

TECHNICAL REPORT

Assessing the health burden of infections with antibiotic-resistant bacteria in the EU/EEA, 2016-2020

ECDC TECHNICAL REPORT

Assessing the health burden of infections with antibiotic-resistant bacteria in the EU/EEA, 2016-2020



This report of the European Centre for Disease Prevention and Control (ECDC) was coordinated by Tommi Kärki.

Contributing authors

Hanna Merk, Liselotte Diaz Högberg, Diamantis Plachouras, Carl Suetens, Dominique L. Monnet

Acknowledgements

ECDC would like to thank all participating laboratories and hospitals for providing data used for this report. The national focal points and the operational contact points are acknowledged for facilitating data transfer to EARS-Net. ECDC would also like to acknowledge all participating hospitals and the national focal points and operational contact points collecting and providing data in the ECDC Point Prevalence Survey 2016-2017.

Data checks, contributions to the analysis and review of the report were provided by:

Cyprus	Despo Pieridou, MD, Microbiologist, PHD, Director, Microbiology Department, National Reference Laboratory for Antimicrobial Resistance Surveillance, Nicosia General Hospital, Cyprus Panagiota Maikanti – Charalampous, MD, Microbiologist, Microbiology Department, National Reference Laboratory for Antimicrobial Resistance Surveillance, Nicosia General Hospital, Cyprus
Finland	Jari Jalava, National Institute for Health and Welfare, Helsinki, Finland Outi Lyytikäinen, National Institute for Health and Welfare, Helsinki, Finland
Greece	Michalis Polemis, Central Public Health Laboratory, National Public Health Organization, Athens, Greece Dr Kyriaki Tryfinopoulou, Central Public Health Laboratory, National Public Health Organization, Athens, Greece
France	Mélanie Colomb-Cotinat, Santé Publique France, Paris, France
Hungary	Ákos Tóth, Dept. of Microbiological Reference Laboratory, National Public Health Center, Budapest, Hungary Ágnes Hajdu, Dept. of Communicable Disease Epidemiology and Infection Control, National Public Health Center, Budapest, Hungary
Iceland	Anna Margrét Halldórsdóttir, Centre for Health Security and Communicable Disease Control, Directorate of Health, Reykjavik, Iceland Kristján Orri Helgason, Dept of Microbiology, Landspítali, University Hospital of Iceland, Reykjavik, Iceland
Netherlands	Jos Monen, National Institute for Public Health and the Environment, Bilthoven, the Netherlands Sjoukje Woudt, National Institute for Public Health and the Environment, Bilthoven, the Netherlands
Norway	Gunnar Skov Simonsen, University Hospital of North Norway, Tromsø, Norway Frode Width Gran, St. Olav University Hospital, Trondheim, Norway
Poland	Waleria Hryniewicz, National Medicines Institute, Warsaw, Poland Dorota Żabicka, National Medicines Institute, Warsaw, Poland
Portugal	Manuela Caniça, National Institute of Health Dr Ricardo Jorge, Lissabon, Portugal José-Artur Paiva, Directorate-General of Health, Lissabon, Portugal
Romania	Prof Gabriel Adrian Popescu, National Institute for Infectious Diseases "Prof.Dr.Matei Bals", Bucharest, Romania Roxana Ioana Serban, PhD, National Institute of Public Health, Bucharest, Romania
Slovenia	Uroš Glavan, Communicable Diseases Centre, National Institute of Public Health, Ljubljana, Slovenia
Spain	Belén Aracil, National Center for Microbiology, Instituto de Salud Carlos III, Madrid, Spain Jesús Oteo-Iglesias, National Center for Microbiology, Instituto de Salud Carlos III, Madrid, Spain
Sweden	Hanna Billström, The Public Health Agency of Sweden
Other	Alessandro Cassini, Deputy Cantonal Doctor, Public Health Department, Canton of Vaud, Lausanne, Switzerland/Infection Prevention and Control Unit, Infectious Diseases Service, Lausanne University Hospital, Switzerland Michele Cecchini, Organisation for Economic Co-operation and Development (OECD), Paris, France Marcello Gelomini, World Health Organisation (WHO) Regional Office for Europe, Copenhagen, Denmark Aliénor Lerouge, Organisation for Economic Co-operation and Development (OECD), Paris, France

Suggested citation: European Centre for Disease Prevention and Control. Assessing the health burden of infections with antibiotic-resistant bacteria in the EU/EEA, 2016-2020. Stockholm: ECDC; 2022.

Stockholm, November 2022

PDF

ISBN 978-92-9498-591-0

doi: 10.2900/73460

Catalogue number TQ-04-22-166-EN-N

© European Centre for Disease Prevention and Control, 2022

Reproduction is authorised, provided the source is acknowledged

Contents

Abbreviations	iv
Executive summary	1
Background	2
Methods	2
Bacterium–antibiotic resistance combinations	2
Outcome measure	3
Estimation of incidence	3
Disease models and attributable mortality	4
Computational analysis and uncertainty	4
Discussion	13
Conclusions and potential implications	14
References	16

Figures

Figure 1. Estimated number of cases, deaths and disability-adjusted life years for the selected antibiotic-resistant bacteria, EU/EEA, 2016-2020 (logarithmic x- and y-scale)	6
Figure 2. Estimated average burden of infections expressed in disability-adjusted life years (DALYs) per 100 000 population, by age group and antibiotic-resistant bacterium, 2016-2020	8
Figure 3. Estimations of the burden of infections with antibiotic-resistant bacteria presented as disability-adjusted life years (DALYs) per 100 000 population by country*, EU/EEA, 2016-2020	10
Figure 4. Estimations of the burden of infections with antibiotic-resistant bacteria presented as disability-adjusted life years (DALYs) per 100 000 population by country*, EU/EEA, 2020	11
Figure 5. Estimations of the burden of infections with antibiotic-resistant bacteria presented as attributable deaths per 100 000 population by country*, EU/EEA, 2020	12

Tables

Table 1. Bacteria and antibiotic resistance combinations included in the study	3
Table 2. Total number of blood isolates of the selected antibiotic-resistant bacteria as reported to EARS-Net, and estimated number of bloodstream infections, number of infections, number of attributable deaths and number of disability-adjusted life years (DALYs), EU/EEA, 2016-2020	5

Abbreviations

BCoDE	Burden of Communicable Diseases in Europe
BSI	Bloodstream infection
CI	Confidence interval
COVID-19	Coronavirus disease
DALY	Disability-adjusted life-year
EARS-Net	European Antimicrobial Resistance Surveillance Network
EEA	European Economic Area
EU	European Union
HAI	Healthcare-associated infection
IHME	Institute for Health Metrics and Evaluation
MRSA	Meticillin-resistant <i>Staphylococcus aureus</i>
PPS	Point prevalence survey
UI	Uncertainty interval
YLD	Years lived with disability
YLL	Years of life lost

Executive summary

Infections caused by antibiotic-resistant bacteria are considered a major global health threat. Previous studies have consistently described these infections having a considerable public health burden in terms of attributable deaths and disability-adjusted life years (DALYs). This report aims to provide updated estimates of the burden of infections with selected bacterium–antibiotic resistance combinations in the EU/EEA in 2016–2020 and assess how this burden has changed from previous estimates.

Our study methods were based on the methodology to estimate the burden of infections with antibiotic-resistant bacteria from the Burden of Communicable Diseases in Europe (BCoDE)ⁱ, using data on bloodstream infections (BSIs) caused by selected antibiotic-resistant bacteria, as reported to the European Antimicrobial Resistance Surveillance Network (EARS-Net). We estimated the total incidence of infections by taking the annual number of BSIs with antibiotic-resistant bacteria, adjusted the data with the estimated population coverage reported to EARS-Net, converted the population coverage-corrected number of BSIs to other types of infections, and deducted the estimated number of secondary BSI. The conversion multipliers and reduction factors were derived from the ECDC point prevalence survey of 2016–2017 and from previous literature. We then used the estimated annual number of infections with disease models based on literature reviews and ran 10 000 iterations of Monte Carlo simulations to acquire the health burden estimates and their respective 95% uncertainty intervals (UIs).

Our main results include the annual number of infections with antibiotic-resistant bacteria, the number of attributable deaths, the number and rate of disability-adjusted life years (DALYs), and the age-group-specific DALY rates. We used the median estimates derived from the simulations, and reported the 95% uncertainty interval (UI) derived using 2.5% and 97.5% percentiles for the uncertainties. The trends were assessed using Poisson-regression. The proportion of healthcare-associated infections was estimated by information derived from the literature and, when using existing data, defined as infections for which the onset of symptoms was on day three or later after the start of the current admission, or where the patient has been re-admitted less than 48 hours after a previous discharge or transfer from a healthcare facility.

