World Health Organization
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Central Asian and European Surveillance of Antimicrobial Resistance

Annual report 2020

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Abstract

This report describes resistance data from isolates obtained in 2019 from 12 countries in the WHO European Region - Armenia, Belarus, Bosnia and Herzegovina, Georgia, Montenegro, North Macedonia, the Republic of Moldova, the Russian Federation, Serbia, Switzerland, Turkey, Ukraine - and Kosovo[1]. The sixth Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) report includes resistance data from the Republic of Moldova for the first time, as well as information on the status of the overall coordination and surveillance of antimicrobial resistance (AMR) for all network members, results from the CAESAR external quality assessment (EQA) exercise in 2019, and a summary of the seven EQA exercises performed between 2013 and 2019. Furthermore, as in previous editions a reader's guide is included that supports cautious interpretation of surveillance data, taking data reliability and representativeness into account. WHO and partners are committed through the CAESAR network and its activities, to improve AMR surveillance in the region, to encourage the international sharing of data, and to guide countries that are building and improving AMR surveillance.

Keywords

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

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1 All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

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Acknowledgements

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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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Abbreviations

A. baumannii	*Acinetobacter baumannii*
AMR	antimicrobial resistance
AST	antimicrobial susceptibility testing
CAESAR	Central Asian and European Surveillance of Antimicrobial Resistance
cfr	chloramphenicol-florfenicol resistance
CLSI	Clinical and Laboratory Standards Institute
COVID-19	coronavirus disease
CSF	cerebrospinal fluid
E. coli	*Escherichia coli*
E. faecalis	*Enterococcus faecalis*
E. faecium	*Enterococcus faecium*
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EQA	external quality assessment
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GLASS	Global Antimicrobial Resistance and Use Surveillance System
IPC	infection prevention and control
ISO	International Organization for Standardization
K. pneumoniae	*Klebsiella pneumoniae*
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
P. aeruginosa	*Pseudomonas aeruginosa*

P. fluorescens	*Pseudomonas fluorescens*
S. aureus	*Staphylococcus aureus*
S. epidermidis	*Staphylococcus epidermidis*
S. mitis	*Streptococcus mitis*
S. pneumoniae	*Streptococcus pneumoniae*
spp.	species (for specific bacteria)
susceptibility category (S/I/R)	susceptibility of a pathogen to an antimicrobial agent according to clinical breakpoints S = susceptible, standard dosing regimen I = susceptible, increased exposure R = resistant
TrACSS	Tripartite AMR country self-assessment survey
UK NEQAS	United Kingdom National External Quality Assessment Service for Microbiology

Summary

The Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) network is an initiative of the WHO Regional Office for Europe, the Netherlands National Institute for Public Health and the Environment, and the European Society of Clinical Microbiology and Infectious Diseases. CAESAR 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]. Twelve countries (Armenia, Belarus, Bosnia and Herzegovina, Georgia, Montenegro, North Macedonia, the Republic of Moldova, the Russian Federation, Serbia, Switzerland, Turkey and Ukraine) and Kosovo[1] submitted AMR data from isolates obtained in 2019 to the CAESAR database. The Republic of Moldova reported AMR data for the first time during this reporting period.

Chapter 2 contains 10 selected AMR maps of the WHO European Region, combining data collected by CAESAR and the European Antimicrobial Resistance Surveillance Network. Chapters 6 and 7 present country- and area-specific proportions of resistance observed for the nine pathogens under surveillance in 2019. 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 WHO 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 quality of antimicrobial susceptibility testing performed or the selection of patients eligible for blood culturing. 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 provides an overview of recent progress made by network members. 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. However, more

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investment in networks, laboratories and standardization, and properly outfitted reference laboratories are needed.

Strong political support is needed to continue making progress. One challenge that remains year after year is the limited routine antimicrobial susceptibility testing performed in many countries caused by the underutilization of microbiological diagnostics in clinical practice. The proof-of-principle AMR routine diagnostics surveillance project was established in 2015, 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. Armenia and Georgia have successfully completed proof-of-principle projects in recent years, which was a starting point for national AMR surveillance and contributing data to CAESAR. Currently proof-of-principle projects are ongoing in Tajikistan and Uzbekistan, and also other countries beyond the WHO European Region.

Chapter 8 describes the results from the CAESAR external quality assessment exercise conducted in 2019. Overall, the results were good, and the number of participants has increased from 120 laboratories in eight countries/areas in 2013 to 240 laboratories in 18 countries/areas in 2019. 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 12% in 2013 to 89% in 2019. 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

The CAESAR 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). 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 one area, Kosovo[1], are engaged in the CAESAR network, with more than 50% of them providing data.

AMR is a slow but steadily growing health crisis, and the CAESAR network is committed to provide tailored assistance to all countries and areas in the WHO European Region planning to build or improve their AMR surveillance systems. Despite steady progress, a look back shows a challenging year for the fight against AMR to which all are committed. The coronavirus disease (COVID-19) pandemic and its effects on health and health care have demonstrated just how urgently investments for a comprehensive approach to AMR, including quality of care and AMR surveillance, are needed.

Reportedly, misuse and overuse of antibiotics have amplified in the Region during the pandemic. Many of the routine clinical practices relied on for laboratory-based AMR surveillance were largely abandoned and efforts and resources directed elsewhere. It will be in 2021, when looking back at CAESAR data from 2020, when the real impact of COVID-19 on national health systems and surveillance networks' efforts to carry out antimicrobial susceptibility testing and surveillance activities will be evident.

On a positive note, all CAESAR network members managed, despite great difficulty and conflicting demands on time and resources in many cases, to report network updates. Furthermore, all 12 countries and areas that submitted 2018 data to CAESAR were able to submit 2019 data as well, and one additional country submitted data for the first time during this reporting period. Given that data for this report have been generated during 2019, no major impact on data outputs was observed. At the time of publication of this report, 25 countries and areas of the WHO European Region had enrolled in the Global Antimicrobial Resistance and Use Surveillance System (GLASS), and hopefully by November 2021 this number will have further increased.

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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 2019. In 2019, 12 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)*. Data for Serbia and Kosovo[1] were combined for this chapter. 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/areas 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 2019, 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%. Resistance of 50% or higher was found in North Macedonia,[2] the Republic of Moldova,[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 2019, resistance proportions exceeding 50% were observed in Georgia,[2] North Macedonia[2], the Republic of Moldova[2] and Turkey, whereas the Scandinavian countries, Austria, Belgium, France, the Netherlands and Slovenia reported the lowest resistance proportions (5-10%, Fig 2.2). The recent emergence of carbapenem-resistant *E. coli* is of serious concern. Belarus,[2] Georgia,[2] North Macedonia,[2] the

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2 CAESAR country with level B data

Republic of Moldova,[2] the Russian Federation,[2] Spain, Turkey and Ukraine reported resistance proportions of 1% or higher in 2019 (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. Third-generation cephalosporin resistance in *K. pneumoniae* has become quite widespread in the WHO European Region. In general, countries in the southern and eastern parts of the Region report high proportions, while proportions below 10% were observed in the Scandinavian countries, the Netherlands and Switzerland (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, Bosnia and Herzegovina, Bulgaria, Georgia,[2] Italy, Romania, the Russian Federation,[2] Serbia and Turkey reported proportions between 25% and 50%, and Belarus,[2] Greece, the Republic of Moldova[2] and Ukraine[2] reported proportions exceeding 50% (Fig. 2.5). These high proportions of third-generation cephalosporin 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. Large differences are seen in the proportions of carbapenem-resistant *P. aeruginosa* within the WHO European Region (Fig. 2.6). Resistance <5% was observed in Iceland and Denmark, whereas Belarus,[2] Georgia,[2] the Republic of Moldova,[2] Romania, the Russian Federation,[2] Serbia and Ukraine[2] reported proportions exceeding 50%.

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. *Acinetobacter* spp. can persist in the health care environment and are difficult to eradicate once established. The proportions of carbapenem-resistant *Acinetobacter* spp. vary widely within the WHO European Region, from <1% in Belgium, Denmark, Finland, Malta, the Netherlands and Norway to >50% in many countries in southern and eastern Europe (Fig. 2.7). These high proportions of carbapenem resistance are concerning, may reflect the spread of resistant strains in the health care setting and indicate 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. Denmark, Estonia, Finland, the Netherlands, Norway, Sweden, 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.

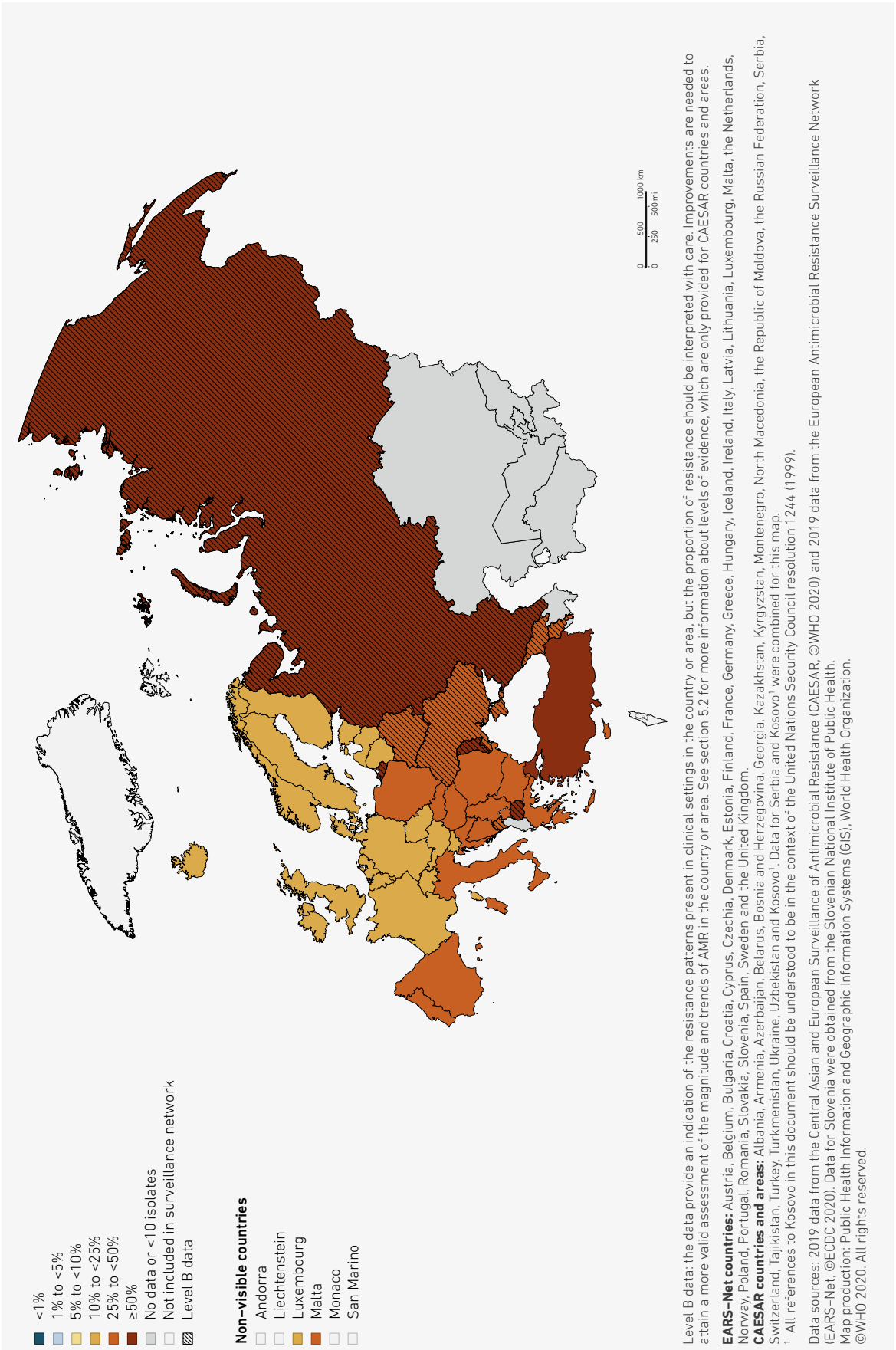
2.2.6 *Streptococcus pneumoniae*

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). Czechia, Denmark, Estonia and the Netherlands report proportions lower than 5%, whereas proportions >25% were found in Belarus,[2] Bosnia and Herzegovina, France, Malta, North Macedonia,[2] 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 Belgium, Finland, France, Iceland, Malta, the Netherlands and Ukraine,[2] 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 WHO European Region (EARS–Net and CAESAR), by country or area, 2019



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.

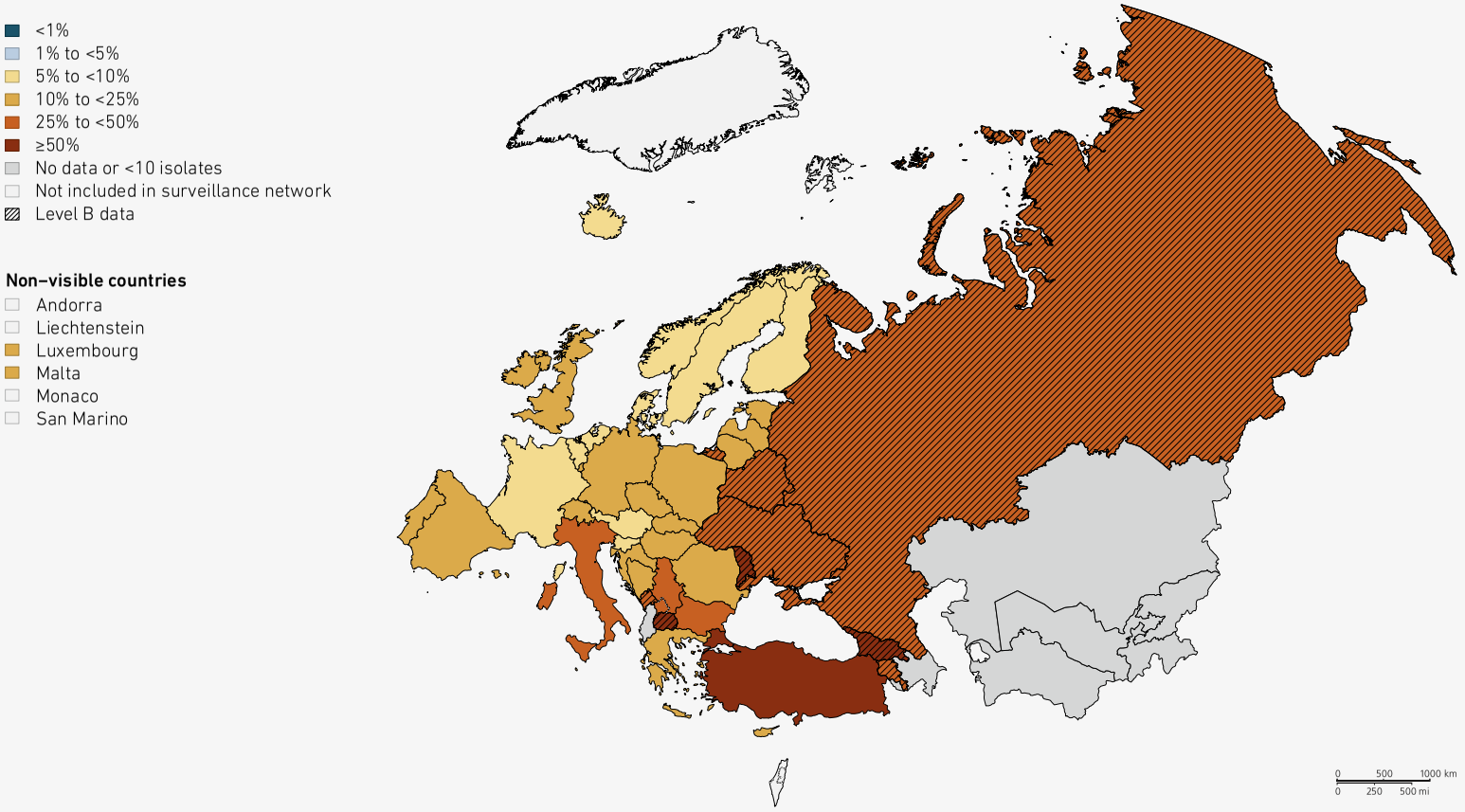
EARS–Net countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.

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 in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

Data sources: 2019 data from the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2020) and 2019 data from the European Antimicrobial Resistance Surveillance Network (EARS–Net, ©ECDC 2020). Data for Slovenia were obtained from the Slovenian National Institute of Public Health.
Map production: Public Health Information and Geographic Information Systems (GIS), World Health Organization.

Fig. 2.2 Percentage of invasive *E. coli* isolates resistant to third-generation cephalosporins in the WHO European Region (EARS-Net and CAESAR), by country or area, 2019



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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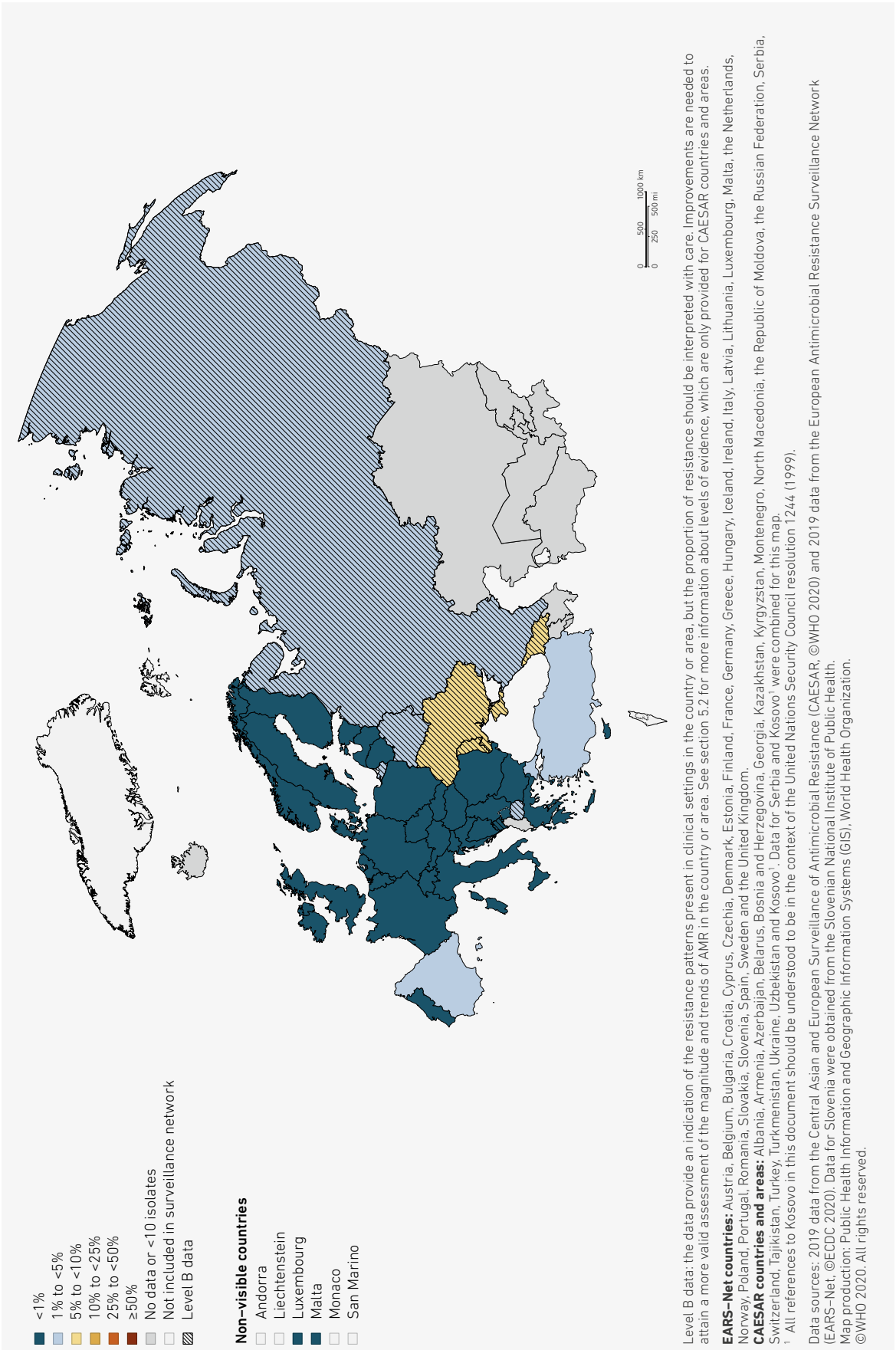
Map production: Public Health Information and Geographic Information Systems (GIS), World Health Organization.

Fig. 2.3 Percentage of invasive *E. coli* isolates resistant to carbapenems in the WHO European Region (EARS–Net and CAESAR), by country or area, 2019



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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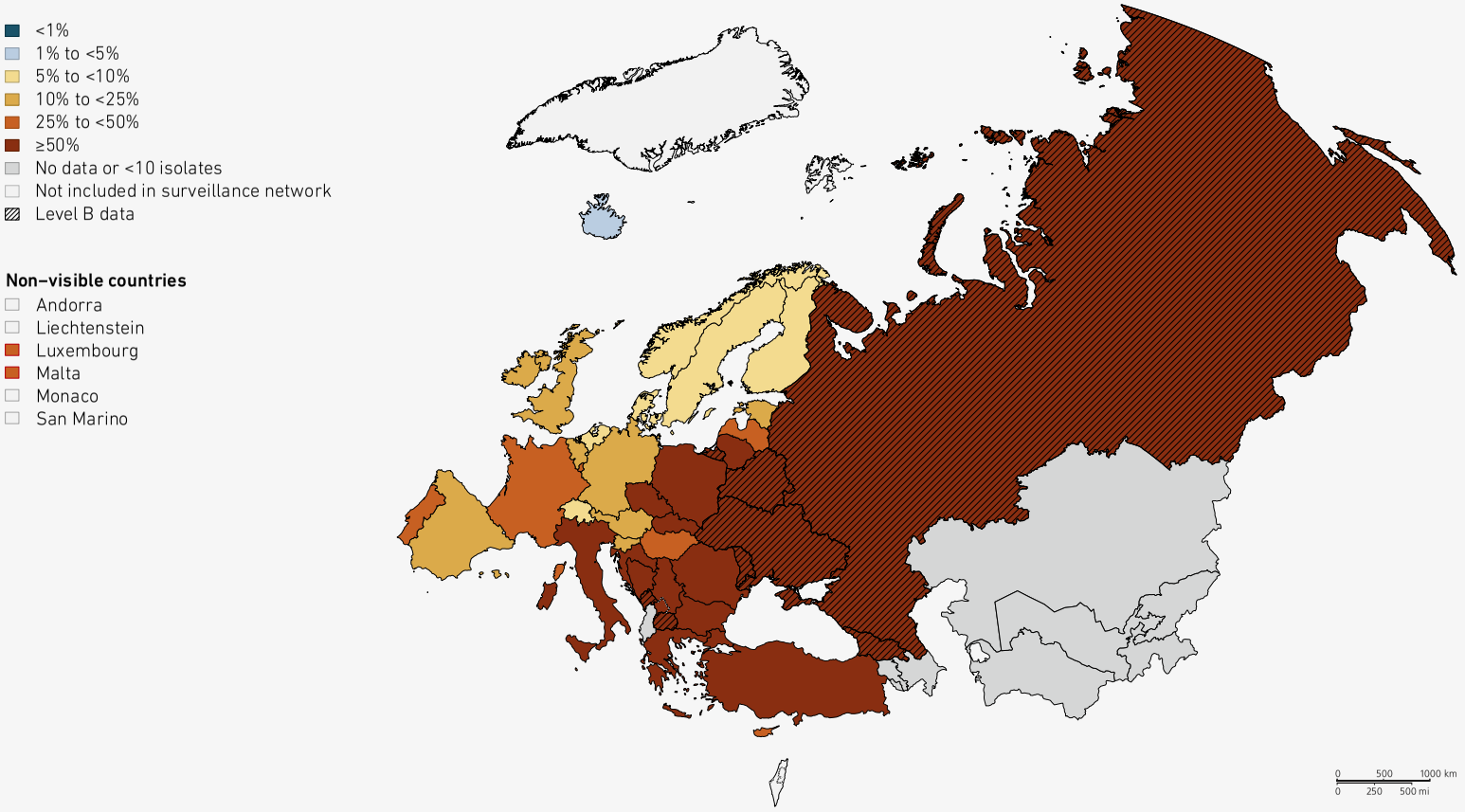
Map production: Public Health Information and Geographic Information Systems (GIS), World Health Organization.

Fig. 2.4 Percentage of invasive *K. pneumoniae* isolates resistant to third-generation cephalosporins in the WHO European Region (EARS-Net and CAESAR), by country or area, 2019



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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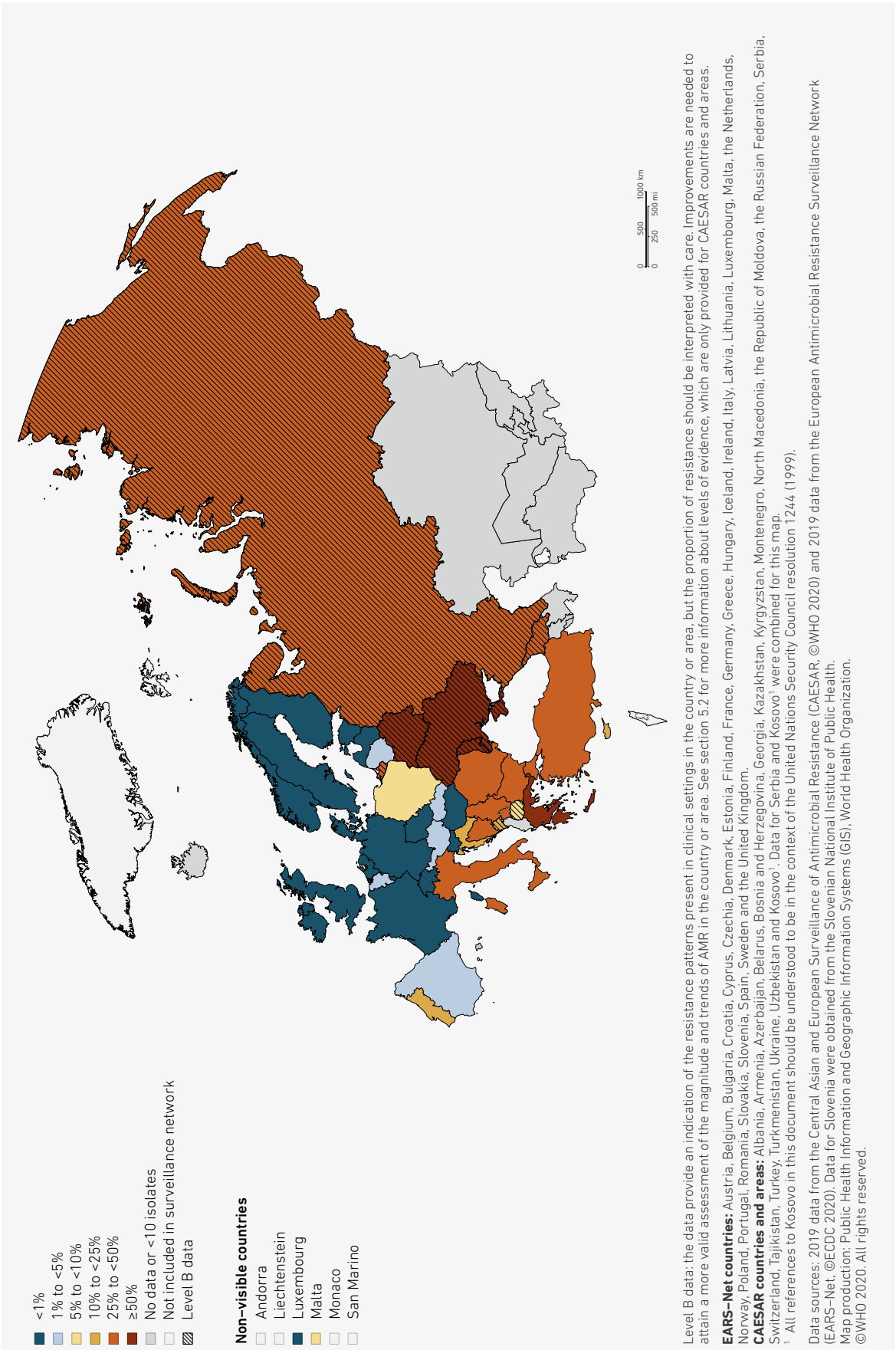
Data sources: 2019 data from the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2020) and 2019 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2020). Data for Slovenia were obtained from the Slovenian National Institute of Public Health.
Map production: Public Health Information and Geographic Information Systems (GIS), World Health Organization.

