R	100	100	100	100	100	100	100	100	100	100	100	–	98	100	100	83	100
Rifampicin	≥128	R/R	100	100	100	100	100	100	100	100	100	100	100	–	100	100	100	83	100
Teicoplanin	≤0.25–0.5	S/S	–	100	91	100	–	–	–	93	100	–	100	–	94	–	100	100	–
Tetracycline	≤0.12–0.25	S/S	67	100	100	100	100	100	100	100	100	95	100	–	98	100	100	100	100
Vancomycin	1	S/S	–	100	92	100	89	–	83	88	100	96	96	–	96	67	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.

satisfactorily. However, laboratories had issues in AST of ceftazidime (MIC = 4 mg/L), piperacillin-tazobactam (MIC = 16 mg/L) and colistin (MIC = 1 and 2 mg/L – as determined independently by two reference laboratories), which were all S by both EUCAST and CLSI.

Ceftazidime susceptibility was reported by 244 laboratories of which 138 (56.6%) correctly reported results as S, and piperacillin-tazobactam susceptibility was reported by 227 laboratories of which 108 (47.6%) correctly reported results as S. Ceftazidime and piperacillin-tazobactam are among the first-line antimicrobials used in the treatment of *P. aeruginosa* infections. Reporting these primary agents as non-susceptible may lead to use of agents with broader spectrum or with increased toxicity.

The concordance for colistin susceptibility results was very high; 126 out of 138 laboratories (91.3%) correctly reported results as S. However, 46.3% (*n* = 119) of laboratories failed to provide results for colistin susceptibility.

Satisfactory performance was obtained for the identification; 244 (95%) of the laboratories correctly identified the strain as *P. aeruginosa*, and another six laboratories provided an identification as *Pseudomonas* spp. Misidentifications were observed in four laboratories: *A. baumannii*, *n* = 1; *S. maltophilia*, *n* = 1; and *Proteus* spp., *n* = 2. Three laboratories did not provide an identification result for this strain.

Table 9.6 *P. aeruginosa* (specimen 4930): 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)	Belarus (12)	Bosnia and Herzegovina (10)	Georgia (17)	Kyrgyzstan (6)	Montenegro (8)	North Macedonia (17)	Republic of Moldova (14)	Russian Federation (33)	Serbia (24)	Tajikistan (6)	Turkey (67)	Turkmenistan (4)	Ukraine (5)	Uzbekistan (6)	Kosovo[a] (7)
Identification	–	–	90	100	100	100	100	100	88	94	100	91	96	67	97	100	100	100	86
Amikacin	4	S/S	71	100	100	100	100	100	100	100	100	94	100	100	99	100	100	100	100
Ceftazidime	4	S/S	14	82	70	80	88	33	0	88	14	62	75	–	43	100	60	17	71
Ciprofloxacin	8–16	R/R	100	100	100	100	100	100	100	100	100	100	100	67	100	100	100	100	100
Colistin	1–2	S/S	–	0	100	100	–	–	–	100	–	–	100	–	97	–	100	100	–
Gentamicin	2	S/S	86	100	83	90	100	100	100	94	100	90	100	83	97	100	100	67	86
Imipenem	16	R/R	75	100	100	100	100	100	88	100	93	100	100	–	99	100	100	100	100
Levofloxacin[b]	–	R/R	100	100	100	100	100	100	100	100	100	100	100	–	100	100	100	100	100
Meropenem	16	R/R	88	100	100	100	100	100	100	100	100	97	100	–	100	100	100	100	100
Piperacillin-tazobactam	16	S/S	38	64	67	50	100	50	57	35	7	72	42	–	39	–	25	0	71
Tobramycin	1	S/S	88	100	100	100	100	100	86	94	100	100	100	–	96	100	100	67	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.