We estimated that between 2016 and 2020, the annual number of cases of infections with the included bacterium–antibiotic resistance combinations in the EU/EEA ranged from 685 433 (95% UI 589 451 – 792 873) in 2016 to 865 767 (95% UI 742 802 – 1 003 591) in 2019, with an annual number of attributable deaths ranging from 30 730 (95% UI 26 935 – 34 836) in 2016 to 38 710 (95% UI 34 053 – 43 748) in 2019. When analysed as DALYs, the infections led to an annual health burden ranging from 909 488 (95% UI 813 858 – 1 013 060) in 2016 to 1 101 288 (95% UI 988 703 – 1 222 498). We estimated that 70.9% of cases of infections with antibiotic-resistant bacteria (95% confidence interval (CI) 68.2 – 74.0%) were healthcare-associated infections.

Between 2016 and 2020 in the EU/EEA, there were significantly increasing trends in the estimated number of infections ($p < 0.001$), attributable deaths ($p < 0.001$) and DALYs ($p < 0.001$) per 100 000 population due to antibiotic-resistant bacteria, although numbers decreased slightly from 2019 to 2020. There was a significant increasing trend in estimated number of infections for almost all bacterium–antibiotic resistance combinations. To note, at both EU/EEA and national level, the estimates had wide uncertainty intervals (UIs).

The largest burden of disease was caused by third-generation cephalosporin-resistant *Escherichia coli*, followed by methicillin-resistant *Staphylococcus aureus* and third-generation cephalosporin-resistant *Klebsiella pneumoniae*. The total age-group-specific burden was the highest in infants and the elderly. Adjusted for population size, the overall burden of infections with antibiotic-resistant bacteria was estimated to be the highest in Greece, Italy and Romania.

This study confirms the considerable health burden of infections with antibiotic-resistant bacteria in the EU/EEA. It also highlights the increasing burden of these infections, with an exception in 2020 when the overall burden was estimated to decrease. Changes in annual burden estimates can be affected by changes in surveillance, or changes in healthcare practices, such as in 2020 when the COVID-19 pandemic put pressure on all health services in EU/EEA countries. Part of the decrease in 2020 can also be explained by measures taken to control the spread of COVID-19, including changes in infection prevention and control, and changes in the patient mix in hospitals due to the different hospitalisation practice during the pandemic.

ⁱ The Burden of Communicable Diseases in Europe (BCoDE) project was initiated by ECDC in 2009 and developed an evidence-based methodology to estimate the burden of infectious diseases in EU/EEA countries.

Our estimates for the burden of antibiotic-resistant bacteria for 2016 remains similar to 2015 data, whilst the estimate has increased in the following years. Also, for individual bacterium–antibiotic resistance combinations, our results were similar with the previous burden analysis and other published sources for data. For example, the observed increase in the burden of vancomycin-resistant *E. faecalis*/*E. faecium* is in line with what is reported elsewhere. Also, as reported in EARS-Net data, most of the individual bacterium–carbapenem resistance combinations showed an increasing trend in 2016-2020.

The limitations of this study include the limitations in the data and the evidence used for estimating the burden of disease. For example, data on the age-specific effects of different infections with antibiotic-resistant bacteria remain relatively scarce. Also, whilst some countries have surveillance systems with good population coverage, the incidence of BSIs often remains a crude estimate if the population coverage is low and the representativeness is poor. Furthermore, the changes in the surveillance and the participation in surveillance in general, affect year-to-year comparisons, and our uncertainty estimates at EU/EEA level remain comparatively wide.

Our main strength is the well-established, internationally approved methodology and a strong collaboration with participating national networks. Updated studies on the burden of antibiotic resistance in the EU/EEA, including relevant updates on the evidence and methodology, can provide important evidence for policy formulation and evaluation.

Background

Infections caused by antibiotic-resistant bacteria are considered a major global health threat in the 21st century [1, 2]. For this reason, antibiotic resistance in pathogens of greatest public health significance is included in continuous surveillance efforts globally, as well as in the European Union (EU) and the European Economic Area (EEA). In the EU/EEA, data from national antibiotic resistance surveillance networks have been collated by the European Antimicrobial Resistance Surveillance Network (EARS-Net) since the late 1990s, and has been coordinated by the ECDC since 2010 [3, 4].

The wide concern caused by antibiotic resistance and its impact on public health has also led to the adoption of action plans on how to mitigate the threat, at global, European and national level [2, 5]. In recent years, in part driven by action plans calling for impact assessments, estimates of the burden associated with infections caused by antibiotic-resistant bacteria has started to emerge from various national, European, and global modelling studies and reviews [6-10]. The studies consistently reported on the considerable health burden of infections with antibiotic-resistant bacteria in comparison with several other infectious diseases, in part due to the fact that it is related to the overall burden of healthcare-associated infections (HAIs) [8, 11-13].

Assessment of the burden of disease is essential for policymakers and public health officials to perform evidence-based, informed prioritisation of resource allocation and to plan accordingly for the mitigation of health threats. The Burden of Communicable Diseases in Europe (BCoDE) study aimed to provide a methodology for this burden assessment, a methodology upon which many later national and international analyses have been built, including our present study [14]. The present study aimed to provide updated estimates of the burden of infections with selected antibiotic-resistant bacteria in the EU/EEA, in the period 2016-2020, and assess how this burden changed from previous estimates [8]. The analysis was based on available surveillance data from EU/EEA countries as well as previous work to identify clinical outcome and infection-specific data for selected antibiotic-resistant bacteria [8].

Methods

The methods were based on the adapted BCoDE methodology [8] to estimate the burden of infections with antibiotic-resistant bacteria. We therefore only present a short description of the methods, with emphasis on the further adaptations made for this study.

Bacterium–antibiotic resistance combinations

The study was based on data on bloodstream infections (BSIs) caused by selected bacterium–antibiotic resistance combinations as reported to EARS-Net for 2016-2020 by all EU/EEA countries except Liechtenstein which does not report data to EARS-Net and the United Kingdom that was only an EU Member State until 31 January 2020. The included bacterium–antibiotic resistance combinations were the same as in the adapted BCoDE methodology [8], apart from colistin-resistant bacteria which were not included separately as they are difficult to assess through EARS-Net, as colistin susceptibility testing is generally not part of the initial routine antimicrobial susceptibility testing panel for *Enterobacterales* [3] (Table 1).

Table 1. Bacteria and antibiotic resistance combinations included in the study

Bacteria	Antibiotic resistance*
<i>Acinetobacter</i> species	Carbapenem-resistant
	Aminoglycoside and fluoroquinolone-resistant (excluding isolates also resistant to carbapenems)
<i>Enterococcus faecalis</i> and <i>E. faecium</i>	Vancomycin-resistant
<i>Escherichia coli</i>	Carbapenem-resistant
	Third-generation cephalosporin-resistant (excluding isolates also resistant to carbapenems)
<i>Klebsiella pneumoniae</i>	Carbapenem-resistant
	Third-generation cephalosporin-resistant (excluding isolates also resistant to carbapenems)
<i>Pseudomonas aeruginosa</i>	Carbapenem-resistant
	Resistant to three or more antibiotic groups (piperacillin-tazobactam, ceftazidime, fluoroquinolones, aminoglycosides; excluding isolates also resistant to carbapenems)
<i>Staphylococcus aureus</i>	Meticillin-resistant
<i>Streptococcus pneumoniae</i>	Penicillin-non-wild-type**
	Penicillin-non-wild-type and macrolide-resistant (excluding isolates being only penicillin-non-wild-type)

*For more information on the antibiotics included in each antibiotic group, please refer to the EARS-Net reporting protocol [4].

** *S. pneumoniae* isolates reported by local laboratories as 'susceptible, increased exposure' (I) or resistant (R) to penicillin, assuming a minimum inhibitory concentration to benzylpenicillin above those of wild-type isolates (i.e. >0.06 mg/L).

Outcome measure

We expressed the burden of infections as the number of cases, number of deaths, and number of disability-adjusted life years (DALYs) attributable to infections with antibiotic-resistant bacteria. The latter measure reflects the burden of disabilities and premature deaths, using years lived with disabilities following the onset of a disease (YLD) and years of life lost due to premature mortality (YLL), compared to a standardised life expectancy derived from the Global Burden of Disease 2017 standard reference life table, with the same life expectancy for males and females, based on the lowest observed death rate for any age group [8, 15].