Fig. 2.5 Percentage of invasive *K. pneumoniae* isolates resistant to carbapenems in the WHO European Region (EARS–Net and CAESAR), by country or area, 2019



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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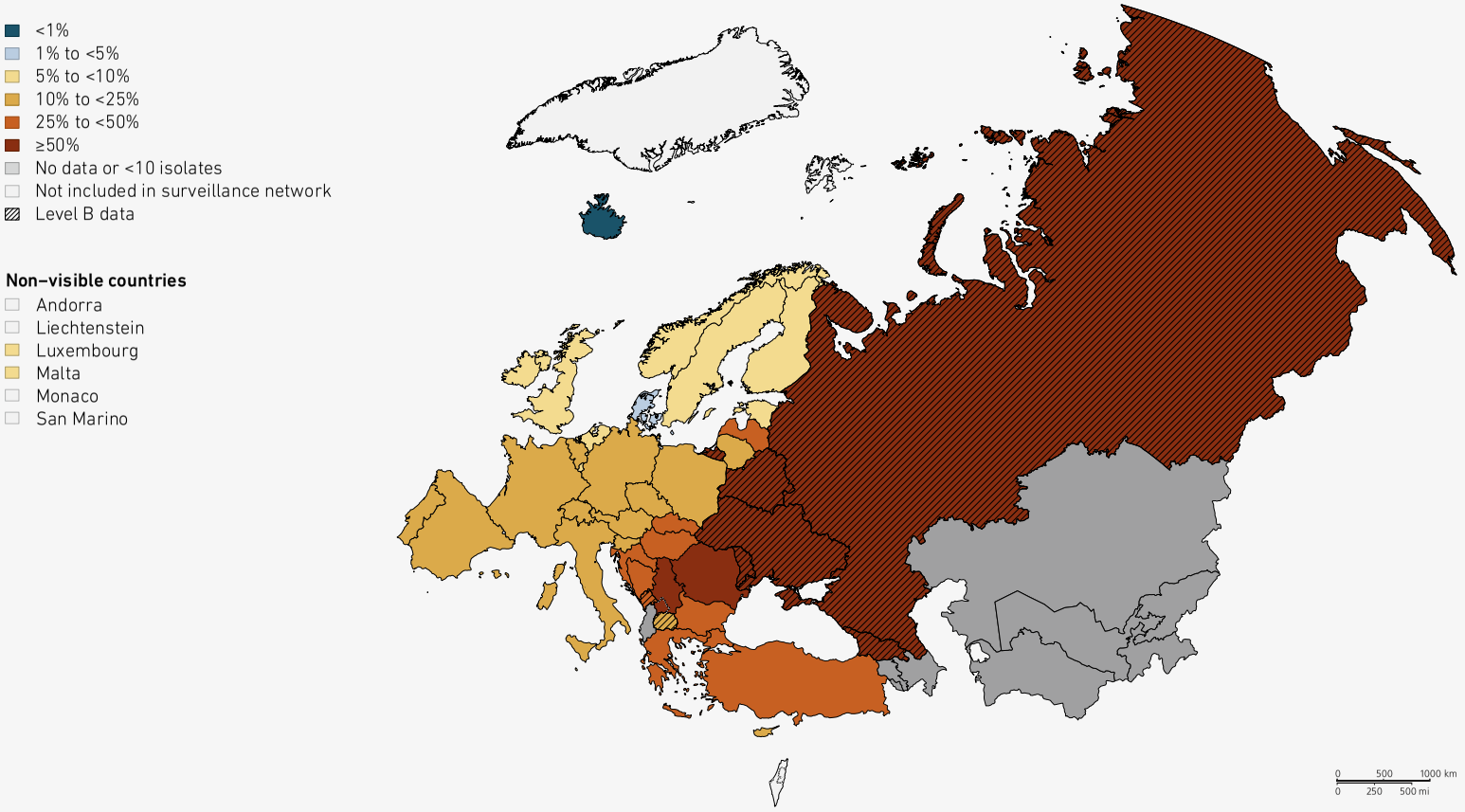
Map production: Public Health Information and Geographic Information Systems (GIS), World Health Organization.



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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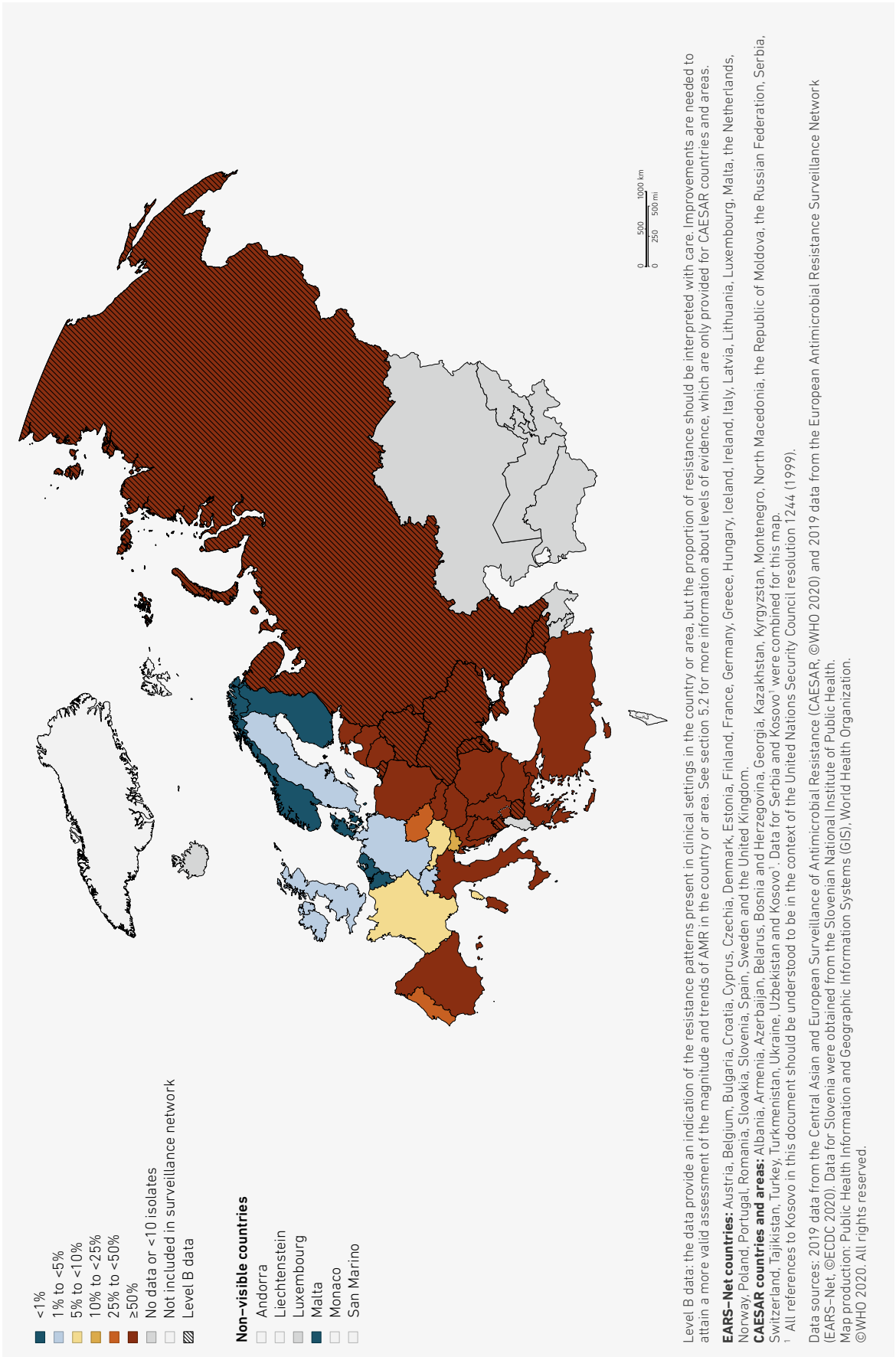
Map production: Public Health Information and Geographic Information Systems (GIS), World Health Organization.

Fig. 2.6 Percentage of invasive *P. aeruginosa* isolates resistant to carbapenems in the WHO European Region (EARS–Net and CAESAR), by country or area, 2019

Fig. 2.7 Percentage of invasive *Acinetobacter* spp. isolates resistant to carbapenems in the WHO European Region (EARS–Net and CAESAR), by country or area, 2019



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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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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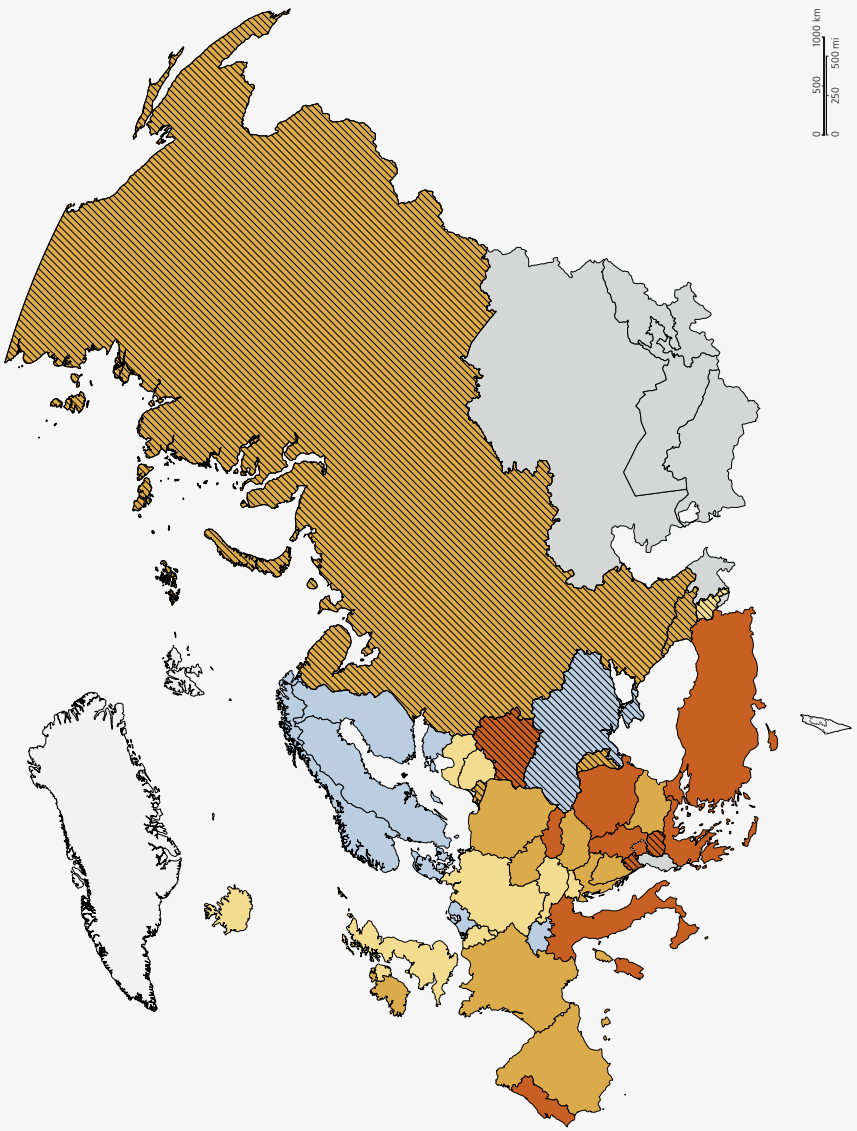
Data sources: 2019 data from the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2020) and 2019 data from the European Antimicrobial Resistance Surveillance Network (EARS–Net, ©ECDC 2020). Data for Slovenia were obtained from the Slovenian National Institute of Public Health.
Map production: Public Health Information and Geographic Information Systems (GIS), World Health Organization.

Fig. 2.8 Percentage of invasive *S. aureus* isolates resistant to methicillin (MRSA) in the WHO European Region (EARS–Net and CAESAR), by country or area, 2019



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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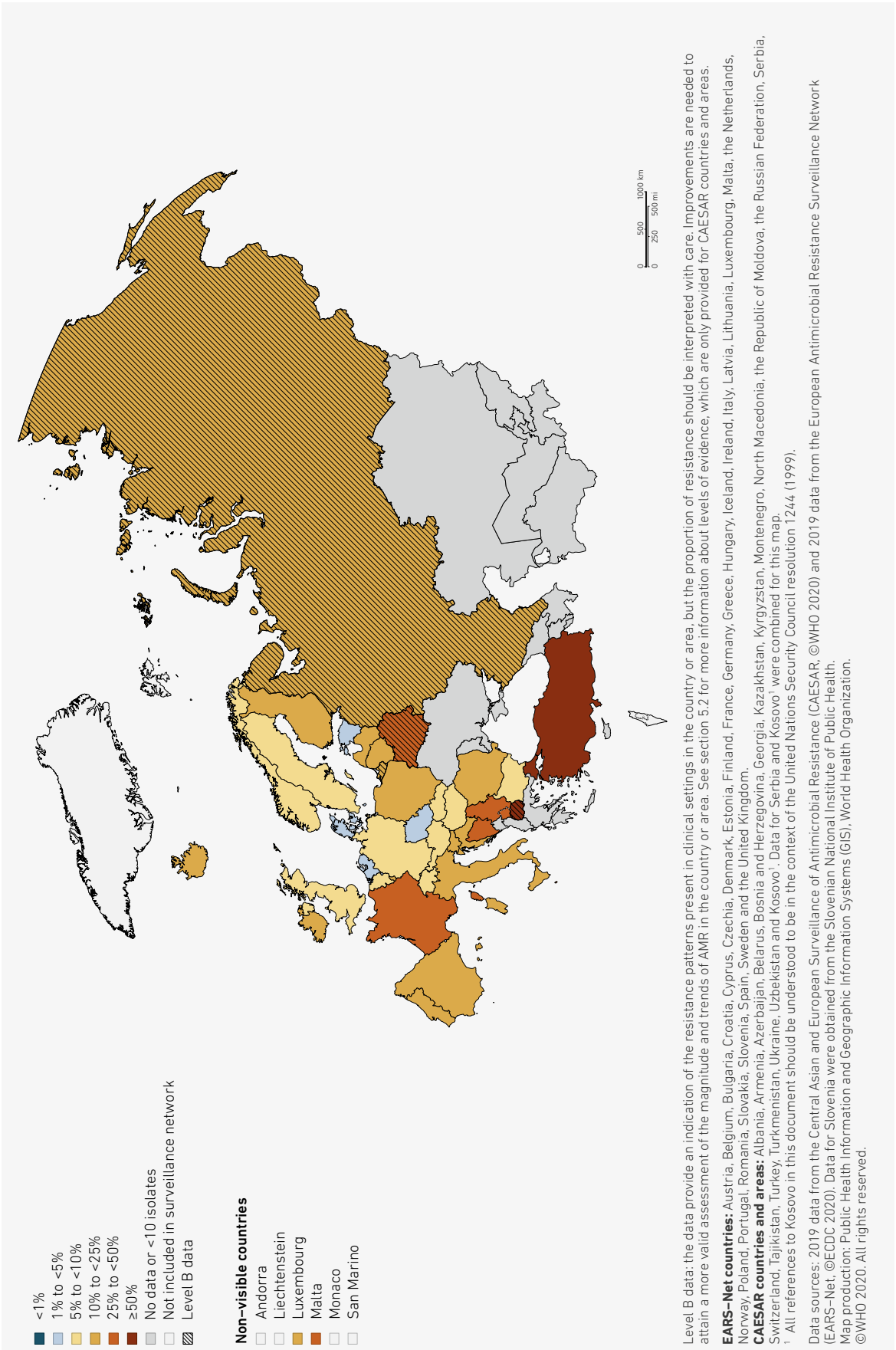
CAESAR countries and areas: Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, North Macedonia, the Republic of Moldova, the Russian Federation, Serbia, Switzerland, Tajikistan, Turkey, Turkmenistan, Ukraine, Uzbekistan and Kosovo[1]. Data for Serbia and Kosovo[1] were combined for this map.
[1] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

Data sources: 2019 data from the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2020) and 2019 data from the European Antimicrobial Resistance Surveillance Network (EARS–Net, ©ECDC 2020). Data for Slovenia were obtained from the Slovenian National Institute of Public Health.
Map production: Public Health Information and Geographic Information Systems (GIS), World Health Organization.

Fig. 2.9 Percentage of invasive penicillin non–wild type *S. pneumoniae* isolates in the WHO European Region (EARS–Net and CAESAR), by country or area, 2019



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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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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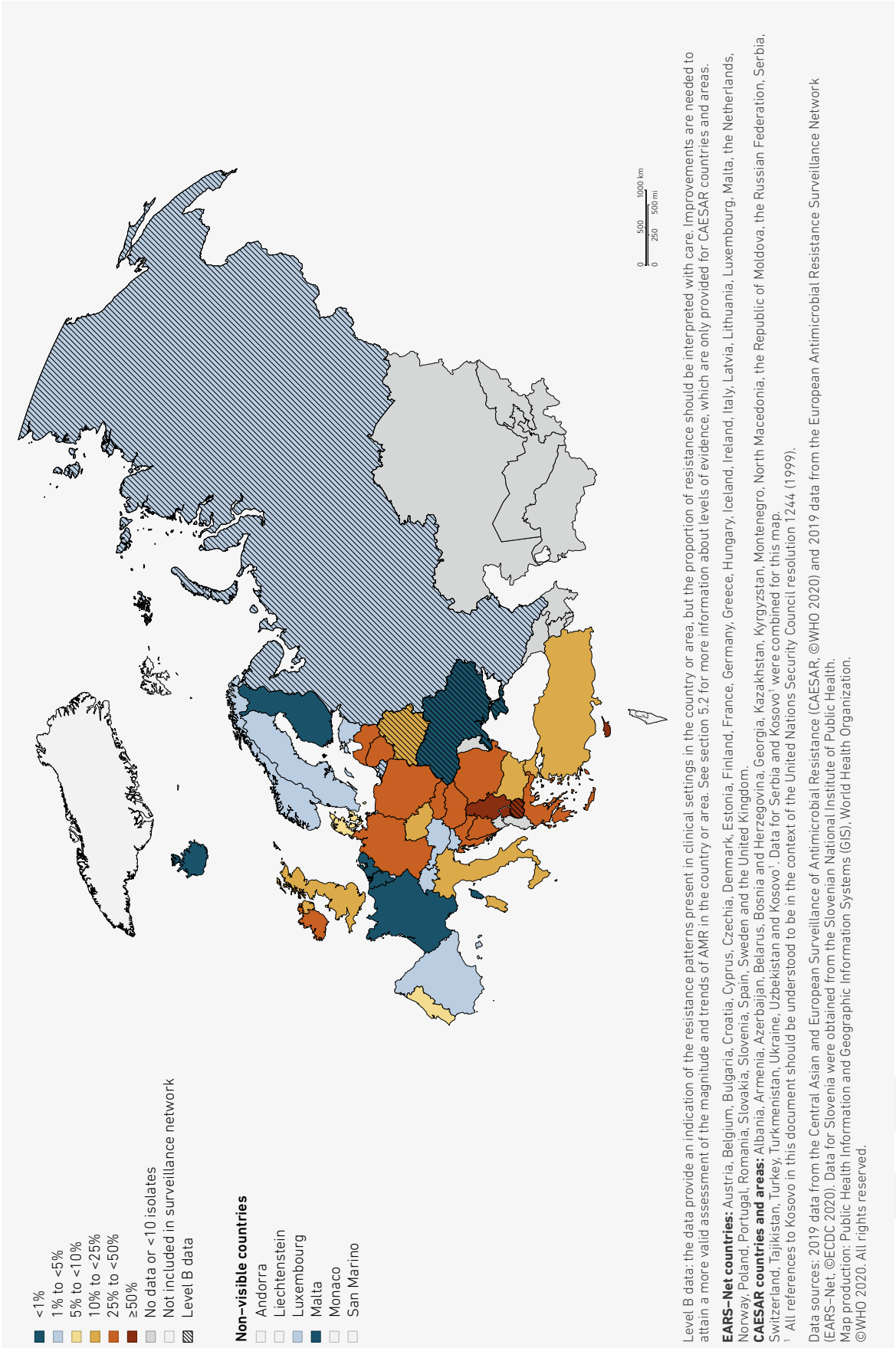
Map production: Public Health Information and Geographic Information Systems (GIS), World Health Organization.

Fig. 2.10 Percentage of invasive *E. faecium* isolates resistant to vancomycin in the WHO European Region (EARS–Net and CAESAR), by country or area, 2019



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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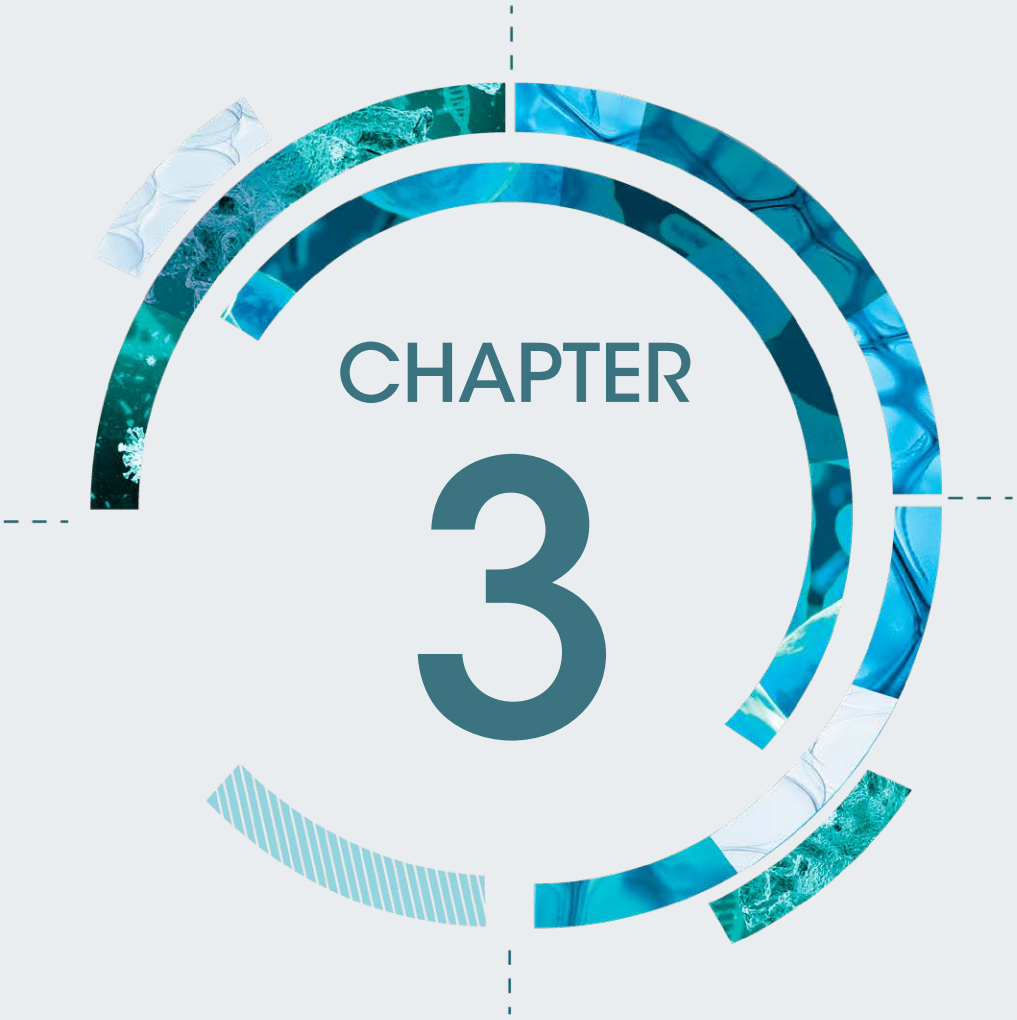
Map production: Public Health Information and Geographic Information Systems (GIS), World Health Organization.


CHAPTER
3

Progress in CAESAR

3.1 Progress indicators for overall coordination and surveillance of AMR

Information on the status of the overall coordination and surveillance of AMR presented in this report (Tables 3.1 and 3.2) either originates from the fourth round of the tripartite AMR country self-assessment survey (TrACSS), which launched on 10 December 2019 and concluded on 31 May 2020, or from similar surveys. The TrACSS is coordinated by WHO, the Food and Agriculture Organization of the United Nations and the World Organisation for Animal Health *(1)*. The survey aims at providing a comparable and periodic assessment of country progress on AMR in line with the WHO global action plan on AMR *(2)*, and is designed to be answered through self-assessment and consultation among all the relevant sectors involved at the national level. Each country submits one official response through a contact established by WHO, who coordinates with the WHO AMR focal points at each country's health ministry. Although Bosnia and Herzegovina did not participate in the TrACSS, concordant responses from the Federation of Bosnia and Herzegovina and Republika Srpska are reported in Table 3.2; otherwise results are reported as not available. The AMR focal point from Kosovo[1] filled out a questionnaire similar to that used by the TrACCS. Information about enrolment in GLASS was obtained from its updated list of members *(3)*.

The progress indicators selected for this report refer to four main components of AMR activities: (i) overall coordination on AMR; (ii) AMR surveillance; (iii) infection prevention and control (IPC); and (iv) antimicrobial stewardship. A description of the progress indicators is provided in Table 3.1. For presentation in this report, the information on progress indicators 2, 4, 8 and 9 has been re-coded using a five-point scale (poor; fair; good; very good; excellent). The original questions and answer categories are accessible through the publicly available TrACSS database *(4)*.

3.1.1 Progress on overall AMR coordination

Multisectoral and One Health collaboration/coordination

Overall, the results from the surveys show that coordination between the human health sector and the other sectors relevant for AMR – namely the animal health, food production and environmental sectors – is good. Whereas some members of the CAESAR network have only established the structure of the multisectoral working groups, the majority report having fully functional multisectoral working groups, with funding allocated and clear terms of reference in place. In a few cases, this multisectoral collaboration demonstrates a desirable integrated approach to implementing the national/area AMR action plan.

National/area AMR action plan

Among survey respondents, all CAESAR members reported having developed their AMR national/area action plan. This result is encouraging on its own, but it calls for a necessary distinction. Some of those who have developed an AMR action plan have also made provision for the required financial resources and have started the implementation of the activities, with a defined monitoring and evaluation process in place. Others, instead, after achieving the first milestone of developing the action plan have still not been able to progress to the next stage of operationalizing the objectives of the plan. This is where one of the main challenges for the coming years lays: supporting CAESAR members in implementing the activities included in the AMR action plan and in monitoring and evaluating the results generated.