Table 9.7 *S. pneumoniae* (specimen 4931): 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)	Belarus (12)	Bosnia and Herzegovina (10)	Georgia (17)	Kyrgyzstan (6)	Montenegro (8)	North Macedonia (17)	Republic of Moldova (14)	Russian Federation (33)	Serbia (24)	Tajikistan (6)	Turkey (67)	Turkmenistan (4)	Ukraine (5)	Uzbekistan (6)	Kosovo[a] (7)
Identification	–	–	90	100	100	100	100	100	100	100	100	85	100	33	91	100	100	100	100
Cefotaxime	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Cefotaxime (meningitis)	–	I/I	–	–	50	13	0	0	–	–	–	–	13	–	26	–	60	20	0
Cefotaxime (pneumonia)	–	I/S	–	–	40	22	44	–	–	33	–	–	24	–	29	–	60	40	0
Ceftriaxone	1–2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Ceftriaxone (meningitis)	–	I/I–R	–	43	67	0	0	0	0	11	–	–	9	–	–	–	60	50	0
Ceftriaxone (pneumonia)	–	I/S–I	–	43	50	22	44	–	0	9	–	–	17	–	–	–	60	67	20
Clindamycin[b]	–	R/R	83	100	82	88	50	50	63	94	86	–	88	–	78	–	100	67	57
Erythromycin	≥128	R/R	87	100	83	100	88	100	88	100	86	88	100	–	92	100	100	100	83
Levofloxacin	1	S/S	100	100	83	100	100	100	100	94	100	93	100	–	95	100	100	100	100
Moxifloxacin	0.12	S/S	100	100	100	100	100	–	100	94	100	100	100	–	94	100	100	100	–
Norfloxacinb	–	S/S	–	100	–	100	–	100	100	86	100	100	100	–	–	–	100	100	–
Penicillin	4	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Penicillin (meningitis)	–	R/R	100	–	100	100	–	–	60	100	100	100	100	–	94	–	100	83	50
Penicillin (pneumonia)	–	R/I	–	83	22	10	–	–	0	22	8	–	4	–	26	–	67	0	0

[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 4931 contained a strain of *S. pneumoniae* that was susceptible to levofloxacin and moxifloxacin but expressed reduced susceptibility to cefotaxime (MIC = 1 mg/L) and ceftriaxone (MIC = 1 and 2 mg/L – as determined independently by two reference laboratories) and was resistant to erythromycin, clindamycin and penicillin (MIC = 4 mg/L).

A very good concordance was achieved for levofloxacin and moxifloxacin; correct results were reported by 97.4% (223/229) of laboratories for levofloxacin and 97.4% (187/192) of laboratories for moxifloxacin. As in previous years, problems were observed with results for beta-lactam antibiotics in a strain of

S. pneumoniae with reduced susceptibility to cefotaxime/ceftriaxone (MIC = 1–2 mg/L) and resistant to penicillin (MIC = 4 mg/L) by EUCAST categorization. For each agent, participants found the strain to be more susceptible than was the case.

For penicillin and meningitis, the intended result was R with both EUCAST and CLSI clinical breakpoints. Among 176 laboratories that returned results, 166 (94.3%) reported the correct result. For penicillin and pneumonia (EUCAST: R and CLSI: I), 163 laboratories returned results. Among laboratories following EUCAST, a correct result (R) was reported by 22.2% (32/144 laboratories), and among laboratories following CLSI, a correct result (I) was reported by 10.5% (2/19 laboratories), whereas 47.4% (9/19) of laboratories reported S.

Similar problems were noticed in results for cefotaxime and ceftriaxone in meningitis and pneumonia. In meningitis, correct results for cefotaxime (I with both EUCAST and CLSI) were received from 20.1% (27/134) of laboratories, whereas 61.2% (82/134) of laboratories reported S. In pneumonia, correct results for cefotaxime (EUCAST: I and CLSI: S) were received from 28.6% (38/133) of laboratories. The low concordance observed was mainly due to laboratories following EUCAST among which 71.8% (84/117) reported the result as S. In meningitis, correct result for ceftriaxone (EUCAST: I and CLSI: I or R) was received from 19.4% (28/144) of laboratories. In pneumonia, correct result for ceftriaxone (EUCAST: I and CLSI: S or I) was received from 25.5% (36/141) of laboratories, whereas 76.2% (96/126) of laboratories following the EUCAST methodology reported the result as S.