Estimation of incidence

EARS-Net is a network of clinical microbiology laboratories in EU/EEA countries which reports on the percentage of antibiotic resistance by bacterial species. In 2020, the population coverage of participating laboratories ranged from 16% to 100% depending on the country, as countries can report data from sentinel laboratories if it was not possible to include data from all their relevant laboratories [16]. EARS-Net collects routine antimicrobial susceptibility testing data on the first invasive isolate of patients with a BSI, or meningitis, due to the bacteria under EARS-Net surveillance. In this study, we excluded meningitis cases reported to EARS-Net, as the incidence for other types of infection was based on the conversion from BSIs (described below). A large part of the laboratories in most countries were already using the clinical breakpoints set by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in 2016-2018, and which since 2019 EARS-Net, only includes data reported using EUCAST clinical breakpoints [4]. Regarding bacterium-antibiotic resistance combinations, Greece did not report data to EARS-Net on antibiotic-resistant *Streptococcus pneumoniae* isolates.

For estimating the total incidence of infections, we used the four-step approach developed in the adapted BCoDE methodology [8]. First, we took the age-group- and sex-specific annual number of BSIs reported to EARS-Net with antibiotic-resistant bacteria in 2016-2020 in each EU/EEA country and, for each antibiotic resistance-bacterium combination, we re-distributed unknown age and sex data based on observed age-gender distribution of the cases in the country [8]. The EARS-Net data aim to represent unique, de-duplicated isolates for each case, as for the same patients duplicated isolate records should be excluded, only considering the first isolate by date and isolate source [4]. For Sweden, data reported to EARS-Net for 2016-2020 could not be checked for possible duplicate cases reported from the same patient.

Following this step, we adjusted the reported number of BSI cases with the estimated population coverage of data reported to EARS-Net provided by the National Focal Points and Operational Contact Points for antimicrobial resistance in EU/EEA countries [4]. This meant applying a correction factor (number of reported cases/estimated coverage) to the number of cases of BSI as reported to EARS-Net. Each country provided estimates of its population coverage, sometimes full coverage, whilst other countries, provided estimates based e.g. on the percentage of general hospitals covered by the national surveillance system.

Thirdly, our methodology required an estimate of the number of other types of infection. We converted the population coverage-corrected number of BSIs to include an additional four types of infections: pneumonias, urinary tract infections, surgical site infections and other infections. For all bacteria apart from *S. pneumoniae*, the conversion multipliers were derived from the ECDC PPS 2016–2017 following similar conversion methodology as implemented in the adapted BCoDE methodology [8, 17]. The EU/EEA incidence of different infections with selected antibiotic-resistant bacteria was calculated by applying the Rhame and Sudderth formula to the ECDC PPS data [18]. The ratio of BSIs to other types of infection (non-BSIs) was estimated based on the cumulative number of infections caused by the selected antibiotic-resistant bacteria, and the uncertainty around these conversion factors was assessed using bootstrap resampling. For each antibiotic resistance-bacterium combination, the BSIs/non-BSIs ratio was then used to estimate the number of included infections converted from the BSIs. For *S. pneumoniae*, the conversion factors were derived directly from the literature review [8].

Finally, a certain number of these non-BSIs were expected to result in a secondary BSI (S-BSI), and to be reported to EARS-Net as a BSI. Therefore, we also estimated the percentage of S-BSIs from each of the other types of infection to acquire reducing factors derived from the variable 'origin of BSI' in the ECDC PPS 2016–2017 data [17]. We then deducted the number of infections according to the reduction factor from other types of infections. The conversion multipliers and reducing factors were only assessed at the EU/EEA level using data from available countries to provide pooled estimates and no country-specific estimations were made.

The proportion of HAIs of all cases of infections and outcomes were assessed based on literature, with the exception of using the ECDC PPS 2016–2017 data to inform the proportion of infections present at hospital admission for third-generation cephalosporin-resistant *Escherichia coli*, third-generation cephalosporin-resistant *Klebsiella pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA) [8, 17]. Healthcare-associated infections were defined as having the onset of symptoms on day three or later after the start of the current admission, or where the patient has been re-admitted less than 48 hours after a previous discharge or transfer from a healthcare facility.

Disease models and attributable mortality

In the analysis, we used the disease models for infections with the selected antibiotic-resistant bacteria [8, 19]. These disease models define the progress and the estimated duration and severity of a disease, depending on the selected antibiotic-resistant bacteria and on the type of infection. Detailed information is available in Cassini et al., supplementary material pp. 168–190, and in the BCoDE-toolkit version 2.0.0 [8, 20].

Computational analysis and uncertainty

The disease models, including their model parameters and uncertainties, and infection incidence data with the selected antibiotic-resistant bacteria were inserted into the BCoDE modelling toolkit v 2.0.0, and each model was run for 10 000 Monte Carlo simulations [8, 20].

The results are presented as total numbers, or as rates per 100 000 population. The population data were derived from Eurostat 2016–2020 [21]. For reporting of point estimates, we used the median estimates derived from the simulations, and for the uncertainties we reported the 95% uncertainty interval (UI) derived using 2.5% and 97.5% percentiles from the simulation output. Data were further analysed with R 4.0.2, with the trends in annual numbers of cases per population assessed using Poisson-regression, and a significance level of 0.05 was considered in the study, and the proportion of HAIs was reported with 95% confidence intervals (CI) [22].

Results

Based on the data reported to EARS-Net, we estimated that between 2016 and 2020, the number of cases of infections with the included antibiotic-resistant bacteria in the EU/EEA increased from 685 433 (95% UI 589 451–792 873) in 2016 to 865 767 (95% UI 742 802–1 003 591) in 2019, with a lower number of reported cases for 2020 and therefore a decrease in the median estimate for 2020 to 801 517 cases (95% UI 684 955–932 213) (Table 2). Based on our simulations, these infections with antibiotic-resistant bacteria resulted in an annual number of attributable deaths from 30 730 (95% UI 26 935–34 836) in 2016 to 38 710 (95% UI 34 053–43 748) in 2019, with a small decrease to 35 813 deaths (95% UI 31 395–40 584) in 2020. When analysed as DALYs, the infections led to an annual health burden ranging from 909 488 (95% UI 813 858–1 013 060) in 2016 to 1 101 288 (95% UI 988 703–1 222 498) in 2019, with a small decrease to 1 014 799 DALYs (95% UI 908 022–1 129 999) in 2020. Each year, 84–85% of these DALYs were caused by years of life lost (YLLs) and 67–68% were due to BSIs. We estimated that 70.9% of cases of infections with antibiotic-resistant bacteria (95% CI 68.2–74.0%) were healthcare-associated infections, with 71.4% attributable deaths (95% CI 69.0–74.4%) and 73.0% DALYs (95% CI 70. –75.8%), respectively, being linked to healthcare-associated infections.

Table 2. Total number of blood isolates of the selected antibiotic-resistant bacteria as reported to EARS-Net, and estimated number of bloodstream infections, number of infections, number of attributable deaths and number of disability-adjusted life years (DALYs), EU/EEA, 2016-2020

	2016	2017	2018	2019	2020
Number of blood isolates as reported to EARS-Net*	39 729	44 306	53 557	54 450	51 798
Estimated number of bloodstream infections after correction for population coverage	107 404	109 556	127 896	134 277	122 070
Estimated median number of infections, all types (95% UI)	685 433 (589 451 - 792 873)	701 816 (603 052 - 811 925)	822 075 (706 070 - 951 816)	865 767 (742 802 - 1 003 591)	801 517 (684 955 - 932 213)
Estimated median number of attributable deaths (95% UI)	30 730 (26 935 - 34 836)	31 178 (27 388 - 35 296)	36 605 (32 227 - 41 352)	38 710 (34 053 - 43 748)	35 813 (31 395 - 40 584)
Estimated median number of DALYs (95% UI)	909 488 (813 858 - 1 013 060)	918 117 (820 200 - 1 024 443)	1 046 858 (940 859 - 1 161 268)	1 101 288 (988 703 - 1 222 498)	1 014 799 (908 022 - 1 129 999)

