EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

SURVEILLANCE

Results of the survey of carbapenem- and/or colistin-resistant Enterobacterales, 2019

European Antimicrobial Resistance Genes Surveillance Network (EURGen-Net)

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

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Abbreviations

AMR	Antimicrobial resistance
AST	Antimicrobial susceptibility testing
CCRE	Carbapenem- and/or colistin-resistant Enterobacterales
cgMLST	Core genome multi-locus sequence typing
CGPS	Centre for Genomic Pathogen Surveillance
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPE	Carbapenemase-producing Enterobacterales
CRE	Carbapenem-resistant Enterobacterales
DTR	Difficult-to-treat resistance
EEA	European Economic Area
ENA	European Nucleotide Archive
EQA	External quality assessment
ESBL	Extended-spectrum beta-lactamase
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EURGen-Net	European Antimicrobial Resistance Genes Surveillance Network
EuSCAPE	European Survey of Carbapenemase-producing *Enterobacteriaceae*
FDR	Fully drug-resistant
I	Susceptible, increased exposure
IBBL	Integrated Biobank of Luxembourg
KL	K locus
MBL	Metallo-beta-lactamase
MDR	Multidrug-resistant
MIC	Minimum inhibitory concentration
MLST	Multilocus sequence typing
NRL	National reference laboratory
NUTS-2	Nomenclature of Territorial Units for Statistics, level 2
QC	Quality control
R	Resistant
S	Susceptible, standard dosing regimen
SC	Species complex
SLV	Single locus variant
SNP	Single nucleotide polymorphism
ST	Sequence type
wgMLST	Whole-genome multilocus sequence typing
WGS	Whole genome sequencing

Executive summary

In response to the increasing threat of antimicrobial resistance, standardised genomic surveys such as the survey of carbapenem- and/or colistin-resistant Enterobacterales (CCRE survey) play an important role to detect emerging resistance patterns and high-risk clones, including in countries and/or regions that may not be covered by routine molecular surveillance. In the CCRE survey, we obtained a total of 2 973 *Klebsiella pneumoniae* species complex and 548 *Escherichia coli* isolates with clinical and epidemiological data together with high-quality whole-genome sequencing (WGS) data from 323 hospitals in 36 European countries in 2019. Analysis of these isolates provided a wealth of results, which give further insight into the continued spread and new emergence of carbapenemase-producing *K. pneumoniae* and *E. coli* high-risk clones in the European Union/European Economic Area (EU/EEA) and have direct implications for control. Comparison over time with the results from the European Survey of Carbapenemase-producing *Enterobacteriaceae* (EuSCAPE) conducted in 2013–2014 was especially valuable.

Although the analysis was delayed because of the COVID-19 pandemic, this CCRE survey was the first study to detect the increase of $bla_{\text{NDM-5}}$-carrying *E. coli* in the EU/EEA and the emergence of the new clade of *K. pneumoniae* sequence type (ST)39 carrying $bla_{\text{KPC-2}}$ in Greece. In both cases, follow-up investigations have already confirmed the signal from the CCRE survey and provided relevant further insights. The CCRE survey also detected an increase of *K. pneumoniae* ST307 and insights into the geo-temporal spread of *K. pneumoniae* ST11. In addition, the CCRE survey showed that there was not one single epidemic of carbapenem-R/I *K. pneumoniae* SC in the 36 participating countries, but heterogenous epidemiological situations ranging from sporadic cases to endemicity, involving a varying mix of *K. pneumoniae* STs and carbapenemases at the national level. Further analysis and comparison with national data may yield additional relevant results. In this respect, the data set can serve as a reference for further genomic studies.

The model of repeated structured genomic surveys is now an established element of European genomic surveillance and may be used for future national and EU-level surveys for carbapenem-resistant Enterobacterales and other multidrug-resistant pathogens. At the same time, efforts to establish faster and more comprehensive genomic surveillance should continue, including those related to capacity building at the national level.

1. Background

Carbapenem-resistant Enterobacterales (CRE) including *Klebsiella pneumoniae* and *Escherichia coli* pose a significant threat to patients and healthcare systems in all EU/EEA countries [1]. Carbapenem-resistant *K. pneumoniae* infections are associated with high mortality [2] related to delays in the administration of effective treatment and limited availability of treatment options. Hypervirulent carbapenem-resistant *K. pneumoniae* have also emerged in Europe and present an additional threat [3]. To date, carbapenem resistance has been less prevalent in *E. coli* than in *K. pneumoniae*, with rates of 0.2% and 11.7% in each species, respectively, across the EU/EEA in 2021 (population-weighted mean) [4]. However, several reports suggest an increasing spread of *E. coli* carrying carbapenemase genes in recent years [5-8]. Carbapenem resistance is mostly conferred by the acquisition of carbapenemase genes, which are typically encoded on plasmids. The spread of high-risk clones in healthcare settings has been identified as a major route of dissemination of carbapenemase genes among *K. pneumoniae* in EU/EEA countries [9]. In addition, epidemic plasmids such as the pOXA-48-like and pKpQIL-like plasmids have also played an important role [10,11].

Whole genome sequencing (WGS) can improve surveillance and control of antimicrobial resistance (AMR) by enabling early detection of transmission events and outbreaks, tracking of transmission pathways, and characterisation of associated pathogens and resistance mechanisms [12,13]. However, national WGS-based surveillance for the detection and control of bacterial pathogens is at various stages of implementation and national coverage and sampling protocols are heterogeneous [14]. The EuSCAPE project developed a consistent sampling framework at the European level and demonstrated the feasibility of a structured survey of carbapenem-resistant *K. pneumoniae* and *E. coli* in hospitals in 36 European countries in 2013–2014 [9]. The prevalence of carbapenem resistance among these species differed greatly between countries, while resistant *K. pneumoniae* isolates outnumbered those of *E. coli* by a ratio of 11:1 [15]. Genomic analysis of the *K. pneumoniae* isolates described the major sequence types (STs) and associated carbapenemase genes, and demonstrated that more than half of the participating hospitals likely experienced within-hospital transmission of carbapenemase-positive *K. pneumoniae* within the six-month sampling time frame [9,15]. To investigate the changing epidemiology and identify newly-emerging threats, the survey of carbapenem- and/or colistin-resistant Enterobacterales (CCRE survey) was launched in 2019, building on the EuSCAPE methodology with a few modifications [16].

The primary public health objective of the CCRE survey was to determine the occurrence, geographic distribution, and population dynamics of high-risk *K. pneumoniae* and *E. coli* clones and transmissible resistance elements of critical public health importance in Europe. The resulting information is intended to raise awareness, support risk assessment, and target infection prevention and control policies.

Secondary objectives were to identify the epidemiological risk factors for infection or colonisation with CCRE at the bacterial, clonal and sub-genomic level, and to support countries in developing technical capabilities and proficiency in genomic-based surveillance and risk assessment of multidrug-resistant (MDR) pathogens [16]. For the CCRE survey, high-risk clones/plasmids were defined as (i) ecologically successful clonal types carrying resistance determinants with high or increasing population prevalence across surveys and/or (ii) displaying extensive or expanding geographical distribution (interregional or international spread), and/or (iii) associated with multiple hospital outbreaks reported in the literature.

The CCRE survey was accompanied by several capacity-building activities, training, and external quality assessments (EQA). An assessment of the national capacity for laboratory detection, surveillance and containment was conducted at the start of activities [14]. After the development of and agreement on the epidemiological and microbiological protocols for the CCRE survey within the network [16-18], a related training workshop was conducted in September 2018 with an emphasis on colistin susceptibility testing. Two EQAs were conducted, with a focus on carbapenem and colistin susceptibility testing. The first EQA was a reverse EQA exercise conducted in 2018, where countries shared isolates fulfilling a set of predefined criteria from their national collection for retesting at the EUCAST development laboratory. The results were used for capacity building and were discussed at the workshop mentioned above. The second EQA was a classical EQA conducted in 2019 to ensure the quality and comparability of the national AST ahead of the CCRE survey and determine the need for central retesting of isolates. Finally, three training sessions of local clinical laboratories on the selection of isolates per protocol and reporting of the associated epidemiological data in the online database were held in 2019, at the start of the isolate and data collection for the CCRE survey.

This is the final report of the CCRE survey, which details the results of the epidemiological, phenotypic and genomic analyses of the *K. pneumoniae* and *E. coli* isolates. It includes information on the prevalence and incidence of carbapenem-resistant or susceptible-increased exposure *K. pneumoniae* and *E. coli* across 36 European countries in 2019, and describes the geographic distribution of STs, carbapenemase genes, and other relevant resistance and virulence determinants in each species. The K- and O-loci distributions among *K. pneumoniae* isolates are also reported due to the relevance of the encoded antigens as vaccine candidates. Associations between plasmid incompatibility (Inc) types and particular carbapenemase genes are described for both species, and pOXA-48-like

plasmids that typically carry *bla*$_{\text{OXA-48-like}}$ carbapenemase genes are reported using the available short-read sequencing data. Results from the CCRE survey were compared to those from EuSCAPE to investigate changes in the epidemiology and pathogen populations. Finally, isolates from both surveys were analysed together with additional public genomes to further investigate specific findings of interest, including the increasing prevalence of carbapenem-resistant *K. pneumoniae* ST307, the emergence of a novel clade of *K. pneumoniae* ST39 carrying *bla*$_{\text{KPC-2}}$, the increase of *bla*$_{\text{NDM-1}}$-carrying *K. pneumoniae* ST11, and the emergence and spread of *bla*$_{\text{NDM-5}}$ in multiple STs of *E. coli*.

2. Methods

2.1 Protocol modifications compared to EuSCAPE

The methodology of the CCRE survey was based on EuSCAPE conducted in 2013–2014 [15]. Details of the epidemiological definitions, variables collected, and microbiological testing for the CCRE survey were outlined in the study protocol, the expert consensus protocols for carbapenem- and colistin susceptibility testing and the laboratory manual for the CCRE survey [16-19]. A few modifications were introduced including acceptance of isolates from screening samples (instead of only from clinical cultures as in EuSCAPE), a stricter approach for more consistent geographic coverage (described below) and the addition of ceftazidime-avibactam to the panel of antimicrobials to be tested. In addition, the CCRE survey included a voluntary study for the collection of colistin-resistant isolates independent of the main survey, which focused on carbapenem resistance. The results of this voluntary additional isolate collection are not described in the present report.

2.2 Hospital recruitment

Hospitals were recruited by designated national coordinators in 37 countries to include one acute care hospital per National Territorial Units for Statistics level 2 (NUTS-2) region [20] for consistent geographical coverage. Depending on the countries' population size and distribution, the number of hospitals included varied between 1–39 sentinel hospitals per country.

2.3 Isolate collection and antimicrobial susceptibility testing

Each hospital microbiology laboratory was asked to collect the first ten non-duplicate isolates of carbapenem-resistant or carbapenem-susceptible increased exposure (hereafter called carbapenem-R/I) *K. pneumoniae* and/or *E. coli* isolates. These were based on EUCAST breakpoints as defined in the respective consensus protocol for the CCRE survey [17], and from clinical or screening samples of individual consecutive patients (case isolates). For each included carbapenem-R/I isolate, a carbapenem-susceptible (carbapenem-S) comparator isolate of the same species was collected. Isolate collection started in spring 2019 with three possible starting dates to be chosen by each country (1 March 2019, 1 April 2019 or 1 May 2019) and ended either on the date of collection of the tenth carbapenem-R/I isolate and its respective comparator within each hospital or after a maximum period of six months. The epidemiological and clinical information for cases and comparators, as outlined in the protocol [16], were reported via an online database hosted by the Public Health Agency of Sweden.

The collected isolates were sent from the hospital microbiology laboratories to the respective national reference or expert laboratory for confirmatory testing as outlined in the above-mentioned consensus protocols [17,18]. Antimicrobial susceptibility testing (AST) was performed by one or more methods including disk diffusion, broth microdilution (BMD), gradient tests or automated methods. EUCAST 2019 breakpoints were applied [21], and results interpreted by National Reference Laboratories (NRLs). As the inclusion criteria and classification into carbapenem-R/I and carbapenem-S categories depended on AST results for carbapenems, a re-analysis of the SIR categorisation according to EUCAST breakpoint table v9.0 [22] was performed at PHAS. The PHAS interpretation was based primarily on minimum inhibitory concentrations (MIC) for carbapenems reported from NRLs. If no MIC was available, zone diffusion diameters reported from NRLs were used for categorisation. If the NRL had not reported any carbapenem testing results, MICs obtained by re-testing at the Integrated Biobank of Luxembourg (IBBL) were used, if available.

Confirmed case and comparator isolates were shipped to a central strain collection managed by IBBL and the Laboratoire National de Santé in Luxembourg, where additional testing of isolates for purity of the culture and species identification by MALDI-TOF were carried out for all isolates, and AST was performed for selected isolates. After confirmation of species and purity of culture, isolates were shipped for DNA extraction to Eurofins Genomics, Germany, followed by WGS at the Centre for Genomic Pathogen Surveillance (CGPS), Wellcome Sanger Institute, except for a small test batch of 96 isolates, which were sequenced by Eurofins Genomics.

2.4 Definitions

While the inclusion criteria for isolates in the case and comparator groups were kept identical throughout the project, the categorisation of AST results has changed since the publication of the EuSCAPE results and the preparation of the CCRE survey analysis plan. The reason for the change in the terminology to carbapenem-R/I and carbapenem-S is the change in the naming of SIR categories introduced by EUCAST in 2019 [22] referring to isolates in the 'I' category as 'susceptible, increased exposure', instead of the previously used term 'intermediate'. In practice, this meant a change from the category 'I' being grouped together with 'R' as non-susceptible (as also in the CCRE survey protocol) to 'I' being considered together with the category 'S' as susceptible [23].

Hence, the category 'susceptible' in line with EUCAST terminology now includes both 'susceptible, standard dosing regimen' and 'susceptible, increased exposure' isolates. To adjust to these new categories and minimise confusion, the categories carbapenem-R/I and carbapenem-S are used in the present report to describe the carbapenem susceptibility results for the case (carbapenem-R/I) and comparator (carbapenem-S) groups for the CCRE survey and EuSCAPE results.

Table 1. Definitions used in the CCRE survey analysis plan and final report

CCRE survey analysis plan	CCRE survey final report	Definition
Carbapenem non-susceptible	Carbapenem-R/I	Minimum of one carbapenem phenotypically tested. Resistant (R) or 'Susceptible, increased exposure' (I) for any tested carbapenem according to EUCAST breakpoint table v9, 2019
Carbapenem susceptible	Carbapenem-S	Minimum of one carbapenem phenotypically tested. 'Susceptible, standard dosing regimen' (S) for all tested carbapenems according to EUCAST breakpoint table v9, 2019.
K. pneumoniae	*K. pneumoniae* SC	All species within the *K. pneumoniae* species complex (SC) are included, i.e. species confirmed as *K. pneumoniae*, *K. quasipneumoniae*, *K. variicola*, *K. quasivariicola* or *K. africana*.
E. coli	*E. coli*	Species confirmed as *E. coli*.

The category of carbapenem-R/I based on clinical breakpoints was a proxy for the identification of potential carbapenemase-producing isolates in the CCRE survey. Ideally, the screening breakpoint for meropenem should have been used to correctly detect as many carbapenemase-producing isolates as possible [24]. The use of the EUCAST screening breakpoint for meropenem was considered during the planning stage but not implemented. This was to enable all countries and individual hospitals to participate based on their routine AST results and to facilitate comparison with the EuSCAPE study. Species within the *K. pneumoniae* species complex (SC) are closely related and not all laboratories could easily differentiate between them [25]. Although this was not clearly stated in the analysis plan, all species within the *K. pneumoniae* SC were accepted and this was communicated to participating laboratories during the study.

2.5 Whole genome sequencing, assembly and quality control

Whole genome sequencing data were generated using Illumina NovaSeq 6 000 instruments with 150 bp paired-end reads at both Eurofins and the CGPS. Analyses of the WGS data were carried out at CGPS, University of Oxford. All raw reads were assembled using SPAdes v3.10.0 with the '—careful' flag and the '--cov-cutoff' flag set to 'auto' [26]. Assemblies were annotated using Prokka v1.5 [27]. Species designations and assembly metrics were obtained from the genome assemblies using Kleborate v2.1.0 [28]. Isolates with species designations that were inconsistent with the species provided by the NRLs, as well as those with ≥1 000 contigs or an assembly length outside of 4.5-6.5 Mb, were discarded. Kleborate was also used to determine the presence of carbapenemase genes in the assembled genomes and any inconsistencies with the results from the NRLs that could not be resolved led to the exclusion of isolates.

Raw sequence data for all isolates that passed our quality control (QC) criteria (n=3 521) are available in the European Nucleotide Archive (ENA) under accession numbers ERP123517 and ERP135831. *K. pneumoniae* SC and *E. coli* genomes from isolates obtained during EuSCAPE (2013-14) were also analysed and compared with the CCRE survey genomes. Assembly and QC of the *K. pneumoniae* SC isolates, which resulted in a collection of 1717 genomes, have been previously described [9]. The *E. coli* genomes from EuSCAPE, which have not been reported to date, were subjected to the same assembly and QC procedures described above and are available in the ENA under accession number ERP011196.

2.6 Phylogenetic analysis

To construct phylogenetic trees of the *K. pneumoniae* SC and *E. coli* isolates from the CCRE survey, we first identified sets of core genes using Panaroo v1.2.9 in the 'moderate' mode. In the case of the *E. coli* genomes, the default core gene alignment generated by Panaroo (i.e. containing genes present in ≥95% of isolates) was used directly for phylogenetic tree construction with RAxML-NG v1.0.3 [29]. For the *K. pneumoniae* SC genomes, a bespoke alignment was generated that contained genes present in ≥95% of isolates from each of the four identified species. This was used to construct a tree using Mashtree [30]. Panaroo was also used to generate a separate core genome alignment for only *K. pneumoniae* isolates containing all genes present in ≥95% of the genomes. This alignment was then used to build an additional tree of this species with RAxML-NG v1.0.3 [29].

Additional phylogenetic trees were constructed for selected lineages, including *K. pneumoniae* clonal complex (CC)258 (comprising multiple constituent STs), ST39 and ST307, and *E. coli* ST167, ST361, ST405, ST410 and ST648. For each lineage, all isolates from EuSCAPE and the CCRE survey were included, as well as those from other STs that were nested within these main STs in the species-wide phylogenies. We also incorporated other genomes from these STs that were publicly available in Pathogenwatch [31], as well as additional *E. coli* genomes from a recent report [32]. However, for CC258, only ST258/512 genomes from the CCRE survey were included to maximise representation of other STs (in particular ST11). Additional CCRE survey isolates that formed closely related outgroups to each of the clones (as determined using the species-wide trees) were also included to enable accurate rooting of the trees where required. Raw reads of isolates were mapped to an ST-specific reference genome: CP003200.1 (*K. pneumoniae* CC258), CP094991.1 (*K. pneumoniae* ST39), CP026495.1 (*K. pneumoniae* ST307), CP074120.1 (*E. coli* ST167), CP083701.1 (*E. coli* ST361), CP090074.1 (*E. coli* ST405), NZ_CP013112.1 (*E. coli* ST410) and CP023815.1 (*E. coli* ST648). Mapping and single nucleotide polymorphism (SNP)-calling were performed using Burrows Wheeler Aligner [33] and SAMtools v1.2 mpileup and BCFtools v1.2 [34]. Isolates were excluded from downstream analyses if they had <20x mapping coverage or ≥25% missing sites in the alignment. Gubbins v3.0.0 [35] was used to remove recombined regions from the resulting pseudo-genome alignments and generate maximum likelihood trees. All phylogenetic trees were visualised together with available metadata and genotypic data using Microreact [36].

2.7 Genomic typing and identification of antimicrobial resistance and virulence loci

Multilocus sequence typing (MLST) and core genome (cg)MLST profiles, as well as life identification number (LIN) codes, were obtained for *K. pneumoniae* SC genomes using BIGSdb-Pasteur (https://bigsdb.pasteur.fr) with new STs, alleles and/or codes defined where necessary. MLST profiles ('Warwick' scheme) and cgMLST profiles were obtained from *E. coli* genomes using Enterobase [37] with new STs and alleles defined where necessary. Kleborate v2.1.0 [28] was used to identify the K- and O-loci (via Kaptive [38]), and antimicrobial resistance and virulence gene loci from the *K. pneumoniae* SC genomes. The *ompK36* gene was also identified in the short-read assemblies of *K. pneumoniae* SC isolates using BLASTn v2.6.0 [39] to determine the presence of loop 3 insertions, including those that are not reported by Kleborate. We required a single hit per assembly that matched ≥10% of the query length (accession CP009208), had ≥90% nucleotide similarity and possessed a start codon. Nucleotide sequences were translated to protein sequences using Seaview v4.7 [40] with the standard genetic code. Alignments were generated of the non-truncated protein sequences (i.e. those with ≥95% of the query length) and used to identify loop 3 insertions. Resistance genes and mutations were identified in *E. coli* genomes using AMRFinderPlus v3.10.23 [41]. Novel carbapenemase variants identified among *K. pneumoniae* SC and *E. coli* genomes were submitted to Genbank and new allele numbers were assigned. Phylogroups were assigned to *E. coli* genomes using Clermontyper v20.03 [42]. O- and H- antigen loci were determined from *E. coli* genomes using SRST2 v0.2.0 [43]. Replicon typing data were obtained for all isolates from the short sequencing reads using Pathogenwatch v12.2.1 [31] with the PlasmidFinder database [44].

2.8 Identification of pOXA-48-like plasmids

The presence of a pOXA-48-like plasmid among isolates was determined by mapping short sequencing reads to the pOXA48a plasmid from strain Kp11978 (accession JN626286.1) using Burrows Wheeler Aligner [33]. SNPs were identified using SAMtools v1.2 mpileup and BCFtools v1.2 [34]. The length of the reference plasmid that was mapped by at least one sequence read was then determined from the binary alignment map (BAM) file of each isolate.

2.9 Statistical analysis and visualisation

Univariate multilevel logistic regression was used to estimate unadjusted odds ratios for each potential risk factor on the different outcomes. A multivariate multilevel logistic regression was applied to estimate mutually adjusted odds ratios. In both the univariate and multivariate models, 'country' was estimated as a random effect. Assessment of the goodness of fit of the model was performed using the likelihood ratio test. Missing data ('unknown', 'information not available' and 'missing') was handled using an indicator variable of combined missing data for each variable.

The variable 'Previous travel' was recoded into a new variable used in the analysis, in order to accommodate travel-related data entered related to fields related to direct hospital transfer and previous hospitalisation in another country. 'Previous travel' thus includes any travel to another country, including hospitalisation in or direct transfer from another country. 'Hospitalisation within six months' includes 'direct transfer from another hospital'. For 'Previous travel' all categories where information on travel was lacking (i.e. missing data, no travel, no information available), was combined into the category 'No reported travel or information not available', which was used as reference.

This approach was chosen due to few counts as 'no travel' and a likely high variation between countries in the reporting of the travel variable. For details, see Annex, section 'Limitations and modifications of the multilevel multivariate logistic regression analysis described in Tables 8a-i'.

The multilevel approach was taken by using a mixed model, with 'country' as a random effect in both univariate and multivariate analysis. This was due to the nature of the data collection procedure where patients were sampled at the national level. Since patients within a country can be expected to be more similar than patients from different countries (due to country-shared factors), the standard estimation of variance may underestimate the true variance. However, this is accounted for in a mixed model with 'country' as a random effect. Odds ratios were estimated with a confidence level of 95% and two-sided p-values less than 0.05 were considered statistically significant.

The investigated outcomes were carbapenem-R/I *K. pneumoniae* SC versus carbapenem-S *K. pneumoniae* SC (Annex Table 8a), carbapenem-R/I *E. coli* versus carbapenem-S *E. coli* (Annex Table 8b), and several sub-analyses within carbapenem-R/I *K. pneumoniae* SC (Annex Tables 8c-i). All statistical calculations for Annex Tables 1-6 and 8 were made using RStudio v4.3.1. The function 'glmer' in package lme4 (version 1.1-34) was used to estimate a multilevel (by country) logistic regression.

Figures were made using Microsoft Excel 2016 or RStudio v2022.12.0+353, including the package ComplexUpset v1.3.5 used for illustrating genotypic combinations. Microreact [36] was used to generate figures of phylogenetic trees with metadata and genotypic data. Figures were annotated using Illustrator v27.7.

3. Results

3.1 Hospital recruitment and processing of isolates

3.1.1 Recruited hospitals

The national coordinators in 37 countries initially recruited 527 hospitals to participate in the study. Of these, 346 hospitals registered isolates, while 181 hospitals did not. One country (Albania) collected isolates in one hospital but did not ship them to the central strain collection for further analysis. Therefore, isolates from this country are not included in the final data set. Of the 181 hospitals that did not register isolates, 44 hospitals said that they did not detect any carbapenem-R/I isolates matching the inclusion criteria for the survey. These hospitals were in Austria, Belgium, Bulgaria, Finland, Hungary, the Netherlands, Poland, Serbia and Sweden. Isolates from 23 of the 346 hospitals that registered isolates were excluded due to quality control procedures as depicted in Figure 1. Overall, 323 hospitals across 36 countries contributed isolates to the final data set (Table 2).

Table 2. Registered hospitals by country and hospitals with isolates in the final dataset

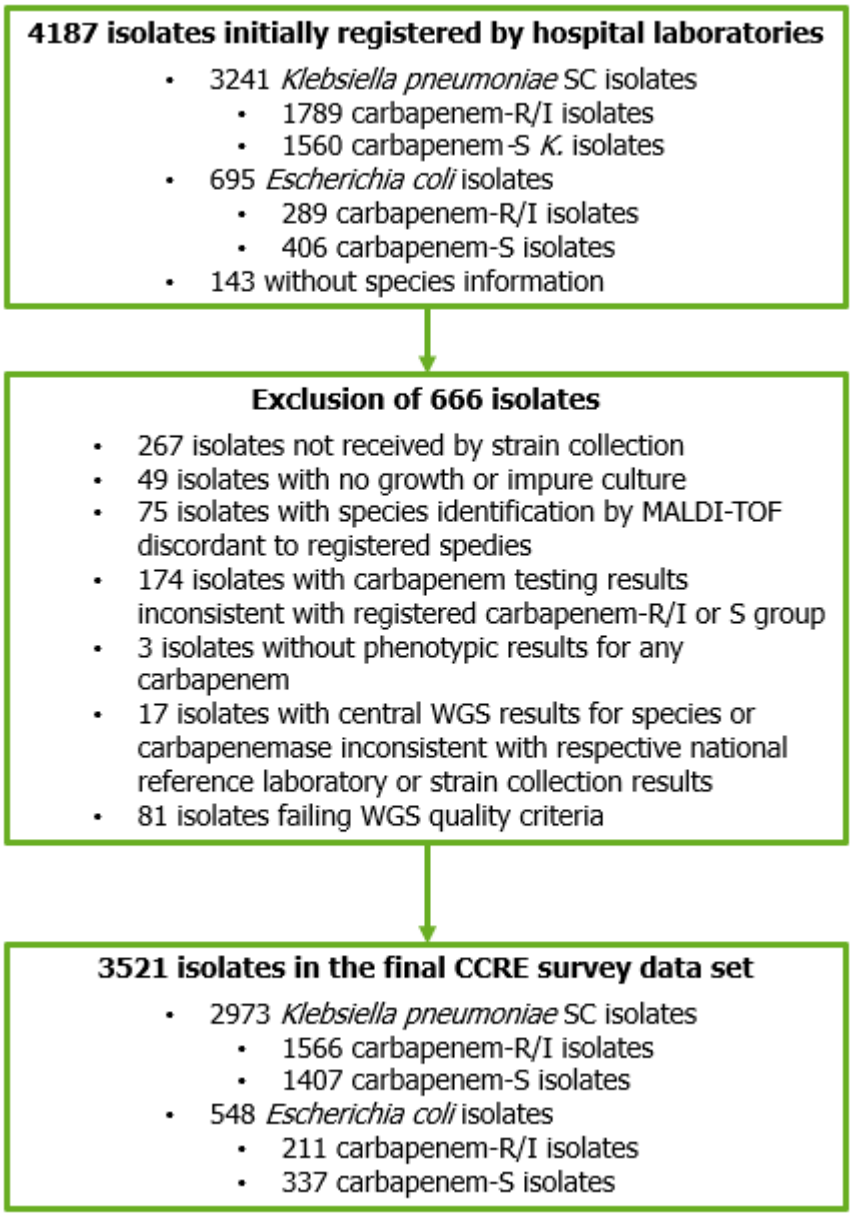
Country	Registered hospitals n	Hospitals in the final dataset n	Country	Registered hospitals n	Hospitals in the final dataset n
Albania	1	0	Latvia	1	1
Austria	9	8	Lithuania	4	1
Belgium	20	14	Luxembourg	4	2
Bosnia and Herzegovina	1	1	Malta	1	1
Bulgaria	11	10	Montenegro	1	1
Croatia	16	9	Netherlands	38	16
Cyprus	1	1	North Macedonia	3	2
Czechia	10	8	Norway	19	5
Denmark	5	5	Poland	27	12
Estonia	1	1	Portugal	7	7
Finland	20	9	Romania	11	9
France	18	12	Serbia	14	9
Germany	35	18	Slovakia	3	3
Greece	18	16	Slovenia	14	7
Hungary	10	8	Spain	26	25
Iceland	1	1	Sweden	10	10
Ireland	8	6	Türkiye	28	25
Italy	46	32	United Kingdom	84	27
Kosovo*	1	1	Total	527	323

**This designation is without prejudice to positions on status and is in line with United Nations Security Council Resolution 1244/99 and the International Court of Justice Opinion on the Kosovo declaration of independence.*

3.1.2 Processing of isolates

The isolates for the CCRE survey were collected in 2019 over a six-month period with variable starting dates (1 March, 1 April or 1 May 2019) depending on the choice of the country. One country was not able to collect isolates in the planned collection period due to delayed national approval of participation in the survey, but collected isolates in 2020 instead. Isolates were directly registered by local hospital laboratory coordinators into the database. Of the 4 438 registered isolates, 4 187 were registered as part of the main survey, including carbapenem-R/I case isolates and carbapenem-S comparator isolates, while 251 isolates were part of the voluntary additional study investigating colistin resistance, which is not reported here. Of the 4 187 isolates from the main survey, 2 141 were registered as carbapenem-R/I cases and 2 046 as carbapenem-S comparator isolates. During processing, 666 isolates were excluded for various reasons including not being received at the strain collection, no growth, contaminated culture, or incorrect species identification upon testing at the central strain collection at IBBL. Isolates with missing or inconsistent carbapenem susceptibility testing results (i.e. isolates registered as carbapenem-S but AST results showing resistance to at least one carbapenem or isolates registered as carbapenem-R/I but AST results showing susceptibility to all tested carbapenems) were also discarded. Isolates with associated WGS data that did not meet the required quality criteria or with central WGS results inconsistent with reported NRL results regarding the species and carbapenemase genes were also excluded (Figure 1).

Figure 1. Flowchart of isolates in the CCRE survey*



The flowchart does not include 251 isolates registered for the "voluntary colistin collection".

3.1.3 Final dataset

The final dataset after exclusion consisted of 1 566 carbapenem-R/I *K. pneumoniae* SC isolates, 1 407 carbapenem-S *K. pneumoniae* SC, 211 carbapenem-R/I *E. coli* and 337 carbapenem-S *E. coli*. These were collected in 323 hospitals in 36 countries, with 302 hospitals contributing *K. pneumoniae* SC isolates and 156 hospitals contributing *E. coli* isolates. The country distributions of the included isolates stratified by species are shown in Table 3 and Figures 2A-D. Further breakdown of registered and included isolates by country is provided in Tables A1 and A2 in the Annex.

Table 3. *Klebsiella pneumoniae* SC (n=2 973) and *Escherichia coli* (n=548) isolates by country

Country	*K. pneumoniae* SC isolates n	*E. coli* isolates n	Country	*K. pneumoniae* SC isolates n	*E. coli* isolates n
Albania	0	0	Latvia	6	2
Austria	36	10	Lithuania	16	4
Belgium	100	23	Luxembourg	6	6
Bosnia and Herzegovina	17	3	Malta	19	0
Bulgaria	168	14	Montenegro	18	0
Croatia	119	4	Netherlands	44	19
Cyprus	17	2	North Macedonia	5	3
Czechia	55	18	Norway	14	10
Denmark	3	6	Poland	113	4
Estonia	5	5	Portugal	85	8
Finland	11	10	Romania	117	7
France	88	19	Serbia	107	10
Germany	68	35	Slovakia	54	0
Greece	254	8	Slovenia	47	12
Hungary	65	1	Spain	357	35
Iceland	2	3	Sweden	39	37
Ireland	22	8	Türkiye	261	71
Italy	509	61	United Kingdom	124	90
Kosovo*	2	0	Total	2 973	548

**This designation is without prejudice to positions on status and is in line with United Nations Security Council Resolution 1244/99 and the International Court of Justice Opinion on the Kosovo declaration of independence.*

For *K. pneumoniae* SC, the distribution of countries was similar for carbapenem-S and carbapenem-R/I isolates and about 50% of the isolates in both groups originated from Italy, Spain, Türkiye, Greece and Bulgaria (Figure 2A-B). For *E. coli,* the distribution of countries differed between carbapenem-R/I and carbapenem-S isolates. This was mainly due to the exclusion of isolates and deviation from the protocol in terms of the selection of comparator isolates (submitting carbapenem-S *E. coli* as comparators for *K. pneumoniae*) in some countries. Isolates from the UK, Sweden, Spain and Germany combined made up 40% of carbapenem-R/I *E. coli* isolates, but only 33% of carbapenem-S isolates, while isolates from Türkiye and Italy represented only 14% of carbapenem-R/I *E. coli* isolates, but 31% of carbapenem-S isolates (Figure 2D-C).

Figure 2A-B. Country distribution for carbapenem-R/I (n=1 566) and carbapenem-S (n=1 407) *Klebsiella pneumoniae* SC isolates

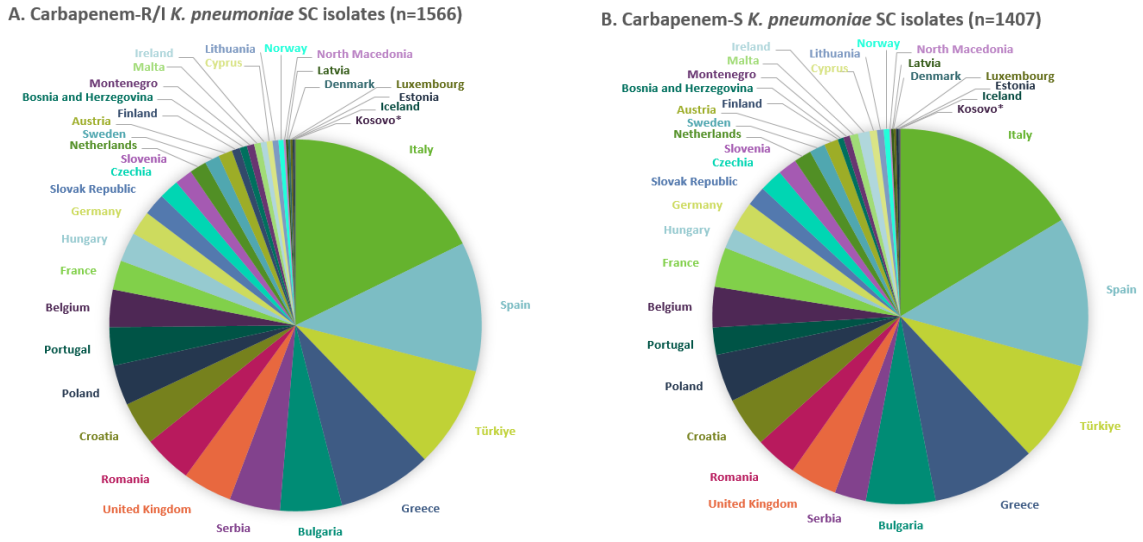
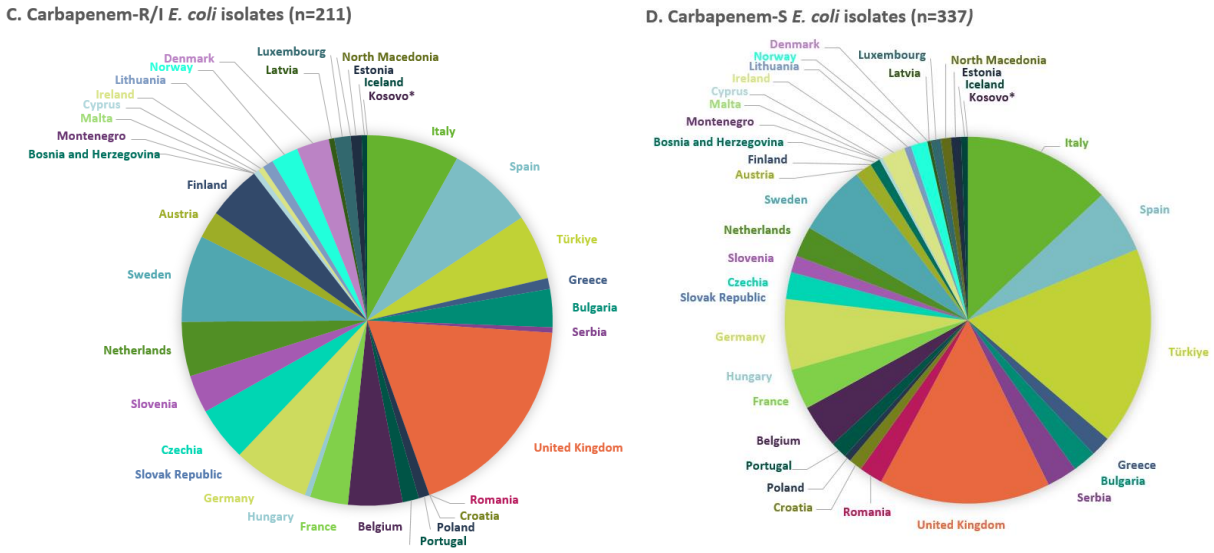


Figure 2C-D. Country distribution for carbapenem-R/I (n=211) and carbapenem-S (n=337) *Escherichia coli* isolates

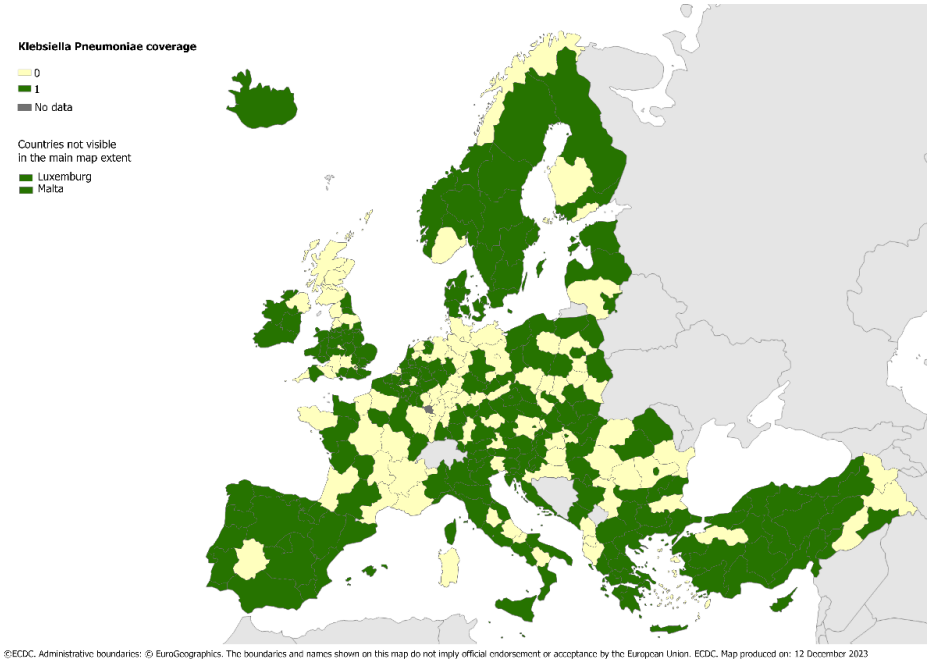


Data from Annex table A1 and A2. E. coli *isolates from Kosovo*, Malta, Montenegro and Slovakia were not present in the final dataset. Albania did not submit any isolates. *This designation is without prejudice to positions on status and is in line with United Nations Security Council Resolution 1244/99 and the International Court of Justice Opinion on the Kosovo declaration of independence.*

3.1.4 Geographic coverage based on NUTS-2 regions

The aim of the CCRE survey was to include one sentinel hospital per NUTS-2 unit. However, for various reasons, ranging from non-recruitment and non-participation of recruited hospitals to loss of isolates during the various processing stages, full coverage could not be achieved. The NUTS-2 coverage of the final *K. pneumoniae* SC dataset is displayed in Figure 3. For *E. coli*, the dataset is much smaller and includes four countries fewer than the *K. pneumoniae* dataset. The *E. coli* dataset is therefore not geographically representative.

Figure 3. National Territorial Units for Statistics (NUTS) level 2 coverage (dark green) for *Klebsiella pneumoniae* SC



3.2 Data completeness

3.2.1 Data completeness for microbiological variables

The microbiological variables (sampling date, type of clinical specimen) were submitted with a high completeness, as this information was easily accessible for the clinical microbiological laboratories submitting the information to the CCRE survey database. The variable 'location of infection' was not always reported (missing in 12% of isolates), indicating that this information was not always provided by the clinicians. A detailed description of the data completeness related to AST is provided in sections 3.4.2.2 and 3.4.2.3 and Figure 8 below.

3.2.2 Data completeness for epidemiological and clinical variables

Completeness of information on age, gender, type of patient, type of unit/ward, date of hospitalisation, clinical significance, organ system or location of infection/colonisation, community or hospital acquisition, healthcare exposure/referral history and travel history are described in Table 4. Regarding the patient data, the most difficult information to collect was the healthcare exposure/referral history and travel history. This information requires clinicians to record this information, and the patient to remember it. Not all laboratories reporting data to the CCRE database had access to medical records, limiting information on clinical variables.

Table 4. Data completeness for microbiological, epidemiological and clinical variables

Variable	Isolates with complete information[A] n (%)
Sample collection date	3 482 (98.9)
Type of specimen	3 503 (99.5)
Type of clinical specimen	3 456 (98.2)
Clinical significance	3 396 (96.4)
Location of infection/colonisation	3 108 (88.3)
Gender	3 394 (96.4)
Age	3 381 (96.0)
In- or outpatient status	3 377 (95.9)
Unit/ward	3 303 (93.8)
Hospital- or community acquisition	2 953 (83.9)
Hospitalisation date	2 667 (75.7)
Hospital transfer	2 448 (69.5)
Previous hospitalisation	2 332 (66.2)
Previous residence in long-term facility	1 952 (55.4)
Recent travel to another country[B]	1 984 (56.3)
Total number of isolates	**3 521**

[A]In complete information a response such as "information not available" is counted for some variables.
[B]For recent travel to another country, this refers to raw data, not the combined variable used in the logistic regression analyses.

3.2.3 Data completeness for hospital variables

Completeness of data on sampling period, total number of admissions and number of occupied bed days during the sampling period, total number of patients colonised or infected with *K. pneumoniae* SC or *E. coli* was calculated for the hospitals with at least one isolate included in the final dataset (n=323). This information was difficult to access for some hospitals and countries despite repeated attempts to collect this information. Completeness of hospital variables is outlined in Table 5. Data on admitted patient days and occupied bed days was especially incomplete or inconsistent for many hospitals, affecting the calculation of incidence and prevalence. For more details regarding exclusion of data for admissions and occupied bed days, see section 3.3.

Table 5. Data completeness for hospital variables

Variable	Hospitals with complete information n (%)
Population in catchment area	209 (64.7)
Admitted patients during sample period	220 (68.1)
Occupied bed days during sampling period	226 (70.0)
Total number of patients colonised/ infected with *E. coli*	204 (63.2)
Total number of patients colonised/ infected with *K. pneumoniae* SC	207 (64.1)
Total number of hospitals	323 (100.0)

3.3 Epidemiological results

3.3.1 Prevalence and incidence

Data on admissions and occupied bed patient-days were incomplete and might have been variably calculated in different countries. Therefore, the following calculations on prevalence and incidence of carbapenem-resistant *K. pneumoniae* SC and *E. coli* should be interpreted with caution. Data on prevalence and incidence with 95% confidence intervals are shown in Figures 4 and 5 and in Annex tables A3a-b.

Prevalence

Prevalence was defined as the number of isolates collected per 10 000 hospital admissions. For various reasons, there were no data available for the calculation of prevalence for *K. pneumoniae* SC and *E. coli* for Czechia, France, Ireland, Latvia, Lithuania and Türkiye. For *E. coli*, additional countries lacking prevalence data were Austria, Bosnia and Herzegovina, Croatia, Kosovo, Malta, Montenegro, North Macedonia, Romania and Slovakia. In addition, to allow comparison between countries, data were only included for hospitals if the number of admitted patients and the number of occupied bed days during the sampling period were >100. For carbapenem-R/I *K. pneumoniae* SC isolates, the mean period prevalence for all included countries was 2.4 isolates per 10 000 hospital admissions. The prevalence varied between 0.0 for Denmark and 21.7 for Slovakia (Figure 4A). The mean period prevalence for all included countries was lower for carbapenem-R/I *E. coli* with 0.4 per 10 000 hospital admissions, ranging between 0.1 for Denmark and 1.8 for Greece (Figure 5A).

Incidence

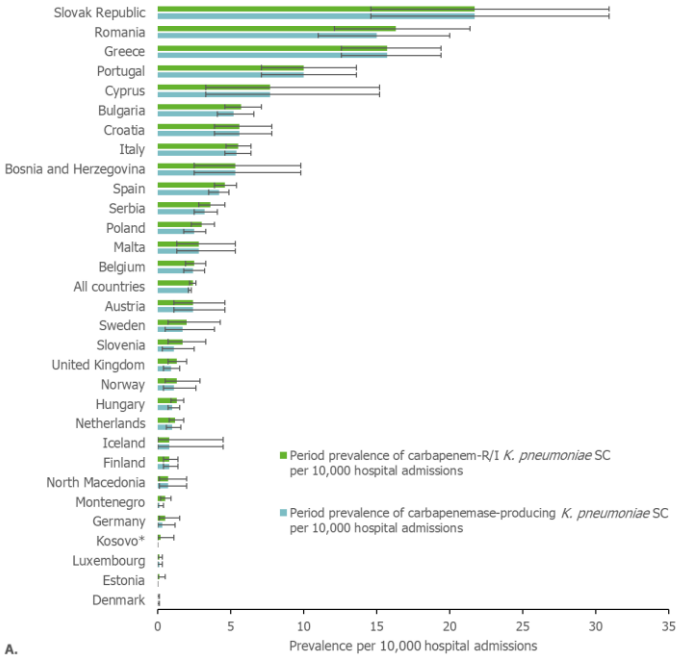
Incidence was defined as the number of isolates collected per 100 000 occupied bed patient-days. Data that could be evaluated were, for various reasons, not available for either *E. coli* or *K. pneumoniae* SC for Cyprus, Czechia, France, Ireland, Latvia, Lithuania, Montenegro and Türkiye. For *E. coli*, additional countries lacking data were Austria, Bosnia and Herzegovina, Croatia, Kosovo, North Macedonia, Malta, Slovakia and Romania. To allow comparison between countries, data were only included for hospitals if the number of occupied bed days during the sampling period was between 100 and 10 000 000, and the number of admitted patients during the sampling period was >100 and [the number of admitted patients during sampling period] / [the number of occupied bed days during sampling period] was <10. For the countries included in the analysis, the mean incidence of *K. pneumoniae* SC carbapenem-R/I isolates was 6.1 per 100 000 patient-days, ranging from 0.1 for Denmark to 43.2 for Portugal (Figure 4B). For *E. coli* carbapenem-R/I the mean incidence was 1.1 isolates per 100 000 patient days, with the lowest incidence in Denmark (0.2 per 100 000 patient-days) and the highest in Greece (9.0 per 100 000 patient-days) (Figure 5B).

Comparison with EuSCAPE

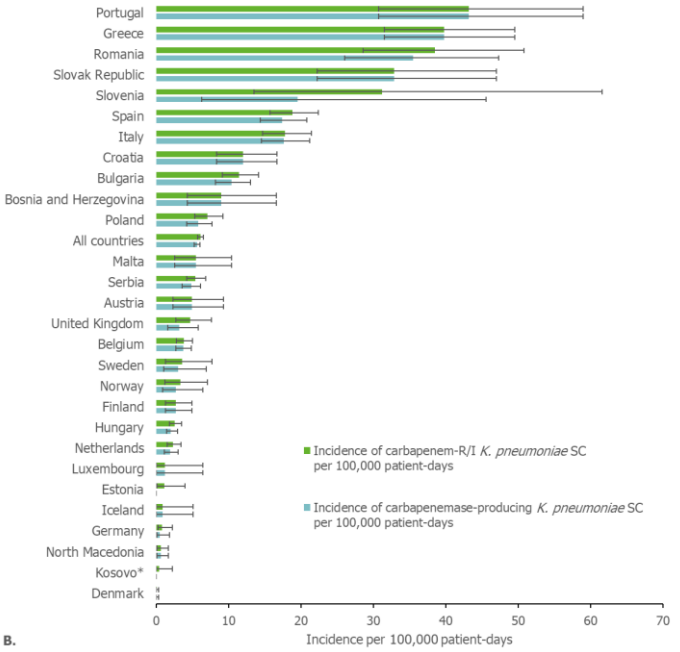
Calculation of prevalence (isolates per 10 000 admissions) and incidence (isolates per 100 000 patient-days) were hampered by lack of data. Nevertheless, in comparison with the EuSCAPE study performed in 2013-2014 [15], we estimate that the combined mean prevalence for carbapenemase-producing *E. coli* and *K. pneumoniae* SC increased from 1.3 per 10 000 hospital admissions to 2.5 isolates per 10 000 hospital admissions in the CCRE survey in 2019. The estimated combined mean incidence of carbapenemase-producing *E. coli* and *K. pneumoniae* SC increased from 2.5 isolates per 100 000 patient days in 2013-2014 (EuSCAPE) to 6.6 per 100 000 patient-days in 2019 (CCRE survey).

Figure 4. Carbapenem-R/I and carbapenemase-producing *Klebsiella pneumoniae* SC during the sampling period per country

Period prevalence per 10 000 hospital admissions



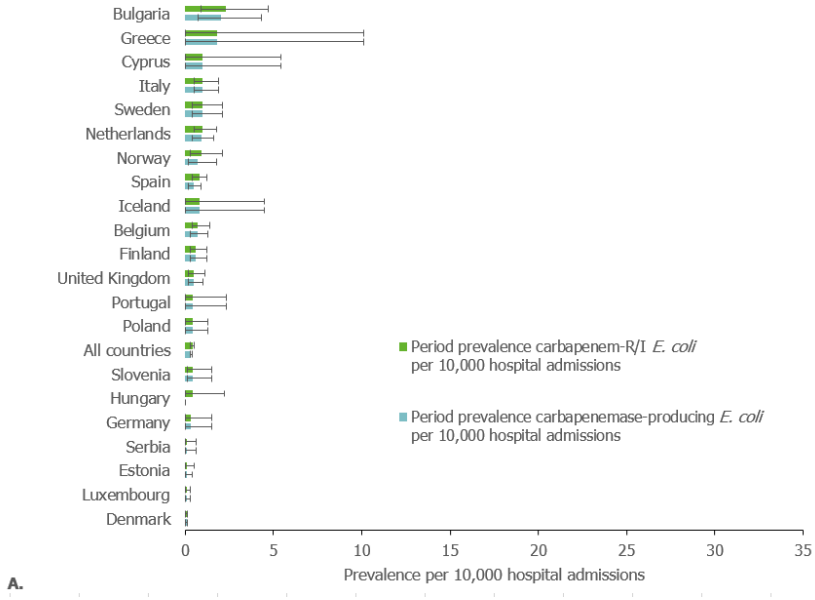
Incidence per 100 000 patient-days



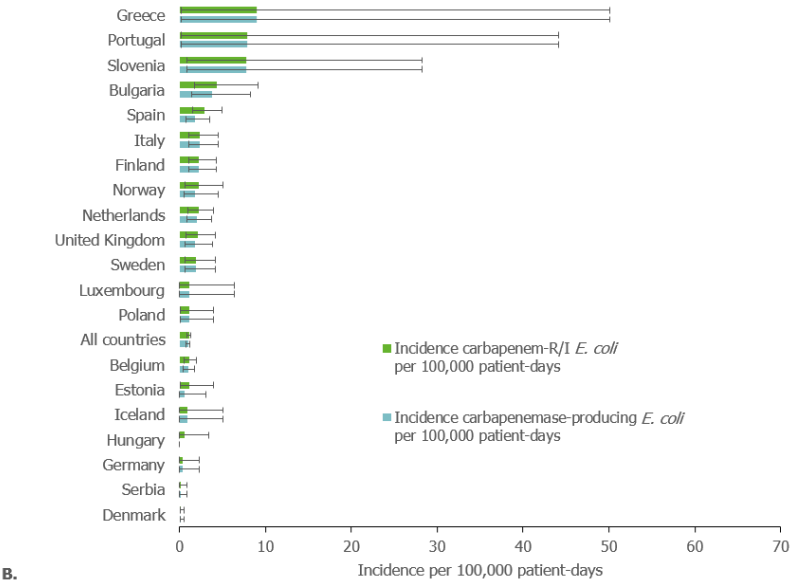
Note: Graphs based on data in Annex table A3a. Black bars show the 95%-confidence interval. Data are only shown for countries with at least one carbapenem-R/I K. pneumoniae isolate in a hospital with data on hospital admission/patient-days. To allow comparison between countries, data were included for calculation of prevalence for hospitals only if the number of admitted patients during sampling period was > 100 and the number of occupied bed days during the sampling period was >100.
For calculation of incidence, data were included for hospitals only if the number of occupied bed days during sampling period was between 100 and 10 000 000 and the number of admitted patients during sampling period was >100 and [the number of admitted patients during sampling period] / [the number of occupied bed days during sampling period] was <10.
Excluded countries due to lack of data: Czechia, France, Latvia, Lithuania and Türkiye, and additionally, for incidence only, Cyprus and Montenegro.

Figure 5. Carbapenem-R/I and carbapenemase-producing *Escherichia coli* during the sampling period per country

Period prevalence per 10 000 hospital admissions



Incidence per 100 000 patient days



Note: Graphs based on data in Annex table A3b. Black bars show 95% CI. Data are only shown for countries with at least one carbapenem-R/I E. coli in a hospital with data on hospital admission/patient-days. To allow comparison between countries, data were included for calculation of prevalence for hospitals only if the number of admitted patients during sampling period was > 100 and the number of occupied bed days during the sampling period was >100.
For calculation of incidence, data were included for hospitals only if the number of occupied bed days during sampling period was between 100 and 10 000 000 and the number of admitted patients during sampling period was >100 and [the number of admitted patients during sampling period] / [the number of occupied bed days during sampling period] was <10.
Excluded countries due to lack of data: Austria, Bosnia and Herzegovina, Croatia, Czechia, France, Ireland, Kosovo, Latvia, Lithuania, North Macedonia, Malta, Slovak Republic, Romania, Türkiye and, additionally, for incidence only, Cyprus.

3.3.2 Descriptive and risk factor analysis

Descriptive analysis

Epidemiological information and potential risk factors for acquisition of carbapenem-R/I *K. pneumoniae* SC and *E. coli* infections including gender, age, hospitalisation status, type of ward, infection/carriage status, organ/system or location of infection/colonization, hospital/community acquisition, hospital transfer, previous hospitalisation, previous residence in a long-term care facility and travel are shown in Table 6.