Correct identification at the species level was achieved by 241 (94%) of the laboratories, and a number of misidentifications were observed: *S. mitis*, *n* = 2; *S. salivarius*, *n* = 4; *S. epidermidis*, *n* = 2; and *Klebsiella* spp., *n* = 2. Additionally, one laboratory reported the strain as *Streptococcus* spp. and one another as viridans group *Streptococcus*. Four laboratories did not provide an identification result for this strain.

9.3 Summary of the first six years of CAESAR EQA (2013–2018)

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.

9.3.1 Expansion of the CAESAR EQA

Between 2013 and 2018, the number of participating laboratories in the CAESAR EQA exercise increased to 287 laboratories in 18 countries or areas (Table 9.8). The CAESAR EQA started in 2013 with 128 laboratories from eight countries or areas (Belarus, Georgia, Kyrgyzstan, Montenegro, Serbia, North Macedonia, Turkey and Kosovo[1]). In 2014, the number of laboratories increased to 184 with the inclusion of four countries (Albania, Azerbaijan, Bosnia and Herzegovina and the Russian Federation). In 2015, the number of laboratories increased to 252 with the Republic of Moldova, Tajikistan and Turkmenistan joining the EQA exercise. In 2016, three more countries (Armenia, Ukraine and Uzbekistan) enrolled in the exercise, and the number of laboratories increased to 272. No new countries have joined the EQA exercise since 2016, and 290 and 287 laboratories participated in 2017 and 2018 exercises, respectively.

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 are strongly encouraged to put more efforts into correct identification at the species level. The EQA

Table 9.8 Countries or areas participating in the CAESAR EQA exercise, 2013–2018

Country or area	Year (no. of returned results/total no. of laboratories)					
	2013	2014	2015	2016	2017	2018
Belarus	8/8	6/8	8/8	9/9	13/13	12/13
Georgia	1/1	5/9	10/10	10/11	0/13[b]	17/17
Kyrgyzstan	3/3	5/5	5/5	6/6	6/6	6/6
Montenegro	1/1	6/7	8/9	9/10	7/8	8/8
North Macedonia	15/16	13/17	16/17	19/21	19/21	17/18
Serbia	14/14	14/14	14/14	21/22	22/22	24/24
Turkey	72/78	68/77	98/106	81/90	81/87	67/71
Kosovo[a]	6/7	7/7	7/7	7/7	7/7	7/7
Albania	–	2/2	6/7	7/9	10/11	10/10
Azerbaijan	–	3/3	3/3	3/3	3/3	0/3[b]
Bosnia and Herzegovina	–	4/4	7/7	9/9	10/10	10/10
Russian Federation	–	26/31	31/39	40/41	33/47	33/53
Republic of Moldova	–	–	12/12	12/12	12/12	14/14
Tajikistan	–	–	1/5	4/5	0/5[b]	6/7
Turkmenistan	–	–	3/3	3/3	3/3	4/4
Armenia	–	–	–	5/5	11/11	11/11
Ukraine	–	–	–	3/3	5/5	5/5
Uzbekistan	–	–	–	6/6	6/6	6/6
Total	120/128 (94%)	159/184 (86%)	229/252 (91%)	254/272 (93%)	248/290 (91%)[c]	257/287 (91%)[c]

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

[b] Laboratories in Georgia (2017), Tajikistan (2017) and Azerbaijan (2018) could not take part in the 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 for 2017 and n = 284 for 2018).

strains distributed and the percentage of correct identification among the participating laboratories by year 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 six 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 as well.