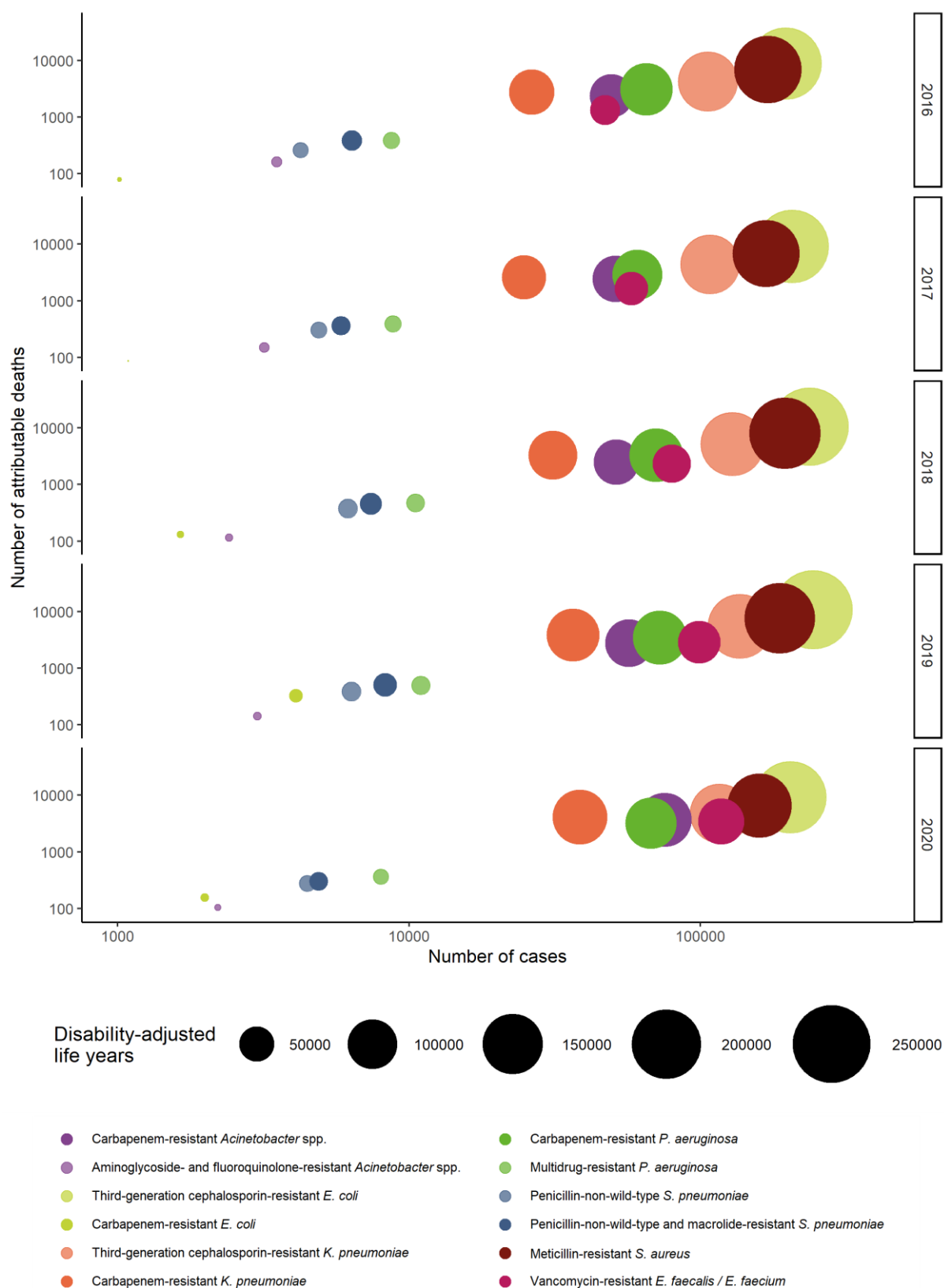
*After de-duplication to exclude repeat isolates from the same patient.

EARS-Net, European Antimicrobial Resistance Surveillance Network; UI, uncertainty interval;

DALYs, disability-adjusted life years

In the EU/EEA in 2016-2020, there were significantly increasing trends in the estimated number of infections per 100 000 population ($p < 0.001$), attributable deaths per 100 000 population ($p < 0.001$) and DALYs per 100 000 population ($p < 0.001$) due to antibiotic-resistant bacteria, although numbers decreased slightly from 2019 to 2020. In individual countries between 2016 and 2020, a significant increasing trend in the estimated number of infections was observed in 18 countries (Cyprus, Czechia, Denmark, Finland, Germany, Greece, Hungary, Iceland, Italy, Latvia, Lithuania, the Netherlands, Norway, Poland, Spain, Romania, Slovakia and Sweden), and a significant decreasing trend was observed in ten countries (Austria, Belgium, Bulgaria, Croatia, France, Ireland, Luxembourg, Malta, Portugal and Slovenia). Overall in the EU/EEA, there was a significant increasing trend in the estimated number of infections for all bacterium-antibiotic resistance combinations except MRSA, aminoglycoside- and fluoroquinolone-resistant *Acinetobacter* spp. and penicillin-non-wild-type and macrolide-resistant *S. pneumoniae*, although for *Acinetobacter* spp. the increase in the carbapenem-resistant infections far exceeds the decrease in aminoglycoside- and fluoroquinolone-resistant *Acinetobacter* spp. To note, at EU/EEA level, the UIs for the annual number of infections, attributable deaths, and DALY estimates were wide, and even on the national level, wide uncertainty was observed. In individual countries, and in less common bacterium-antibiotic resistance combinations, the trends in numbers of attributable deaths were less often significant due to lower estimated numbers. Even after adjusting for the reported population coverage, which remained relatively stable in 2016-2019, and increased in 2020, the number of reported BSIs with antibiotic-resistant bacteria reported to EARS-Net increased, especially in 2018-2019 compared to 2016-2017, thus providing an explanation for the observed increases in the health burden estimates (Table 2).

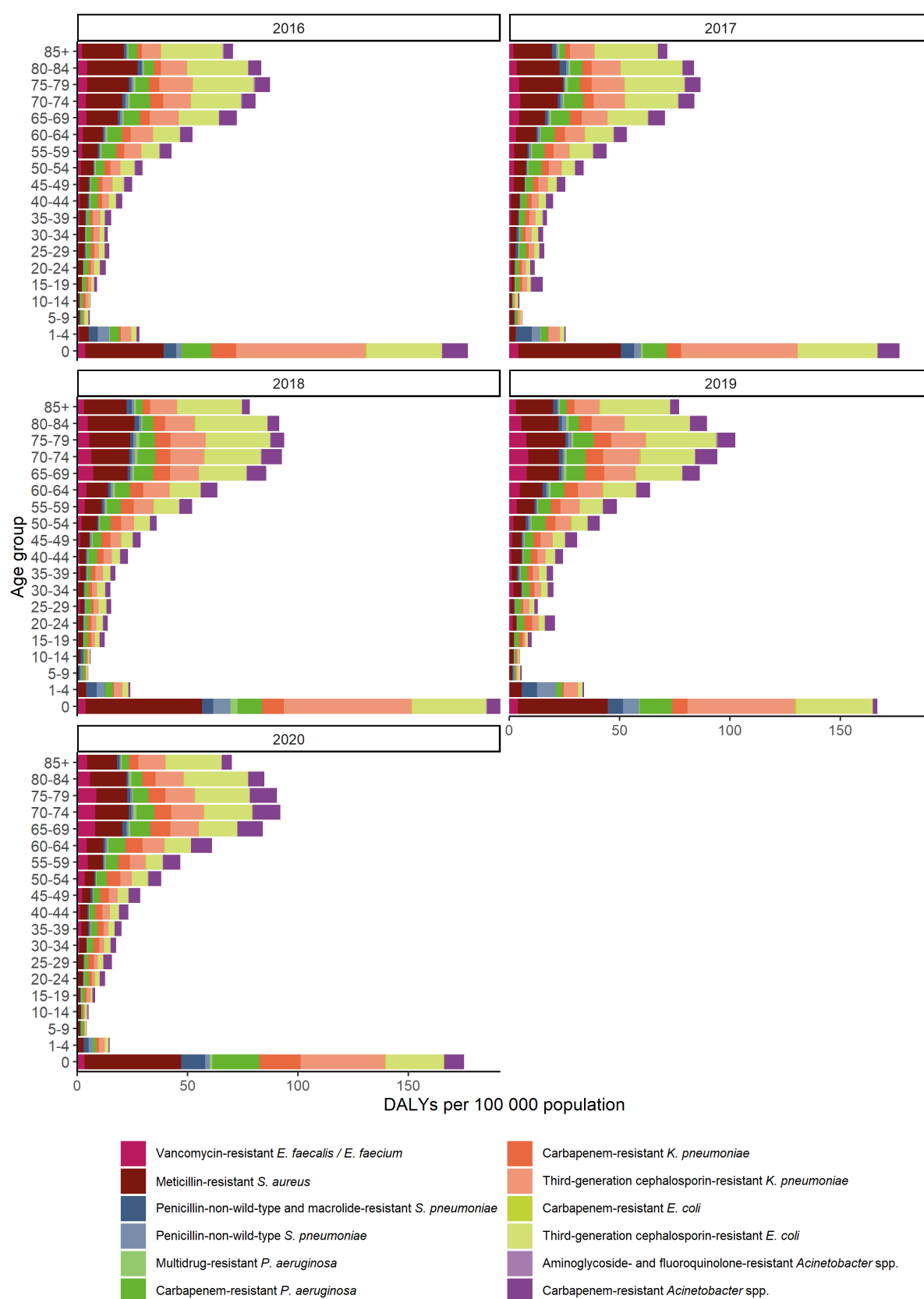
The largest burden of disease was caused by third-generation cephalosporin-resistant *Escherichia coli*, followed by MRSA and third-generation cephalosporin-resistant *Klebsiella pneumoniae*, with these three antibiotic-resistant bacteria resulting in the largest health impact and generating 58.2% of the total burden as measured in DALYs (Figure 1). In total, 30.9% of the total burden in DALYs was from infections with carbapenem-resistant bacteria, i.e. carbapenem-resistant *K. pneumoniae*, *E. coli*, *Pseudomonas aeruginosa* and *Acinetobacter* spp. Almost two thirds (62.4%) of the total number of DALYs was estimated to occur among men, ranging from 56.0% (third-generation cephalosporin-resistant *E. coli*) to 66.6% (carbapenem-resistant *K. pneumoniae*). Year and antibiotic resistance-bacterium combination specific tables of burden results are available in Annex 1.