Table 6. Overview of epidemiological variables for *Escherichia coli* and *Klebsiella pneumoniae* SC isolates

Variable	*E. coli*			*K. pneumoniae* SC		
	Total n (%)	Carbapenem-R/I n (%)	Carbapenem-S n (%)	Total n (%)	Carbapenem-R/I n (%)	Carbapenem-S n (%)
n	548	211	337	2973	1 566	1 407
Gender						
Male	246 (44.9)	119 (56.4)	127 (37.7)	1553 (52.2)	903 (57.7)	650 (46.2)
Female	273 (49.8)	84 (39.8)	189 (56.1)	1322 (44.5)	619 (39.5)	703 (50.0)
Missing	29 (5.3)	8 (3.8)	21 (6.2)	98 (3.3)	44 (2.8)	54 (3.8)
Age class (years)						
0-19	47 (8.6)	15 (7.1)	32 (9.5)	157 (5.3)	57 (3.6)	100 (7.1)
20-39	61 (11.1)	27 (12.8)	34 (10.1)	218 (7.3)	106 (6.8)	112 (8.0)
40-59	103 (18.8)	40 (19.0)	63 (18.7)	517 (17.4)	283 (18.1)	234 (16.6)
60-79	204 (37.2)	93 (44.1)	111 (32.9)	1332 (44.8)	733 (46.8)	599 (42.6)
≥80	102 (18.6)	28 (13.3)	74 (22.0)	638 (21.5)	343 (21.9)	295 (21.0)
Missing	31 (5.7)	8 (3.8)	23 (6.8)	111 (3.7)	44 (2.8)	67 (4.8)
Child/adult (years)						
>19	470 (85.8)	188 (89.1)	282 (83.7)	2705 (91.0)	1465 (93.6)	1240 (88.1)
0-19	47 (8.6)	15 (7.1)	32 (9.5)	157 (5.3)	57 (3.6)	100 (7.1)
Missing	31 (5.7)	8 (3.8)	23 (6.8)	111 (3.7)	44 (2.8)	67 (4.8)
Hospitalisation status						
Outpatient	129 (23.5)	44 (20.9)	85 (25.2)	559 (18.8)	215 (13.7)	344 (24.4)
Inpatient	389 (71.0)	154 (73.0)	235 (69.7)	2 300 (77.4)	1 291 (82.4)	1 009 (71.7)
Missing	30 (5.5)	13 (6.2)	17 (5.0)	114 (3.8)	60 (3.8)	54 (3.8)
Type of ward						
Medical	247 (45.1)	82 (38.9)	165 (49.0)	1257 (42.3)	624 (39.8)	633 (45.0)
Intensive care	74 (13.5)	39 (18.5)	35 (10.4)	637 (21.4)	436 (27.8)	201 (14.3)
Surgical	99 (18.1)	35 (16.6)	64 (19.0)	452 (15.2)	239 (15.3)	213 (15.1)
Other	87 (15.9)	38 (18.0)	49 (14.5)	450 (15.1)	183 (11.7)	267 (19.0)
Missing	41 (7.5)	17 (8.1)	24 (7.1)	177 (6.0)	84 (5.4)	93 (6.6)
Infection/carriage status						
Colonisation	119 (21.7)	82 (38.9)	37 (11.0)	496 (16.7)	313 (20.0)	183 (13.0)
Infection	363 (66.2)	105 (49.8)	258 (76.6)	2 135 (71.8)	1 087 (69.4)	1 048 (74.5)
Undetermined clinical significance	40 (7.3)	13 (6.2)	27 (8.0)	243 (8.2)	119 (7.6)	124 (8.8)
Missing	26 (4.7)	11 (5.2)	15 (4.5)	99 (3.3)	47 (3.0)	52 (3.7)
Organ/system or location of infection/ carriage						
Urinary tract	218 (39.8)	67 (31.8)	151 (44.8)	1 252 (42.1)	598 (38.2)	654 (46.5)
Lower respiratory tract	19 (3.5)	8 (3.8)	11 (3.3)	363 (12.2)	203 (13.0)	160 (11.4)
Intra-abdominal	37 (6.8)	18 (8.5)	19 (5.6)	130 (4.4)	78 (5.0)	52 (3.7)
Bloodstream	86 (15.7)	14 (6.6)	72 (21.4)	439 (14.8)	231 (14.8)	208 (14.8)
Skin and soft tissue	34 (6.2)	17 (8.1)	17 (5.0)	228 (7.7)	131 (8.4)	97 (6.9)
Other	85 (15.5)	57 (27.0)	28 (8.3)	217 (7.3)	138 (8.8)	79 (5.6)
Missing	69 (12.6)	30 (14.2)	39 (11.6)	344 (11.6)	187 (11.9)	157 (11.2)
Hospital-acquired/community-onset						
Community-onset	243 (44.3)	68 (32.2)	175 (51.9)	1 018 (34.2)	359 (22.9)	659 (46.8)
Hospital-acquired	180 (32.8)	87 (41.2)	93 (27.6)	1512 (50.9)	971 (62.0)	541 (38.5)
Missing	125 (22.8)	56 (26.5)	69 (20.5)	443 (14.9)	236 (15.1)	207 (14.7)
Direct hospital transfer						
No direct hospital transfer	306 (55.8)	99 (46.9)	207 (61.4)	1862 (62.6)	929 (59.3)	933 (66.3)
From another hospital in the same country	17 (3.1)	8 (3.8)	9 (2.7)	211 (7.1)	148 (9.5)	63 (4.5)
From a hospital in an EU/EEA country[A]	2 (0.4)	2 (0.9)	0 (0.0)	16 (0.5)	15 (1.0)	1 (0.1)
From a hospital in a non-EU/EEA country[A]	12 (2.2)	12 (5.7)	0 (0.0)	21 (0.7)	21 (1.3)	0 (0.0)

Variable	*E. coli*			*K. pneumoniae* SC		
	Total n (%)	Carbapenem-R/I n (%)	Carbapenem-S n (%)	Total n (%)	Carbapenem-R/I n (%)	Carbapenem-S n (%)
From a hospital in another country (country not specified)[A]	1 (0.2)	1 (0.5)	0 (0.0)	4 (0.1)	4 (0.3)	0 (0.0)
Missing	210 (38.3)	89 (42.2)	121 (35.9)	859 (28.9)	449 (28.7)	410 (29.1)
Previous hospital admission within six months						
No previous hospital admission	166 (30.3)	34 (16.1)	132 (39.2)	857 (28.8)	343 (21.9)	514 (36.5)
In the same hospital	103 (18.8)	51 (24.2)	52 (15.4)	745 (25.1)	433 (27.7)	312 (22.2)
In another hospital in the same country	24 (4.4)	13 (6.2)	11 (3.3)	284 (9.6)	189 (12.1)	95 (6.8)
In a hospital in an EU/EEA country[A]	1 (0.2)	1 (0.5)	0 (0.0)	24 (0.8)	22 (1.4)	2 (0.1)
In a hospital in a non-EU/EEA country[A]	19 (3.5)	18 (8.5)	1 (0.3)	31 (1.0)	31 (2.0)	0 (0.0)
In a hospital in another country (country not specified)[A]	4 (0.7)	3 (1.4)	1 (0.3)	21 (0.7)	18 (1.1)	3 (0.2)
Unknown hospital	13 (2.4)	6 (2.8)	7 (2.1)	88 (3.0)	48 (3.1)	40 (2.8)
Missing	218 (39.8)	85 (40.3)	133 (39.5)	923 (31.0)	482 (30.8)	441 (31.3)
Previous residence in a long-term/elderly care facility within six months						
No previous residence in care facility	235 (42.9)	84 (39.8)	151 (44.8)	1 487 (50.0)	731 (46.7)	756 (53.7)
In the same country	17 (3.1)	7 (3.3)	10 (3.0)	187 (6.3)	131 (8.4)	56 (4.0)
In an EU/EEA country[A]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
In a non-EU/EEA country[A]	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	2 (0.1)	0 (0.0)
Missing	296 (54.0)	120 (56.9)	176 (52.2)	1 297 (43.6)	702 (44.8)	595 (42.3)
Previous travel within 6 months[B]						
No reported travel or information not available	512 (93.4)	181 (85.8)	331 (98.2)	2894 (97.3)	1500 (95.8)	1394 (99.1)
To an EU/EEA country[B]	3 (0.5)	2 (0.9)	1 (0.3)	30 (1.0)	26 (1.7)	4 (0.3)
To a non-EU/EEA country[B]	33 (6.0)	28 (13.3)	5 (1.5)	49 (1.6)	40 (2.6)	9 (0.6)

[A]Hospitals in an EU/EEA country and a non-EU/EEA country refers to countries other than the country of sampling.
[B]Previous travel is a combined variable on all information on travel within 6 months, combining travel information entered concerning direct transfer, previous hospital admission and travel. For details see Annex section "Limitations and modifications of the multilevel multivariate logistic regression analysis described in tables 8a-i.

Limitations and modifications of the multilevel multivariate logistic regression analysis

The multivariate multilevel model had convergence problems and some estimates and confidence intervals were very wide and could not be interpreted. This may be due to several factors, such as small sample size in some sub-analyses and rare outcomes, but could also be due to a high correlation between several factors in the model. For this reason, several adaptations were made, for example, the variable 'direct hospital transfer' was removed from the multivariate analysis to reduce the risk of multicollinearity and small counts. For details of the multivariate analysis, see Annex Tables 8a-i.

Results of the multilevel multivariate logistic regression analysis

Overall, most isolates were associated with infections (71.8% of *K. pneumoniae* SC and 66.2% of *E. coli* isolates), although there were differences in the proportion of isolates associated with infection by country. Colonisation (as compared to infection) was more common in carbapenem-R/I than carbapenem-S isolates, which was a statistically significant difference for both *K. pneumoniae* SC (multivariate OR 0.77 [95%CI 0.60-0.99]) and *E. coli* (OR 0.40 [95%CI 0.18-0.85]). Carbapenem-R/I isolates were more often from male patients (57.7% of *K. pneumoniae* SC and 56.4% of *E. coli* isolates) than the carbapenem-S isolates (46.2% of *K. pneumoniae* SC and 37.7%*E. coli* isolates). Overall, the most frequent age group was 60-79 years-old; for *K. pneumoniae* SC, 44.8% of isolates were from patients in this age group, and for *E. coli* 37.2%.

Carbapenem-R/I K. pneumoniae *SC compared to carbapenem-S* K. pneumoniae *SC*

Detailed results of this analysis are presented in Annex table A8a. For *K. pneumoniae* SC, variables with the statistically strongest association with carbapenem-R/I isolates in the multilevel multivariate logistic regression analysis were related to different aspects of hospital acquisition. Overall, 62.0% of carbapenem-R/I *K. pneumoniae* SC isolates were reported to be hospital-acquired, compared to 38.5% of carbapenem-S isolates (OR 3.37 [2.71-4.19]). All types of hospital acquisition had a statistically significant association, including previous hospital admission within six months in the same hospital, another hospital in the same country or a hospital in another country and previous residence in a long-term/elderly care facility in the same or another country. The type of

ward was intensive care for 27.8% of carbapenem-R/I *K. pneumoniae* SC isolates, but only for 14.3% of carbapenem-S *K. pneumoniae* SC isolates (OR for intensive care compared to medical ward 2.07 [1.64-2.61]). The combined variable travel to another country (including healthcare related travel and unspecified travel) was significantly associated with carbapenem-R/I *K. pneumoniae* SC isolates compared with the combined variable for no reported travel or information not available. However, data on travel could be influenced by information bias and data was recorded as "missing" or "information not available" in 87.2% of *K. pneumoniae* SC.

Carbapenem-R/I E. coli *compared to carbapenem-S* E. coli

Detailed results are presented in Annex table A8b. Hospital acquisition of infection/carriage was documented for 41.2% of carbapenem-R/I *E. coli* and 27.6% of carbapenem-S *E. coli* (OR 3.52 [1.92-6.46]). For *E. coli*, previous hospital admission within six months had a statistically significant association in the multilevel multivariate logistic regression analysis, regardless of whether the hospital was the same, or another hospital in the same country, or a hospital in another country. The combined variable travel to another country (including hospitalisation in and direct hospital transfer from another country and unspecified travel) was significantly associated with carbapenem-R/I *E. coli* isolates compared with the combined variable for no reported travel or information not available. However, data on travel could be influenced by information bias and data was recorded as "missing" or "information not available" in 80.8% of *E. coli*.

Multilevel multivariate logistic regression analysis comparing major STs within carbapenem-R/I K. pneumoniae *SC*

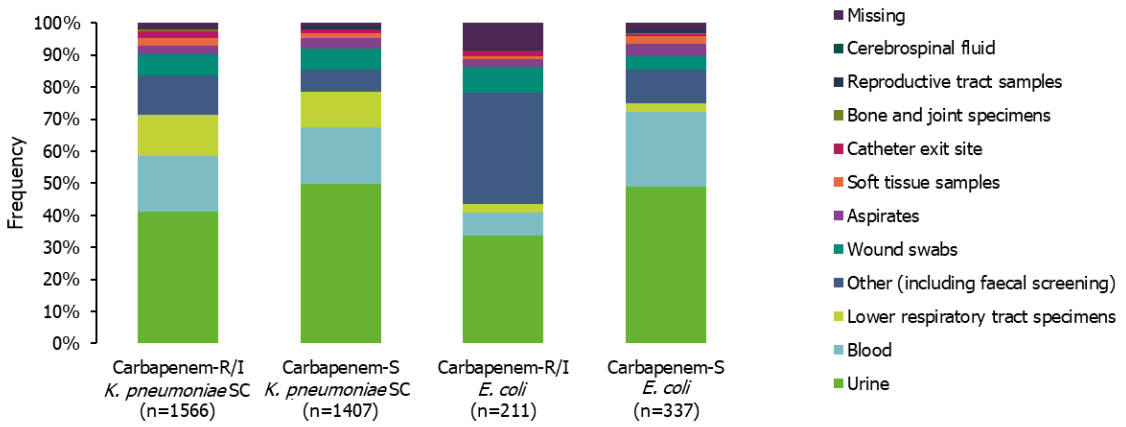
An in-depth multilevel multivariate logistic regression analysis was performed within the carbapenem-R/I *K. pneumoniae* SC to identify differences in risk factors between major STs among carbapenem-R/I *K. pneumoniae* SC (Annex tables A8c-i). The six dominant STs of carbapenem-R/I *K. pneumoniae* SC (ST258/512, ST307, ST11, ST101, ST147, ST15) were called 'epidemic STs' and risk factors associated with these STs compared to other 'non-epidemic' carbapenem-R/I *K. pneumoniae* SC STs were investigated. Within the carbapenem-R/I *K. pneumoniae* SC group, the multilevel multivariate analysis did not reveal major differences between the combined epidemic STs and the non-epidemic STs. Although a few variables had a significant statistical association in this analysis, those were mostly variables with few observations, which makes the results difficult to interpret (A8c). When looking at the individual epidemic STs compared to non-epidemic STs, some kind of healthcare association was found for ST258/512, ST307, and ST15. Previous hospital admission in the same hospital or a hospital in another EU/EEA country, as well as surgical ward (with medical ward as reference) was associated with ST258/512 (Table A8d). Previous residence in a long-term/elderly care facility in the same country was associated with ST307 (Table A8e) and ST15 (Table A8i). Previous hospitalisation in another country was associated with ST147 (Table A8h). On the other hand, hospital acquisition had a negative association with ST11 (Table A8f). For ST101 (Table A8g), associated variables were surgical ward and skin and soft tissue infection.

3.4 Microbiological results

3.4.1 Sample type

Most isolates analysed in the CCRE survey (3 147/3 521, 89.4%), and specifically *K. pneumoniae* SC isolates (2 718/2 973, 91.4%), originated from clinical samples. The type of clinical specimens from which the isolates originated were largely similar for carbapenem-R/I and carbapenem-S *K. pneumoniae* SC (Figure 6). For *E. coli* isolates, the proportion of clinical samples was lower (429/548, 78.3%), especially for the carbapenem-R/I isolates (126/211, 59.7%) (Figure 6).

Figure 6. Type of clinical specimens for isolates of *Klebsiella pneumoniae* and *Escherichia coli* in the final CCRE survey dataset



Data from Annex Table 6.

3.4.2 Phenotypic AST results

3.4.2.1 AST methods and interpretation

Phenotypic AST was performed at the NRLs as described above using various AST methods including BMD, disk diffusion, automated and other methods (Table 7). MIC and disc diffusion zones were submitted together with the NRL interpretation according to the EUCAST breakpoint table version 9.0, 2019 [22]. For carbapenem susceptibility testing, laboratories were recommended to use BMD primarily or disk diffusion, if BMD was not available [17]. For colistin AST, BMD was recommended exclusively [18]. The NRL interpretation according to EUCAST breakpoint table 9.0, 2019 was used. Of note, since 2022, the colistin breakpoints are shown in brackets in the EUCAST breakpoint tables. This means that for isolates classified as colistin-S in this report, colistin is now only recommended as combination treatment with another active antimicrobial agent [45].

The methods available for the different carbapenems varied and not all countries reported the methods used for colistin susceptibility testing. Some laboratories used more than one AST method per isolate and reported disk diffusion zone diameters and MICs for the same sample. NRLs reported S/I/R-interpretation based on obtained results. Reported AST results for tigecycline and fosfomycin for *K. pneumoniae* SC were not used in the analysis. EUCAST breakpoints for tigecycline and *K. pneumoniae* were removed in the EUCAST breakpoint table version 9.0, 2019 [22], and fosfomycin AST for *K. pneumoniae* is discouraged in the EUCAST breakpoint table version 14.0, 2024 [46]. For colistin, 22% of the samples in the final dataset lacked AST results. As the inclusion criteria and classification into carbapenem-R/I and carbapenem-S categories depended on AST results for carbapenems, a re-analysis according to EUCAST breakpoint table v9.0 [22] was performed at PHAS. The PHAS interpretations were based on MICs (first choice) or disc diffusion results (second choice) reported from the NRLs when available. If no results from an NRL were reported, MICs obtained at IBBL were used, if available. For all other antibiotic agents, the AST interpretation reported by the NRL was used for the analysis below.

Table 7. Methods reported from national reference or expert laboratories for carbapenem and colistin susceptibility testing

AST methods	Meropenem n (%)	Imipenem n (%)	Ertapenem n (%)	Colistin n (%)
BMD	2 361 (67.1)	1 680 (47.7)	1 283 (36.4)	2 643 (75.1)
Disk diffusion	474 (13.5)	684 (19.4)	1 318 (37.4)	12 (0.3)
Automated system	348 (9.9)	177 (5.0)	410 (11.6)	68 (1.9)
Gradient strip test	95 (2.7)	42 (1.2)	80 (2.3)	13 (0.4)
Other*	167 (4.7)	191 (5.4)	192 (5.5)	17 (0.5)

*The online database allowed the submission of both - disk diffusion and MIC results and results for both methods were submitted by some countries. However, in the method section of the online database, only one method could be recorded for each antibiotic. Hence, the numbers in the table are approximations and may include reporting errors. *Other includes e.g. agar dilution.*

Table 8. Availability of MIC and disk diffusion zone diameter results for carbapenems and colistin

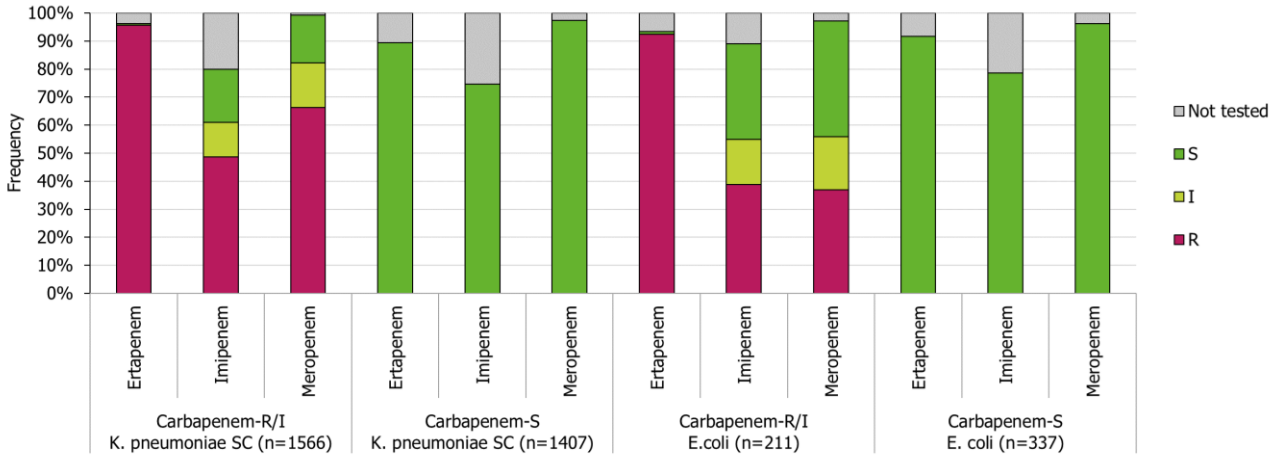
Variable	Isolates with available results n (%)
Colistin MIC	2 759 (78)
Ertapenem MIC	2 015 (57)
Ertapenem zone	1 454 (41)
Imipenem MIC	2 193 (62)
Imipenem zone	1 026 (29)
Meropenem MIC	3 035 (86)
Meropenem zone	1 073 (30)

More than one method was applied in some countries, therefore the percentages do not add up to 100.

3.4.2.2 Carbapenems

In total, 98.1% of isolates had an AST result for meropenem, 92.9% for ertapenem and 88.2% for imipenem. Based on the inclusion criteria, all carbapenem-R/I isolates had to be in the categories R or I for at least one carbapenem tested. This inclusion procedure resulted in most (99.5%) of the carbapenem-R/I *K. pneumoniae SC* being resistant (R) to ertapenem, while only 60.9% were resistant (R) to imipenem and 66.7% were resistant (R) to meropenem according to EUCAST clinical breakpoints and based on tested isolates (Figure 7 and Annex Table 4). For carbapenem-R/I *E. coli,* the proportion of resistance (R) was lower with 99.0% for ertapenem, 43.6% for imipenem and 38% for meropenem, based on tested isolates. As per the inclusion criteria, all carbapenem-S isolates had an AST result for at least one carbapenem and all tested carbapenems were in the category S. Due to the study set-up and applied inclusion criteria relying exclusively on clinical breakpoints, the performance of EUCAST screening breakpoints for carbapenemase production for meropenem [24] cannot be evaluated for this dataset, and this information is not included.

Figure 7. Phenotypic antimicrobial susceptibility testing results for carbapenems for *Klebsiella pneumoniae* SC and *Escherichia coli*



Note. The displayed carbapenem AST results were performed at the NRLs and reanalysed by PHAS according to the EUCAST breakpoint table from 2019. Phenotypic criteria for inclusion of isolates submitted as carbapenem-S were that all tested carbapenems were in the susceptible category. For isolates submitted as carbapenem-R/I at least one carbapenem had to be classified as susceptible increased exposure or resistant according to EUCAST breakpoints.

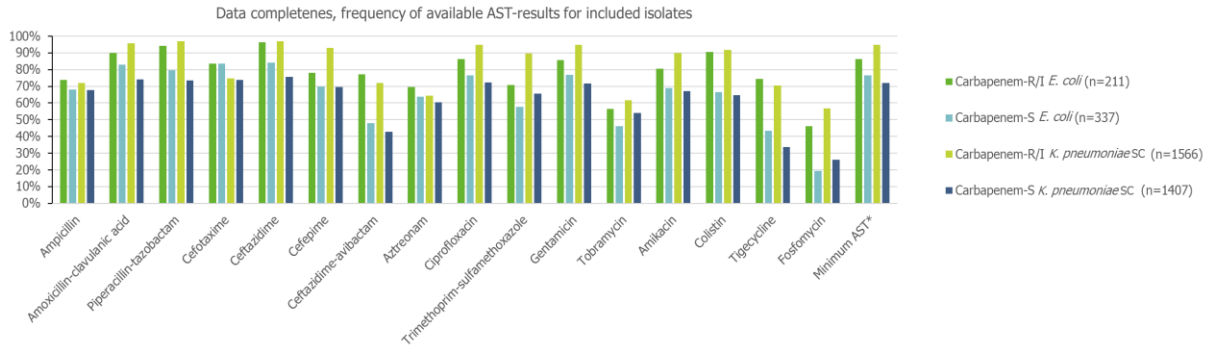
3.4.2.3 Other key antibiotics

For antimicrobial agents other than carbapenems, the data completeness for AST-results was lower, but was generally higher for the carbapenem-R/I than for the carbapenem-S isolates. Overall, more than 75% of isolates were tested for amoxicillin-clavulanic acid, piperacillin-tazobactam, cefotaxime, ceftazidime, cefepime, ciprofloxacin, trimethoprim-sulfamethoxazole, gentamicin, amikacin and colistin, while less than 75% of isolates had AST results for ampicillin, ceftazidime-avibactam, aztreonam, tobramycin, tigecycline and fosfomycin. Data on AST completeness are shown in Figure 8 and the proportion of S/I/R among tested isolates for each antimicrobial agent is shown in figures 9A-D, based on data in Annex table 5a-b.

Results for fosfomycin and tobramycin are not included in Figure 9 due to low completeness. The tigecycline breakpoint in the EUCAST breakpoint table v.9.0 is restricted to *E. coli* and *Citrobacter* spp., thus AST results for tigecycline for *K. pneumoniae* SC are not shown. Resistance levels to other antibiotics were generally higher among carbapenem-R/I *K. pneumoniae* SC isolates than carbapenem-R/I *E. coli* isolates. For carbapenem-R/I *K. pneumoniae* SC, 76.7% of the tested isolates remained susceptible (S) to colistin and 75.4% to ceftazidime-avibactam, which were the two most active antimicrobial agents. For carbapenem-S *K. pneumoniae* SC, 97.7% of isolates were susceptible (S) to colistin and 99.2% to ceftazidime-avibactam. For the carbapenem-R/I *E. coli*, 96.9% of tested isolates remained susceptible to colistin and 96.2% to tigecycline, while only 62.6% were susceptible to ceftazidime-avibactam. For carbapenem-S *E. coli*, 98.7% were susceptible (S) to colistin, 99.3% to tigecycline, and 100% to ceftazidime-avibactam.

Of note, among the carbapenem-S isolates there were many isolates with phenotypic resistance to other agents. The frequency of cefotaxime resistance (R) was 26.6% among carbapenem-S *E. coli* and 27.2% among carbapenem-S *K. pneumoniae* SC (Figure 9A-D). Resistance (R) proportions for carbapenem-R/I compared to carbapenem-S *K. pneumoniae* SC isolates were 94.2% vs 26.7% for ciprofloxacin, 77.1% vs 33.2% for trimethoprim-sulfamethoxazole, 54.6% vs 15.0% for gentamicin and 40.6% vs 3.7% for amikacin. Resistance levels were somewhat lower for *E. coli*. Resistance (R) proportions for carbapenem-R/I compared to carbapenem-S *E. coli* isolates were 68.1% vs 29.5% for ciprofloxacin, 69.1% vs 33.5% for trimethoprim-sulfamethoxazole, 35.4% vs 15.4% for gentamicin and 15.9% vs 3.0% for amikacin.

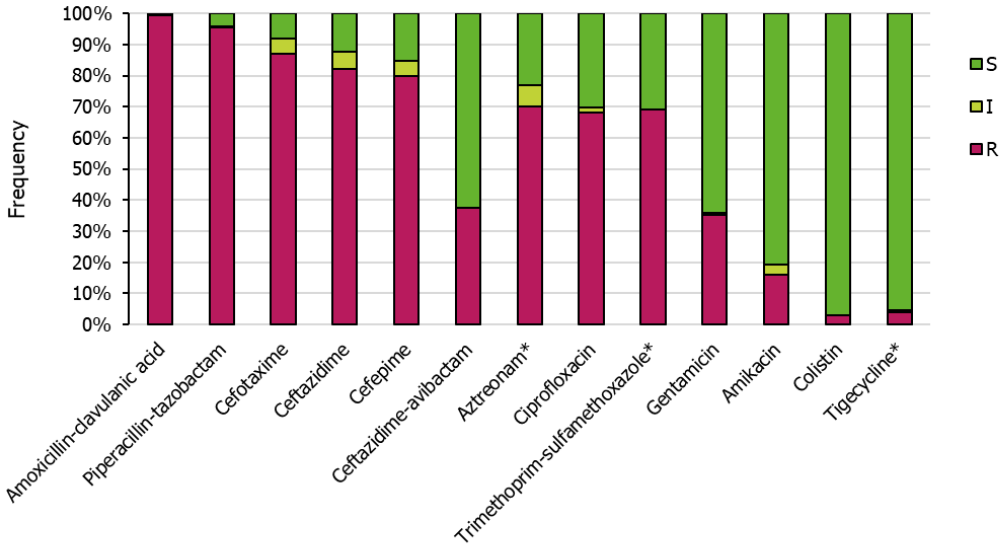
Figure 8. Data completeness for reported phenotypic antimicrobial susceptibility testing results



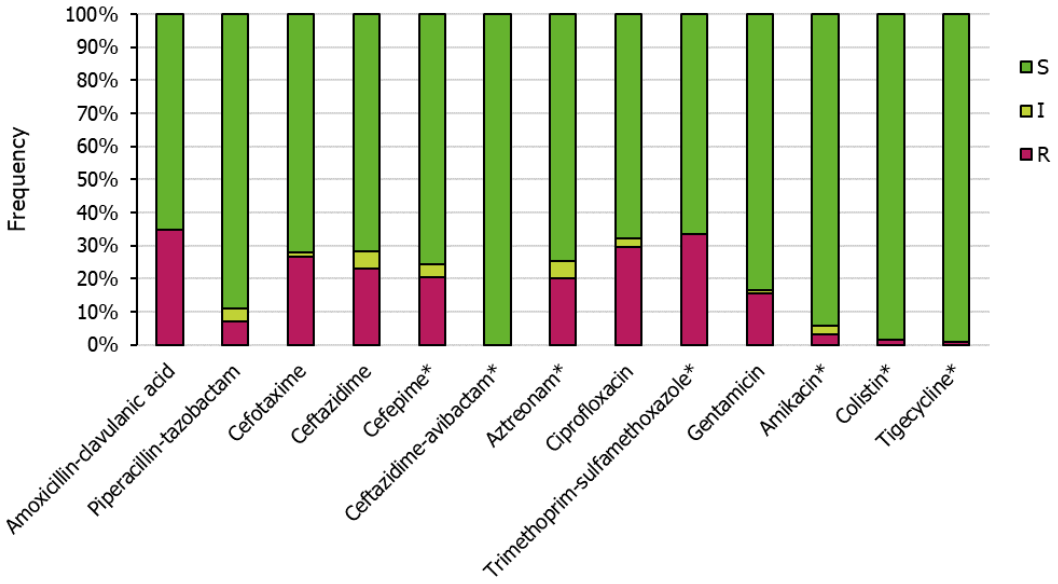
**Minimum AST was defined as AST for ≥1 carbapenem, ≥1 extended-spectrum cephalosporin and ≥1 fluoroquinolone for calculation of difficult-to-treat- and fully drug-resistance. K. pneumoniae SC AST results for tigecycline and fosfomycin were not included in analysis.*

Figure 9 A-D. Phenotypic antimicrobial susceptibility testing results for carbapenem-R/I and carbapenem-S *Escherichia coli* and *Klebsiella pneumoniae* SC isolates

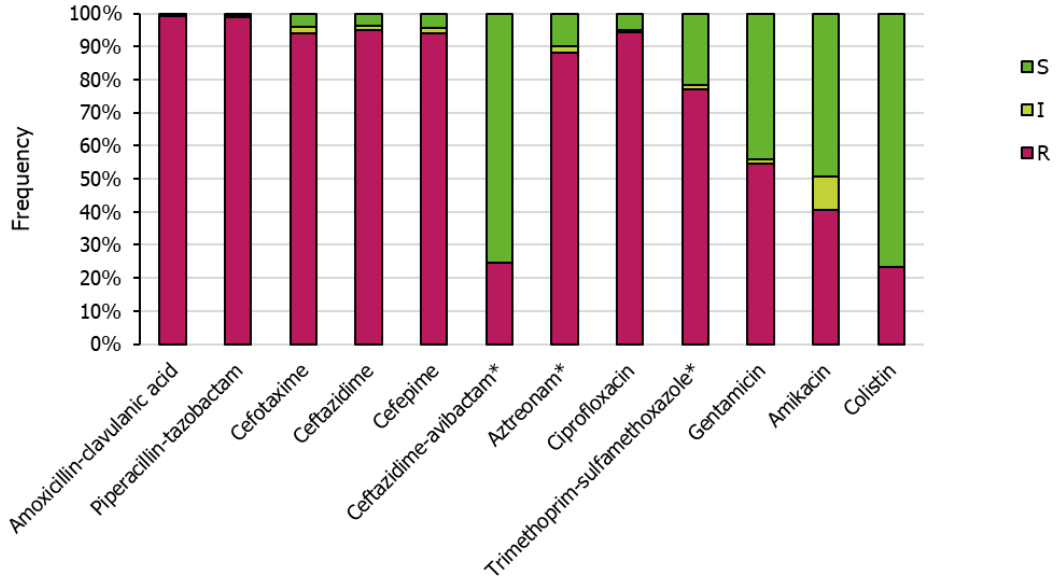
A. Carbapenem-R/I *E. coli*



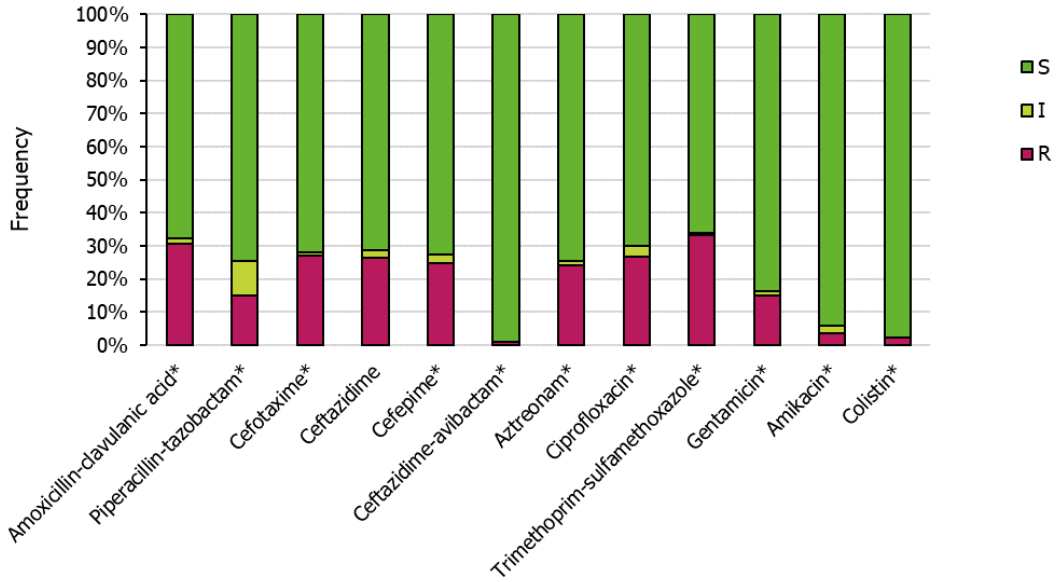
B. Carbapenem-S *E. coli*



C. Carbapenem-R/I *K. pneumoniae* SC



D. Carbapenem-S *K. pneumoniae* SC



**Antimicrobials with AST-results available for <75% of isolates are marked with an asterisk.*
Note: Susceptibility interpretation is according to reported AST, performed and interpreted by the NRLs, according to EUCAST breakpoint table v9.0, 2019.
Graphs show the proportion of S, R and I out of tested isolates. The number of isolates with AST varies between antibiotic agents, see figure 8 for data completeness for each group and antimicrobial agent. For colistin breakpoints are in brackets since the EUCAST breakpoint table v12.0, 2022 which means that for isolates categorised as colistin S in the graphs, combination treatment with another active agent would be required.

As expected, resistance to other antibiotics varied between isolates with different carbapenemases. Co-resistance to other antimicrobials such as ciprofloxacin, trimethoprim-sulfamethoxazole and aminoglycosides were most frequent in isolates carrying *bla*$_{NDM}$, and least frequent in isolates carrying *bla*$_{OXA-48-like}$ carbapenemase genes. Since avibactam has no inhibitory effect on metallo-beta-lactamases (MBL), it is expected that isolates with *bla*$_{NDM}$ or *bla*$_{VIM}$ are resistant to ceftazidime-avibactam. In *E. coli*, ceftazidime-avibactam resistance was explained by the carriage of MBL genes for all isolates and not detected in any isolates carrying only *bla*$_{OXA-48-like}$ or *bla*$_{KPC}$. However, 7.6% of tested *K. pneumoniae* SC isolates with *bla*$_{KPC}$ and 3.2% of tested *K. pneumoniae* SC isolates with *bla*$_{OXA-48}$-like were resistant to ceftazidime-avibactam. In these isolates, *bla*$_{KPC-3}$ was the most common carbapenemase (Table 9). Ceftazidime-avibactam resistance was found in 13 different STs of *K. pneumoniae* SC not carrying an MBL gene, with ST512 being the most frequent ST.

Table 9. Carbapenemase gene distribution in ceftazidime-avibactam-resistant *Klebsiella pneumoniae* isolates without carriage of metallo-beta-lactamase genes

Carbapenemase gene	Carbapenem-R/I *K. pneumoniae* n	Carbapenem-S *K. pneumoniae* n
bla$_{KPC-2}$	10	-
bla$_{KPC-3}$	23	-
bla$_{KPC-31}$	2	-
bla$_{KPC-58}$	1	-
bla$_{KPC-66}$	1	-
bla$_{KPC-183}$	1	-
bla$_{OXA-48}$	9	-
bla$_{KPC-3}$; *bla*$_{OXA-48}$	1	-
None	10	5

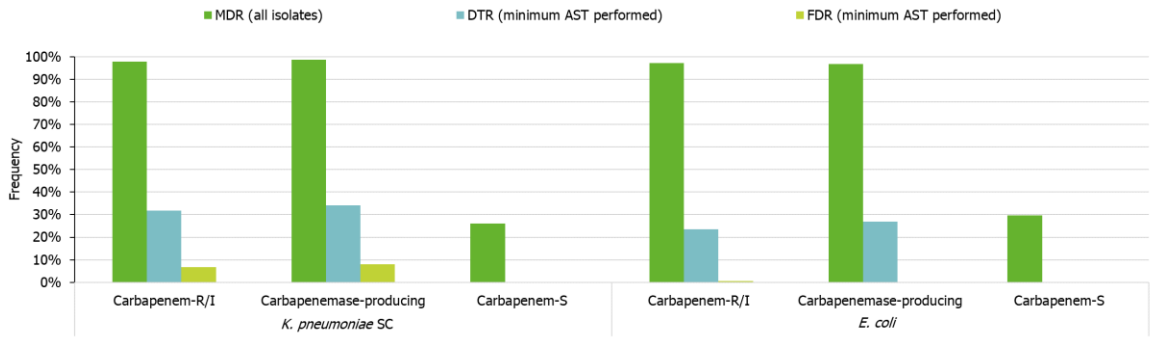
3.4.2.5 Multidrug resistance

The prevalence of multidrug-resistant (MDR) and fully drug-resistant (FDR) isolates as well as isolates with difficult-to-treat resistance (DTR) was examined. The related definitions varied over time and were also affected by the changed EUCAST definition in 2019, when category I-isolates were no longer considered as non-susceptible [22]. On the other hand, in 2020, EUCAST lowered the R-breakpoint for aminoglycosides reclassifying isolates previously categorised as I to R [47]. Moreover, the categorisations are heavily influenced by the number and choice of antimicrobials tested at the NRLs. Hence, the definitions for MDR, FDR and DTR were applied as described in the original CCRE analysis plan. The analysis is based on the S/I/R-interpretation reported by each NRL (except for carbapenems as described above) and has not been confirmed with central testing.

MDR defined as R or I to at least one agent from three or more antimicrobial categories (excluding intrinsic resistance), as described by Magiorakos *et al.* in 2012 [21], was observed in 97.8% of carbapenem-R/I *K. pneumoniae* SC and 97.2% of carbapenem-R/I *E. coli* isolates. MDR was also common in the carbapenem-S isolates, present in 26.1% and 29.7% of *K. pneumoniae* SC and *E. coli,* respectively (Figure 10 and Annex Table A5d).

For isolates with a minimum set of available AST results, i.e. AST performed for at least ≥1 carbapenem, ≥1 extended-spectrum cephalosporin and ≥1 fluoroquinolone, the frequency of isolates with DTR (defined as R/I to all beta-lactams and fluoroquinolones [48]) and FDR (defined as R/I to all tested antimicrobials, for *K. pneumoniae* disregarding reported AST results for tigecycline and fosfomycin) was calculated. For carbapenem-R/I *K. pneumoniae* SC, 95% of isolates had minimum AST results as per the definition above. Of these, 31.7% were classified as having DTR and 7.5% (91 isolates) as FDR. Among carbapenemase-producing isolates, the frequencies of isolates with DTR and FDR isolates were slightly higher (34.2% and 7.9%, respectively). In carbapenem-R/I *E. coli*, 86% had minimum AST results, of which 23.6% had DTR and only one isolate (0.5%) was classified as FDR. As the inclusion criteria for carbapenem-S isolates included susceptibility for all tested carbapenems, none of the carbapenem-S isolates were classified as having DTR or were FDR.

Figure 10. Frequency of multidrug-resistant, difficult-to-treat and fully drug-resistant isolates in *Klebsiella pneumoniae* SC and *Escherichia coli* isolates



The frequency of multidrug-resistance (R/I to at least one agent from three or more antimicrobial categories, excluding intrinsic resistance) was calculated for all isolates. Difficult-to-treat resistant bacteria (R/I to all ß-lactams and fluoroquinolones) and fully drug-resistance (R/I to all tested antimicrobials) was based only on isolates with minimum AST results, defined as AST for ≥1 carbapenem, ≥1 extended-spectrum cephalosporin and ≥1 fluoroquinolone. The number of isolates with minimum AST results/total number of isolates were for carbapenem-R/I K. pneumoniae SC: 1484/1531; carbapenemase-producing K. pneumoniae SC 1339/1379; carbapenem-S K. pneumoniae SC 1014/1407; carbapenem-R/I E. coli 182/211; carbapenemase-producing E. coli 157/182; carbapenem-S E. coli 258/337.

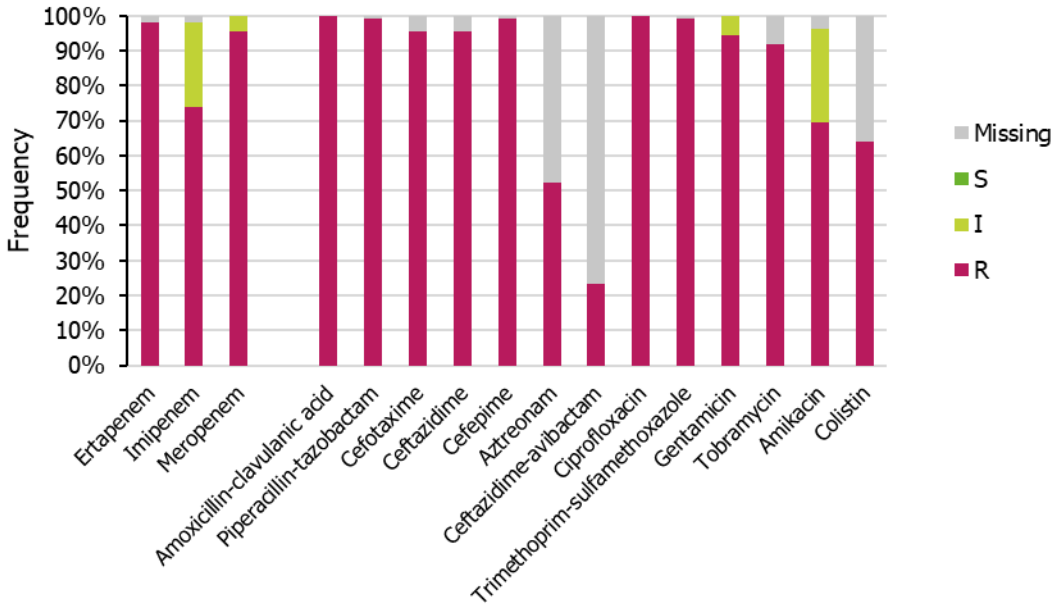
3.4.2.6 Fully drug-resistant isolates

In total, 111 *K. pneumoniae* SC isolates and one *E. coli* isolate were classified as FDR among isolates with AST performed for ≥1 carbapenem, ≥1 extended-spectrum cephalosporin and ≥1 fluoroquinolone. The variable number of agents tested affected the classification of FDR. Reported AST results for tigecycline and fosfomycin were disregarded since EUCAST breakpoints for tigecycline for *K. pneumoniae* were removed in the 2019 breakpoint table and AST for fosfomycin is no longer recommended (EUCAST breakpoint table 2024). EUCAST breakpoints for colistin are in brackets since 2022, thus isolates reported as colistin S in this report imply that colistin could only be used in combination therapy and must be supported by another active antimicrobial. Importantly, the CCRE survey did not include AST for newer agents such as imipenem-relebactam, meropenem-vaborbactam and cefiderocol, which were not widely available in 2019. Isolates classified as FDR could therefore still be susceptible to one or several of these newer agents; however, this mainly applies to the few FDR isolates not carrying MBL genes.

Figure 11A shows the completeness of AST results for *K. pneumoniae* SC isolates classified as FDR (n=111). Of these isolates, 64% had an AST result (R) for colistin, while only 23% had AST results (R) for ceftazidime-avibactam. For amikacin, 27% were classified as I; however, amikacin monotherapy would not have been an option for those isolates. Due to EUCAST breakpoint changes in 2020, isolates classified as I for aminoglycosides in 2019 (MIC breakpoint for amikacin S≤8, R>16 mg/L, gentamicin S≤2, R>4 mg/L) would be classified as R from 2020 onwards (MIC breakpoint amikacin S≤8, R>8 mg/L, gentamicin S≤2, R>2).

The 111 FDR *K. pneumoniae* SC isolates represented 20 different STs (Figure 11B), of which ST101 was the most common (36 isolates, 32%), followed by ST11 (20 isolates, 18%). Among the 85 isolates lacking AST for ceftazidime-avibactam, the most common carbapenemase gene was *bla*$_{\text{OXA-48}}$ (45 isolates) of which most belonged to ST101 (n=32) or ST437 (n=8). It is likely that at least some of these isolates would be susceptible to ceftazidime-avibactam and perhaps colistin, if tested. Out of the 45 *bla*$_{\text{OXA-48}}$ isolates without AST results for ceftazidime-avibactam, 20 isolates were also resistant to colistin while 25 isolates lacked AST results for colistin. For isolates carrying *bla*$_{\text{NDM-1,}}$ ceftazidime-avibactam is not an alternative, regardless if is tested or not. Seventeen of the ST11 isolates carrying *bla*$_{\text{NDM-1}}$ were colistin resistant, while two lacked colistin AST results.

Figure 11A. Antimicrobial susceptibility testing results for fully drug-resistant *Klebsiella pneumoniae* SC isolates (n=111)

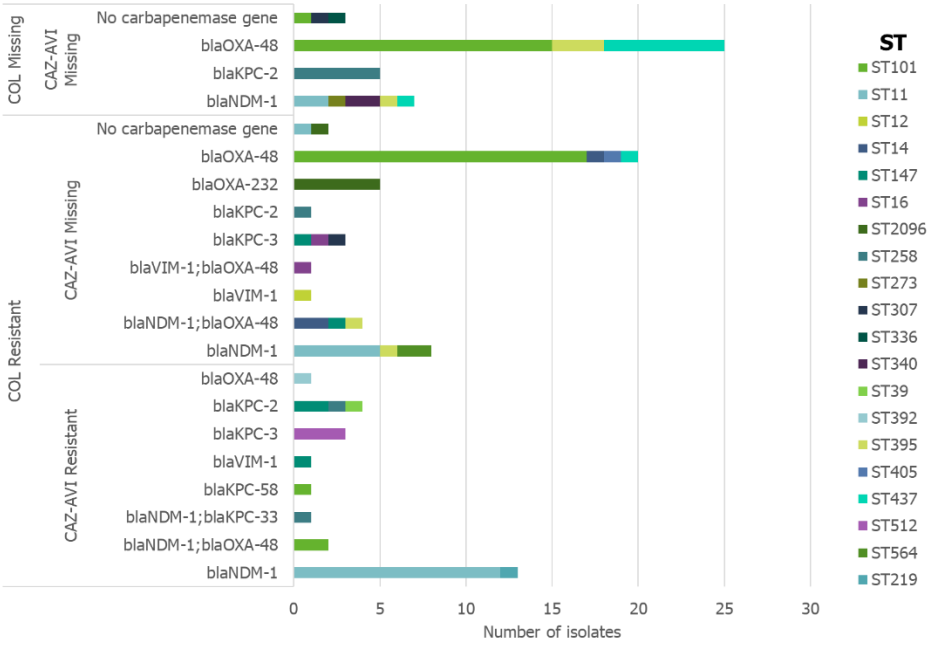


Note: Susceptibility is presented according to reported AST, performed and interpreted by the NRLs, according to EUCAST breakpoint table v9.0, 2019 (except for carbapenems, see method section). Graphs show the proportion of S, R and I out of tested isolates. Due to breakpoint changes, isolates classified as I for aminoglycosides in 2019 (MIC breakpoint for amikacin S≤8, R>16 mg/L, gentamicin S≤2, R>4 mg/L) would be classified as R from 2020 (MIC breakpoint amikacin S≤8, R>8 mg/L, gentamicin S≤2, R>2). Hence, aminoglycosides would not be a treatment option for the isolates categorised as I for aminoglycosides in the Figure. Note that for colistin, breakpoints are in brackets since the later version of EUCAST breakpoint table v12.0, 2022. For an isolate categorised as colistin S, combination with another active agent would be required.

Twenty-six *K. pneumoniae* SC isolates were classified as FDR and had results for both colistin and ceftazidime-avibactam. Details of these isolates are presented in Table 9 in the Annex. All except three of these isolates originated from clinical samples, and seven were from blood cultures indicating invasive infection. Sixteen of these FDR isolates carried $bla_{\text{NDM-1}}$ of which 12 belonged to ST11, while nine isolates carried carbapenemase genes other than MBL genes including $bla_{\text{KPC-2}}$, $bla_{\text{KPC-3}}$, $bla_{\text{KPC-58}}$ and $bla_{\text{OXA-48}}$. Ceftazidime-avibactam resistance has been associated with $bla_{\text{KPC-31}}$ [49]. Truncation of the colistin resistance-associated *mgrB* gene was detected in 15 isolates, but *mcr* genes were not identified.

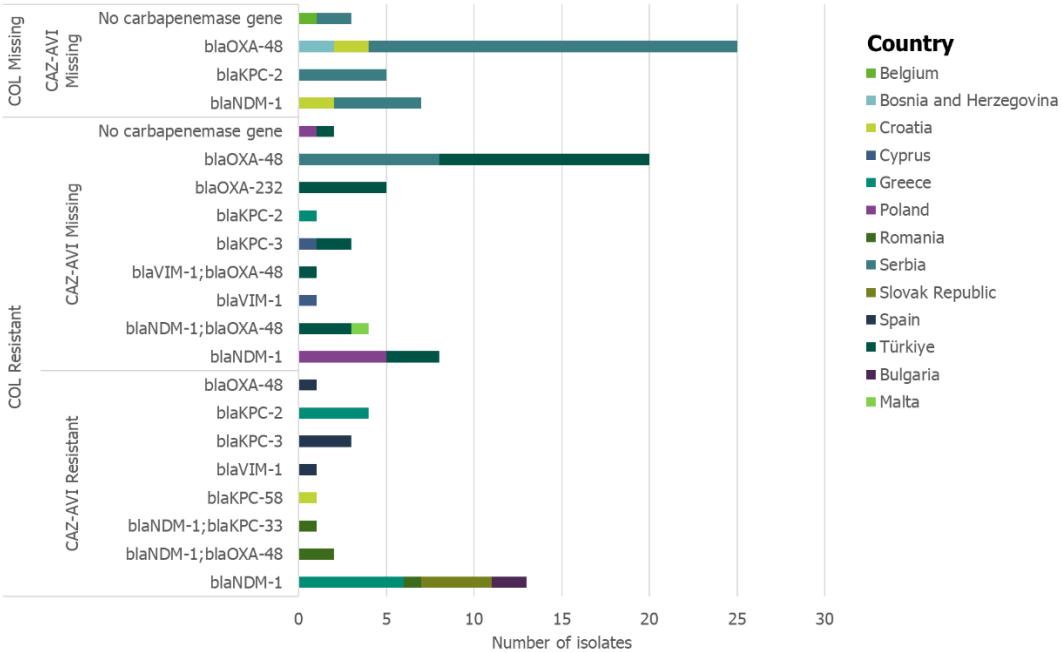
Overall, the 26 FDR *K. pneumoniae* SC isolates that were resistant to both colistin and ceftazidime-avibactam originated from six countries including Greece (n=10), Spain (n=5), Slovakia (n=4), Romania (n=4), Bulgaria (n=2) and Croatia (n=1) (Table A9 in the Annex). The single *E. coli* isolate classified as FDR was resistant to colistin (MIC 8 mg/L), but did not have AST results for tigecycline, fosfomycin and ceftazidime-avibactam. The isolate originated from a clinical urinary tract sample, belonged to ST648 and did neither carry carbapenemase nor extended-spectrum beta-lactamase (ESBL) genes.

Figure 11B. Carbapenemase genes and sequence types for fully drug-resistant *Klebsiella pneumoniae* SC FDR isolates (n=111)



Carbapenemase genes in K. pneumoniae SC *FDR isolates, stratified by resistance or missing AST results for colistin and ceftazidime-avibactam. The classification of an isolate as FDR is affected by the availability of AST results for colistin and ceftazidime-avibactam as these agents retain activity in many isolates resistant to other agents. Note that for colistin, breakpoints are in brackets since EUCAST breakpoint table v12.0, 2022.*
COL, colistin; CAZ-AVI, ceftazidime-avibactam; FDR, fully drug-resistant;

Figure 11C. Carbapenemase genes and country for *Klebsiella pneumoniae* SC FDR isolates (n=111)



Carbapenemase in detected K. pneumoniae SC *FDR isolates, stratified by resistance or missing AST results for colistin and ceftazidime-avibactam. The classification of an isolate as FDR is affected by the availability of AST results for colistin and ceftazidime-avibactam since these agents retain activity in many isolates resistant to other agents. COL, colistin; CAZ-AVI, ceftazidime-avibactam; FDR, fully drug-resistant; Note that for colistin, breakpoints are in brackets since EUCAST breakpoint table v12.0, 2022.*

3.5 Whole genome sequencing results

3.5.1 Species distribution

The species designations of all Enterobacterales included in the CCRE survey (n=3 521), as determined from the assembled genomes, were concordant with those provided by the NRLs (any discordant isolates were discarded as described above). These comprised 2 973 *K. pneumoniae* SC and 548 *E. coli* isolates (Table 10). The *K. pneumoniae* SC isolates were from four species including *K. pneumoniae*, *K. quasipneumoniae*, *K. variicola* and *K. quasivariicola*. The *K. quasipneumoniae* isolates could further be divided into two subspecies, *K. quasipneumoniae subsp. quasipneumoniae* and *K. quasipneumoniae subsp. similipneumoniae*. A total of 98.7% (1 545/1 566) and 91.6% (1 289/1 407) of the carbapenem-R/I and carbapenem-S *K. pneumoniae* SC isolates, respectively, belonged to *K. pneumoniae* (Table 10).