1 All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

Table 3.1 Description of indicators of overall coordination and surveillance of AMR

Area	Indicators	Description
Overall AMR coordination	1. WHO AMR focal point appointed by the health ministry/authority	The health ministry/authority appoints an AMR focal point to play a leading role in the formation of an intersectoral coordinating mechanism to contain AMR.
	2. Multisectoral and One Health collaboration/coordination	Based on the One Health approach, a multisectoral coordinating mechanism should be created to contain AMR at the national/area level. This committee should ideally include representatives of relevant government/area sectors, representatives of local professional associations, authorities and leading scientific institutions.
	3. National/area AMR action plan developed	The AMR action plan is the key document detailing the characteristics and objectives of the overall national/area strategy to combat AMR.
AMR surveillance	4. National/area surveillance system for AMR in humans	Existence of a national/area surveillance system to identify patterns and trends of AMR, generate evidence-based clinical guidelines and recognize emerging pathogens
	5. Submits AMR data to CAESAR, the regional surveillance network	Participation in the regional network for AMR surveillance (CAESAR)
	6. Participates in a regional external quality assessment (EQA) scheme	Participation in the CAESAR regional EQA scheme
	7. Enrolled in GLASS	Participation in GLASS for monitoring AMR globally
IPC	8. IPC in human health care	Status of development and implementation of the main IPC measures at the national/area level
Antimicrobial stewardship	9. Optimizing antimicrobial use in human health	Status of development and implementation of policies and guidelines for antimicrobial stewardship at the national/area level

Table 3.2 Overview of selected progress indicators

CAESAR member	1. AMR focal point appointed by the health ministry/authority	2. Multisectoral and One Health collaboration/ coordination	3. AMR action plan developed	4. National/area surveillance system for AMR in humans	5. Submits AMR data to CAESAR, the regional surveillance network	6. Participates in the regional EQA scheme	7. Enrolled in GLASS	8. IPC in human health care	9. Optimizing antimicrobial use in human health
	Yes / No	Excellent / Very good / Good / Fair / Poor	Yes / In progress / No	Excellent / Very good / Good / Fair / Poor	Yes / No	Yes / No	Yes / No	Excellent / Very good / Good / Fair / Poor	Excellent / Very good / Good / Fair / Poor
Albania	■	■	■	■	■	■	■	■	■
Armenia	■	■	■	■	■	■	■	■	■
Azerbaijan	■	■	■	■	■	■	■	■	■
Belarus	■	■	■	■	■	■	■	■	■
Bosnia and Herzegovina	■	NA	NA	NA	■	■	■	NA	NA
Georgia	■	■	■	■	■	■	■	■	■
Kazakhstan	■	■	■	■	■	■	■	■	■
Kyrgyzstan	■	■	■	■	■	■	■	■	■
Montenegro	■	■	■	■	■	■	■	■	■
North Macedonia	■	■	■	■	■	■	■	■	■
Republic of Moldova	■	■	■	■	■	■	■	■	■
Russian Federation	■	■	■	■	■	■	■	■	■
Serbia	■	■	■	■	■	■	■	■	■
Switzerland	■	■	■	■	■	■	■	■	■
Tajikistan	■	■	■	■	■	■	■	■	■
Turkey	■	■	■	■	■	■	■	■	■
Turkmenistan	■	■	■	NA	■	■	■	■	■
Ukraine	■	■	■	NA	■	■	■	NA	NA
Uzbekistan	■	■	■	■	■	■	■	■	■
Kosovo[1]	■	■	■	■	■	■	■	■	■

NA = not available.

[1] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

3.1.2 Progress on surveillance networks and AMR laboratories

National/area surveillance system for AMR in humans

Results from the surveys show two different clusters within the CAESAR network. One is composed of those that have a national/area AMR surveillance system for common bacterial infections, with a national/area reference laboratory involved in external quality assurance exercises. The other is composed of those whose surveillance system for AMR in humans has a limited scope, usually only at the local level, and lacks national coordination and quality management. Having a well-functioning and geographically representative surveillance network for AMR is crucial for generating reliable information on the spread of resistant bacteria, and it is the very reason why the CAESAR network was established. Therefore, it is only natural that renewed efforts will be channelled to this objective in the coming years.

Participate in the regional EQA scheme

Most CAESAR members regularly take part in the regional EQA scheme. This is a remarkable achievement that has been built over the years through constant support and guidance. Some obstacles remain towards the sustainability of the CAESAR EQA. These are mostly related to logistics and national/area regulations, which can sometimes restrict the ability to share laboratory sampling and testing panels internationally. A regional administrative agreement paired with strong national/area leadership would be needed to lower these barriers and to strengthen continued EQA activities.

Submitting AMR data to CAESAR, the regional surveillance network

Out of 20 network members, only 13 (65%) currently submit AMR data to the regional surveillance network. This situation reflects the state of the national/area surveillance system. When the surveillance system for AMR is weak or does not have a proper geographical coverage, it hampers the possibility of sharing reliable information about AMR. The great majority of CAESAR members who submit their data to the regional network have a well-established national/area surveillance network. At the same time, it is worth mentioning that substantial improvements to AMR surveillance have been achieved within the CAESAR network through the implementation of laboratory training and the proof-of-principle AMR routine diagnostics surveillance project. In particular, Armenia and Georgia benefitted from taking part in the project to kick off a functional national sentinel laboratory-based surveillance system for AMR.

Enrolled in GLASS

Currently, only six (30%) of the 20 CAESAR members are also enrolled in GLASS. This does not prevent international collaboration in reporting and data sharing, but it might reduce the opportunities for countries and areas in the region to receive global support in standardizing the collection, analysis and sharing of AMR data. The CAESAR network actively promotes GLASS participation and anticipates a rise in GLASS enrollment in the coming years.

3.1.3 Progress on IPC programmes and antimicrobial stewardship

IPC in human health care

Among the CAESAR members that provided a response to the surveys, seven (37%) either have no national/area IPC programme or have an operational plan that has not been fully implemented. IPC is key for avoiding the mass spreading of infectious diseases – as became evident during the COVID-19 pandemic – and is a central tool in curbing AMR. Increased efforts within the CAESAR network will be devoted, in the coming years, towards an integrated surveillance whose main pillars should include IPC.

Optimizing antimicrobial use in human health

The optimizing of antimicrobial use refers to the coordinated efforts of antimicrobial stewardship, which includes proper diagnostics and appropriate use of antimicrobial drugs, improved patients' outcomes, containment of resistance and reduced spread of resistant infections. It is a comprehensive indicator, and a good sign that many of the respondents have indicated the availability of guidelines for appropriate use of antimicrobials and the implementation of antimicrobial stewardship practices in some health care

facilities. At the same time, there is still much to be done. To exercise real antimicrobial stewardship based on evidence-informed local treatment guidelines both national/area and local surveillance data are urgently needed. This in turn can only be achieved with stronger national/area surveillance systems.


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 antimicrobial susceptibility testing (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 the European Committee on Antimicrobial Susceptibility Testing (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 Clinical and Laboratory Standards Institute (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 2019.

Table 5.2 Level of evidence and scoring of factors affecting the validity of CAESAR data in 2019

		Armenia	Belarus	Bosnia and Herzegovina	Georgia	Montenegro	North Macedonia	Republic of Moldova	Russian Federation	Serbia	Switzerland	Turkey	Ukraine	Kosovo[1]
Level of evidence		B	B	A	B	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	+	–	+	+/–	+	+	+	+	+	+	+	+	+

[1] All references to Kosovo in this document should be understood to be in the context of the 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

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 2019. 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 2019

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 (2 973 000)[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[b] number of blood samples taken per 1000 patient days: median 7, range 2–9 in the four hospitals providing denominator data; - the small total number of isolates; and - the large proportion of isolates from intensive care units (67%). *Patient characteristics of isolates from Armenia are available in Fig. 6.1.*
	Sample size	–	• The total number of isolates is 36. • Fewer than 30 isolates are available for all pathogens.
Laboratory procedures	AST methods	+/-	• The national standard for AST is EUCAST. • The method for AST is disk diffusion (all laboratories). • Not all isolates are tested for each relevant antibiotic (as listed in the minimum panel for CAESAR reporting *(1)*). • Regulations on confirmatory testing of isolates are under development. • Internal quality control is not regularly performed in most laboratories. • All 11 laboratories (100%) participated in the CAESAR EQA in 2019.
	AST breakpoints	+	• EUCAST breakpoints are used in all 11 laboratories (100%).

[a] Estimated population January 2018, United Nations *(2)*.
[b] Compared with EARS-Net countries: median 36.8, range 5.3–206.9 in 2018 *(3)*.

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 2019. Resistance percentages for these isolates are presented in Tables 6.2–6.7.

Fig. 6.1 Patient characteristics of isolates in Armenia in 2019, by pathogen

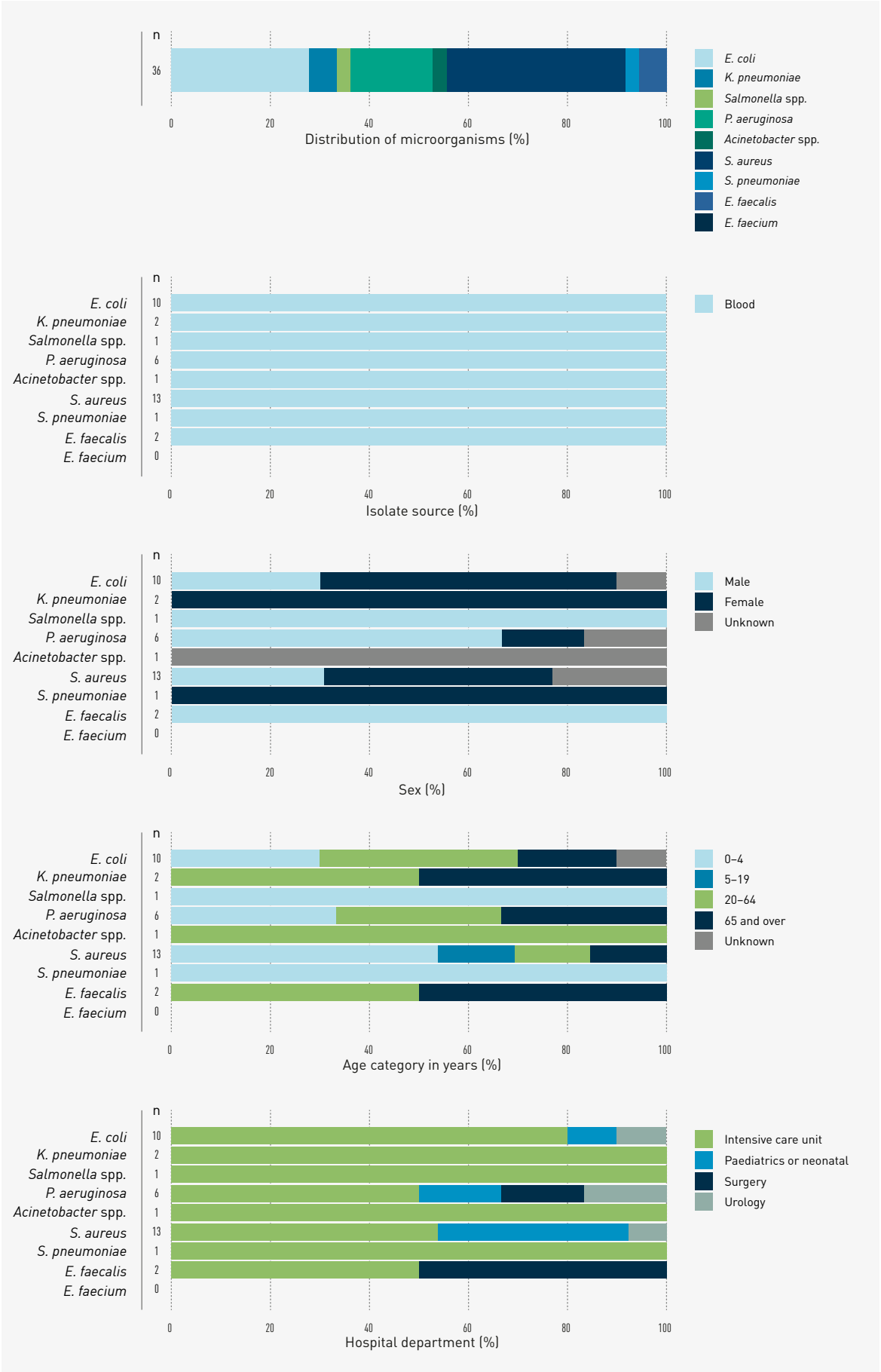


Table 6.2 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Armenia in 2019

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	10	40*	0*	NA	NA	NA
Amoxicillin-clavulanic acid	10	40*	0*	2	100*	0*
Piperacillin-tazobactam	8	13*	0*	2	0*	0*
Cefotaxime/ceftriaxone	10	30*	0*	2	100*	0*
Ceftazidime	10	30*	0*	2	100*	0*
Ertapenem	5	0* **	0* **	2	0*	0*
Imipenem/meropenem	9	0*	0*	2	0*	0*
Gentamicin/tobramycin	7	0*	0*	2	50*	0*
Amikacin	9	0*	0*	2	0*	0*
Ciprofloxacin/levofloxacin/ofloxacin	10	30*	30*	2	50*	0*
Multidrug resistance[a]	7	0*	NA	2	50*	NA

NA = not applicable.

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

** Less than 70% of isolates were tested for this antibiotic (group), 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 *Salmonella* spp. among blood and CSF isolates in Armenia in 2019

Antibiotic (group)	*Salmonella* spp.		
	N	%R	%I
Cefotaxime/ceftriaxone	1	100*	0*
Ceftazidime	1	100*	0*
Ertapenem	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 6.4 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Armenia in 2019

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	6	0*	0*	NA	NA	NA
Ceftazidime	5	40*	0*	NA	NA	NA
Cefepime	6	50*	0*	NA	NA	NA
Imipenem/meropenem	5	40*	0*	1	100*	0*
Gentamicin/tobramycin	5	60*	0*	1	100*	0*
Amikacin	6	33*	17*	1	100*	0*
Ciprofloxacin/levofloxacin	6	50*	0*	1	100*	0*
Multidrug resistance[a]	3	67* **	NA	1	100*	NA

NA = not applicable.

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

** Less than 70% of isolates were tested for this antibiotic (group), 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 6.5 Resistance levels for *S. aureus* among blood and CSF isolates in Armenia in 2019

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	13	8*	NA
Ciprofloxacin/levofloxacin/ofloxacin	13	15*	0*
Vancomycin	6	0* **	0* **
Rifampicin	7	0* **	0* **
Linezolid	10	0*	NA

NA = not applicable.

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

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

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

Table 6.6 Resistance levels for *S. pneumoniae* among blood and CSF isolates in Armenia in 2019

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%IR
Penicillin[a]	1	NA	NA	0*
Cefotaxime/ceftriaxone	1	0*	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.

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

[a] The percentage IR to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage IR should be interpreted as the percentage R. For non-meningitis indications, the percentage IR 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 6.7 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in Armenia in 2019

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	2	0*	0*	0	–	–
High-level gentamicin	2	50*	0*	0	–	–
Vancomycin	2	50*	0*	0	–	–
Linezolid	1	0* **	0* **	0	–	–

– = no data available.

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

** Less than 70% of isolates were tested for this antibiotic (group), 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 seem reliable.

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, resistance levels for third-generation cephalosporins (cefotaxime/ceftriaxone and ceftazidime) and fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin) were moderately high in *E. coli* (although based on a small number of isolates, Table 6.2). The percentage of MRSA was low, although based on a small number of isolates (Table 6.5). Too few results were available for *K. pneumoniae* (Table 6.2), *Salmonella* spp. (Table 6.3), *P. aeruginosa*, *Acinetobacter* spp. (Table 6.4), *S. pneumoniae* (Table 6.6), *E. faecalis* and *E. faecium* (Table 6.7) to allow interpretation.

6.2 Belarus

6.2.1 Surveillance set-up and data quality assessment

Table 6.8 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from Belarus in 2019. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.8 Level of evidence and scoring of factors affecting the validity of CAESAR data from Belarus in 2019

Level of evidence: B			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+	• The surveillance network comprises 93 laboratories providing blood culture diagnostic services (>90% of hospitals), of which 49 submitted data eligible for CAESAR. • Laboratories are geographically spread throughout Belarus; some regions are underrepresented. • The estimated coverage of the total population (9 492 000)[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 likely small number of blood samples taken per 1000 patient days in most hospitals, although exact data are not available; - the relatively large proportion of isolates (53%) that come from the capital (20% of population); - the large proportion of isolates from intensive care units (57%); - the large proportion of nosocomial pathogens (33% *K. pneumoniae*, 21% *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 1722. • 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 methods for AST are disk diffusion (64 laboratories) and a semi-automated system (29 laboratories). • Not all isolates are tested for each relevant antibiotic (as listed in the minimum panel for CAESAR reporting *(1)*). • 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. • Thirteen out of 93 laboratories (14%) participated in the CAESAR EQA in 2019.
	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-2018, United Nations *(2)*.

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 2019. Resistance percentages for these isolates are presented in Tables 6.9–6.14.

Fig. 6.2 Patient characteristics of isolates in Belarus in 2019, by pathogen

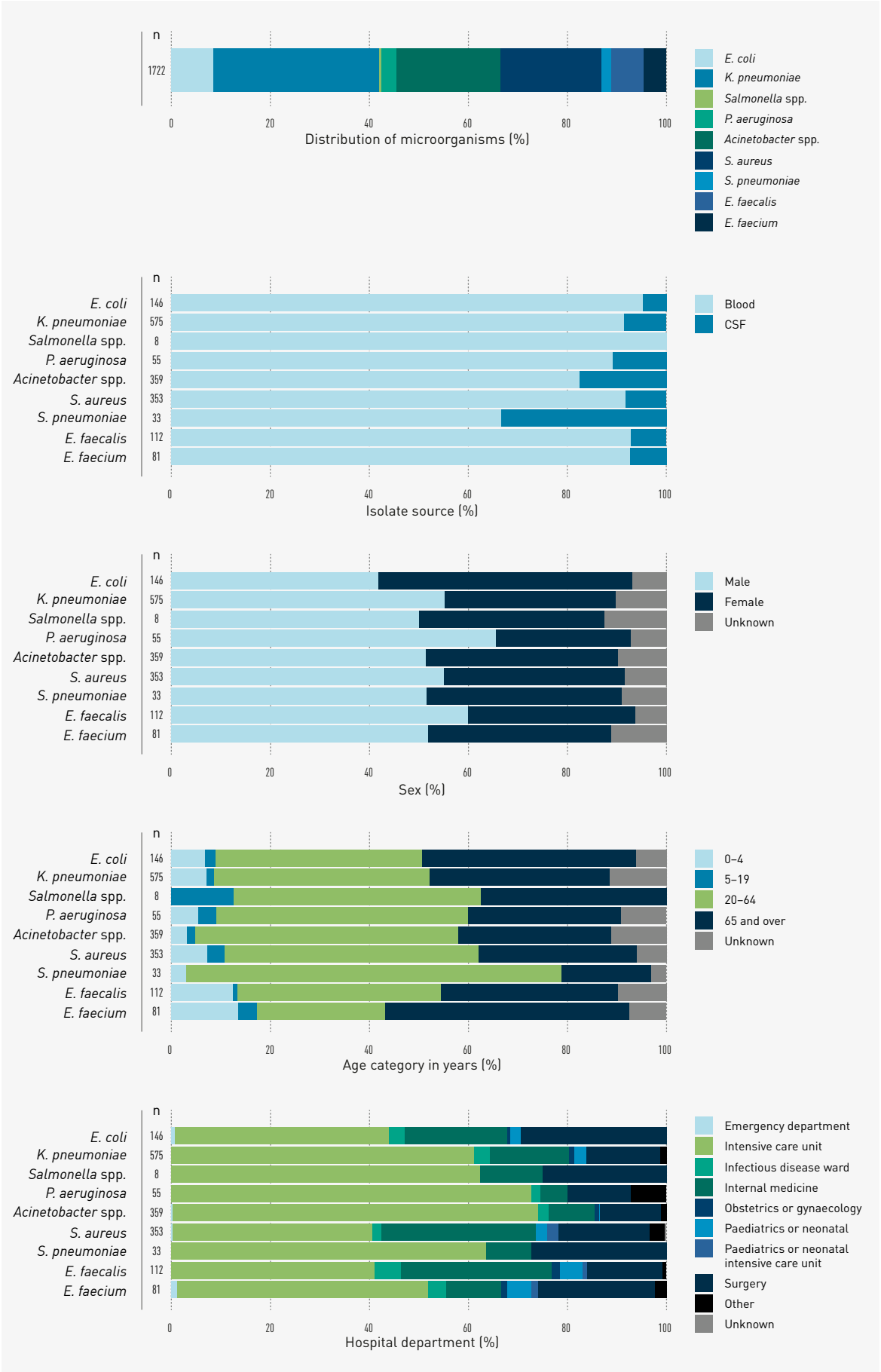


Table 6.9 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Belarus in 2019

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	89	65**	3**	NA	NA	NA
Amoxicillin-clavulanic acid	78	15**	17**	201	81**	4**
Piperacillin-tazobactam	87	3**	6**	260	83**	1**
Cefotaxime/ceftriaxone	123	40	5	478	87	2
Ceftazidime	99	34**	3**	334	84**	1**
Ertapenem	43	0**	0**	87	67**	1**
Imipenem/meropenem	137	4	2	551	75	2
Gentamicin/tobramycin	109	13	4	360	70**	3**
Amikacin	65	2**	0**	268	64**	1**
Ciprofloxacin/levofloxacin/ofloxacin	139	42	4	533	87	1
Multidrug resistance[a]	101	9**	NA	324	71**	NA

NA = not applicable.

** Less than 70% of isolates were tested for this antibiotic (group), 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 6.10 Resistance levels for *Salmonella* spp. among blood and CSF isolates in Belarus in 2019

Antibiotic (group)	*Salmonella* spp.		
	N	%R	%I
Cefotaxime/ceftriaxone	7	0*	0*
Ceftazidime	6	0*	0*
Ertapenem	1	0* **	0* **
Imipenem/meropenem	8	0*	0*
Ciprofloxacin/levofloxacin	7	14*	57*

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

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

Table 6.11 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Belarus in 2019

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	24	46* **	0* **	NA	NA	NA
Ceftazidime	43	63	2	NA	NA	NA
Cefepime	42	57	10	NA	NA	NA
Imipenem/meropenem	52	83	4	347	93	3
Gentamicin/tobramycin	31	68**	0**	182	68**	7**
Amikacin	38	50**	5**	136	82**	3**
Ciprofloxacin/levofloxacin	46	80	7	346	95	3
Multidrug resistance[a]	17	53* **	NA	167	66**	NA

NA = not applicable.

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

** Less than 70% of isolates were tested for this antibiotic (group), 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 6.12 Resistance levels for *S. aureus* among blood and CSF isolates in Belarus in 2019

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	305	36	NA
Ciprofloxacin/levofloxacin/ofloxacin	326	24	2
Vancomycin	266	0	0
Rifampicin	244	16**	0**
Linezolid	283	2	NA

NA = not applicable.

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

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

Table 6.13 Resistance levels for *S. pneumoniae* among blood and CSF isolates in Belarus in 2019

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%IR
Penicillin[a]	16	NA	NA	38* **
Cefotaxime/ceftriaxone	13	8* **	8* **	NA
Levofloxacin/moxifloxacin	29	3*	0*	NA
Erythromycin/clarithromycin/azithromycin	25	32*	0*	NA
Multidrug resistance[b]	13	NA	NA	15* **

NA = not applicable.

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

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

[a] The percentage IR to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage IR should be interpreted as the percentage R. For non-meningitis indications, the percentage IR 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 6.14 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in Belarus in 2019

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	93	14	0	65	89	0
High-level gentamicin	87	67	0	49	73**	0**
Vancomycin	108	2	4	77	22	0
Linezolid	96	2	0	69	3	1

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

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 enough for robust estimates of resistance in most pathogens.

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, recently updated 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 moderately high in *E. coli*, but very high in *K. pneumoniae* (Table 6.9). 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 6.11) are concerning and likely reflect the spread of resistant clones in the health care setting. The proportion of MRSA was moderately high and higher than that in neighbouring countries (Table 6.12, Fig. 2.8). In *S. pneumoniae*, the level of penicillin non-wild type was moderately high, as was resistance to macrolides (erythromycin/clarithromycin/azithromycin, Table 6.13). In *E. faecium*, resistance to vancomycin was moderately high (Table 6.14).

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 6.15 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from Bosnia and Herzegovina in 2019. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.15 Level of evidence and scoring of factors affecting the validity of CAESAR data from Bosnia and Herzegovina in 2019

Level of evidence: A			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+	• The two surveillance networks comprise 12 laboratories providing blood culture diagnostic services: - six (50% of) laboratories in the Federation of Bosnia and Herzegovina, all of which submitted data; and - six (86% of) laboratories in Republika Srpska, all of which submitted data. • Laboratories are geographically spread throughout 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[a] number of blood samples taken per 1000 patient days: median 8, range 3–30 in the seven hospitals providing denominator data; and - in Republika Srpska 87% of data are from the main tertiary care centre in Banja Luka. *Patient characteristics of isolates from Bosnia and Herzegovina are available in Fig. 6.3.*
	Sample size	+	• The total number of isolates is 1247. • 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 - disk diffusion (five laboratories) and a semi-automated system (expert laboratory) in Republika Srpska. • Not all isolates are tested for each relevant antibiotic (as listed in the minimum panel for CAESAR reporting *(1)*). • 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. • Eleven out of 12 laboratories (92%) participated in the CAESAR EQA in 2019: - all six laboratories (100%) in the Federation of Bosnia and Herzegovina - five out of six laboratories (83%) in Republika Srpska.
	AST breakpoints	+	• EUCAST breakpoints are used in 11 out of 12 laboratories (92%): - Five out of six laboratories in the Federation of Bosnia and Herzegovina (83%) - All six laboratories in Republika Srpska (100%).

[a] Compared with EARS-Net countries: median 36.8, range 5.3–206.9 in 2018.

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 2019. Resistance percentages for these isolates are presented in Tables 6.16–6.21.

Fig. 6.3 Patient characteristics of isolates in Bosnia and Herzegovina in 2019, by pathogen

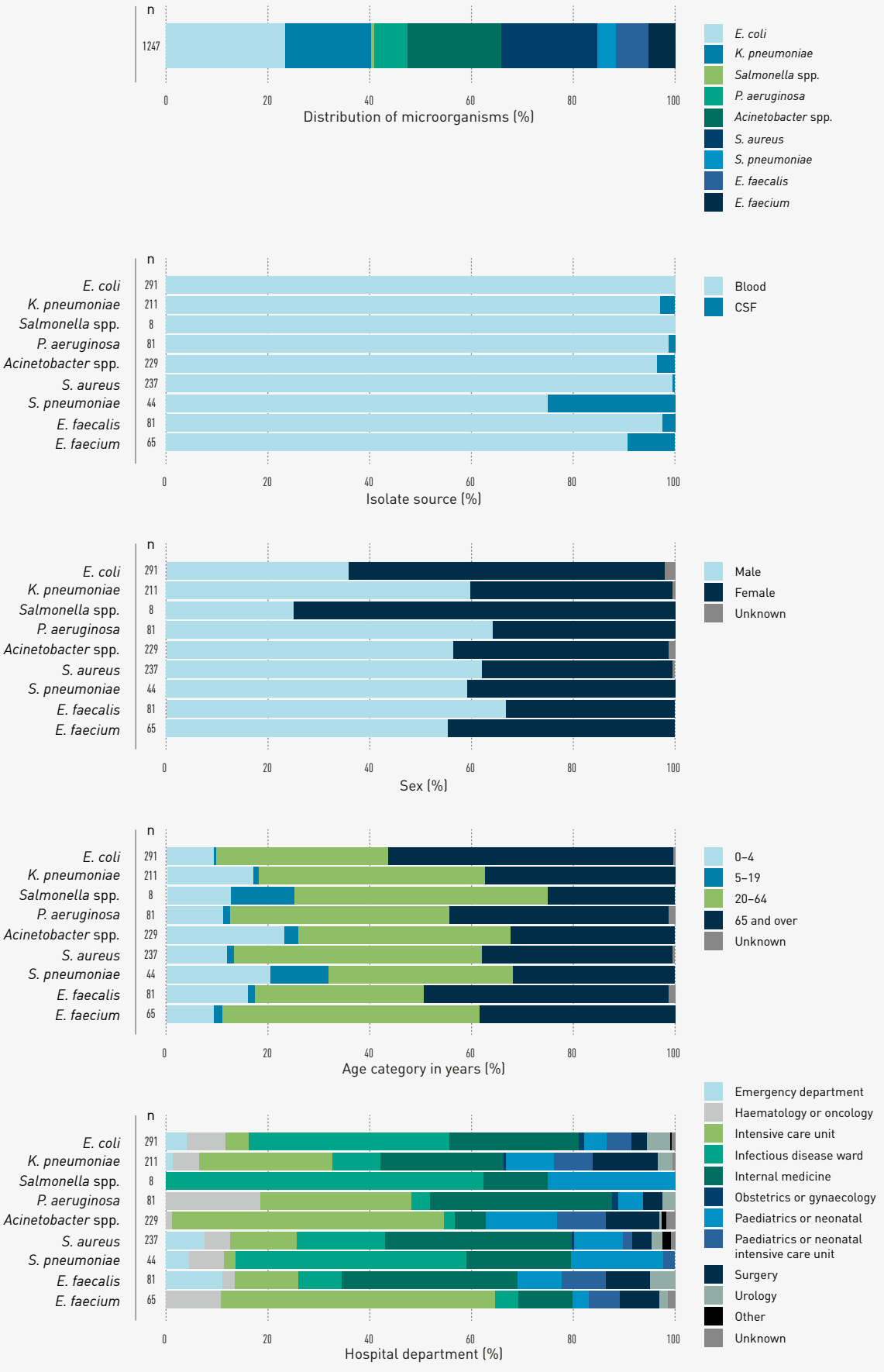


Table 6.16 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Bosnia and Herzegovina in 2019

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	290	71	0	NA	NA	NA
Amoxicillin-clavulanic acid	288	37	0	211	85	0
Piperacillin-tazobactam	278	8	1	208	54	6
Cefotaxime/ceftriaxone	290	20	0	211	79	0
Ceftazidime	289	17	2	211	77	0
Ertapenem	137	0**	0**	62	23**	2**
Imipenem/meropenem	290	0	0	211	42	0
Gentamicin/tobramycin	290	20	2	211	79	0
Amikacin	289	4	2	210	10	9
Ciprofloxacin/levofloxacin/ofloxacin	289	30	0	210	68	0
Multidrug resistance[a]	289	10	NA	210	63	NA

NA = not applicable.