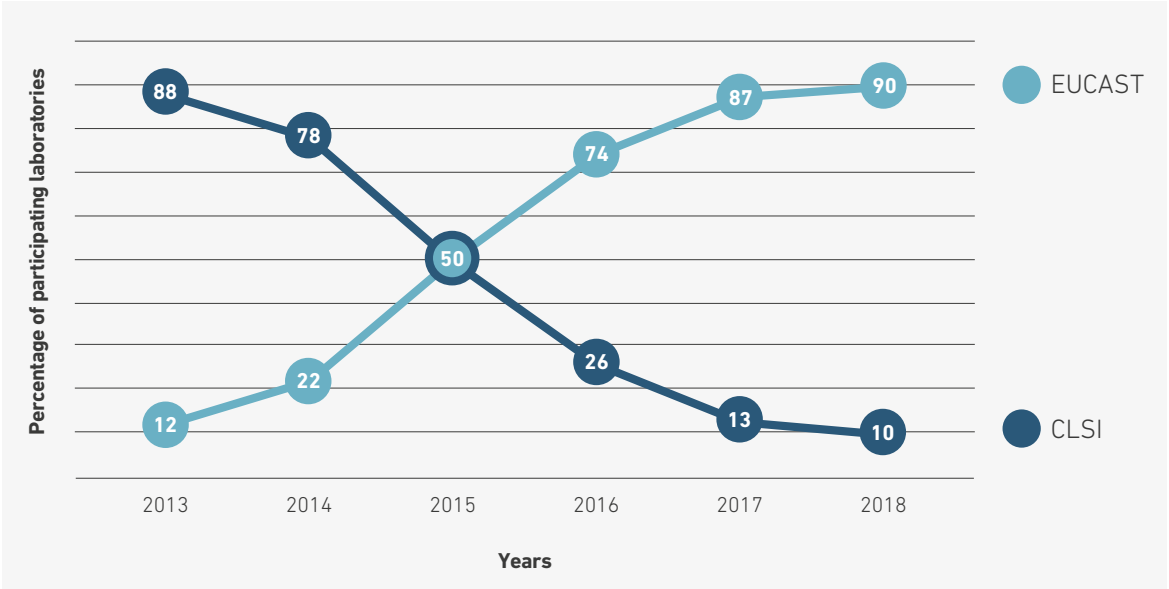
9.3.3 Trends in AST guidelines

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 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 2018, was used as the guideline in 90% of 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

Table 9.9 Specimens distributed as part of the CAESAR EQA and the percentage of correct identification at the species level among participating laboratories, 2013–2018

Organism	Year											
	2013		2014		2015		2016		2017		2018	
	Specimen no.	%	Specimen no.	%	Specimen no.	%	Specimen no.	%	Specimen no.	%	Specimen no.	%
E. coli	1951	100	2496	100	3092	94	3682	99	4326	99	4928	97
K. pneumoniae	1952	97	2497	92	3089	99	3683	91	4327	98	4927	96
P. aeruginosa	1956	100	–	–	3093	99	3684	100	–	–	4930	95
A. baumannii complex	1950	87	2501	98	–	–	3686	91	4328	96	–	–
S. aureus	1953	100	2498	99	3090	99	3685	98	4324	100	4929	97
S. pneumoniae	1954	99	2499	99	3091	100	3687	98	4323	99	4931	94
E. faecium	–	–	2500	87	–	–	–	–	4325	88	4926	91
E. faecalis	–	–	–	–	3088	98	–	–	–	–	–	–

Fig. 9.3 Trends in AST guidelines used by CAESAR EQA participating laboratories, 2013–2018



EUCAST documents into local languages such as Russian, Serbian and Turkish may have contributed to the uptake of the EUCAST methodology in those settings.