Table 10. Species distribution for *Klebsiella pneumoniae* SC and *Escherichia coli* isolates (n=3 521)

Species/subspecies		Carbapenem-R/I isolates n	Carbapenem-S isolates n	Total n
K. pneumoniae SC	All	1 566	1 407	2 973
	K. pneumoniae	1 545	1 289	2 834
	K. quasipneumoniae subsp. quasipneumoniae	4	23	27
	K. quasipneumoniae subsp. similipneumoniae	8	15	23
	K. variicola	9	79	88
	K. quasivariicola	0	1	1
E. coli	All	211	337	548
Total		1 777	1 744	3 521

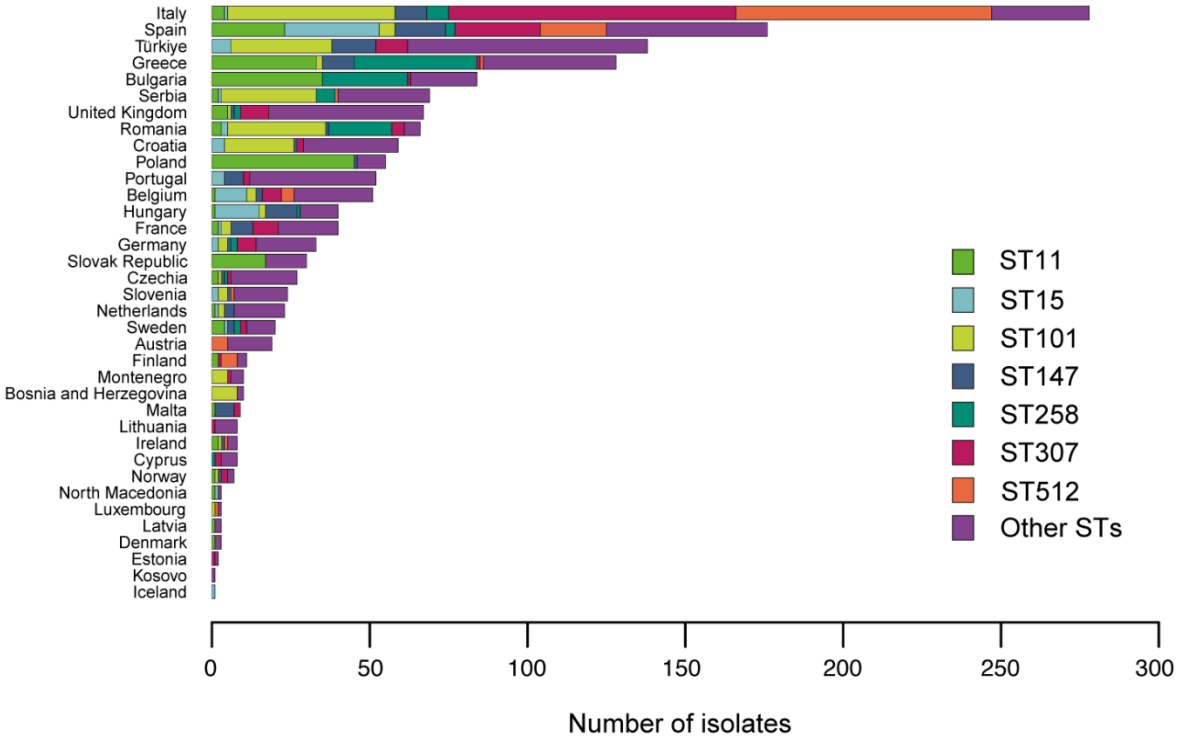
3.5.2 Sequence type distribution

STs could be unambiguously determined for 98.3% (2 922/2 973) of *K. pneumoniae* SC isolates and 100% (548/548) of *E. coli* isolates (Table 11). These included 53 novel STs from the *K. pneumoniae* SC and 12 novel STs of *E. coli*, which were newly assigned by BIGSdb-Pasteur and Enterobase, respectively. The carbapenem-R/I *K. pneumoniae* SC isolates (which all use the same scheme) belonged to a total of 152 different STs, of which the most common all belonged to *K. pneumoniae* and included ST258/ST512 (14.8%; 232/1 566), ST101 (13.3%; 209/1 566), ST11 (11.9%; 187/1 566), ST307 (11.5%; 180/1 566), ST147 (6.1%; 95/1 566) and ST15 (5.2%; 81/1 566) (Table 12). ST258 and ST512, which are single locus variants, are grouped together as they have been shown to form a single clone with no significant evolutionary separation between them [9]. Together, these six ST groupings comprised 62.8% (984/1 566) of carbapenem-R/I *K. pneumoniae* SC isolates. They were geographically widespread across the EU/EEA region, having each been isolated from between 18 and 28 countries, considering both carbapenem-R/I and -S groups (see Figure 12 and Annex Table 7a for full country distributions). The *K. pneumoniae* SC carbapenem-S isolates were more diverse as they belonged to 478 different STs, of which the most common were ST307 (4.4%; 62/1 407), ST35 (3.4%; 48/1 407), ST37 (3.0%; 42/1 407), ST45 (3.0%; 42/1 407) and ST20 (2.8%; 40/1 407). These were isolated from between 14 and 28 countries, considering both carbapenem-R/I and -S groups (see Annex Table 7a).

Table 11. Sequence types among carbapenem-R/I and carbapenem-S *Klebsiella pneumoniae* SC and *Escherichia coli* isolates

Species	Isolates in final dataset n	Isolates with designated ST n (%)	Different STs n
K. pneumoniae SC			
All isolates	2 973	2 922 (98.3)	538
Carbapenem-R/I isolates	1 566	1 552 (99.1)	152
Carbapenem-S isolates	1 407	1 370 (97.4)	478
E. coli			
All isolates	548	548 (100)	146
Carbapenem-R/I isolates	211	211 (100)	74
Carbapenem-S isolates	337	337 (100)	101

Figure 12. Country distribution of major sequence types detected among carbapenem-R/I *Klebsiella pneumoniae* SC isolates (n=1 566)*



**The raw data used for this figure is available in Annex Table 7a.*

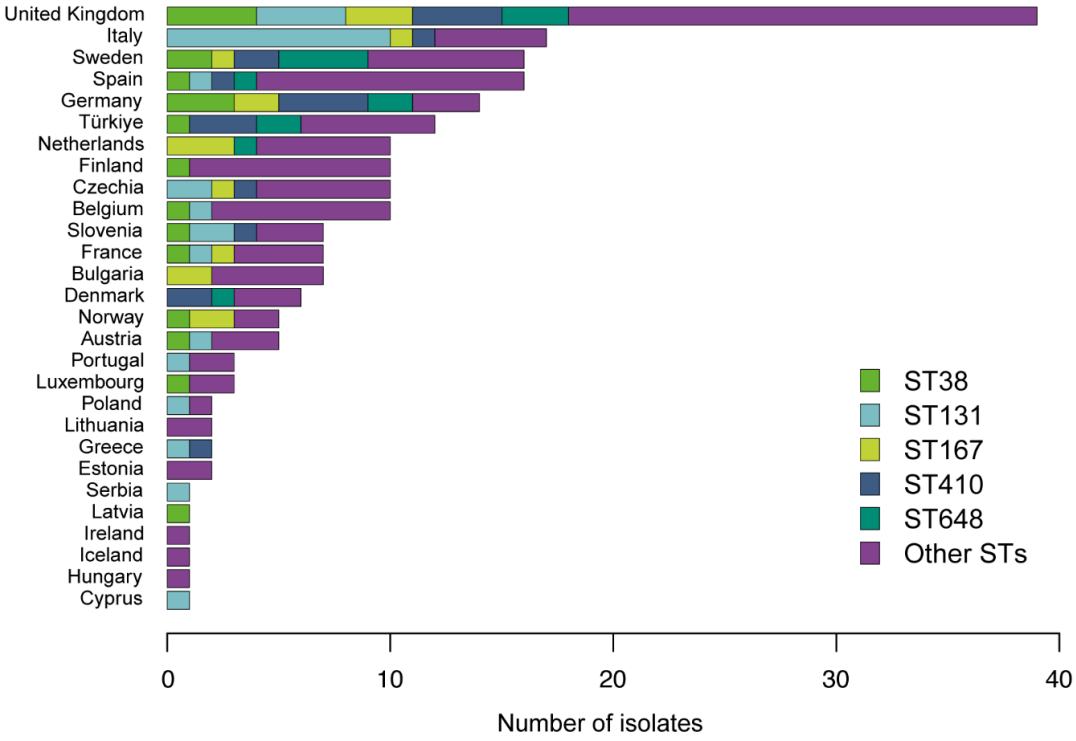
Table 12. Geographic distribution and major carbapenemase gene variants among the most common sequence types (STs) of carbapenem-R/I *Klebsiella pneumoniae* SC (n=2 973)

ST	Isolates n (%)	Carbapenem-R/I isolates n (%)	Countries (all isolates) n	Countries with ≥10% of isolates (n)	Hospitals (all isolates) n	Carbapenemase gene variants found in ≥10% of isolates of this ST (n)
ST307	242 (8.1)	180 (11.5)	28	Italy (n=103), Spain (n=33)	108	bla_{KPC-3} (n=91), bla_{OXA-48} (n=38)
ST258/ 512	237 (8.0)	232 (14.8)	18	Bulgaria (n=28), Greece (n=42), Italy (n=90), Spain (n=24)	72	bla_{KPC-2} (n=92), bla_{KPC-3} (n=131)
ST258	114 (3.8)	111 (7.1)	12	Bulgaria (n=28), Greece (n=41), Romania (n=20)	37	bla_{KPC-2} (n=92), bla_{KPC-3} (n=14)
ST512	123 (4.1)	121 (7.7)	10	Italy (n=83), Spain (n=21)	41	bla_{KPC-3} (n=117)
ST101	216 (7.3)	209 (13.3)	21	Croatia (n=22), Italy (n=53), Romania (n=32), Serbia (n=31), Türkiye (n=32)	89	bla_{KPC-2} (n=34), bla_{KPC-3} (n=32), bla_{OXA-48} (n=119)
ST11	202 (6.8)	187 (11.9)	23	Bulgaria (n=37), Greece (n=37), Poland (n=47), Spain (n=26)	73	bla_{NDM-1} (n=136), bla_{OXA-48} (n=29)
ST147	110 (3.7)	95 (6.1)	21	Greece (n=11), Italy (n=11), Spain (n=17), Türkiye (n=18)	57	bla_{KPC-3} (n=13), bla_{NDM-1} (n=37), bla_{OXA-48} (n=21)
ST15	105 (3.5)	81 (5.2)	20	Belgium (n=11), Hungary (n=14), Spain (n=33)	59	bla_{OXA-48} (n=50), bla_{VIM-4} (n=13)

In *E. coli*, the carbapenem-R/I isolates belonged to 74 different STs, of which the most common were ST131 (12.8%; 27/211), ST410 (9.5%; 20/211), ST38 (9.0%; 19/211), ST167 (7.6%; 16/211) and ST648 (6.6%; 14/211) (Table 13). These five STs together comprised 45.5% (96/211) of the carbapenem-R/I isolates. They were each found in between eight and 21 countries, taking into account both carbapenem-R/I and -S groups (see Figure 13

and Annex Table 7b for full country distributions). The carbapenem-S *E. coli* isolates belonged to 101 different STs. The most common were ST131 (16.6%; 56/337), ST69 (8.9%; 30/337), ST73 (8.6%; 29/337), ST95 (4.7%; 16/337) and ST141 (3.9%; 13/337). These were isolated from between nine and 21 countries, including both carbapenem-R/I and -S groups (see Annex Table 7b).

Figure 13. Country distribution of major sequence types detected among carbapenem-R/I *Escherichia coli* isolates (n=211)*



**The raw data used for this figure is available in Annex Table 7b.*

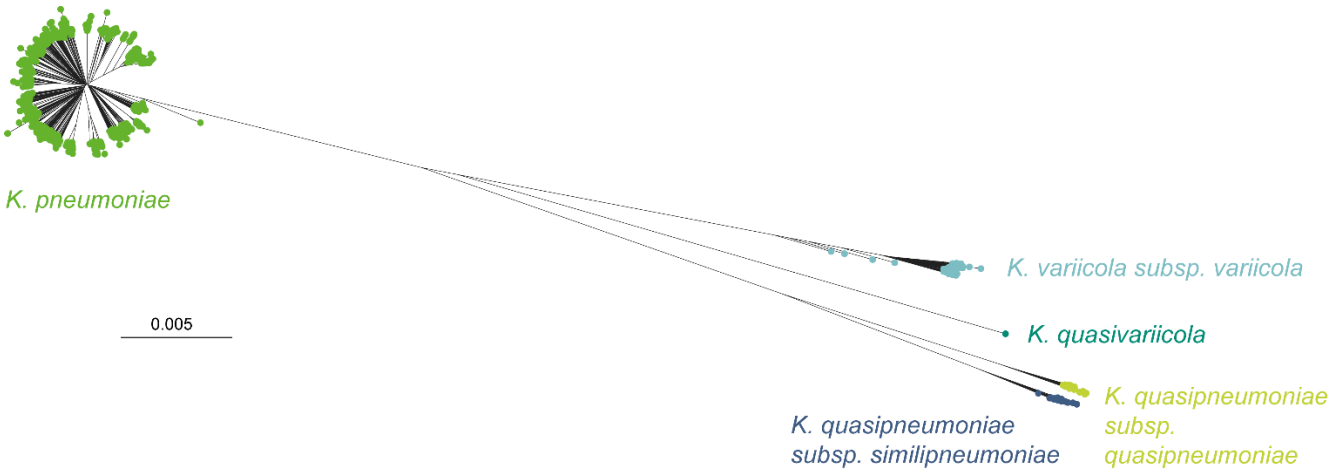
Table 13. Geographic distribution and major carbapenemase gene variants among the most common sequence types (STs) of carbapenem-R/I *Escherichia coli* (n=548)

ST	Isolates n (%)	Carbapenem-R/I isolates n (%)	Countries (all isolates) n	Countries with ≥10% of isolates n	Hospitals (all isolates) n	Carbapenemase gene variants found in ≥10% of isolates of this ST (n)
ST131	83 (15.1)	27 (12.8)	21	Italy (n=21), Türkiye (n=11), UK (n=11)	58	bla_{KPC-3} (n=10)
ST38	24 (4.4)	19 (9.0)	15	Germany (n=3), UK (n=4)	22	$bla_{OXA-244}$ (n=9), bla_{OXA-48} (n=6)
ST410	22 (4.0)	20 (9.5)	10	Germany (n=4), Türkiye (n=3), UK (n=5)	21	bla_{NDM-5} (n=7), $bla_{OXA-181}$ (n=6), bla_{OXA-48} (n=3)
ST648	19 (3.5)	14 (6.6)	8	France (n=2), Germany (n=3), Sweden (n=5), Türkiye (n=3), UK (n=3)	17	bla_{NDM-5} (n=9), bla_{OXA-48} (n=3)
ST167	16 (2.9)	16 (7.6)	9	Bulgaria (n=2), Germany (n=2), Netherlands (n=3), Norway (n=2), UK (n=3)	15	bla_{NDM-1} (n=2), bla_{NDM-5} (n=14)

3.5.3 Population structure

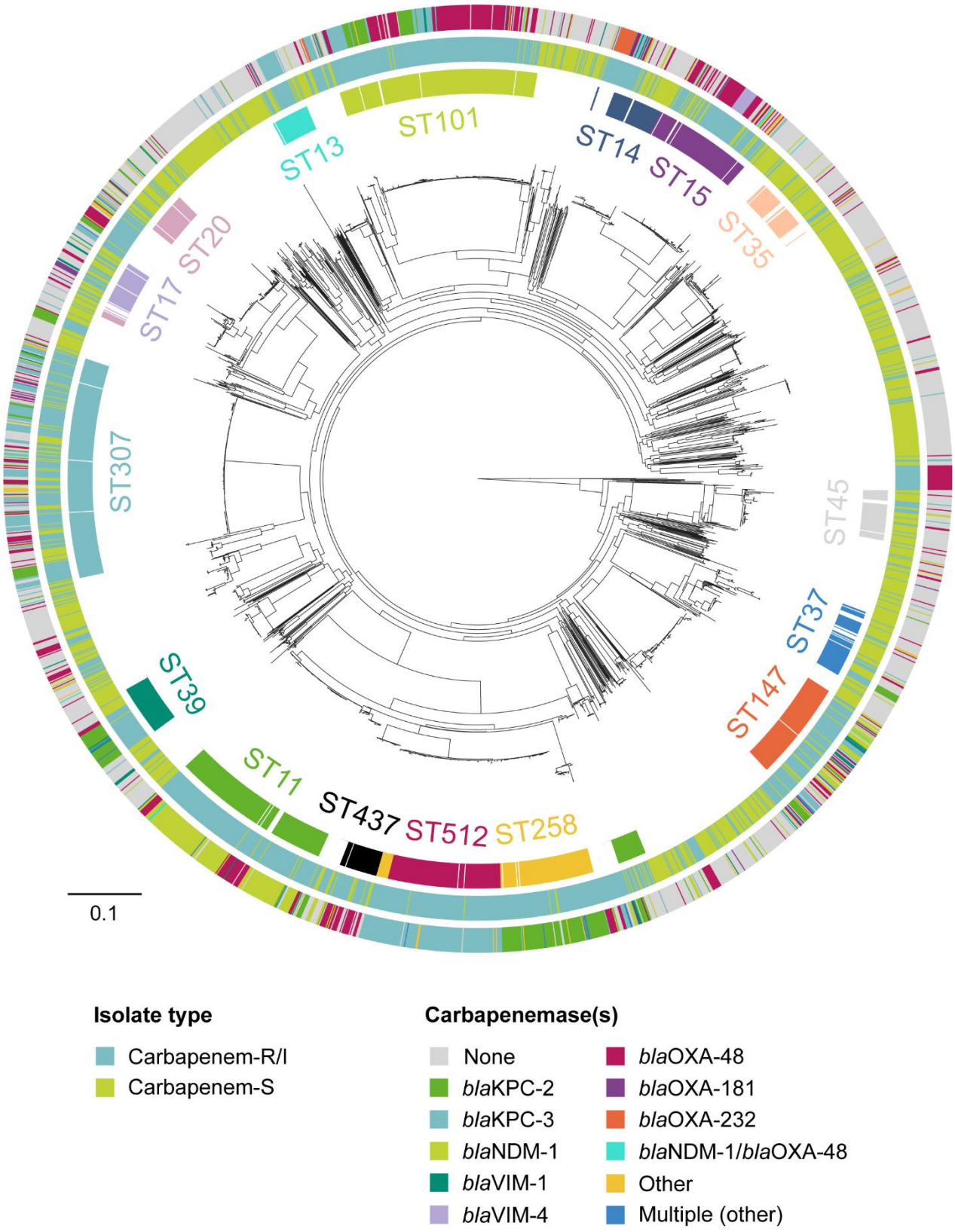
A tree of all 2973 *K. pneumoniae* SC isolates generated using Mashtree [30] showed a clear division by species and subspecies (Figure 14). A phylogenetic tree of the *K. pneumoniae* isolates only (n=2 834) generated with RAxML-NG [29] demonstrated numerous distinct lineages (Figure 15), reflecting the high number of STs identified across the species. Carbapenem-R/I isolates were mostly concentrated in different clonal lineages distributed across the species, representing major high-risk STs including those described above.

Figure 14. Mash tree of *Klebsiella pneumoniae* SC isolates (n = 2 973)



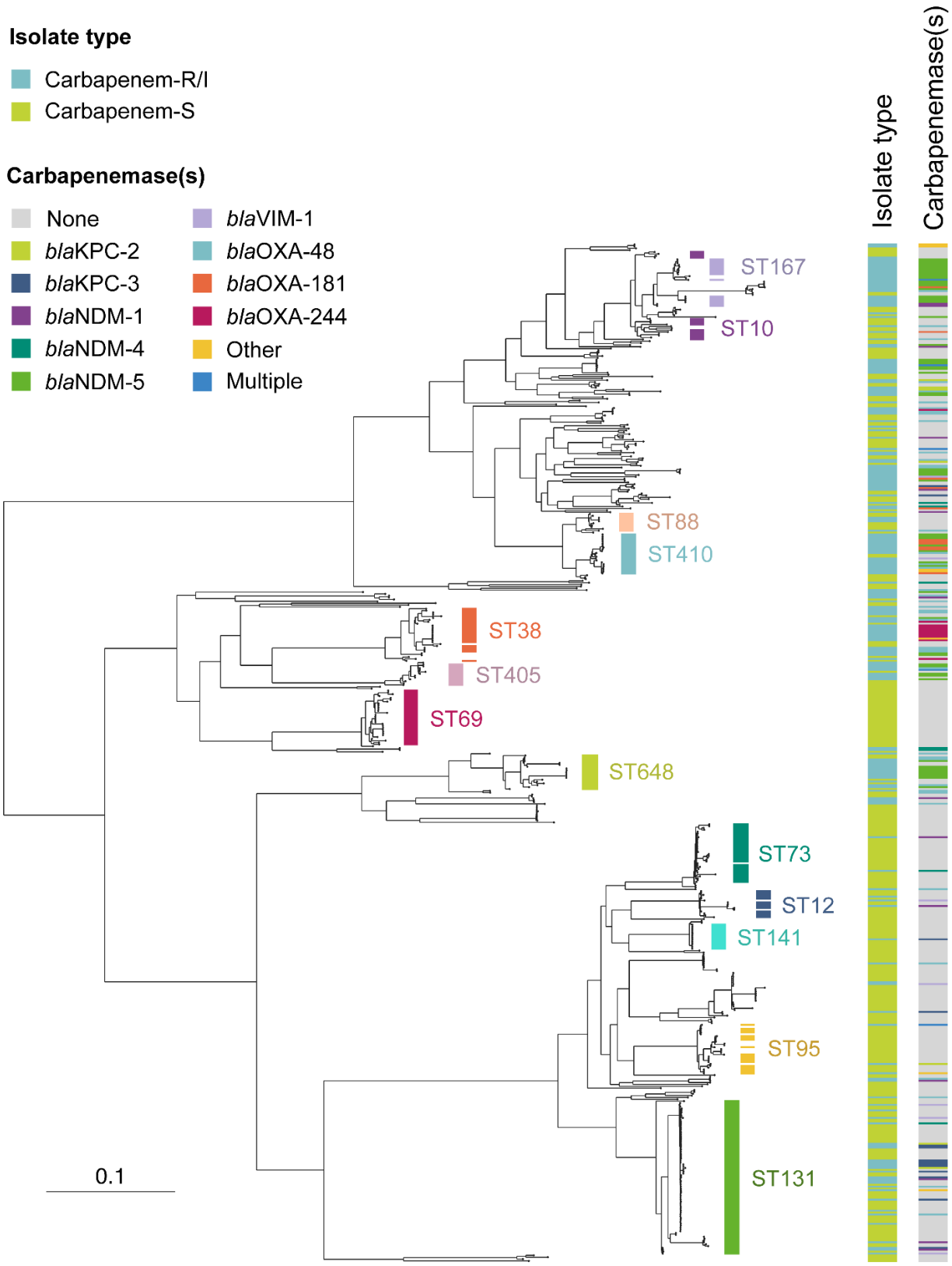
Isolates are coloured by species/subspecies. The scale bar represents the Mash distance between isolates. An interactive version of the tree with additional metadata and genotyping data is available at: https://microreact.org/project/klebsiella-ccre-survey

Figure 15. Phylogenetic tree of *Klebsiella pneumoniae* isolates (n= 2 834) with major sequence types highlighted on the tree and metadata rings showing the isolate type (carbapenem-R/I or -S) and carbapenemase gene



The scale bar represents the numbers of SNPs per variable site. An interactive version of the tree with additional metadata and genotyping data is available at: https://microreact.org/project/kpneumoniae-ccre-survey

Figure 16. Phylogenetic tree of *Escherichia coli* isolates (n=548) with major sequence types highlighted on the tree and metadata columns showing the isolate type (carbapenem-R/I or -S) and carbapenemase gene



The scale represents the number of SNPs per variable site. An interactive version of the tree with additional metadata and genotyping data is available at: https://microreact.org/project/ecoli-ccre-survey

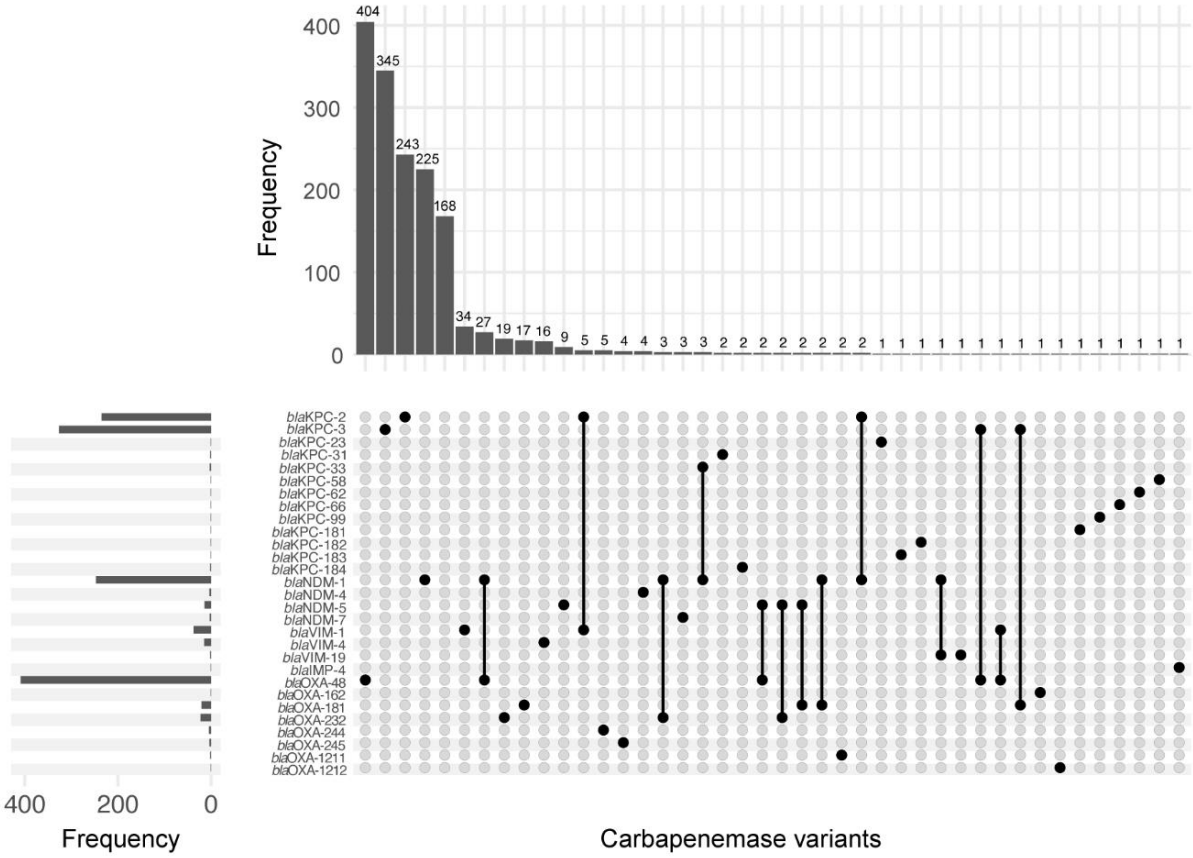
A phylogenetic tree of all 548 *E. coli* isolates also showed high diversity (Figure 16). Clonal lineages representing high-risk STs enriched with carbapenem-R/I isolates were observed, although the dominance of these lineages was not as pronounced as for the major high-risk clones observed among *K. pneumoniae*. We also found that it was common to have isolates from different STs nested among isolates from some of the high-risk STs (e.g. ST167, ST38), possibly reflecting the high genomic diversity among these lineages.

3.5.4 Distribution of carbapenemase gene variants

3.5.4.1 Identification of carbapenemase gene variants

For carbapenem-R/I *K. pneumoniae* SC, 89.3% (1 398/1 566) of genomes carried one or more known or suspected carbapenemase gene variants. These genes were found among all three species with carbapenem-R/I isolates, most notably *K. pneumoniae* (1 384/1 398) but also *K. quasipneumoniae* (8/1 398) and *K. variicola* (6/1 398). A total of 23 known carbapenemase gene variants were found, belonging to the gene families *bla*$_{KPC}$, *bla*$_{NDM}$, *bla*$_{VIM}$, *bla*$_{OXA-48-like}$ and *bla*$_{IMP}$ (Figure 17). The most common were *bla*$_{OXA-48}$ (31.1%; 435/1 398), *bla*$_{KPC-3}$ (24.8%; 347/1 398), *bla*$_{NDM-1}$ (18.8%; 263/1 398) and *bla*$_{KPC-2}$ (17.9%; 250/1 398), which together made up 90.5% (1 265/1 398) of all carbapenem-R/I *K. pneumoniae* SC isolates carrying a carbapenemase gene. A further six variants with high similarity to known carbapenemase genes were newly detected among the carbapenem-R/I *K. pneumoniae* SC isolates in this study and assigned new allele numbers (*bla*$_{KPC-181}$, *bla*$_{KPC-182}$, *bla*$_{KPC-183}$, *bla*$_{KPC-184}$, *bla*$_{OXA-1211}$, *bla*$_{OXA-1212}$). Carbapenemase activities of these new variants have not been further investigated yet. Fifty-two carbapenem-R/I isolates were found to carry two carbapenemase genes; the most common combination was *bla*$_{NDM-1}$/*bla*$_{OXA-48}$ found in 27 isolates. A further ten carbapenem-S *K. pneumoniae* SC isolates (0.7%; 10/1407) also carried a single carbapenemase gene including *bla*$_{OXA-48}$ (n=6), *bla*$_{KPC-2}$ (n=3) and *bla*$_{VIM-1}$ (n=1). All of these isolates except one were not only susceptible according to EUCAST clinical breakpoints but also had a meropenem MIC of ≤0.12 mg/L, below the screening cut-off recommended by EUCAST for suspected carbapenemase production, according to NRL results. None of these isolates were tested by meropenem disk diffusion [24].

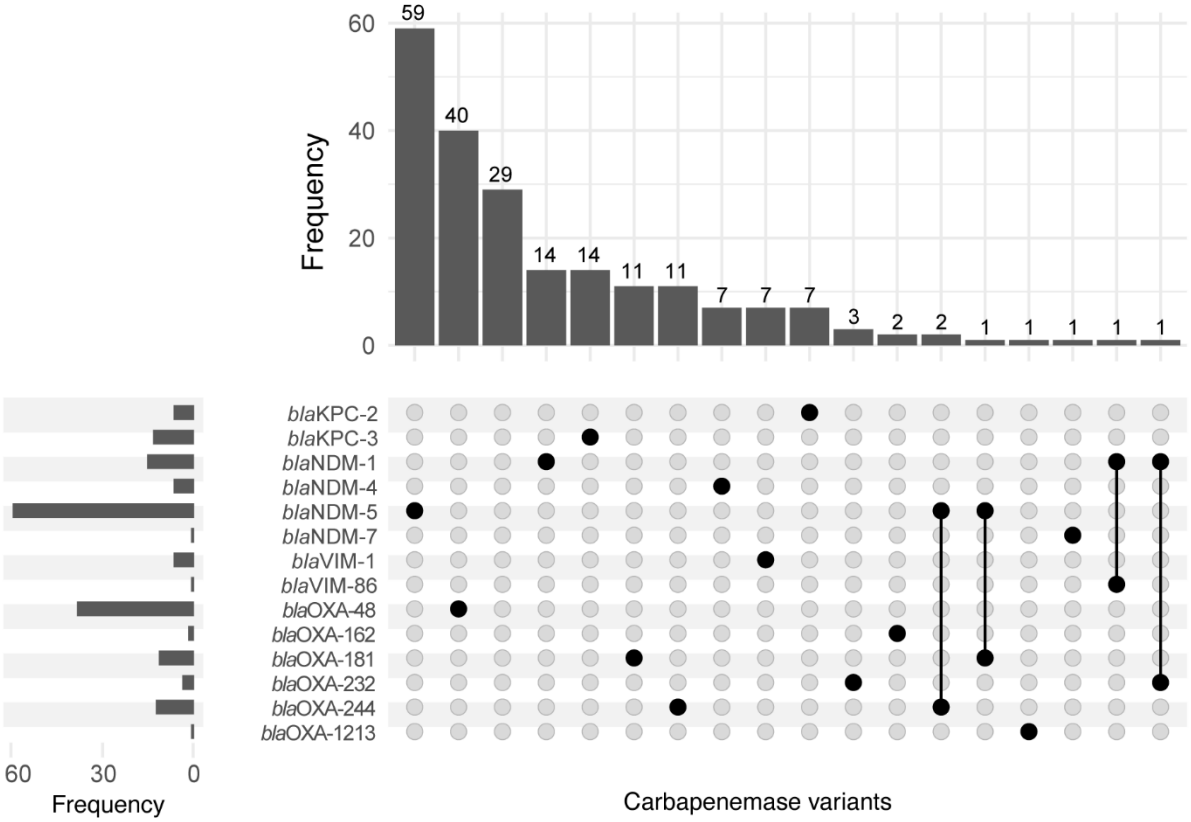
Figure 17. Distribution of carbapenemase gene variants among the carbapenem-R/I *Klebsiella pneumoniae* SC isolates (n=1 566)



The frequencies of all the combinations identified are shown in the upper bar plot, while the frequencies of individual genes are shown on the left.

For carbapenem-R/I *E. coli* , 86.3% (182/211) of the genomes carried one or more known or suspected carbapenemase gene variants. Twelve different known carbapenemase gene variants were found, belonging to the gene families *bla*$_{KPC}$, *bla*$_{NDM}$, *bla*$_{VIM}$ and *bla*$_{OXA-48}$-like (Figure 18). The most common variants were *bla*$_{NDM-5}$ (34.1%; 62/182) and *bla*$_{OXA-48}$ (22.0%; 40/182), which together comprised 56.0% (102/182) of all carbapenem-R/I *E. coli* isolates with a carbapenemase gene. A further two variants with high similarity to known carbapenemase genes were newly detected among the carbapenem-R/I *E. coli* isolates in this study and assigned new allele numbers (*bla*$_{VIM-86}$, *bla*$_{OXA-1213}$). Five carbapenem-R/I *E. coli* genomes were found to contain two carbapenemase genes. A further two carbapenem-S *E. coli* genomes (0.6%; 2/337) also contained a single carbapenemase gene (*bla*$_{OXA-48}$ in both).

Figure 18. Distribution of carbapenemase gene variants the carbapenem-R/I *Escherichia coli* isolates (n=211)



The frequencies of all the combinations identified are shown in the upper bar plot, while the frequencies of individual genes are shown on the left.

3.5.4.2 Geographic distribution of carbapenemase gene variants

Many of the carbapenemase genes found among *K. pneumoniae* SC isolates showed a wide geographic distribution across the EU/EEA, most notably *bla*$_{OXA-48}$, which was identified in isolates from 30 countries and 144 hospitals (Table 14 and Figure 19). *bla*$_{OXA-48}$ was also the most common carbapenemase gene variant among carbapenem-R/I *K. pneumoniae* SC isolates in some countries including Spain (63.1%; 111/176), Serbia (62.3%; 43/69), Croatia (67.8%; 40/59) and Belgium (68.6%; 35/51). *bla*$_{KPC}$ variants dominated in other countries, including *bla*$_{KPC-3}$ in Italy (71.9%; 200/278) and Portugal (80.8%; 42/52), and *bla*$_{KPC-2}$ in Greece (57.0%; 73/128), while most carbapenem-R/I *K. pneumoniae* SC isolates from Poland (74.5%; 41/55) and Slovakia (66.7%; 20/30) carried *bla*$_{NDM-1}$.

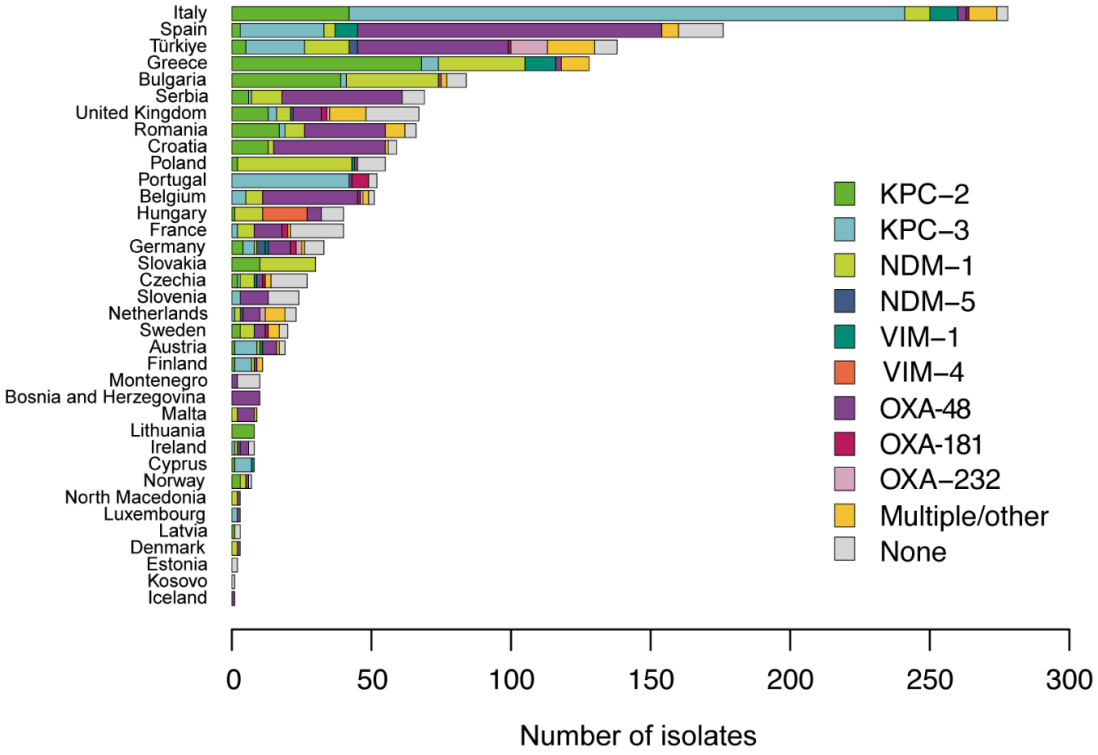
Individual carbapenemase gene variants were distributed widely across different lineages of the *K. pneumoniae* SC (Table 14 and Figure 15). A variety of gene variants from the *bla*$_{\text{OXA-48-like}}$, *bla*$_{\text{KPC}}$, *bla*$_{\text{NDM}}$ and *bla*$_{\text{VIM}}$ families were also identified among *K. quasipneumoniae* and *K. variicola* isolates, as well as in *K. pneumoniae*. The *bla*$_{\text{OXA-48}}$ gene was the most widespread in terms of STs, and was identified among 60 STs within the *K. pneumoniae* SC. However, carbapenemase gene variants were typically associated with one or more of the high-risk STs, in particular those described in section 3.5.2 above, with the specific associations depending on the carbapenemase gene variant (Table 14). These included *bla*$_{\text{KPC-2}}$ with *K. pneumoniae* ST258, *bla*$_{\text{KPC-3}}$ with ST307 and ST512, *bla*$_{\text{NDM-1}}$ with ST11 and ST147, *bla*$_{\text{VIM-4}}$ with ST15 and *bla*$_{\text{OXA-48}}$ with ST101. Notably, we also detected associations of *bla*$_{\text{KPC-2}}$ genes with ST39 and *bla*$_{\text{OXA-232}}$ genes with ST2096, which are two less frequent *K. pneumoniae* SC STs in the collection (comprising 2.6% and 3.7% of the carbapenem-R/I isolates, respectively).

Table 14. Geographical distribution and major sequence types among the most common carbapenemase gene variants across all *Klebsiella pneumoniae* SC isolates (n=2 973)

Carbapenemae gene variant	Isolates n	Carbapenem-R/I isolates n (%)	STs* (all isolates) n	STs with ≥10% of isolates (n)	Countries (all isolates) n	Countries with ≥10% of isolates (n)	Hospitals (all isolates) n
bla$_{\text{KPC-2}}$	253	250 (16.0)	25	ST39 (n=35), ST101 (n=34), ST258 (n=92)	21	Bulgaria (n=40), Greece (n=73), Italy (n=42)	72
bla$_{\text{KPC-3}}$	347	347 (22.2)	38	ST307 (n=91), ST512 (n=117)	20	Italy (n=200), Portugal (n=42)	86
bla$_{\text{NDM-1}}$	263	263 (16.8)	35	ST11 (n=136), ST147 (n=37)	25	Bulgaria (n=34), Greece (n=34), Poland (n=41), Türkiye (n=31)	106
bla$_{\text{NDM-5}}$	15	15 (1.0)	9	ST147 (n=2), ST16 (n=2), ST383 (n=3), ST4069 (n=2)	8	Germany (n=3), Netherlands (n=2), Türkiye (n=3), UK (n=3)	13
bla$_{\text{VIM-1}}$	41	40 (2.6)	19	ST147 (n=8), ST17 (n=4), ST39 (n=5)	9	Greece (n=16), Italy (n=10), Spain (n=9)	23
bla$_{\text{VIM-4}}$	16	16 (1.0)	4	ST15 (n=13)	1	Hungary (n=16)	5
bla$_{\text{OXA-48}}$	441	435 (27.8)	60	ST15 (n=50), ST101 (n=119)	30	Spain (n=115), Türkiye (n=71)	144
bla$_{\text{OXA-181}}$	22	22 (1.4)	13	ST17 (n=6), ST147 (n=2), ST307 (n=3)	9	Belgium (n=2), France (n=2), Germany (n=3), Italy (n=2), Portugal (n=6), UK (n=4)	18
bla$_{\text{OXA-232}}$	24	24 (1.5)	6	ST147 (n=2), ST2096 (n=16), ST231 (n=3)	7	Germany (n=2), Netherlands (n=3), Türkiye (n=13), UK (n=3)	16

*Genes comprising ≥1% of all carbapenemase genes are shown. Isolates with multiple carbapenemase gene variants are included and thus may be counted in multiple rows. *Isolates with no fully designated ST were excluded from the ST counts.*

Figure 19. Country distribution of carbapenemase gene variants detected among carbapenem-R/I *Klebsiella pneumoniae* SC isolates (n=1 566)



Genes comprising ≤1% of all carbapenemase genes are included in the 'Multiple/other' category.

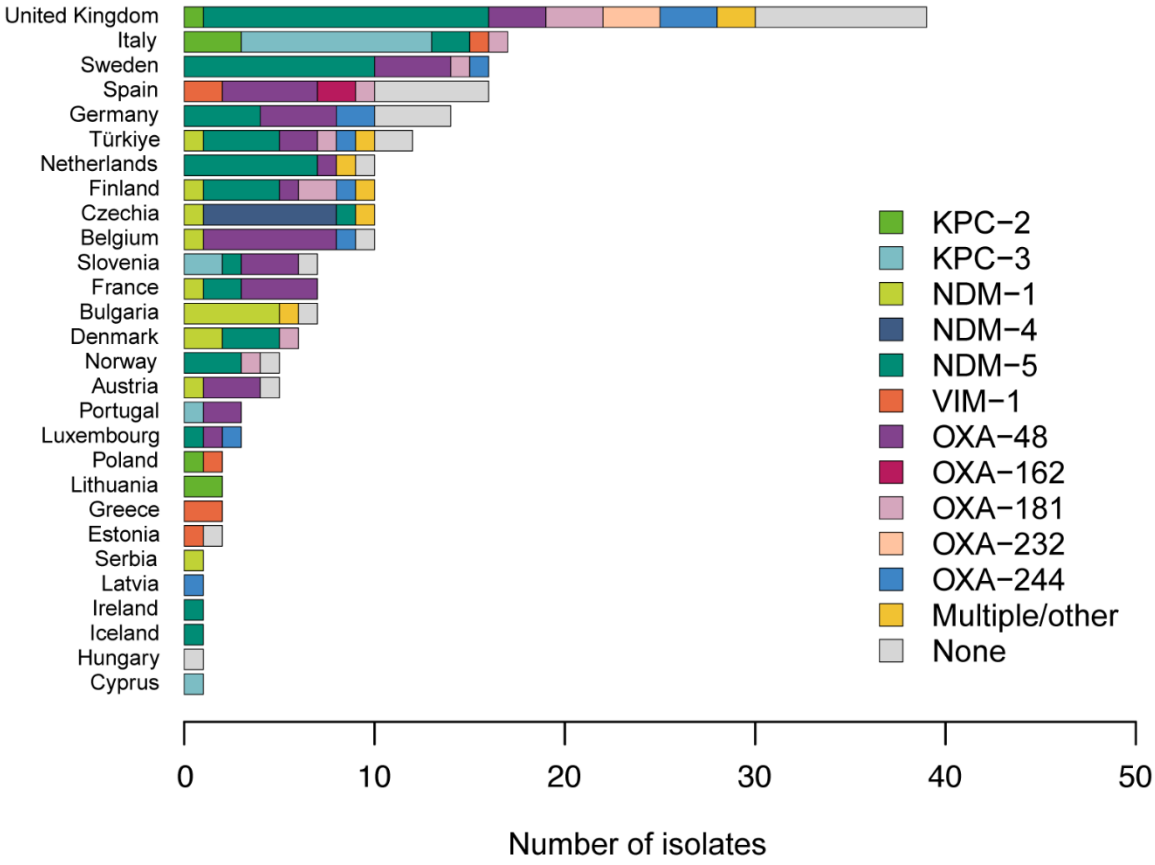
Among the *E. coli* isolates, the two most common carbapenemase genes (*bla*$_{\text{NDM-5}}$ and *bla*$_{\text{OXA-48}}$), were also the most widely distributed, and were recovered from 45 hospitals in 15 countries and 32 hospitals in 13 countries, respectively (Table 15 and Figure 20). *bla*$_{\text{NDM-5}}$ was particularly prevalent among carbapenem-R/I isolates from the Netherlands (70.0%; 7/10), Sweden (62.5%; 10/16) and the UK (41.0%; 16/39), while *bla*$_{\text{OXA-48}}$ was common in Belgium (70.0%; 7/10) and Spain (31.3%; 5/16). More than half (58.8%; 10/17) of carbapenem-R/I isolates from Italy carried *bla*$_{\text{KPC-3}}$ while those from Bulgaria (85.7%; 6/7) and Czechia (70.0%; 7/10) mostly carried *bla*$_{\text{NDM-1}}$ and *bla*$_{\text{NDM-4}}$, respectively. *bla*$_{\text{OXA-48}}$ was also the most widely distributed carbapenemase gene variant among *E. coli* isolates in terms of STs, recovered from isolates in 28 STs (Table 15 and Figure 16). We also noted associations of carbapenemases with high-risk STs, largely those described in section 3.5.2 above, including *bla*$_{\text{KPC-3}}$ with ST131, *bla*$_{\text{NDM-5}}$ with ST167 and *bla*$_{\text{OXA-244}}$ with ST38.

Table 15. Geographical distribution and major sequence types among the most common carbapenemase gene variants across all *Escherichia coli* isolates (n=548)

Carbapenemase gene variant	Isolates n	Carbapenem-R/I isolates n (%)	STs (all isolates) n	STs with ≥10% of isolates (n)	Countries (all isolates) n	Countries with ≥10% of isolates (n)	Hospitals (all isolates) n
bla$_{KPC-2}$	7	7 (3.3)	6	ST1495 (n=1), ST131 (n=2), ST641 (n=1), ST46 (n=1), ST12865 (n=1), ST11240 (n=1)	4	Italy (n=3), Lithuania (n=2), Poland (n=1), UK (n=1)	6
bla$_{KPC-3}$	14	14 (6.6)	5	ST131 (n=10)	4	Italy (n=10), Slovenia (n=2)	11
bla$_{NDM-1}$	16	16 (7.6)	13	ST131 (n=3), ST167 (n=2)	9	Bulgaria (n=6), Denmark (n=2), Türkiye (n=2)	12
bla$_{NDM-4}$	7	7 (3.3)	6	ST57 (n=1), ST58 (n=1), ST73 (n=1), ST131 (n=1), ST1158 (n=2), ST5903 (n=1)	1	Czechia (n=7)	1
bla$_{NDM-5}$	62	62 (29.4)	17	ST167 (n=14), ST361 (n=7), ST405 (n=6), ST410 (n=7), ST648 (n=9)	15	Netherlands (n=7), Sweden (n=10), UK (n=16)	45
bla$_{OXA-48}$	42	40 (19.0)	28	ST38 (n=6), ST224 (n=4)	13	Belgium (n=7), France (n=4), Germany (n=6), Spain (n=5), Sweden (n=4)	32
bla$_{OXA-162}$	2	2 (0.9)	1	ST5968 (n=2)	1	Spain (n=2)	2
bla$_{OXA-181}$	12	12 (5.7)	7	ST410 (n=6)	8	Finland (n=2), UK (n=4)	12
bla$_{OXA-232}$	4	4 (1.9)	3	ST410 (n=2), ST131 (n=1), ST1431 (n=1)	2	UK (n=3), Türkiye (n=1)	3
bla$_{OXA-244}$	13	13 (6.2)	5	ST38 (n=9)	9	Finland (n=2), Germany (n=2), UK (n=3)	13
bla$_{VIM-1}$	7	7 (3.3)	5	ST12860 (n=1), ST8578 (n=1), ST5528 (n=1), ST410 (n=1), ST131 (n=3)	5	Estonia (n=1), Spain (n=2), Greece (n=2), Italy (n=1), Poland (n=1)	6

Genes comprising ≥1% of all carbapenemase genes are shown. Isolates with multiple carbapenemase gene variants are included and thus may be counted in multiple rows.

Figure 20. Country distribution of carbapenemase gene variants detected among carbapenem-R/I *Escherichia coli* (n=211)



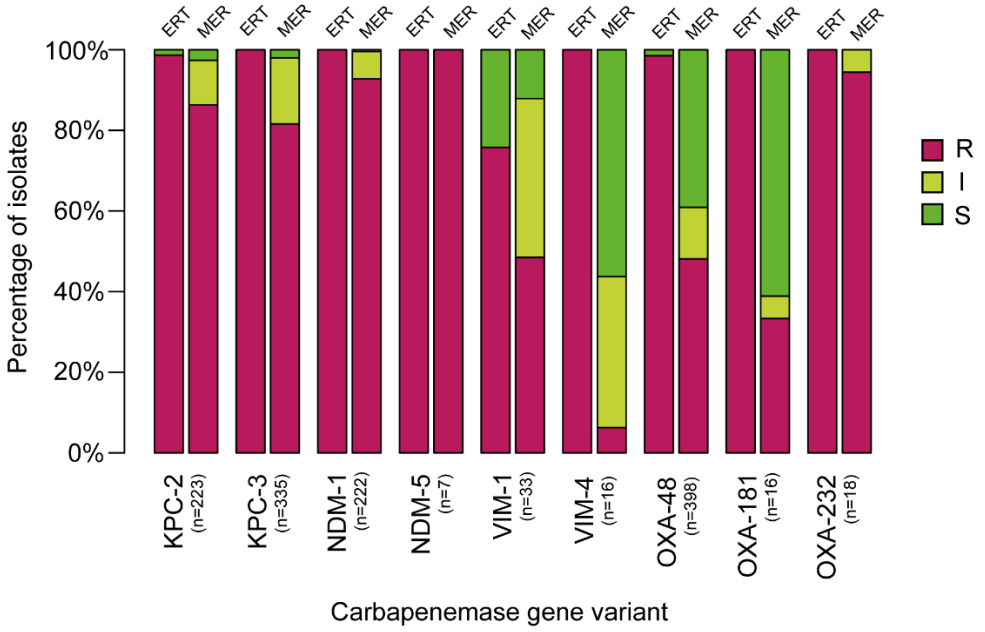
Genes comprising ≤1% of all carbapenemase genes are included in the 'Multiple/other' category.

3.5.4.3 Correlation between phenotypic carbapenem testing results and carbapenemase gene variants

We next investigated the carbapenem susceptibility patterns of isolates with different carbapenemase gene variants among those isolates that had both ertapenem and meropenem susceptibility results available. We found that almost all *K. pneumoniae* SC isolates (98.7%; 1283/1300) and *E. coli* isolates (97.5%; 157/161) carrying a single carbapenemase gene variant of any type were phenotypically resistant (R) to ertapenem (Figures 21 and 22). However, there was more variability in the resistance of isolates to meropenem depending on the carbapenemase gene. For some carbapenemase genes, fewer than half of the tested isolates were resistant (R) to meropenem, including *K. pneumoniae* SC isolates with $bla_{\text{VIM-1}}$ (48.5%; 16/33), $bla_{\text{VIM-4}}$ (6.3%; 1/16), $bla_{\text{OXA-48}}$ (48.0%; 191/398) and $bla_{\text{OXA-181}}$ (25.0%; 4/16), and *E. coli* isolates with $bla_{\text{KPC-2}}$ (20.0%; 1/5), $bla_{\text{KPC-3}}$ (15.4%; 2/13), $bla_{\text{NDM-4}}$ (0%; 0/6), $bla_{\text{VIM-1}}$ (28.6%; 2/7), $bla_{\text{OXA-48}}$ (2.6%; 1/39), $bla_{\text{OXA-181}}$ (0%; 0/11) and $bla_{\text{OXA-244}}$ (9.1%; 1/11). Carbapenemase-encoding isolates that were susceptible (S) to meropenem were typically diverse and not restricted to specific clones. For example, meropenem-susceptible isolates with $bla_{\text{OXA-48}}$ were identified in 48 STs of *K. pneumoniae* SC and 25 STs of *E. coli*.

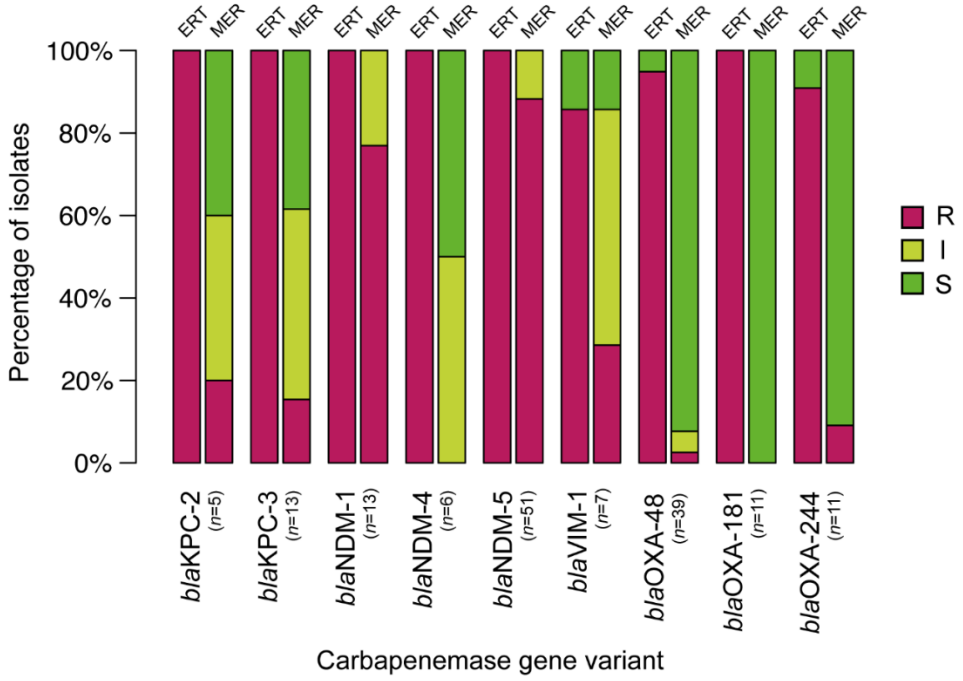
Overall, a higher proportion of isolates from the *K. pneumoniae* SC (71.2%; 925/1 300) with a single carbapenemase were resistant to meropenem compared with *E. coli* (38.5%; 62/161), potentially due to the presence of additional resistance mechanisms such as porin mutations in *K. pneumoniae* SC. Among isolates lacking a carbapenemase gene, from the carbapenem-R/I group only, 99.4% (155/156) of the *K. pneumoniae* SC isolates and 100% (28/28) of the *E. coli* isolates were resistant (R) to ertapenem. However, only 13.5% (21/156) and 14.3% (4/28) of isolates from the same groups were resistant (R) to meropenem.