** Less than 70% of isolates were tested for this antibiotic (group), 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 6.17 Resistance levels for *Salmonella* spp. among blood and CSF isolates in Bosnia and Herzegovina in 2019

Antibiotic (group)	*Salmonella* spp.		
	N	%R	%I
Cefotaxime/ceftriaxone	8	0*	0*
Ceftazidime	8	0*	0*
Ertapenem	5	0* **	0* **
Imipenem/meropenem	6	0*	0*
Ciprofloxacin/levofloxacin	8	0*	0*

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

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

Table 6.18 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Bosnia and Herzegovina in 2019

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	77	14	0	NA	NA	NA
Ceftazidime	81	35	1	NA	NA	NA
Cefepime	81	23	1	NA	NA	NA
Imipenem/meropenem	81	47	1	229	97	0
Gentamicin/tobramycin	81	48	1	229	97	0
Amikacin	81	26	1	221	90	2
Ciprofloxacin/levofloxacin	81	57	0	229	98	0
Multidrug resistance[a]	77	43	NA	229	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 6.19 Resistance levels for *S. aureus* among blood and CSF isolates in Bosnia and Herzegovina in 2019

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	237	11	NA
Ciprofloxacin/levofloxacin/ofloxacin	237	13	0
Vancomycin	237	0	0
Rifampicin	194	3	0
Linezolid	222	0	NA

NA = not applicable.

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

Table 6.20 Resistance levels for *S. pneumoniae* among blood and CSF isolates in Bosnia and Herzegovina in 2019

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%IR
Penicillin[a]	44	NA	NA	34
Cefotaxime/ceftriaxone	41	12	2	NA
Levofloxacin/moxifloxacin	35	0	0	NA
Erythromycin/clarithromycin/azithromycin	44	34	0	NA
Multidrug resistance[b]	44	NA	NA	25

NA = not applicable.

[a] The percentage IR to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage IR should be interpreted as the percentage R. For non-meningitis indications, the percentage IR 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 6.21 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in Bosnia and Herzegovina in 2019

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	81	0	1	65	97	0
High-level gentamicin	81	70	0	65	45	0
Vancomycin	81	0	0	65	38	0
Linezolid	81	0	0	63	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;
- the number of isolates is large enough for robust estimates of resistance in most pathogens; 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 6.16) and *Acinetobacter* spp. (Table 6.18), very high levels of resistance were observed for all selected agents, including carbapenems (imipenem/meropenem). In addition, in *E. faecium* resistance to vancomycin was high (Table 6.21). These findings suggest the dissemination of resistant clones in the health care setting. Furthermore, in *S. pneumoniae*, concerningly high levels of resistance were observed for all selected agents (Table 6.20). On the other hand, the resistance levels in *E. coli* (Table 6.16) and *S. aureus* (Table 6.19) were only moderately high. In *P. aeruginosa*, moderate to high resistance levels were found (Table 6.18). Too few results were available for *Salmonella* spp. (Table 6.17) to allow interpretation.

6.4 Georgia

6.4.1 Surveillance set-up and data quality assessment

Table 6.22 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from Georgia in 2019. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.22 Level of evidence and scoring of factors affecting the validity of CAESAR data from Georgia in 2019

Level of evidence: B			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+/–	• The surveillance network comprises 23 laboratories (80% of hospitals), of which seven submitted data. • Most laboratories are located in or close to the capital. • The estimated coverage of the total population (3 730 000)[a] is 80%.
	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[b] number of blood samples taken per 1000 patient days: median 6, range 2–13 in the 17 hospitals providing denominator data; - the large proportion of isolates from intensive care units (58%); and - the relatively large proportion of nosocomial pathogens (17% *Acinetobacter* spp., 27% *K. pneumoniae*). *Patient characteristics of isolates from Georgia are available in Fig. 6.4.*
	Sample size	+/–	• The total number of isolates is 501. • Fewer than 30 isolates are available for some pathogens.
Laboratory procedures	AST methods	+/–	• There is no national standard for AST. • The 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 (as listed in the minimum panel for CAESAR reporting *(1)*). • Confirmatory testing of some exceptional phenotypes is performed at the reference laboratory. • Internal quality control is regularly performed in all laboratories. • Twenty-two out of 23 laboratories (96%) participated in the CAESAR EQA in 2019.
	AST breakpoints	+/–	• EUCAST breakpoints are used in 14 out of 23 laboratories (61%).

[a] Estimated population mid-2018, United Nations *(2)*.
[b] Compared with EARS-Net countries: median 36.8, range 5.3–206.9 in 2018 *(3)*.

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 2019. Resistance percentages for these isolates are presented in Tables 6.23–6.27.

Fig. 6.4 Patient characteristics of isolates in Georgia in 2019, by pathogen

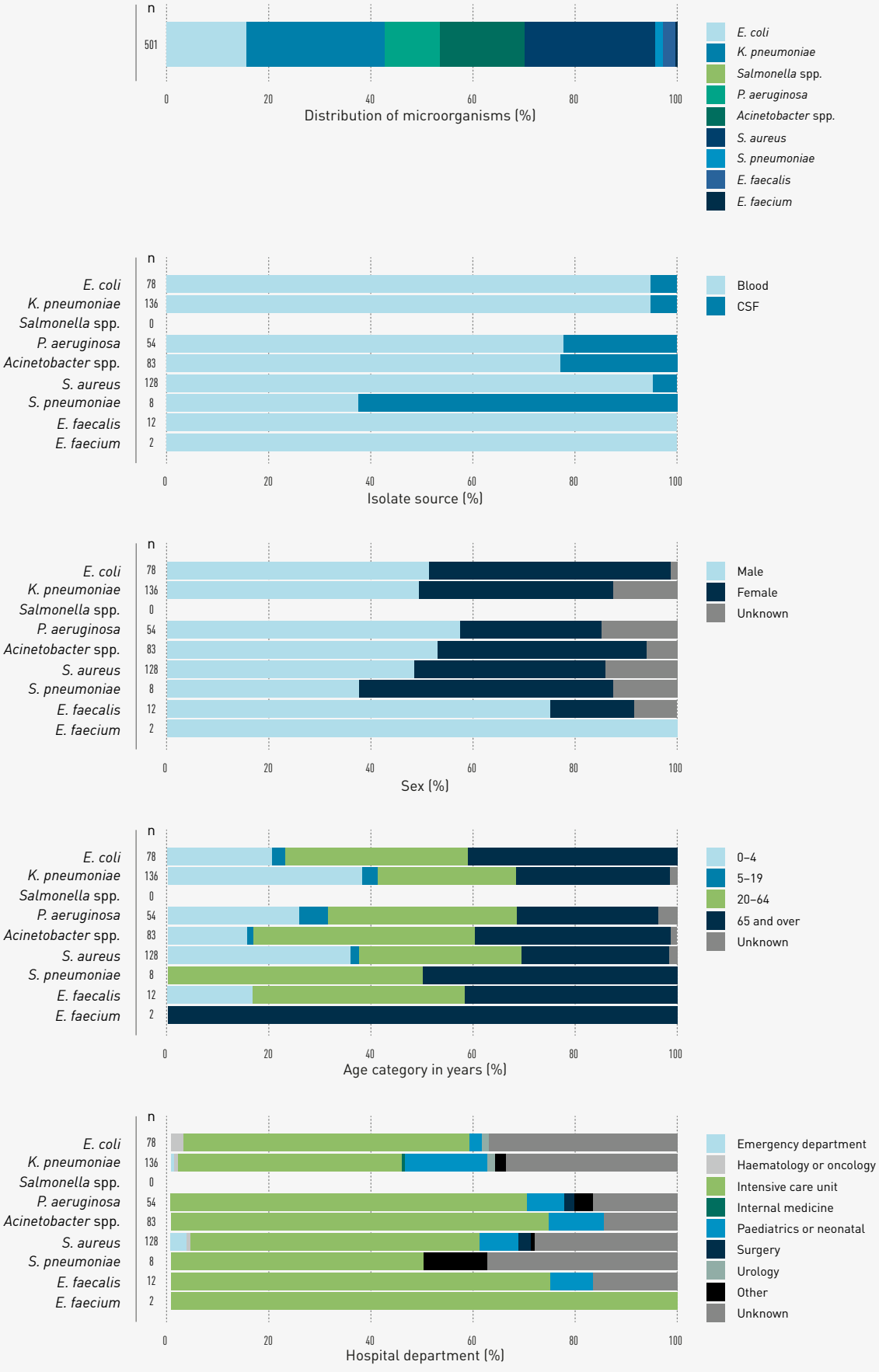


Table 6.23 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Georgia in 2019

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	77	74	1	NA	NA	NA
Amoxicillin-clavulanic acid	76	26	11	122	61	12
Piperacillin-tazobactam	77	14	1	133	50	8
Cefotaxime/ceftriaxone	78	56	0	135	77	0
Ceftazidime	78	55	1	133	77	1
Ertapenem	57	2	0	99	42	0
Imipenem/meropenem	78	8	0	136	37	0
Gentamicin/tobramycin	65	17	2	133	41	2
Amikacin	66	9	2	131	28	2
Ciprofloxacin/levofloxacin/ofloxacin	78	42	1	136	50	3
Multidrug resistance[a]	65	6	NA	132	25	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 6.24 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Georgia in 2019

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	49	43	2	NA	NA	NA
Ceftazidime	48	48	4	NA	NA	NA
Cefepime	51	49	2	NA	NA	NA
Imipenem/meropenem	51	55	2	83	76	5
Gentamicin/tobramycin	53	45	0	83	40	4
Amikacin	52	17	10	38	55**	5**
Ciprofloxacin/levofloxacin	51	51	4	80	80	3
Multidrug resistance[a]	43	56	NA	80	31	NA

NA = not applicable.

** Less than 70% of isolates were tested for this antibiotic (group), 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 2019

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	96	17	NA
Ciprofloxacin/levofloxacin/ofloxacin	128	20	5
Vancomycin	52	0**	0**
Rifampicin	121	7	0
Linezolid	121	1	NA

NA = not applicable.

** Less than 70% of isolates were tested for this antibiotic (group), 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 2019

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%IR
Penicillin[a]	5	NA	NA	0* **
Cefotaxime/ceftriaxone	1	0* **	0* **	NA
Levofloxacin/moxifloxacin	6	0*	0*	NA
Erythromycin/clarithromycin/azithromycin	7	71*	14*	NA
Multidrug resistance[b]	5	NA	NA	0* **

NA = not applicable.

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

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

[a] The percentage IR to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage IR should be interpreted as the percentage R. For non-meningitis indications, the percentage IR 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 2019

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	11	64*	0*	2	100*	0*
High-level gentamicin	5	60* **	0* **	2	100*	0*
Vancomycin	12	0*	0*	2	0*	0*
Linezolid	11	9*	0*	2	0*	0*

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

** Less than 70% of isolates were tested for this antibiotic (group), 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 of some pathogens 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, in the patient population sampled, high resistance levels were found for third-generation cephalosporins (cefotaxime/ceftriaxone and ceftazidime) and fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin) in *E. coli* (Table 6.23). In *K. pneumoniae*, high resistance levels were observed for all selected agents, including carbapenems (imipenem/meropenem/ertapenem). The high levels of resistance in *P. eruginosa* and *Acinetobacter* spp. are concerning and may reflect the dissemination of resistant clones in the health care setting (Table 6.24). On the other hand, the proportion of MRSA was moderately low (Table 6.25). Too few results were available for *Salmonella* spp. (no isolates), *S. pneumoniae* (Table 6.26), *E. faecalis* and *E. faecium* (Table 6.27) 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 2019. 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 2019

Level of evidence: B			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+	• The surveillance network comprises eight (100% of) laboratories providing blood culture diagnostic services, of which six submitted data. • Laboratories are geographically spread throughout 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[b] number of blood samples taken per 1000 patient days: median 4, range 0–18 in the eight hospitals providing denominator data; - the large proportion of isolates (94%) that come from the main tertiary care centre in the capital; and - the relatively large proportion of isolates from (neonatal/paediatric) intensive care units (58%). *Patient characteristics of isolates from Montenegro are available in Fig. 6.5.*
	Sample size	–	• The total number of isolates is 161. • Fewer than 30 isolates are available for most pathogens.
Laboratory procedures	AST methods	+	• The national standard for AST is EUCAST. • The methods for AST are disk diffusion (regional laboratories) and a combination of disk diffusion and a semi-automated system (reference laboratory). • Not all isolates are tested for each relevant antibiotic (as listed in the minimum panel for CAESAR reporting *(1)*). • 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 eight laboratories (100%) participated in the CAESAR EQA in 2019.
	AST breakpoints	+	• EUCAST breakpoints are used in seven out of eight laboratories (88%).

[a] Estimated population mid-2018, United Nations *(2)*.
[b] Compared with EARS-Net countries: median 36.8 in 2018 *(3)*.

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 2019. Resistance percentages for these isolates are presented in Tables 6.29–6.34.

Fig. 6.5 Patient characteristics of isolates in Montenegro in 2019, by pathogen

Table 6.29 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Montenegro in 2019

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	23	74*	0*	NA	NA	NA
Amoxicillin-clavulanic acid	24	33*	0*	22	77*	5*
Piperacillin-tazobactam	23	0*	13*	22	50*	5*
Cefotaxime/ceftriaxone	24	38*	0*	23	87*	0*
Ceftazidime	24	33*	4*	23	48*	22*
Ertapenem	19	0*	0*	18	28*	6*
Imipenem/meropenem	24	0*	0*	23	17*	4*
Gentamicin/tobramycin	24	33*	0*	23	78*	0*
Amikacin	24	0*	4*	23	30*	9*
Ciprofloxacin/levofloxacin/ofloxacin	24	46*	0*	23	48*	9*
Multidrug resistance[a]	24	29*	NA	23	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 6.30 Resistance levels for *Salmonella* spp. among blood and CSF isolates in Montenegro in 2019

Antibiotic (group)	*Salmonella* spp.		
	N	%R	%I
Cefotaxime/ceftriaxone	2	0*	0*
Ceftazidime	2	0*	0*
Ertapenem	1	0* **	0* **
Imipenem/meropenem	2	0*	0*
Ciprofloxacin/levofloxacin	0	–	–

– = no data available.

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

** Less than 70% of isolates were tested for this antibiotic (group), 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 2019

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	16	44*	0*	NA	NA	NA
Ceftazidime	16	31*	0*	NA	NA	NA
Cefepime	15	53*	0*	NA	NA	NA
Imipenem/meropenem	16	44*	0*	32	97	0
Gentamicin/tobramycin	16	50*	0*	32	81	0
Amikacin	16	19*	0*	32	94	3
Ciprofloxacin/levofloxacin	15	53*	0*	32	97	3
Multidrug resistance[a]	15	53*	NA	32	81	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 2019

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	43	26	NA
Ciprofloxacin/levofloxacin/ofloxacin	43	12	0
Vancomycin	41	0	0
Rifampicin	32	3	0
Linezolid	31	0	NA

NA = not applicable.

[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 2019

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%IR
Penicillin[a]	4	NA	NA	50*
Cefotaxime/ceftriaxone	4	25*	0*	NA
Levofloxacin/moxifloxacin	1	0* **	0* **	NA
Erythromycin/clarithromycin/azithromycin	4	25*	0*	NA
Multidrug resistance[b]	4	NA	NA	25*

NA = not applicable.

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

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

[a] The percentage IR to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage IR should be interpreted as the percentage R. For non-meningitis indications, the percentage IR 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 2019

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	9	0*	0*	7	100*	0*
High-level gentamicin	9	56*	0*	6	100*	0*
Vancomycin	9	0*	0*	8	50*	0*
Linezolid	4	0* **	0* **	7	0*	0*

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

** Less than 70% of isolates were tested for this antibiotic (group), 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 in a single tertiary care hospital in the capital, who are more likely to be referred patients and therefore more severely ill and possibly had unsuccessful previous antibiotic treatment; 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) and aminoglycosides (gentamicin/tobramycin) were moderately high in *E. coli* but very high in *K. pneumoniae* (Table 6.29). The proportion of resistance to fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin) was high in both *E. coli* and *K. pneumoniae*. Resistance in *P. aeruginosa* was high as well, although based on a small number of isolates (Table 6.31). The high levels of resistance in and *Acinetobacter* spp. are concerning and may reflect the expansion of resistant clones in the health care setting. The proportion of MRSA was moderately high (Table 6.32). Too few results 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 2019. 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 2019

Level of evidence: B			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+	• The surveillance network comprises 18 (100% of) laboratories providing blood culture diagnostic services, of which 12 submitted data. • Laboratories are geographically spread throughout 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 likely small number of blood samples taken per 1000 patient days, although data from 2019 are not available[b]; - the relatively large proportion of isolates (57%) 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 368. • Fewer than 30 isolates are available for some pathogens.
Laboratory procedures	AST methods	+	• The national standard for AST is EUCAST. • The method for AST is a combination of a semi-automated system and disk diffusion (all laboratories). • Not all isolates are tested for each relevant antibiotic (as listed in the minimum panel for CAESAR reporting *(1)*). • Confirmatory and additional testing for some strains is performed in two laboratories. • Internal quality control is regularly performed in eight out of 18 laboratories (44%). • Fourteen out of 18 (78%) laboratories participated in the CAESAR EQA in 2019.
	AST breakpoints	+	• EUCAST breakpoints are used in 17 out of 18 laboratories (94%).

[a] Estimated population mid-2018, United Nations *(2)*.

[b] Median 4, range 0–30 in 2018; in comparison: median 36.8, range 5.3–206.9 in 2018 in EARS-Net countries *(3)*.

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 2019. Resistance percentages for these isolates are presented in Tables 6.36–6.41.

Fig. 6.6 Patient characteristics of isolates in North Macedonia in 2019, by pathogen

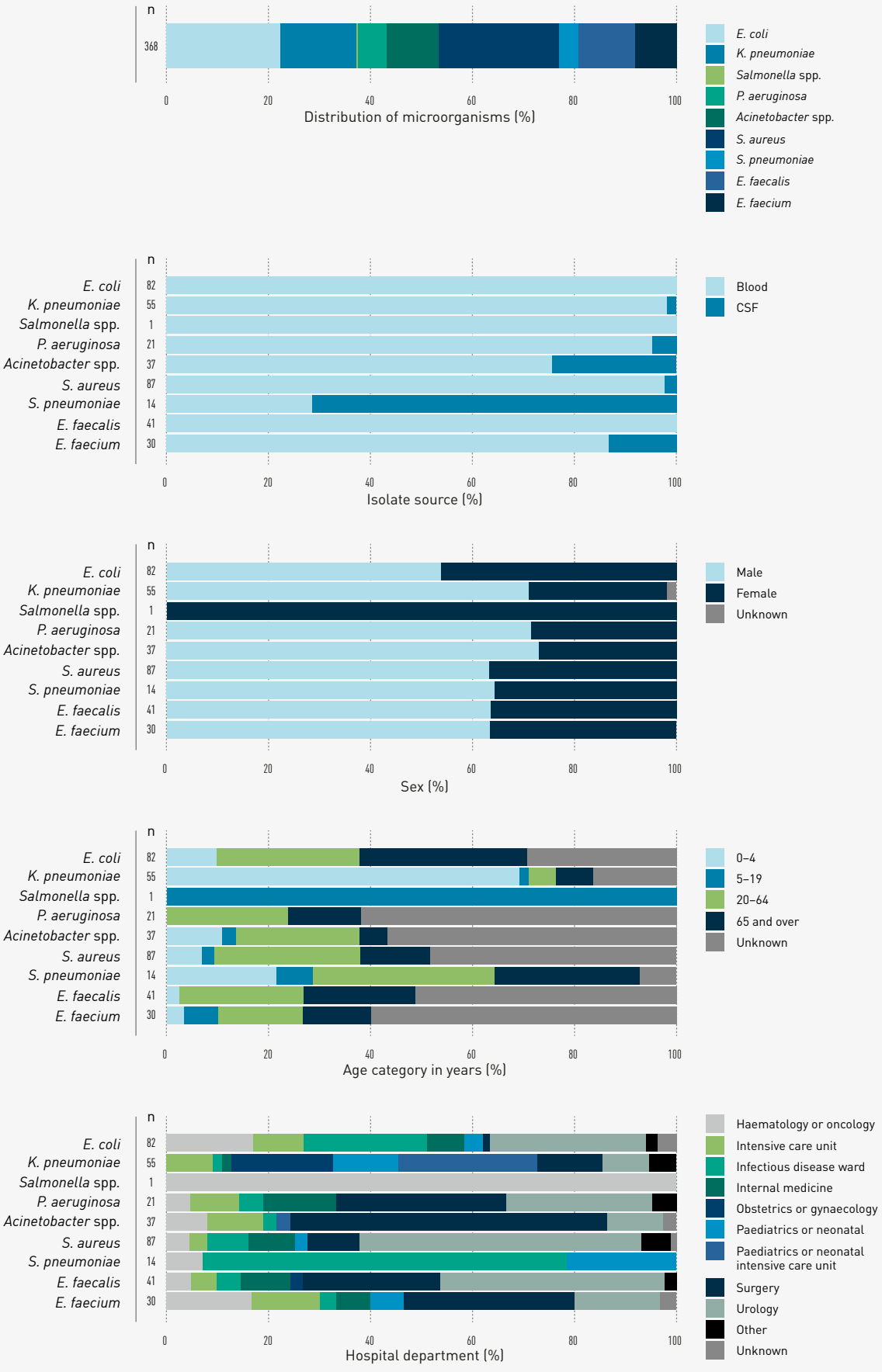


Table 6.36 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in North Macedonia in 2019

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	66	88	0	NA	NA	NA
Amoxicillin-clavulanic acid	71	63	0	54	96	0
Piperacillin-tazobactam	77	26	1	55	93	2
Cefotaxime/ceftriaxone	74	61	3	49	96	0
Ceftazidime	71	49	17	54	94	0
Ertapenem	48	8**	2**	49	18	18
Imipenem/meropenem	82	1	0	55	7	4
Gentamicin/tobramycin	82	39	1	55	96	0
Amikacin	70	6	7	54	7	22
Ciprofloxacin/levofloxacin/ofloxacin	80	59	3	55	87	5
Multidrug resistance[a]	80	24	NA	55	85	NA

NA = not applicable.

** Less than 70% of isolates were tested for this antibiotic (group), 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 *Salmonella* spp. among blood and CSF isolates in North Macedonia in 2019

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

– = no data available.

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

Table 6.38 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in North Macedonia in 2019

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	21	19*	0*	NA	NA	NA
Ceftazidime	21	24*	0*	NA	NA	NA
Cefepime	21	24*	0*	NA	NA	NA
Imipenem/meropenem	21	14*	0*	37	89	0
Gentamicin/tobramycin	20	30*	0*	37	73	0
Amikacin	20	20*	10*	34	71	18
Ciprofloxacin/levofloxacin	21	38*	5*	37	97	0
Multidrug resistance[a]	20	25*	NA	37	73	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 6.39 Resistance levels for *S. aureus* among blood and CSF isolates in North Macedonia in 2019

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	87	45	NA
Ciprofloxacin/levofloxacin/ofloxacin	87	18	1
Vancomycin	77	0	0
Rifampicin	75	5	4
Linezolid	84	0	NA

NA = not applicable.

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

Table 6.40 Resistance levels for *S. pneumoniae* among blood and CSF isolates in North Macedonia in 2019

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%IR
Penicillin[a]	14	NA	NA	57*
Cefotaxime/ceftriaxone	9	11* **	56* **	NA
Levofloxacin/moxifloxacin	11	0*	0*	NA
Erythromycin/clarithromycin/azithromycin	14	43*	0*	NA
Multidrug resistance[b]	14	NA	NA	43*

NA = not applicable.

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

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

[a] The percentage IR to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage IR should be interpreted as the percentage R. For non-meningitis indications, the percentage IR 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 6.41 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in North Macedonia in 2019

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	41	10	0	29	93*	3*
High-level gentamicin	35	54	0	28	89*	0*
Vancomycin	40	8	0	28	64*	0*
Linezolid	36	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 in the main tertiary care hospital in the capital, who are more likely to be referred patients and therefore more severely ill and possibly had unsuccessful previous antibiotic treatment; 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, 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 very high in *K. pneumoniae* (Table 6.36). Resistance in *P. aeruginosa* was moderately high (Table 6.38). The very high levels of resistance in *Acinetobacter* spp. (Table 6.38) and *E. faecium* (Table 6.41) are concerning and may reflect the dissemination of resistant clones in the health care setting. The percentage of MRSA was high and higher than that in most neighbouring countries (Table 6.39, Fig 2.8). Although based on a small number of isolates, resistance levels in *S. pneumoniae* were rather high and concerning (Table 6.40). Too few results were available for *Salmonella* spp. (Table 6.37) to allow interpretation.

6.7 Republic of Moldova

6.7.1. Surveillance set up and data quality assessment

Table 6.42 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from the Republic of Moldova in 2019. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.42 Level of evidence and scoring of factors affecting the validity of CAESAR data from the Republic of Moldova in 2019

Level of evidence: B			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+	• The surveillance network comprises 12 laboratories providing blood culture diagnostic services, of which seven submitted data. • Laboratories are geographically spread throughout the Republic of Moldova. • The estimated coverage of the total population (2 706 000)[a] is not available.
	Hospital types	+	• The network comprises tertiary (25%), secondary (25%), and primary (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[b] number of blood samples taken per 1000 patient days: median 1, range 0–7 in the seven hospitals providing denominator data; - the relatively large proportion of isolates (63%) that come from the main tertiary care hospital in the capital; and - the large proportion of isolates from intensive care units (70%). *Patient characteristics of isolates from the Republic of Moldova are available in Fig 6.7.*
	Sample size	–	• The total number of isolates is 115. • Fewer than 30 isolates are available for most pathogens.
Laboratory procedures	AST methods	+	• The national standard for AST is EUCAST. • The 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 (as listed in the minimum panel for CAESAR reporting *(1)*). • Confirmatory and additional testing of exceptional phenotypes is performed at the reference laboratory (both identification and AST). • Internal quality control is regularly performed in all laboratories. • All 12 laboratories (100%) participated in the CAESAR EQA in 2019.
	AST breakpoints	+	• EUCAST breakpoints are used in all 12 laboratories (100%).

[a] Estimated population mid-year 2018, United Nations *(2)*.
[b] Compared with EARS-Net countries: median 36.8, range 5.3–206.9 in 2018 *(3)*.