Figure 1. Estimated number of cases, deaths and disability-adjusted life years for the selected antibiotic-resistant bacteria, EU/EEA, 2016-2020 (logarithmic x- and y-scale)

The relationship between the number of cases, the number of attributable deaths, and the total burden expressed in DALYs varied by antibiotic resistance-bacterium combination. For example, carbapenem-resistant *K. pneumoniae* only represented a small proportion (4-5%) of the estimated number of cases in the EU/EEA but represented a relatively larger proportion of the number of attributable deaths (8-11%) and DALYs (9-12%). The estimates for the EU/EEA varied not only between antibiotic-resistant bacteria, but also between years. In particular, for vancomycin-resistant *Enterococcus faecalis*/*E. faecium*, the burden increased from 47 124 estimated infections, 1 335 attributable deaths and 36 542 DALYs in 2016, to 117 866 cases, 3 414 attributable deaths and 87 375 DALYs in 2020. During the same period, MRSA showed a rather stable trend in the numbers of infections, attributable deaths and of DALYs, yet a decrease in its contribution to the total estimated burden when compared to other pathogens, especially third-generation cephalosporin-resistant *E. coli*, or vancomycin-resistant *E. faecalis*/*E. faecium* (Figure 1).

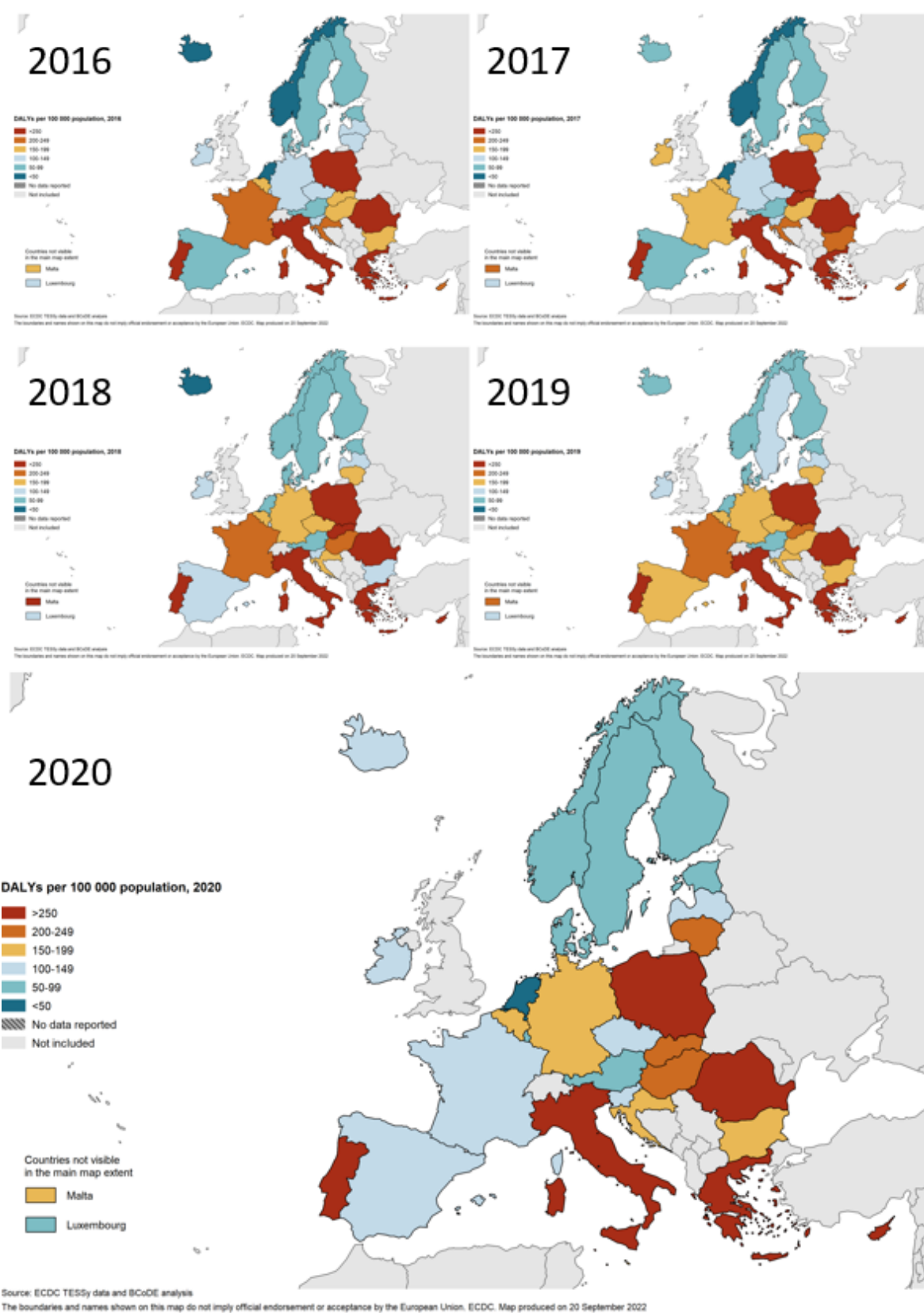
The total age-group-specific burden was invariably the highest in infants (children under one year of age), varying from 167 DALYs per 100 000 population in 2019 to 192 DALYs per 100 000 population in 2018. The elderly (age 65 years and older) had a considerably higher estimated population-specific burden than younger age groups (apart from infants) (Figure 2). In infants, the largest rate of DALYs was caused by third-generation cephalosporin-resistant *K. pneumoniae* in years 2016-2019, and MRSA in 2020, whilst in the elderly third-generation cephalosporin-resistant *E. coli* was responsible for the highest burden. In the group aged 1-4 years, there was also a large overall rate of DALYs per 100 000 population, with the largest proportional burden caused by penicillin-non-wild-type and macrolide-resistant *S. pneumoniae*.

Figure 2. Estimated average burden of infections expressed in disability-adjusted life years (DALYs) per 100 000 population, by age group and antibiotic-resistant bacterium, 2016-2020