Figure 21. Phenotypic ertapenem and meropenem susceptibility results by carbapenemase gene variant for *Klebsiella pneumoniae* SC isolates (n=1 268)



Isolates were excluded if either of the ertapenem and meropenem results were unavailable, or if they carried multiple carbapenemase gene variants. The carbapenemase gene variants shown include those comprising ≥1% of all carbapenemase gene variants and found in a minimum of five isolates.

Figure 22. Phenotypic ertapenem and meropenem susceptibility results by carbapenemase gene variant for *Escherichia coli* isolates (n=156)



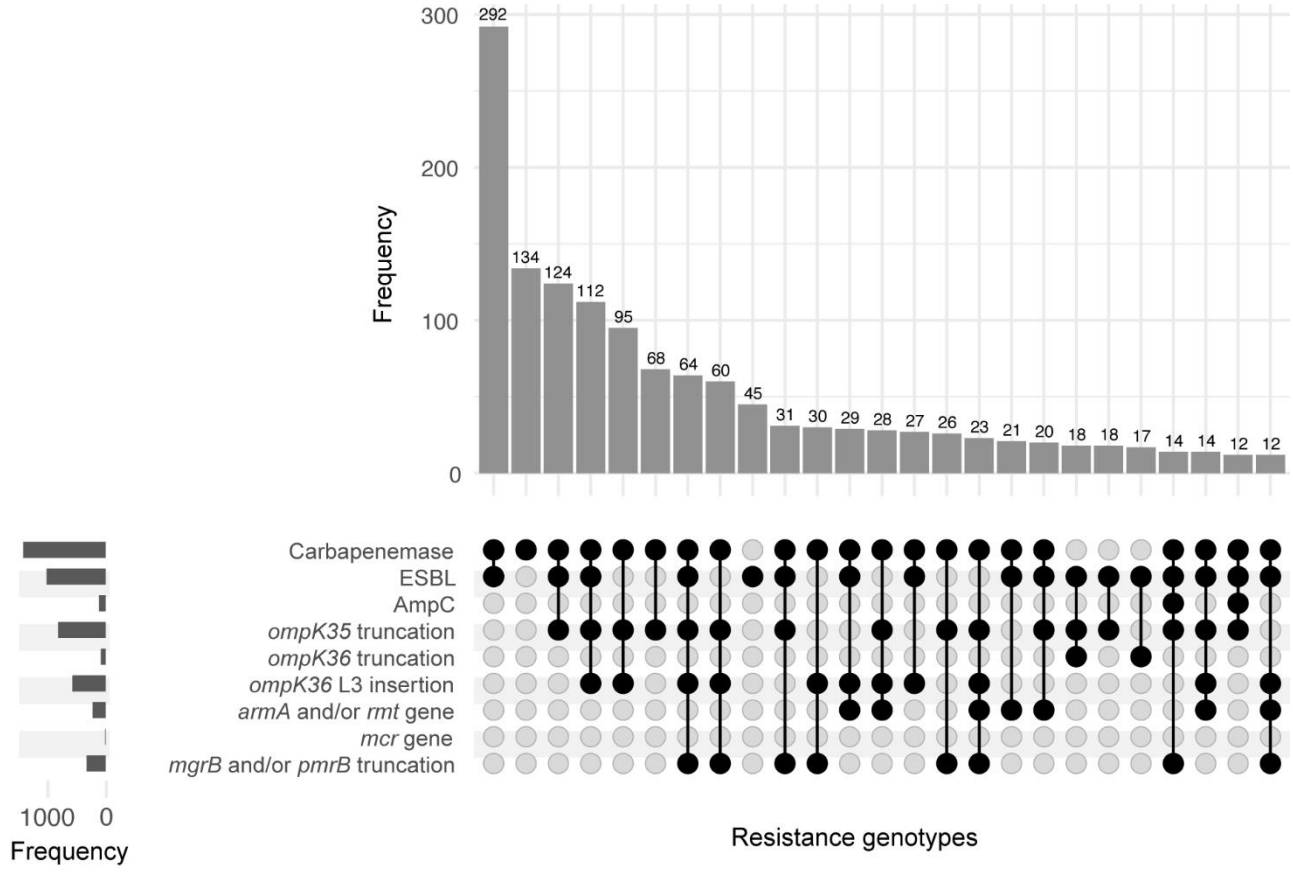
Isolates were excluded if either of the ertapenem and meropenem results were unavailable, or if they carried multiple carbapenemase gene variants. The carbapenemase gene variants shown include those comprising ≥1% of all carbapenemase gene variants and found in a minimum of five isolates.

3.5.5 Distribution of other resistance genes

We examined the presence of other selected resistance mechanisms in the *K. pneumoniae* SC and *E. coli* genomes. For the *K. pneumoniae* SC, these included ESBL and AmpC genes (typically plasmid-encoded) and chromosomally encoded porin mutations (*ompK35* and *ompK36* truncations and *ompK36* loop 3 insertions), which affect susceptibility to beta-lactam antibiotics. We also investigated the presence of plasmid-encoded *mcr* genes and chromosomally encoded *mgrB*/*pmrB* truncations, which affect susceptibility to colistin, as well as *armA* and *rmt* genes, which are plasmid-encoded 16S rRNA methyltransferases conferring high-level aminoglycoside resistance. A full breakdown of all other resistance genes and/or mutations identified with Kleborate among the *K. pneumoniae* SC genomes is available from Microreact (https://microreact.org/project/klebsiella-ccre-survey).

We found that carbapenem-R/I *K. pneumoniae* SC isolates commonly possessed one or more of these other mechanisms (Figure 23). In particular, 64.0% (1 003/1 566) carried an ESBL gene and 58.2% (911/1 566) had one or more porin mutations, although AmpC genes were rarer (7.2%; 113/1 566). Of the 167 carbapenem-R/I *K. pneumoniae* isolates that lacked a carbapenemase gene, we found that 60.5% (101/167) had an ESBL gene and/or AmpC gene in combination with one or more porin mutations, which could potentially explain the carbapenem-R/I phenotype. Among the colistin resistance mechanisms, *mgrB*/*pmrB* truncations were found more commonly than *mcr* genes, with a prevalence of 20.7% (324/1 566) and 0.6% (9/1 566), respectively, among the carbapenem-R/I isolates. An *armA* and/or *rmt* gene was found in 14.1% (221/1566) of the carbapenem-R/I isolates. High-risk STs accounted for most carbapenem-R/I isolates that carried multiple of the selected resistance mechanisms. For example, of 74 isolates that carried a carbapenemase gene, an ESBL gene, *ompK35* truncation, *ompK36* L3 insertion and a *mgrB*/*pmrB* truncation (+/- other mechanisms), 59.5% (44/74) belonged to ST258, 35.1% (26/74) to ST101, 2.7% (2/74) to ST14 and 2.7% (2/74) to ST147.

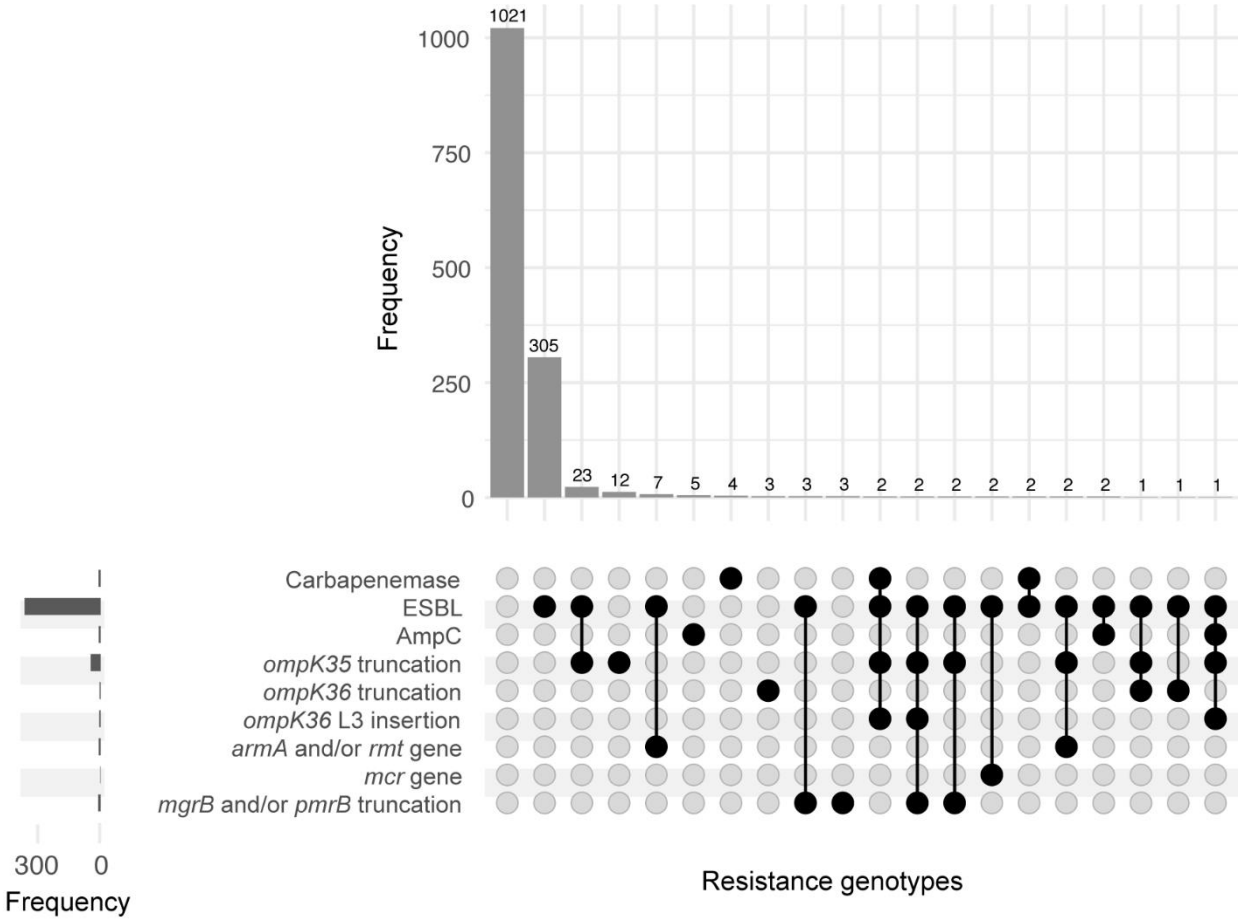
Figure 23. Combinations of resistance genes and mutations among the carbapenem-R/I *Klebsiella pneumoniae* SC isolates (n=1 566)



Frequencies of the top 25 combinations are shown in the upper bar plot, while frequencies of individual genes/mutations are shown on the left.

By contrast, most (72.6%; 1 021/1 407) carbapenem-S *K. pneumoniae* SC isolates carried none of the additional selected resistance mechanisms (Figure 24). An ESBL gene (+/- other mechanisms) was carried by 25.4% (357/1 407) of these isolates while all other mechanisms were found at low frequency (<4%).

Figure 24. Combinations of resistance genes and mutations among the carbapenem-S *Klebsiella pneumoniae* SC isolates (n=1 407)



Frequencies of the top 20 combinations are shown in the upper bar plot, while frequencies of individual genes/mutations are shown on the left.

Overall, most (86.0%; 1170/1360) carbapenem-R/I and -S *K. pneumoniae* SC isolates with an ESBL gene carried the *bla*$_{\text{CTX-M-15}}$ variant. The most common AmpC gene variants were *bla*$_{\text{CMY-4}}$ (33.6%; 41/122) and *bla*$_{\text{DHA-1}}$ (25.4%; 31/122). Truncations were 9.9x more common in *ompK35* (n=853) than *ompK36* (n=86). Of the total 571 isolates with an *ompK36* loop 3 insertion, 80.9% (462/571) had the amino acid insertion glycine-aspartate (GD), 12.1% (69/571) had threonine-aspartate (TD), 5.1% (29/571) had aspartate (D), 1.8% (10/571) had serine-aspartate (SD), and 0.2% (1/571) had serine-aspartate-asparagine-phenylalanine-leucine (SDNFL).

A total of 230 *K. pneumoniae* SC isolates carried an *armA* and/or *rmt* gene, including 221 carbapenem-R/I and nine carbapenem-S isolates. Among these, 74.8% (172/230) carried an *armA* gene, 23.9% (55/230) carried a *rmt* gene and 1.3% (3/230) carried both an *armA* and *rmt* gene. The *rmt* genes were comprised of *rmtB* (n=10), *rmtC* (n=22) and *rmtF* (n=26) variants. Of the 230 isolates with *armA* and/or *rmt*, we found that 57.4% (132/230) also carried either *bla*$_{\text{NDM-1}}$/*bla*$_{\text{NDM-5}}$, a *bla*$_{\text{OXA-48-like}}$ gene or a combination of both carbapenemase gene types. A further 18.7% (43/230) and 13.9% (32/230) carried a single *bla*$_{\text{KPC-2}}$ or *bla*$_{\text{KPC-3}}$ carbapenemase gene, respectively.

A total of 11 *K. pneumoniae* SC genomes possessed a match to an *mcr* gene, including nine carbapenem-R/I isolates and an additional two carbapenem-S isolates. Of the 11 isolates, one had *mcr-8*, one had *mcr-8** (inexact nucleotide and amino acid match to *mcr-8*), four had *mcr-9*, four had an incomplete match to *mcr-9*, and one had *mcr-9** (inexact nucleotide and amino acid match to *mcr-9*). However, the effect of these variants on colistin susceptibility remains uncertain; in one study the *mcr-9* variant was found not to confer colistin resistance in *E. coli* and *Salmonella* [50]. Among all carbapenem-R/I and -S isolates with *mgrB* and/or *pmrB* truncations (n=336), we found that *mgrB* truncations were more common accounting for 95.2% (320/336), while 2.1% (7/336) had only a *pmrB* truncation and 2.7% (9/336) had both *mgrB* and *pmrB* truncations.

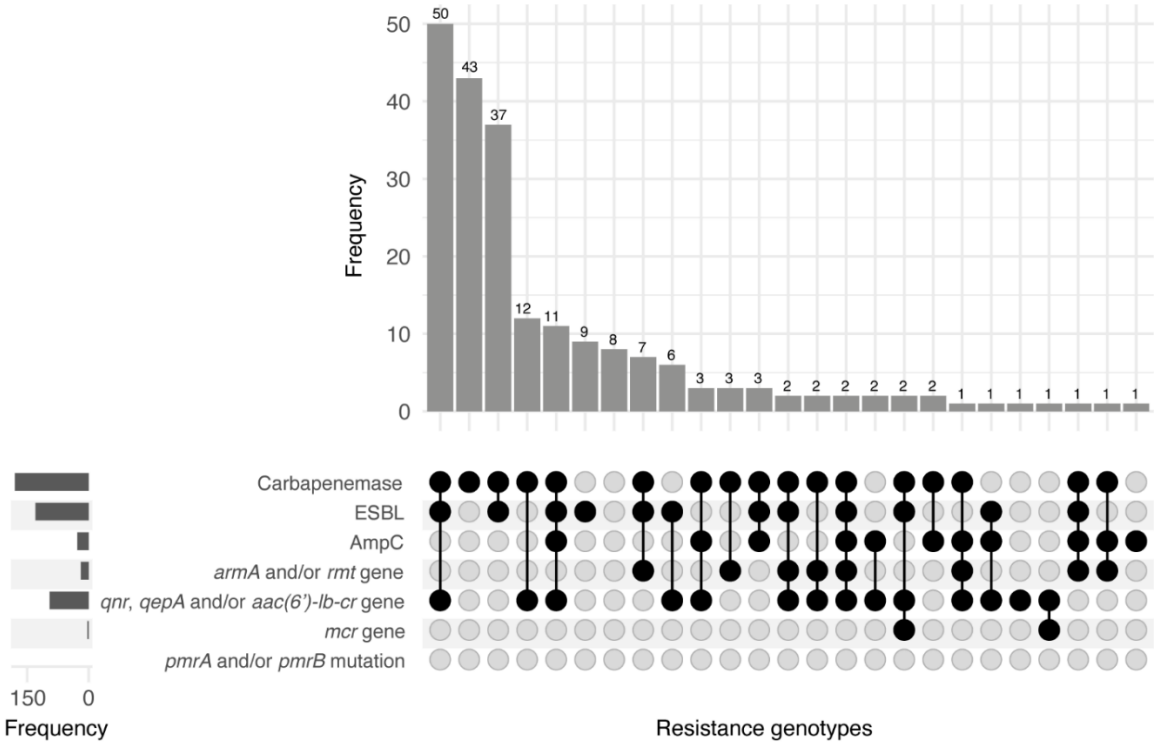
As with the *K. pneumoniae* SC isolates, we also examined a selection of key resistance mechanisms among the *E. coli* genomes with a particular focus on those that are plasmid-encoded due to their potential for rapid spread. The selected mechanisms included ESBL and AmpC genes, which mediate resistance to beta-lactams, and *mcr* genes and the chromosomally encoded *pmrA*/*pmrB* mutations, which mediate resistance to colistin.

We also investigated the presence of the aminoglycoside resistance genes, *armA* and *rmt*. Finally, we assessed the presence of *qnr*, *qepA* and *aac(6')-Ib-cr* genes, which represent the primary plasmid-encoded mechanisms contributing to quinolone resistance. A full breakdown of all other resistance genes and/or mutations identified with AMRFinderPlus among the *E. coli* genomes is available from Microreact (https://microreact.org/project/ecoli-ccre-survey).

As with *K. pneumoniae* SC isolates, the carbapenem-R/I *E. coli* commonly carried one or more of these other resistance mechanisms (Figure 25). In particular, ESBL genes were carried by 62.1% (131/211), while *qnr*, *qepA* and/or *aac(6')-Ib-cr* genes were found in 45.5% (96/211). However, AmpC genes were found less frequently (13.3%; 28/211), together also with *armA* and/or *rmt* genes (9.0%; 19/211). The *mcr* genes were rare (1.4%; 3/211) and *pmrA*/*pmrB* mutations were absent from this group (0%; 0/211). Most (70.6%; 238/337) carbapenem-S *E. coli* genomes carried none of the genes encoding for additional selected resistance mechanisms (Figure 26). An ESBL gene was carried by 23.7% (80/337) of this group and 18.7% (63/337) carried a *qnr*, *qepA* and/or *aac(6')-Ib-cr* gene. All other genes were found at low frequency (<4%).

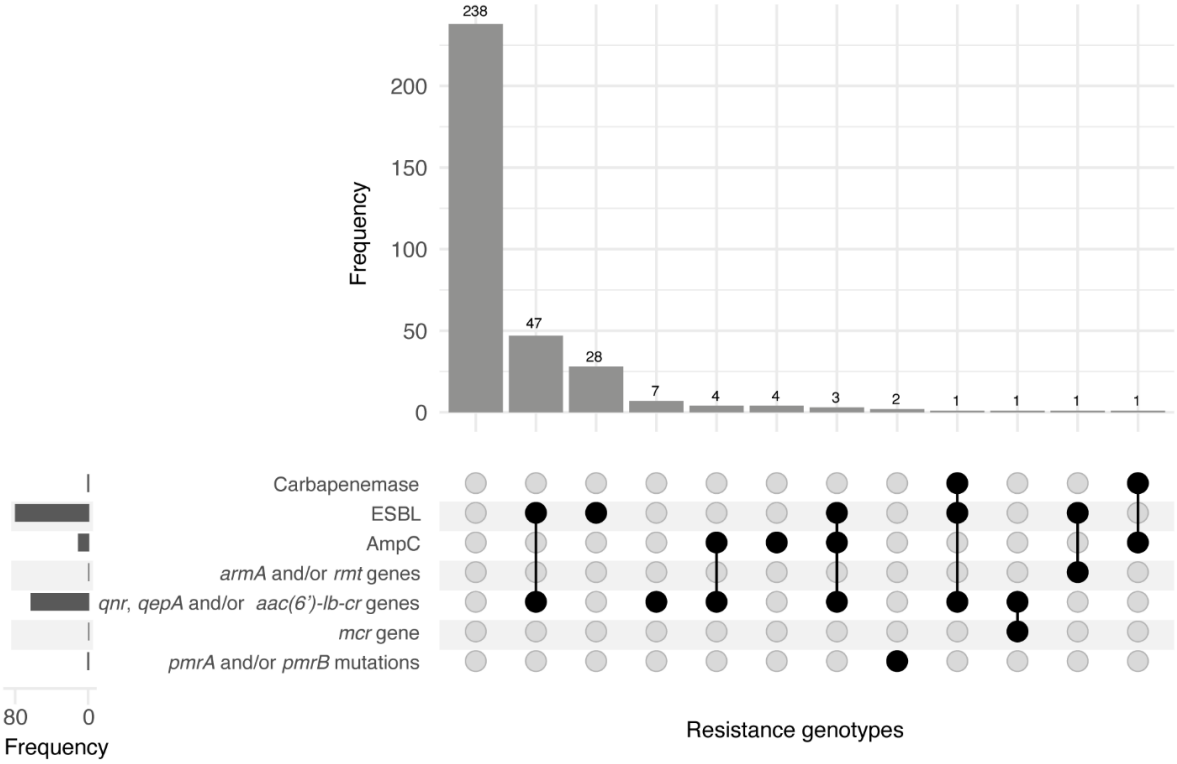
Most of the ESBL gene variants identified among the carbapenem-R/I and -S *E. coli* isolates were $bla_{\text{CTX-M-15}}$ (66.4%; 140/211) although other notable variants included $bla_{\text{CTX-M-27}}$ (11.4%; 24/211) and $bla_{\text{CMY-42}}$ (10.0%; 21/211). The most frequent AmpC gene variants were $bla_{\text{CMY-2}}$ (30.0%; 12/40), $bla_{\text{CMY-4}}$ (27.5%; 11/40) and $bla_{\text{DHA-1}}$ (30.0%; 12/40). The aminoglycoside resistance genes identified included *rmtB1* (55.0%; 11/20), *rmtC* (25.0%; 5/20), *rmtF1* (5%; 1/20) and *armA* (15.0%; 3/20). We found that most of the isolates with an *armA* and/or *rmt* gene also carried either $bla_{\text{NDM-5}}$ (50.0%; 10/20) or $bla_{\text{NDM-1}}$ (40.0%; 8/20). Among the 159 carbapenem-R/I and -S isolates with plasmid-borne quinolone resistance genes, *aac(6')-Ib-cr* genes were the most common, found among 61.0% (97/159) of the genomes. In addition, *qnrS* genes were found in 34.6% (55/159), *qnrB* in 13.2% (21/159), *qepA* in 3.8% (6/159) and *qnrA* in 1.9% (3/159). Of the four *mcr* genes identified, two were *mcr-1* while two were *mcr-9*. Only one of the *pmrA* and *pmrB* mutations each were found (both among carbapenem-S isolates).

Figure 25. Combinations of resistance genes and mutations among the carbapenem-R/I *Escherichia coli* isolates (n=211)



Frequencies of all the combinations are shown in the upper bar plot, while the frequencies of individual genes/mutations are shown on the left.

Figure 26. Combinations of resistance genes and mutations among the carbapenem-S *Escherichia coli* isolates (n=337)



Frequencies of all the combinations are shown in the upper bar plot, while frequencies of individual genes/mutations are shown on the left.

3.5.6 Virulence genes (*Klebsiella pneumoniae* SC only)

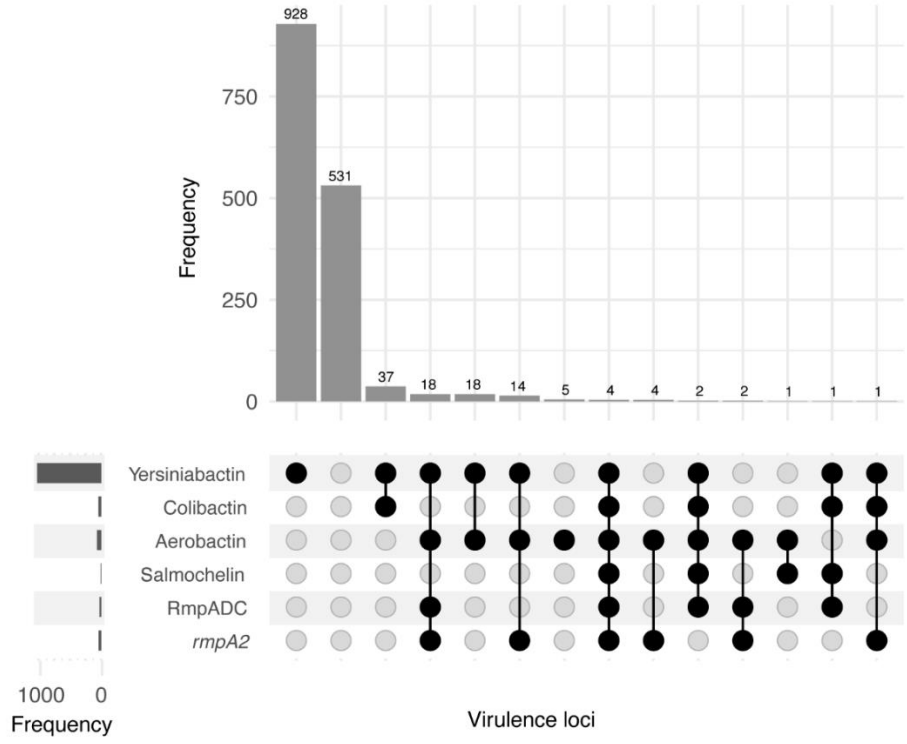
We examined the presence of virulence factors among the *K. pneumoniae* SC genomes using Kleborate (Table 16 and Figures 27 and 28). We found that 65.3% (1 023/1 566) of the carbapenem-R/I genomes carried a yersiniabactin locus compared with 36.5% (514/1 407) of the carbapenem-S genomes. This difference could be largely attributed to the high prevalence of yersiniabactin in some of the STs enriched with carbapenem-R/I isolates. In particular, 97.7% (211/216) of ST101 genomes, 92.9% (52/56) of ST39 genomes and 88.1% (178/202) of ST11 genomes carried the locus. All other virulence factors were found at a prevalence of <6% in both groups.

A total of 40 isolates were designated the highest virulence score of five by Kleborate, due to simultaneous carriage of the yersiniabactin, colibactin and aerobactin loci. These all belonged to *K. pneumoniae* and comprised 0.4% (7/1566) of carbapenem-R/I and 2.3% (33/1407) of carbapenem-S isolates. The seven carbapenem-R/I isolates belonged to ST23 (n=2), ST65 (n=2), ST147 (n=1), ST380 (n=1) and an undesignated SLV of ST23 (n=1). Five of the seven carbapenem-R/I isolates carried a carbapenemase gene which included $bla_{\text{KPC-3}}$ (n=2) and $bla_{\text{OXA-48}}$ (n=3). Four of the seven isolates (ST23, n=2; ST23-1LV, n=1; ST65, n=1) carried all six virulence loci reported by Kleborate, although all four carried a truncated copy of *rmpA2* while one also carried a truncated copy of the RmpADC locus. Across all 40 isolates with a virulence score of five (from both carbapenem-R/I and -S groups), the most prevalent STs were ST23 (47.5%; 19/40), ST380 (20.0%; 8/40), ST65 (10.0%; 4/40) and ST268 (7.5%; 3/40), with all other isolates belonging to single STs. More than half (55.0%; 22/40) of the isolates possessed the capsular loci KL1, followed by KL2 (35.0%; 14/40), KL10 (2.5%; 1/40) and KL20 (7.5%; 3/40). The 19 ST23 isolates were obtained from 15 hospitals in 11 countries, while the eight ST380 isolates were obtained from six hospitals in five countries.

Table 16. Summary of virulence loci identified among all *Klebsiella pneumoniae* SC isolates (n=2 973)

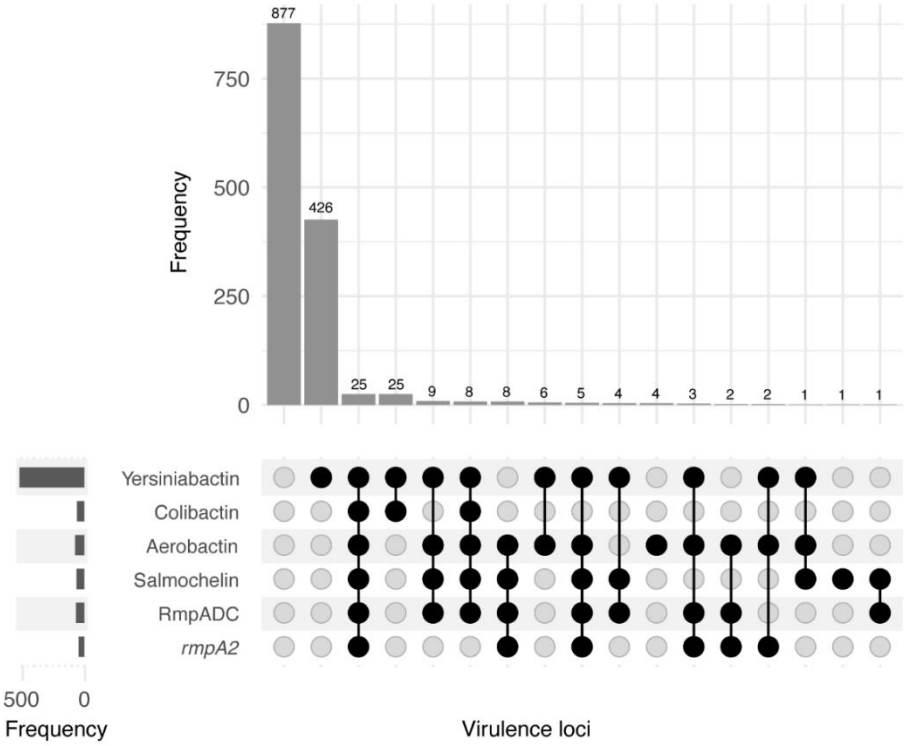
Virulence locus	Isolates n (%)	Carbapenem-R/I isolates n (%)	Carbapenem-S isolates n (%)	Major STs, i.e. with≥10% of isolates (n)
Yersiniabactin	1 537 (51.7)	1 023 (65.3)	514 (36.5)	ST101 (n=211), ST11 (n=178)
Colibactin	103 (3.5)	45 (2.9)	58 (4.1)	ST13 (n=24), ST23 (n=19), ST792 (n=10)
Aerobactin	142 (4.8)	69 (4.4)	73 (5.2)	ST147 (n=19), ST2096 (n=15), ST23 (n=22)
Salmochelin	70 (2.4)	8 (0.5)	62 (4.4)	ST23 (n=20), ST380 (n=9)
RmpADC	92 (3.1)	27 (1.7)	65 (4.6)	ST147 (n=17), ST23 (n=20), ST380 (n=9)
rmpA2	88 (3.0)	43 (2.7)	45 (3.2)	ST147 (n=19), ST2096 (n=15), ST23 (n=20)

Figure 27. Combinations of virulence loci among the carbapenem-R/I *Klebsiella pneumoniae* SC isolates (n=1 566)



Frequencies of all the combinations are shown in the upper bar plot, while frequencies of individual loci are shown on the left.

Figure 28. Combinations of virulence loci among the carbapenem-S *Klebsiella pneumoniae* SC isolates (n=1 407)



Frequencies of all the combinations are shown in the upper bar plot, while frequencies of individual loci are shown on the left.

3.5.7 O and K loci (*Klebsiella pneumoniae* SC only)

The lipopolysaccharide and capsular polysaccharide antigens, encoded by O loci and K loci respectively, were typed in the *K. pneumoniae* SC genomes using Kaptive. Most isolates encoded O loci corresponding to an O1 or O2 subtype, including 81.6% (1278/1566) of carbapenem-R/I and 62.3% (876/1407) of carbapenem-S isolates (Figure 29). Carbapenem-R/I isolates from each of the major high-risk STs mostly encoded the same O locus type (Figure 30). Some STs shared the same dominant O locus subtype, including ST258/512 and ST307, which shared O2v2, ST101 and ST15, which shared O1v1, and ST11 and ST147, which shared O2v1.

Figure 29. Frequency of O locus types encoded by carbapenem-R/I (n=1 566) and carbapenem-S (n=1 407) *Klebsiella pneumoniae* SC isolates

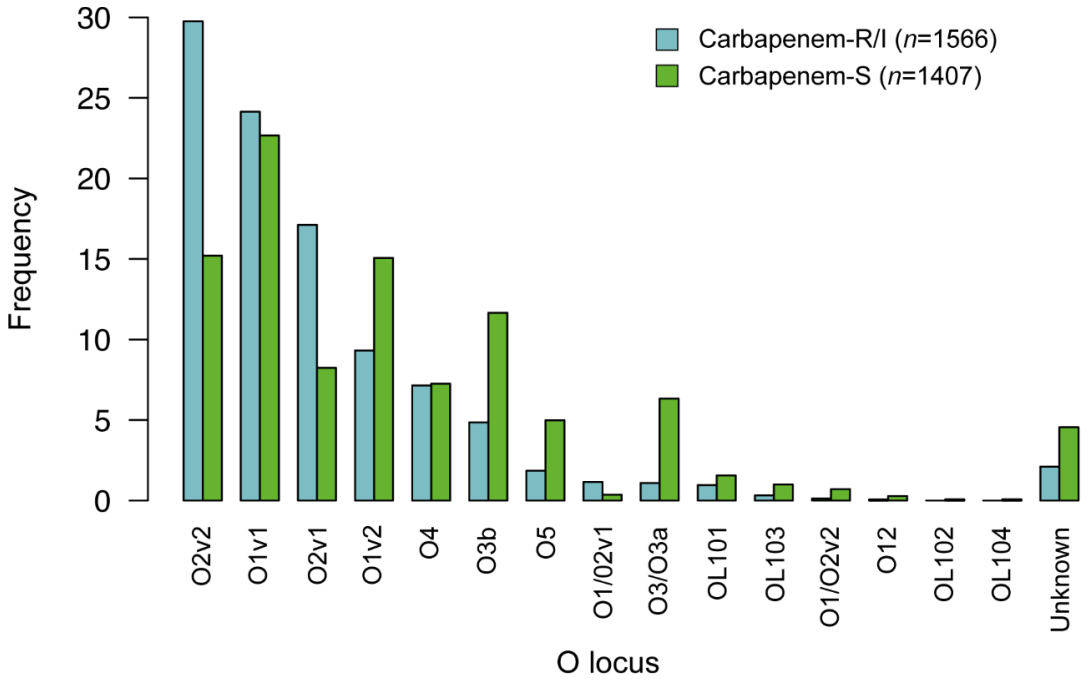
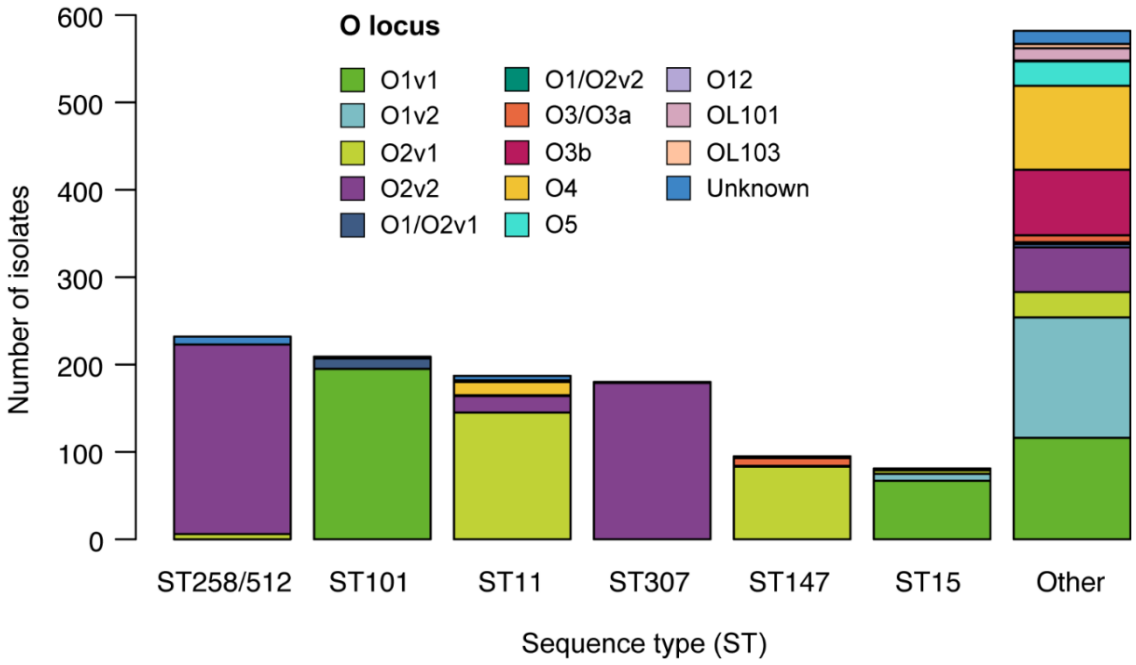
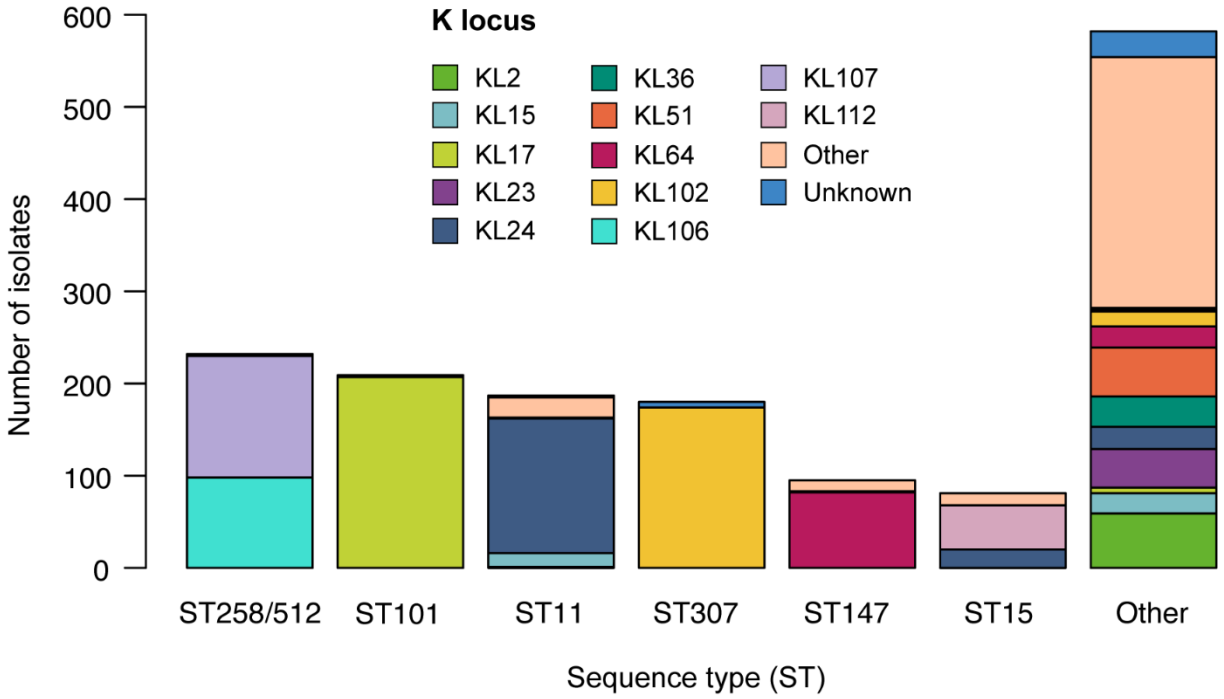


Figure 30. O locus types encoded by carbapenem-R/I isolates belonging to major high-risk STs and all other STs from the *Klebsiella pneumoniae* SC (n=1 566)



The diversity of K locus (KL) types was higher, with 74 known KL types among the 1 566 carbapenem-R/I isolates and 103 known KL types among the 1407 carbapenem-S isolates. The most frequent KL types among carbapenem-R/I isolates were KL17 (13.6%; 213/1566), KL102 (12.1%; 190/1566), KL24 (12.1%; 190/1566), KL107 (8.6%; 134/1566) and KL64 (6.8%; 106/1566), which together comprised 53.2% (833/1566) of the isolates. The most numerous among the carbapenem-S group were KL102 (5.7%; 80/1407), KL2 (4.9%; 69/1407), KL24 (4.4%; 62/1407), KL22 (3.6%; 50/1407) and KL28 (3.1%; 43/1407), which together made up 21.6% (304/1407) of these isolates. As with O locus types, carbapenem-R/I isolates from each of the major high-risk STs largely possessed the same KL type, with the exception of ST258/512 isolates which mostly carried either KL106 (42.2%; 98/232) or KL107 (56.9%; 132/232) (Figure 31). However, there was little sharing of KL types among the different high-risk STs.

Figure 31. K locus (KL) types encoded by carbapenem-R/I isolates belonging to major high-risk STs and all other STs from the *Klebsiella pneumoniae* SC (n=1 566)



KL types present in ≤30 isolates were grouped into the 'Other' category.

3.5.8 Plasmid replicons

We examined the plasmid replicons observed among both the *K. pneumoniae* SC and *E. coli* genomes using the short-read assemblies. Among the *K. pneumoniae* SC, the mean number of plasmid replicons was greater among carbapenem-R/I isolates (mean 4.1, range 0-11) than carbapenem-S isolates (mean 2.1, range 0-11), which may be due to carriage of additional resistance plasmids or greater carriage of multi-replicon plasmids. However, in *E. coli*, the number of replicons was similar among carbapenem-R/I isolates (mean 3.3, range 0-8) and carbapenem-S isolates (mean 3.4, range 0-9).

We examined associations between particular carbapenemase gene variants and replicon types (Tables 17 and 18), with the limitation that observed associations could be an artefact of lineage effects (i.e. where both a carbapenemase gene variant and a plasmid replicon are commonly present within a lineage due to clonal replication, without the carbapenemase necessarily being carried by that plasmid). However, we considered associations that held across both *K. pneumoniae* SC and *E. coli*, or multiple STs of a species, to more likely represent carriage of a carbapenemase gene variant by a plasmid.

We found that 75.1% (331/441) of *K. pneumoniae* SC genomes and 59.5% (25/42) of *E. coli* genomes with a $bla_{\text{OXA-48}}$ gene carried an IncL replicon, compared with 1.0% (25/2532) and 0.6% (3/506), respectively, of those that lack $bla_{\text{OXA-48}}$. Both the *K. pneumoniae* SC and *E. coli* genomes with $bla_{\text{OXA-48}}$ and an IncL replicon belonged to many STs (56 and 22, respectively). The two *E. coli* genomes with $bla_{\text{OXA-162}}$, which differs from $bla_{\text{OXA-48}}$ by a single point mutation, were also found to carry only IncL replicons. This suggests frequent carriage of $bla_{\text{OXA-48}}$ and $bla_{\text{OXA-162}}$ genes on pOXA-48-like plasmids, which are typically highly-conserved IncL plasmids that have been previously shown to be the dominant vector of $bla_{\text{OXA-48}}$ genes in Europe [10,51,52].

We found that most isolates with $bla_{\text{OXA-181}}$ from both species, including 72.7% (16/22) of *K. pneumoniae* SC isolates and 75.0% (9/12) of *E. coli* isolates, carried the IncX3 replicon. This compared to only 6.1% (180/2951) and 5.8% (31/536) of the remaining isolates lacking $bla_{\text{OXA-181}}$, respectively. The isolates with both $bla_{\text{OXA-181}}$ and an IncX3 replicon belonged to nine and five different STs of *K. pneumoniae* SC and *E. coli*, respectively.

In *K. pneumoniae* SC, $bla_{\text{OXA-232}}$ was associated with multiple replicons including Col(pHAD28), IncHI1B(pNDM-Mar), IncFIB(pNDM-Mar) and ColKP3. However, the strongest association was with ColKP3, which was carried by 100% (24/24) of $bla_{\text{OXA-232}}$ isolates, compared with 0.1% (2/2949) of the remaining genomes. ColKP3 plasmids of approximately 6.1kb are known to be dominant vectors of $bla_{\text{OXA-232}}$ genes [53-55]. Some of the other associations may have arisen from the fact that most of the $bla_{\text{OXA-232}}$ isolates (16/24) belonged to a single lineage, ST2096, which also harbours these plasmid replicons, rather than reflecting carriage of $bla_{\text{OXA-232}}$ genes on the respective

plasmids. Indeed, ST2096 accounted most of *bla*$_{OXA-232}$ isolates with IncHI1B(pNDM-Mar) (82.4%; 14/17) and IncFIB(pNDM-Mar) (83.3%; 15/18) replicons.

We found associations of *bla*$_{KPC-2}$ and *bla*$_{KPC-3}$ genes in *K. pneumoniae* SC isolates with IncFIB(K), IncFII(K), IncFIB(pQIL), ColRNAI and IncX3 replicons. These replicons were previously shown to be commonly harboured by plasmids in ST258/512 isolates, with *bla*$_{KPC-2}$ and *bla*$_{KPC-3}$ genes frequently mobilised between the different plasmids in this lineage [10]. Here we found that non-ST258/512 isolates, in addition to ST258/512 isolates, also drove some of observed associations. In particular, 84.6% (319/377) of non-ST258/512 isolates with *bla*$_{KPC-2}$/*bla*$_{KPC-3}$ carried IncFII(K), 52.3% (197/377) carried IncFIB(pQIL) and 44.8% (169/377) carried ColRNAI replicons. This compared with 39.0% (926/2373), 5.7% (136/2373), and 9.4% (224/2373), respectively, among the remaining isolates lacking *bla*$_{KPC-2}$/*bla*$_{KPC-3}$. However, the proportion of non-ST258/512 isolates with *bla*$_{KPC-2}$/*bla*$_{KPC-3}$ that carried the IncFIB(K) replicon was similar to that among all *K. pneumoniae* SC isolates without one of these carbapenemases (61.0% (230/377) vs 56.7% (1345/2373)), thus it remained unclear if these plasmids may be carrying *bla*$_{KPC-2}$/*bla*$_{KPC-3}$ outside of ST258/512. The IncX3 replicon was also largely restricted to *bla*$_{KPC-2}$/*bla*$_{KPC-3}$ isolates from ST258/512 (96.0%; 144/150), demonstrating a specific association with this lineage.

While only seven *bla*$_{KPC-2}$ isolates were detected among the *E. coli* genomes, we found that two carried both the IncFII(K) and IncFIB(pQIL) replicons (which were associated with *bla*$_{KPC-2}$/*bla*$_{KPC-3}$ genes in *K. pneumoniae* SC isolates, as above), while another carried IncFIB(pQIL) without IncFII(K). These replicons were otherwise rare in *E. coli*, found in 2.8% (15/541) (IncFII(K)) and 2.2% (12/541) (IncFIB(pQIL)) of isolates lacking *bla*$_{KPC-2}$. A further three of the seven (42.9%) *bla*$_{KPC-2}$ -encoding *E. coli* isolates, from three different STs, carried an IncN replicon, which was otherwise rare among *E. coli* without *bla*$_{KPC-2}$ (1.7%; 9/541). Of the 14 *E. coli* isolates with a *bla*$_{KPC-3}$ gene, 64.3% (9/14) carried both IncFII(K) and IncFIB(pQIL) replicons (albeit 8/9 of which were from the ST131 lineage).

We found that *bla*$_{VIM-1}$ genes were associated with multiple replicons. Some of these were more species-specific (e.g. IncHI1B(pNDM-Mar) and IncFIB(pNDM-Mar) in the *K. pneumoniae* SC), while others were found across both *K. pneumoniae* SC and *E. coli*. The latter included IncHI2 and IncHI2A (which were always present together), found in 19.5% (8/41) of *K. pneumoniae* SC isolates and 28.6% (2/7) of *E. coli* genomes with *bla*$_{VIM-1}$, compared with 0.4% (13/2932) and 0.9% (5/541) of those without *bla*$_{VIM-1}$. We also found strong associations of *bla*$_{VIM-4}$ in the *K. pneumoniae* SC with the IncFIB(K) and IncR replicons, which were carried by 93.8% (15/16) and 81.3% (13/16) of *bla*$_{VIM-4}$ isolates, respectively, compared with 59.9% (1770/2957) and 21.1% (623/2957) of the remaining isolates. As in EuSCAPE, most (13/16) of the *bla*$_{VIM-4}$-encoding *K. pneumoniae* SC isolates belonged to ST15 and were submitted from Hungary. Long-read sequencing analysis showed that *bla*$_{VIM-4}$ was carried on an IncR plasmid among ST15 isolates from Hungary in EuSCAPE [10].

bla$_{NDM-1}$-carrying isolates from both the *K. pneumoniae* SC and *E. coli* were associated with the IncC_1 replicon, which was found in 24.0% (63/263) and 56.3% (9/16) of the isolates, respectively. This compared with 2.1% (58/2710) and 0.6% (3/532) among isolates lacking *bla*$_{NDM-1}$ from each of these species. Isolates with both *bla*$_{NDM-1}$ and the IncC_1 replicon were found in 14 STs of the *K. pneumoniae* SC and 8 STs of *E. coli*. We also found an association of *bla*$_{NDM-1}$ with the IncFII(pKPX1) replicon, which was found in 30.0% (79/263) of the *K. pneumoniae* SC isolates and 25.0% (4/16) of the *E. coli* isolates with *bla*$_{NDM-1}$, compared with 0.7% (19/2710) and 0% (0/532), respectively, of isolates lacking *bla*$_{NDM-1}$. Furthermore, IncFIB(pB171) was found in 6.1% (16/263) of *K. pneumoniae* SC isolates and 18.8% (3/16) of the *E. coli* with *bla*$_{NDM-1}$, compared with 0.1% (3/2710) and 0.9% (5/532) of isolates without *bla*$_{NDM-1}$. Isolates with *bla*$_{NDM-1}$ and IncFIB(pB171) were found in 11 STs of *K. pneumoniae* SC and 3 STs of *E. coli*. Finally, all seven *bla*$_{NDM-4}$ isolates in *E. coli*, from six different STs, carried an IncX3 replicon, compared with 6.1% (33/541) of *E. coli* isolates lacking *bla*$_{NDM-4}$.

We found some shared associations of *bla*$_{NDM-5}$ with particular plasmid replicons across the *K. pneumoniae* SC and *E. coli* isolates. These included with the IncFII replicon, found in 33.3% (5/15) and 66.1% (41/62) of *bla*$_{NDM-5}$-carrying *K. pneumoniae* SC and *E. coli* isolates, respectively, compared with 1.1% (34/2958) and 34.6% (168/486) of isolates lacking the carbapenemase. They also included the IncX3 replicon, found in 26.7% (4/15) and 22.6% (14/62) of *bla*$_{NDM-5}$-encoding *K. pneumoniae* SC and *E. coli* genomes, respectively, compared with 6.5% (192/2958) and 5.3% (26/486) of the remaining isolates. However, other replicons showed more species-specific associations with *bla*$_{NDM-5}$ including Col(MG828) and ColKP3 among *K. pneumoniae* SC isolates, and IncFIA and Col(BS512) in *E. coli*.