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 Republic of Moldova in 2019. Resistance percentages for these isolates are presented in Tables 6.43–6.47.

Fig. 6.7 Patient characteristics of isolates in the Republic of Moldova in 2019, by pathogen

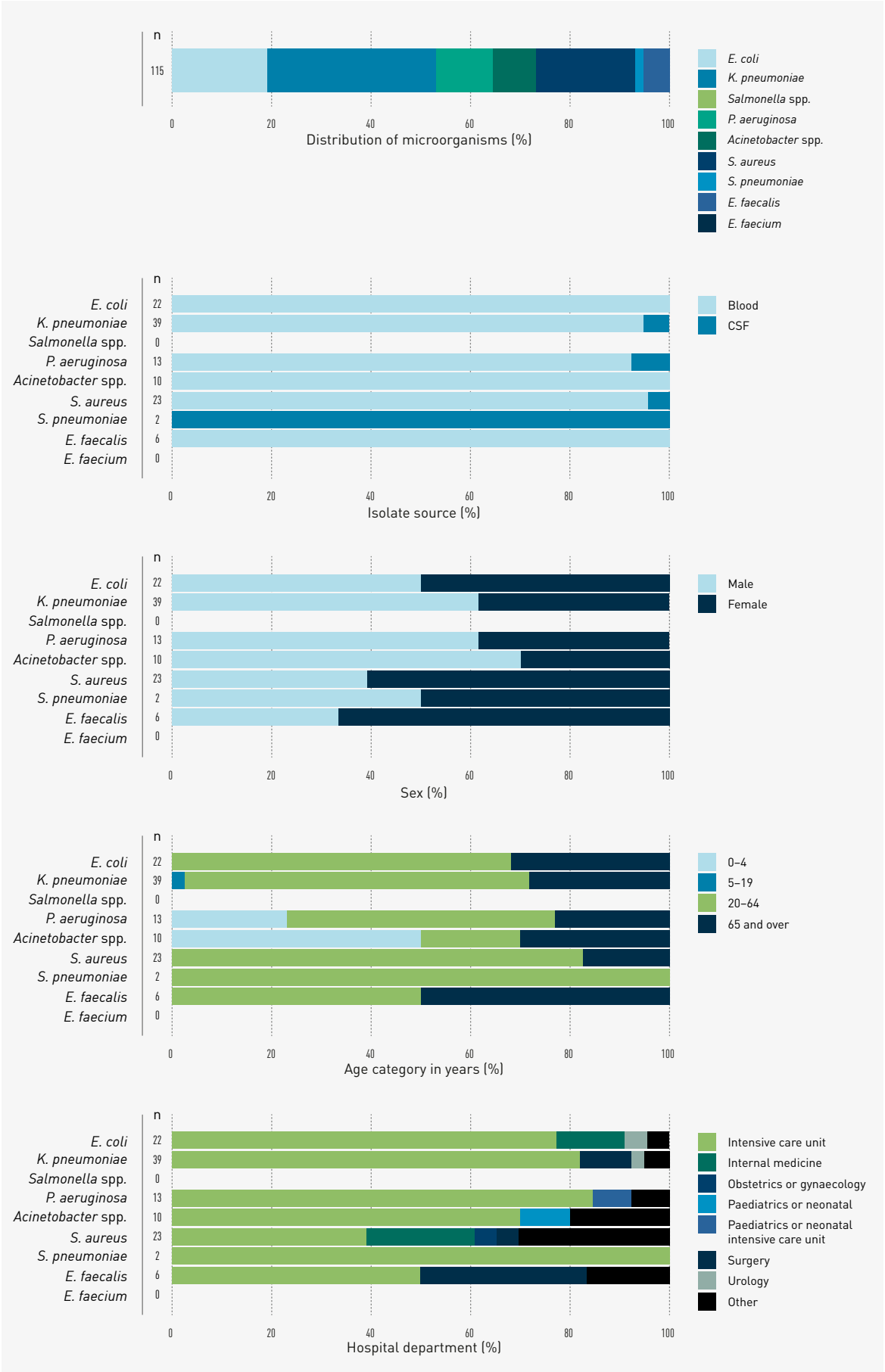


Table 6.43 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in the Republic of Moldova in 2019

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	11	100* **	0* **	NA	NA	NA
Amoxicillin-clavulanic acid	17	53*	0*	27	85* **	0* **
Piperacillin-tazobactam	18	17*	0*	35	80	0
Cefotaxime/ceftriaxone	22	59*	0*	39	79	0
Ceftazidime	22	55*	5*	39	79	0
Ertapenem	12	17* **	0* **	20	80* **	0* **
Imipenem/meropenem	22	9*	0*	39	54	3
Gentamicin/tobramycin	22	18*	5*	39	69	5
Amikacin	22	5*	0*	39	31	13
Ciprofloxacin/levofloxacin/ofloxacin	22	50*	5*	39	82	0
Multidrug resistance[a]	22	9*	NA	39	69	NA

NA = not applicable.

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

** Less than 70% of isolates were tested for this antibiotic (group), 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 6.44 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in the Republic of Moldova in 2019

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	13	77*	0*	NA	NA	NA
Ceftazidime	11	91*	0*	NA	NA	NA
Cefepime	10	70*	10*	NA	NA	NA
Imipenem/meropenem	13	77*	0*	10	50*	0*
Gentamicin/tobramycin	13	85*	0*	10	50*	0*
Amikacin	12	50*	0*	5	80* **	0* **
Ciprofloxacin/levofloxacin	13	85*	0*	9	56*	0*
Multidrug resistance[a]	11	91*	NA	9	56*	NA

NA = not applicable.

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

** Less than 70% of isolates were tested for this antibiotic (group), 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 6.45 Resistance levels for *S. aureus* among blood and CSF isolates in the Republic of Moldova in 2019

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	23	22*	NA
Ciprofloxacin/levofloxacin/ofloxacin	16	13* **	0* **
Vancomycin	11	0* **	0* **
Rifampicin	8	0* **	0* **
Linezolid	14	0* **	NA

NA = not applicable.

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

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

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

Table 6.46 Resistance levels for *S. pneumoniae* among blood and CSF isolates in the Republic of Moldova in 2019

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%IR
Penicillin[a]	2	NA	NA	50*
Cefotaxime/ceftriaxone	0	–	–	NA
Levofloxacin/moxifloxacin	2	0*	0*	NA
Erythromycin/clarithromycin/azithromycin	2	0*	0*	NA
Multidrug resistance[b]	2	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 IR to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage IR should be interpreted as the percentage R. For non-meningitis indications, the percentage IR 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 6.47 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in the Republic of Moldova in 2019

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	6	17*	0*	0	–	–
High-level gentamicin	4	100* **	0* **	0	–	–
Vancomycin	6	17*	0*	0	–	–
Linezolid	5	0*	20*	0	–	–

– = no data available.

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

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

6.7.3 Conclusion

Data from the Republic of Moldova 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 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 in the main tertiary care hospital in the capital, who are more likely to be referred patients and therefore more severely ill and possibly had unsuccessful previous antibiotic treatment; 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 the Republic of Moldova, especially patients with community-acquired infections.

Nevertheless, in the patient population sampled, high levels of resistance to third-generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime) and fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin) were observed in *E. coli* and *K. pneumoniae* (Table 6.43). In *K. pneumoniae* in addition, resistance to aminoglycosides (gentamicin/tobramycin) and carbapenems (imipenem/meropenem) was high. 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 dissemination of resistant clones in the health care setting (Table 6.44). The proportion of MRSA was moderately high (Table 6.45). Too few results were available for *Salmonella* spp. (no isolates), *S. pneumoniae* (Table 6.46), *E. faecalis* and *E. faecium* (Table 6.47) to allow interpretation.

6.8 Russian Federation

6.8.1 Surveillance set-up and data quality assessment

Table 6.48 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from the Russian Federation in 2019. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.48 Level of evidence and scoring of factors affecting the validity of CAESAR data from the Russian Federation in 2019

Level of evidence: B			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+/–	• The surveillance network comprises 46 (1% of) laboratories, of which 13 submitted data. • Laboratories are geographically spread throughout 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[b] number of blood samples taken per 1000 patient days in some hospitals: median 15, range 12–55 in the four hospitals providing denominator data; - the large proportion of isolates from intensive care units (60%); and - the relatively large proportion of nosocomial pathogens (13% *Acinetobacter* spp., 30% *K. pneumoniae*), with high resistance percentages. *Patient characteristics of isolates from the Russian Federation are available in Fig. 6.8.*
	Sample size	+	• The total number of isolates is 1412. • At least 30 isolates are available for most pathogens.
Laboratory procedures	AST methods	+/–	• The national standard for AST is EUCAST. • The 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 (as listed in the minimum panel for CAESAR reporting *(1)*). • Confirmatory testing and additional characterization of exceptional phenotypes is performed at the reference laboratory. • Internal quality control is regularly performed in all laboratories. • None of the 46 laboratories participated in the CAESAR EQA in 2019.
	AST breakpoints	+	• EUCAST breakpoints are used in all 13 laboratories that submitted data (100%).

[a] Estimated population mid-2013, United Nations *(2)*.

[b] Compared with EARS-Net countries: median 36.8, range 5.3–206.9 in 2018 *(3)*.

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 the Russian Federation in 2019. Resistance percentages for these isolates are presented in Tables 6.49–6.54.

Fig. 6.8 Patient characteristics of isolates in the Russian Federation in 2019, by pathogen

Table 6.49 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in the Russian Federation in 2019

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	121	65**	0**	NA	NA	NA
Amoxicillin-clavulanic acid	153	39	0	238	79**	0**
Piperacillin-tazobactam	37	22**	5**	107	86**	3**
Cefotaxime/ceftriaxone	166	53	0	308	81	4
Ceftazidime	167	40	7	322	79	1
Ertapenem	122	4**	0**	196	61**	0**
Imipenem/meropenem	210	2	0	415	47	7
Gentamicin/tobramycin	143	25**	2**	295	62	3
Amikacin	205	3	5	405	39	8
Ciprofloxacin/levofloxacin/ofloxacin	207	50	3	407	83	3
Multidrug resistance[a]	133	25**	NA	283	57**	NA

NA = not applicable.

** Less than 70% of isolates were tested for this antibiotic (group), 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 6.50 Resistance levels for *Salmonella* spp. among blood and CSF isolates in the Russian Federation in 2019

Antibiotic (group)	*Salmonella* spp.		
	N	%R	%I
Cefotaxime/ceftriaxone	5	0*	0*
Ceftazidime	5	0*	0*
Ertapenem	0	–	–
Imipenem/meropenem	5	0*	0*
Ciprofloxacin/levofloxacin	5	20*	0*

– = no data available.

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

Table 6.51 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in the Russian Federation in 2019

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	23	43* **	0* **	NA	NA	NA
Ceftazidime	68	43	28	NA	NA	NA
Cefepime	60	43	0	NA	NA	NA
Imipenem/meropenem	76	53	0	174	78	3
Gentamicin/tobramycin	45	42**	0**	106	89**	0**
Amikacin	71	35	1	118	81**	1**
Ciprofloxacin/levofloxacin	75	43	0	173	81	5
Multidrug resistance[a]	10	40* **	NA	104	87**	NA

NA = not applicable.

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

** Less than 70% of isolates were tested for this antibiotic (group), 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 6.52 Resistance levels for *S. aureus* among blood and CSF isolates in the Russian Federation in 2019

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	320	23	NA
Ciprofloxacin/levofloxacin/ofloxacin	279	23	0
Vancomycin	135	0**	0**
Rifampicin	49	22**	0**
Linezolid	170	0**	NA

NA = not applicable.

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

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

Table 6.53 Resistance levels for *S. pneumoniae* among blood and CSF isolates in the Russian Federation in 2019

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%IR
Penicillin[a]	22	NA	NA	14*
Cefotaxime/ceftriaxone	11	0* **	0* **	NA
Levofloxacin/moxifloxacin	20	0*	0*	NA
Erythromycin/clarithromycin/azithromycin	21	38*	0*	NA
Multidrug resistance[b]	20	NA	NA	5*

NA = not applicable.

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

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

[a] The percentage IR to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage IR should be interpreted as the percentage R. For non-meningitis indications, the percentage IR 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 6.54 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in the Russian Federation in 2019

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	99	2	0	60	97	0
High-level gentamicin	77	39	0	43	79**	0**
Vancomycin	98	1	0	62	5	0
Linezolid	54	2**	0**	37	3**	0**

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

6.8.3 Conclusion

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

The strengths are:

- the network has coverage in the entire country (although data are available for thirteen laboratories only);
- the number of isolates is large enough for robust estimates of resistance in most pathogens.

The limitation is:

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

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 levels for third-generation cephalosporins (cefotaxime/ceftriaxone and ceftazidime) and fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin) were high in *E. coli*, and very high in *K. pneumoniae* (Table 6.49). In *K. pneumoniae* in addition, high levels of resistance to carbapenems (imipenem/meropenem) were observed. Resistance in *P. aeruginosa* was high (Table 6.51). The very high percentages of resistance in *Acinetobacter* spp. are concerning and may reflect dissemination of resistant clones in the health care setting. The percentage of MRSA was moderately high (Table 6.52). In *S. pneumoniae*, the percentage of penicillin non-wild type was moderately low (Table 6.53). In *E. faecium*, vancomycin resistance was low (Table 6.54). Too few results were available for *Salmonella* spp. (Table 6.50) to allow interpretation.

6.9 Serbia

6.9.1 Surveillance set-up and data quality assessment

Table 6.55 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from Serbia in 2019. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.55 Level of evidence and scoring of factors affecting the validity of CAESAR data from Serbia in 2019

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 throughout Serbia. • The estimated coverage of the total population (7 001 000)[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[b] number of blood samples taken per 1000 patient days in some hospitals: median 17, range 1–88 in the 24 hospitals providing denominator data; and - the relatively large proportion of nosocomial pathogens (18% *Acinetobacter* spp., 18% *K. pneumoniae*, 14% *Enterococcus* spp.) with high resistance percentages. *Patient characteristics of isolates from Serbia are available in Fig. 6.9.*
	Sample size	+	• The total number of isolates is 2909. • 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 disk diffusion (most laboratories) and a combination of a semi-automated system and disk diffusion. • Not all isolates are tested for each relevant antibiotic (as listed in the minimum panel for CAESAR reporting *(1)*). • 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. • Twenty-three out of 24 laboratories (96%) participated in the CAESAR EQA in 2019.
	AST breakpoints	+	• EUCAST breakpoints are used in all 24 laboratories (100%).

[a] Annual average population in 2018, based on results of 2011 population census, United Nations *(2)*.
[b] Compared with EARS-Net countries: median 36.8, range 5.3–206.9 in 2018 *(3)*.

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 Serbia in 2019. Resistance percentages for these isolates are presented in Tables 6.56–6.61.

Fig. 6.9 Patient characteristics of isolates in Serbia in 2019, by pathogen

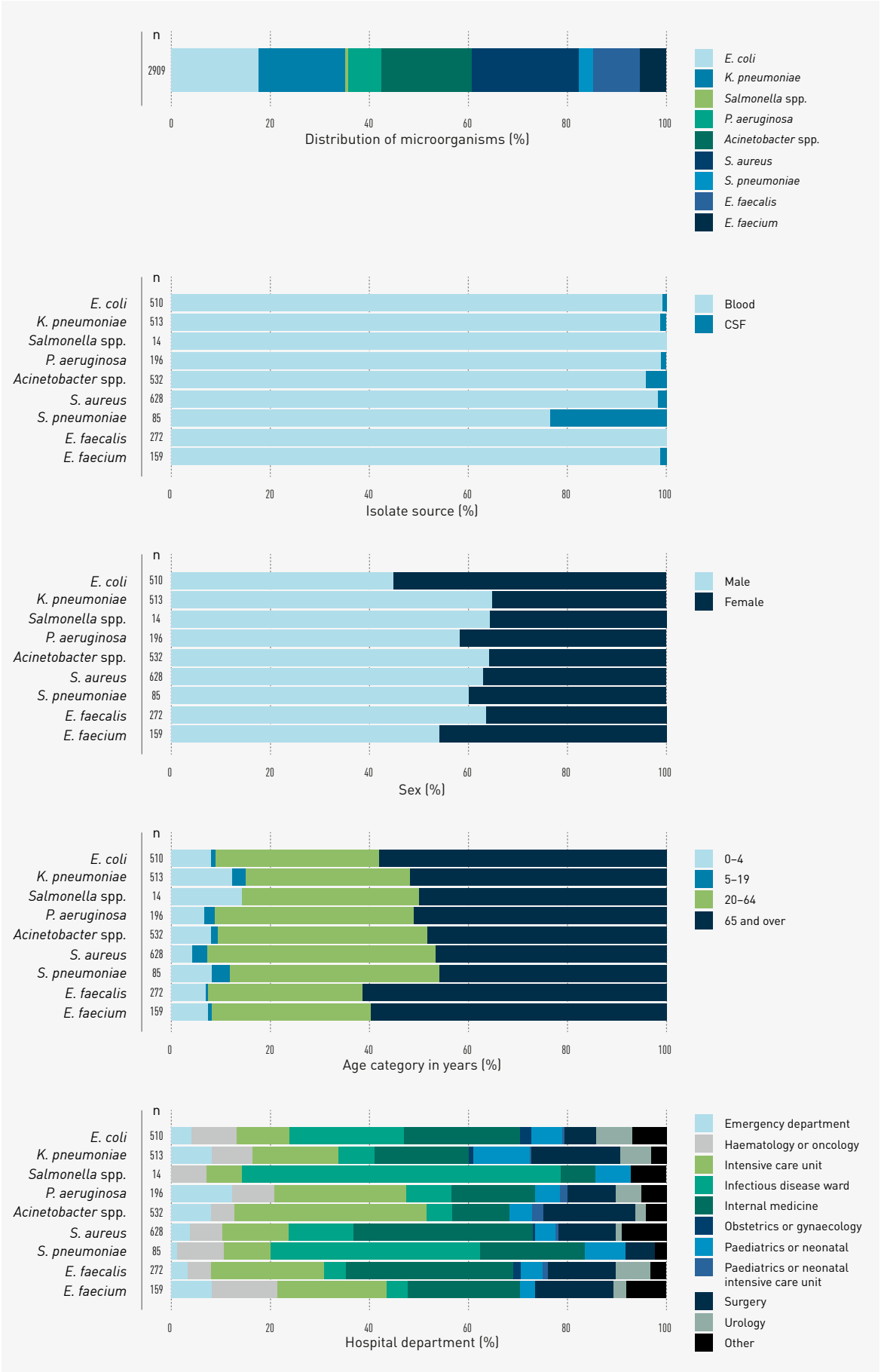


Table 6.56 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Serbia in 2019

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	474	64	0	NA	NA	NA
Amoxicillin-clavulanic acid	328	35**	0**	367	89	0
Piperacillin-tazobactam	477	10	2	447	77	3
Cefotaxime/ceftriaxone	497	25	0	479	87	1
Ceftazidime	473	21	2	444	85	1
Ertapenem	437	1	0	383	59	0
Imipenem/meropenem	502	0	1	512	39	7
Gentamicin/tobramycin	491	30	5	466	77	3
Amikacin	491	7	11	465	37	20
Ciprofloxacin/levofloxacin/ofloxacin	509	35	3	508	78	2
Multidrug resistance[a]	489	13	NA	461	65	NA

NA = not applicable.

** Less than 70% of isolates were tested for this antibiotic (group), 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 6.57 Resistance levels for *Salmonella* spp. among blood and CSF isolates in Serbia in 2019

Antibiotic (group)	*Salmonella* spp.		
	N	%R	%I
Cefotaxime/ceftriaxone	13	0*	0*
Ceftazidime	12	0*	0*
Ertapenem	10	0*	0*
Imipenem/meropenem	11	0*	0*
Ciprofloxacin/levofloxacin	12	17*	0*

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

Table 6.58 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Serbia in 2019

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	191	54	0	NA	NA	NA
Ceftazidime	195	59	0	NA	NA	NA
Cefepime	194	55	0	NA	NA	NA
Imipenem/meropenem	195	55	3	532	96	0
Gentamicin/tobramycin	195	58	0	509	92	0
Amikacin	194	40	11	507	88	3
Ciprofloxacin/levofloxacin	194	59	0	532	97	2
Multidrug resistance[a]	188	56	NA	509	90	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 6.59 Resistance levels for *S. aureus* among blood and CSF isolates in Serbia in 2019

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	628	26	NA
Ciprofloxacin/levofloxacin/ofloxacin	626	21	0
Vancomycin	589	0	0
Rifampicin	537	12	3
Linezolid	614	0	NA

NA = not applicable.

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

Table 6.60 Resistance levels for *S. pneumoniae* among blood and CSF isolates in Serbia in 2019

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%IR
Penicillin[a]	85	NA	NA	36
Cefotaxime/ceftriaxone	77	4	6	NA
Levofloxacin/moxifloxacin	70	1	0	NA
Erythromycin/clarithromycin/azithromycin	77	35	1	NA
Multidrug resistance[b]	77	NA	NA	26

NA = not applicable.

[a] The percentage IR to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage IR should be interpreted as the percentage R. For non-meningitis indications, the percentage IR 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 6.61 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in Serbia in 2019

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	272	0	0	158	100	0
High-level gentamicin	263	60	0	152	82	0
Vancomycin	272	6	0	159	60	0
Linezolid	269	0	0	157	0	0

6.9.3 Conclusion

Data from Serbia 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 number of isolates is large enough for robust estimates of resistance in most pathogens
- 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 antimicrobial 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 pre-treated 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 6.56). High levels of resistance, including carbapenem (imipenem/meropenem) resistance, were seen in *K. pneumoniae*. The high percentages of resistance in *P. aeruginosa*, *Acinetobacter* spp. (Table 6.58) and *E. faecium* (Table 6.61) are concerning and may reflect the dissemination of resistant clones in the health care setting. The proportion of MRSA was moderately high (Table 6.59). In *S. pneumoniae*, the level of penicillin non-wild type was moderately high, as was resistance to macrolides (erythromycin/clarithromycin/azithromycin, Table 6.60).

6.10 Switzerland

6.10.1 Surveillance set-up and data quality assessment

Table 6.62 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from Switzerland in 2019. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.62 Level of evidence and scoring of factors affecting the validity of CAESAR data from Switzerland in 2019

Level of evidence: A			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+	• The surveillance network comprises 33 laboratories providing blood culture diagnostic services, all of which submitted data. • Laboratories are geographically spread throughout Switzerland. • The estimated coverage of the total population (8 484 000)[a] is 86% of hospitalized patients and >30% of ambulatory practitioners' patients.
	Hospital types	+	• The network comprises tertiary/specialized (7%), secondary (10%) 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. 6.10.*
	Sample size	+	• The total number of isolates is 11 651. • 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 (as listed in the minimum panel for CAESAR reporting *(1)*). • 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 32 out of 33 laboratories (97%).

[a] Estimated population 1 January 2018, United Nations *(2)*.

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 Switzerland in 2019. Resistance percentages for these isolates are presented in Tables 6.63–6.68.

Fig. 6.10 Patient characteristics of isolates Switzerland in 2019, by pathogen

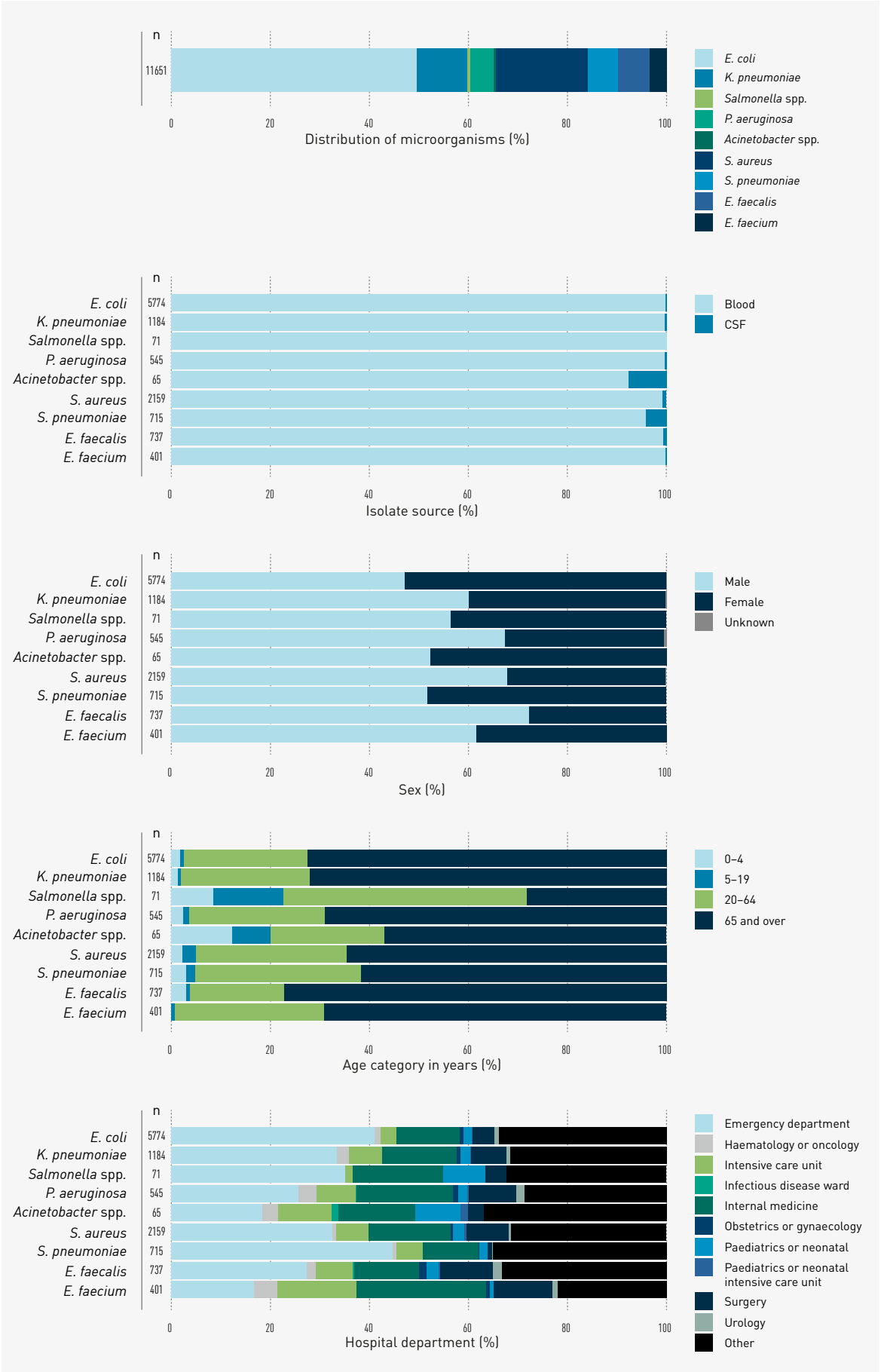


Table 6.63 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Switzerland in 2019

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	5407	49	1	NA	NA	NA
Amoxicillin-clavulanic acid	5757	24	5	1180	12	2
Piperacillin-tazobactam	5539	5	3	1129	7	5
Cefotaxime/ceftriaxone	5763	10	0	1179	7	0
Ceftazidime	5655	8	2	1164	7	1
Ertapenem	3712	0**	0**	733	1**	0**
Imipenem/meropenem	5734	0	0	1179	0	0
Gentamicin/tobramycin	5675	9	0	1169	4	0
Amikacin	4208	2	2	891	1	1
Ciprofloxacin/levofloxacin/ofloxacin	5765	16	2	1183	9	1
Multidrug resistance[a]	5667	4	NA	1169	3	NA

NA = not applicable.