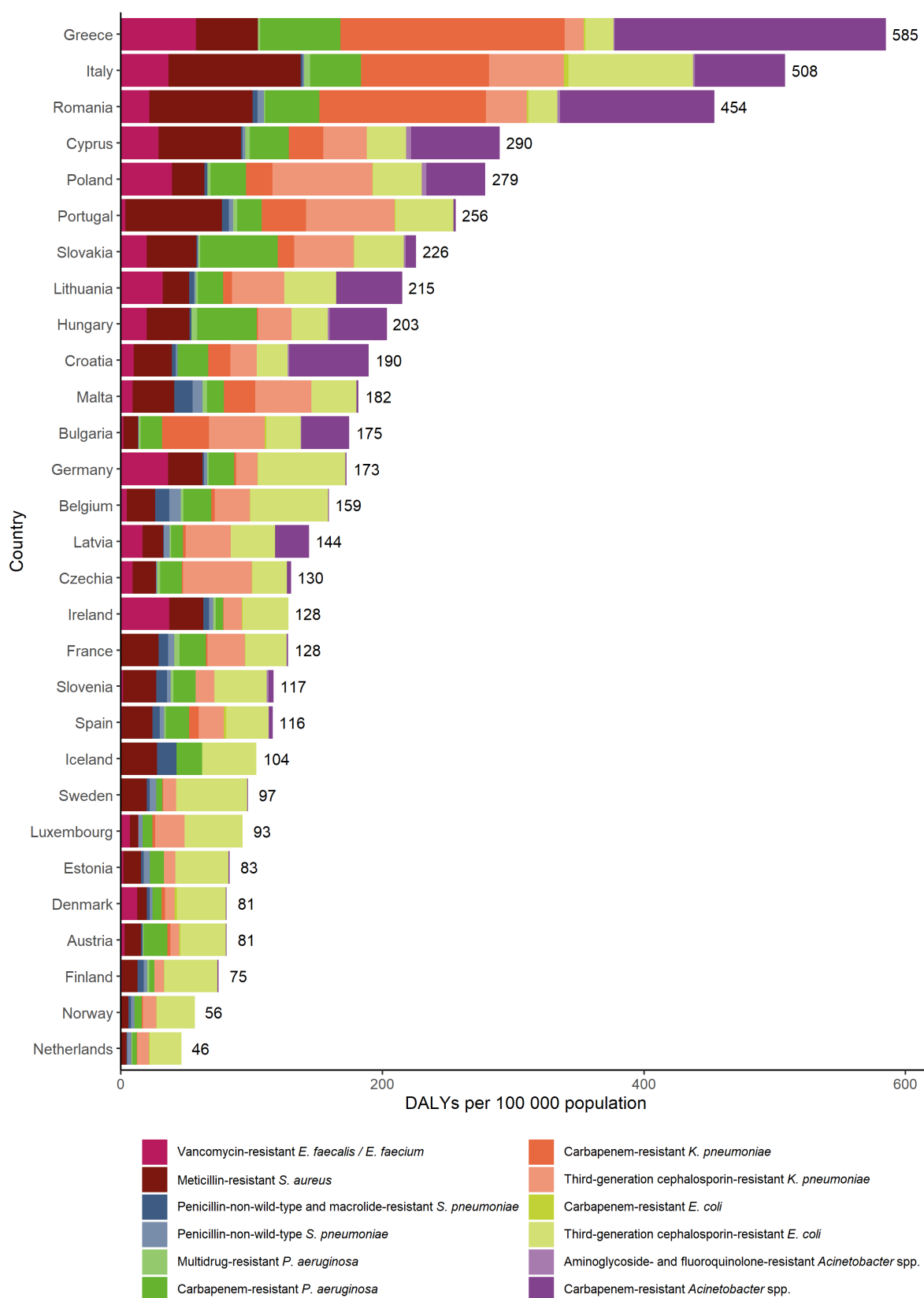
The largest burden of infections with antibiotic-resistant bacteria was estimated to be in southern and eastern European countries, as illustrated by the number of DALYs (Figure 3, Figure 4). Nevertheless, all the countries in North and West Europe also had an estimated annual burden of 50 DALYs or more per 100 000 population, at least once in 2018, 2019 or 2020 (Figure 3). Adjusted for population size, the overall burden of infections with antibiotic-resistant bacteria was estimated to be the highest in Greece, Italy, and Romania, each having in total more than 2 000 estimated DALYs per 100 000 population in 2016-2020, with the highest individual yearly estimates occurring in Romania in 2018-2019, Greece in 2020 and Italy in 2019-2020. In most EU/EEA countries, third-generation cephalosporin-resistant *E. coli* was among the most common combinations accounting for the burden, both in DALYs and attributable deaths (Figure 4, Figure 5). In Greece, Italy, and Romania, carbapenem-resistant *K. pneumoniae* was responsible for a large part of the DALYs at the national level; and in many countries, carbapenem-resistant *Acinetobacter* spp. and carbapenem-resistant *P. aeruginosa* were also among the antibiotic-resistant bacteria with a comparatively high number of DALYs. In addition, in Denmark, Germany and Ireland in 2016-2020, vancomycin-resistant *E. faecalis*/*E. faecium* was among the combinations with the highest number of DALYs, while in some countries such as Portugal and Romania, MRSA remained the antibiotic-resistant bacterium with the highest number of DALYs for multiple years in 2016-2020. Detailed information on results per country is available in Annex 2.

Figure 3. Estimations of the burden of infections with antibiotic-resistant bacteria presented as disability-adjusted life years (DALYs) per 100 000 population by country*, EU/EEA, 2016-2020



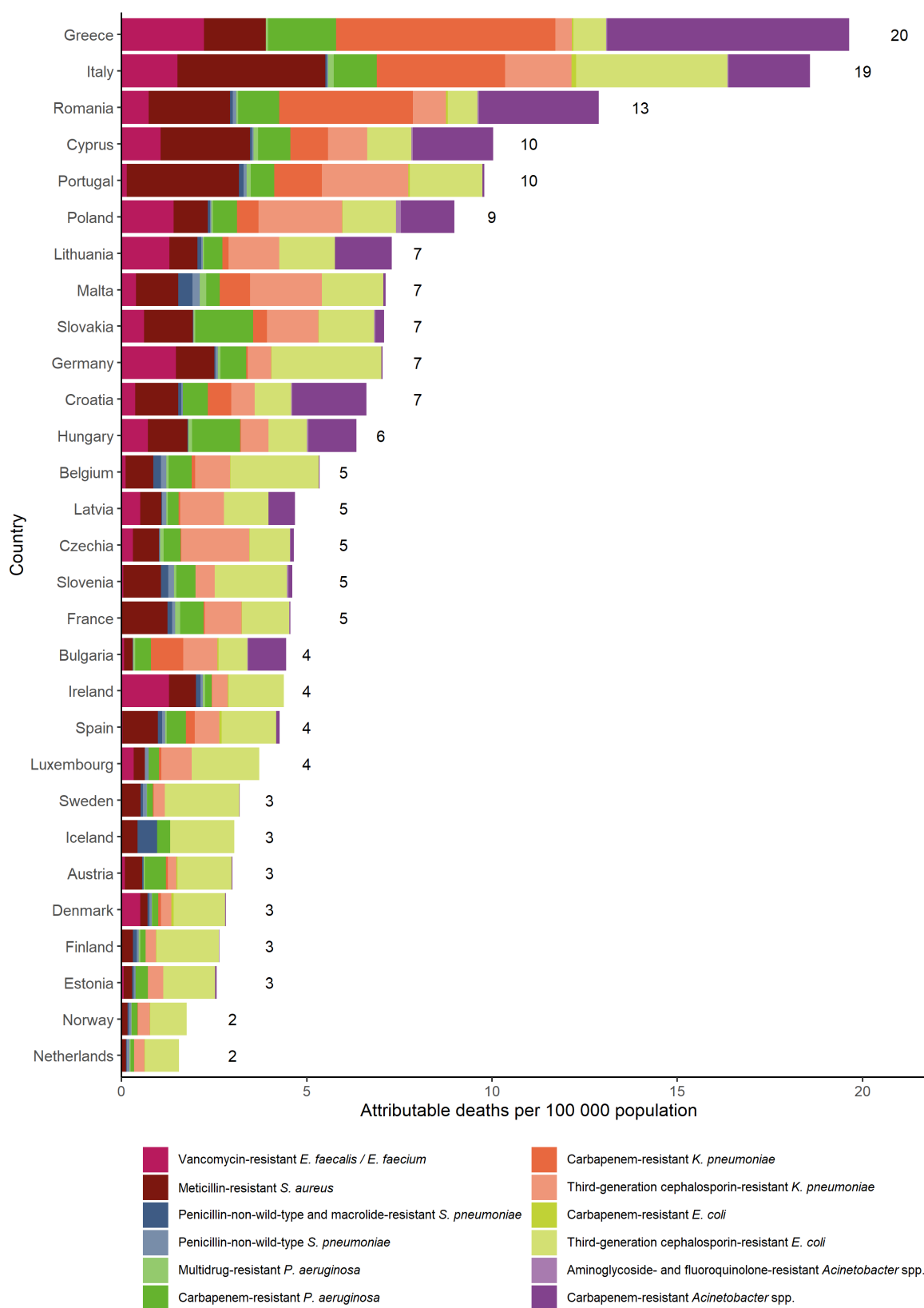
*For Sweden, data reported to EARS-Net for 2016-2020 could not be checked for possible duplicate cases reported from the same patient

Figure 4. Estimations of the burden of infections with antibiotic-resistant bacteria presented as disability-adjusted life years (DALYs) per 100 000 population by country*, EU/EEA, 2020



*For Sweden, data reported to EARS-Net for 2016-2020 could not be checked for possible duplicate cases reported from the same patient.

Figure 5. Estimations of the burden of infections with antibiotic-resistant bacteria presented as attributable deaths per 100 000 population by country*, EU/EEA, 2020



*For Sweden, data reported to EARS-Net for 2016-2020 could not be checked for possible duplicate cases reported from the same patient.

Discussion

This study confirms the considerable health burden of infections with antibiotic-resistant bacteria in the EU/EEA. Spanning over 2016-2020, this report highlights the continuous and increasing burden of these infections, with an exception in 2020 when the overall burden was estimated to decrease in comparison with previous years. Annual changes in the burden estimates must, however, be interpreted with caution considering the wide uncertainty intervals. Changes in annual burden estimates can be affected by changes in surveillance, use of different antimicrobial susceptibility testing guidelines, as well as potential changes or issues in the data reporting at national level as well as population coverage of the surveillance. This is especially relevant for 2020 data, with data submission in 2021, when the COVID-19 pandemic placed pressure on all public health services in EU/EEA countries.