Table 17. Proportion of all *Klebsiella pneumoniae* SC genomes (n=2 973) with and without particular carbapenemase gene variants carrying individual plasmid replicons

	Carbapenemase	KPC-2		KPC-3		NDM-1		NDM-5		VIM-1		VIM-4		OXA-48		OXA-181		OXA-232	
		Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Plasmid replicon	No. of isolates	253	2720	347	2626	263	2710	15	2958	41	2932	16	2957	441	2532	22	2951	24	2949
IncFIB(K)_1__JN233704	1785	66.8	59.4	78.1	57.7	45.2	61.5	33.3	60.2	63.4	60.0	93.8	59.9	53.1	61.3	72.7	59.9	66.7	60.0
IncFII(K)_1__CP000648	1461	92.9	45.1	86.5	44.2	49.0	49.2	66.7	49.1	68.3	48.9	12.5	49.3	43.5	50.1	54.5	49.1	25.0	49.3
Col(pHAD28)_1__KU674895	687	11.1	24.2	11.8	24.6	30.8	22.4	40.0	23.0	29.3	23.0	6.3	23.2	47.6	18.8	31.8	23.0	91.7	22.6
IncR_1__DQ449578	636	22.9	21.3	14.1	22.4	35.0	20.1	20.0	21.4	19.5	21.4	81.3	21.1	51.9	16.1	40.9	21.2	8.3	21.5
ColRNAI_1__DQ298019	600	68.8	15.7	58.2	15.2	14.8	20.7	20.0	20.2	36.6	20.0	0.0	20.3	15.4	21.0	0.0	20.3	16.7	20.2
IncFIB(pQil)_1__JN233705	481	50.6	13.0	62.5	10.1	21.3	15.7	20.0	16.2	12.2	16.2	0.0	16.3	9.3	17.4	9.1	16.2	20.8	16.1
FIA(pBK30683)_1__KF954760	400	13.4	13.5	20.2	12.6	30.0	11.8	13.3	13.5	4.9	13.6	0.0	13.5	30.2	10.5	27.3	13.4	0.0	13.6
IncL__1__JN626286	356	0.0	13.1	0.6	13.5	10.3	12.1	20.0	11.9	9.8	12.0	0.0	12.0	75.1	1.0	0.0	12.1	0.0	12.1
Col440II_1__CP023921	307	7.1	10.6	16.1	9.6	7.6	10.6	0.0	10.4	7.3	10.4	0.0	10.4	34.2	6.2	9.1	10.3	4.2	10.4
Col440I_1__CP023920	296	5.9	10.3	5.8	10.5	9.5	10.0	13.3	9.9	9.8	10.0	6.3	10.0	12.2	9.6	13.6	9.9	16.7	9.9
IncFIB(K)(pCAV1099-114)_1__CP011596	271	1.6	9.8	1.4	10.1	5.3	9.5	26.7	9.0	14.6	9.0	0.0	9.2	5.2	9.8	18.2	9.0	0.0	9.2
IncFIB(pKPHS1)_1__CP003223	236	4.0	8.3	4.6	8.4	15.6	7.2	6.7	7.9	2.4	8.0	0.0	8.0	5.7	8.3	18.2	7.9	8.3	7.9
IncHI1B(pNDM-MAR)_1__JN420336	231	4.0	8.1	8.9	7.6	17.1	6.9	20.0	7.7	26.8	7.5	0.0	7.8	10.9	7.2	13.6	7.7	70.8	7.3
IncFIB(pNDM-Mar)_1__JN420336	220	5.5	7.6	9.2	7.2	15.6	6.6	20.0	7.3	26.8	7.1	0.0	7.4	10.7	6.8	22.7	7.3	75.0	6.8
IncX3_1__JN247852	196	28.9	4.5	22.2	4.5	2.3	7.0	26.7	6.5	2.4	6.7	0.0	6.6	0.0	7.7	72.7	6.1	0.0	6.6
IncC_1__JN157804	121	3.6	4.1	1.4	4.4	24.0	2.1	0.0	4.1	19.5	3.9	0.0	4.1	4.8	3.9	4.5	4.1	0.0	4.1
IncFIA(HI1)_1__AF250878	119	1.2	4.3	0.3	4.5	1.5	4.2	6.7	4.0	14.6	3.9	0.0	4.0	3.2	4.1	0.0	4.0	0.0	4.0
IncFII(pKPX1)_1__AP012055	98	0.0	3.6	0.0	3.7	30.0	0.7	0.0	3.3	0.0	3.3	0.0	3.3	1.4	3.6	0.0	3.3	0.0	3.3
IncN_1__AY046276	69	4.7	2.1	4.6	2.0	0.8	2.5	0.0	2.3	17.1	2.1	6.3	2.3	1.1	2.5	0.0	2.3	0.0	2.3
FII(pBK30683)_1__KF954760	60	0.4	2.2	11.2	0.8	0.4	2.2	0.0	2.0	9.8	1.9	0.0	2.0	0.5	2.3	4.5	2.0	0.0	2.0
repB_KLEB_VIR_AP006726	59	0.0	2.2	0.3	2.2	0.8	2.1	0.0	2.0	0.0	2.0	0.0	2.0	0.7	2.2	4.5	2.0	0.0	2.0
IncM2_1__AF550415	57	5.9	1.5	0.0	2.2	5.3	1.6	0.0	1.9	0.0	1.9	0.0	1.9	1.1	2.1	0.0	1.9	0.0	1.9
Col156_1__NC_009781	55	1.2	1.9	8.4	1.0	1.1	1.9	0.0	1.9	0.0	1.9	0.0	1.9	0.9	2.0	4.5	1.8	0.0	1.9
IncM1_1__U27345	54	1.2	1.9	1.2	1.9	1.1	1.9	0.0	1.8	0.0	1.8	12.5	1.8	5.7	1.1	0.0	1.8	0.0	1.8
IncFII(pKP91)_1__CP000966	51	0.4	1.8	0.0	1.9	0.4	1.8	0.0	1.7	2.4	1.7	0.0	1.7	0.7	1.9	0.0	1.7	0.0	1.7
ColpVC_1__JX133088	45	1.2	1.5	1.2	1.6	0.8	1.6	6.7	1.5	0.0	1.5	0.0	1.5	7.0	0.6	4.5	1.5	0.0	1.5
IncFIB(AP001918)_1__AP001918	40	11.5	0.4	0.3	1.5	0.8	1.4	0.0	1.4	12.2	1.2	0.0	1.4	0.2	1.5	0.0	1.4	0.0	1.4
IncFII_1__AY458016	39	0.4	1.4	0.3	1.4	4.6	1.0	33.3	1.1	0.0	1.3	0.0	1.3	1.6	1.3	4.5	1.3	8.3	1.3
IncFIC(FII)_1__AP001918	31	11.5	0.1	0.0	1.2	0.0	1.1	0.0	1.0	12.2	0.9	0.0	1.0	0.0	1.2	0.0	1.1	0.0	1.1
Col(MG828)_1__NC_008486	29	0.4	1.0	0.3	1.1	1.9	0.9	26.7	0.8	0.0	1.0	0.0	1.0	0.7	1.0	4.5	0.9	8.3	0.9
ColKP3_1__JN205800	26	0.0	1.0	0.0	1.0	1.1	0.8	20.0	0.8	0.0	0.9	0.0	0.9	0.0	1.0	9.1	0.8	100.0	0.1
IncFII(Yp)_1__CP000670	24	0.0	0.9	0.3	0.9	6.1	0.3	0.0	0.8	2.4	0.8	0.0	0.8	1.1	0.8	0.0	0.8	0.0	0.8
IncHI2_1__BX664015	21	0.4	0.7	0.9	0.7	1.1	0.7	0.0	0.7	19.5	0.4	0.0	0.7	0.5	0.8	0.0	0.7	0.0	0.7
IncHI2A_1__BX664015	21	0.4	0.7	0.9	0.7	1.1	0.7	0.0	0.7	19.5	0.4	0.0	0.7	0.5	0.8	0.0	0.7	0.0	0.7
Col(BS512)_1__NC_010656	20	0.4	0.7	1.7	0.5	1.1	0.6	0.0	0.7	0.0	0.7	0.0	0.7	0.9	0.6	4.5	0.6	4.2	0.6
IncFIB(pB171)_1__AB024946	19	0.0	0.7	0.3	0.7	6.1	0.1	0.0	0.6	0.0	0.6	0.0	0.6	1.1	0.6	0.0	0.6	0.0	0.6
IncI1-I(Gamma)_1__AP005147	16	0.0	0.6	0.0	0.6	0.8	0.5	0.0	0.5	0.0	0.5	6.3	0.5	0.5	0.6	0.0	0.5	4.2	0.5
IncX4_1__CP002895	16	0.4	0.6	1.7	0.4	0.4	0.6	0.0	0.5	0.0	0.5	0.0	0.5	0.0	0.6	0.0	0.5	0.0	0.5
IncX1_1__EU370913	13	0.0	0.5	0.0	0.5	1.1	0.4	0.0	0.4	0.0	0.4	0.0	0.4	0.5	0.4	4.5	0.4	0.0	0.4
IncFII(pCRY)_1__NC_005814	10	0.0	0.4	0.0	0.4	0.0	0.4	0.0	0.3	0.0	0.3	0.0	0.3	0.0	0.4	4.5	0.3	0.0	0.3

Genes comprising ≥1% of all carbapenemase genes are shown, while plasmid replicons found in ≥10 genomes are shown and ordered by their frequency.

Table 18. Proportion of all *Escherichia coli* genomes (n=548) with and without particular carbapenemase gene variants carrying individual plasmid replicons

	Carbapenemase	KPC-2		KPC-3		NDM-1		NDM-4		NDM-5		VIM-1		OXA-48		OXA-162		OXA-181		OXA-232		OXA-244	
		Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Plasmid replicon	No. of isolates	7	541	14	534	16	532	7	541	62	486	7	541	42	506	2	546	12	536	4	544	13	535
IncFIB(AP001918)_1__AP001918	331	85.7	60.1	71.4	60.1	50.0	60.7	71.4	60.3	54.8	61.1	71.4	60.3	45.2	61.7	0.0	60.6	66.7	60.3	50.0	60.5	76.9	60.0
IncFII_1__AY458016	209	28.6	38.3	28.6	38.4	25.0	38.5	42.9	38.1	66.1	34.6	42.9	38.1	21.4	39.5	0.0	38.3	8.3	38.8	50.0	38.1	84.6	37.0
IncFIA_1__AP001918	175	14.3	32.2	57.1	31.3	12.5	32.5	14.3	32.2	77.4	26.1	28.6	32.0	28.6	32.2	0.0	32.1	58.3	31.3	75.0	31.6	23.1	32.1
Col156_1__NC_009781	157	28.6	28.7	35.7	28.5	18.8	28.9	0.0	29.0	16.1	30.2	42.9	28.5	28.6	28.7	0.0	28.8	0.0	29.3	25.0	28.7	15.4	29.0
Col(MG828)_1__NC_008486	82	14.3	15.0	14.3	15.0	12.5	15.0	0.0	15.2	22.6	14.0	14.3	15.0	19.0	14.6	0.0	15.0	0.0	15.3	25.0	14.9	0.0	15.3
IncI1-I(Gamma)_1__AP005147	67	0.0	12.4	21.4	12.0	31.3	11.7	57.1	11.6	14.5	11.9	0.0	12.4	19.0	11.7	0.0	12.3	8.3	12.3	25.0	12.1	7.7	12.3
IncFII(pRSB107)_1__AJ851089	63	0.0	11.6	35.7	10.9	6.3	11.7	0.0	11.6	9.7	11.7	0.0	11.6	2.4	12.3	0.0	11.5	0.0	11.8	25.0	11.4	0.0	11.8
Col(BS512)_1__NC_010656	60	0.0	11.1	0.0	11.2	0.0	11.3	0.0	11.1	30.6	8.4	14.3	10.9	14.3	10.7	0.0	11.0	41.7	10.3	50.0	10.7	7.7	11.0
Col(pHAD28)_1__KU674895	52	14.3	9.4	7.1	9.6	12.5	9.4	0.0	9.6	30.6	6.8	0.0	9.6	7.1	9.7	0.0	9.5	16.7	9.3	25.0	9.4	7.7	9.5
IncFII(pSE11)_1__AP009242	40	0.0	7.4	7.1	7.3	25.0	6.8	28.6	7.0	1.6	8.0	28.6	7.0	7.1	7.3	0.0	7.3	0.0	7.5	0.0	7.4	0.0	7.5
IncX3_1__JN247852	40	0.0	7.4	28.6	6.7	12.5	7.1	100.0	6.1	22.6	5.3	14.3	7.2	0.0	7.9	0.0	7.3	75.0	5.8	0.0	7.4	0.0	7.5
IncFII(29)_1__CP003035	39	14.3	7.0	0.0	7.3	12.5	7.0	14.3	7.0	1.6	7.8	14.3	7.0	2.4	7.5	0.0	7.1	0.0	7.3	0.0	7.2	0.0	7.3
IncX1_1__EU370913	32	0.0	5.9	7.1	5.8	12.5	5.6	0.0	5.9	0.0	6.6	0.0	5.9	11.9	5.3	0.0	5.9	0.0	6.0	0.0	5.9	7.7	5.8
ColRNAI_1__DQ298019	31	14.3	5.5	0.0	5.8	0.0	5.8	0.0	5.7	11.3	4.9	28.6	5.4	4.8	5.7	0.0	5.7	0.0	5.8	0.0	5.7	0.0	5.8
IncFII(pCoo)_1__CR942285	31	14.3	5.5	0.0	5.8	6.3	5.6	0.0	5.7	6.5	5.6	0.0	5.7	11.9	5.1	0.0	5.7	16.7	5.4	0.0	5.7	0.0	5.8
IncY_1__K02380	29	14.3	5.2	14.3	5.1	6.3	5.3	0.0	5.4	11.3	4.5	0.0	5.4	7.1	5.1	0.0	5.3	16.7	5.0	50.0	5.0	7.7	5.2
IncL__1__JN626286	28	0.0	5.2	0.0	5.2	0.0	5.3	0.0	5.2	0.0	5.8	0.0	5.2	59.5	0.6	100.0	4.8	0.0	5.2	0.0	5.1	0.0	5.2
p0111_1__AP010962	28	0.0	5.2	0.0	5.2	6.3	5.1	0.0	5.2	8.1	4.7	0.0	5.2	14.3	4.3	0.0	5.1	0.0	5.2	0.0	5.1	0.0	5.2
IncFII(pAMA1167-NDM-5)_1__CP024805	22	0.0	4.1	0.0	4.1	0.0	4.1	0.0	4.1	14.5	2.7	0.0	4.1	14.3	3.2	0.0	4.0	58.3	2.8	0.0	4.0	7.7	3.9
IncX4_2__FN543504	20	0.0	3.7	7.1	3.6	0.0	3.8	0.0	3.7	6.5	3.3	14.3	3.5	2.4	3.8	0.0	3.7	8.3	3.5	0.0	3.7	0.0	3.7
IncB/O/K/Z_1__CU928147	18	0.0	3.3	0.0	3.4	0.0	3.4	14.3	3.1	3.2	3.3	0.0	3.3	2.4	3.4	0.0	3.3	0.0	3.4	0.0	3.3	7.7	3.2
IncFIB(H89-PhagePlasmid)_1__HG530657	18	0.0	3.3	0.0	3.4	0.0	3.4	0.0	3.3	16.1	1.6	0.0	3.3	0.0	3.6	0.0	3.3	0.0	3.4	0.0	3.3	15.4	3.0
IncFII(K)_1__CP000648	17	28.6	2.8	64.3	1.5	12.5	2.8	0.0	3.1	1.6	3.3	0.0	3.1	2.4	3.2	0.0	3.1	0.0	3.2	0.0	3.1	0.0	3.2
IncB/O/K/Z_2__GU256641	17	0.0	3.1	0.0	3.2	6.3	3.0	0.0	3.1	1.6	3.3	0.0	3.1	2.4	3.2	0.0	3.1	0.0	3.2	0.0	3.1	0.0	3.2
ColpVC_1__JX133088	16	0.0	3.0	0.0	3.0	0.0	3.0	28.6	2.6	3.2	2.9	0.0	3.0	7.1	2.6	0.0	2.9	0.0	3.0	0.0	2.9	0.0	3.0
IncFIB(pQil)_1__JN233705	15	42.9	2.2	64.3	1.1	6.3	2.6	0.0	2.8	1.6	2.9	0.0	2.8	0.0	3.0	0.0	2.7	0.0	2.8	0.0	2.8	0.0	2.8
Col440I_1__CP023920	13	0.0	2.4	0.0	2.4	0.0	2.4	0.0	2.4	3.2	2.3	0.0	2.4	9.5	1.8	0.0	2.4	8.3	2.2	0.0	2.4	0.0	2.4
IncI2(Delta)_1__AP002527	13	0.0	2.4	0.0	2.4	6.3	2.3	0.0	2.4	3.2	2.3	0.0	2.4	2.4	2.4	0.0	2.4	8.3	2.2	0.0	2.4	0.0	2.4
IncX4_1__CP002895	13	0.0	2.4	0.0	2.4	0.0	2.4	0.0	2.4	1.6	2.5	0.0	2.4	2.4	2.4	0.0	2.4	8.3	2.2	0.0	2.4	0.0	2.4
IncN_1__AY046276	12	42.9	1.7	0.0	2.2	6.3	2.1	0.0	2.2	0.0	2.5	14.3	2.0	0.0	2.4	0.0	2.2	0.0	2.2	0.0	2.2	0.0	2.2
IncFIC(FII)_1__AP001918	12	28.6	1.8	0.0	2.2	0.0	2.3	0.0	2.2	0.0	2.5	0.0	2.2	2.4	2.2	0.0	2.2	0.0	2.2	0.0	2.2	0.0	2.2
IncC_1__JN157804	12	0.0	2.2	0.0	2.2	56.3	0.6	0.0	2.2	1.6	2.3	14.3	2.0	0.0	2.4	0.0	2.2	0.0	2.2	0.0	2.2	0.0	2.2
Col8282_1__DQ995352	11	0.0	2.0	0.0	2.1	0.0	2.1	0.0	2.0	3.2	1.9	0.0	2.0	4.8	1.8	0.0	2.0	0.0	2.1	0.0	2.0	0.0	2.1
IncFIB(K)_1__JN233704	9	0.0	1.7	7.1	1.5	0.0	1.7	0.0	1.7	1.6	1.6	0.0	1.7	2.4	1.6	0.0	1.6	0.0	1.7	0.0	1.7	0.0	1.7
IncFII(pHN7A8)_1__JN232517	9	0.0	1.7	0.0	1.7	6.3	1.5	0.0	1.7	0.0	1.9	0.0	1.7	4.8	1.4	0.0	1.6	0.0	1.7	0.0	1.7	15.4	1.3
IncFIB(pB171)_1__AB024946	8	0.0	1.5	0.0	1.5	18.8	0.9	0.0	1.5	4.8	1.0	0.0	1.5	0.0	1.6	0.0	1.5	0.0	1.5	25.0	1.3	0.0	1.5
IncB/O/K/Z_4__FN868832	8	0.0	1.5	0.0	1.5	14.3	1.3	0.0	1.6	0.0	1.5	0.0	1.6	0.0	1.6	0.0	1.5	0.0	1.5	0.0	1.5	7.7	1.3
IncHI2_1__BX664015	7	0.0	1.3	0.0	1.3	0.0	1.3	0.0	1.3	0.0	1.4	28.6	0.9	7.1	0.8	0.0	1.3	0.0	1.3	0.0	1.3	0.0	1.3
IncHI2A_1__BX664015	7	0.0	1.3	0.0	1.3	0.0	1.3	0.0	1.3	0.0	1.4	28.6	0.9	7.1	0.8	0.0	1.3	0.0	1.3	0.0	1.3	0.0	1.3
IncR_1__DQ449578	6	14.3	0.9	7.1	0.9	0.0	1.1	0.0	1.1	0.0	1.2	0.0	1.1	2.4	1.0	0.0	1.1	8.3	0.9	0.0	1.1	0.0	1.1
IncHI1A_1__AF250878	5	14.3	0.7	0.0	0.9	0.0	0.9	0.0	0.9	0.0	1.0	0.0	0.9	0.0	1.0	0.0	0.9	0.0	0.9	0.0	0.9	0.0	0.9
IncHI1B(R27)_1_R27_AF250878	5	14.3	0.7	0.0	0.9	0.0	0.9	0.0	0.9	0.0	1.0	0.0	0.9	0.0	1.0	0.0	0.9	0.0	0.9	0.0	0.9	0.0	0.9
Col440II_1__CP023921	5	0.0	0.9	0.0	0.9	6.3	0.8	0.0	0.9	0.0	1.0	0.0	0.9	0.0	1.0	0.0	0.9	0.0	0.9	0.0	0.9	0.0	0.9
IncX1_4__JN935898	5	28.6	0.6	0.0	0.9	0.0	0.9	0.0	0.9	1.6	0.8	14.3	0.7	0.0	1.0	0.0	0.9	0.0	0.9	0.0	0.9	0.0	0.9

Genes comprising ≥1% of all carbapenemase genes are shown, while plasmid replicons found in ≥5 genomes are shown and ordered by their frequency.

3.5.9 Association of *bla*$_{\text{OXA-48-like}}$ genes with pOXA-48-like plasmids

We further investigated the association between *bla*$_{\text{OXA-48-like}}$ genes and pOXA-48-like plasmids using the short-read sequencing data. Due to the high stability of the pOXA-48-like plasmid backbone, it is possible to infer the presence of this plasmid among isolates by mapping their short sequence reads to the pOXA48a reference plasmid [51]. Correlation between the presence of the plasmid via this mapping approach and the presence of the IncL replicon was strong; 97.9% (320/327) of isolates in *K. pneumoniae* SC and 100% (27/27) in *E. coli* with ≥90% plasmid mapping (the threshold over which we deemed the plasmid to be 'present') also possessed the IncL replicon. In both species, we found a strong association of several of the *bla*$_{\text{OXA-48-like}}$ variants with presence of the pOXA-48-like plasmid (Table 19).

Most notably, 69.8% (308/441) and 59.5% (25/42) of *K. pneumoniae* SC and *E. coli* isolates with the *bla*$_{\text{OXA-48}}$ gene, respectively, had mapping across the length of pOXA48a of ≥90%. This compared with 0.4% (10/2473) and 0% (0/474) of isolates from these species carrying no *bla*$_{\text{OXA-48}}$ or other *bla*$_{\text{OXA-48-like}}$ genes. We also detected ten *K. pneumoniae* SC isolates lacking any *bla*$_{\text{OXA-48-like}}$ gene that had ≥90% mapping to the plasmid, which included six isolates with no carbapenemase, three isolates that carried *bla*$_{\text{VIM-1}}$ and one isolate that carried *bla*$_{\text{NDM-5}}$. Of note, *bla*$_{\text{VIM-1}}$ genes have been previously observed within IncL plasmid backbones [56], although long-read sequencing would be required to further confirm IncL plasmid carriage of the three *bla*$_{\text{VIM-1}}$ genes identified here and the relatedness of these putative plasmids to pOXA-48-like plasmids.

We also found that some *K. pneumoniae* SC isolates, including 11.6% (51/441) of those with *bla*$_{\text{OXA-48}}$ and 20.0% (1/5) of those with *bla*$_{\text{OXA-244}}$, mapped to 70-90% of the pOXA48a plasmid, and were scored as having the plasmid 'partially present'. This lower amount of mapping could reflect deletions within the pOXA-48-like plasmid, which have been observed previously among *K. pneumoniae* ST307 isolates in Wales [57], or may represent sequence variation in the plasmid backbone. Interestingly, we found that 42.3% (22/52) of the isolates carrying *bla*$_{\text{OXA-48}}$/*bla*$_{\text{OXA-244}}$ in *K. pneumoniae* SC with 70-90% mapping did not carry an IncL replicon. Of these, 95.5% (21/22) instead carried either an IncM1 (n=18) or IncM2 (n=3) replicon, which were grouped with IncL replicons into the "IncL/M" group until recently [58]. IncM plasmids have been shown previously to share substantial albeit not complete homology with IncL plasmids [57].

Table 19. Presence/absence of pOXA-48-like plasmids among *Klebsiella pneumoniae* SC (n=2 973) and *Escherichia coli* (n=548) isolates as inferred from short-read mapping

Isolate subset	Isolates with the pOXA-48-like plasmid, n (%)		
	Present, ≥90% mapping	Partially present, 70-90% mapping	Absent, <70% mapping
K. pneumoniae SC (n=2 973)			
bla$_{\text{OXA-48}}$ (n=441)	308 (69.8)	51 (11.6)	82 (18.6)
bla$_{\text{OXA-162}}$ (n=1)	1 (100)	0 (0)	0 (0)
bla$_{\text{OXA-181}}$ (n=22)	0 (0)	0 (0)	22 (100)
bla$_{\text{OXA-232}}$ (n=24)	0 (0)	0 (0)	24 (100)
bla$_{\text{OXA-244}}$ (n=5)	4 (80.0)	1 (20.0)	0 (0)
bla$_{\text{OXA-245}}$ (n=4)	3 (75.0)	0 (0)	1 (25.0)
bla$_{\text{OXA-1211}}$ (n=2)	0 (0)	0 (0)	2 (100)
bla$_{\text{OXA-1212}}$ (n=1)	1 (100)	0 (0)	0 (0)
All other isolates (n=2 473)	10 (0.4)	85 (3.4)	2378 (96.2)
E. coli (n=548)			
bla$_{\text{OXA-48}}$ (n=42)	25 (59.5)	0 (0)	17 (40.5)
bla$_{\text{OXA-162}}$ (n=2)	2 (100)	0 (0)	0 (0)
bla$_{\text{OXA-181}}$ (n=12)	0 (0)	0 (0)	12 (100)
bla$_{\text{OXA-232}}$ (n=4)	0 (0)	0 (0)	4 (100)
bla$_{\text{OXA-244}}$ (n=13)	0 (0)	0 (0)	13 (100)
bla$_{\text{OXA-1213}}$ (n=1)	0 (0)	0 (0)	1 (100)
Other (n=474)	0 (0)	3 (0.6)	471 (99.4)

3.5.10 Development over time (comparison to the EuSCAPE dataset)

Overview

We compared the results of the CCRE survey (2019) with those from the EuSCAPE survey (2013-14) in which isolates were collected according to a similar protocol with a few modifications as outlined in section 2.1. While the *K. pneumoniae* SC genomes from the EuSCAPE survey have been previously analysed [9], the *E. coli* genomes are newly reported here, with all metadata and additional genotyping data available from Microreact (https://microreact.org/project/ecoli-euscape-ccre).

Overall, the number of sequenced isolates included in the final curated dataset was higher in the CCRE survey (n=3 521) compared with EuSCAPE (n=1 938) (Table 20). This reflects the increased number of countries and hospitals that participated in the CCRE survey and contributed isolates to the final dataset (323 hospitals in 36 countries in the CCRE survey, compared with 260 hospitals in 32 countries in EuSCAPE). Of note, while the recruited hospitals varied in each survey, 113 hospitals contributed *K. pneumoniae* SC isolates to both the EuSCAPE and CCRE survey data sets, while 24 hospitals contributed *E. coli* isolates to both. The *K. pneumoniae* SC isolates substantially outnumbered *E. coli* isolates in both surveys (Table 20). *K. pneumoniae* was also the dominant species among carbapenem-R/I and carbapenem-S isolates from the *K. pneumoniae* SC in both surveys. It accounted for 99.5% (939/944) and 98.7% (1545/1566) of the carbapenem-R/I isolates among EuSCAPE and the CCRE survey isolates, respectively.

Table 20. Species distribution of Enterobacterales isolates in EuSCAPE (n=1 938) and the CCRE survey (n=3 521)

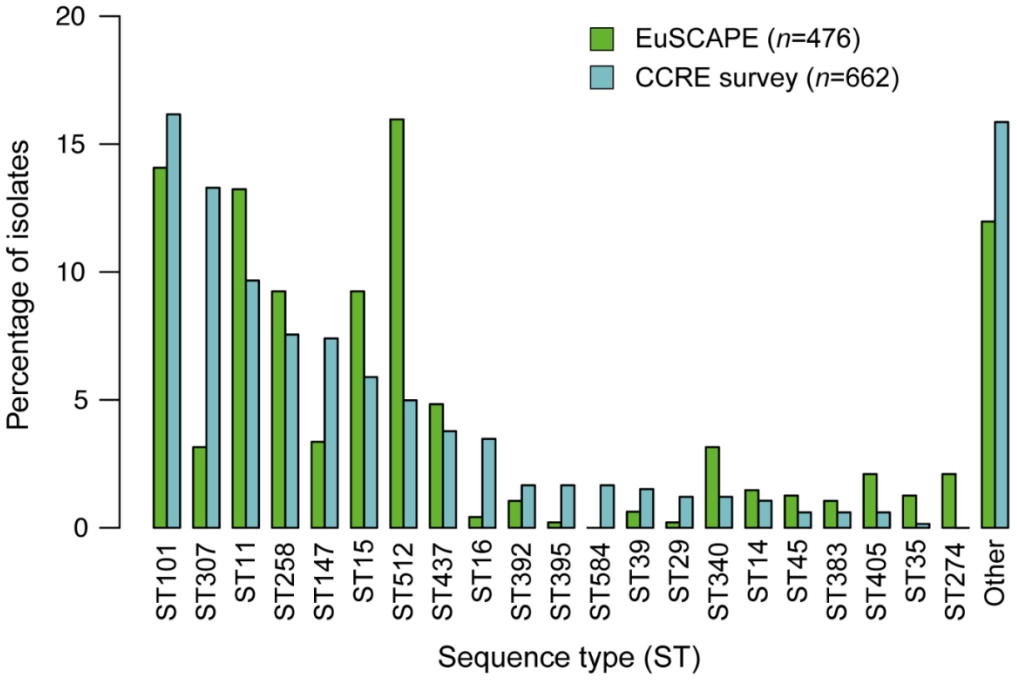
Species		EuSCAPE (2013-14)			CCRE survey (2019)		
		Carbapenem-R/I n	Carbapenem-S n	Total n	Carbapenem-R/I n	Carbapenem-S n	Total n
K. pneumoniae SC	All	944	773	1 717	1 566	1 407	2 973
	K. pneumoniae	939	710	1 649	1 545	1 289	2 834
	K. quasipneumoniae	2	15	17	12	38	50
	K. variicola	3	45	48	9	79	88
	K. quasivariicola	0	3	3	0	1	1
E. coli	All	99	122	221	211	337	548
Total		1 043	895	1 938	1 777	1 744	3 521

Comparison of sequence type distribution

We compared the distribution of STs among isolates collected during EuSCAPE and the CCRE survey. As the recruited hospitals varied between the two surveys, we restricted this analysis to hospitals that contributed isolates to both. The 113 hospitals that submitted *K. pneumoniae* SC isolates to both surveys contributed a total of 1 246 isolates to the CCRE survey data set (including 662 carbapenem-R/I isolates) and 876 to the EuSCAPE data set (including 476 carbapenem-R/I isolates). The 24 hospitals that submitted *E. coli* to both surveys contributed a total of 100 isolates to the CCRE survey data set (including 42 carbapenem-R/I isolates) and 59 to the EuSCAPE data set (including 29 carbapenem-R/I isolates). Due to the low numbers of *E. coli* isolates available for comparison, we largely restricted these comparisons to the *K. pneumoniae* SC isolates only.

We found several of the STs among *K. pneumoniae* SC isolates that were dominant among carbapenem-R/I isolates in EuSCAPE were still dominant in the CCRE survey, albeit with some changes in their overall proportions (Figure 32). These included ST11, ST15, ST101 and ST258, which each comprised ≥5% of carbapenem-R/I isolates from both surveys. However, notable increases of ST147 (3.4% to 7.4%) and particularly ST307 (3.2% to 13.3%) meant that these were among the most frequent STs detected in the CCRE survey. We also observed more than a two-fold increase in the proportion of carbapenem-R/I isolates from ST16 (0.4% to 3.5%), ST29 (0.2% to 1.2%), ST39 (0.6% to 1.5%), ST395 (0.2% to 1.7%) and ST584 (0% to 1.7%). By contrast, we observed at least a two-fold decline in the proportion of carbapenem-R/I isolates belonging to ST35 (1.3% to 0.2%), ST45 (1.3% to 0.6%), ST274 (2.1% to 0%), ST340 (3.2% to 1.2%), ST405 (2.1% to 0.6%) and ST512 (16.0% to 5.0%). However, trends in specific countries may differ from the overall trends on the European level.

Figure 32. Proportion of STs among carbapenem-R/I *Klebsiella pneumoniae* SC isolates from EuSCAPE (2013-14; n=476) and the CCRE survey (2019, n=662)



Only isolates from 113 hospitals that contributed K. pneumoniae SC isolates to both data sets were included. STs making up ≥1% of carbapenem-R/I isolates in either of the sample sets are shown.

Comparison of carbapenemase distribution

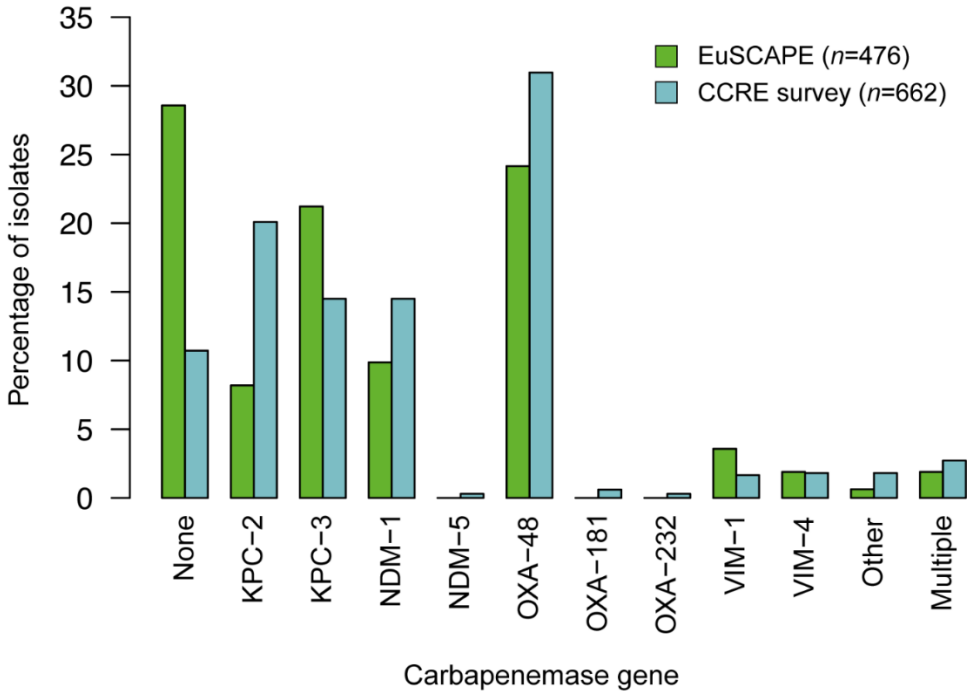
We also compared the distribution of carbapenemase genes among isolates from hospitals that contributed to both EuSCAPE and the CCRE survey. Among *K. pneumoniae* SC isolates from the 113 shared hospitals, we found that a higher proportion of carbapenem-R/I isolates carried a carbapenemase gene among CCRE survey isolates compared with EuSCAPE isolates (89.3% vs 69.6%, respectively). Among the 24 hospitals that contributed *E. coli* isolates to both surveys, this pattern was even more pronounced (88.1% vs 27.6%, respectively). We attribute these differences largely to the improved screening procedures and increasing spread of carbapenemase-producing high-risk clones.

We found some differences in the proportions of the major carbapenemase gene variants among carbapenem-R/I *K. pneumoniae* SC isolates from the shared hospitals, with increases observed for $bla_{\text{KPC-2}}$ (9.0% to 20.1%), $bla_{\text{NDM-1}}$ (10.7% to 16.5%) and $bla_{\text{OXA-48}}$ (25.6% to 32.8%), and a decrease for $bla_{\text{KPC-3}}$ (21.2% to 14.7%) from EuSCAPE to the CCRE survey. More than two-thirds (67.4%; 29/43) of the isolates from EuSCAPE which carried $bla_{\text{KPC-2}}$ belonged to ST258 while those from the CCRE survey were more widely distributed across different STs, with significant proportions from ST258 (33.8%; 45/133), ST101 (21.1%; 28/133), ST307 (12.0%; 16/133), ST39 (7.5%; 10/133) and ST584 (7.5%; 10/133). ST11 was the most frequent ST among isolates carrying $bla_{\text{NDM-1}}$ in both surveys, accounting for 41.2% (21/51) of the isolates in EuSCAPE and 37.6% (41/109) of the isolates in the CCRE survey. However, the proportion of ST147 among isolates carrying $bla_{\text{NDM-1}}$ increased from 0% (0/51) in EuSCAPE to 21.1% (23/109) in the CCRE survey.

The number of carbapenem-R/I *K. pneumoniae* SC isolates carrying two carbapenemases from the 113 shared hospitals increased from 1.9% (9/476) in EuSCAPE to 2.7% (18/662) in the CCRE survey. The most common combination of carbapenemase genes in both surveys was $bla_{\text{NDM-1}}$/$bla_{\text{OXA-48}}$, accounting for 44.4% (4/9) of these isolates in EuSCAPE and 50.0% (9/18) in the CCRE survey. Among the 24 hospitals that contributed *E. coli* to both surveys, we found no carbapenem-R/I *E. coli* isolates (0/29) with ≥2 carbapenemase genes from EuSCAPE, while one isolate (2.4%; 1/42) was found in the CCRE survey.

While we performed no formal comparison of the carbapenemase distribution among *E. coli* isolates in the two surveys, we did note a large increase in the proportion of carbapenem-R/I *E. coli* isolates from all hospitals carrying $bla_{\text{NDM-5}}$ from 2.0% (2/99) in EuSCAPE to 29.4% (62/211) in the CCRE survey. This observation also held when analysing isolates from the 24 shared hospitals only (0% to 31.0%).

Figure 33. Proportion of carbapenemase gene variants among carbapenem-R/I *Klebsiella pneumoniae* SC isolates from EuSCAPE (2013-14; n=476) and the CCRE survey (2019, n=662)



Only isolates from 113 hospitals that contributed K. pneumoniae SC isolates to both data sets were included. Genes comprising ≥1% of carbapenemase genes in the CCRE survey isolates are shown.

Epidemiology of high-risk STs

Increase of Klebsiella pneumoniae *ST307*

The most notable increase of any ST among the *K. pneumoniae* SC was that of ST307. Among 113 hospitals that contributed *K. pneumoniae* SC isolates to both EuSCAPE and the CCRE survey, the proportion of ST307 among carbapenem-R/I isolates increased from 3.2% (15/476) to 13.3% (88/662). The increase in ST307 between surveys was particularly notable in Italy and Spain where the proportion among carbapenem-R/I isolates from all hospitals increased from 3.2% (5/154) to 32.7% (91/278) and from 0% (0/69) to 15.3% (27/176), respectively. In the CCRE survey, carbapenem-R/I ST307 isolates were obtained from 81.3% (26/32) of the participating hospitals in Italy and 58.3% (14/24) of those in Spain. ST307 isolates were also the most widely distributed ST in the CCRE survey, collected from 108 hospitals in 28 countries. Notably, ST307 was also the most common ST among carbapenem-S isolates in the CCRE survey, representing 4.4% (62/1407) of this group. However, we found that the proportion of ST307 isolates carrying a carbapenemase gene increased between the surveys from 35.6% (16/45) to 68.2% (165/242).

To further investigate the diversity, geo-temporal spread and emergence of carbapenem resistance within ST307, we combined genomes of ST307 (and closely related STs) from the EuSCAPE (n=45) and CCRE (n=245) surveys with additional publicly available ST307 genomes from Pathogenwatch (n=986) to create a collection of 1 276 genomes. We generated a core genome alignment by mapping sequence reads to an ST307 reference genome (accession CP026495.1). After the removal of recombined regions from this alignment, we found a maximum of 718 SNPs between any pair of genomes. A phylogenetic tree, constructed using the recombination-free alignment, demonstrated that the isolates were primarily divided into two clades, except four isolates that formed a distinct outgroup lineage (Figure 34; https://microreact.org/project/kp-st307-ccre-survey). The first clade contained isolates almost exclusively from the US (99.6%; 503/505) collected between 2011 and 2020, with most (93.4%; 470/503) of these isolates being from the Houston Methodist Hospital system in Texas, which have been described previously [59]. The second clade contained isolates collected from diverse global locations (56 countries) between 2009 and 2020 and included all isolates from EuSCAPE and the CCRE survey. Interestingly, there was greater genomic diversity among isolates from the US clade (which differed by a maximum of 708 SNPs) than those from the global clade (which differed by a maximum of 356 SNPs). Despite the wide geographic spread of isolates from the global clade, we found substantial phylogenetic clustering by hospital and country, suggestive of spread within national hospital networks. Indeed, of 13 hospitals that submitted ST307 isolates in both surveys, we identified four with phylogenetic clustering of isolates from the two surveys (hospital codes FR01 (France), MT01 (Malta), ES09 and ES14 (Spain), suggestive of local persistence of these lineages over the time period.

The phylogeny also demonstrated that, despite the substantial clustering by location, isolates from many individual countries (including Italy, Spain and the US) were found in many distinct lineages of the global clade, demonstrating multiple introductions of ST307 into each of these countries.

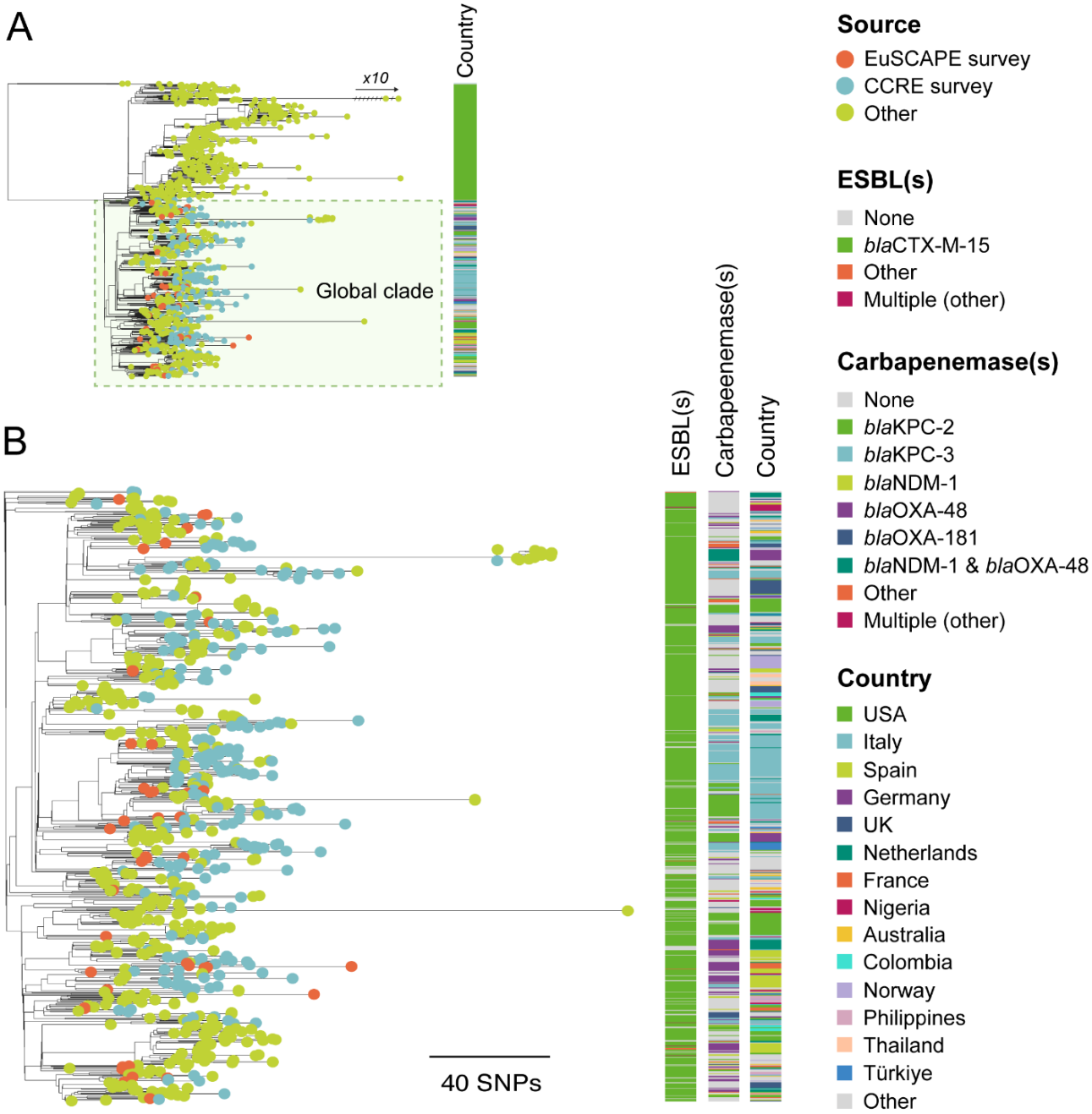
We found that isolates from both EuSCAPE and the CCRE survey were widely distributed across many different lineages of the global ST307 clade. Isolates from the CCRE survey were typically closely related to those sampled during the EuSCAPE survey, with no major new lineages observed. This suggests that ST307 remained endemic among European hospitals during the time period between the surveys, with the ST307s circulating in 2019 being closely related descendants of the circulating lineages from 2013-14.

Most (90.4%; 1 153/1 276) ST307 isolates carried a *bla*$_{\text{CTX-M-15}}$ gene and these were distributed across the phylogeny. The few isolates lacking this gene were sporadically distributed across the ST307 population, having likely lost the associated plasmid. Carbapenem-R/I and -S isolates from EuSCAPE and the CCRE survey were both widely distributed across the global ST307 clade, demonstrating many independent emergences of carbapenem resistance. We detected a high number of different carbapenemase genes in the global clade, as well as many independent acquisitions of particular carbapenemase gene variants. The types of carbapenemase gene variants varied by country, with most isolates from Italy carrying *bla*$_{\text{KPC-2}}$ or *bla*$_{\text{KPC-3}}$ (82.8%; 135/163) and most isolates from Spain carrying *bla*$_{\text{OXA-48}}$ (63.9%; 39/61), despite isolates from these individual countries belonging to different lineages. Approximately one third (33.7%; 170/505) of isolates from the US clade carried a carbapenemase gene, most of which (96.5%; 164/170) were *bla*$_{\text{KPC-2}}$.

We also investigated the presence of loci encoding virulence factors among the combined collection of ST307 genomes using Kleborate. We found that 20.9% (267/1 276) carried the yersiniabactin locus. Multiple yersiniabactin locus types were found, with isolates possessing the same type typically clustering together in the phylogeny. None of the genomes carried colibactin or salmochelin loci. We detected aerobactin, RmpADC and *rmpA2* loci among 1.4% (18/1276), 1.2% (15/1 276) and 1.1% (14/1 276) isolates, respectively. Most of these occurred within a single phylogenetic clade of 15 isolates submitted from Germany (n=13) and Finland (n=2). All 15 isolates within this clade carried the *iuc1* locus (aerobactin) and *rmp1* (RmpADC), while 13/15 carried a truncated version of *rmpA2*. Of concern, all 15 isolates also carried both *bla*$_{\text{NDM-1}}$ and *bla*$_{\text{OXA-48}}$.

Altogether, this analysis suggests that ST307 is a globally distributed, healthcare-associated clone that is prevalent within European hospitals and which has been successful even prior to the acquisition of carbapenem resistance. However, it also possesses the ability to rapidly gain additional resistance determinants (including carbapenemase genes), which has occurred frequently in recent years.

Figure 34. A) Phylogenetic tree of 1 276 *Klebsiella pneumoniae* ST307 isolates from the EuSCAPE survey (n=45), CCRE survey (n=245) and additional public databases (n=986). B) Larger version of the 'Global clade' highlighted in (A).



The tree was constructed using variable sites from a pseudo-genome alignment generated by mapping sequence reads to an ST307 reference genome (CP026495.1) and removing recombined regions. The tree was rooted using an outgroup isolate (ST1235) that was subsequently removed. Isolate tips are coloured by the data source and the metadata columns show ESBL gene variant, carbapenemase gene variant and/or the country of origin. Branches leading to two isolates have been shortened for visualisation purposes in (A). The scale represents the number of SNPs. An interactive version of the tree with additional metadata and genotyping data is available at: https://microreact.org/project/kp-st307-ccre-survey

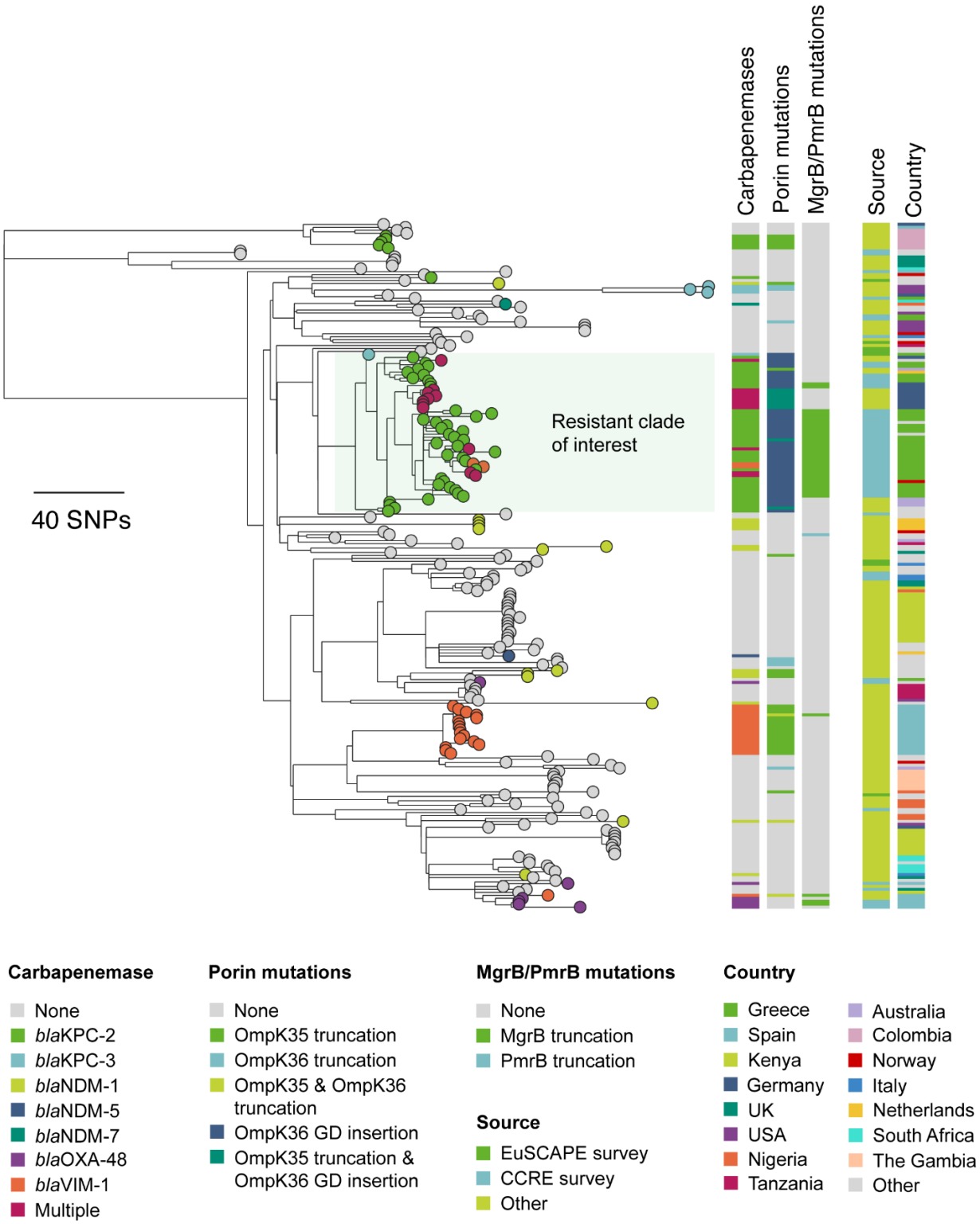
Emergence of K. pneumoniae *ST39*

Among the 113 hospitals that contributed *K. pneumoniae* SC isolates to both surveys, we observed an increase in the proportion of ST39 among carbapenem-R/I isolates from 0.6% (3/476) in EuSCAPE to 1.5% (10/662) in the CCRE survey. *K. pneumoniae* ST39 isolates, which totalled 56 across the full CCRE survey data set (including 41 carbapenem-R/I isolates), were mainly from Greece (64.3%; 36/56) where they were obtained from 14/15 of the participating hospitals. Most of the carbapenem-R/I ST39 isolates from the CCRE survey possessed a worrisome resistance profile including the bla_{KPC-2} gene (82.9%; 34/41), porin mutations (87.8%; 36/41) and an MgrB truncation (80.5%; 33/41).

To further investigate the emergence of ST39 and its association with resistance loci, we analysed the ST39 genomes from both surveys with 168 public ST39 genomes from Pathogenwatch. We mapped sequence reads of all isolates to an ST39 reference genome (CP094991.1) and removed recombined regions from the resulting pseudo-genome alignment. A total of 394 SNPs were found among any pair of these ST39 genomes after disregarding those that occurred in the predicted recombination regions. We used the vertically-inherited SNPs to construct a phylogenetic tree, which included isolates from 44 countries sampled between 2005 and 2020 (Figure 35; https://microreact.org/project/kp-st39-ccre-survey).

The phylogenetic tree showed that many of the CCRE survey isolates (66.1%; 37/56) were clustered into a single clade, including most of the isolates from Greece (n=32) but also some from Bulgaria (n=1), Cyprus (n=1), Germany (n=2) and Norway (n=1). This clade, which comprised of 54 isolates from 2013-2019, included one isolate from the EuSCAPE survey (from Greece), as well as another 16 public genomes (from Australia, Germany, the Netherlands and Russia). The isolates differed by a mean of 33.7 SNPs (range, 0-69). All the isolates in this clade carried at least one carbapenemase gene (mostly bla_{KPC-2}) and porin mutations (mostly an OmpK36 GD insertion +/- an OmpK35 truncation). A subset (59.3%; 32/54) had also acquired an MgrB truncation. One fifth (20.4%; 11/54) of the isolates carried two carbapenemases (bla_{KPC-2}/bla_{NDM-1}, n=7; bla_{KPC-2}/bla_{VIM-1}, n=3; bla_{KPC-2}/bla_{OXA-48}, n=1). The CCRE survey isolates in this clade were detected from 12/15 of the participating hospitals in Greece, which were widespread across the country. Analysis of the phenotypic AST results for the 37 CCRE survey isolates from this clade showed high levels of resistance to piperacillin-tazobactam (97.3%; 36/37 isolates with available results), ceftazidime (97.3%; 36/37), meropenem (97.2%; 35/36), ciprofloxacin (100%; 35/35) and tobramycin (83.8%; 31/37), while resistance to ceftazidime-avibactam (25%; 9/36), colistin (11.1%; 4/36), fosfomycin (36.4%; 12/33) and tigecycline (68.6%; 24/35) was more variable.

Figure 35. Phylogenetic tree of 232 *Klebsiella pneumoniae* ST39 isolates from the EuSCAPE survey (n=8), CCRE survey (n=56) and additional public databases (n=168)



The tree was constructed using variable sites from a pseudo-genome alignment generated by mapping sequence reads to an ST39 reference genome (CP094991.1) and removing recombined regions. The tree was rooted using an outgroup isolate (ST364) that was subsequently removed. Isolate tips are coloured by the carbapenemase variant, while metadata columns show the carbapenemase variant, porin mutations (OmpK35/OmpK36) and colistin resistance mutations (MgrB/PmrB), and the data source and country of origin. The scale bar represents the number of SNPs. An interactive version of the tree with additional metadata and genotyping data is available at: https://microreact.org/project/kp-st39-ccre-survey

Due to the recent emergence and apparent rapid spread of this *K. pneumoniae* ST39 clade across Greece, we sought to determine its prevalence via a rapid follow-up survey in Greece [60]. This survey was conducted to determine the prevalent STs of carbapenem-R/I *K. pneumoniae* SC in the same 15 Greek hospitals that participated in the CCRE survey, to generate more timely data to inform public health action. The protocol included isolate and data collection based on the CCRE survey protocol with a few modifications to decrease the turn-around time from isolate collection to WGS results. The continued circulation of this clade was confirmed by the detection of ST39 isolates in 13 of 15 participating hospitals in 2022, despite the total number of isolates being lower in 2022 (n=23) than in the same hospitals in 2019 (n=36). In addition, all 15 participating hospitals had collected at least one isolate of this clade in 2019 and/or 2022, highlighting that ST39 was now established in hospitals in Greece. Due to the rapid increase in ST39 between the two surveys, and its spread to all 15 participating hospitals in Greece and internationally, *K. pneumoniae* ST39 carrying *bla*$_{KPC-2}$ may be considered an emerging high-risk clone.

Diversity and geo-temporal spread of K. pneumoniae *ST11 carrying carbapenemase genes*

The proportion of *K. pneumoniae* ST11 was high in both the EuSCAPE and the CCRE survey, constituting 13.2% (63/476) and 9.7% (64/662) of carbapenem-R/I isolates, respectively, from the 113 hospitals that contributed *K. pneumoniae* SC isolates to both surveys. A variety of carbapenemase gene variants were observed among all carbapenem-R/I ST11 isolates from the CCRE survey, although most (72.7%; 136/187) carried *bla*$_{NDM-1}$. Notably, among the shared hospitals, we observed a rise in the proportion of carbapenem-R/I isolates with *bla*$_{NDM-1}$ from 10.7% (51/476) in EuSCAPE to 16.5% (109/662) in the CCRE survey, a trend which also held across the entire data set. Since ST11 was the most prevalent ST among *bla*$_{NDM-1}$ isolates in both surveys, we aimed to investigate its potential role in the increase of *bla*$_{NDM-1}$ isolates and better understand its diversity, geo-temporal spread and resistance dynamics.

We analysed ST11 genomes from both surveys with publicly available ST11 genomes from Pathogenwatch. Since ST11 is not a monophyletic group, we also incorporated survey and public genomes belonging to closely related STs from the same clonal complex (CC258) including ST340, ST395 and ST437 in our phylogenetic analysis. Genomes from ST258 and ST512, also part of CC258, were included, but due to the high frequency of these, we included only those from the CCRE survey. All sequence reads from CC258 isolates were mapped to an ST11 reference genome, HS11286 (accession CP003200.1), and recombined regions were removed from the resulting pseudo-genome alignment. Using the vertically inherited SNPs, we generated a phylogenetic tree of 3962 CC258 genomes (https://microreact.org/project/kp-cc258-ccre-survey). This is shown in Figure 36, albeit with all isolates from ST395 (n=228) and ten isolates from ST11 excluded as they formed distant outgroups.