** Less than 70% of isolates were tested for this antibiotic (group), 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 6.64 Resistance levels for *Salmonella* spp. among blood and CSF isolates in Switzerland in 2019

Antibiotic (group)	*Salmonella* spp.		
	N	%R	%I
Cefotaxime/ceftriaxone	69	0	0
Ceftazidime	56	0	0
Ertapenem	32	0**	0**
Imipenem/meropenem	54	0	0
Ciprofloxacin/levofloxacin	66	11	2

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

Table 6.65 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Switzerland in 2019

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	521	10	1	NA	NA	NA
Ceftazidime	522	8	0	NA	NA	NA
Cefepime	534	8	0	NA	NA	NA
Imipenem/meropenem	542	10	3	64	3	2
Gentamicin/tobramycin	543	5	0	63	11	0
Amikacin	480	1	2	55	5	0
Ciprofloxacin/levofloxacin	543	10	0	65	8	40
Multidrug resistance[a]	494	6	NA	63	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 6.66 Resistance levels for *S. aureus* among blood and CSF isolates in Switzerland in 2019

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	2099	3	NA
Ciprofloxacin/levofloxacin/ofloxacin	2154	5	2
Vancomycin	1921	0	0
Rifampicin	2049	0	0
Linezolid	757	0**	NA

NA = not applicable.

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

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

Table 6.67 Resistance levels for *S. pneumoniae* among blood and CSF isolates in Switzerland in 2019

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%IR
Penicillin[a]	671	NA	NA	6
Cefotaxime/ceftriaxone	491	0**	0**	NA
Levofloxacin/moxifloxacin	510	1	0	NA
Erythromycin/clarithromycin/azithromycin	587	8	0	NA
Multidrug resistance[b]	543	NA	NA	3

NA = not applicable.

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

[a] The percentage IR to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage IR should be interpreted as the percentage R. For non-meningitis indications, the percentage IR 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 6.68 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in Switzerland in 2019

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	683	0	0	338	73	1
High-level gentamicin	413	10**	0**	250	27**	0**
Vancomycin	732	0	0	399	2	0
Linezolid	400	0**	0**	218	0**	0**

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

6.10.3 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 enough for robust estimates of resistance in all pathogens; 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.

In *E. coli* and *K. pneumoniae*, resistance levels for third-generation cephalosporins (cefotaxime/ceftriaxone and ceftazidime), aminoglycosides (gentamicin/tobramycin) and fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin) were moderately low, and resistance to carbapenems (imipenem/meropenem) was low (Table 6.63). In *P. aeruginosa* and *Acinetobacter* spp., resistance levels were moderately low (Table 6.65). The proportion of MRSA was low and lower than in neighbouring countries (Table 6.66, Fig. 2.8). In *S. pneumoniae*, the percentage penicillin non-wild type was low (Table 6.67). In *E. faecium*, resistance to vancomycin was low as well (Table 6.68).

6.11 Turkey

6.11.1 Surveillance set-up and data quality assessment

Table 6.69 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from Turkey in 2019. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.69 Level of evidence and scoring of factors affecting the validity of CAESAR data from Turkey in 2019

Level of evidence: A			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+	• The surveillance network comprises 120 (15% of) laboratories providing blood culture diagnostic services, of which 69 submitted data. • Laboratories are geographically spread throughout Turkey. • The estimated coverage of the total population (81 339 000)[a] is 28%.
	Hospital types	+	• The network comprises tertiary (75%) and secondary (25%) 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[b] number of blood samples taken per 1000 patient days in some hospitals: median 23, range 1–99 in the 69 hospitals providing denominator data; and - the relatively large proportion of nosocomial pathogens (12% *Acinetobacter* spp., 20% *K. pneumoniae*, 18% *Enterococcus* spp.). *Patient characteristics of isolates from Turkey are available in Fig. 6.11.*
	Sample size	+	• The total number of isolates is 20 945. • At least 30 isolates are available for all pathogens.
Laboratory procedures	AST methods	+	• The national standard for AST is EUCAST. • The methods for AST are a semi-automated system (most laboratories), a combination of a semi-automated system and disk diffusion, and a combination of disk diffusion and gradient strip tests. • Not all isolates are tested for each relevant antibiotic (as listed in the minimum panel for CAESAR reporting *(1)*). • Confirmatory testing of exceptional phenotypes is performed at the reference laboratory. • Internal quality control is regularly performed in all laboratories. • Seventy out of 120 laboratories (58%) participated in the CAESAR EQA in 2019.
	AST breakpoints	+	• EUCAST breakpoints are used in all 120 laboratories (100%).

[a] Estimated population mid-2018, United Nations *(2)*.
[b] Compared with EARS-Net countries: median 36.8, range 5.3–206.9 in 2018 *(3)*.

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 Turkey in 2019. Resistance percentages for these isolates are presented in Tables 6.70–6.75.

Fig. 6.11 Patient characteristics of isolates in Turkey in 2019, by pathogen

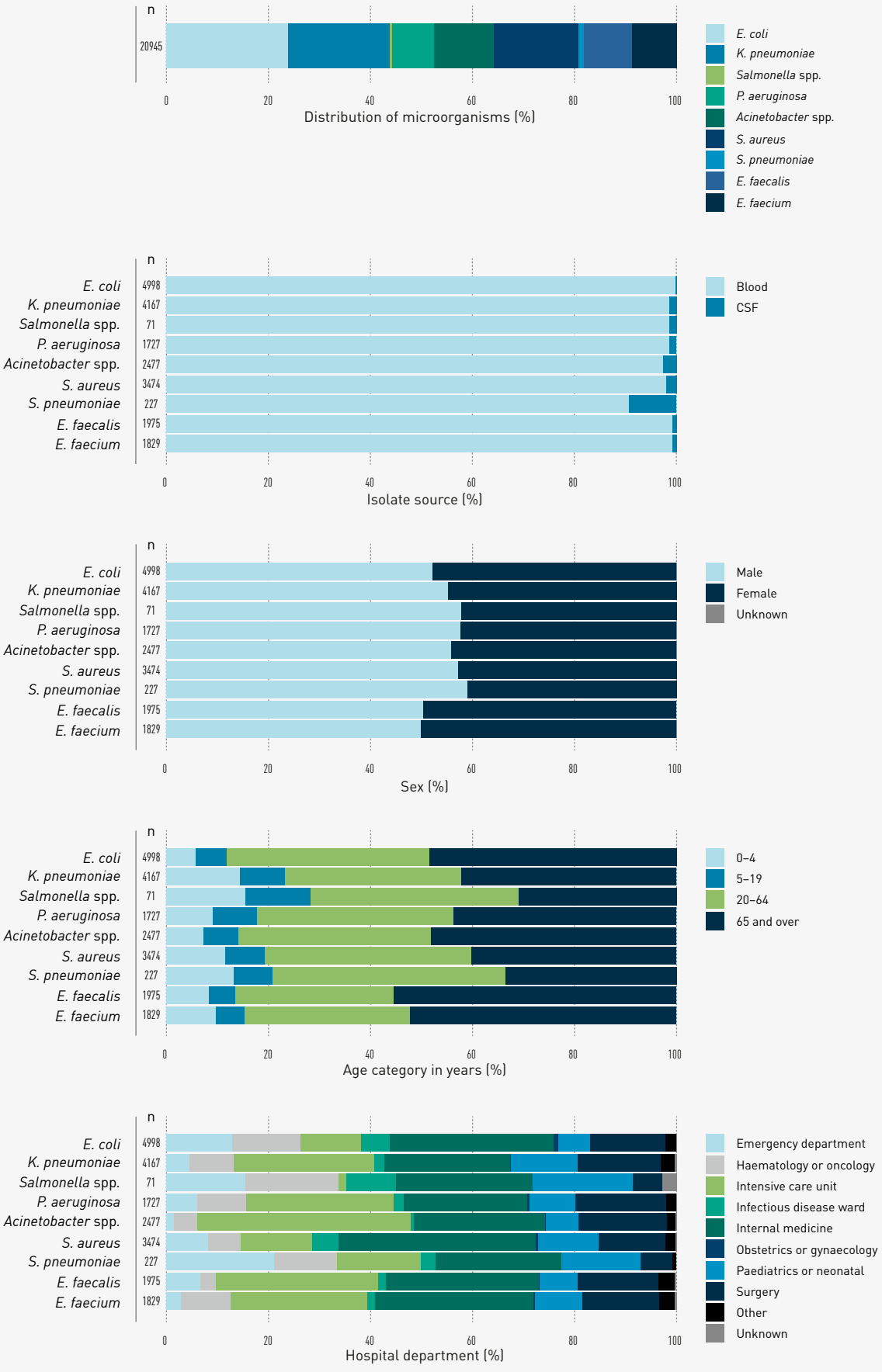


Table 6.70 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Turkey in 2019

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	4289	79	0	NA	NA	NA
Amoxicillin-clavulanic acid	3487	61**	0**	2772	75**	0**
Piperacillin-tazobactam	4369	22	4	3565	60	7
Cefotaxime/ceftriaxone	4598	53	1	3602	73	1
Ceftazidime	4537	47	6	3742	70	3
Ertapenem	4559	9	0	3647	51	0
Imipenem/meropenem	4965	3	1	4028	39	6
Gentamicin/tobramycin	4616	26	1	3925	45	2
Amikacin	4552	2	4	3760	27	5
Ciprofloxacin/levofloxacin/ofloxacin	4852	52	5	3933	65	5
Multidrug resistance[a]	4495	18	NA	3689	40	NA

NA = not applicable.

** Less than 70% of isolates were tested for this antibiotic (group), 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 6.71 Resistance levels for *Salmonella* spp. among blood and CSF isolates in Turkey in 2019

Antibiotic (group)	*Salmonella* spp.		
	N	%R	%I
Cefotaxime/ceftriaxone	60	13	7
Ceftazidime	35	14**	6**
Ertapenem	31	3**	0**
Imipenem/meropenem	44	2**	0**
Ciprofloxacin/levofloxacin	56	20	0

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

Table 6.72 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Turkey in 2019

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	1533	34	0	NA	NA	NA
Ceftazidime	1645	28	0	NA	NA	NA
Cefepime	1630	31	0	NA	NA	NA
Imipenem/meropenem	1712	38	3	2390	90	1
Gentamicin/tobramycin	1681	21	0	2404	80	0
Amikacin	1579	14	4	2179	70	5
Ciprofloxacin/levofloxacin	1637	35	0	2391	91	6
Multidrug resistance[a]	1424	30	NA	2362	80	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 6.73 Resistance levels for *S. aureus* among blood and CSF isolates in Turkey in 2019

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	3406	31	NA
Ciprofloxacin/levofloxacin/ofloxacin	3130	13	0
Vancomycin	3396	0	0
Rifampicin	1218	9**	2**
Linezolid	3418	0	NA

NA = not applicable.

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

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

Table 6.74 Resistance levels for *S. pneumoniae* among blood and CSF isolates in Turkey in 2019

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%IR
Penicillin[a]	212	NA	NA	51
Cefotaxime/ceftriaxone	158	8**	15**	NA
Levofloxacin/moxifloxacin	189	4	0	NA
Erythromycin/clarithromycin/azithromycin	211	37	3	NA
Multidrug resistance[b]	200	NA	NA	33

NA = not applicable.

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

[a] The percentage IR to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage IR should be interpreted as the percentage R. For non-meningitis indications, the percentage IR 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 6.75 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in Turkey in 2019

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	1915	5	0	1627	89	1
High-level gentamicin	1913	34	0	1745	55	0
Vancomycin	1939	1	0	1797	13	0
Linezolid	1954	0	0	1771	0	0

6.11.3 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 enough for robust estimates of resistance in most pathogens
- 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 pre-treated 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 6.70). In *K. pneumoniae* in addition, high levels of resistance to carbapenems (imipenem/meropenem) were seen. The high levels of resistance in *Acinetobacter* spp. (Table 6.72) are concerning and likely reflect the dissemination of resistant clones in the health care setting. The proportion of MRSA was moderately high (Table 6.73). In *S. pneumoniae*, the level of penicillin non-wild type was high, as was resistance to macrolides (erythromycin/clarithromycin/azithromycin (Table 6.74). Resistance in *P. aeruginosa* was moderately high in general (Table 6.72), as was vancomycin resistance in *E. faecium* (Table 6.75).

6.12 Ukraine

6.12.1 Surveillance set-up and data quality assessment

Table 6.76 shows the level of evidence and scoring of factors affecting the validity of CAESAR data from Ukraine in 2019. More information on the assessment criteria is in Chapter 5 and Annex 2.

Table 6.76 Level of evidence and scoring of factors affecting the validity of CAESAR data from Ukraine in 2019

Level of evidence: B			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+/–	• The surveillance network comprises seven (0.9% of) laboratories, all of which submitted data. • Laboratories are located in four (out of 24) different regions spread throughout Ukraine. • The estimated coverage of the total population (42 386 000)[a] is 0.74%.
	Hospital types	+/–	• The network comprises tertiary (86%) and secondary (14%) 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[b] number of blood samples per 1000 patient days: median 3, range 1–12 in the five hospitals providing denominator data; - the large proportion of isolates from intensive care units (46%); and - the relatively large proportion of nosocomial pathogens (14% *Acinetobacter* spp., 24% *K. pneumoniae*, 19% *Enterococcus* spp.), with high resistance percentages. *Patient characteristics of isolates from Ukraine are available in Fig. 6.12.*
	Sample size	–	- The total number of isolates is 307. - Fewer than 30 isolates are available for some pathogens.
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 (five laboratories) and disk diffusion only (two laboratories). • Not all isolates are tested for each relevant antibiotic (as listed in the minimum panel for CAESAR reporting *(1)*). • 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 seven laboratories (100%) participated in the CAESAR EQA in 2019.
	AST breakpoints	+	• EUCAST breakpoints are used in all seven laboratories (100%).

[a] Estimated population mid-2018, United Nations *(2)*.

[b] Compared with EARS-Net countries: median 36.8, range 5.3-206.9 in 2018 *(3)*.

6.12.2 Results

Fig. 6.12 shows the distribution of CAESAR microorganisms and the characteristics of patients (broken down by pathogen) of blood and CSF isolates in Ukraine in 2019. Resistance percentages for these isolates are presented in Tables 6.77–6.81.

Fig. 6.12 Patient characteristics of isolates in Ukraine in 2019, by pathogen

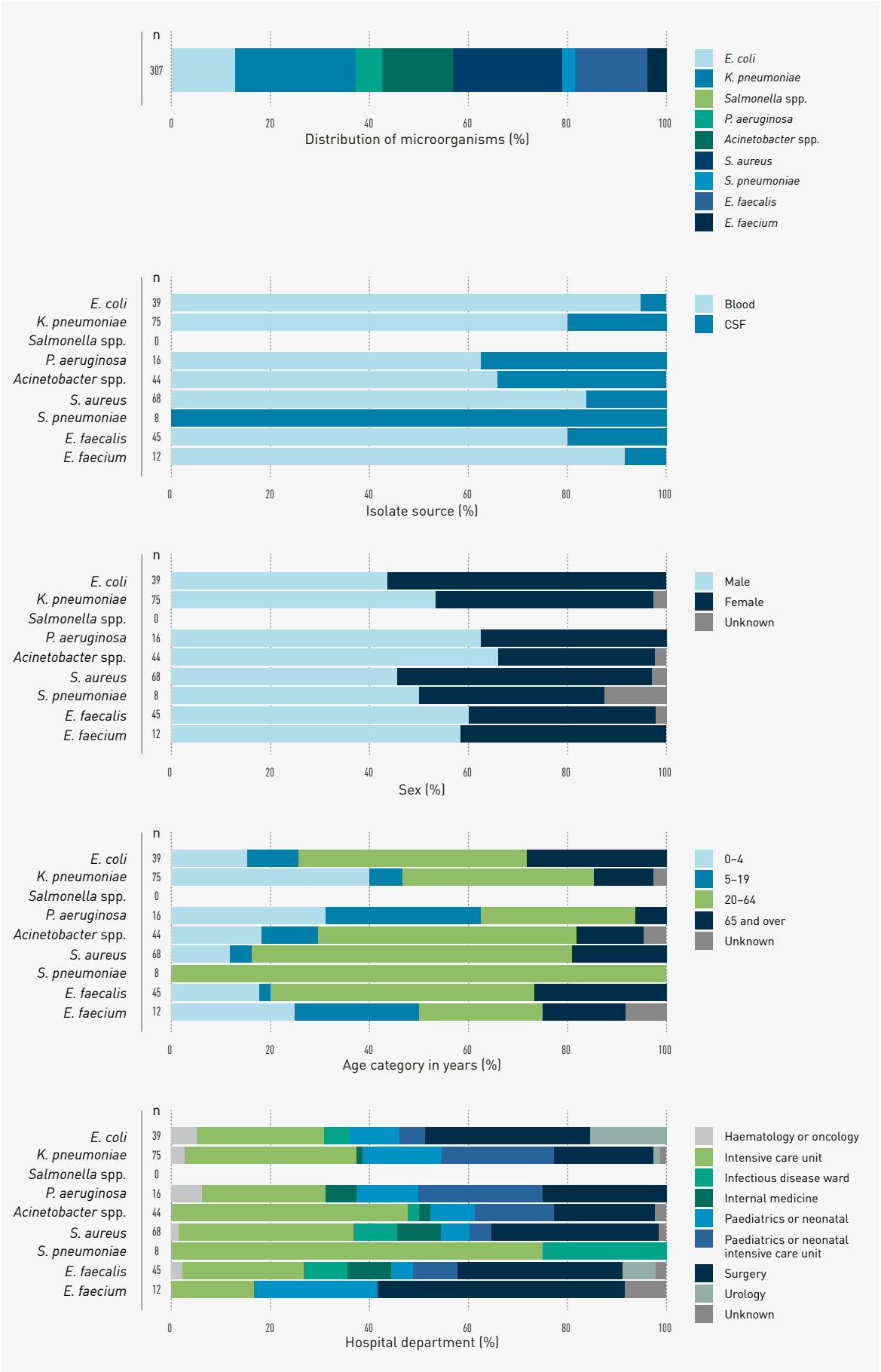


Table 6.77 Resistance levels for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Ukraine in 2019

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	17	76* **	0* **	NA	NA	NA
Amoxicillin-clavulanic acid	38	66	0	61	95	0
Piperacillin-tazobactam	25	8* **	8* **	53	81	0
Cefotaxime/ceftriaxone	38	42	0	67	93	0
Ceftazidime	37	35	3	70	91	1
Ertapenem	22	5* **	0* **	57	72	0
Imipenem/meropenem	31	6	0	67	61	9
Gentamicin/tobramycin	35	20	0	69	77	0
Amikacin	33	3	9	69	65	6
Ciprofloxacin/levofloxacin/ofloxacin	37	35	0	71	83	1
Multidrug resistance[a]	34	12	NA	68	71	NA

NA = not applicable.

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

** Less than 70% of isolates were tested for this antibiotic (group), 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 6.78 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Ukraine in 2019

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	12	42*	0*	NA	NA	NA
Ceftazidime	15	60*	0*	NA	NA	NA
Cefepime	16	56*	0*	NA	NA	NA
Imipenem/meropenem	16	56*	0*	44	73	7
Gentamicin/tobramycin	15	53*	0*	40	85	0
Amikacin	15	40*	0*	36	86	0
Ciprofloxacin/levofloxacin	15	73*	0*	41	90	2
Multidrug resistance[a]	12	42*	NA	38	76	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 6.79 Resistance levels for *S. aureus* among blood and CSF isolates in Ukraine in 2019

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	60	2	NA
Ciprofloxacin/levofloxacin/ofloxacin	46	17**	7**
Vancomycin	36	8**	0**
Rifampicin	26	0* **	0* **
Linezolid	40	5**	NA

NA = not applicable.

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

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

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

Table 6.80 Resistance levels for *S. pneumoniae* among blood and CSF isolates in Ukraine in 2019

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%IR
Penicillin[a]	8	NA	NA	13*
Cefotaxime/ceftriaxone	7	0*	0*	NA
Levofloxacin/moxifloxacin	7	14*	0*	NA
Erythromycin/clarithromycin/azithromycin	8	13*	0*	NA
Multidrug resistance[b]	8	NA	NA	13*

NA = not applicable.

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

[a] The percentage IR to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage IR should be interpreted as the percentage R. For non-meningitis indications, the percentage IR 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 6.81 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in Ukraine in 2019

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	42	19	0	12	83*	0*
High-level gentamicin	28	50* **	0* **	11	55*	0*
Vancomycin	38	8	0	12	0*	0*
Linezolid	38	8	0	12	0*	0*

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

** Less than 70% of isolates were tested for this antibiotic (group), and the percentage resistance should be interpreted with caution.

6.12.3 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 different regions of the country; and
- AST results seem reliable and comparable, although some exceptional phenotypes were not confirmed at the reference laboratory.

The limitations are:

- the representativeness of results is limited by overrepresentation of severely ill and pre-treated patients with nosocomial infections in tertiary care 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 Ukraine, especially patients with community-acquired infections.

Nevertheless, in the patient population sampled, resistance levels for third-generation cephalosporins (cefotaxime/ceftriaxone and ceftazidime), aminoglycosides (gentamicin/tobramycin) and fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin) were moderately high in *E. coli* (Table 6.77). The very high levels of resistance in *K. pneumoniae* (Table 6.77) and *Acinetobacter* spp. (Table 6.78) are concerning and may reflect the dissemination of resistant clones in the health care setting. Resistance levels in *P. aeruginosa* were high, although based on a small number of isolates (Table 6.78). The percentage MRSA was low and lower than in neighbouring countries (Table 6.79, Fig. 2.8). In *E. faecium*, although based on a small number of isolates, vancomycin resistance was not observed (Table 6.81). Too few results were available for *Salmonella* spp. (no isolates) and *S. pneumoniae* (Table 6.80) to allow interpretation.


CHAPTER
7

Area-specific data on AMR

7.1 Kosovo[1]

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 2019. 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[1] in 2019

Level of evidence: B			
Assessment criteria		**Score**	**Factors**
Surveillance system	Geographic coverage	+	• The surveillance network comprises two (100% of) laboratories providing blood culture diagnostic services, both of which submitted data. • Laboratories are geographically spread throughout Kosovo[1]. • The estimated coverage of the total population (1 800 000)[a] is 90%.
	Hospital types	+	• The network comprises tertiary (14%) and secondary (86%) 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 (particularly in patients other than neonates and in regional hospitals) are indicated by: - the small[b] number of blood samples taken per 1000 patient days: median 5, range 5–6 in the two hospitals providing denominator data; - the relatively large proportion of isolates (86%) that come from the main tertiary care hospital; and - the relatively large proportion of isolates from neonatal/paediatric intensive care units (57%). *Patient characteristics of isolates from Kosovo1 are available in Fig. 7.1.*
	Sample size	–	• The total number of isolates is 188. • Fewer than 30 isolates are available for most pathogens.
Laboratory procedures	AST methods	+	• The unified standard for AST is EUCAST. • The methods for AST are a combination of a semi-automated system and disk diffusion (expert laboratory) and disk diffusion only (regional laboratory). • All isolates are tested for each relevant antibiotic (as listed in the minimum panel for CAESAR reporting *(1)*). • Confirmatory testing of exceptional phenotypes or highly resistant microorganisms is performed at the expert laboratory. • Internal quality control is regularly performed in both laboratories. • Both laboratories (100%) participated in the CAESAR EQA in 2019.
	AST breakpoints	+	• EUCAST breakpoints are used in both laboratories (100%).

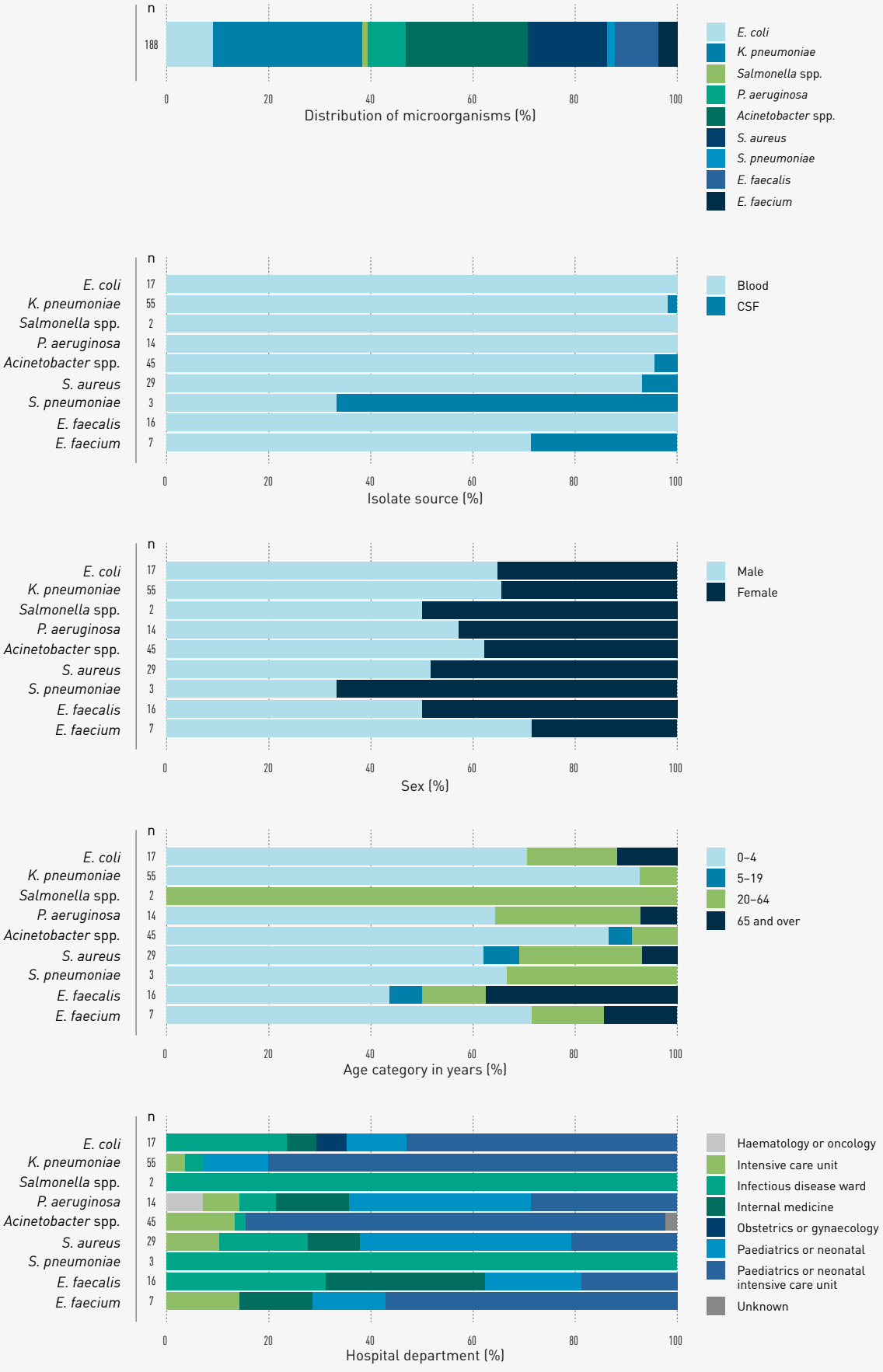
[a] Sergy Koryak, WHO Country Office in Serbia, personal communication, 5 August 2020.
[b] Compared with EARS-Net countries: median 36.8, range 5.3–206.9 in 2018 *(2)*.

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 2019. Resistance percentages for these isolates are presented in Tables 7.2–7.6.