In addition, the wide range of national, regional, and local COVID-19 control and mitigation measures that were implemented in 2020, affected practices both in the community and the healthcare sector [23]. Changes in contact patterns between various age groups compared to preceding years likely contributed to changes in disease transmission, and consequently decreases in incidence for certain pathogens, such as *S. pneumoniae* [24]. In addition, the changes in healthcare seeking patterns, and postponement of elective surgery and non-urgent care, will have led to less surgical site infections and different types of healthcare-associated infections caused by different pathogens in general. Especially in 2020, early in the COVID-19 pandemic, health system inefficiencies aggravated the situation in healthcare, probably also affecting non-COVID-19 related care [25]. This could also be more pronounced for some types of infection, especially lower respiratory tract infections, only partially reflected in our analysis as per the constant conversion factors derived from ECDC PPS 2016-2017, which allows us to estimate the considerable burden in healthcare but might neither reflect all the changes in the community, nor the changes in HAIs during the pandemic.

Nevertheless, when comparing with previous analysis which estimated a total burden of 33 110 deaths and 874 541 DALYs for the EU/EEA for 2015 [8], our estimate for 2016 of 30 700 deaths and over 900 000 DALYs is very close, given that we updated the life expectancy tables with increased life expectancy in all age groups, resulting in a higher estimate of DALYs in 2016. Another important consideration to the previous analysis, is that the United Kingdom is no longer included, and therefore, the population included in the study substantially decreased. Other changes possibly affecting the comparison of the burden estimates to those of 2015, include the exclusion of colistin resistance leading to a very minor decrease in burden for the relevant bacteria. The exclusion, from EARS-Net data, of antibiotic-resistant isolates derived from cerebrospinal fluid samples, also had an impact on decreases for antibiotic-resistant *S. pneumoniae* compared with the 2015 estimates where these were included in the numbers preceding the conversion to other types of infection. The updated conversion factors, based on the ECDC PPS 2016-2017 resulted in an overall increase in the number of infections for most antibiotic-resistant bacteria. However, as mentioned above, from 2016 until 2019, the health burden estimates in the EU/EEA have increased.

An international modelling initiative to estimate the burden of antimicrobial resistance, conducted by the Institute for Health Metrics and Evaluation (IHME), compared its 2019 results with the 2015 analysis from ECDC both in their global analysis and for subsequent analysis for the WHO European Region [6, 26]. IHME reported that ECDC estimates fell between the low and high estimate from their analysis, but overall was closer to the lower estimate, i.e. of the burden of 'attributable to resistance' rather than the burden of 'association with resistance' (in the latter, attributability of deaths, and in general of burden of disease, to the infection itself or to another cause was not considered). Also, considering the increases seen from 2015 to 2019, our estimate for 2019 was again closer to the lower IHME estimates 'attributable to resistance' for 2019. Whilst the range of the different estimates varied widely, differences were expected as different modelling methods were used, and both IHME analysis outcomes, 'attributable to resistance' and 'associated with resistance', differ from the outcome in our analysis outcome 'attributable to infections with antibiotic-resistant bacteria'. Such analyses can be seen as complementary and providing information from different perspectives on the magnitude of the problem.

For individual bacterium-antibiotic resistance combinations, our results from 2016 were also similar with the previous ECDC estimates for 2015, and the increases in 2016-2019 follow increases reported in other published sources for data. For example, the observed increase in the burden of vancomycin-resistant *E. faecalis*/*E. faecium* in 2016-2020 is in line with what was reported elsewhere, also in the EARS-Net surveillance [3, 27-29]. Also, whilst there have been some indications of stabilisation in the proportions of resistance to antibiotics especially in *E. coli*, this does not translate to stabilisation in the total number of antibiotic-resistant *E. coli* infections, which have been nevertheless increasing. *E. coli* remains the most frequently reported pathogen in EARS-Net, thus also having the highest burden estimate in our analysis. The larger gap between third-generation cephalosporin-resistant *E. coli* and MRSA in the 2015 analysis than in this update is partly explained by the exclusion of the United Kingdom, where the MRSA proportion was relatively low in 2015 [3, 8, 30, 31].

The increase in reported numbers of carbapenem-resistant infections was also observed in the previous ECDC study [8]. Each of the individual bacterium–carbapenem resistance combinations also showed an increasing trend in 2016-2020, where for carbapenem-resistant *Acinetobacter spp.* and for carbapenem-resistant *K. pneumoniae*, the highest number of infections and subsequently the highest burden was indeed estimated in 2020, the year when many other pathogens were estimated to have a slightly decreased burden in comparison with 2019. Also as previously noted, a majority of the infections with antibiotic resistance were estimated to be healthcare-associated infections, and as indicated by the ECDC prevalence surveys 2016-2017, an additional significant contribution is likely to be associated with long-term care [8, 13].

The limitations of this study include the usual limitations of modelling analyses of the burden of antibiotic resistance. The prior evidence, for example for age-specific effects of different infections with antibiotic-resistant bacteria, remains relatively scarce, thus the assumptions in the disease models remain open for improvements when further evidence accumulates and becomes publicly available. Secondly, whilst some countries have surveillance systems with good population coverage that would pick up virtually all severe infections with the relevant pathogens, the incidence of BSIs remains a crude estimate if the population coverage is low and the representativeness is poor. Also, the subsequent extrapolation to other types of infection using generic EU/EEA level conversion factors introduces further uncertainties to the incidence estimation for these other types of infections. To obtain the estimates for non-BSIs, we used conversion factors that are fixed for all countries and years, as no further data on these types of infection with antibiotic-resistant bacteria were available at the EU/EEA level.

Thirdly, the changes of EARS-Net to only accept from 2019 onwards, results interpreted according to the EUCAST guidelines, as well as changes in the participation in surveillance in general (such as changes in the national networks as reported by France), affect year-to-year comparisons. Fourthly, our uncertainty estimates at EU/EEA level remain comparatively wide, thus further complicating the interpretation of annual and national estimates. To note, our uncertainties do not consider the aleatoric uncertainty of the infections or random severe outcomes affecting the model estimates. Finally, both the burden and uncertainty estimations in our disease models draw heavily from existing scientific literature and place trust on the best possible estimates available in published studies, which remains valid but are also subject to biases and reporting effects of those individual studies and reviews.

The main strength of this study is the well-established, internationally approved methodology derived from the BCoDE project, and from previous work by Cassini et al. [8, 14]. This work allowed us to have a strong collaboration with participating national networks and national focal points as well as operational contact points, and to include a validation step of the results with EU/EEA countries. However, some changes in surveillance data remained challenging to interpret after this validation step, such as decreases in 2020 reported in France and Spain. In addition, all EU/EEA countries (except Liechtenstein) report data to EARS-Net, and thus our initial surveillance data offer a well-established starting point for estimating the incidence and the burden of infections with antibiotic-resistant bacteria in the EU/EEA [3]. The main objective of EARS-Net is to collect and report representative and accurate data on bacterial isolates from BSI and meningitis cases and corresponding antibiotic resistance proportions. This ongoing collection of validated surveillance data allowed us to perform the analysis over several years and report on changes and trends in the health burden of antibiotic resistance, and to confirm previous estimates with new, updated and validated data from each EU/EEA country [3].

Conclusions and potential implications

The results of this study confirm that further public health efforts are urgently needed to reduce the burden of antibiotic resistance in the EU/EEA. Reducing the spread of antibiotic-resistant bacteria will have a significant positive impact on population health and future healthcare expenditure in the EU/EEA. As a major part of the burden of infections with antibiotic-resistant bacteria is associated with healthcare, further surveillance, as well as further improvements in infection prevention and control, both in hospitals and in long-term care, remain essential. In addition, areas of inappropriate antibiotic use need to be addressed within comprehensive antimicrobial stewardship, and programmes targeting both the community and healthcare settings play an important role. Relatively little investment per capita in prevention and control of antibiotic resistance and antimicrobial stewardship could pay itself back within a year, allowing thousands of deaths to be avoided, and producing savings in healthcare costs in the long run [32, 33]. Putting into practice national and European-level action plans remains important in several areas, and further updates and renewal of the plans should be undertaken when necessary [5].