We found significant clustering by country among the CC258 genomes including ST11. In particular, 96.1% (1018/1059) of ST11 isolates from China belonged to a single monophyletic clade, which contained only a small proportion (3.4%; 36/1054) of isolates from elsewhere. Three CCRE survey isolates belonged to this clade, including two isolates from Spain with 0 SNPs difference and one unrelated isolate from Sweden. Most isolates from this clade carried *bla*$_{CTX-M-65}$ (80.1%; 844/1054) and *bla*$_{KPC-2}$ (98.3%; 1036/1054). All possessed an OmpK35 truncation while 98.1% (1 034/1054) also had an OmpK36 GD insertion. We also observed another large clade of ST11 isolates in which 98.7% (303/307) of the isolates were from Spain. CCRE survey isolates accounted for 9.8% (30/307) of isolates from this clade, which included 29 isolates from seven hospitals across Spain. 98.0% (301/307) of isolates in this clade carried *bla*$_{CTX-M-15}$ while 87.9% (270/307) carried *bla*$_{OXA-48}$.

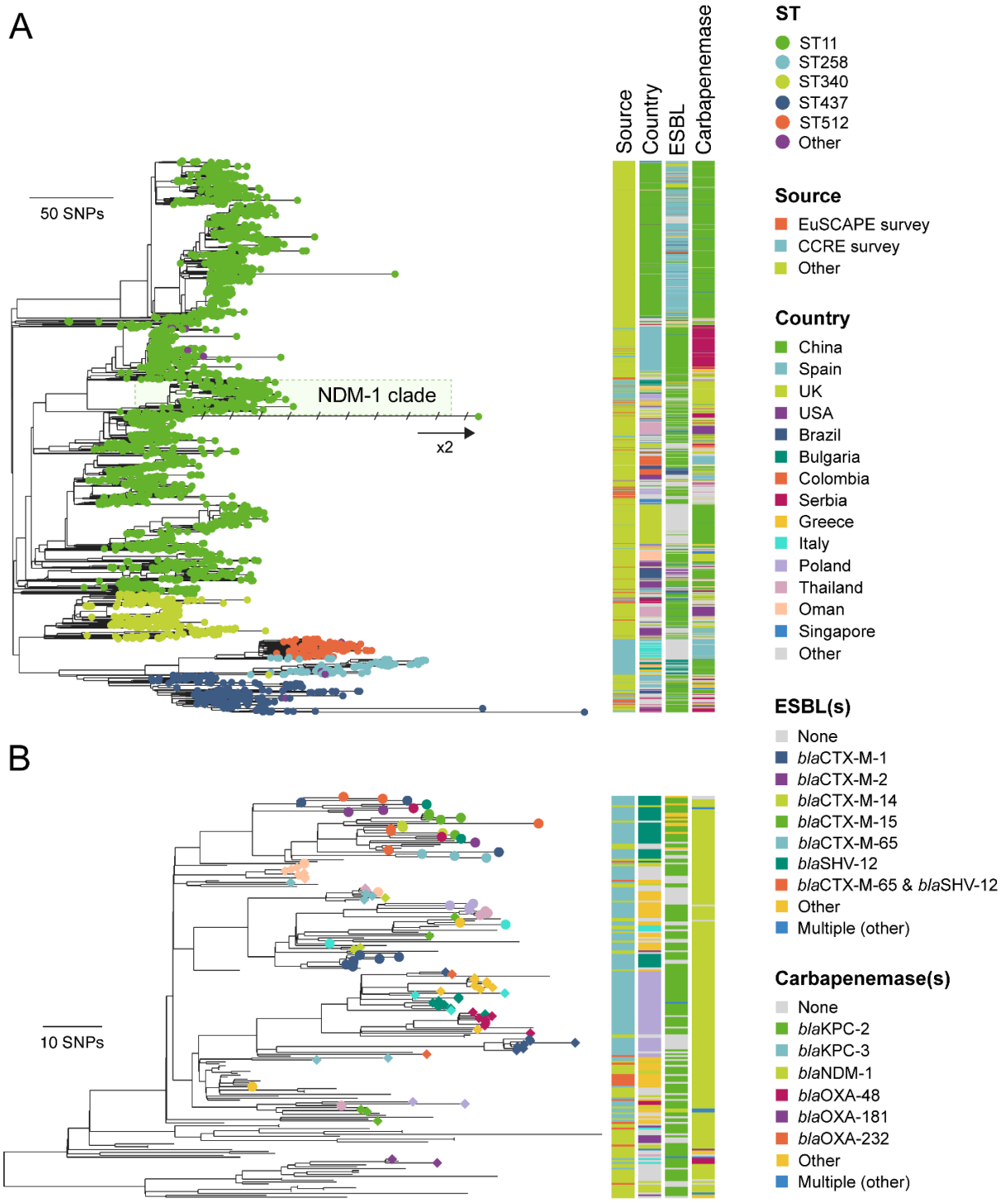
We also detected a cluster of ST11 isolates exclusively from the North-West region of England, UK. Most of these (98.1%; 255/260) were from public data, although five isolates were also submitted during the CCRE survey (from two different hospitals). All 260 isolates in this cluster carried a *bla*$_{KPC-2}$ gene. We suspect that these isolates are linked to the long-term outbreak of *bla*$_{KPC-2}$-producing *Enterobacterales* that has been described in this region [11]. ST11 isolates from this clade accounted for five of the ten isolates carrying *bla*$_{KPC-2}$ submitted from North-West England in the CCRE survey, while different STs were represented among the other five isolates (ST17, ST48, ST258, ST268, ST307).

We investigated the distribution of *bla*$_{NDM-1}$ isolates across the collection of CC258 genomes. Overall, we found that *bla*$_{NDM-1}$ genes were distributed among many different lineages of ST11 (and other STs of CC258). However, 44.6% (197/442) of all *bla*$_{NDM-1}$-carrying ST11 isolates in the combined collection belonged to a single clade of 211 isolates, highlighted in Figure 36A, which comprised isolates from EuSCAPE (n=5), the CCRE survey (n=128) and other public data (n=68). Of the 211 isolates in this clade, 93.4% (197/211) carried *bla*$_{NDM-1}$. Most also had a *bla*$_{CTX-M-15}$ gene (68.7%; 145/211), while a subset (32.2%; 68/211) also had either an MgrB or PmrB truncation. The 211 isolates were from a total of 27 countries. We found substantial clustering of isolates by country, with larger clusters observed in Greece, Poland and Bulgaria, which contributed 21.8% (46/211), 19.9% (42/211) and 17.1% (36/211) of the isolates, respectively. CCRE survey isolates submitted from the same hospital also frequently clustered together, as shown in Figure 36B, with a mean of 24.8 SNPs between the same-hospital pairs.

This compared to a mean of 69.5 SNPs among all pairs of isolates from this clade. Moreover, among 26 hospitals that contributed at least two CCRE survey isolates to this clade, 18 had ≤20 SNPs (and 17 with ≤10 SNPs) among all or some of their isolates. This is suggestive of recent transmission, based on a previously defined threshold for ST258/512 isolates that was found to optimise the discrimination of hospital clusters [9].

Finally, we also investigated the distribution of virulence factors across the CC258 genomes. Most of the genomes possessed either none of the virulence factors identified by Kleborate (29.9%; 1 183/3 962) or yersiniabactin only (53.7%; 2 128/3 962). However, among the ST11 clade associated with China, 41.6% (438/1 054) of the isolates encoded aerobactin, 25.3% (267/1 054) had a *rmpADC* locus and 38.3% (404/1 054) had a *rmpA2* locus, with most of these clustered into a single subclade. We also detected colibactin in 3.1% (123/3 962) of all CC258 genomes, most of which belonged to two different clades of ST11 associated with Brazil and the US, respectively.

Figure 36. A) Phylogenetic tree of 3 724 *Klebsiella pneumoniae* CC258 isolates from the EuSCAPE survey (n=207), CCRE survey (n=518) and additional public databases (n=2 999). B) Larger version of the "NDM-1 clade" (n=211) highlighted in (A), indicating CCRE survey isolates from individual hospitals that contributed ≥2 isolates to this clade with a particular shape/colour



Only ST258/512 isolates from the CCRE survey were included in the phylogenetic tree to maximize representation of other STs. The tree was constructed using variable sites from a pseudo-genome alignment generated by mapping sequence reads to an ST11 reference genome (CP003200.1) and removing recombined regions. The tree was rooted with additional ST11 and ST395 genomes not shown here. Isolate tips in (A) are coloured by the ST while metadata columns in (A) and (B) show the data source, country of origin, ESBL variant and carbapenemase gene variant. One branch in (A) has been shortened for visualisation purposes. The scale bars represent the number of SNPs. An interactive version of the full tree (including outgroup isolates excluded here) with additional metadata and genotyping data is available at: https://microreact.org/project/kp-cc258-ccre-survey

Recurrent acquisition and clonal spread of bla$_{NDM-5}$ in Escherichia coli

In the CCRE survey, *bla*$_{NDM-5}$ was the most commonly identified carbapenemase gene in *E. coli*, found in 29.4% (62/211) of carbapenem-R/I isolates. While a formal comparison of the *E. coli* isolates from EuSCAPE and the CCRE survey was not possible due to the low numbers, it is nevertheless noteworthy that *bla*$_{NDM-5}$ was found in only 2.0% (2/99) of the carbapenem-R/I isolates from EuSCAPE and thus appears to have increased in prevalence. Notably, *bla*$_{NDM-5}$ was also not detected among any carbapenem-R/I *K. pneumoniae* SC isolates from EuSCAPE but found among 1.0% (15/1 566) of this group in the CCRE survey. These included isolates from *K. pneumoniae* (n=14) and *K. quasipneumoniae subsp. quasipneumoniae* (n=1). No *bla*$_{NDM-5}$ genes were identified among carbapenem-S isolates of either *E. coli* or the *K. pneumoniae* SC in the CCRE survey.

We therefore aimed to investigate the potential emergence and spread of *bla*$_{NDM-5}$. The 62 *E. coli* isolates carrying *bla*$_{NDM-5}$ from the CCRE survey were obtained from 45 hospitals in 15 countries (Czechia, Denmark, Estonia, Finland, France, Germany, Iceland, Italy, Luxembourg, the Netherlands, Norway, Slovenia, Sweden, Türkiye, and the UK). The most commonly represented countries were the UK (n=16), Sweden (n=10) and the Netherlands (n=7). Across all countries, only 12 hospitals contributed ≥2 *E. coli* isolates with *bla*$_{NDM-5}$, while the maximum number submitted by any one hospital was four. Of the 12 hospitals with ≥2 *bla*$_{NDM-5}$-carrying *E. coli* isolates, only one hospital contributed isolates from the same ST (one UK hospital had two isolates of ST1284). The 15 *Klebsiella* SC isolates with *bla*$_{NDM-5}$ were also widely distributed across Europe, obtained from 13 hospitals in eight countries (Austria, Belgium, Germany, Ireland, the Netherlands, Sweden, Türkiye and the UK), with no hospital contributing more than two isolates.

Availability of data on travel and prior hospitalisation was very limited due to missing information; however, 13 patients with *bla*$_{NDM-5}$-carrying *E. coli* and three patients with *bla*$_{NDM-5}$-carrying *K. pneumoniae* had a reported link to another country (either direct hospital transfer, previous hospitalisation, or travel) within the six months prior to sample collection. The countries mentioned at least once as a link were Cambodia, Egypt, Germany, India, Iran, Iraq, Russia, Syria, Somalia, and Thailand. 40.3% (25/62) of the *bla*$_{NDM-5}$-carrying *E. coli* were isolated from samples recorded as clinical samples, with urine being the most frequent sample type, and 35.1% (20/57) of cases with available information were classified as infections. 80.0% (12/15) of the *K. pneumoniae* SC isolates with *bla*$_{NDM-5}$ were recorded as from clinical samples, with urine also being the most frequent sample type, and 72.7% (8/11) of cases with available information were classified as infections.

Among the CCRE survey isolates, we found *bla*$_{NDM-5}$ in 17 different STs of *E. coli* although five STs accounted for 69.4% (43/62) of the isolates. These were ST167 (n=14), ST648 (n=9), ST361 (n=7), ST410 (n=7) and ST405 (n=6). In the *Klebsiella* SC, *bla*$_{NDM-5}$ was identified in nine STs with only four STs accounting for ≥1 isolate: ST383 (n=3), ST147 (n=2), ST16 (n=2) and ST4069 (n=2). Based on available phenotypic AST results, all *E. coli* isolates carrying *bla*$_{NDM-5}$ showed 'resistant' or 'susceptible, increased exposure', as defined in the CCRE survey consensus protocol, to penicillins, cephalosporins and carbapenems. They also showed high percentages of resistance to aztreonam (83.8%; 31/37 tested isolates), trimethoprim-sulfamethoxazole (91.9%; 34/37), ciprofloxacin (96.1%; 49/51) and tobramycin (57.1%; 20/35). The percentages of 'resistant' or 'susceptible, increased exposure' were lower for tigecycline (7.0%; 3/43), fosfomycin (14.3%; 3/21) and colistin (3.6%; 2/55).

We further investigated the emergence and spread of *bla*$_{NDM-5}$ in *E. coli* through combined analysis of all EuSCAPE and CCRE survey genomes with other public genomes from the five most common STs from which *bla*$_{NDM-5}$ was found in the CCRE survey. Of note, the public genomes included a substantial number of sequenced isolates from our follow-up investigation (see below) [61] that were obtained due to their carriage of the *bla*$_{NDM-5}$ gene, thus contributing to a bias towards *bla*$_{NDM-5}$-carrying isolates in these sample collections. A wide distribution of countries were represented among the combined collections (ST167 – 54; ST361 – 40; ST405 – 61; ST410 – 64; ST648 – 50). We included public genomes sampled as far back as 1971 (ST648), 1975 (ST410), 1981 (ST405), 1986 (ST361) and 1999 (ST167), and up until 2022 (all STs), although *bla*$_{NDM-5}$ was only found in genomes from 2013 onwards across all five STs (two years after the first description of the gene variant [62].

Phylogenetic analysis was performed separately on each of the five STs. We included additional isolates from closely related STs (e.g. single-locus variants) from EuSCAPE and the CCRE survey, including outgroup isolates that enabled rooting of the trees. We first mapped sequence reads from each ST (and related STs) to an ST-specific reference genome (see Methods section 2.6) and constructed phylogenetic trees after the removal of recombined regions from the pseudo-genome alignments. Among the different STs, we found that isolates with *bla*$_{NDM-5}$ mostly clustered together, indicative of clonal spread of this carbapenemase (Figures 37 and 38; see Microreact URLs below). However, in each of the STs, *bla*$_{NDM-5}$ was found in multiple clades, suggesting that the gene has been acquired independently, multiple times.

The clonal expansions of *bla*$_{NDM-5}$-encoding isolates were typically associated with the presence of other genes conferring resistance to antibiotics including beta-lactams, aminoglycosides, fluoroquinolones, trimethoprim and sulfonamide (see Microreact URLs below). For example, among the ST167 genomes that carried *bla*$_{NDM-5}$, 73.6% (404/549) carried an ESBL gene, 62.1% (341/549) carried *aac(6')-Ib-cr* , 27.9% (153/549) carried *rmtB*, 100% (549/549) had a *gyrA*, *parC* and/or *parE* resistance mutation, 97.8% (537/549) carried a *sul* gene and 97.3% (534/549) carried a *dfrA* gene.

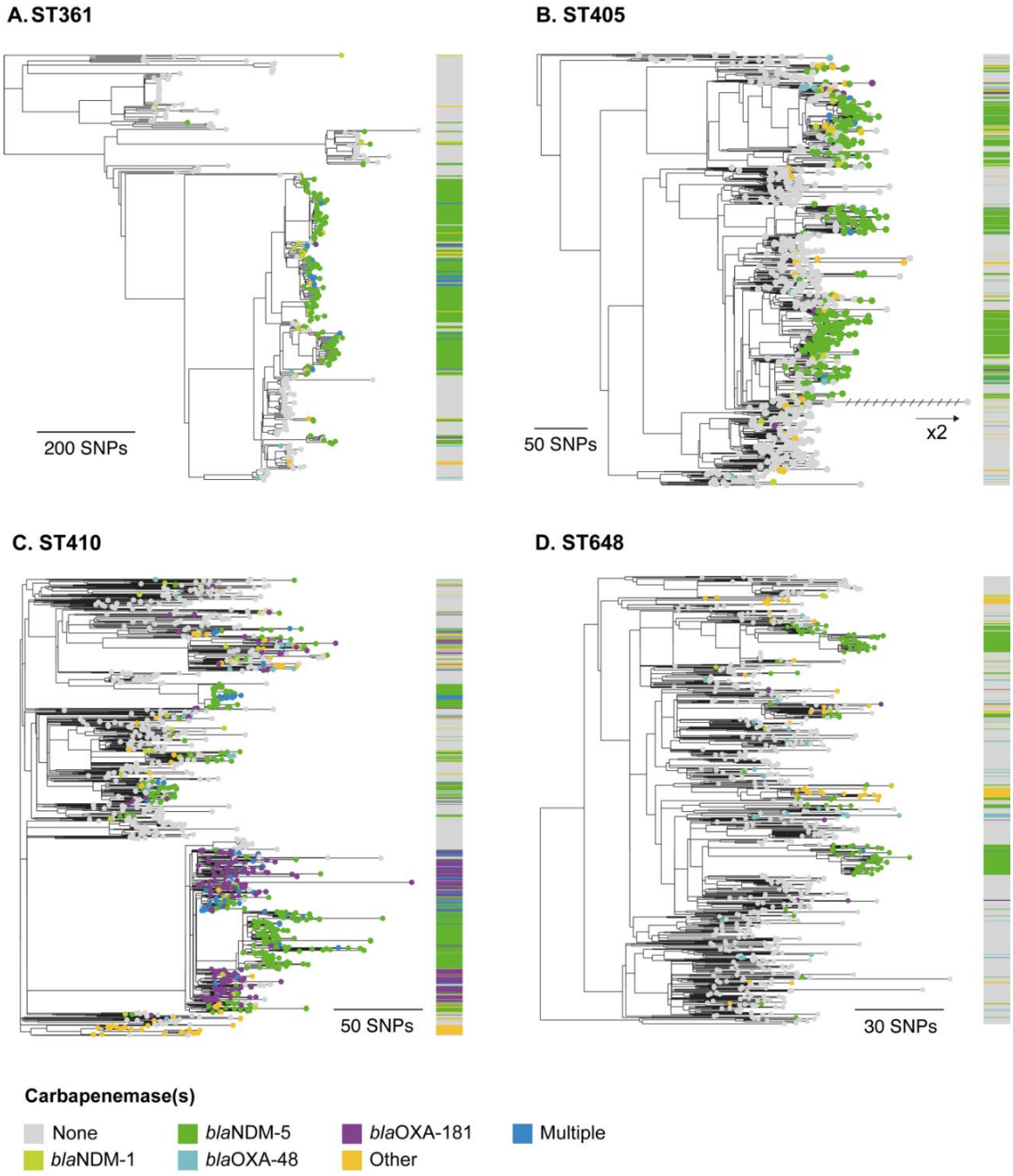
Notably, we found that isolates from individual countries, including those from the EU/EEA, were distributed widely across the phylogenies of each of the five STs, typically appearing as singletons or within small clusters of isolates from the same country (Figure 37; see Microreact URLs below). This demonstrates that numerous introductions of *bla*$_{NDM-5}$-carrying *E. coli* into each country have occurred, yet significant onward spread has been scarcely detected. However, an exception to this was two substantial clusters of ST167 genomes from the US. CCRE survey isolates were also widely distributed across the phylogenies of each of the five STs with few transmission clusters (i.e. clusters of isolates from single hospitals/countries) observed.

Of note, we also detected a cluster of *bla*$_{KPC-2}$-carrying ST410 isolates (n=25), all but one of which were obtained from the UK between 2010 and 2016 (the other from the US, 2015). It is likely these were part of the large outbreak of *bla*$_{KPC-2}$-encoding *Enterobacterales* in North-West England [11]. Furthermore, we detected a cluster of *bla*$_{NDM-7}$-carrying ST648 isolates (n=15), sampled across nine countries between 2013 and 2020. No CCRE survey isolates were detected from either of these clusters.

Figure 37. Phylogenetic tree of 899 *Escherichia coli* isolates belonging to ST167 (and other closely related STs) from EuSCAPE (n=3), the CCRE survey (n=26) and additional public databases (n=870)

The phylogenetic tree was constructed using variable sites from a pseudo-genome alignment generated by mapping sequence reads to an ST167 reference genome (CP074120.1) and removing recombined regions. The tree was rooted using isolates from closely related STs (e.g. ST10) that form an outgroup and which have been removed from this figure. Isolate tips are coloured by the carbapenemase gene variant, while the metadata columns show the carbapenemase gene variant, ESBL gene variant, data source and country of origin. The scale bar represents the number of SNPs. An interactive version of the tree with additional metadata and genotyping data is available at: https://microreact.org/project/ecoli-st167-ccre-survey

Figure 38. Phylogenetic trees of *Escherichia coli* from A) ST361 (n=374), B) ST405 (n=974), C) ST410 (n=1 182) and D) ST648 (n=789)



The phylogenetic trees (and above stated numbers) include a small number of isolates from related STs that are nested among the main STs. The illustrated trees of ST405, ST410 and ST648 represent subtrees of the full phylogenetic trees that are available using the Microreact URLs below. The trees were constructed using variable sites from pseudo-genome alignments generated by mapping sequence reads to ST-specific reference genomes (see Methods section 2.6) and removing recombined regions. One branch in (B) has been shortened for visualisation purposes. The isolate tips and metadata columns are coloured by the carbapenemase variants. The scale bars represent the number of SNPs. Interactive versions of these trees with additional metadata and genotyping data are available at: https://microreact.org/project/ecoli-st361-ccre-survey (ST361), https://microreact.org/project/ecoli-st405-ccre-survey (ST405), https://microreact.org/project/ecoli-st410-ccre-survey (ST410), https://microreact.org/project/ecoli-st648-ccre-survey (ST648).

The increased detection of *bla*$_{NDM-5}$ among *E. coli* in the CCRE survey was of concern and warranted a rapid investigation to examine the extent of *bla*$_{NDM-5}$ spread and describe the epidemiological and microbiological characteristics of the associated isolates. In 2022, ECDC requested WGS and epidemiological data on *E. coli* carrying *bla*$_{NDM-5}$ from EU/EEA countries via its EpiPulse platform. In response, high-quality data for 874 *E. coli* isolates with *bla*$_{NDM-5}$ were received from 13 countries between 2012 and June 2022 (Table 21).

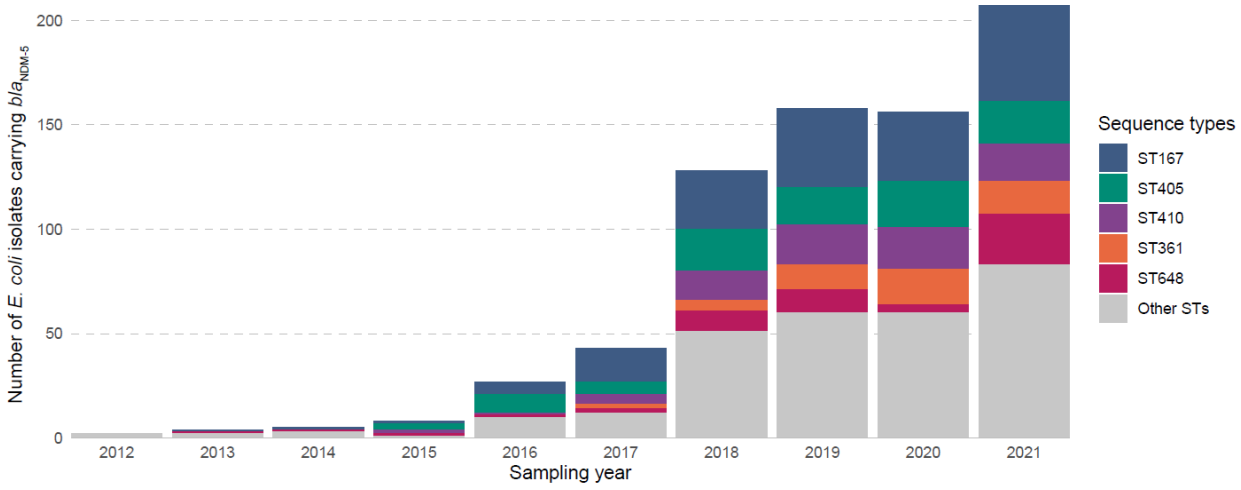
Table 21. Isolates of the dominant sequence types of *Escherichia coli* isolates carrying *bla*$_{NDM-5}$ submitted from national collections (n=874), by country and period covered*

E. coli sequence type	No. of isolates by country (period covered)													
	AT (2019–2022)	DE (2019)	DK (2015–2022)	ES (2014–2021)	FI (2016–2022)	FR (2017–2022)	HU (2020)	IE (2017–2022)	IT (2017–2018)	NL (2012–2022)	NO (2021–2022)	PT (2017–2020)	SE (2021–2022)	Total (2012–2022)
ST167	0	2	23	1	5	95	0	8	4	42	3	6	11	200
ST405	0	2	8	2	8	49	0	15	0	24	0	0	7	115
ST410	0	2	7	0	3	54	1	8	2	13	0	1	5	96
ST361	0	1	9	0	3	42	0	5	0	6	2	0	2	70
ST648	0	1	5	0	6	18	0	11	0	12	1	0	11	65
Other STs	4	2	30	2	20	145	1	33	0	61	6	6	18	328
Total	4	10	82	5	45	403	2	80	6	158	12	13	54	874

*ST – sequence type. AT, Austria; DE, Germany; DK, Denmark; ES, Spain; FI, Finland; FR, France; HU, Hungary; IE, Ireland; IT, Italy; NL, Netherlands; NO, Norway; PT, Portugal; SE, Sweden. * Data collection until June 2022.*

Eighty-three *E. coli* STs were present in the 874 isolates from national collections, with the same five STs observed in the CCRE survey predominating: ST167 (22.9%; n=200), ST405 (13.2%; n=115), ST410 (11.0%; n=96), ST361 (8.0%; n=70) and ST648 (7.4%; n=65). The five dominant STs were detected in all countries that submitted more than 20 isolates, i.e. Denmark, Finland, France, Ireland, the Netherlands and Sweden (Table 21). The number of *E. coli* isolates carrying *bla*$_{NDM-5}$ from these collections increased over time (Figure 39). The findings related to the CCRE survey follow-up study on *bla*$_{NDM-5}$-encoding *E. coli* are described and discussed in more detail in the respective ECDC surveillance report [32] and Eurosurveillance article [61].

Figure 39. Frequency of sequence types of *Escherichia coli* isolates carrying *bla*$_{NDM-5}$ from national collections by year of sampling, 2012-2021* (n=741).



*ST – sequence type. *The time distribution illustrated above should not be interpreted as an epidemic curve as year-to-year variation is likely affected by detection and reporting biases and may not reflect true temporal trends in incidence. Isolates (n=133) from 2022 are not displayed as data for this year was incomplete at the time of analysis. Seventy STs other than the dominant ones were grouped as "Other STs".*

4 Discussion

Standardised genomic-based surveys such as the CCRE survey can play an important role in the response to the increasing threat of AMR by detecting emerging resistance patterns and high-risk clones, including in countries and/or regions that may not be covered by routine molecular surveillance. The final data set of the CCRE survey includes 2 973 *K. pneumoniae* SC and 548 *E. coli* isolates with clinical and epidemiological data together with high-quality WGS data from a total of 323 hospitals in 36 European countries. The survey provided an important opportunity to re-assess the prevalence and incidence of carbapenem resistance among these species since the 2013-14 EuSCAPE survey [9,15], as well as identify changes in the epidemiology and pathogen populations. The resulting analysis of the epidemiological, phenotypic and genomic data from the CCRE survey described in this report will help to review and re-prioritise surveillance and control efforts.

Epidemiological analysis

While the calculations of prevalence and incidence were hampered by a lack of data for some hospitals and countries, we found that the mean prevalence of carbapenemase-producing *K. pneumoniae* SC and *E. coli* (combined) increased from 1.3 isolates per 10 000 hospital admissions in EuSCAPE to 2.5 per 10 000 hospital admissions in the CCRE survey. Moreover, the mean incidence of carbapenemase-producing *K. pneumoniae* SC and *E. coli* (combined) increased from 2.5 isolates per 100 000 patient days in EuSCAPE to 6.6 per 100 000 patient days in the CCRE survey. The prevalence and incidence per country were highly variable in the CCRE survey, similar to the EuSCAPE survey. In addition, comparability between the two surveys is also limited due to different participating hospitals. However, the detected increase in the incidence and prevalence is in line with data reported from national surveillance systems and smaller scale studies.

In contrast to the EuSCAPE, which only included clinical samples, both clinical and screening samples were accepted in the CCRE survey. Overall, more than two thirds of isolates in the CCRE survey were reported as associated with infections, although there were differences in the proportion of isolates associated with infection by country. However, this number may not reflect the real distribution of infection and carriage for various reasons, for example due to inclusion bias related to preferential collection of isolates originating from infections or limited surveillance for CPE carriage in some countries or hospitals. Although the inclusion of screening samples enabled countries with low CPE prevalence to contribute isolates, this difference also decreases the comparability with the EuSCAPE, and within the CCRE survey. Additionally, there were significant differences in the submitted sample types, both between countries and between carbapenem-R/I and carbapenem-S isolates in the CCRE survey. While some countries submitted clinical samples exclusively for both carbapenem-R/I and S isolates, other countries submitted >50% carbapenem-R/I isolates *K. pneumoniae* SC from samples collected for screening. This effect was most notable for *E. coli*.

The results of the multilevel multivariate analysis of risk factors associated with carbapenem-R/I isolates corroborate results from the EuSCAPE survey, highlighting that hospital spread is a major driver of transmission. For *K. pneumoniae* SC, all investigated types of hospital acquisition had a statistically significant association with carbapenem-R/I isolates. Furthermore, the comparison of individual epidemic STs with non-epidemic STs found a healthcare association for *K. pneumoniae* ST258/512, ST307 and ST15 but not for ST11 or ST101. For *E. coli*, we found an association with previous hospital admission within the last six months (regardless of previous hospital location). However, community-acquired cases and those without a documented healthcare exposure are also a cause of concern, as spread of carbapenemase genes, especially via *E. coli* in the community, could result in broader and very difficult-to-control dissemination in the healthy population. However, as community-onset is determined via a time cutoff of sampling within 48h after admission, prior healthcare contact may have been underestimated as a risk factor for example in case of readmissions. There may also have been hospital acquisition of carriage, but community-onset of infection. Travel to other countries had a statistically significant association with carbapenem-R/I isolates for both *K. pneumoniae SC* and *E. coli*, but data were very incomplete in this regard and could be subject to information bias.

Phenotypic resistance

Resistance levels to other antibiotics than carbapenems were generally higher among carbapenem-R/I *K. pneumoniae* SC than *E. coli* isolates. For the carbapenem-R/I *K. pneumoniae* SC, the two most active agents were colistin and ceftazidime-avibactam with proportions of resistance of 23.3% and 24.6%, respectively. For the carbapenem-R/I *E. coli*, the proportion of resistance to ceftazidime-avibactam was higher (37.4%), but lower for colistin (3.1%). Most of the ceftazidime-avibactam resistance was explained by the presence of MBL genes, although 7.6% of tested *K. pneumoniae* SC isolates with bla_{KPC} and 3.8% of tested *K. pneumoniae* SC isolates with $bla_{OXA\text{-}48\text{-}like}$ genes were also resistant to ceftazidime-avibactam. In EuSCAPE, colistin resistance was reported in 28% of tested carbapenem-R/I *K. pneumoniae* and 5.3% of carbapenem-R/I *E. coli*. This indicates that colistin-resistance in carbapenem-R/I *K. pneumoniae* SC and *E. coli* has not increased between the two studies, although

comparability is limited due to missing colistin AST results, especially in the EuSCAPE survey. EuSCAPE did not include AST for ceftazidime-avibactam which was only authorised for use in the EU/EEA in 2016 [63].

The occurrence of FDR isolates with few remaining treatment options is of concern. However, AST for newer agents such as cefiderocol, imipenem-relebactam and meropenem-vaborbactam was not included in the CCRE survey. These antibiotics could still represent a treatment option for isolates defined as FDR in the CCRE survey; however, this applies mainly to the few FDR isolates not producing MBLs. Classification of the categories of MDR and FDR used in this report may also change in the future when updates of the respective definitions with inclusion of recently approved antimicrobials become available.

Sequence type distribution

In the CCRE survey, we found that carbapenem-R/I isolates from *K. pneumoniae* SC were largely concentrated within a few high-risk STs of *K. pneumoniae*, including ST11, ST15, ST101, ST147, ST258/512 and ST307. Each of these ST groups were geographically widespread across EU/EEA countries. While many of these ST groups were also dominant among EuSCAPE isolates [9], in the CCRE survey, notable increases of ST147 and particularly of ST307 which represented 6.1% and 11.5% of the carbapenem-R/I isolates, respectively, were observed. *K. pneumoniae* ST147 and ST307 are both recently emerged resistant clones that have become prominent global pathogens within a short time frame, likely in part due to their association with the *bla*$_{\text{CTX-M-15}}$ ESBL gene and other resistance loci [64,65]. In *E. coli*, carbapenem-R/I isolates from the CCRE survey were also concentrated among a few major STs, including ST38, ST131, ST167, ST410 and ST648. While a robust comparison of *E. coli* isolates from the two surveys was not possible due to the smaller number of isolates, we found that ST131 was the most common ST among carbapenem-R/I isolates from both. ST131 is a globally distributed MDR clone, associated with the *bla*$_{\text{CTX-M-15}}$ gene, and the most common lineage found among extraintestinal pathogenic *E. coli* (ExPEC) isolates worldwide [66].

K. pneumoniae ST11

The increase of *bla*$_{\text{NDM-1}}$ among carbapenem-R/I *K. pneumoniae* SC isolates led us to investigate ST11, which represented a major ST among carbapenem-R/I isolates in both surveys and contributed over half (51.7%) of the *bla*$_{\text{NDM-1}}$ isolates in the CCRE survey. ST11 is known to be a globally distributed high-risk clone [67], that has been especially reported as a dominant *bla*$_{\text{KPC}}$-producing clone in China, where it has been associated with outbreaks of MDR, hypervirulent *K. pneumoniae* [68-70]. Phylogenetic analysis of survey isolates with other public data, showed that *bla*$_{\text{NDM-1}}$ genes are carried by many distinct lineages of ST11, but that a single clade of 211 isolates was responsible for 44.6% of all *bla*$_{\text{NDM-1}}$-carrying ST11 isolates in the combined genome collection. Isolates from this clade were geographically widespread (collected from 27 countries), although substantial clustering by country and hospital was observed, indicating healthcare-associated transmission as the primary means of spread. We also observed other significant country-specific clusters of ST11 isolates, including from China (associated with *bla*$_{\text{KPC-2}}$ and different virulence loci), Spain (associated with *bla*$_{\text{OXA-48}}$) and the North-West region of England (associated with *bla*$_{\text{KPC-2}}$). The latter is likely related to the long-term outbreak of *bla*$_{\text{KPC-2}}$-carrying Enterobacterales in North-West England described previously [11]. However, this outbreak has been reported to be largely driven by horizontal exchange of plasmids and other mobile elements, combined with clonal spread of *bla*$_{\text{KPC-2}}$-encoding ST11 as described previously [71] and confirmed by our analysis. We also detected a cluster of *bla*$_{\text{KPC-2}}$ carrying *E. coli* ST410 isolates (all from public data), also likely linked to this outbreak.

We also investigated the detected increase of *bla*$_{\text{NDM-5}}$-carrying *E. coli* isolates among carbapenem-R/I isolates between EuSCAPE and the CCRE survey. Our phylogenetic analyses of multiple STs of *E. coli*, which included both survey and additional public data, showed that *bla*$_{\text{NDM-5}}$ has been acquired multiple times by each ST, and has been involved in substantial amounts of clonal spread. Clonal spread of carbapenemase-producing *E. coli* is of deep concern as this species spreads more readily in the community than *K. pneumoniae* and could be significantly more difficult to control as hospital infection control policies are less effective. We also anticipate that the spread of *bla*$_{\text{NDM-5}}$ may increasingly spill-over into *K. pneumoniae* and other Enterobacterales species. This spill-over may already have begun as *bla*$_{\text{NDM-5}}$ genes were detected among 1.0% (15/1566) of the carbapenem-R/I *K. pneumoniae* SC isolates from the CCRE survey, despite not being found in EuSCAPE. Analysis of plasmid replicons across the CCRE survey data set showed no single association of *bla*$_{\text{NDM-5}}$ genes with a particular replicon but suggested that several plasmid types, including IncFII, IncX3, Col(MG828), ColKP3, IncFIA and Col(BS512), may be implicated in gene spread. Our phylogenetic analyses showed that numerous introductions of *bla*$_{\text{NDM-5}}$-carrying *E. coli* has occurred into different countries (including EU/EEA countries) but detected limited local onward transmission in most cases. Further surveillance is required to understand the extent to which cases in EU/EEA countries may be currently related to travel and to which *bla*$_{\text{NDM-5}}$-carrying *E. coli* is spreading in both hospital and community settings within Europe.

K. pneumoniae ST307

The increased frequency of ST307 among the CCRE survey isolates is in line with numerous recent reports relating to the high prevalence of this ST among clinical isolate collections globally [57,59,72-74]. In the CCRE survey, we found that ST307 was the most widely distributed of any *K. pneumoniae* ST, found in 108 hospitals in 28 countries. The increase in ST307 among carbapenem-R/I isolates between the two surveys was particularly notable in Italy (3.2% to 32.7%) and Spain (0% to 15.3%), taking account of isolates submitted from all hospitals. In Italy, we also observed a concomitant decline in ST258/512 (85.7% to 31.7%), the previously dominant ST group among carbapenem-R/I isolates in the country, which was in line with observations from a country-wide survey [74]. Notably, we also found that the proportion of all ST307 isolates that carried one or more carbapenemase genes increased from 35.6% in EuSCAPE to 68.2% in the CCRE survey. Phylogenetic analysis of the survey isolates with other public ST307 genomes showed that there have been numerous acquisitions of different carbapenemase genes within this ST. The analysis also showed that ST307 isolates from the CCRE survey belonged to pre-existing lineages already represented by EuSCAPE isolates, with no major new lineages detected.

Substantial clustering of the isolates by country and hospital suggested that ST307 spread has largely occurred via hospital networks. Indeed, we found long-term persistence of the same ST307 lineage in four hospitals in the EU/EEA, identified via phylogenetic clustering of isolates from the two surveys. We also detected a clade of ST307 isolates comprising isolates from Germany (n=13) and Finland (n=2) carrying *bla*$_{\text{NDM-1}}$, *bla*$_{\text{OXA-48}}$ and multiple virulence loci, from both public and CCRE survey genomes. The particular resistance and virulence profile of these isolates suggests that they are likely related to isolates from a previously described outbreak clone of ST307 from north-eastern Germany associated with extensive drug resistance and hypervirulence [75]. While we detected an low number of isolates with virulence loci indicative of a hypervirulence phenotype among carbapenem-R/I isolates in the CCRE survey, these findings reinforce the need for vigilant monitoring and rapid containment of any emergent hypervirulent/MDR *K. pneumoniae* clones, which have been increasing especially in Asia [70,76] and more recently in Europe [77].

K. pneumoniae ST39

We also detected a small but notable increase in the frequency of *K. pneumoniae* ST39, which represented 2.6% of carbapenem-R/I *K. pneumoniae* SC isolates in the CCRE survey. The resistance profile of the ST39 CCRE survey isolates was concerning, with most harbouring porin mutations, a MgrB truncation and at least one carbapenemase gene, usually *bla*$_{\text{KPC-2}}$ alone but combinations of *bla*$_{\text{KPC-2}}$/ *bla*$_{\text{VIM-1}}$, *bla*$_{\text{KPC-2}}$/ *bla*$_{\text{NDM-1}}$ and *bla*$_{\text{KPC-2}}$/ *bla*$_{\text{OXA-48}}$ were also observed. Our phylogenetic analysis which included additional public data showed that most of the CCRE survey ST39 genomes belonged to a single clade. Twelve of the fifteen participating hospitals from Greece contributed CCRE survey isolates to this clade, but spread to other countries was also observed (including Australia, Bulgaria, Cyprus, Germany, Netherlands, Norway and Russia). Only one ST39 isolate from the EuSCAPE survey (from Greece) belonged to this clade. We therefore suggest that this clade has likely spread rapidly over recent years, particularly in Greek hospitals. The clinical importance of this clade was recognised in a report that investigated four clonally related ST39 isolates from individual patients obtained from a retrospective analysis of carbapenemase-producing *K. pneumoniae* in a Greek tertiary hospital in 2018-19 [78]. The four isolates carried both *bla*$_{\text{KPC-2}}$ and *bla*$_{\text{VIM-1}}$, and were designated as either pan-drug-resistant (three isolates) or extensively drug resistant (one isolate). We also further confirmed the continued dominance and circulation of ST39 within hospitals in Greece via a follow-up study in 2022 [60]. Due to the apparent rapid spread of this clade and its high levels of resistance, we urge vigilant global monitoring of ST39 to prevent its onward spread.

Carbapenemase variants

We detected one or more carbapenemase gene variants in 89.3% (1398/1566) of carbapenem-R/I *K. pneumoniae* SC and 86.3% (182/211) of carbapenem-R/I *E. coli* isolates from the CCRE survey. These proportions were significantly higher than those observed in EuSCAPE (70.2% and 35.4% among all isolates, respectively), which we suspect reflects more widespread dissemination of high-risk clones. We could rule out potential differences between hospitals because the findings also held when we included only isolates from hospitals that contributed to both survey data sets. Among the *K. pneumoniae* SC isolates from the CCRE survey, the dominant gene variants found were *bla*$_{\text{OXA-48}}$, *bla*$_{\text{KPC-3}}$, *bla*$_{\text{NDM-1}}$ and *bla*$_{\text{KPC-2}}$, which together comprised 90.5% of all carbapenemase genes found among the carbapenem-R/I isolates. Among the 113 hospitals that contributed *K. pneumoniae* SC isolates to both surveys, we observed notable increases of isolates with *bla*$_{\text{KPC-2}}$ (9.0% to 20.1%) and *bla*$_{\text{NDM-1}}$ (10.7% to 16.5%) among carbapenem-R/I isolates. Among *E. coli* from the CCRE survey, the main carbapenemases found were *bla*$_{\text{NDM-5}}$ and *bla*$_{\text{OXA-48}}$, identified in 29.4% and 19.0%, respectively, of the carbapenem-R/I isolates. Our rapid follow-up study confirmed an increase in the detection of *bla*$_{\text{NDM-5}}$-carrying *E. coli* isolates across EU/EEA countries using national routine WGS data [61].

Our findings also suggested that most *bla*$_{\text{OXA-48}}$ genes were carried on pOXA-48-like plasmids in both *K. pneumoniae* SC (69.8%) and *E. coli* (59.5%), which have previously been shown to be the dominant vector of *bla*$_{\text{OXA-48}}$ genes in Europe [10]. We also detected an increase in the number of carbapenem-R/I isolates from all hospitals carrying two carbapenemase gene variants between the surveys, from 1.9% to 3.3% among *K. pneumoniae* SC, and 0% to 2.4% among *E. coli*. This finding also held when we included only isolates from a

subset of hospitals that contributed to both surveys. Carbapenemase gene variants were widely distributed across different STs of both *K. pneumoniae* SC and *E. coli*, although we also observed strong associations of carbapenemase gene variants with specific STs. Among *K. pneumoniae* SC isolates, these included *bla*$_{KPC-2}$ with ST258 and ST39, *bla*$_{KPC-3}$ and to a lesser extent *bla*$_{OXA-48}$ with ST307, *bla*$_{NDM-1}$ with ST11 and ST147, *bla*$_{VIM-4}$ with ST15, *bla*$_{OXA-48}$ with ST101 and *bla*$_{OXA-232}$ with ST2096. These or similar associations have been described previously but may also vary by country or geographic region [67,79]. In *E. coli*, we found associations of *bla*$_{NDM-5}$ with ST167, *bla*$_{KPC-3}$ with ST131, *bla*$_{OXA-181}$ with ST410 and *bla*$_{OXA-244}$ with ST38.

National epidemiology

This report mainly focuses on the epidemiological situation of *K. pneumoniae* and *E. coli* and related changes compared to EuSCAPE that were noticeable on the European level. The CCRE survey cannot substitute for more detailed national surveillance and genomic epidemiology of CRE. However, the CCRE survey also showed that there was not one single epidemic of carbapenem-R/I *K. pneumoniae* SC in the 36 participating countries but heterogenous epidemiological situations ranging from sporadic cases to endemicity involving a varying mix of *K. pneumoniae* STs and carbapenemases on the national level. Firstly, there was a > 200-fold difference in prevalence and a > 400-fold difference in incidence between the country with the lowest and highest incidence and prevalence of carbapenem-resistant *K. pneumoniae* SC. Secondly, while the dominant STs were all widely distributed throughout participating countries, there were nevertheless considerable differences in the dominant high-risk STs by country, for example in Italy carbapenem-R/I *K. pneumoniae* were clearly dominated by ST101, ST307 and ST512, while Spain had a more diverse mix of ST11, ST147, ST15, ST307, ST15, ST512 and other STs and in Türkiye other 'non-epidemic' STs were the most frequent group, followed by smaller proportions of ST101, ST147 and ST307 as shown in Figure 12. Thirdly, the frequency of carbapenemase gene variants differed by country, with for example, *bla*$_{KPC-3}$ being most frequently detected in Italy while *bla*$_{OXA-48}$ was the most frequent variant in Spain and Türkiye, as shown in Figure 19. This description of predominant STs and carbapenemase gene variants could be continued for countries with less isolates in the CCRE survey than Italy, Spain and Türkiye, resulting in a variety of unique combinations. More in-depth analysis may also reveal further differences in resistance genes and virulence genes as well as regional differences within countries but is outside the scope of this report. A more detailed national level genomic analysis using CCRE survey and follow-up study results has been conducted in Greece [60].

Limitations of CCRE survey

There are several limitations of the CCRE survey. Firstly, many registered isolates were excluded from the final validated dataset for various reasons which included failure of receipt of the isolates by the NRLs or the strain collection, contaminated cultures, inconsistencies in species identification and/or carbapenemase results between national and central testing and/or the WGS data not meeting the required quality criteria. However, despite the isolate processing stages falling into the early part of the COVID-19 pandemic, it was a success that 36 of the 37 registered countries contributed isolates. Another limitation is the uneven distribution of isolates obtained from different countries, with some countries contributing large numbers (e.g. Italy, Spain, Türkiye, Greece) and others being underrepresented. This is partially due to differences in the prevalence of carbapenem-R/I *K. pneumoniae* and *E. coli* between countries, but also partially due to an under-recruitment of hospitals in some countries. The completeness of the clinical, epidemiological, microbiological and AST data are also variable. Many of these limitations relate to the high time and resource consumption required for the CCRE survey, which is based on voluntary efforts by the participating NRLs and sentinel hospitals. We also acknowledge that this report only becomes available more than four years after the isolate and data collection in 2019, which is not fast enough for real-time surveillance and rapid institution of control measures.

The strength of EuSCAPE and the CCRE survey lies in the standardised large dataset based on harmonised sampling and data collection in 36 countries. However, due to the inclusion of one hospital per NUTS-2 unit and the restricted number of ten consecutive carbapenem-R/I and carbapenem-S *K. pneumoniae* isolates per hospital, these surveys had a limited geographic resolution within each country and a very limited power to detect outbreaks in participating hospitals. The implementation of comprehensive WGS-based surveillance targeting multidrug-resistant organisms in all EU/EEA countries remains the overarching goal. While the establishment of the required capacity is ongoing in many countries, the CCRE survey not only serves as a model for genomic surveillance for CRE, but potentially for other multidrug-resistant organisms of concern, at the European level. A recently conducted CCRE follow-up survey in Greece showed that a modified protocol could be implemented much faster at the national level and generate near real-time data useful for IPC [60]. New or increasing resistance threats, potential outbreaks and/or high-risk areas for transmission that are identified could then be followed-up with more targeted and detailed epidemiological and genomic studies to determine the sources and transmission pathways.

Suggested improvements to CRE surveillance

So far, the CCRE survey and EU-level molecular surveillance for CRE have focused on *K. pneumoniae* and *E. coli* as most frequent species of CRE/CPE, however, clonal spread and outbreaks of other Enterobacterales species carrying carbapenemases have also been reported in recent years [80-83]. One example is the investigation of *Providencia stuartii* carrying bla_{NDM} imported into ten EU/EEA countries and related to prior healthcare exposure in Ukraine [84]. In a recent ECDC questionnaire focusing mainly on NDM-producing Enterobacterales, NRLs reported the detection of a number of NDM-producing Enterobacterales species other than *K. pneumoniae* and *E. coli* including *Citrobacter freundii* complex, *Enterobacter cloacae* complex, *K. oxytoca, Proteus* spp., *Providencia stuartii* and *Serratia marcescens.* Related findings from national surveillance have also been published [85]. These species may need more attention in future surveillance activities at the European level. However, related data collection may require a different approach than the current model used for the CCRE survey, which included the collection of ten consecutive carbapenem-R/I isolates of *K. pneumoniae* SC or *E. coli* from individual patients and ten carbapenem-S control isolates of the same species per participating hospital. While this resulted in a more representative dataset for *K. pneumoniae* SC with 2 973 isolates from 36 countries, representativeness was less for *E. coli* with 548 isolates from 32 countries. Extending the inclusion criteria to include additional Enterobacterales species among the ten carbapenem-R/I Enterobacterales isolates collected per hospital according to the protocol for the 2019 CCRE survey may therefore not lead to representative datasets for these other species while reducing the data available for *K. pneumoniae* SC and *E. coli.* Different approaches may therefore be considered such as a pilot study of isolates of carbapenem-resistant Enterobacterales species other than *E. coli* and *K. pneumoniae* already available at NRLs or modifying the survey inclusion criteria to allow the inclusion of ten carbapenem-resistant isolates per species. Input in this regard will be sought from the national EURGen-Net contact points and the NRLs.

5 Conclusions and potential implications

The CCRE survey provided a wealth of results, which give further insight into the continued spread and new emergence of carbapenemase-producing high-risk clones in the EU/EEA and have direct implications for control. Comparison over time with the European Survey of Carbapenemase-producing Enterobacteriaceae (EuSCAPE) results conducted in 2013-2014 was especially valuable in this respect. Although the analysis was delayed because of the COVID-19 pandemic, the CCRE survey was the first study to detect the increase of bla_{NDM-5}-producing *E. coli* in the EU/EEA and the emergence of the new clade of *K. pneumoniae* ST39 carrying bla_{KPC-2} in Greece. In both cases, follow-up investigations have already confirmed the signal of the CCRE survey and provided relevant further insights. The CCRE survey also detected an increase of *K. pneumoniae* ST307 and improved mapping of the geo-temporal spread of *K. pneumoniae* ST11.

The CCRE survey showed that there was not one single epidemic of carbapenem-R/I *K. pneumoniae* SC in the 36 participating countries but heterogenous epidemiological situations ranging from sporadic cases to endemicity involving a varying mix of *K. pneumoniae* STs and carbapenemases on the national level. Further analysis and comparison with national data may yield additional relevant findings and the dataset can serve as a reference for further genomic studies. The model of repeated structured genomic surveys is now an established element of European genomic surveillance and may be used for future national surveys as well as EU-level surveys for CRE and other multidrug-resistant pathogens. At the same time, efforts to establish faster and more comprehensive genomic surveillance should continue, including related capacity building at the national level.