1 All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

Fig. 7.1 Patient characteristics of isolates in Kosovo[1] in 2019, by pathogen



1 All references to Kosovo in this document should be understood to be in the context of the 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[1] in 2019

Antibiotic (group)	*E. coli*			*K. pneumoniae*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	17	76*	0*	NA	NA	NA
Amoxicillin-clavulanic acid	17	35*	0*	55	69	0
Piperacillin-tazobactam	17	6*	0*	55	40	11
Cefotaxime/ceftriaxone	17	41*	12*	55	85	0
Ceftazidime	17	29*	18*	55	62	13
Ertapenem	17	0*	0*	55	2	0
Imipenem/meropenem	17	0*	0*	55	0	2
Gentamicin/tobramycin	17	29*	0*	55	82	4
Amikacin	17	0*	12*	55	65	2
Ciprofloxacin/levofloxacin/ofloxacin	17	35*	6*	55	16	4
Multidrug resistance[a]	17	24*	NA	55	16	NA

[1] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).
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 7.3 Resistance levels for *Salmonella* spp. among blood and CSF isolates in Kosovo[1] in 2019

Antibiotic (group)	*Salmonella* spp.		
	N	%R	%I
Cefotaxime/ceftriaxone	2	0*	0*
Ceftazidime	2	0*	0*
Ertapenem	2	0*	0*
Imipenem/meropenem	2	0*	0*
Ciprofloxacin/levofloxacin	2	0*	0*

[1] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

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

Table 7.4 Resistance levels for *P. aeruginosa* and *Acinetobacter* spp. among blood and CSF isolates in Kosovo1 in 2019

Antibiotic (group)	*P. aeruginosa*			*Acinetobacter* spp.		
	N	%R	%I	N	%R	%I
Piperacillin-tazobactam	14	14*	0*	NA	NA	NA
Ceftazidime	14	14*	0*	NA	NA	NA
Cefepime	14	14*	0*	NA	NA	NA
Imipenem/meropenem	14	14*	0*	45	93	0
Gentamicin/tobramycin	14	14*	0*	45	91	0
Amikacin	14	14*	0*	45	91	2
Ciprofloxacin/levofloxacin	14	21*	0*	45	91	0
Multidrug resistance[a]	14	14*	NA	45	91	NA

[1] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

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 7.5 Resistance levels for *S. aureus* among blood and CSF isolates in Kosovo[1] in 2019

Antibiotic (group)	*S. aureus*		
	N	%R	%I
MRSA[a]	29	34*	NA
Ciprofloxacin/levofloxacin/ofloxacin	29	10*	0*
Vancomycin	29	0*	0*
Rifampicin	29	7*	0*
Linezolid	29	0*	NA

[1] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

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 7.6 Resistance levels for *S. pneumoniae* among blood and CSF isolates in Kosovo[1] in 2019

Antibiotic (group)	*S. pneumoniae*			
	N	%R	%I	%IR
Penicillin[a]	3	NA	NA	67*
Cefotaxime/ceftriaxone	3	0*	0*	NA
Levofloxacin/moxifloxacin	3	33*	0*	NA
Erythromycin/clarithromycin/azithromycin	3	0*	0*	NA
Multidrug resistance[b]	3	NA	NA	0*

[1] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

NA = not applicable.

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

[a] The percentage IR to penicillin is based on penicillin or, if not available, on oxacillin. For meningitis, the percentage IR should be interpreted as the percentage R. For non-meningitis indications, the percentage IR 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 7.7 Resistance levels for *E. faecalis* and *E. faecium* among blood and CSF isolates in Kosovo[1] in 2019

Antibiotic (group)	*E. faecalis*			*E. faecium*		
	N	%R	%I	N	%R	%I
Ampicillin/amoxicillin	16	0*	0*	7	86*	0*
High-level gentamicin	16	50*	0*	7	86*	0*
Vancomycin	16	0*	0*	7	57*	0*
Linezolid	16	0*	0*	7	0*	0*

[1] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

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

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; and
- AST results seem reliable and comparable.

The limitations are:

- the representativeness of results is limited by overrepresentation of neonates and other patients in a single tertiary care hospital in Pristina, who are more likely to be referred patients and therefore more severely ill and possibly had unsuccessful previous antibiotic treatment; 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 moderately high in *E.coli* (although based on a small number of isolates), but very high in *K. pneumoniae* (Table 7.2). However, the proportion of *K. pneumoniae* resistant to carbapenems (imipenem/meropenem) was low. Resistance in *P. aeruginosa* was moderately low, although based on a small number of isolates (Table 7.4). The high levels of resistance in *Acinetobacter* spp. are concerning and may reflect the dissemination of resistant clones in the health care setting. The proportion of MRSA was moderately high (Table 7.5). Too few results were available for *Salmonella* spp. (Table 7.3), *S. pneumoniae* (Table 7.6), and *E. faecium* (Table 7.7) to allow interpretation.


CHAPTER
8

CAESAR EQA

8.1 Introduction

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.

The annual EQA for the laboratories in the CAESAR network is coordinated by the United Kingdom National External Quality Assessment Service for Microbiology (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/area network, thereby enabling the independent assessment of performance and the identification of problem areas.

Participation in the CAESAR EQA serves as a capacity-building exercise supporting the formation of national/area surveillance networks, and also 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 laboratory studies.

Participation in the annual EQA exercises allows 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.

This chapter describes the results from the CAESAR EQA exercise conducted in 2019 and provides a summary of the seven exercises performed between 2013 and 2019.

8.2 CAESAR EQA in 2019

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: *A. baumannii* complex (specimen 5588), *E. coli* (specimen 5589), *K. pneumoniae* (specimen 5590), *P. aeruginosa* (specimen 5591), *S. aureus* (specimen 5592), and *S. pneumoniae* (specimen 5593). The EQA panels were dispatched on 30 September 2019 to all participating laboratories in 18 countries or areas participating in the CAESAR network. All laboratories in Switzerland participate in at least one national or international EQA programme; Switzerland was not included in the 2019 CAESAR EQA but might participate in future rounds. Participating laboratories were requested to return results within four weeks. Results were returned from 18 countries/areas by 240 of 245 (98%) participating laboratories: Albania(10/10 laboratories), Armenia (11/11), Azerbaijan (3/3), Belarus (13/13), Bosnia and Herzegovina (11/11), Georgia (22/23), Kazakhstan (1/1), Kyrgyzstan (6/6), Montenegro (8/8), North Macedonia (14/14), the Republic of Moldova (13/13), Serbia (23/24), Tajikistan (7/8), Turkey (70/72), Turkmenistan (4/4), Ukraine (10/10), Uzbekistan (7/7) and Kosovo[1] (7/7). Laboratories in the Russian Federation could not take part in the 2019 EQA exercise due to logistical problems experienced in delivery of the EQA samples.

8.2.1 Methods and guidelines used

Fig. 8.1 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 (11%) and EUCAST (89%). Homogenous adherence to one guideline was observed in nine countries and areas. All participating laboratories in Armenia, Kyrgyzstan, North Macedonia, the Republic of Moldova, Serbia, Turkmenistan, Ukraine and Kosovo[1] used the EUCAST guidelines, whereas the only participating laboratory in Kazakhstan used the CLSI guidelines.

Among participating laboratories that specified the susceptibility testing method used for the survey strains (n = 240), the breakdown of the methods used revealed that 55% (n = 131) of the laboratories used a disk diffusion susceptibility testing method and 45% (n = 108) used a semi-automated AST instrument (Fig. 8.2). Additionally, one laboratory used the gradient strip test method.

8.2.2 Antimicrobial susceptibility results

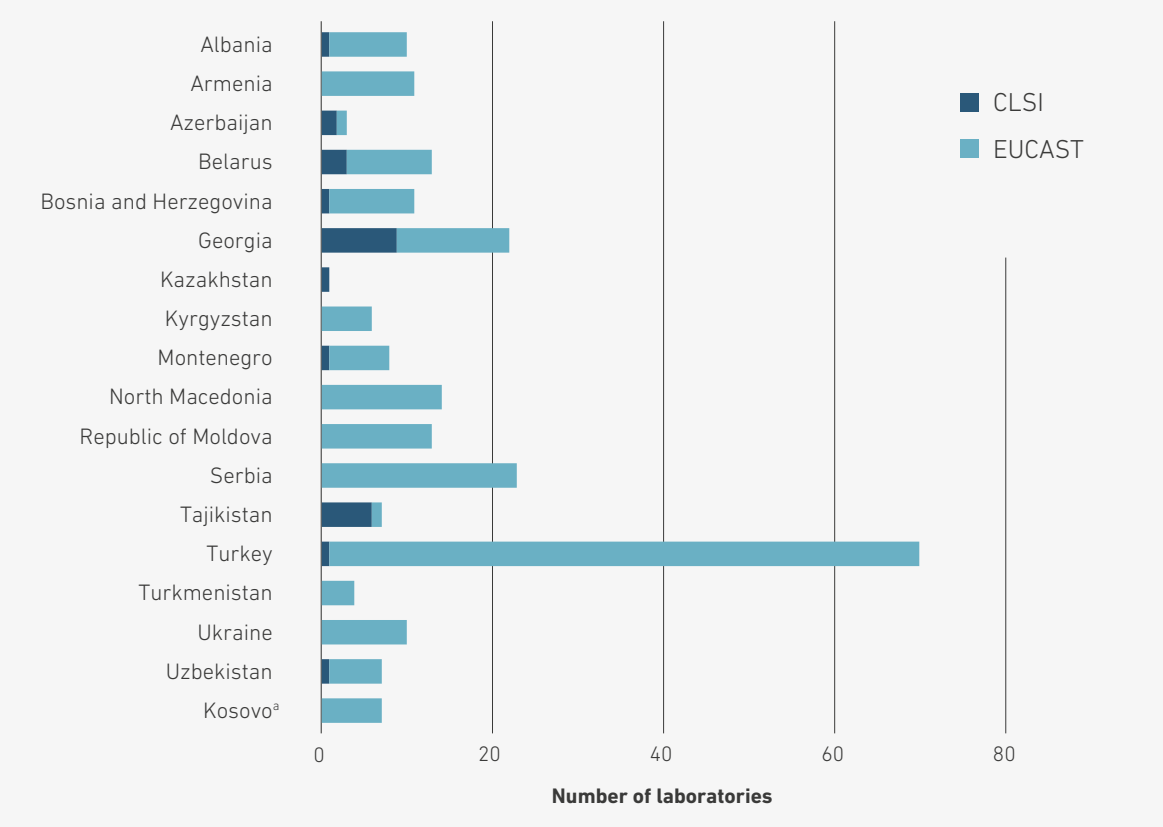
Participating laboratories' results were collated, analysed and presented in individual laboratory reports, which were available on the secure UK NEQAS website. The reports display the individual laboratory's results and the overall results for all laboratories, which give laboratories the opportunity to make suitable comparisons. Laboratories can access their reports at any time, as well as download a printable copy.

In general, performance was very good and consistent with that seen in previous EQA surveys among laboratories in the European Region *(1)*. The major problems encountered in the current exercise are:

- borderline susceptibility (ceftazidime in *E. coli* (specimen 5589), amikacin, ceftazidime and colistin in *P. aeruginosa* (specimen 5591));
- determination of susceptibility to beta-lactam/beta-lactamase inhibitor combinations (notably susceptibility to piperacillin-tazobactam in *K. pneumoniae* (specimen 5590));
- detection of linezolid resistance in *S. aureus* (specimen 5592); and
- determination of susceptibility to beta-lactam agents in *S. pneumoniae* (specimen 5593).

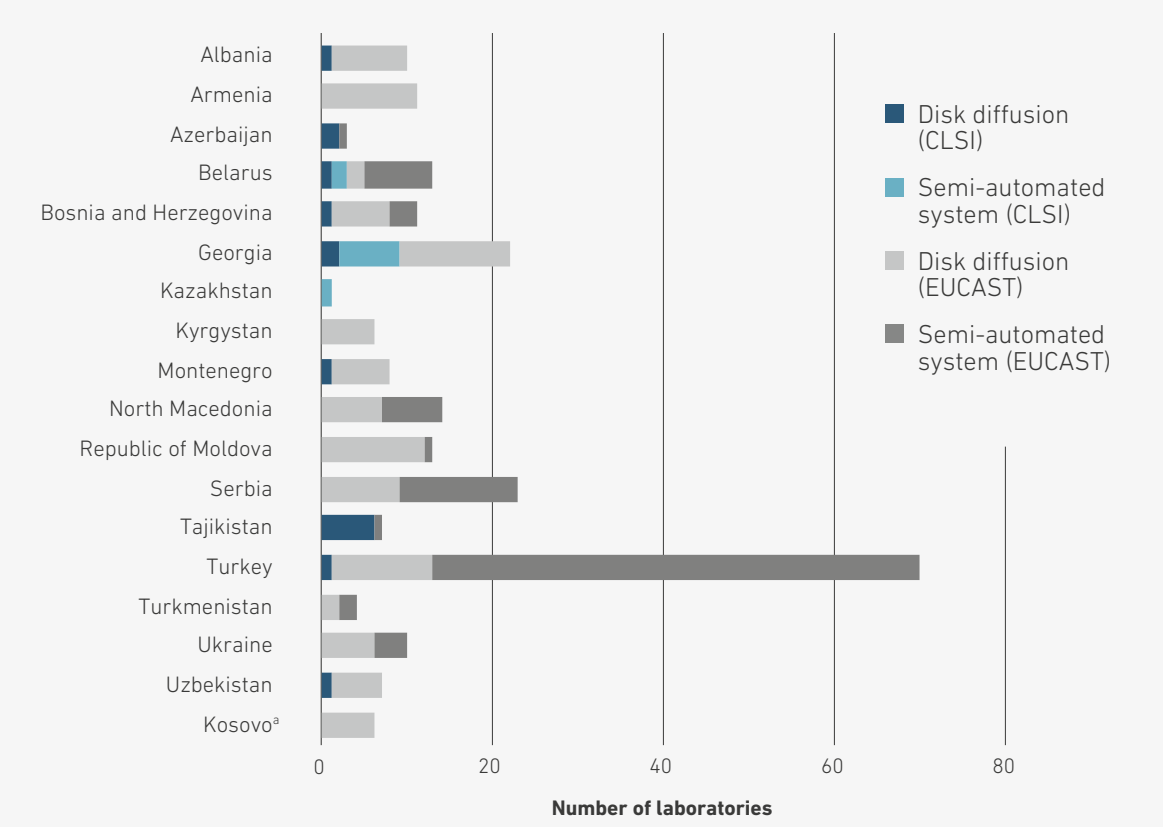
1 All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

Fig. 8.1 Number of laboratories and type of susceptibility testing method per country or area



[a] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

Fig. 8.2 Trends in AST guidelines used by CAESAR EQA participating laboratories, 2013–2019



[a] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

Table 8.1 Specimens distributed in the CAESAR EQA survey in 2019, evaluation of laboratory performance for identification and important antimicrobial susceptibility features of the strains

Specimen	Organism	Correct identification among participating laboratories (*n* = 240)		Failures in identification at species level	Important antimicrobial susceptibility features of the strain
		%	*n*		
5588	*A. baumannii* complex	90	216	*Acinetobacter* spp. (*n* = 14) *Burkholderia* spp. (*n* = 1) *Enterobacter* spp. (*n* = 1) *E. coli* (*n* = 2) *K. pneumoniae* (*n* = 2) *E. faecalis* (*n* = 3) *E. faecium* (*n* = 1)	• Resistant to carbapenems (imipenem and meropenem) due to increased production of chromosomal OXA-51-like oxacillinase • Resistant to fluoroquinolones (ciprofloxacin and levofloxacin) • Resistant to gentamicin but susceptible to amikacin and tobramycin • Susceptible to colistin
5589	*E. coli*	99	239	*K. pneumoniae* (*n* = 1)	• Resistant to aminopenicillins, amoxicillin-clavulanic acid and piperacillin-tazobactam due to hyperexpression of TEM-1 ß-lactamase • Borderline susceptibility with ceftazidime
5590	*K. pneumoniae*	95	229	*Acinetobacter baumannii* complex (*n* = 2) *E. coli* (*n* = 2) *Klebsiella* spp. (*n* = 4) Gram negative rod (*n* = 1) *E. faecium* (*n* = 1) *S. aureus* (*n* = 1)	• Wide MIC range from reference laboratories for piperacillin-tazobactam (4–16 mg/L) • Resistant to gentamicin and tobramycin but susceptible to amikacin
5591	*P. aeruginosa*	98	235	*Pseudomonas* spp. (*n* = 4) *P. fluorescens* (*n* = 1)	• Colistin MIC values from reference laboratories (2 and 4 mg/L) spanning the clinical breakpoints (S ≤2 mg/L, R >2 mg/L) • Resistant to carbapenems (imipenem and meropenem) due to a combination of reduced porin expression, efflux systems and increased production of AmpC ß-lactamase
5592	*S. aureus*	99	237	*S. epidermidis* (*n* = 1) No result provided (*n* = 2)	• MRSA • Resistant to linezolid • Susceptible to erythromycin but resistant to clindamycin
5593	*S. pneumoniae*	96	230	*Streptococcus mitis* (*n* = 1) *Streptococcus* spp. (*n* = 1) *Neisseria meningitidis* (*n* = 1) No result provided (*n* = 7)	• Penicillin MIC = 4 mg/L • Reduced susceptibility to cefotaxime and ceftriaxone • Susceptible to fluoroquinolones but resistant to erythromycin and clindamycin

The specimens distributed and their important antimicrobial susceptibility features are outlined in Table 8.1. The different isolates are described in more detail on the next pages, and the results by country or area are given in Tables 8.2–8.7. The following susceptibility categories were used to categorize susceptibility of the challenge strains tested against the antimicrobial agents:

- S ("susceptible, standard dosing regimen" according to EUCAST and "susceptible" according to CLSI);
- I ("susceptible, increased exposure" according to EUCAST and "intermediate" according to CLSI); or
- R ("resistant" according to both EUCAST and CLSI).

Specimen 5588 was an international clone II *A. baumannii* complex strain. The strain was resistant to carbapenems (imipenem and meropenem), fluoroquinolones (ciprofloxacin and levofloxacin) and gentamicin but susceptible to amikacin, tobramycin and colistin.

The mechanism causing carbapenem resistance in this strain was the production of the chromosomal OXA-51-like oxacillinase with increased expression due to the insertion sequence IS*Aba1*.

The concordance attained with intended results was overall excellent or very good for all eight antimicrobials tested. As for colistin, >50% of the participating laboratories in 10 out of 18 countries/areas failed to provide a result, highlighting the need for improved laboratory capacity for AST of colistin.

Table 8.2 *A. baumannii* complex (specimen 5588): MIC and intended results reported by the reference laboratories and the percentage of laboratories giving the correct result per country or area

Agent	MIC range (mg/L), reference laboratory	Intended interpretation	Percentage of laboratories giving the correct result																	
		EUCAST/ CLSI	Albania (10)	Armenia (11)	Azerbaijan (3)	Belarus (13)	Bosnia and Herzegovina (11)	Georgia (22)	Kazakhstan (1)	Kyrgyzstan (6)	Montenegro (8)	North Macedonia (14)	Republic of Moldova (13)	Serbia (23)	Tajikistan (7)	Turkey (70)	Turkmenistan (4)	Ukraine (10)	Uzbekistan (7)	Kosovo[1] (7)
Identification	–	–	90	100	67	100	73	95	100	67	75	93	100	96	14	97	50	100	86	86
Amikacin	4	S/S	70	100	100	100	91	82	–	100	100	92	100	100	–	84	100	100	100	86
Ciprofloxacin	32–>64	R/R	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Colistin	0.5	S/S	–	100	–	100	100	–	–	–	–	78	–	100	–	96	–	100	100	–
Gentamicin	>64	R/R	100	100	100	83	100	95	100	83	88	100	100	100	57	100	75	100	86	86
Imipenem	32	R/R	100	100	100	100	100	90	0	100	75	100	100	100	–	96	33	100	86	100
Levofloxacin[a]	–	R/R	89	100	33	83	100	84	100	83	75	100	100	100	–	100	67	100	71	100
Meropenem	64–>64	R/R	100	100	100	100	100	100	–	100	86	100	92	100	–	100	100	100	71	100
Tobramycin	1	S/S	78	100	–	92	89	93	100	100	100	100	100	100	–	94	67	100	86	100

[1] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).
[a] 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.

Identification at the species level was achieved by 90% (216/240) of the participating laboratories. Additionally, 14 laboratories, most of which used conventional methods for identification, could identify the strain at genus level and reported the identification result as *Acinetobacter* spp. Furthermore, numerous misidentifications (*n* = 10) were encountered (*Burkholderia* spp., *n* = 1; *E. coli*, *n* = 2; *Enterobacter* spp., *n* = 1; *K. pneumoniae*, *n* = 2; *E. faecalis*, *n* = 3; and *E. faecium*, *n* = 1). All misidentifications were reported from laboratories using conventional methods for identification.

Specimen 5589 was a strain of *E. coli* resistant to ampicillin, amoxicillin, amoxicillin-clavulanic acid and piperacillin-tazobactam. The strain was susceptible to cefotaxime and ceftriaxone but was either 'I' with EUCAST guidelines or 'S' with CLSI guidelines to ceftazidime. The strain was susceptible to all of the remaining agents tested: carbapenems (ertapenem, imipenem and meropenem), fluoroquinolones (ciprofloxacin, levofloxacin and ofloxacin), aminoglycosides (amikacin, gentamicin and tobramycin) and colistin.

There was overall very good concordance attained with intended results for all agents except amoxicillin-clavulanic acid, piperacillin-tazobactam and more strikingly, ceftazidime.

For amoxicillin-clavulanic acid and piperacillin-tazobactam, the intended result was resistant (MIC ≥128 mg/L for both agents). Among laboratories that returned results for amoxicillin-clavulanic acid (*n* = 223), the following results were provided; R: 80.3% (*n* = 179), I: 1.3% (*n* = 3) and S: 18.4% (*n* = 41). Similarly, among laboratories that returned result for piperacillin-tazobactam (*n* = 218), the following results were provided: R: 77.1% (*n* = 168), I: 4.1% (*n* = 9) and S: 18.8% (*n* = 41).

Interestingly, two laboratories that stated that they followed the EUCAST guidelines reported I for amoxicillin-clavulanic acid; however, there is no I category for amoxicillin-clavulanic acid in the 2019 EUCAST clinical breakpoint tables. Additionally, five laboratories that stated that they followed the CLSI guidelines reported results for colistin; however, there are no interpretative criteria for colistin with *Enterobacterales* in the 2019 CLSI breakpoint tables. These laboratories may need to review and update their methodology.

For ceftazidime the intended result was I with EUCAST guidelines and S with CLSI guidelines. The strain had an MIC of 4 mg/L for ceftazidime, which was at the border between I and R categories with EUCAST guidelines (S ≤1 mg/L and R >4 mg/L) and between S and I categories with CLSI guidelines (S ≤4 mg/L, I = 8 mg/L and R ≥16 mg/L). Only 9.9% (*n* = 20) of participating laboratories using the EUCAST guidelines (*n* = 203) provided the intended category I, whereas 76.8% (*n* = 156) reported the result as S and 13.3% (*n* = 27) reported the result as R. Among participating laboratories reporting the result using the CLSI guidelines (*n* = 22), the intended category S was reported by 72.7% (*n* = 16) of the laboratories, whereas 4.6% (*n* = 1) reported the result as I and 22.7% (*n* = 5) reported the result as R.

Correct identification at the species level was achieved by 239 of the 240 participating laboratories (99%), and only one misidentification (*K. pneumoniae*) was observed.

Specimen 5590 contained a *K. pneumoniae* strain that was resistant to amoxicillin, ampicillin, amoxicillin-clavulanic acid and fluoroquinolones (ciprofloxacin, levofloxacin and ofloxacin). The strain was susceptible to third-generation cephalosporins (cefotaxime, ceftriaxone and ceftazidime), carbapenems (ertapenem, imipenem and meropenem), amikacin and colistin. For gentamicin and tobramycin, the intended susceptibility category was R with EUCAST guidelines, but I or R for gentamicin and I for tobramycin with CLSI guidelines.

For piperacillin-tazobactam, the intended result was S or I with EUCAST guidelines and S with CLSI guidelines. The reason for that was a wide MIC range (4–16 mg/L) was obtained for this strain from the reference laboratories. The technical challenges associated with AST of *Enterobacterales* against piperacillin-tazobactam have been addressed by EUCAST in its 2019 update of clinical breakpoint tables when the context of "area of technical uncertainty" was first introduced. As observed with this challenge strain, piperacillin-tazobactam MIC results of 16 mg/L (and zone diameter results of 17–19 mm) with *Enterobacterales* isolates fall into the "area of technical uncertainty". In these cases, the susceptibility category is uncertain and EUCAST advises laboratories to follow certain steps to resolve these uncertainties.

Table 8.3 *E. coli* (specimen 5589): MIC and intended results reported by the reference laboratories and the percentage of laboratories giving the correct result per country or area

Agent	MIC range (mg/L), reference laboratory	Intended interpretation	Percentage of laboratories giving the correct result																	
		EUCAST/ CLSI	Albania (10)	Armenia (11)	Azerbaijan (3)	Belarus (13)	Bosnia and Herzegovina (11)	Georgia (22)	Kazakhstan (1)	Kyrgyzstan (6)	Montenegro (8)	North Macedonia (14)	Republic of Moldova (13)	Serbia (23)	Tajikistan (7)	Turkey (70)	Turkmenistan (4)	Ukraine (10)	Uzbekistan (7)	Kosovo[1] (7)
Identification	–	–	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	86
Amikacin	2	S/S	80	100	100	92	91	95	–	100	100	93	92	100	–	99	75	100	100	100
Amoxicillin	≥128	R/R	100	100	100	86	100	–	–	–	100	100	100	100	–	–	100	100	100	100
Amoxicillin-clavulanic acid[a]	≥128	R/R	80	91	–	15	80	80	0	83	88	64	85	75	–	94	67	80	86	86
Ampicillin	≥128	R/R	100	100	100	100	100	100	100	100	100	100	100	100	50	100	100	100	100	100
Cefotaxime	0.125	S/S	90	100	100	92	100	94	–	100	100	83	100	100	60	93	–	90	57	86
Ceftazidime	4	I/S	22	0	100	31	18	40	100	0	0	0	0	0	–	22	0	10	0	29
Ceftriaxone	0.25	S/S	80	91	100	100	100	88	100	75	100	83	100	100	80	93	100	90	57	100
Ciprofloxacin	0.016	S/S	89	100	100	100	100	95	100	100	100	100	100	100	80	97	100	100	100	83
Colistin	0.5–1	S/–	–	100	–	100	100	–	–	–	–	78	–	100	–	98	–	100	100	–
Ertapenem	0.008–0.016	S/S	75	100	100	91	100	93	100	100	88	100	100	96	–	100	100	100	86	100
Gentamicin	0.5	S/S	70	100	67	100	82	95	100	100	100	100	92	96	86	99	100	100	71	86
Imipenem	0.125	S/S	44	91	67	100	100	95	100	100	100	100	100	100	–	100	100	90	100	100
Levofloxacin[b]	–	S/S	89	100	100	100	100	100	100	100	100	100	100	100	–	100	100	100	100	86
Meropenem	0.016	S/S	56	100	100	100	100	95	–	100	100	100	100	100	–	100	100	100	100	100
Ofloxacin[b]	–	S/S	67	100	67	–	100	–	–	100	100	–	100	100	100	–	100	100	86	86
Piperacillin-tazobactam	≥128	R/R	75	0	–	83	80	85	100	50	50	100	62	91	–	91	100	78	43	29
Tobramycin	0.5–1	S/S	56	100	–	92	88	100	100	100	100	100	92	85	–	97	67	100	86	100

[1] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).
[a] Reference results for amoxicillin-clavulanic acid minimum inhibitory concentrations relate to tests with a fixed concentration of 2 mg/L clavulanic acid.
[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.

For gentamicin, the intended result was R with EUCAST guidelines but the MIC values obtained from the reference laboratories (8 and 16 mg/L) fell into two categories with CLSI clinical breakpoints (S ≤4 mg/L, I = 8 mg/L, R ≥16 mg/L), namely I and R.

Interestingly, one laboratory using the EUCAST guidelines, reported I for amoxicillin-clavulanic acid; however, there is no I category for amoxicillin-clavulanic acid in the 2019 EUCAST clinical breakpoint

tables. Additionally, four laboratories using the CLSI guidelines reported results for colistin; however, there are no interpretative criteria for colistin with *Enterobacterales* in the 2019 CLSI breakpoint tables. These laboratories may need to review and update their methodology.

Correct identification at the species level was achieved by 229 (95%) of the participating laboratories. Additionally, four laboratories reported *Klebsiella* spp. and one laboratory reported Gram-negative rod. A few misidentifications were observed: *A. baumannii* complex, *n* = 2; *E. coli*, *n* = 2; *E. faecium*, *n* = 1; and *S. aureus*, *n* = 1.