Updated studies on the burden of antibiotic resistance in the EU/EEA performed at regular intervals, including relevant updates on the evidence and methodology, both on the side of the initial surveillance and incidence estimation, as well as the disease progression in the affected population/individuals, can provide important evidence for policy formulation and evaluation. Further updates can include attempts to estimate the attributability of the health burden to antibiotic resistance rather than to infections, or including more bacterium–antibiotic resistance combinations. Further studies are also needed to estimate the effects of the COVID-19 pandemic on the burden of antibiotic resistance, including further pandemic years into the analysis. The ECDC methodology is openly available for further work via the latest releases of the BCoDE toolkit, which already allows for estimations and updates for different antibiotic-resistance bacteria and infections [20].

References

1. Jonas OBI, Alec; Berthe, Franck Cesar Jean; Le Gall, Francois G.;Marquex, Patricio V. Drug-resistant infections : a threat to our economic future (Vol. 2) : final report (English). Washington, D.C.: HNP/Agriculture Global Antimicrobial Resistance Initiative. World Bank Group; 2017.
2. World Health Organization. Global Action Plan on Antimicrobial resistance. Geneva, Switzerland: World Health Organization; 2015.
3. WHO Regional Office for Europe/European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2022 – 2020 data. Copenhagen: WHO Regional Office for Europe; 2022.
4. European Centre for Disease Prevention and Control. TESSy, The European Surveillance System – Antimicrobial resistance (AMR) reporting protocol 2020 – European Antimicrobial Resistance Surveillance Network (EARS-Net) surveillance data for 2019. Solna, Sweden: European Centre for Disease Prevention and Control; 2020.
5. European Commission. A European One Health Action Plan against Antimicrobial Resistance,. Brussels, Belgium: European Commission; 2017.
6. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399(10325):629-55.
7. Gasser M, Zingg W, Cassini A, Kronenberg A, Swiss Centre for Antibiotic R. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in Switzerland. *Lancet Infect Dis*. 2019;19(1):17-8.
8. Cassini A, Hogberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis*. 2019;19(1):56-66.
9. Naylor NR, Atun R, Zhu N, Kulasabanathan K, Silva S, Chatterjee A, et al. Estimating the burden of antimicrobial resistance: a systematic literature review. *Antimicrob Resist Infect Control*. 2018;7:58.
10. Hay SI, Rao PC, Dolecek C, Day NPJ, Stergachis A, Lopez AD, et al. Measuring and mapping the global burden of antimicrobial resistance. *BMC Med*. 2018;16(1):78.
11. Cassini A, Plachouras D, Eckmanns T, Abu Sin M, Blank HP, Ducomble T, et al. Burden of Six Healthcare-Associated Infections on European Population Health: Estimating Incidence-Based Disability-Adjusted Life Years through a Population Prevalence-Based Modelling Study. *PLoS Med*. 2016;13(10):e1002150.
12. Cassini A, Colzani E, Pini A, Mangen MJ, Plass D, McDonald SA, et al. Impact of infectious diseases on population health using incidence-based disability-adjusted life years (DALYs): results from the Burden of Communicable Diseases in Europe study, European Union and European Economic Area countries, 2009 to 2013. *Euro Surveill*. 2018;23(16).
13. Suetens C, Latour K, Karki T, Ricchizzi E, Kinross P, Moro ML, et al. Prevalence of healthcare-associated infections, estimated incidence and composite antimicrobial resistance index in acute care hospitals and long-term care facilities: results from two European point prevalence surveys, 2016 to 2017. *Euro Surveill*. 2018;23(46).
14. Kretzschmar M, Mangen MJ, Pinheiro P, Jahn B, Fevre EM, Longhi S, et al. New methodology for estimating the burden of infectious diseases in Europe. *PLoS Med*. 2012;9(4):e1001205.
15. G. B. D. Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1736-88.
16. European Centre for Disease Prevention and Control. Antimicrobial resistance in the EU/EEA (EARS-Net) - Annual Epidemiological Report 2020. ECDC; 2022.
17. European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals – protocol version 5.3. Solna, Sweden: European Centre for Disease Prevention and Control; 2016.
18. Rhame FS, Sudderth WD. Incidence and prevalence as used in the analysis of the occurrence of nosocomial infections. *Am J Epidemiol*. 1981;113(1):1-11.
19. Colzani E, Cassini A, Lewandowski D, Mangen MJ, Plass D, McDonald SA, et al. A Software Tool for Estimation of Burden of Infectious Diseases in Europe Using Incidence-Based Disability Adjusted Life Years. *PLoS One*. 2017;12(1):e0170662.
20. European Centre for Disease Prevention and Control. The Burden of Communicable Disease in Europe (BCoDE) toolkit 2.0.0: European Centre for Disease Prevention and Control; 2019 [Available from: <https://www.ecdc.europa.eu/en/publications-data/toolkit-application-calculate-dalys>].
21. Eurostat. Population on 1 January by age and sex: Eurostat; 2022 [Available from: <https://ec.europa.eu/eurostat/data/database>].
22. R Core Team. R 4.0.2. Vienna, Austria: R Foundation for Statistical Computing; 2022.

23. European Centre for Disease Prevention and Control; Joint Research Centre of the European Commission. The Response Measures Database Solna, Sweden: European Centre for Disease Prevention and Control; Joint Research Centre of the European Commission; 2022 Available from: <https://www.ecdc.europa.eu/en/publications-data/response-measures-database-rmd> .
24. Liu CY, Berlin J, Kiti MC, Del Fava E, Grow A, Zagheni E, et al. Rapid Review of Social Contact Patterns During the COVID-19 Pandemic. *Epidemiology*. 2021;32(6):781-91.
25. Lupu D, Tiganasu R. COVID-19 and the efficiency of health systems in Europe. *Health Econ Rev*. 2022;12(1):14.
26. European Antimicrobial Resistance Collaborators. The burden of bacterial antimicrobial resistance in the WHO European region in 2019: a cross-country systematic analysis. *Lancet Public Health*. 2022.
27. Ayobami O, Willrich N, Reuss A, Eckmanns T, Markwart R. The ongoing challenge of vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* in Europe: an epidemiological analysis of bloodstream infections. *Emerg Microbes Infect*. 2020;9(1):1180-93.
28. Piezzi V, Gasser M, Atkinson A, Kronenberg A, Vuichard-Gysin D, Harbarth S, et al. Increasing proportion of vancomycin-resistance among enterococcal bacteraemias in Switzerland: a 6-year nation-wide surveillance, 2013 to 2018. *Euro Surveill*. 2020;25(35).
29. Remschmidt C, Schroder C, Behnke M, Gastmeier P, Geffers C, Kramer TS. Continuous increase of vancomycin resistance in enterococci causing nosocomial infections in Germany - 10 years of surveillance. *Antimicrob Resist Infect Control*. 2018;7:54.
30. Penalva G, Hogberg LD, Weist K, Vlahovic-Palcevski V, Heuer O, Monnet DL, et al. Decreasing and stabilising trends of antimicrobial consumption and resistance in *Escherichia coli* and *Klebsiella pneumoniae* in segmented regression analysis, European Union/European Economic Area, 2001 to 2018. *Euro Surveill*. 2019;24(46).
31. Gagliotti C, Hogberg LD, Billstrom H, Eckmanns T, Giske CG, Heuer OE, et al. *Staphylococcus aureus* bloodstream infections: diverging trends of methicillin-resistant and methicillin-susceptible isolates, EU/EEA, 2005 to 2018. *Euro Surveill*. 2021;26(46).
32. European Centre for Disease Prevention and Control/Organisation for Economic Co-operation and Development. Antimicrobial Resistance - Tackling the Burden in the European Union. Paris, France: European Centre for Disease Prevention and Control/Organisation for Economic Co-operation and Development;; 2019.
33. Organisation for Economic Co-operation and Development. Stemming the Superbug Tide - Just A Few Dollars More. Paris, France: Organisation for Economic Co-operation and Development;; 2018.

**European Centre for Disease
Prevention and Control (ECDC)**

Gustav III:s Boulevard 40, 16973 Solna, Sweden

Tel. +46 858601000

Fax +46 858601001

www.ecdc.europa.eu

An agency of the European Union

www.europa.eu

Subscribe to our publications

www.ecdc.europa.eu/en/publications

Contact us

publications@ecdc.europa.eu

🐦 Follow us on Twitter

[@ECDC_EU](https://twitter.com/ECDC_EU)

📘 Like our Facebook page

www.facebook.com/ECDC.EU

ECDC is committed to ensuring the transparency and independence of its work

In accordance with the *Staff Regulations for Officials and Conditions of Employment of Other Servants of the European Union* and the *ECDC Independence Policy*, ECDC staff members shall not, in the performance of their duties, deal with matters in which they may, directly or indirectly, have a personal interest that could impair their independence. Declarations of interest must be received from any prospective contractor before a contract can be awarded.

www.ecdc.europa.eu/en/aboutus/transparency



Publications Office
of the European Union