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Annex

Table A1. Number of carbapenem-R/I *Klebsiella pneumoniae* SC isolates and involved resistance mechanisms by country

Country	Registered carbapenem-R/I isolates n	Included carbapenem-R/I isolates n	Included isolates carrying carbapenemase genes n (%)	Included isolates carrying *bla*KPC n (%)	Included isolates carrying *bla*NDM n (%)	Included isolates carrying *bla*OXA-48-like n (%)	Included carrying *bla*NM isolates n (%)	Included isolates carrying other or multiple carbapenemmase genes n (%)	Included other carbapenem-R/I isolates n (%)	Included carbapenem-S comparator isolates n
Albania	8	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0
Austria	19	19	17 (89)	9 (47)	1 (5)	5 (26)	1 (5)	1 (5)	2 (11)	17
Belgium	54	51	49 (96)	5 (10)	6 (12)	36 (71)	0 (0)	2 (4)	2 (4)	49
Bosnia and Herzegovina	10	10	10 (100)	0 (0)	0 (0)	10 (100)	0 (0)	0 (0)	0 (0)	7
Bulgaria	84	84	77 (92)	42 (50)	33 (39)	1 (1)	0 (0)	1 (1)	7 (8)	84
Croatia	71	59	56 (95)	14 (24)	2 (3)	40 (68)	0 (0)	0 (0)	3 (5)	60
Cyprus	9	8	8 (100)	7 (88)	0 (0)	0 (0)	1 (12)	0 (0)	0 (0)	9
Czechia	30	27	14 (52)	3 (11)	7 (26)	3 (11)	1 (4)	0 (0)	13 (48)	28
Denmark	3	3	3 (100)	0 (0)	2 (67)	1 (33)	0 (0)	0 (0)	0 (0)	0
Estonia	2	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)	3
Finland	13	11	11 (100)	7 (64)	2 (18)	1 (9)	0 (0)	1 (9)	0 (0)	0
France	49	40	21 (52)	2 (5)	6 (15)	12 (30)	0 (0)	1 (2)	19 (48)	48
Germany	45	33	26 (79)	8 (24)	4 (12)	12 (36)	1 (3)	1 (3)	7 (21)	35
Greece	140	128	128 (100)	75 (59)	31 (24)	2 (2)	12 (9)	8 (6)	0 (0)	126
Hungary	40	40	32 (80)	1 (2)	10 (25)	5 (12)	16 (40)	0 (0)	8 (20)	25
Iceland	1	1	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	1
Ireland	14	8	6 (75)	1 (12)	2 (25)	3 (38)	0 (0)	0 (0)	2 (25)	14
Italy	293	278	274 (99)	248 (89)	9 (3)	4 (1)	10 (4)	3 (1)	4 (1)	231
Kosovo*	1	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	1
Latvia	6	3	1 (33)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	2 (67)	3
Lithuania	8	8	8 (100)	8 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8
Luxembourg	3	3	3 (100)	2 (67)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	3
Malta	10	9	9 (100)	0 (0)	2 (22)	6 (67)	0 (0)	1 (11)	0 (0)	10
Montenegro	10	10	2 (20)	0 (0)	0 (0)	2 (20)	0 (0)	0 (0)	8 (80)	8
Netherlands	24	23	18 (83)	1 (4)	6 (30)	8 (35)	0 (0)	3 (13)	5 (17)	21
North Macedonia	14	3	3 (100)	0 (0)	2 (67)	1 (33)	0 (0)	0 (0)	0 (0)	2
Norway	7	7	6 (86)	3 (43)	2 (29)	1 (14)	0 (0)	0 (0)	1 (14)	7
Poland	64	55	45 (82)	2 (4)	41 (75)	1 (2)	1 (2)	0 (0)	10 (18)	58
Portugal	53	52	49 (94)	42 (81)	0 (0)	7 (13)	0 (0)	0 (0)	3 (6)	33
Romania	74	66	62 (94)	20 (30)	7 (11)	30 (45)	0 (0)	5 (8)	4 (6)	51
Serbia	70	69	61 (88)	7 (10)	11 (16)	43 (62)	0 (0)	0 (0)	8 (12)	38
Slovakia	30	30	30 (100)	10 (33)	20 (67)	0 (0)	0 (0)	0 (0)	0 (0)	24
Slovenia	23	24#	13 (54)	3 (12)	0 (0)	10 (42)	0 (0)	0 (0)	11 (46)	23
Spain	188	176	160 (91)	34 (19)	4 (2)	112 (64)	8 (5)	2 (1)	16 (9)	181
Sweden	21	20	17 (85)	3 (15)	6 (30)	6 (30)	0 (0)	2 (10)	3 (15)	19
Türkiye	212	138	130 (94)	26 (19)	19 (14)	69 (50)	0 (0)	16 (12)	8 (6)	123
United Kingdom	86	67	48 (72)	16 (24)	6 (9)	20 (30)	0 (0)	6 (9)	19 (28)	57
All countries	1 789	1 566	1 398 (89)	600 (38)	241 (15)	453 (29)	51 (3)	53 (3)	168 (11)	1 407

**This designation is without prejudice to positions on status and is in line with United Nations Security Council Resolution 1244/99 and the International Court of Justice Opinion on the Kosovo declaration of independence.*

 # The reason for the number of included K. pneumoniae *isolates being higher than the number of registered* K. pneumoniae *isolates is that for one isolate the species was initially erroneously registered as* E. coli *and later corrected to* K. pneumoniae*.*

Table A2. Number of carbapenem-R/I *Escherichia coli* isolates and involved resistance mechanisms by country

Country	Registered carbapenem-R/I isolates n	Included carbapenem-R/I isolates n	Included isolates carrying carbapenemase genes n (%)	Included isolates carrying *bla*$_{KPC}$ n (%)	Included isolates carrying *bla*$_{NDM}$ n (%)	Included isolates carrying *bla*$_{OXA-48-like}$ n (%)	Included carrying *bla*$_{VIM}$ n (%)	Included isolates carrying other or multiple carbapenemase genes n (%)	Included other carbapenem-R/I isolates n (%)	Included carbapenem-S comparator isolates n
Albania	2	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0
Austria	5	5	4 (80)	0 (0)	1 (20)	3 (60)	0 (0)	0 (0)	1 (20)	5
Belgium	13	10	9 (90)	0 (0)	1 (10)	8 (80)	0 (0)	0 (0)	1 (10)	13
Bosnia and Herzegovina	0	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3
Bulgaria	7	7	6 (86)	0 (0)	5 (71)	0 (0)	0 (0)	1 (14)	1 (14)	7
Croatia	3	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4
Cyprus	1	1	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1
Czechia	10	10	10 (100)	0 (0)	9 (90)	0 (0)	0 (0)	1 (10)	0 (0)	8
Denmark	8	6	6 (100)	0 (0)	5 (83)	1 (17)	0 (0)	0 (0)	0 (0)	0
Estonia	3	2	1 (50)	0 (0)	0 (0)	0 (0)	1 (50)	0 (0)	1 (50)	3
Finland	13	10	10 (100)	0 (0)	5 (50)	4 (40)	0 (0)	1 (10)	0 (0)	0
France	10	7	7 (100)	0 (0)	3 (43)	4 (57)	0 (0)	0 (0)	0 (0)	12
Germany	23	14	10 (71)	0 (0)	4 (29)	6 (43)	0 (0)	0 (0)	4 (29)	21
Greece	2	2	2 (100)	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	6
Hungary	1	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0
Iceland	2	1	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	2
Ireland	9	1	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	7
Italy	20	17	17 (100)	13 (76)	2 (12)	1 (6)	1 (6)	0 (0)	0 (0)	44
Kosovo*	0	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0
Latvia	1	1	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	1
Lithuania	2	2	2 (100)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2
Luxembourg	3	3	3 (100)	0 (0)	1 (33)	2 (67)	0 (0)	0 (0)	0 (0)	3
Malta	0	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0
Montenegro	0	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0
Netherlands	10	10	9 (90)	0 (0)	8 (80)	1 (10)	0 (0)	0 (0)	1 (10)	9
North Macedonia	0	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3
Norway	5	5	4 (80)	0 (0)	3 (60)	1 (20)	0 (0)	0 (0)	1 (20)	5
Poland	2	2	2 (100)	1 (50)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	2
Portugal	3	3	3 (100)	1 (33)	0 (0)	2 (67)	0 (0)	0 (0)	0 (0)	5
Romania	0	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7
Serbia	1	1	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	9
Slovakia	0	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0
Slovenia	8	7	6 (86)	2 (29)	1 (14)	3 (43)	0 (0)	0 (0)	1 (14)	5
Spain	20	16	10 (62)	0 (0)	0 (0)	8 (50)	2 (12)	0 (0)	6 (38)	19
Sweden	25	16	16 (100)	0 (0)	10 (62)	6 (38)	0 (0)	0 (0)	0 (0)	21
Türkiye	30	12	10 (83)	0 (0)	5 (42)	4 (33)	0 (0)	1 (8)	2 (17)	59
United Kingdom	47	39	30 (77)	1 (3)	15 (38)	13 (33)	0 (0)	1 (3)	9 (23)	51
All countries	289	211	182 (86)	21 (10)	81 (38)	68 (32)	7 (3)	5 (2)	29 (14)	337

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Table A3a. Prevalence and incidence of carbapenem-R/I *Klebsiella pneumoniae* SC

Country	Participating hospitals n	Participating hospitals with information on admission n	Hospital admissions[1] during the sampling period n	Period prevalence carbapenem-R/I *K. pneumoniae* SC isolates n per 10 000 hospital admissions (95% CI)	Period prevalence *K. pneumoniae* SC carrying carbapenemase genes n per 10 000 hospital admissions (95% CI)	Participating hospitals with information on patient-days n	Patient-days[2] during the sampling period n	Incidence carbapenem-R/I *K. pneumoniae* SC isolates n per 100 000 patient-days (95% CI)	Incidence *K. pneumoniae* SC carrying carbapenemmase genes n per 100 000 patient-days (95% CI)
Albania	NA	NA	NA	NA	NA	NA	NA	NA	NA
Austria	7	1	37 161	2.4 (1.1-4.6)	2.4 (1.1-4.6)	1	182 852	4.9 (2.3-9.3)	4.9 (2.3-9.3)
Belgium	14	14	202 684	2.5 (1.9-3.3)	2.4 (1.8-3.2)	14	1 341 909	3.8 (2.8-5.0)	3.7 (2.7-4.8)
Bosnia and Herzegovina	1	1	18 834	5.3 (2.5-9.8)	5.3 (2.5-9.8)	1	110 656	9.0 (4.3-16.6)	9.0 (4.3-16.6)
Bulgaria	10	10	146 843	5.7 (4.6-7.1)	5.2 (4.1-6.6)	10	737 854	11.4 (9.1-14.1)	10.4 (8.2-13.0)
Croatia	9	6	61 022	5.6 (3.9-7.8)	5.6 (3.9-7.8)	6	284 308	12.0 (8.3-16.7)	12.0 (8.3-16.7)
Cyprus	1	1	10 344	7.7 (3.3-15.2)	7.7 (3.3-15.2)	NA	NA	NA	NA
Czechia	8	NA	NA	NA	NA	NA	NA	NA	NA
Denmark	3	3	841 881	0.0 (0.0-0.1)	0.0 (0.0-0.1)	3	2 544 870	0.1 (0.0-0.3)	0.1 (0.0-0.3)
Estonia	1	1	135 673	0.1 (0.0-0.5)	NA	1	178 993	1.1 (0.1-4.0)	NA
Finland	5	4	129 056	0.8 (0.4-1.4)	0.8 (0.4-1.4)	4	371 531	2.7 (1.3-4.9)	2.7 (1.3-4.9)
France	12	NA	NA	NA	NA	NA	NA	NA	NA
Germany	18	3	59 199	0.5 (0.1-1.5)	0.3 (0-1.2)	3	397 630	0.8 (0.2-2.2)	0.5 (0.1-1.8)
Greece	15	10	55 354	15.7 (12.6-19.4)	15.7 (12.6-19.4)	9	198 741	39.8 (31.5-49.5)	39.8 (31.5-49.5)
Hungary	8	8	308 217	1.3 (0.9-1.8)	1.0 (0.7-1.5)	8	1 571 421	2.5 (1.8-3.5)	2.0 (1.4-2.9)
Iceland	1	1	12 252	0.8 (0-4.5)	0.8 (0-4.5)	1	108 895	0.9 (0.0-5.1)	0.9 (0.0-5.1)
Ireland	6	1	35 023	NA	NA	1	87 596	NA	NA
Italy	32	18	284 833	5.5 (4.7-6.4)	5.4 (4.6-6.4)	13	635 478	17.8 (14.7-21.4)	17.6 (14.5-21.2)
Kosovo*	1	1	49 466	0.2 (0.0-1.1)	NA	1	249217	0.4 (0.0-2.2)	NA
Latvia	1	NA	NA	NA	NA	NA	NA	NA	NA
Lithuania	1	NA	NA	NA	NA	NA	NA	NA	NA
Luxembourg	2	1	188 860	0.1 (0.0-0.3)	0.1 (0.0-0.3)	1	86 723	1.2 (0.0-6.4)	1.2 (0.0-6.4)
Malta	1	1	32 052	2.8 (1.3-5.3)	2.8 (1.3-5.3)	1	164 045	5.5 (2.5-10.4)	5.5 (2.5-10.4)
Montenegro	1	1	197 926	0.5 (0.2-0.9)	0.1 (0.0-0.4)	NA	NA	NA	NA
Netherlands	13	13	191 101	1.2 (0.8-1.8)	1.0 (0.6-1.6)	13	1 003 997	2.3 (1.5-3.4)	1.9 (1.1-3.0)
North Macedonia	1	1	44 866	0.7 (0.1-2.0)	0.7 (0.1-2.0)	1	517 226	0.6 (0.1-1.7)	0.6 (0.1-1.7)
Norway	3	2	44 855	1.3 (0.5-2.9)	1.1 (0.4-2.6)	2	182 787	3.3 (1.2-7.1)	2.7 (0.9-6.4)
Poland	12	12	183 594	3.0 (2.3-3.9)	2.5 (1.8-3.3)	12	778 456	7.1 (5.3-9.2)	5.8 (4.2-7.7)
Portugal	7	5	39 118	10.0 (7.1-13.6)	10.0 (7.1-13.6)	5	90 330	43.2 (30.7-59)	43.2 (30.7-59.0)
Romania	9	7	30 724	16.3 (12.1-21.4)	15.0 (11.0-20.0)	7	129 714	38.5 (28.6-50.8)	35.5 (26.0-47.3)
Serbia	9	9	189 876	3.6 (2.8-4.6)	3.2 (2.5-4.1)	9	1 278 731	5.4 (4.2-6.8)	4.8 (3.6-6.1)
Slovakia	3	3	13 845	21.7 (14.6-30.9)	21.7.0 (14.6-30.9)	3	91 198	32.9 (22.2-47.0)	32.9 (22.2-47.0)
Slovenia	7	1	47 600	1.7 (0.7-3.3)	1.1 (0.3-2.5)	1	25 600	31.2 (13.5-61.6)	19.5 (6.3-45.6)
Spain	24	22	339 483	4.6 (3.9-5.4)	4.2 (3.5-4.9)	18	695 473	18.8 (15.7-22.4)	17.4 (14.4-20.8)
Sweden	7	1	30 300	2.0 (0.7-4.3)	1.7 (0.5-3.9)	1	169 000	3.6 (1.3-7.7)	3.0 (1.0-6.9)
Türkiye	25	NA	NA	NA	NA	NA	NA	NA	NA
United Kingdom	24	4	127 523	1.3 (0.7-2.0)	0.9 (0.4-1.5)	4	339 997	4.7 (2.7-7.6)	3.2 (1.6-5.8)
All countries	302	166	4 089 565	2.4 (2.2-2.6)	2.2 (2.1-2.3)	154	14 555 228	6.1 (5.7-6.5)	5.6 (5.2-6.0)

[1]Data on hospital admissions were incompletely and, in some cases, erroneously registered. To allow comparison between countries, data was included for hospitals only if the number of admitted patients during sampling period was > 100 and the number of occupied bed days during the sampling period was >100.

[2]Data on patient days were incompletely and, in some cases, erroneously registered. To allow comparison between countries, data was included for hospitals only if the number of occupied bed days during sampling period was between 100 and 10,000,000 and the number of admitted patients during sampling period was >100 and [the number of admitted patients during sampling period] / [the number of occupied bed days during sampling period] was <10

NA: not available.

***This designation is without prejudice to positions on status and is in line with United Nations Security Council Resolution 1244/99 and the International Court of Justice Opinion on the Kosovo declaration of independence*

Table A3b. Prevalence and incidence of carbapenem-R/I *Escherichia coli*

Country	Participating hospitals n	Participating hospitals with information on admission n	Hospital admissions[1] during the sampling period n	Period prevalence carbapenem-R/I *E. coli* isolates n per 10 000 hospital admissions (95% CI)	Period prevalence *E. coli* carrying carbapenemmase genes n per 10 000 hospital admissions (95% CI)	Participating hospitals with information on patient-days[2] n	Patient-days during the sampling period n	Incidence carbapenem-R/I *E. coli* isolates n per 100 000 patient-days (95% CI)	Incidence *E. coli* carrying carbapenemmase genes n per 100 000 patient-days (95% CI)
Albania	NA	NA	NA	NA	NA	NA	NA	NA	NA
Austria	4	NA	NA	NA	NA	NA	NA	NA	NA
Belgium	8	8	135 534	0.7 (0.4-1.4)	0.7 (0.3-1.3)	8	928 578	1.1 (0.5-2.0)	1.0 (0.4-1.8)
Bosnia and Herzegovina	1	1	18 834	NA	NA	1	110 656	NA	NA
Bulgaria	2	2	30 681	2.3 (0.9-4.7)	2.0 (0.7-4.3)	2	157 673	4.4 (1.8-9.1)	3.8 (1.4-8.3)
Croatia	1	1	24 678	NA	NA	1	146 159	NA	NA
Cyprus	1	1	10 344	1.0 (0.0-5.4)	1.0 (0.0-5.4)	NA	NA	NA	NA
Czechia	4	NA	NA	NA	NA	NA	NA	NA	NA
Denmark	4	4	889 756	0.1 (0.0-0.1)	0.1 (0.0-0.1)	4	2 460 777	0.2 (0.1-0.5)	0.2 (0.1-0.5)
Estonia	1	1	135 673	0.1 (0.0-0.5)	0.1 (0.0-0.4)	1	178 993	1.1 (0.1-4.0)	0.6 (0.0-3.1)
Finland	5	5	159 602	0.6 (0.3-1.2)	0.6 (0.3-1.2)	5	428 924	2.3 (1.1-4.3)	2.3 (1.1-4.3)
France	5	NA	NA	NA	NA	NA	NA	NA	NA
Germany	12	2	37 728	0.3 (0.0-1.5)	0.3 (0.0-1.5)	2	245 157	0.4 (0.0-2.3)	0.4 (0.0-2.3)
Greece	4	2	5 529	1.8 (0.0-10.1)	1.8 (0.0-10.1)	2	11 113	9.0 (0.2-50.1)	9.0 (0.2-50.1)
Hungary	1	1	25 125	0.4 (0.0-2.2)	NA	1	162 664	0.6 (0.0-3.4)	NA
Iceland	1	1	12 252	0.8 (0.0-4.5)	0.8 (0.0-4.5)	1	108 895	0.9 (0.0-5.1)	0.9 (0.0-5.1)
Ireland	2	NA	NA	NA	NA	NA	NA	NA	NA
Italy	17	10	95 833	1.0 (0.5-1.9)	1.0 (0.5-1.9)	9	382 647	2.4 (1.1-4.5)	2.4 (1.1-4.5)
Kosovo*	NA	NA	NA	NA	NA	NA	NA	NA	NA
Latvia	1	NA	NA	NA	NA	NA	NA	NA	NA
Lithuania	1	NA	NA	NA	NA	NA	NA	NA	NA
Luxembourg	2	1	188 860	0.1 (0.0-0.3)	0.1 (0.0-0.3)	1	86 723	1.2 (0.0-6.4)	1.2 (0.0-6.4)
Malta	NA	NA	NA	NA	NA	NA	NA	NA	NA
Montenegro	NA	NA	NA	NA	NA	NA	NA	NA	NA
Netherlands	8	8	104 630	1.0 (0.5-1.8)	0.9 (0.4-1.6)	8	458 932	2.2 (1.0-4.0)	2.0 (0.9-3.7)
North Macedonia	2	2	58 343	NA	NA	2	603 243	NA	NA
Norway	3	3	55 893	0.9 (0.3-2.1)	0.7 (0.2-1.8)	3	228 326	2.2 (0.7-5.1)	1.8 (0.5-4.5)
Poland	1	1	54 442	0.4 (0.0-1.3)	0.4 (0.0-1.3)	1	181 818	1.1 (0.1-4.0)	1.1 (0.1-4.0)
Portugal	3	2	23 948	0.4 (0.0-2.3)	0.4 (0.0-2.3)	2	12 622	7.9 (0.2-44.1)	7.9 (0.2-44.1)
Romania	1	1	5 297	NA	NA	1	29 027	NA	NA
Serbia	2	2	96 918	0.1 (0.0-0.6)	0.1 (0.0-0.6)	2	648 493	0.2 (0.0-0.9)	0.2 (0.0-0.9)
Slovakia	NA	NA	NA	NA	NA	NA	NA	NA	NA
Slovenia	5	1	47 600	0.4 (0.1-1.5)	0.4 (0.1-1.5)	1	25 600	7.8 (0.9-28.2)	7.8 (0.9-28.2)
Spain	10	10	210 834	0.8 (0.4-1.2)	0.5 (0.2-0.9)	9	451 346	2.9 (1.5-4.9)	1.8 (0.8-3.5)
Sweden	7	3	61 910	1.0 (0.4-2.1)	1.0 (0.4-2.1)	3	311 574	1.9 (0.7-4.2)	1.9 (0.7-4.2)
Türkiye	17	NA	NA	NA	NA	NA	NA	NA	NA
United Kingdom	20	4	127 523	0.5 (0.2-1.1)	0.5 (0.2-1.0)	4	339 997	2.1 (0.8-4.2)	1.8 (0.6-3.8)
All countries	156	77	2 617 767	0.4 (0.3-0.5)	0.3 (0.3-0.4)	74	8 699 937	1.1 (0.9-1.3)	1.0 (0.8-1.2)

[1]Data on hospital admissions were incompletely and, in some cases, erroneously registered. To allow comparison between countries, data was included for hospitals only if the number of admitted patients during sampling period was > 100 and the number of occupied bed days during the sampling period was >100.

[2]Data on patient days were incompletely and, in some cases, erroneously registered. To allow comparison between countries, data was included for hospitals only if the number of occupied bed days during sampling period was between 100 and 10,000,000 and the number of admitted patients during sampling period was >100 and [the number of admitted patients during sampling period] / [the number of occupied bed days during sampling period] was <10

NA: not available.

***This designation is without prejudice to positions on status and is in line with United Nations Security Council Resolution 1244/99 and the International Court of Justice Opinion on the Kosovo declaration of independence*

Table A4. *Escherichia coli* and *Klebsiella pneumoniae* SC isolates resistant (R) and 'susceptible, increased exposure' (I) to carbapenems

Category	Included isolates n	Ertapenem (R+I) n/N tested (%)	Imipenem (R+I) n/N tested (%)	Meropenem (R+I) n/N tested (%)
Carbapenem-R/I *E. coli*	211	195/197 (99.0)	116/188 (61.7)	118/205 (57.6)
E. coli carrying carbapenemase genes	182	167/169 (98.8)	107/160 (66.9)	105/176 (59.7)
Carbapenem-S *E. coli*	337	0/309 (0.0)	0/265 (0.0)	0/324 (0.0)
Carbapenem-R/I *K. pneumoniae* SC	1 566	1 498/1 506 (99.5)	956/1 252 (76.4)	1 287/1 555 (82.8)
K. pneumoniae SC carrying carbapenemase genes	1 399	1 341/1 348 (99.5)	926/1 095 (84.6)	1 198/1 390 (86.2)
Carbapenem-S *K. pneumoniae* SC	1 407	0/1 258 (0.0)	0/1 050 (0.0)	0/1 371 (0.0)

Table A5a. *Escherichia coli* and *Klebsiella pneumoniae* SC isolates: resistant (R) to other antibiotics

Category	Included isolates n	Amoxicillin-clavulanic acid-R n/N tested (%)	Piperacillin-tazobactam-R n/N tested (%)	Cefotaxime-R n/N tested (%)	Ceftazidime-R n/N tested (%)	Cefepime-R n/N tested (%)	Ceftazidime-avibactam-R n/N tested (%)	Aztreonam-R n/N tested (%)	Ciprofloxacin-R n/N tested (%)	Trimethoprim-sulfamethoxazole-R n/N tested (%)	Gentamicin-R n/N tested (%)	Tobramycin-R n/N tested (%)	Amikacin-R n/N tested (%)	Colistin-R n/N tested (%)	Tigecycline-R n/N tested (%)	Fosfomycin-R n/N tested (%)
Carbapenem-R/I *E. coli*	211	189/190 (99.5)	190/199 (95.5)	153/176 (86.9)	167/203 (82.3)	132/165 (80.0)	61/163 (37.4)	103/147 (70.1)	124/182 (68.1)	103/149 (69.1)	64/181 (35.4)	47/119 (39.5)	27/170 (15.9)	6/191 (3.1)	6/157 (3.8)	9/97 (9.3)
E. coli carrying carbapenemase genes	182	160/161 (99.4)	168/170 (98.8)	127/147 (86.4)	143/174 (82.2)	108/137 (78.8)	61/138 (44.2)	82/120 (68.3)	103/157 (65.6)	93/133 (69.9)	54/156 (34.6)	44/106 (41.5)	26/146 (17.8)	4/168 (2.4)	5/136 (3.7)	6/85 (7.1)
Carbapenem-S *E. coli*	337	97/279 (34.8)	19/268 (7.1)	75/282 (26.6)	65/284 (22.9)	48/235 (20.4)	0/162 (0.0)	43/215 (20.0)	76/258 (29.5)	65/194 (33.5)	40/259 (15.4)	33/155 (21.3)	7/232 (3.0)	3/224 (1.3)	1/146 (0.7)	5/65 (7.7)
Carbapenem-R/I *K. pneumoniae* SC	1566	1490/1500 (99.3)	1502/1516 (99.1)	1103/1171 (94.2)	1442/1520 (94.9)	1369/1457 (94.0)	277/1126 (24.6)	888/1007 (88.2)	1398/1484 (94.2)	1082/1404 (77.1)	811/1484 (54.6)	834/966 (86.3)	571/1407 (40.6)	336/1439 (23.3)	N.A.	466/891 (52.3)
K. pneumoniae SC carrying carbapenemase genes	1399	1350/1352 (99.9)	1365/1367 (99.9)	971/1029 (94.4)	1298/1371 (94.7)	1241/1318 (94.2)	267/1017 (26.3)	784/891 (88.0)	1274/1339 (95.1)	977/1282 (76.2)	722/1339 (53.9)	755/868 (87.0)	538/1271 (42.3)	317/1306 (24.3)	N.A.	414/825 (50.2)
Carbapenem-S *K. pneumoniae* SC	1407	318/1041 (30.5)	154/1036 (14.9)	282/1037 (27.2)	282/1064 (26.5)	242/977 (24.8)	5/601 (0.8)	204/850 (24.0)	271/1015 (26.7)	306/922 (33.2)	151/1007 (15.0)	173/760 (22.8)	35/943 (3.7)	21/911 (2.3)	N.A.	155/365 (42.5)

Table A5b. *Escherichia coli* and *Klebsiella pneumoniae* SC isolates: 'susceptible, increased exposure (I)' to other antibiotics

Category	Included isolates n	Amoxicillin-clavulanic acid-I n/N	Piperacillin-tazobactam-I n/N tested (%)	Cefotaxime-I n/N tested (%)	Ceftazidime-I n/N tested (%)	Cefepime-I n/N tested (%)	Ceftazidime-avibactam-I n/N tested (%)	Aztreonam-I n/N tested (%)	Ciprofloxacin-I n/N tested (%)	Trimethoprim-sulfamethoxazole-I n/N tested (%)	Gentamicin-I n/N tested (%)	Tobramicin-I n/N tested (%)	Amikacin-I n/N tested (%)	Colistin-I n/N tested (%)	Tigecycline-I n/N tested (%)	Fosfomicin-I n/N tested (%)
Carbapenem-R/I *E. coli*	211	0/190 (0.0)	1/199 (0.5)	9/176 (5.1)	11/203 (5.4)	8/165 (4.8)	0/163 (0.0)	10/147 (6.8)	3/182 (1.6)	0/149 (0.0)	1/181 (0.6)	4/119 (3.4)	6/170 (3.5)	0/191 (0.0)	1/157 (0.6)	0/97 (0.0)
E. coli carrying carbapenemase genes	182	0/161 (0.0)	0/170 (0.0)	8/147 (5.4)	8/174 (4.6)	7/137 (5.1)	0/138 (0.0)	7/120 (5.8)	3/157 (1.9)	0/133 (0.0)	1/156 (0.6)	4/106 (3.8)	6/146 (4.1)	0/168 (0.0)	1/136 (0.7)	0/85 (0.0)
Carbapenem-S *E. coli*	337	0/279 (0.0)	10/268 (3.7)	4/282 (1.4)	15/284 (5.3)	9/235 (3.8)	0/162 (0.0)	11/215 (5.1)	7/258 (2.7)	0/194 (0.0)	3/259 (1.2)	4/155 (2.6)	6/232 (2.6)	0/224 (0.0)	0/146 (0.0)	0/65 (0.0)
Carbapenem-R/I *K. pneumoniae* SC	1566	0/1500 (0.0)	6/1516 (0.4)	22/1171 (1.9)	20/1520 (1.3)	23/1457 (1.6)	0/1126 (0.0)	18/1007 (1.8)	11/1484 (0.7)	18/1404 (1.3)	18/1484 (1.2)	9/966 (0.9)	140/1407 (10.0)	0/1439 (0.0)	N.A.	0/891 (0.0)
K. pneumoniae SC carrying carbapenemase genes	1399	0/1352 (0.0)	0/1367 (0.0)	18/1029 (1.7)	17/1371 (1.2)	19/1318 (1.4)	0/1017 (0.0)	12/891 (1.3)	5/1339 (0.4)	17/1282 (1.3)	17/1339 (1.3)	8/868 (0.9)	127/1271 (10.0)	0/1306 (0.0)	N.A.	0/825 (0.0)
Carbapenem-S *K. pneumoniae* SC	1407	18/1041 (1.7)	108/1036 (10.4)	7/1037 (0.7)	23/1064 (2.2)	25/977 (2.6)	0/601 (0.0)	13/850 (1.5)	33/1015 (3.3)	8/922 (0.9)	14/1007 (1.4)	16/760 (2.1)	21/943 (2.2)	0/911 (0.0)	N.A.	0/365 (0.0)

Table A5c. Multidrug-resistant, difficult-to-treat and fully drug-resistant isolates of *Escherichia coli* and *K. pneumoniae* SC

Category	Included isolates n	Multidrug-resistant (MDR)[1] isolates n (%)	Isolates with AST performed for ≥1 carbapenem, ≥1 extended-spectrum cephalosporin and ≥1 fluoroquinolone n	Isolates with difficult-to-treat resistance (DTR)[2] n (%)	Isolates fully drug-resistant (FDR) for tested antimicrobials[3] n (%)
Carbapenem-R/I *E. coli*	211	205 (97.2)	182	43 (23.6)	1 (0.5)
Carbapenemase-producing *E. coli*	182	176 (96.7)	157	42 (26.8)	0 (0.0)
Carbapenem-S *E. coli*	337	100 (29.7)	258	0 (0.0)	0 (0.0)
Carbapenem-R/I *K. pneumoniae* SC	1 566	1 531 (97.8)	1 484	470 (31.7)	111 (7.5)
Carbapenemase-producing *K. pneumoniae* SC	1 399	1 379 (98.6)	1 339	458 (34.2)	106 (7.9)
Carbapenem-S *K. pneumoniae* SC	1 407	367 (26.1)	1 014	0 (0.0)	0 (0.0)

[1]Multidrug-resistant (MDR): R/I to at least one agent from three or more antibiotic classes (table A5d) [21].
[2]Difficult-to-treat resistance (DTR): R/I to all ß-lactams and fluoroquinolones, definition by Kadri et al. [48]. Based on isolates that have AST performed for ≥1 carbapenem, ≥1 extended-spectrum cephalosporin and ≥1 fluoroquinolone.
[3]FDR for tested antimicrobials, R/I to all tested antimicrobials, based on isolates that have AST performed for ≥1 carbapenem, ≥1 extended-spectrum cephalosporin and ≥1 fluoroquinolone. For K. pneumoniae *SC, AST-results for tigecycline and fosfomycin were disregarded. AST: Antimicrobial susceptibility testing.*

Table A5d. Antimicrobial categories used for categorisation of multidrug-resistant (MDR) isolates

Antimicrobial category	Antimicrobial agents	SIR for fullfilling MDR criteria
Aminoglycosides	Amikacin, gentamicin or tobramycin	I or R
Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam	I or R
Carbapenems	Ertapenem, imipenem, meropenem	I or R
Extended-spectrum cephalosporins; 3rd- and 4th-generation cephalosporins	Cefepime, cefotaxime, ceftazidime	I or R
Fluoroquinolones	Ciprofloxacin	I or R
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole	I or R
Glycylcyclines	Tigecycline	I or R
Monobactams	Aztreonam	I or R
Penicillins[1]	Ampicillin[1]	R
Penicillins + β-lactamase inhibitors	Amoxicillin-clavulanic acid	I or R
Phosphonic acids	Fosfomycin	R
Polymyxins	Colistin	R

[1]Ampicillin-resistance was not counted for K. pneumoniae SC due to intrinsic resistance.
Isolates were defined as MDR if R or I to ≥1 agent in ≥3 antimicrobial categories [21].

Table A6. Distribution of carbapenem-R/I and carbapenem-S *Escherichia coli* and *Klebsiella pneumoniae* isolates by specimen type

Type of clinical specimen	*Escherichia coli*		*Klebsiella pneumoniae* SC	
	Carbapenem-R/I n (%)	Carbapenem-S n (%)	Carbapenem-R/I n (%)	Carbapenem-S n (%)
Blood	15 (7.1)	79 (23.4)	270 (17.2)	247 (17.6)
Wound swabs	17 (8.1)	14 (4.2)	103 (6.6)	93 (6.6)
Urine	71 (33.6)	165 (49)	646 (41.3)	702 (49.9)
Lower respiratory tract specimens	6 (2.8)	9 (2.7)	200 (12.8)	156 (11.1)
Soft tissue samples	2 (0.9)	8 (2.4)	36 (2.3)	20 (1.4)
Aspirates	5 (2.4)	13 (3.9)	41 (2.6)	47 (3.3)
Bone and joint specimens	0 (0)	1 (0.3)	8 (0.5)	2 (0.1)
Catheter exit site	4 (1.9)	2 (0.6)	35 (2.2)	17 (1.2)
Reproductive tract samples	1 (0.5)	4 (1.2)	1 (0.1)	13 (0.9)
Cerebrospinal fluid	0 (0)	0 (0)	1 (0.1)	1 (0.1)
Other	73 (34.6)	35 (10.4)	195 (12.5)	97 (6.9)
Missing	17 (8.1)	7 (2.1)	30 (1.9)	12 (0.9)
Total	211 (100)	337 (100)	1 566 (100)	1 407 (100)

Table A7a. Dominant sequence types among carbapenem-R/I (n=1 566) and carbapenem-S (n=1 407) *Klebsiella pneumoniae* SC isolates

Country	Carbapenem R/I *K. pneumoniae* SC								Carbapenem-S *K. pneumoniae* SC						
	Total	STs	ST258/512	ST101	ST11	ST30	ST147	ST15	Total	STs	ST307	ST35	ST37	ST45	ST20
	n	n	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n	n	n (%)	n (%)	n (%)	n (%)	n (%)
Albania	0	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA
Austria	19	10	5 (26.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	17	16	0 (0)	1 (5.9)	0 (0)	1 (5.9)	1 (5.9)
Belgium	51	25	4 (7.8)	3 (5.9)	1 (2.0)	6 (11.8)	2 (3.9)	10 (19.6)	49	37	0 (0)	1 (2.0)	1 (2.0)	2 (4.1)	2 (4.1)
Bosnia and Herzegovina	10	2	0 (0)	8 (80.0)	0 (0)	0 (0)	0 (0)	0 (0)	7	6	2 (28.6)	0 (0)	1 (14.3)	0 (0)	0 (0)
Bulgaria	84	10	27 (32.1)	0 (0)	35 (41.7)	1 (1.2)	0 (0)	0 (0)	84	58	6 (7.1)	1 (1.2)	2 (2.4)	1 (1.2)	0 (0)
Croatia	59	14	0 (0)	22 (37.3)	0 (0)	2 (3.4)	1 (1.7)	4 (6.8)	60	42	5 (8.3)	1 (1.7)	2 (3.3)	3 (5.0)	0 (0)
Cyprus	8	6	1 (12.5)	0 (0)	0 (0)	2 (25.0)	0 (0)	0 (0)	9	9	0 (0)	0 (0)	1 (11.1)	0 (0)	0 (0)
Czechia	27	22	1 (3.7)	1 (3.7)	2 (7.4)	1 (3.7)	1 (3.7)	0 (0)	28	23	0 (0)	1 (3.6)	0 (0)	1 (3.6)	2 (7.1)
Denmark	3	3	0 (0)	0 (0)	1 (33.3)	0 (0)	0 (0)	0 (0)	0	NA	NA	NA	NA	NA	NA
Estonia	2	2	0 (0)	0 (0)	0 (0)	1 (50.0)	0 (0)	0 (0)	3	3	0 (0)	0 (0)	1 (33.3)	0 (0)	0 (0)
Finland	11	6	5 (45.5)	0 (0)	2 (18.2)	1 (9.1)	0 (0)	0 (0)	0	NA	NA	NA	NA	NA	NA
France	40	20	0 (0)	3 (7.5)	2 (5.0)	8 (20.0)	7 (17.5)	1 (2.5)	48	39	3 (6.3)	1 (2.1)	3 (6.3)	1 (2.1)	4 (8.3)
Germany	33	18	2 (6.1)	3 (9.1)	0 (0)	6 (18.2)	1 (3.0)	2 (6.1)	35	28	0 (0)	0 (0)	3 (8.6)	0 (0)	3 (8.6)
Greece	128	10	40 (31.3)	2 (1.6)	33 (25.8)	1 (0.8)	10 (7.8)	0 (0)	126	82	3 (2.4)	7 (5.6)	4 (3.2)	1 (0.8)	3 (2.4)
Hungary	40	13	1 (2.5)	2 (5.0)	1 (2.5)	0 (0)	10 (25.0)	14 (35.0)	25	23	0 (0)	0 (0)	0 (0)	1 (4.0)	2 (8.0)
Iceland	1	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100.0)	1	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ireland	8	7	1 (12.5)	1 (12.5)	2 (25.0)	0 (0)	1 (12.5)	0 (0)	14	13	1 (7.1)	0 (0)	0 (0)	0 (0)	1 (7.1)
Italy	278	27	88 (31.7)	53 (19.1)	4 (1.4)	91 (32.7)	10 (3.6)	1 (0.4)	231	143	12 (5.2)	10 (4.3)	2 (0.9)	7 (3.0)	7 (3.0)
Kosovo*	1	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Latvia	3	2	0 (0)	0 (0)	1 (33.3)	0 (0)	0 (0)	0 (0)	3	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Lithuania	8	2	0 (0)	0 (0)	0 (0)	1 (12.5)	0 (0)	0 (0)	8	6	1 (12.5)	0 (0)	0 (0)	0 (0)	0 (0)
Luxembourg	3	3	1 (33.3)	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	3	2	2 (66.7)	0 (0)	0 (0)	0 (0)	0 (0)
Malta	9	3	0 (0)	0 (0)	1 (11.1)	2 (22.2)	6 (66.7)	0 (0)	10	9	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Montenegro	10	4	0 (0)	5 (50.0)	0 (0)	1 (10.0)	0 (0)	0 (0)	8	8	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Netherlands	23	18	0 (0)	2 (8.7)	1 (4.3)	0 (0)	3 (13.0)	1 (4.3)	21	19	1 (4.8)	2 (9.5)	0 (0)	1 (4.8)	2 (9.5)
North Macedonia	3	3	0 (0)	0 (0)	1 (33.3)	0 (0)	0 (0)	1 (33.3)	2	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Norway	7	6	0 (0)	1 (14.3)	1 (14.3)	2 (28.6)	1 (14.3)	0 (0)	7	6	0 (0)	0 (0)	1 (14.3)	1 (14.3)	0 (0)
Poland	55	8	0 (0)	0 (0)	45 (81.8)	0 (0)	1 (1.8)	0 (0)	58	35	2 (3.4)	2 (3.4)	0 (0)	1 (1.7)	3 (5.2)
Portugal	52	13	0 (0)	0 (0)	0 (0)	2 (3.8)	6 (11.5)	4 (7.7)	33	25	2 (6.1)	3 (9.1)	0 (0)	0 (0)	1 (3.0)
Romania	66	11	20 (30.3)	31 (47.0)	3 (4.5)	4 (6.1)	1 (1.5)	2 (3.0)	51	34	0 (0)	4 (7.8)	1 (2.0)	2 (3.9)	0 (0)
Serbia	69	11	7 (10.1)	30 (43.5)	2 (2.9)	0 (0)	0 (0)	1 (1.4)	38	28	2 (5.3)	0 (0)	1 (2.6)	0 (0)	0 (0)
Slovakia	30	4	0 (0)	0 (0)	17 (56.7)	0 (0)	0 (0)	0 (0)	24	15	0 (0)	0 (0)	2 (8.3)	2 (8.3)	2 (8.3)
Slovenia	24	13	1 (4.2)	3 (12.5)	0 (0)	0 (0)	1 (4.2)	2 (8.3)	23	13	6 (26.1)	0 (0)	0 (0)	0 (0)	0 (0)
Spain	176	35	24 (13.6)	5 (2.8)	23 (13.1)	27 (15.3)	16 (9.1)	30 (17.0)	181	101	6 (3.3)	9 (5.0)	8 (4.4)	4 (2.2)	3 (1.7)
Sweden	20	14	2 (10.0)	0 (0)	4 (20.0)	2 (10.0)	2 (10.0)	1 (5.0)	19	16	0 (0)	0 (0)	1 (5.3)	3 (15.8)	0 (0)
Türkiye	138	22	0 (0)	32 (23.2)	0 (0)	10 (7.2)	14 (10.1)	6 (4.3)	123	78	3 (2.4)	5 (4.1)	5 (4.1)	6 (4.9)	1 (0.8)
United Kingdom	67	38	2 (3.0)	1 (1.5)	5 (7.5)	9 (13.4)	1 (1.5)	0 (0)	57	41	5 (8.8)	0 (0)	3 (5.3)	4 (7.0)	3 (5.3)
All countries	1 566	152	232 (14.8)	209 (13.3)	187 (11.9)	180 (11.5)	95 (6.1)	81 (5.2)	1407	478	62 (4.4)	48 (3.4)	42 (3.0)	42 (3.0)	40 (2.8)

**This designation is without prejudice to positions on status and is in line with United Nations Security Council Resolution 1244/99 and the International Court of Justice Opinion on the Kosovo declaration of independence.*
NA: not available.
The number of STs includes only those that could be unambiguously determined, which accounted for 1552/1566 (99.1%) carbapenem-R/I and 1370/1407 (97.4%) carbapenem-S isolates.

Table A7b. Dominant sequence types among carbapenem-R/I (n=211) and carbapenem-S (n=211) *Escherichia coli* isolates

Country	Carbapenem-R/I *E. coli*							Carbapenem-S *E. coli*						
	Total n	STs n	ST131 n (%)	ST38 n (%)	ST410 n (%)	ST648 n (%)	ST16 n (%)	Total n	STs n	ST131 n (%)	ST69 n (%)	ST73 n (%)	ST95 n (%)	ST141 n (%)
Albania	0	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA
Austria	5	5	1 (20.0)	1 (20.0)	0 (0)	0 (0)	0 (0)	5	4	0 (0)	0 (0)	2 (40.0)	1 (20.0)	1 (20.0)
Belgium	10	10	1 (10.0)	1 (10.0)	0 (0)	0 (0)	0 (0)	13	12	2 (15.4)	0 (0)	1 (7.7)	0 (0)	1 (7.7)
Bosnia and Herzegovina	0	NA	NA	NA	NA	NA	NA	3	3	1 (33.3)	0 (0)	1 (33.3)	0 (0)	0 (0)
Bulgaria	7	6	0 (0)	0 (0)	0 (0)	0 (0)	2 (28.6)	7	4	4 (57.1)	0 (0)	0 (0)	0 (0)	0 (0)
Croatia	0	NA	NA	NA	NA	NA	NA	4	1	4 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)
Cyprus	1	1	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1	1	1 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)
Czechia	10	8	2 (20)	0 (0)	1 (10.0)	0 (0)	1 (10.0)	8	7	1 (12.5)	2 (25.0)	1 (12.5)	0 (0)	0 (0)
Denmark	6	5	0 (0)	0 (0)	2 (33.3)	1 (16.7)	0 (0)	0	NA	NA	NA	NA	NA	NA
Estonia	2	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3	3	0 (0)	0 (0)	0 (0)	1 (33.3)	0 (0)
Finland	10	8	0 (0)	1 (10.0)	0 (0)	0 (0)	0 (0)	0	NA	NA	NA	NA	NA	NA
France	7	7	1 (14.3)	1 (14.3)	0 (0)	0 (0)	1 (14.3)	12	11	0 (0)	1 (8.3)	1 (8.3)	0 (0)	1 (8.3)
Germany	14	7	0 (0)	3 (21.4)	4 (28.6)	2 (14.3)	2 (14.3)	21	16	1 (4.8)	3 (14.3)	1 (4.8)	3 (14.3)	0 (0)
Greece	2	2	1 (50)	0 (0)	1 (50.0)	0 (0)	0 (0)	6	6	1 (16.7)	0 (0)	1 (16.7)	1 (16.7)	0 (0)
Hungary	1	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0	NA	NA	NA	NA	NA	NA
Iceland	1	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ireland	1	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7	7	1 (14.3)	0 (0)	1 (14.3)	1 (14.3)	0 (0)
Italy	17	8	10 (58.8)	0 (0)	1 (5.9)	0 (0)	1 (5.9)	44	26	11 (25.0)	5 (11.4)	2 (4.5)	2 (4.5)	2 (4.5)
Kosovo*	0	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA
Latvia	1	1	0 (0)	1 (100.0)	0 (0)	0 (0)	0 (0)	1	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Lithuania	2	2	0 (0)	0	0 (0)	0 (0)	0 (0)	2	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Luxembourg	3	3	0 (0)	1 (33.3)	0 (0)	0 (0)	0 (0)	3	3	0 (0)	1 (33.)	1 (33.3)	1 (33.3)	0 (0)
Malta	0	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA
Montenegro	0	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA
Netherlands	10	7	0 (0)	0 (0)	0 (0)	1 (10.0)	3 (30.0)	9	7	2 (22.2)	0 (0)	0 (0)	0 (0)	0 (0)
North Macedonia	0	NA	NA	NA	NA	NA	NA	3	3	0 (0)	1 (33.3)	0 (0)	0 (0)	0 (0)
Norway	5	4	0 (0)	1 (20.0)	0 (0)	0 (0)	2 (40.0)	5	5	0 (0)	1 (20.0)	1 (20.0)	0 (0)	0 (0)
Poland	2	2	1 (50.0)	0 (0)	0 (0)	0 (0)	0 (0)	2	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Portugal	3	3	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	5	4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Romania	0	NA	NA	NA	NA	NA	NA	7	6	1 (14.3)	2 (28.6)	0 (0)	1 (14.3)	0 (0)
Serbia	1	1	1 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)	9	9	1 (11.1)	1 (11.1)	0 (0)	0 (0)	1 (11.1)
Slovakia	0	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA
Slovenia	7	6	2 (28.6)	1 (14.3)	1 (14.3)	0 (0)	0 (0)	5	3	3 (60.0)	1 (20.0)	0 (0)	0 (0)	1 (20.0)
Spain	16	14	1 (6.3)	1 (6.3)	1 (6.3)	1 (6.3)	0 (0)	19	13	4 (21.1)	1 (5.3)	0 (0)	0 (0)	1 (5.3)
Sweden	16	11	0 (0)	2 (12.5)	2 (25.0)	4 (25.0)	1 (6.3)	21	14	0 (0)	2 (9.5)	5 (23.8)	2 (9.5)	0 (0)
Türkiye	12	9	0 (0)	1 (8.3)	3 (25.0)	2 (16.7)	0 (0)	59	30	11 (18.6)	5 (8.5)	3 (5.1)	0 (0)	1 (1.7)
United Kingdom	39	21	4 (10.3)	4 (10.3)	4 (10.3)	3 (7.7)	3 (7.7)	51	25	7 (13.7)	4 (7.8)	8 (15.7)	3 (5.9)	4 (7.8)
All countries	211	74	27 (12.8)	19 (9.0)	20 (9.5)	14 (6.6)	16 (7.6)	337	101	56 (16.6)	30 (8.9)	29 (8.6)	16 (4.7)	13 (3.9)

**This designation is without prejudice to positions on status and is in line with United Nations Security Council Resolution 1244/99 and the International Court of Justice Opinion on the Kosovo declaration of independence*
NA: not available.

Limitations and modifications of the multilevel multivariate logistic regression analysis described in tables 8a-i

The multivariate multilevel model had convergence problems and some estimates and confidence intervals were very wide and could not be interpreted. This is due to several factors, such as small sample size in some sub-analyses and rare outcomes.

Another important factor is that since many of the variables, especially variables related to hospitalization and travel, are highly correlated to each other, there is an issue with multicollinearity, i.e. inflation of the variance of parameter estimates. Both 'Direct hospital transfer' and 'Hospitalisation status' were removed from the multivariate analysis to reduce the risk of multicollinearity. Moreover, complete case analysis was used for gender and age since missing entries on these two variables were strongly correlated. We also estimated the multivariate model twice for each analysis with mutual exclusion of 'Previous travel' and 'Previous hospital admission within six months' in order to avoid inflated variance by multicollinearity.

The variable 'Previous travel' used in the analyses, is a variable combining travel information entered under the variables direct transfer, previous hospital admission and travel. Information from 'Direct hospital transfer' was used to recode inconsistent answers to 'Hospitalization within 6 months', since a direct hospital transfer indicates a previous hospitalization. Moreover, hospitalization withing 6 months in another country indicates previous travel and information from the variable 'Hospitalization within 6 months' was used to recode previous travel. Although this recoding enhances the multicollinearity between the variables, it increases consistency in coding between countries and standardisation of the variables. 'Previous travel' thus includes any travel to another country, including travel with hospitalisation. 'Hospitalization within 6 months' includes 'direct transfer from another hospital'. For 'Previous travel' all categories where information on travel was lacking (i.e. missing data, no travel, no information available), was combined to the category 'No reported travel or information not available', which was used as reference. This strategy was chosen due to few recordings of 'no travel' and a likely high variation between countries in the reporting of the travel variable.

Moreover, due to the large number of parameters to be estimated with relatively few observations a warning message 'Model is nearly unidentifiable: large eigenvalue ratio - Rescale variables' is given for the multivariate model in all outcomes except outcomes in table 8f. For the univariate models in table 8f some risk factors do not seem to have any variation over country with an estimated random effect standard deviation of 0 which yields the warning 'boundary (singular) fit'. For these models results were compared with results obtained using a logistic regression model. As results were very similar, the multilevel model was kept as country differences were considered important to take into account and the model was more similar for all outcomes.

Due to few observations there were major convergence problems in table 8b, 8c and 8g. To address this the categories 'Hospital in another EU/EEA country' and 'Hospital in a non-EU/EEA country' in 'Previous hospital admission within six months in' were combined into the new variable 'Hospital in another country'. In addition, the categories 'In the same country' and 'Non-EU/EEA country' in the variable 'Previous residence in a long-term/elderly care facility in' were combined into the new variable 'In the same or Non-EU/EEA country'.

Table A8a. Results of multilevel univariate and multilevel multivariate logistic regression analysis: carbapenem-R/I *versus* carbapenem-S *Klebsiella pneumoniae* SC

Variable	Overall n (%)	Carbapenem-R/I K. *pneumoniae* SC n (%)	Carbapenem-S K. *pneumoniae* SC n (%)	Unadjusted odds ratio	Unadjusted odds ratio 95% confidence interval	Unadjusted p-value	Adjusted odds ratio	Adjusted odds ratio 95% confidence interval	Adjusted p-value
n	2973	1566	1407						
Gender									
Male	1553 (52.2)	903 (57.7)	650 (46.2)	Ref					
Female	1322 (44.5)	619 (39.5)	703 (50.0)	0.63	0.55-0.73	<0.001	0.68	0.57-0.80	<0.001
Missing	98 (3.3)	44 (2.8)	54 (3.8)	NA	NA	NA	NA	NA	NA
Age[A]									
0-19	157 (5.3)	57 (3.6)	100 (7.1)	Ref					
20-39	218 (7.3)	106 (6.8)	112 (8.0)	1.67	1.09-2.54	0.018			
40-59	517 (17.4)	283 (18.1)	234 (16.6)	2.13	1.47-3.09	<0.001			
60-79	1332 (44.8)	733 (46.8)	599 (42.6)	2.16	1.53-3.05	<0.001			
≥80	638 (21.5)	343 (21.9)	295 (21.0)	2.06	1.43-2.96	<0.001			
Missing	111 (3.7)	44 (2.8)	67 (4.8)	NA	NA	NA	NA	NA	NA
Children/adult									
Adult (>19)	2705 (91.0)	1465 (93.6)	1240 (88.1)	Ref					
Children (0-19)	157 (5.3)	57 (3.6)	100 (7.1)	0.48	0.34-0.67	<0.001	0.49	0.33-0.72	<0.001
Missing	111 (3.7)	44 (2.8)	67 (4.8)	NA	NA	NA	NA	NA	NA
Type of ward									
Medical	1257 (42.3)	624 (39.8)	633 (45.0)	Ref					
Intensive care	637 (21.4)	436 (27.8)	201 (14.3)	2.22	1.81-2.72	<0.001	2.07	1.64-2.61	<0.001
Surgical	452 (15.2)	239 (15.3)	213 (15.1)	1.14	0.92-1.42	0.230	0.98	0.77-1.25	0.874
Other	450 (15.1)	183 (11.7)	267 (19.0)	0.69	0.55-0.86	0.001	0.76	0.58-0.99	0.046
Missing	177 (6.0)	84 (5.4)	93 (6.6)	0.91	0.66-1.25	0.560	1.24	0.75-2.06	0.401
Hospitalisation status									
Outpatient	559 (18.8)	215 (13.7)	344 (24.4)	Ref					
Inpatient	2300 (77.4)	1291 (82.4)	1009 (71.7)	2.05	1.69-2.47	<0.001	0.82	0.63-1.08	0.153
Missing	114 (3.8)	60 (3.8)	54 (3.8)	1.78	1.19-2.67	0.005	3.51	1.29-9.57	0.014
Infection/colonisation status									
Colonisation	496 (16.7)	313 (20.0)	183 (13.0)	Ref					
Infection	2135 (71.8)	1087 (69.4)	1048 (74.5)	0.60	0.49-0.74	<0.001	0.77	0.60-0.99	0.042
Undetermined clinical significance	243 (8.2)	119 (7.6)	124 (8.8)	0.55	0.40-0.75	<0.001	0.54	0.37-0.80	0.002
Missing	99 (3.3)	47 (3.0)	52 (3.7)	0.51	0.33-0.80	0.003	0.43	0.18-1.00	0.050
Organ/system or location of infection/colonisation									
Urinary tract	1252 (42.1)	598 (38.2)	654 (46.5)	Ref					
Lower respiratory tract	363 (12.2)	203 (13.0)	160 (11.4)	1.39	1.10-1.76	0.006	0.73	0.55-0.97	0.028
Intra-abdominal	130 (4.4)	78 (5.0)	52 (3.7)	1.64	1.14-2.37	0.008	1.00	0.65-1.52	0.994
Bloodstream	439 (14.8)	231 (14.8)	208 (14.8)	1.21	0.98-1.51	0.080	0.73	0.57-0.95	0.020
Skin and soft tissue	228 (7.7)	131 (8.4)	97 (6.9)	1.48	1.11-1.96	0.007	1.04	0.76-1.44	0.793
Other	217 (7.3)	138 (8.8)	79 (5.6)	1.91	1.42-2.57	<0.001	1.01	0.69-1.46	0.968
Missing	344 (11.6)	187 (11.9)	157 (11.2)	1.30	1.03-1.65	0.030	1.40	0.93-2.11	0.105
Hospital/community acquisition									
Community-onset	1018 (34.2)	359 (22.9)	659 (46.8)	Ref					
Hospital-acquired	1512 (50.9)	971 (62.0)	541 (38.5)	3.36	2.81-4.02	<0.001	3.37	2.71-4.19	<0.001
Missing	443 (14.9)	236 (15.1)	207 (14.7)	2.10	1.67-2.65	<0.001	2.22	1.63-3.02	<0.001
Direct hospital transfer[A]									
No hospital transfer	1862 (62.6)	929 (59.3)	933 (66.3)	Ref					
Another hospital in the same country	211 (7.1)	148 (9.5)	63 (4.5)	2.36	1.73-3.21	<0.001			
Hospital in an EU/EEA country[B]	16 (0.5)	15 (1.0)	1 (0.1)	NA	NA	NA	NA	NA	NA
Hospital in a non-EU/EEA country[B]	21 (0.7)	21 (1.3)	0 (0.0)	NA	NA	NA	NA	NA	NA
Hospital in another country (country not specified)[B]	4 (0.1)	4 (0.3)	0 (0.0)	NA	NA	NA	NA	NA	NA
Hospital in another country[C]	41 (1.4)	40 (2.6)	1 (0.1)	40.17	5.51-292.79	<0.001			
Missing	859 (28.9)	449 (28.7)	410 (29.1)	1.10	0.94-1.29	0.249			
Previous hospital admission within six months									
No hospitalisation	857 (28.8)	343 (21.9)	514 (36.5)	Ref					
Same hospital	745 (25.1)	433 (27.7)	312 (22.2)	2.13	1.74-2.62	<0.001	2.05	1.63-2.56	<0.001
Another hospital in the same country	284 (9.6)	189 (12.1)	95 (6.8)	3.03	2.28-4.03	<0.001	2.43	1.78-3.31	<0.001
Hospital in an EU/EEA country[B]	24 (0.8)	22 (1.4)	2 (0.1)	NA	NA	NA	NA	NA	NA
Hospital in a non-EU/EEA country[B]	31 (1.0)	31 (2.0)	0 (0.0)	NA	NA	NA	NA	NA	NA
Hospital in another country (country not specified)[B]	21 (0.7)	18 (1.1)	3 (0.2)	NA	NA	NA	NA	NA	NA
Hospital in another country[B, C]	76 (2.6)	71 (4.5)	5 (0.4)	22.62	8.95-57.13	<0.001	26.45	10.08-69.40	<0.001
Unknown hospital	88 (3.0)	48 (3.1)	40 (2.8)	1.86	1.17-2.96	0.008	1.76	1.04-2.96	0.034
Missing	923 (31.0)	482 (30.8)	441 (31.3)	1.66	1.37-2.02	<0.001	1.72	1.30-2.27	<0.001
Previous residence in a long-term/elderly care facility									
No residence in care facility	1487 (50.0)	731 (46.7)	756 (53.7)	Ref					
In the same country	187 (6.3)	131 (8.4)	56 (4.0)	NA	NA	NA	NA	NA	NA
In an EU/EEA country[B]	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	NA	NA
In a non-EU/EEA country[B]	2 (0.1)	2 (0.1)	0 (0.0)	NA	NA	NA	NA	NA	NA
In the same or a non-EU/EEA country[C]	189 (6.4)	133 (8.5)	56 (4.0)	2.47	1.77-3.45	<0.001	3.02	2.10-4.35	<0.001
Missing	1297 (43.6)	702 (44.8)	595 (42.3)	1.22	1.05-1.42	0.010	1.14	0.89-1.45	0.292
Previous travel within 6 months[D]									
No reported travel or information not available	2894 (97.3)	1500 (95.8)	1394 (99.1)	Ref					
To an EU/EEA country[B]	30 (1.0)	26 (1.7)	4 (0.3)	6.05	2.11-17.40	0.001	6.08	2.03-18.25	0.001
To a non-EU/EEA country[B]	49 (1.6)	40 (2.6)	9 (0.6)	4.14	2.00-8.58	<0.001	4.88	2.18-10.92	<0.001

The multilevel multivariate logistic analysis was adjusted for random effect by country. Random effect std=0.2169, logLikelihood=-1725, p-value<0.001.
[A] Variables "age" and "direct hospital transfer from" were excluded from the multivariate analysis, due to collinearity with other variables. See section on limitations and modifications above for details.
[B] Hospitals in an EU/EEA country and a non-EU/EEA country refers to countries other than the country of sampling.
[C] Combined category used in the logistic regression analysis to avoid calculation difficulties caused by small group sizes.
[D] Previous travel is a combined variable on all information on travel within 6 months, combining travel information entered concerning direct transfer, previous hospital admission and travel. For details see section on limitations and modifications above.
NA; not available, Ref; reference.