Specimen 5591 contained a strain of *P. aeruginosa* that was resistant to piperacillin-tazobactam, carbapenems (imipenem and meropenem), fluoroquinolones (ciprofloxacin and levofloxacin) and aminoglycosides (amikacin, gentamicin and tobramycin). The strain was susceptible to ceftazidime.

The mechanism causing carbapenem resistance in this strain was a combination of reduced porin expression, efflux systems and increased production of AmpC ß-lactamase.

General performance was excellent for most of the agents but less than satisfactory for amikacin, ceftazidime and colistin.

For colistin, due to MIC values obtained from reference laboratories (2–4 mg/L) that span the clinical breakpoints (S ≤2 mg/L, R >2 mg/L) with both EUCAST and CLSI guidelines, all results were considered correct. An MIC value of 4 mg/L with *P. aeruginosa* is identified as a result falling into EUCAST's "area of technical uncertainty", acknowledging the technical difficulties in correctly categorizing isolates with colistin MIC results close to resistant breakpoint. For *P. aeruginosa*, both EUCAST and CLSI have the same clinical breakpoints (S ≤2 mg/L, R >2 mg/L). The number of laboratories reporting a result for colistin was 140 of which 115 (82.1%) reported S and 25 (17.9%) reported R. It's worth mentioning that gradient strip tests are still considered as an invalid method to determine colistin susceptibility. Both EUCAST and CLSI recommend only the broth microdilution method for AST of colistin.

For ceftazidime and amikacin, the reference MIC values were close to clinical breakpoints separating S and R categories with ceftazidime, and I and R categories with amikacin, which has resulted in overall low concordance with intended results. The percentage of laboratories reporting the correct category (S) was 55.4% (128/231) for ceftazidime, and the percentage of laboratories reporting the correct category (R with EUCAST, I or R with CLSI) was 71.1% (165/232) for amikacin.

Approximately 98% of laboratories (*n* = 235) correctly identified the strain at the species level and four laboratories reported *Pseudomonas* spp. Only one misidentification was observed (*P. fluorescens*).

Specimen 5592 contained a strain of *S. aureus* that was resistant to benzylpenicillin, cefoxitin, clindamycin, linezolid and tetracycline. The strain was susceptible to ciprofloxacin, erythromycin, fusidic acid, gentamicin, rifampicin, teicoplanin and vancomycin.

There was excellent or very good concordance with intended results for most of the agents tested. Cefoxitin susceptibility was reported by only 205 of 240 participating laboratories (85%), indicating the need for better adherence to guidelines in use. However, the correct category (R) was reported by 96.6% (198/205) of the laboratories reporting results for cefoxitin.

This strain exhibited a very rare susceptibility profile: it was susceptible to erythromycin but resistant to clindamycin; additionally, the strain was resistant to linezolid. Although still very rare among clinical isolates, linezolid resistance in *S. aureus* is most commonly conferred due to mutations in the 23S rRNA target site. However, the acquisition of the chloramphenicol-florfenicol resistance (*cfr*) gene can also confer multidrug resistance to linezolid. The methyltransferase gene *cfr* can be horizontally transferred with plasmids and it confers resistance to phenicols (e.g. chloramphenicol), lincosamides (e.g. clindamycin), oxazolidinones (e.g. linezolid and tedizolid), pleuromutilins (e.g. lefamulin), streptogramin

Table 8.4 *K. pneumoniae* (specimen 5590): MIC and intended results reported by the reference laboratories and the percentage of laboratories giving the correct result per country or area

Agent	MIC range (mg/L), reference laboratory	Intended interpretation	Percentage of laboratories giving the correct result																	
		EUCAST/ CLSI	Albania (10)	Armenia (11)	Azerbaijan (3)	Belarus (13)	Bosnia and Herzegovina (11)	Georgia (22)	Kazakhstan (1)	Kyrgyzstan (6)	Montenegro (8)	North Macedonia (14)	Republic of Moldova (13)	Serbia (23)	Tajikistan (7)	Turkey (70)	Turkmenistan (4)	Ukraine (10)	Uzbekistan (7)	Kosovo[1] (7)
Identification	–	–	90	100	100	100	100	100	100	83	75	93	100	96	57	99	100	100	86	100
Amikacin	<0.25	S/S	90	100	100	91	91	95	–	100	100	100	100	100	–	100	50	100	71	100
Amoxicillin	>64	R/R	89	91	100	–	100	–	–	–	100	100	100	100	–	–	100	100	100	100
Amoxicillin-clavulanic acid[a]	64–>64	R/R	80	73	–	69	91	48	0	67	100	79	62	60	–	94	100	100	86	71
Ampicillin	>64	R/R	100	91	100	100	100	100	100	100	100	93	100	100	83	100	100	100	100	100
Cefotaxime	0.5–1	S/S	80	91	67	82	100	89	–	60	100	100	100	95	60	92	–	100	43	100
Ceftazidime	0.125	S/S	70	91	100	85	100	90	0	83	88	93	100	96	–	93	–	100	71	100
Ceftriaxone	0.25	S/S	80	91	100	91	100	100	0	100	100	90	100	95	83	95	75	100	71	100
Ciprofloxacin	32–64	R/R	100	100	100	100	100	100	100	83	88	100	100	100	80	100	100	100	86	100
Colistin	0.5	S/–	–	100	–	100	100	–	–	–	–	100	–	100	–	100	–	100	83	–
Ertapenem	0.25–0.5	S/S	75	100	50	82	100	93	100	60	88	100	92	96	–	85	100	100	71	100
Gentamicin	8–16	R/I–R	56	9	100	75	90	67	100	0	57	93	46	96	50	97	25	90	57	71
Imipenem	0.125–0.25	S/S	80	100	33	92	100	95	100	60	100	100	85	96	–	98	100	100	71	100
Levofloxacin[b]	–	R/R	100	91	100	100	100	100	100	100	86	100	100	100	–	98	75	100	100	100
Meropenem	0.25	S/S	67	100	50	92	100	90	–	100	100	100	100	96	–	94	100	100	86	86
Ofloxacin[b]	–	R/R	100	82	100	100	–	100	–	100	88	100	100	100	–	–	100	100	86	86
Piperacillin-tazobactam	4–16	S–I/S	38	100	–	82	100	70	100	100	75	85	85	91	–	90	50	90	29	86
Tobramycin	8	R/I	67	82	–	50	75	60	100	0	14	100	54	95	–	83	33	89	29	100

[1] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

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

[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.

A (e.g. dalfopristin) and 16-membered macrolides (e.g. josamycin, spiramycin). The 14- or 15-membered macrolides (e.g. erythromycin, clarithromycin and azithromycin), however, can retain their activity if there is no accompanying macrolide resistance mechanism. Given the fact that *cfr*-mediated resistance can be horizontally spread, it is important for laboratories to accurately detect linezolid resistance in these strains, not only to avoid the spread of this resistance determinant but also to properly guide the clinical management of the patient.

Table 8.5 *P. aeruginosa* (specimen 5591): MIC and intended results reported by the reference laboratories and the percentage of laboratories giving the correct result per country or area

Agent	MIC range (mg/L), reference laboratory	Intended interpretation	Percentage of laboratories giving the correct result																	
		EUCAST/ CLSI	Albania (10)	Armenia (11)	Azerbaijan (3)	Belarus (13)	Bosnia and Herzegovina (11)	Georgia (22)	Kazakhstan (1)	Kyrgyzstan (6)	Montenegro (8)	North Macedonia (14)	Republic of Moldova (13)	Serbia (23)	Tajikistan (7)	Turkey (70)	Turkmenistan (4)	Ukraine (10)	Uzbekistan (7)	Kosovo[1] (7)
Identification	–	–	100	100	100	100	100	95	100	100	100	93	100	100	100	99	100	100	100	71
Amikacin	32–>64	R/I–R	70	100	67	83	73	70	–	0	25	100	54	74	–	67	100	100	57	71
Ceftazidime	4–8	S/S	50	0	33	62	73	71	0	17	38	86	23	87	–	53	50	90	43	14
Ciprofloxacin	4–32	R/R	100	100	100	100	100	100	100	100	100	100	100	100	40	100	100	100	100	100
Colistin	2–4	S–R/S–R	–	100	–	100	100	–	–	–	–	100	–	100	–	100	–	100	100	–
Gentamicin	>64	R/R	100	100	100	100	100	100	100	83	100	100	100	100	43	100	75	100	86	100
Imipenem	32	R/R	100	100	67	100	100	100	100	100	88	100	100	100	–	99	100	100	100	100
Levofloxacin[a]	–	R/R	100	100	100	100	100	100	100	100	88	100	100	100	–	100	100	100	100	100
Meropenem	16–32	R/R	89	100	100	100	100	100	–	100	88	100	100	100	–	100	100	100	100	100
Piperacillin-tazobactam	>64	R/R	100	100	–	75	100	100	100	100	100	100	100	100	–	100	100	100	100	100
Tobramycin	>64	R/R	100	100	–	100	100	95	100	80	100	100	92	100	–	98	100	100	71	100

[1] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

[a] 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.

The performance of the participating laboratories to correctly categorize erythromycin and clindamycin was very good: among laboratories returning results for erythromycin and clindamycin, correct susceptibility categories (erythromycin S and clindamycin R) were achieved by 94.0% (219/233) and 98.7% (228/231) of the laboratories, respectively. Correct susceptibility category for linezolid (R) was reported, however, by only 72% (144/200) of the laboratories returning results.

Correct identification at the species level was achieved by 99% (237/240) of the laboratories, and only one misidentification was observed (*S. epidermidis*). No identification result was provided for this strain by two laboratories.

Specimen 5593 contained a strain of *S. pneumoniae* that showed varying degrees of susceptibility to beta-lactam antibiotics, was susceptible to fluoroquinolones but resistant to erythromycin and clindamycin.

As in previous years, problems were observed with results for beta-lactam antibiotics in a strain of *S. pneumoniae* with a penicillin MIC of 4 mg/L. For each beta-lactam antibiotic, 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 183 laboratories that returned results, 179 (97.8%) reported the correct result. For penicillin and pneumonia (EUCAST: R and CLSI: I), 172 laboratories returned results. Among laboratories following

Table 8.6 *S. aureus* (specimen 5592): MIC and intended results reported by the reference laboratories and the percentage of laboratories giving the correct result per country or area

Agent	MIC range (mg/L), reference laboratory	Intended interpretation	Percentage of laboratories giving the correct result																	
		EUCAST/ CLSI	Albania (10)	Armenia (11)	Azerbaijan (3)	Belarus (13)	Bosnia and Herzegovina (11)	Georgia (22)	Kazakhstan (1)	Kyrgyzstan (6)	Montenegro (8)	North Macedonia (14)	Republic of Moldova (13)	Serbia (23)	Tajikistan (7)	Turkey (70)	Turkmenistan (4)	Ukraine (10)	Uzbekistan (7)	Kosovo[1] (7)
Identification	–	–	100	100	100	100	100	100	100	100	88	100	100	100	86	99	100	100	100	100
Penicillin	>0.5	R/R	88	100	100	100	100	100	–	75	100	100	100	100	–	98	67	100	100	100
Cefoxitin	16	R/R	88	100	–	90	91	100	100	100	88	100	100	100	–	100	–	100	100	57
Ciprofloxacin	0.5	S/S	100	91	67	92	91	95	100	100	88	100	100	96	67	100	100	89	86	100
Clindamycin	>4	R/R	100	100	100	100	100	95	–	100	100	100	100	100	–	99	75	100	100	100
Erythromycin	0.5	S/S	56	100	67	85	100	95	100	100	100	100	100	100	50	100	100	90	57	100
Fusidic acid	≤0.125	S/–	–	100	–	100	100	–	–	–	100	100	100	100	–	100	–	100	80	100
Gentamicin	0.5	S/S	60	100	67	100	100	70	100	100	100	93	100	100	83	99	100	90	86	100
Linezolid	16	R/R	50	73	–	80	89	42	–	25	43	77	92	95	–	74	–	70	57	20
Rifampicin	≤0.008	S/S	100	100	100	83	89	72	–	–	100	82	100	95	–	97	100	100	86	100
Teicoplanin	0.5	S/S	–	100	–	100	100	–	–	–	–	100	100	100	–	100	–	100	100	–
Tetracycline	>8	R/R	100	100	100	100	100	100	100	100	100	100	100	100	50	100	100	100	71	86
Vancomycin	1	S/S	–	100	–	100	100	–	–	–	83	92	100	100	–	100	50	100	100	–

[1] All references to Kosovo in this document should be understood to be in the context of the 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.

EUCAST, the correct result (R) was reported by 24.4% (39/160 laboratories), and among laboratories following CLSI, the correct result (I) was reported by 8.3% (1/12 laboratories).

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 26.5% (31/117) of the laboratories, whereas 59.0% (69/117) of the laboratories reported S. In pneumonia, correct results for cefotaxime (EUCAST: I and CLSI: S) were received from 31.9% (38/119) of the laboratories. The low concordance observed was mainly due to the laboratories following EUCAST, among which 62.0% (67/108) reported the result as S. In meningitis, correct results for ceftriaxone (EUCAST: I and CLSI: I or R) were received from 21.1% (28/133) of the laboratories. In pneumonia, correct results for ceftriaxone (EUCAST: I and CLSI: S or I) were received from 27.8% (35/126) of the laboratories, whereas 70.6% (89/126) of the laboratories following the EUCAST methodology reported the result as S.

Furthermore, the strain was susceptible to levofloxacin and moxifloxacin and was resistant to erythromycin and clindamycin. An excellent concordance was achieved for levofloxacin and moxifloxacin; correct results were reported by 98.2% (215/219) of laboratories for levofloxacin and 99.5% (195/196) of laboratories for moxifloxacin. A good concordance was achieved with erythromycin and clindamycin; correct results

were reported by 85.8% (205/239) of laboratories for erythromycin and 92.0% (184/200) of laboratories for clindamycin.

Correct identification at the species level was achieved by 96% (230/240) of the laboratories and one laboratory reported the strain as *Streptococcus* spp. A few misidentifications were observed: *S. mitis*, *n* = 1; *Neisseria meningitidis*, *n* = 1 and no identification result was provided for this strain by seven laboratories.

Table 8.7 *S. pneumoniae* (specimen 5593): MIC and intended results reported by the reference laboratories and the percentage of laboratories giving the correct result per country or area

Agent	MIC range (mg/L), reference laboratory	Intended interpretation	Percentage of laboratories giving the correct result																	
		EUCAST/ CLSI	Albania (10)	Armenia (11)	Azerbaijan (3)	Belarus (13)	Bosnia and Herzegovina (11)	Georgia (22)	Kazakhstan (1)	Kyrgyzstan (6)	Montenegro (8)	North Macedonia (14)	Republic of Moldova (13)	Serbia (23)	Tajikistan (7)	Turkey (70)	Turkmenistan (4)	Ukraine (10)	Uzbekistan (7)	Kosovo[1] (7)
Identification	–	–	90	100	100	100	100	95	100	100	100	100	100	100	–	99	75	100	100	100
Penicillin	4	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Penicillin (meningitis)	–	R/R	100	100	–	90	100	–	–	–	100	92	100	100	–	100	–	100	86	80
Penicillin (pneumonia)	–	R/I	60	0	–	0	0	–	–	–	57	18	83	9	–	23	–	17	14	60
Cefotaxime	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Cefotaxime (meningitis)	–	I/I	–	0	–	25	38	–	–	–	0	–	–	39	–	–	–	20	57	0
Cefotaxime (pneumonia)	–	I/S	–	0	–	13	50	–	–	–	0	–	–	33	–	–	–	20	57	0
Ceftriaxone	1–2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Ceftriaxone (meningitis)	–	I/I–R	–	0	–	13	13	–	–	–	0	13	60	30	–	–	–	17	57	0
Ceftriaxone (pneumonia)	–	I/S–I	–	0	–	13	13	–	–	–	0	25	60	30	–	20	–	17	71	0
Clindamycin[a]	–	R/R	100	100	100	100	90	71	–	100	100	92	92	100	–	89	–	80	100	86
Erythromycin	≥128	R/R	90	100	100	100	100	90	100	83	100	100	92	100	–	97	67	100	100	100
Levofloxacin	1	S/S	67	100	100	100	100	100	0	100	100	100	100	100	–	100	67	100	100	100
Moxifloxacin	0.125	S/S	88	100	100	100	100	100	–	100	100	100	100	100	–	100	–	100	100	100
Norfloxacin[a]	–	S/S	43	18	–	–	75	–	–	–	100	100	92	95	–	–	–	75	100	–

[1] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

[a] 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.

8.3 Summary of CAESAR EQA (2013–2019)

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.

8.3.1 Expansion of the CAESAR EQA

The CAESAR EQA started in 2013 with 128 laboratories from eight countries or areas (Belarus, Georgia, Kyrgyzstan, Montenegro, North Macedonia, Serbia, Turkey and Kosovo[2]) (Table 8.8). 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. In 2017 and 2018 no new countries joined the EQA exercise, with 290 and 287 laboratories participating in the 2017 and 2018 exercises, respectively. In 2019, Kazakhstan participated in the EQA exercise for the first time. However due to problems encountered in transportation of the EQA samples to the Russian Federation, the number of countries or areas participating in the CAESAR EQA exercise remained at 18, as in 2018.

8.3.2 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. Almost half of the laboratories (48.3%, 116/240) used conventional methods for identification in the CAESAR EQA exercise in 2019. This, in some instances, reflects as a failure to provide identification at the species level. For example, correct identification at the species level was lowest (90%) among participating laboratories for *A. baumannii* complex strain (specimen 5588). Among laboratories using a device or a semi-automated system for identification, correct identification at the species level was achieved by 97.6% (121/124) of the laboratories, whereas the remaining three laboratories reported the identification result as *Acinetobacter* spp. Among laboratories using conventional methods, however, correct identification at the species level was achieved by 81.9% (95/116) of the laboratories. Among the remaining 21 laboratories that failed to provide correct identification at the species level, 11 laboratories reported '*Acinetobacter* spp.' and 10 laboratories failed to provide a correct identification even at genus level.

Similar problems in identification due to limited laboratory capacity were also observed in previous years, especially with *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, laboratories are strongly encouraged to put more efforts into correct identification at the species level. The EQA strains distributed and the percentage of correct identification among the participating laboratories by year is summarized in Table 8.9. So far, only organisms whose antimicrobial susceptibility results are collected by CAESAR have been sent to laboratories. A strain of *E. coli*, *K. pneumoniae*, *S. aureus* and *S. pneumoniae* was distributed in all seven surveys conducted so far.

Greater care is needed when processing the samples, 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.

2 All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

Table 8.8 Countries or areas participating in the CAESAR EQA exercise, 2013–2019

Country or area	Year (no. of returned results/total no. of laboratories)						
	2013	2014	2015	2016	2017	2018	2019
Belarus	8/8	6/8	8/8	9/9	13/13	12/13	13/13
Georgia	1/1	5/9	10/10	10/11	0/13[a]	17/17	22/23
Kyrgyzstan	3/3	5/5	5/5	6/6	6/6	6/6	6/6
Montenegro	1/1	6/7	8/9	9/10	7/8	8/8	8/8
North Macedonia	15/16	13/17	16/17	19/21	19/21	17/18	14/14
Serbia	14/14	14/14	14/14	21/22	22/22	24/24	23/24
Turkey	72/78	68/77	98/106	81/90	81/87	67/71	70/72
Kosovo[1]	6/7	7/7	7/7	7/7	7/7	7/7	7/7
Albania	–	2/2	6/7	7/9	10/11	10/10	10/10
Azerbaijan	–	3/3	3/3	3/3	3/3	0/3[a]	3/3
Bosnia and Herzegovina	–	4/4	7/7	9/9	10/10	10/10	11/11
Russian Federation	–	26/31	31/39	40/41	33/47	33/53	–[a]
Republic of Moldova	–	–	12/12	12/12	12/12	14/14	13/13
Tajikistan	–	–	1/5	4/5	0/5[a]	6/7	7/8
Turkmenistan	–	–	3/3	3/3	3/3	4/4	4/4
Armenia	–	–	–	5/5	11/11	11/11	11/11
Ukraine	–	–	–	3/3	5/5	5/5	10/10
Uzbekistan	–	–	–	6/6	6/6	6/6	7/7
Kazakhstan	–	–	–	–	–	–	1/1
Total	120/128 (94%)	159/184 (86%)	229/252 (91%)	254/272 (93%)	248/290 (91%)[b]	257/287 (91%)[b]	240/245 (98%)

[1] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

[a] Laboratories in Georgia (2017), Tajikistan (2017), Azerbaijan (2018) and the Russian Federation (2019) could not take part in the EQA exercise due to problems encountered in transportation and/or delivery of the EQA samples.

[b] 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).

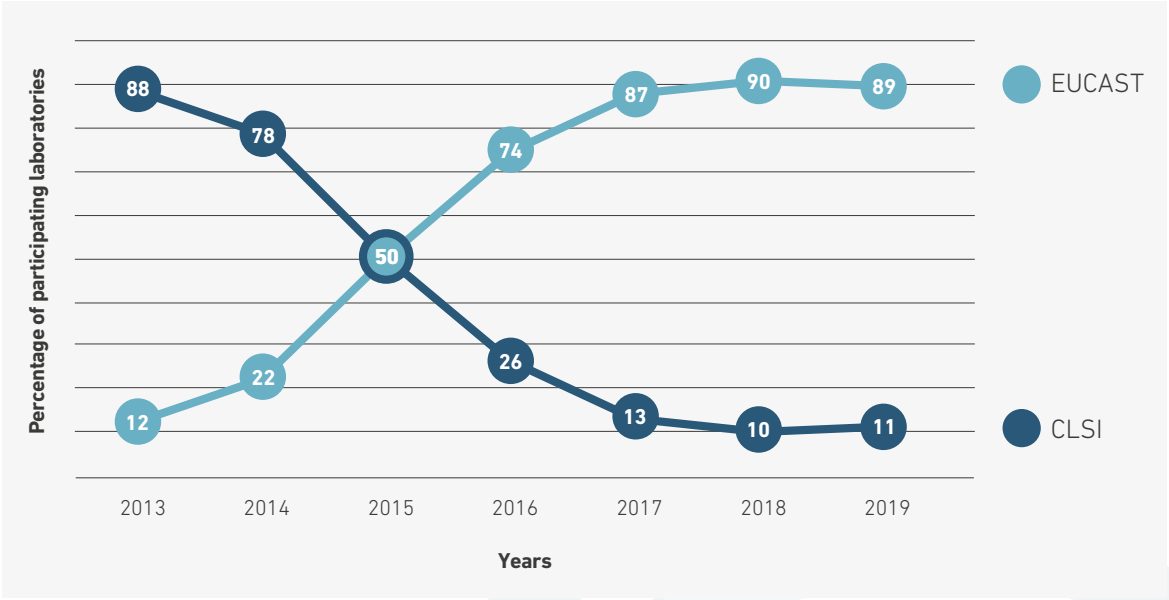
8.3.3 Trends in AST guidelines

Starting from the very beginning, CAESAR aimed to collect reliable and comparable surveillance data on AMR and promoted strict adherence to international guidelines on AST. In 2013, when the first CAESAR EQA exercise was conducted, 88% of the participating laboratories indicated CLSI as their AST guideline and 12% indicated EUCAST. However, a strong shift towards the EUCAST methodology has taken place,

Table 8.9 Specimens distributed as part of the CAESAR EQA and the percentage of correct identification at the species level among participating laboratories, 2013–2019

Organism	Year													
	2013		2014		2015		2016		2017		2018		2019	
	Specimen	%	Specimen	%	Specimen	%	Specimen	%	Specimen	%	Specimen	%	Specimen	%
E. coli	1951	100	2496	100	3092	94	3682	99	4326	99	4928	97	5589	99
K. pneumoniae	1952	97	2497	92	3089	99	3683	91	4327	98	4927	96	5590	95
P. aeruginosa	1956	100	–	–	3093	99	3684	100	–	–	4930	95	5591	98
A. baumannii complex	1950	87	2501	98	–	–	3686	91	4328	96	–	–	5588	90
S. aureus	1953	100	2498	99	3090	99	3685	98	4324	100	4929	97	5592	99
S. pneumoniae	1954	99	2499	99	3091	100	3687	98	4323	99	4931	94	5593	96
E. faecium	–	–	2500	87	–	–	–	–	4325	88	4926	91	–	–
E. faecalis	–	–	–	–	3088	98	–	–	–	–	–	–	–	–

Fig. 8.3 Trends in AST guidelines used by CAESAR EQA participating laboratories, 2013–2019



which, as of 2019, was used as the guideline in 89% of the CAESAR EQA participating laboratories in 18 countries or areas (Fig. 8.3). The fact that all EUCAST documents can be freely accessed and the translation of EUCAST documents into local languages such as Russian, Serbian and Turkish may have contributed to the uptake of the EUCAST methodology in those settings.

8.3.4 Future perspectives and the need for improvement

In general, the CAESAR EQA showed a remarkable growth in the number of participating laboratories between 2013 and 2019, with 245 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;
- even though *Salmonella* spp. is included among the CAESAR pathogens, no *Salmonella* spp. strain was distributed yet; and
- EQA results may not reflect routinely obtained results due to differences in methodology.

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


CHAPTER
9

Concluding remarks

It is not possible to remark on the 2019 CAESAR reporting period, of which data collection was performed mostly in 2020, without mentioning the disruptive effect of the COVID-19 pandemic on the efforts to combat AMR, and on people and systems worldwide.

The CAESAR network is immensely proud to report that despite those challenges all network members were able to contribute to the report in 2020, and that twelve countries (Armenia, Belarus, Bosnia and Herzegovina, Georgia, Montenegro, North Macedonia, the Republic of Moldova, the Russian Federation, Serbia, Switzerland, Turkey and Ukraine) and Kosovo[1] submitted AMR data from isolates obtained in 2019 to the CAESAR database. The Republic of Moldova reported AMR data for the first time during this reporting period. This alone is a remarkable achievement. In addition, 2020 has marked the eighth consecutive year of conducting the CAESAR EQA, preparations of which are currently ongoing. Participation in the 2019 EQA has been steady compared to previous years, with 18 countries and areas participating with 240 out of 245 laboratories (98% response rate).

The proof-of-principle AMR routine diagnostics surveillance projects that are currently ongoing in Tajikistan and Uzbekistan had to be put on a temporary hold due to the disruption of routine activities and services at several project sites, as well as repurposing of clinical staff, due to COVID-19. The disruptions in services experienced during this time provide valuable lessons learned, as they highlight vulnerabilities in systems and services. They also demonstrate how urgently the routines these projects aim to build up need to be strengthened and sustained. Projects will resume once the continuity and quality of proceedings can be guaranteed again. Sustainable investments in AMR response, AMR and antimicrobial consumption surveillance, national AMR reference laboratories and general bacteriological diagnostic services available for patients are urgently needed and cannot be bypassed any longer.

In 2020, for the first time since the initial network kick-off meeting was held in 2013, the CAESAR network was not able to hold a face-to-face meeting due to the COVID-19 pandemic. As unfortunate as this was, the experience has allowed the network to test other means of communication and engagement, which were previously not utilized to their full potential. For example, the network organized a series of technical webinars to discuss updates, findings and topics of interest related to AMR surveillance. While the network remains hopeful that the next CAESAR meeting will take place in Vienna, Austria, in 2021, webinars, regular discussions and capacity building in the way of virtual meetings are very likely here to stay, with great potential in further developing this way of interacting in the future.

From October 2020 to March 2021, the network will have yet another chance to use this new familiarity with virtual meetings, when WHO will hold virtual consultations with countries and areas to inform the future development of GLASS, taking their perspectives into account. A number of new protocols have been developed that complement the core AMR activities, for example the GLASS *Candida* spp. protocol, which is currently undergoing a test phase with many European Region Member States actively participating.

Finally, it remains the plan that – in 2021 – surveillance data from the CAESAR network will be published together with those from EARS-Net, in a report prepared jointly with ECDC. This report is set to provide a comprehensive update of the AMR situation in the WHO European Region.

1 All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

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8. CAESAR EQA

1. External quality assessment (EQA) of performance of laboratories participating in the European Antimicrobial Resistance Surveillance Network (EARS-Net), 2018. Stockholm: European Centre for Disease Prevention and Control, 2019.


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

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