9.3.4 Future perspectives and the need for improvement

The CAESAR EQA showed a remarkable growth in the number of participating laboratories between 2013 and 2018, now including 287 laboratories in 18 countries and areas. Building functioning quality assurance systems in the 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 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 publication of the fifth CAESAR annual report, the 2019 edition, coincides with several major international initiatives for sustaining the global efforts to control AMR. In particular, the Ad hoc Interagency Coordination Group (IACG) on Antimicrobial Resistance released its final report in 2019. The IACG was convened in March 2017 following the political declaration of the United Nations high-level meeting on AMR in 2016. The IACG's mandate is to "provide practical guidance for approaches needed to ensure sustained effective global action to address antimicrobial resistance" *(1)*. The IACG recommendations were presented to the Secretary-General, who reported to the Seventy-first session of the United Nations General Assembly in September 2019. These recommendations highlighted the need for the One Health approach to the threat of AMR, including "integrated monitoring and surveillance systems" at national level. The results achieved since the creation of the CAESAR network in 2012 move undoubtedly towards that direction, pointing at the experience of the WHO European Region as a best practice for regional surveillance of AMR.

Looking at the WHO European Region, the last 12 months were also marked by the publication of a landmark study on the burden of infections associated with antibiotics resistance in the EU/EEA countries *(2)*. Taking into account only the year 2015, the authors estimated that antibiotic-resistant infections caused 33 110 attributable deaths and 874 541 disability-adjusted life-years. The importance of this study is its contribution to generating scientific evidence about the overall impact of AMR on health at population level. More efforts should be devoted to this task to provide essential information for policy-makers. The plan for the coming years is to learn from all the existing international experiences and generate epidemiological estimates on the burden of AMR that are specific to the countries and areas participating in CAESAR.

The reporting period for the current CAESAR annual report includes several essential achievements. First, all members of the CAESAR network have made sustained efforts to enhance surveillance-related activities. Second, compared with the 2018 report, one more member of the surveillance network is reporting AMR data to CAESAR, bringing the total to 12 countries/areas, with an additional two countries in the process of setting up systematic reporting of resistance data. Third, participation in the CAESAR EQA has been expanding further, reaching 257 laboratories from 17 countries/areas.

Since the CAESAR network was established, remarkable results have been achieved through the implementation of the PoP projects. These projects aim at addressing the underutilization of bacteriological diagnostics in clinical practice – a primary obstacle to the expansion of a laboratory-based surveillance network such as CAESAR – with the ultimate goal of improving clinical care for patients admitted with suspected bloodstream infections. Previous PoP projects in Georgia (2015–2016) and Armenia (2017–2018) have provided initial insights into the resistance patterns of these two countries and have eventually led to the inclusion of their AMR surveillance data in the CAESAR database. The interest in the beneficial effects of the PoP project has steadily grown among the members of the CAESAR network. Currently, the project is ongoing in Tajikistan and Uzbekistan, marking a first for the implementation of PoP in central Asia. Preliminary results from the two countries are already showing improvements in laboratory capacity, particularly for blood culture processing and AST. Interest in this regional approach has also grown outside the WHO European Region, as Jordan and Nigeria are considering embarking on similar PoP projects.

CAESAR is a regional surveillance network with a specific geographical focus. At the same time, there is widespread recognition among its members that the goal of establishing and strengthening AMR surveillance systems in the European Region can only be achieved through concerted efforts at the international and global levels. In this perspective, the WHO Regional Office for Europe and ECDC have worked closely to integrate their reporting systems, and they will be issuing next year a joint report on AMR surveillance in the European Region. Moreover, it is important also to acknowledge how much the experience gained from CAESAR has contributed significantly to the development of GLASS, to which more and more CAESAR members are signing up.

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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 localized or systemic impairment of immune defences;
- commonly causes hospital-acquired pneumonia (including ventilator-associated pneumonia) and bloodstream and urinary tract infections;
- is difficult to control in hospitals and institutional environments, because of its ubiquity, enormous versatility and intrinsic tolerance to many detergents, disinfectants and antimicrobial compounds;
- 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 as susceptible, standard dosing regimen/susceptible, increased exposure/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

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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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