Table A8b. Results of multilevel univariate and multilevel multivariate logistic regression analysis: carbapenem-R/I *versus* carbapenem-S *Escherichia coli*

Variable	Overall n (%)	Carbapenem-R/I *E. coli* n (%)	Carbapenem-S *E. coli* n (%)	Unadjusted odds ratio	Unadjusted odds ratio 95% Confidence interval	Unadjusted p-value	Adjusted odds ratio	Adjusted odds ratio 95% confidence interval	Adjusted p-value
n	548	211	337						
Gender									
Male	246 (44.9)	119 (56.4)	127 (37.7)	Ref					
Female	273 (49.8)	84 (39.8)	189 (56.1)	0.50	0.35-0.73	<0.001	0.57	0.36-0.91	0.018
Missing	29 (5.3)	8 (3.8)	21 (6.2)	NA	NA	NA	NA	NA	NA
Age[A]									
0-19	47 (8.6)	15 (7.1)	32 (9.5)	Ref					
20-39	61 (11.1)	27 (12.8)	34 (10.1)	1.44	0.61-3.38	0.404			
40-59	103 (18.8)	40 (19.0)	63 (18.7)	1.29	0.59-2.83	0.518			
60-79	204 (37.2)	93 (44.1)	111 (32.9)	1.70	0.82-3.52	0.153			
≥80	102 (18.6)	28 (13.3)	74 (22.0)	0.71	0.32-1.59	0.401			
Missing	31 (5.7)	8 (3.8)	23 (6.8)	NA	NA	NA	NA	NA	NA
Children/adult									
Adult (>19)	470 (85.8)	188 (89.1)	282 (83.7)	Ref					
Children (0-19)	47 (8.6)	15 (7.1)	32 (9.5)	0.76	0.38-1.52	0.441	0.85	0.38-1.90	0.684
Missing	31 (5.7)	8 (3.8)	23 (6.8)	NA	NA	NA	NA	NA	NA
Type of ward									
Medical	247 (45.1)	82 (38.9)	165 (49.0)	Ref					
Intensive care	74 (13.5)	39 (18.5)	35 (10.4)	2.43	1.37-4.33	0.003	1.14	0.57-2.28	0.720
Surgical	99 (18.1)	35 (16.6)	64 (19.0)	1.08	0.64-1.83	0.778	0.71	0.37-1.35	0.294
Other	87 (15.9)	38 (18.0)	49 (14.5)	1.30	0.75-2.24	0.346	1.71	0.85-3.43	0.132
Missing	41 (7.5)	17 (8.1)	24 (7.1)	0.97	0.44-2.13	0.935	0.70	0.22-2.25	0.545
Hospitalisation status									
Outpatient	129 (23.5)	44 (20.9)	85 (25.2)	Ref					
Inpatient	389 (71.0)	154 (73.0)	235 (69.7)	1.34	0.85-2.11	0.212	0.65	0.33-1.26	0.200
Missing	30 (5.5)	13 (6.2)	17 (5.0)	1.02	0.38-2.74	0.963	3.17	0.54-18.79	0.203
Infection/colonisation status									
Colonisation	119 (21.7)	82 (38.9)	37 (11.0)	Ref					
Infection	363 (66.2)	105 (49.8)	258 (76.6)	0.18	0.11-0.29	<0.001	0.40	0.18-0.85	0.018
Undetermined clinical significance	40 (7.3)	13 (6.2)	27 (8.0)	0.19	0.08-0.43	<0.001	0.34	0.12-0.97	0.043
Missing	26 (4.7)	11 (5.2)	15 (4.5)	0.26	0.10-0.71	0.008	0.83	0.12-5.92	0.852
Organ/system or location of infection/colonisation									
Urinary tract	218 (39.8)	67 (31.8)	151 (44.8)	Ref					
Lower respiratory tract	19 (3.5)	8 (3.8)	11 (3.3)	1.55	0.58-4.15	0.386	0.72	0.23-2.28	0.576
Intra-abdominal	37 (6.8)	18 (8.5)	19 (5.6)	2.03	0.97-4.24	0.060	1.16	0.45-2.95	0.762
Bloodstream	86 (15.7)	14 (6.6)	72 (21.4)	0.44	0.23-0.85	0.015	0.29	0.14-0.63	0.002
Skin and soft tissue	34 (6.2)	17 (8.1)	17 (5.0)	2.13	1.00-4.54	0.050	1.58	0.65-3.86	0.313
Other	85 (15.5)	57 (27.0)	28 (8.3)	4.51	2.48-8.21	<0.001	1.67	0.67-4.12	0.268
Missing	69 (12.6)	30 (14.2)	39 (11.6)	1.62	0.87-3.03	0.131	0.98	0.40-2.39	0.964
Hospital/community acquisition									
Community-onset	243 (44.3)	68 (32.2)	175 (51.9)	Ref					
Hospital-acquired	180 (32.8)	87 (41.2)	93 (27.6)	3.23	2.03-5.14	<0.001	3.52	1.92-6.46	<0.001
Missing	125 (22.8)	56 (26.5)	69 (20.5)	1.92	1.15-3.19	0.012	1.46	0.71-2.97	0.303
Direct hospital transfer[A]									
No hospital transfer	306 (55.8)	99 (46.9)	207 (61.4)	Ref					
Another hospital in the same country	17 (3.1)	8 (3.8)	9 (2.7)	1.95	0.70-5.47	0.202			
Hospital in an EU/EEA country[B]	2 (0.4)	2 (0.9)	0 (0.0)	6.94e+07	0.00-Inf	0.997			
Hospital in a non-EU/EEA country[B]	12 (2.2)	12 (5.7)	0 (0.0)	7.16e+07	0.00-Inf	0.991			
Hospital in another country (country not specified)[B]	1 (0.2)	1 (0.5)	0 (0.0)	3.10e+07	0.00-Inf	0.998			
Missing	210 (38.3)	89 (42.2)	121 (35.9)	1.36	0.89-2.07	0.159			
Previous hospital admission within six months									
No hospitalisation	166 (30.3)	34 (16.1)	132 (39.2)	Ref					
Same hospital	103 (18.8)	51 (24.2)	52 (15.4)	3.85	2.13-6.96	<0.001	3.67	1.90-7.08	<0.001
Another hospital in the same country	24 (4.4)	13 (6.2)	11 (3.3)	5.03	1.95-12.98	0.001	5.59	2.02-15.51	0.001
Hospital in an EU/EEA country[B]	1 (0.2)	1 (0.5)	0 (0.0)	NA	NA	NA	NA	NA	NA
Hospital in a non-EU/EEA country[B]	19 (3.5)	18 (8.5)	1 (0.3)	NA	NA	NA	NA	NA	NA
Hospital in another country (country not specified)[B]	4 (0.7)	3 (1.4)	1 (0.3)	NA	NA	NA	NA	NA	NA
Hospital in another country[B, C]	24 (4.4)	22 (10.4)	2 (0.6)	43.20	9.22-202.47	<0.001	30.65	6.08-154.46	<0.001
Unknown hospital	13 (2.4)	6 (2.8)	7 (2.1)	3.21	0.87-11.78	0.079	3.43	0.84-13.98	0.086
Missing	218 (39.8)	85 (40.3)	133 (39.5)	2.41	1.41-4.12	0.001	2.63	1.27-5.44	0.009
Previous residence in a long-term/elderly care facility									
No residence in care facility	235 (42.9)	84 (39.8)	151 (44.8)	Ref					

Variable	Overall n (%)	Carbapenem-R/I *E. coli* n (%)	Carbapenem-S *E. coli* n (%)	Unadjusted odds ratio	Unadjusted odds ratio 95% Confidence interval	Unadjusted p-value	Adjusted odds ratio	Adjusted odds ratio 95% confidence interval	Adjusted p-value
In the same country	17 (3.1)	7 (3.3)	10 (3.0)	1.15	0.40-3.32	0.790	1.71	0.51-5.76	0.386
In an EU/EEA country[B]	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	NA	NA
In a non-EU/EEA country[B]	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	NA	NA
Missing	296 (54.0)	120 (56.9)	176 (52.2)	1.01	0.66-1.55	0.963	0.79	0.43-1.45	0.449
Previous travel within 6 months[D]									
No reported travel or information not available	512 (93.4)	181 (85.8)	331 (98.2)	Ref					
To an EU/EEA country[B]	3 (0.5)	2 (0.9)	1 (0.3)	2.94	0.25-34.91	0.393	1.47	0.09-24.21	0.788
To a non-EU/EEA country[B]	33 (6.0)	28 (13.3)	5 (1.5)	11.37	3.94-32.83	<0.001	8.55	2.79-26.27	<0.001

The multilevel multivariate logistic analysis was adjusted for random effect by country. Random effect std=0.3114, logLikelihood=-271, p-value<0.001
[A] Variables "age" and "direct hospital transfer from" were excluded from the multivariate analysis, due to collinearity with other variables. See section on limitations and modifications above for details.
[B] Hospitals in an EU/EEA country and a non-EU/EEA country refers to countries other than the country of sampling.
[C] Combined category used in logistic regression analysis to avoid calculation difficulties caused by small group sizes.
[D] Previous travel is a combined variable on all information on travel within 6 months, combining travel information entered concerning direct transfer, previous hospital admission and travel. For details see section on limitations and modifications above.
NA, not available; Ref, reference.

Table A8c. Results of multilevel univariate and multilevel multivariate logistic regression analysis: epidemic *versus* non-epidemic sequence types carbapenem-R/I *Klebsiella pneumoniae* SC

Variable	Overall n (%)	Epidemic ST carbapenem-R/I *K. pneumoniae* SC n (%)	Non-epidemic STs of carbapenem-R/I *K. pneumoniae* SC n (%)	Unadjusted odds ratio	Unadjusted odds ratio 95% confidence interval	Unadjusted p-value	Adjusted odds ratio	Adjusted odds ratio 95% confidence interval	Adjusted p-value
n	1566	984	582						
Gender									
Male	903 (57.7)	571 (58.0)	332 (57.0)	Ref					
Female	619 (39.5)	385 (39.1)	234 (40.2)	0.93	0.73-1.17	0.523	0.94	0.73-1.20	0.617
Missing	44 (2.8)	28 (2.8)	16 (2.7)	NA	NA	NA	NA	NA	NA
Age[A]									
0-19	57 (3.6)	16 (1.6)	41 (7.0)	Ref					
20-39	106 (6.8)	68 (6.9)	38 (6.5)	4.17	1.90-9.13	<0.001			
40-59	283 (18.1)	178 (18.1)	105 (18.0)	3.63	1.80-7.31	<0.001			
60-79	733 (46.8)	469 (47.7)	264 (45.4)	3.73	1.90-7.30	<0.001			
≥80	343 (21.9)	226 (23.0)	117 (20.1)	4.06	2.02-8.16	<0.001			
Missing	44 (2.8)	27 (2.7)	17 (2.9)	NA	NA	NA	NA	NA	NA
Children/adult									
Adult (>19)	1465 (93.6)	941 (95.6)	524 (90.0)	Ref					
Children (0-19)	57 (3.6)	16 (1.6)	41 (7.0)	0.26	0.14-0.51	<0.001	0.25	0.13-0.48	<0.001
Missing	44 (2.8)	27 (2.7)	17 (2.9)	NA	NA	NA	NA	NA	NA
Type of ward									
Medical	624 (39.8)	387 (39.3)	237 (40.7)	Ref					
Intensive care	436 (27.8)	273 (27.7)	163 (28.0)	1.15	0.86-1.54	0.341	1.21	0.88-1.67	0.244
Surgical	239 (15.3)	164 (16.7)	75 (12.9)	1.66	1.17-2.37	0.005	1.76	1.21-2.56	0.003
Other	183 (11.7)	107 (10.9)	76 (13.1)	1.36	0.91-2.02	0.137	1.41	0.90-2.20	0.137
Missing	84 (5.4)	53 (5.4)	31 (5.3)	1.10	0.63-1.93	0.740	1.01	0.44-2.29	0.988
Hospitalisation status									
Outpatient	215 (13.7)	133 (13.5)	82 (14.1)	Ref					
Inpatient	1291 (82.4)	813 (82.6)	478 (82.1)	1.06	0.76-1.50	0.721	1.08	0.69-1.68	0.743
Missing	60 (3.8)	38 (3.9)	22 (3.8)	1.34	0.66-2.69	0.416	3.53	1.02-12.20	0.047
Infection/colonisation status									
Colonisation	313 (20.0)	176 (17.9)	137 (23.5)	Ref					
Infection	1087 (69.4)	710 (72.2)	377 (64.8)	1.14	0.84-1.54	0.411	1.08	0.76-1.53	0.660
Undetermined clinical significance	119 (7.6)	67 (6.8)	52 (8.9)	0.85	0.52-1.40	0.523	0.92	0.52-1.62	0.765
Missing	47 (3.0)	31 (3.2)	16 (2.7)	1.11	0.50-2.49	0.798	1.57	0.35-6.92	0.554
Organ/system or location of infection/colonisation									
Urinary tract	598 (38.2)	378 (38.4)	220 (37.8)	Ref					
Lower respiratory tract	203 (13.0)	142 (14.4)	61 (10.5)	1.20	0.82-1.75	0.341	1.21	0.80-1.83	0.364
Intra-abdominal	78 (5.0)	48 (4.9)	30 (5.2)	1.01	0.59-1.73	0.982	0.91	0.51-1.62	0.752
Blood stream	231 (14.8)	166 (16.9)	65 (11.2)	1.06	0.73-1.54	0.765	1.05	0.70-1.60	0.801
Skin and soft tissue	131 (8.4)	89 (9.0)	42 (7.2)	1.10	0.71-1.72	0.665	0.94	0.59-1.50	0.788
Other	138 (8.8)	75 (7.6)	63 (10.8)	1.09	0.69-1.72	0.722	1.06	0.63-1.78	0.823
Missing	187 (11.9)	86 (8.7)	101 (17.4)	0.58	0.34-0.98	0.042	0.40	0.17-0.93	0.033
Hospital/community acquisition									
Community-onset	359 (22.9)	233 (23.7)	126 (21.6)	Ref					
Hospital-acquired	971 (62.0)	628 (63.8)	343 (58.9)	0.92	0.68-1.24	0.585	0.88	0.61-1.26	0.475
Missing	236 (15.1)	123 (12.5)	113 (19.4)	0.74	0.49-1.10	0.137	0.74	0.45-1.19	0.214
Direct hospital transfer[A]									
No hospital transfer	929 (59.3)	601 (61.1)	328 (56.4)	Ref					
Another hospital in the same country	148 (9.5)	93 (9.5)	55 (9.5)	0.87	0.57-1.33	0.524			
Hospital in an EU/EEA country[B]	15 (1.0)	9 (0.9)	6 (1.0)	1.98	0.60-6.58	0.265			
Hospital in a non-EU/EEA country[B]	21 (1.3)	11 (1.1)	10 (1.7)	0.99	0.39-2.55	0.990			
Hospital in another country (country not specified)[B]	4 (0.3)	2 (0.2)	2 (0.3)	0.56	0.05-6.02	0.633			
Missing	449 (28.7)	268 (27.2)	181 (31.1)	1.07	0.78-1.49	0.662			
Previous hospital admission within six months									
No hospitalisation	343 (21.9)	209 (21.2)	134 (23.0)	Ref					
Same hospital	433 (27.7)	290 (29.5)	143 (24.6)	1.07	0.76-1.50	0.694	1.16	0.82-1.64	0.411
Another hospital in the same country	189 (12.1)	124 (12.6)	65 (11.2)	1.04	0.68-1.58	0.864	1.10	0.71-1.69	0.670
Hospital in an EU/EEA country[B]	22 (1.4)	16 (1.6)	6 (1.0)	5.10	1.67-15.57	0.004	6.60	2.05-21.17	0.002
Hospital in a non-EU/EEA country[B]	31 (2.0)	18 (1.8)	13 (2.2)	1.33	0.58-3.02	0.498	1.63	0.68-3.89	0.273
Hospital in another country (country not specified)[B]	18 (1.1)	9 (0.9)	9 (1.5)	1.60	0.49-5.22	0.435	2.00	0.58-6.88	0.269
Unknown hospital	48 (3.1)	26 (2.6)	22 (3.8)	1.07	0.53-2.18	0.848	1.11	0.53-2.31	0.778
Missing	482 (30.8)	292 (29.7)	190 (32.6)	1.08	0.76-1.53	0.682	1.40	0.91-2.15	0.125
Previous residence in a long-term/elderly care facility									
No residence in care facility	731 (46.7)	470 (47.8)	261 (44.8)	Ref					
In the same country	131 (8.4)	95 (9.7)	36 (6.2)	NA	NA	NA	NA	NA	NA
In an EU/EEA country[B]	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	NA	NA
In a non-EU/EEA country[B]	2 (0.1)	2 (0.2)	0 (0.0)	NA	NA	NA	NA	NA	NA
In the same or a non-EU/EEA country[C]	133 (8.5)	97 (9.9)	36 (6.2)	1.33	0.84-2.10	0.232	1.38	0.85-2.24	0.188
Missing	702 (44.8)	417 (42.4)	285 (49.0)	0.88	0.65-1.17	0.376	0.75	0.52-1.08	0.123
Previous travel within 6 months[D]									
No reported travel or information not available	1500 (95.8)	944 (95.9)	556 (95.5)	Ref					
To an EU/EEA country[B]	26 (1.7)	18 (1.8)	8 (1.4)	3.25	1.24-8.52	0.017	3.30	1.22-8.92	0.019
To a non-EU/EEA country[B]	40 (2.6)	22 (2.2)	18 (3.1)	1.06	0.52-2.16	0.865	1.06	0.51-2.23	0.869

The multilevel multivariate logistic analysis was adjusted for random effect by country. Random effect std=0.9727, logLikelihood=-859, p-value=0.001.
[A] Variables "age" and "direct hospital transfer from" were excluded from the multivariate analysis, due to collinearity with other variables. See section on limitations and modifications above for details.
[B] Hospitals in an EU/EEA country and a non-EU/EEA country refers to countries other than the country of sampling.
[C] Combined category used in logistic regression analysis to avoid calculation difficulties caused by small group sizes.
[D] Previous travel is a combined variable on all information on travel within 6 months, combining travel information entered concerning direct transfer, previous hospital admission and travel. For details see section on limitations and modifications above.
NA, not available; Ref, reference.

Table A8d. Results of multilevel univariate and multilevel multivariate logistic regression analysis: *Klebsiella pneumoniae* ST258-512 *versus* non-epidemic STs of carbapenem-R/I *K. pneumoniae* SC

Variable	Overall n (%)	Epidemic carbapenem-R/I *K. pneumoniae* ST258-512 n (%)	Non-epidemic STs of carbapenem-R/I *K. pneumoniae* SC n (%)	Unadjusted odds ratio	Unadjusted odds ratio 95% confidence interval	Unadjusted p-value	Adjusted odds ratio	Adjusted odds ratio 95% confidence interval	Adjusted p-value
n	814	232	582						
Gender									
Male	471 (57.9)	139 (59.9)	332 (57.0)	Ref					
Female	320 (39.3)	86 (37.1)	234 (40.2)	0.96	0.64-1.45	0.861	0.93	0.59-1.46	0.749
Missing	23 (2.8)	7 (3.0)	16 (2.7)	NA	NA	NA	NA	NA	NA
Age[A]									
0-19	44 (5.4)	3 (1.3)	41 (7.0)	Ref					
20-39	59 (7.2)	21 (9.1)	38 (6.5)	9.75	2.05-46.29	0.004			
40-59	147 (18.1)	42 (18.1)	105 (18.0)	3.49	0.83-14.68	0.088			
60-79	376 (46.2)	112 (48.3)	264 (45.4)	3.54	0.88-14.26	0.075			
≥80	164 (20.1)	47 (20.3)	117 (20.1)	3.46	0.82-14.56	0.090			
Missing	24 (2.9)	7 (3.0)	17 (2.9)	NA	NA	NA	NA	NA	NA
Children/adult									
Adult (>19)	746 (91.6)	222 (95.7)	524 (90.0)	Ref					
Children (0-19)	44 (5.4)	3 (1.3)	41 (7.0)	0.26	0.07-1.03	0.055	0.25	0.05-1.14	0.072
Missing	24 (2.9)	7 (3.0)	17 (2.9)	NA	NA	NA	NA	NA	NA
Type of ward									
Medical	330 (40.5)	93 (40.1)	237 (40.7)	Ref					
Intensive care	223 (27.4)	60 (25.9)	163 (28.0)	1.18	0.71-1.96	0.529	1.23	0.69-2.22	0.483
Surgical	115 (14.1)	40 (17.2)	75 (12.9)	1.75	0.97-3.16	0.063	2.31	1.18-4.54	0.015
Other	98 (12.0)	22 (9.5)	76 (13.1)	1.64	0.82-3.30	0.165	1.84	0.80-4.21	0.149
Missing	48 (5.9)	17 (7.3)	31 (5.3)	0.89	0.39-2.05	0.783	1.68	0.47-6.07	0.425
Hospitalisation status									
Outpatient	112 (13.8)	30 (12.9)	82 (14.1)	Ref					
Inpatient	671 (82.4)	193 (83.2)	478 (82.1)	0.97	0.54-1.74	0.912	0.78	0.34-1.82	0.570
Missing	31 (3.8)	9 (3.9)	22 (3.8)	0.68	0.20-2.24	0.522	2.38	0.15-37.07	0.535
Infection/colonisation status									
Colonisation	174 (21.4)	37 (15.9)	137 (23.5)	Ref					
Infection	537 (66.0)	160 (69.0)	377 (64.8)	1.05	0.61-1.79	0.871	1.06	0.55-2.02	0.868
Undetermined clinical significance	77 (9.5)	25 (10.8)	52 (8.9)	1.23	0.57-2.64	0.599	1.48	0.58-3.79	0.413
Missing	26 (3.2)	10 (4.3)	16 (2.7)	0.72	0.21-2.49	0.599	2.78	0.15-50.66	0.489
Organ/system or location of infection/colonisation									
Urinary tract	300 (36.9)	80 (34.5)	220 (37.8)	Ref					
Lower respiratory tract	98 (12.0)	37 (15.9)	61 (10.5)	1.20	0.64-2.23	0.570	1.36	0.68-2.72	0.378
Intra-abdominal	45 (5.5)	15 (6.5)	30 (5.2)	1.51	0.61-3.72	0.369	1.25	0.46-3.37	0.660
Bloodstream	111 (13.6)	46 (19.8)	65 (11.2)	0.95	0.52-1.71	0.858	1.02	0.51-2.08	0.947
Skin and soft tissue	63 (7.7)	21 (9.1)	42 (7.2)	0.71	0.35-1.45	0.351	0.49	0.23-1.07	0.073
Other	80 (9.8)	17 (7.3)	63 (10.8)	0.96	0.43-2.13	0.913	0.87	0.35-2.19	0.772
Missing	117 (14.4)	16 (6.9)	101 (17.4)	0.44	0.18-1.08	0.072	0.25	0.02-2.61	0.245
Hospital/community acquisition									
Community-onset	171 (21.0)	45 (19.4)	126 (21.6)	Ref					
Hospital-acquired	498 (61.2)	155 (66.8)	343 (58.9)	1.53	0.94-2.51	0.088	1.84	0.96-3.54	0.066
Missing	145 (17.8)	32 (13.8)	113 (19.4)	1.34	0.66-2.72	0.421	1.93	0.73-5.08	0.185
Direct hospital transfer[A]									
No hospital transfer	481 (59.1)	153 (65.9)	328 (56.4)	Ref					
Another hospital in the same country	79 (9.7)	24 (10.3)	55 (9.5)	1.08	0.54-2.14	0.834			
Hospital in an EU/EEA country[B]	9 (1.1)	3 (1.3)	6 (1.0)	NA	NA	NA	NA	NA	NA
Hospital in a non-EU/EEA country[B]	10 (1.2)	0 (0.0)	10 (1.7)	NA	NA	NA	NA	NA	NA
Hospital in another country (country not specified)[B]	2 (0.2)	0 (0.0)	2 (0.3)	NA	NA	NA	NA	NA	NA
Hospital in another country[B, C]	21 (2.6)	3 (1.3)	18 (3.1)	0.62	0.14-2.75	0.533			
Missing	233 (28.6)	52 (22.4)	181 (31.1)	0.77	0.45-1.34	0.356			
Previous hospital admission within six months									
No hospitalisation	173 (21.3)	39 (16.8)	134 (23.0)	Ref					
Same hospital	233 (28.6)	90 (38.8)	143 (24.6)	2.04	1.17-3.57	0.012	2.46	1.33-4.53	0.004
Another hospital in the same country	96 (11.8)	31 (13.4)	65 (11.2)	1.79	0.87-3.67	0.113	2.02	0.94-4.35	0.071
Hospital in an EU/EEA country[B]	12 (1.5)	6 (2.6)	6 (1.0)	18.88	3.96-90.00	<0.001	41.19	7.24-234.34	<0.001
Hospital in a non-EU/EEA country[B]	14 (1.7)	1 (0.4)	13 (2.2)	0.41	0.04-4.47	0.464	0.40	0.03-5.61	0.494
Hospital in another country (country not specified)[B]	10 (1.2)	1 (0.4)	9 (1.5)	0.53	0.04-7.40	0.638	0.75	0.05-11.83	0.836
Unknown hospital	22 (2.7)	0 (0.0)	22 (3.8)	0.00	0.00-Inf	0.995	0.00	0.00-Inf	0.995
Missing	254 (31.2)	64 (27.6)	190 (32.6)	1.32	0.71-2.44	0.382	2.27	1.04-4.97	0.041
Previous residence in a long-term/elderly care facility									
No residence in care facility	386 (47.4)	125 (53.9)	261 (44.8)	Ref					
In the same country	63 (7.7)	27 (11.6)	36 (6.2)	NA	NA	NA	NA	NA	NA
In an EU/EEA country[B]	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	NA	NA
In a non-EU/EEA country[B]	1 (0.1)	1 (0.4)	0 (0.0)	NA	NA	NA	NA	NA	NA
In the same or a non-EU/EEA country[C]	64 (7.9)	28 (12.1)	36 (6.2)	1.89	0.91-3.92	0.088	2.39	1.08-5.29	0.032
Missing	364 (44.7)	79 (34.1)	285 (49.0)	0.70	0.44-1.12	0.139	0.59	0.31-1.11	0.104
Previous travel within 6 months[D]									
No reported travel or information not available	780 (95.8)	224 (96.6)	556 (95.5)	Ref					
To an EU/EEA country[B]	14 (1.7)	6 (2.6)	8 (1.4)	7.07	1.66-30.05	0.008	10.76	2.36-49.09	0.002
To a non-EU/EEA country[B]	20 (2.5)	2 (0.9)	18 (3.1)	0.32	0.06-1.75	0.189	0.31	0.05-1.79	0.188

The multilevel multivariate logistic analysis was adjusted for random effect by country. Random effect std=2.0715, logLikelihood=-306, p-value=0.002.
[A] Variables "age" and "direct hospital transfer from" were excluded from the multivariate analysis, due to collinearity with other variables. See section on limitations and modifications above for details.
[B] Hospitals in an EU/EEA country and a non-EU/EEA country refers to countries other than the country of sampling.
[C] Combined category used in logistic regression analysis to avoid calculation difficulties caused by small group sizes.
[D] Previous travel is a combined variable on all information on travel within 6 months, combining travel information entered concerning direct transfer, previous hospital admission and travel. For details see section on limitations and modifications above.
NA, not available; Ref, reference.

Table A8e. Results of multilevel univariate and multilevel multivariate logistic regression analysis: *Klebsiella pneumoniae* ST307 *versus* non-epidemic STs of carbapenem-R/I *K. pneumoniae* SC

Variable	Overall n (%)	Epidemic carbapenem-R/I *K. pneumoniae* ST307 n (%)	Non-epidemic STs of carbapenem-R/I *K. pneumoniae* SC n (%)	Unadjusted odds ratio	Unadjusted odds ratio 95% confidence interval	Unadjusted p-value	Adjusted odds ratio	Adjusted odds ratio 95% confidence interval	Adjusted p-value
n	762	180	582						
Gender									
Male	433 (56.8)	101 (56.1)	332 (57.0)	Ref					
Female	310 (40.7)	76 (42.2)	234 (40.2)	1.17	0.76-1.79	0.476	1.24	0.78-1.97	0.368
Missing	19 (2.5)	3 (1.7)	16 (2.7)	NA	NA	NA	NA	NA	NA
Age[A]									
0-19	43 (5.6)	2 (1.1)	41 (7.0)	Ref					
20-39	44 (5.8)	6 (3.3)	38 (6.5)	3.09	0.49-19.70	0.232			
40-59	136 (17.8)	31 (17.2)	105 (18.0)	4.20	0.83-21.22	0.083			
60-79	353 (46.3)	89 (49.4)	264 (45.4)	4.85	1.01-23.37	0.049			
≥80	167 (21.9)	50 (27.8)	117 (20.1)	6.77	1.37-33.46	0.019			
Missing	19 (2.5)	2 (1.1)	17 (2.9)	NA	NA	NA	NA	NA	NA
Children/adult									
Adult (>19)	700 (91.9)	176 (97.8)	524 (90.0)	Ref					
Children (0-19)	43 (5.6)	2 (1.1)	41 (7.0)	0.20	0.04-0.95	0.043	0.21	0.04-1.07	0.060
Missing	19 (2.5)	2 (1.1)	17 (2.9)	NA	NA	NA	NA	NA	NA
Type of ward									
Medical	321 (42.1)	84 (46.7)	237 (40.7)	Ref					
Intensive care	214 (28.1)	51 (28.3)	163 (28.0)	1.15	0.68-1.94	0.600	1.17	0.65-2.08	0.603
Surgical	102 (13.4)	27 (15.0)	75 (12.9)	1.46	0.78-2.76	0.238	1.60	0.81-3.17	0.177
Other	86 (11.3)	10 (5.6)	76 (13.1)	0.54	0.24-1.23	0.143	0.75	0.29-1.93	0.552
Missing	39 (5.1)	8 (4.4)	31 (5.3)	0.46	0.17-1.30	0.144	0.73	0.20-2.65	0.634
Hospitalisation status									
Outpatient	100 (13.1)	18 (10.0)	82 (14.1)	Ref					
Inpatient	638 (83.7)	160 (88.9)	478 (82.1)	1.99	1.05-3.77	0.036	1.53	0.62-3.75	0.354
Missing	24 (3.1)	2 (1.1)	22 (3.8)	0.59	0.07-4.66	0.613	0.00	0.00-Inf	0.992
Infection/colonisation status									
Colonisation	168 (22.0)	31 (17.2)	137 (23.5)	Ref					
Infection	501 (65.7)	124 (68.9)	377 (64.8)	0.86	0.49-1.50	0.590	0.69	0.36-1.34	0.271
Undetermined clinical significance	71 (9.3)	19 (10.6)	52 (8.9)	1.30	0.55-3.09	0.554	1.33	0.50-3.53	0.566
Missing	22 (2.9)	6 (3.3)	16 (2.7)	0.46	0.12-1.71	0.245	1.14	0.09-13.88	0.919
Organ/system or location of infection/colonisation									
Urinary tract	280 (36.7)	60 (33.3)	220 (37.8)	Ref					
Lower respiratory tract	86 (11.3)	25 (13.9)	61 (10.5)	1.45	0.73-2.88	0.294	1.25	0.59-2.67	0.560
Intra-abdominal	39 (5.1)	9 (5.0)	30 (5.2)	1.38	0.52-3.64	0.515	1.14	0.40-3.27	0.812
Bloodstream	108 (14.2)	43 (23.9)	65 (11.2)	1.69	0.91-3.14	0.097	1.68	0.83-3.40	0.151
Skin and soft tissue	57 (7.5)	15 (8.3)	42 (7.2)	1.08	0.48-2.43	0.853	0.64	0.27-1.56	0.329
Other	77 (10.1)	14 (7.8)	63 (10.8)	1.23	0.53-2.85	0.623	0.92	0.33-2.50	0.863
Missing	115 (15.1)	14 (7.8)	101 (17.4)	0.58	0.21-1.61	0.293	0.50	0.08-3.17	0.460
Hospital/community acquisition									
Community-onset	158 (20.7)	32 (17.8)	126 (21.6)	Ref					
Hospital-acquired	473 (62.1)	130 (72.2)	343 (58.9)	1.60	0.93-2.74	0.086	1.09	0.55-2.17	0.795
Missing	131 (17.2)	18 (10.0)	113 (19.4)	0.78	0.36-1.71	0.539	0.65	0.25-1.73	0.393
Direct hospital transfer[A]									
No hospital transfer	423 (55.5)	95 (52.8)	328 (56.4)	Ref					
Another hospital in the same country	77 (10.1)	22 (12.2)	55 (9.5)	2.02	0.98-4.19	0.058			
Hospital in an EU/EEA country[B]	6 (0.8)	0 (0.0)	6 (1.0)	NA	NA	NA	NA	NA	NA
Hospital in a non-EU/EEA country[B]	11 (1.4)	1 (0.6)	10 (1.7)	NA	NA	NA	NA	NA	NA
Hospital in another country (country not specified)[B]	3 (0.4)	1 (0.6)	2 (0.3)	NA	NA	NA	NA	NA	NA
Hospital in another country[B, C]	20 (2.6)	2 (1.1)	18 (3.1)	0.53	0.10-2.80	0.455			
Missing	242 (31.8)	61 (33.9)	181 (31.1)	1.98	1.14-3.43	0.015			
Previous hospital admission within six months									
No hospitalisation	167 (21.9)	33 (18.3)	134 (23.0)	Ref					
Same hospital	199 (26.1)	56 (31.1)	143 (24.6)	1.51	0.82-2.80	0.187	1.70	0.89-3.25	0.106
Another hospital in the same country	88 (11.5)	23 (12.8)	65 (11.2)	1.47	0.68-3.20	0.329	1.62	0.73-3.62	0.237
Hospital in an EU/EEA country[B]	6 (0.8)	0 (0.0)	6 (1.0)	NA	NA	NA	NA	NA	NA
Hospital in a non-EU/EEA country[B]	18 (2.4)	5 (2.8)	13 (2.2)	NA	NA	NA	NA	NA	NA
Hospital in another country (country not specified)[B]	9 (1.2)	0 (0.0)	9 (1.5)	NA	NA	NA	NA	NA	NA
Hospital in another country[B, C]	33 (4.3)	5 (2.8)	28 (4.8)	1.35	0.41-4.41	0.618	1.15	0.31-4.33	0.837
Unknown hospital	28 (3.7)	6 (3.3)	22 (3.8)	1.33	0.37-4.76	0.660	1.33	0.36-4.99	0.668
Missing	247 (32.4)	57 (31.7)	190 (32.6)	1.53	0.81-2.89	0.187	1.91	0.91-4.00	0.089
Previous residence in a long-term/elderly care facility									
No residence in care facility	328 (43.0)	67 (37.2)	261 (44.8)	Ref					
In the same country	56 (7.3)	20 (11.1)	36 (6.2)	2.82	1.20-6.62	0.017	3.26	1.33-7.97	0.010
In an EU/EEA country[B]	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	NA	NA
In a non-EU/EEA country[B]	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	NA	NA
Missing	378 (49.6)	93 (51.7)	285 (49.0)	1.40	0.83-2.37	0.202	1.37	0.72-2.60	0.344
Previous travel within 6 months[D]									
No reported travel or information not available	730 (95.8)	174 (96.7)	556 (95.5)	Ref					
To an EU/EEA country[B]	9 (1.2)	1 (0.6)	8 (1.4)	0.35	0.03-3.76	0.383	0.30	0.03-3.40	0.334
To a non-EU/EEA country[B]	23 (3.0)	5 (2.8)	18 (3.1)	1.30	0.41-4.08	0.658	1.09	0.30-3.94	0.901

The multilevel multivariate logistic analysis was adjusted for random effect by country. Random effect std=1.6191, logLikelihood=-291, p-value=0.122.
[A] Variables "age" and "direct hospital transfer from" were excluded from the multivariate analysis, due to collinearity with other variables. See section on limitations and modifications above for details.
[B] Hospitals in an EU/EEA country and a non-EU/EEA country refers to countries other than the country of sampling.
[C] Combined category used in logistic regression analysis to avoid calculation difficulties caused by small group sizes.
[D] Previous travel is a combined variable on all information on travel within 6 months, combining travel information entered concerning direct transfer, previous hospital admission and travel. For details see section on limitations and modifications above.
NA, not available; Ref, reference.

Table A8f. Results of multilevel univariate and multilevel multivariate logistic regression analysis: *Klebsiella pneumoniae* ST11 *versus* non-epidemic STs of carbapenem-R/I *K. pneumoniae* SC

Variable	Overall n (%)	Epidemic carbapenem-R/I *K. pneumoniae* ST11 n (%)	Non-epidemic STs of carbapenem-R/I *K. pneumoniae* SC n (%)	Unadjusted odds ratio	Unadjusted odds ratio 95% confidence interval	Unadjusted p-value	Adjusted odds ratio	Adjusted odds ratio 95% confidence interval	Adjusted p-value
n	769	187	582						
Gender									
Male	433 (56.3)	101 (54.0)	332 (57.0)	Ref					
Female	317 (41.2)	83 (44.4)	234 (40.2)	1.15	0.75-1.77	0.514	1.06	0.66-1.70	0.810
Missing	19 (2.5)	3 (1.6)	16 (2.7)	NA	NA	NA	NA	NA	NA
Age[A]									
0-19	43 (5.6)	2 (1.1)	41 (7.0)	Ref					
20-39	50 (6.5)	12 (6.4)	38 (6.5)	4.70	0.72-30.67	0.106			
40-59	136 (17.7)	31 (16.6)	105 (18.0)	3.57	0.64-19.95	0.148			
60-79	357 (46.4)	93 (49.7)	264 (45.4)	3.85	0.72-20.52	0.114			
≥80	163 (21.2)	46 (24.6)	117 (20.1)	4.26	0.77-23.53	0.096			
Missing	20 (2.6)	3 (1.6)	17 (2.9)	NA	NA	NA	NA	NA	NA
Children/adult									
Adult (>19)	706 (91.8)	182 (97.3)	524 (90.0)	Ref					
Children (0-19)	43 (5.6)	2 (1.1)	41 (7.0)	0.25	0.05-1.34	0.107	0.29	0.05-1.54	0.146
Missing	20 (2.6)	3 (1.6)	17 (2.9)	NA	NA	NA	NA	NA	NA
Type of ward									
Medical	310 (40.3)	73 (39.0)	237 (40.7)	Ref					
Intensive care	216 (28.1)	53 (28.3)	163 (28.0)	1.03	0.60-1.76	0.914	1.53	0.81-2.91	0.189
Surgical	111 (14.4)	36 (19.3)	75 (12.9)	1.56	0.86-2.85	0.146	2.15	1.11-4.17	0.023
Other	96 (12.5)	20 (10.7)	76 (13.1)	0.88	0.42-1.84	0.743	0.86	0.37-2.00	0.728
Missing	36 (4.7)	5 (2.7)	31 (5.3)	0.43	0.13-1.35	0.147	0.40	0.06-2.60	0.339
Hospitalisation status									
Outpatient	107 (13.9)	25 (13.4)	82 (14.1)	Ref					
Inpatient	632 (82.2)	154 (82.4)	478 (82.1)	0.84	0.46-1.56	0.589	0.97	0.44-2.16	0.947
Missing	30 (3.9)	8 (4.3)	22 (3.8)	0.58	0.17-1.99	0.386	7.55	0.53-107.97	0.137
Infection/colonisation status									
Colonisation	187 (24.3)	50 (26.7)	137 (23.5)	Ref					
Infection	508 (66.1)	131 (70.1)	377 (64.8)	0.95	0.58-1.57	0.844	0.75	0.40-1.40	0.373
Undetermined clinical significance	56 (7.3)	4 (2.1)	52 (8.9)	0.34	0.11-1.13	0.079	0.36	0.08-1.50	0.159
Missing	18 (2.3)	2 (1.1)	16 (2.7)	0.60	0.09-3.95	0.595	1.16	0.05-26.23	0.925
Organ/system or location of infection/colonisation									
Urinary tract	311 (40.4)	91 (48.7)	220 (37.8)	Ref					
Lower respiratory tract	88 (11.4)	27 (14.4)	61 (10.5)	0.79	0.41-1.53	0.488	0.92	0.43-1.96	0.823
Intra-abdominal	37 (4.8)	7 (3.7)	30 (5.2)	0.33	0.12-0.95	0.040	0.30	0.10-0.92	0.034
Bloodstream	82 (10.7)	17 (9.1)	65 (11.2)	0.50	0.24-1.05	0.068	0.61	0.26-1.45	0.266
Skin and soft tissue	56 (7.3)	14 (7.5)	42 (7.2)	0.42	0.18-0.96	0.039	0.36	0.15-0.88	0.025
Other	78 (10.1)	15 (8.0)	63 (10.8)	0.84	0.36-1.98	0.689	0.73	0.28-1.92	0.526
Missing	117 (15.2)	16 (8.6)	101 (17.4)	0.24	0.09-0.60	0.002	0.24	0.07-0.89	0.033
Hospital/community acquisition									
Community-onset	184 (23.9)	58 (31.0)	126 (21.6)	Ref					
Hospital-acquired	453 (58.9)	110 (58.8)	343 (58.9)	0.59	0.36-0.98	0.041	0.49	0.26-0.94	0.032
Missing	132 (17.2)	19 (10.2)	113 (19.4)	0.70	0.32-1.53	0.372	1.26	0.46-3.41	0.654
Direct hospital transfer[A]									
No hospital transfer	467 (60.7)	139 (74.3)	328 (56.4)	Ref					
Another hospital in the same country	66 (8.6)	11 (5.9)	55 (9.5)	0.47	0.19-1.17	0.104			
Hospital in an EU/EEA country[B]	8 (1.0)	2 (1.1)	6 (1.0)	NA	NA	NA	NA	NA	NA
Hospital in a non-EU/EEA country[B]	10 (1.3)	0 (0.0)	10 (1.7)	NA	NA	NA	NA	NA	NA
Hospital in another country (country not specified)[B]	2 (0.3)	0 (0.0)	2 (0.3)	NA	NA	NA	NA	NA	NA
Hospital in another country[B, C]	20 (2.6)	2 (1.1)	18 (3.1)	0.62	0.10-3.66	0.597			
Missing	216 (28.1)	35 (18.7)	181 (31.1)	0.63	0.34-1.17	0.143			
Previous hospital admission within six months									
No hospitalisation	186 (24.2)	52 (27.8)	134 (23.0)	Ref					
Same hospital	203 (26.4)	60 (32.1)	143 (24.6)	0.94	0.54-1.65	0.834	0.89	0.49-1.63	0.710
Another hospital in the same country	86 (11.2)	21 (11.2)	65 (11.2)	0.75	0.35-1.60	0.462	0.82	0.36-1.83	0.621
Hospital in an EU/EEA country[B]	9 (1.2)	3 (1.6)	6 (1.0)	NA	NA	NA	NA	NA	NA
Hospital in a non-EU/EEA country[B]	14 (1.8)	1 (0.5)	13 (2.2)	NA	NA	NA	NA	NA	NA
Hospital in another country (country not specified)[B]	9 (1.2)	0 (0.0)	9 (1.5)	NA	NA	NA	NA	NA	NA
Hospital in another country[B, C]	32 (4.2)	4 (2.1)	28 (4.8)	0.70	0.18-2.72	0.608	0.84	0.20-3.54	0.811
Unknown hospital	32 (4.2)	10 (5.3)	22 (3.8)	3.73	0.62-22.39	0.151	3.64	0.54-24.66	0.186
Missing	230 (29.9)	40 (21.4)	190 (32.6)	0.65	0.34-1.22	0.175	0.81	0.36-1.81	0.611
Previous residence in a long-term/elderly care facility									
No residence in care facility	364 (47.3)	103 (55.1)	261 (44.8)	Ref					
In the same country	55 (7.2)	19 (10.2)	36 (6.2)	1.15	0.56-2.37	0.697	1.19	0.55-2.60	0.661
In an EU/EEA country[B]	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	NA	NA
In a non-EU/EEA country[B]	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	NA	NA
Missing	350 (45.5)	65 (34.8)	285 (49.0)	0.72	0.42-1.24	0.239	0.79	0.38-1.65	0.536
Previous travel within 6 months[D]									
No reported travel or information not available	737 (95.8)	181 (96.8)	556 (95.5)	Ref					
To an EU/EEA country[B]	12 (1.6)	4 (2.1)	8 (1.4)	4.41	0.88-22.08	0.071	4.71	0.86-25.80	0.074
To a non-EU/EEA country[B]	20 (2.6)	2 (1.1)	18 (3.1)	0.58	0.11-3.13	0.528	0.56	0.09-3.27	0.516

The multilevel multivariate logistic analysis was adjusted for random effect by country. Random effect std=1.9793, logLikelihood=-285, p-value=0.080.
[A] Variables "age" and "direct hospital transfer from" were excluded from the multivariate analysis, due to collinearity with other variables. See section on limitations and modifications above for details.
[B] Hospitals in an EU/EEA country and a non-EU/EEA country refers to countries other than the country of sampling.
[C] Combined category used in logistic regression analysis to avoid calculation difficulties caused by small group sizes.
[D] Previous travel is a combined variable on all information on travel within 6 months, combining travel information entered concerning direct transfer, previous hospital admission and travel. For details see section on limitations and modifications above.
NA, not available; Ref, reference.

Table A8g. Results of multilevel univariate and multilevel multivariate logistic regression analysis: *Klebsiella pneumoniae* ST101 *versus* non-epidemic STs of carbapenem-R/I *K. pneumoniae* SC

Variable	Overall n (%)	Epidemic carbapenem-R/I *K. pneumoniae* ST101 n (%)	Non-epidemic ST carbapenem-R/I *K. pneumoniae* SC n (%)	Unadjusted odds ratio	Unadjusted odds ratio 95% CI	Unadjusted p-value	Adjusted odds ratio	Adjusted odds ratio 95% confidence interval	Adjusted p-value
n	791	209	582						
Gender									
Male	466 (58.9)	134 (64.1)	332 (57.0)	Ref					
Female	300 (37.9)	66 (31.6)	234 (40.2)	0.58	0.38-0.89	0.012	0.61	0.38-0.98	0.042
Missing	25 (3.2)	9 (4.3)	16 (2.7)	NA	NA	NA	NA	NA	NA
Age[A]									
0-19	48 (6.1)	7 (3.3)	41 (7.0)	Ref					
20-39	56 (7.1)	18 (8.6)	38 (6.5)	3.88	1.20-12.58	0.024			
40-59	148 (18.7)	43 (20.6)	105 (18.0)	2.56	0.92-7.15	0.073			
60-79	357 (45.1)	93 (44.5)	264 (45.4)	2.23	0.83-5.94	0.110			
≥80	155 (19.6)	38 (18.2)	117 (20.1)	2.41	0.85-6.83	0.097			
Missing	27 (3.4)	10 (4.8)	17 (2.9)	NA	NA	NA	NA	NA	NA
Children/adult									
Adult (>19)	716 (90.5)	192 (91.9)	524 (90.0)	Ref					
Children (0-19)	48 (6.1)	7 (3.3)	41 (7.0)	0.41	0.16-1.05	0.064	0.27	0.09-0.80	0.017
Missing	27 (3.4)	10 (4.8)	17 (2.9)	NA	NA	NA	NA	NA	NA
Type of ward									
Medical	307 (38.8)	70 (33.5)	237 (40.7)	Ref					
Intensive care	235 (29.7)	72 (34.4)	163 (28.0)	1.28	0.80-2.07	0.301	1.09	0.62-1.90	0.770
Surgical	117 (14.8)	42 (20.1)	75 (12.9)	2.43	1.35-4.37	0.003	2.21	1.16-4.22	0.016
Other	88 (11.1)	12 (5.7)	76 (13.1)	1.42	0.62-3.27	0.409	1.40	0.49-4.04	0.529
Missing	44 (5.6)	13 (6.2)	31 (5.3)	2.05	0.80-5.25	0.137	0.43	0.08-2.32	0.327
Hospitalisation status									
Outpatient	101 (12.8)	19 (9.1)	82 (14.1)	Ref					
Inpatient	658 (83.2)	180 (86.1)	478 (82.1)	1.21	0.63-2.31	0.562	0.85	0.34-2.16	0.733
Missing	32 (4.0)	10 (4.8)	22 (3.8)	3.73	1.08-12.94	0.038	2.19	0.05-90.98	0.680
Infection/colonisation status									
Colonisation	161 (20.4)	24 (11.5)	137 (23.5)	Ref					
Infection	540 (68.3)	163 (78.0)	377 (64.8)	1.37	0.74-2.51	0.315	1.19	0.55-2.58	0.661
Undetermined clinical significance	65 (8.2)	13 (6.2)	52 (8.9)	0.76	0.30-1.87	0.545	0.72	0.23-2.19	0.560
Missing	25 (3.2)	9 (4.3)	16 (2.7)	2.18	0.63-7.52	0.219	0.00	0.00-Inf	0.995
Organ/system or location of infection/colonisation									
Urinary tract	291 (36.8)	71 (34.0)	220 (37.8)	Ref					
Lower respiratory tract	96 (12.1)	35 (16.7)	61 (10.5)	1.82	0.99-3.35	0.053	1.83	0.90-3.70	0.093
Intra-abdominal	40 (5.1)	10 (4.8)	30 (5.2)	2.02	0.76-5.34	0.157	2.47	0.81-7.54	0.111
Bloodstream	109 (13.8)	44 (21.1)	65 (11.2)	1.60	0.90-2.84	0.107	1.25	0.64-2.47	0.513
Skin and soft tissue	63 (8.0)	21 (10.0)	42 (7.2)	2.86	1.32-6.18	0.008	2.54	1.09-5.92	0.030
Other	79 (10.0)	16 (7.7)	63 (10.8)	1.39	0.63-3.05	0.417	1.25	0.47-3.33	0.654
Missing	113 (14.3)	12 (5.7)	101 (17.4)	1.43	0.51-3.98	0.499	0.14	0.00-4.88	0.281
Hospital/community acquisition									
Community-onset	164 (20.7)	38 (18.2)	126 (21.6)	Ref					
Hospital-acquired	483 (61.1)	140 (67.0)	343 (58.9)	0.87	0.50-1.51	0.613	0.66	0.32-1.38	0.268
Missing	144 (18.2)	31 (14.8)	113 (19.4)	0.65	0.32-1.33	0.237	0.40	0.15-1.07	0.067
Direct hospital transfer[A]									
No hospital transfer	435 (55.0)	107 (51.2)	328 (56.4)	Ref					
Another hospital in the same country	77 (9.7)	22 (10.5)	55 (9.5)	0.95	0.46-1.94	0.884			
Hospital in an EU/EEA country[B]	9 (1.1)	3 (1.4)	6 (1.0)	NA	NA	NA	NA	NA	NA
Hospital in a non-EU/EEA country[B]	17 (2.1)	7 (3.3)	10 (1.7)	NA	NA	NA	NA	NA	NA
Hospital in another country (country not specified)[B]	2 (0.3)	0 (0.0)	2 (0.3)	NA	NA	NA	NA	NA	NA
Hospital in another country[B, C]	28 (3.5)	10 (4.8)	18 (3.1)	5.65	1.89-16.89	0.002			
Missing	251 (31.7)	70 (33.5)	181 (31.1)	1.34	0.79-2.29	0.274			
Previous hospital admission within six months									
No hospitalisation	180 (22.8)	46 (22.0)	134 (23.0)	Ref					
Same hospital	186 (23.5)	43 (20.6)	143 (24.6)	0.79	0.43-1.44	0.437	0.83	0.43-1.61	0.589
Another hospital in the same country	94 (11.9)	29 (13.9)	65 (11.2)	1.09	0.54-2.24	0.804	1.08	0.50-2.34	0.842
Hospital in an EU/EEA country[B]	10 (1.3)	4 (1.9)	6 (1.0)	75.52	7.91-720.70	<0.001	191.98	20.69-1.8e+03	<0.001
Hospital in a non-EU/EEA country[B]	20 (2.5)	7 (3.3)	13 (2.2)	6.00	1.62-22.20	0.007	12.36	3.02-50.59	<0.001
Hospital in another country (country not specified)[B]	11 (1.4)	2 (1.0)	9 (1.5)	3.85	0.52-28.62	0.188	9.95	1.17-84.44	0.035
Unknown hospital	26 (3.3)	4 (1.9)	22 (3.8)	0.74	0.21-2.54	0.628	0.68	0.19-2.48	0.562
Missing	264 (33.4)	74 (35.4)	190 (32.6)	1.54	0.83-2.85	0.167	2.60	1.11-6.07	0.027
Previous residence in a long-term/elderly care facility									
No residence in care facility	358 (45.3)	97 (46.4)	261 (44.8)	Ref					
In the same country	45 (5.7)	9 (4.3)	36 (6.2)	NA	NA	NA	NA	NA	NA
In an EU/EEA country[B]	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	NA	NA
In a non-EU/EEA country[B]	1 (0.1)	1 (0.5)	0 (0.0)	NA	NA	NA	NA	NA	NA
In the same or a non-EU/EEA country[C]	46 (5.8)	10 (4.8)	36 (6.2)	0.50	0.17-1.50	0.217	0.50	0.15-1.74	0.279
Missing	387 (48.9)	102 (48.8)	285 (49.0)	0.94	0.57-1.54	0.802	0.53	0.26-1.07	0.077
Previous travel within 6 months[D]									
No reported travel or information not available	752 (95.1)	196 (93.8)	556 (95.5)	Ref					
To an EU/EEA country[B]	12 (1.5)	4 (1.9)	8 (1.4)	19.04	3.58-101.17	0.001	26.89	5.19-139.38	<0.001
To a non-EU/EEA country[B]	27 (3.4)	9 (4.3)	18 (3.1)	5.63	1.76-17.97	0.004	7.43	2.20-25.12	0.001

The multilevel multivariate logistic analysis was adjusted for random effect by country. Random effect std=2.5882, logLikelihood=-297, p-value<0.001.
[A] Variables "age" and "direct hospital transfer from" were excluded from the multivariate analysis, due to collinearity with other variables. See section on limitations and modifications above for details.
[B] Hospitals in an EU/EEA country and a non-EU/EEA country refers to countries other than the country of sampling.
[C] Combined category used in logistic regression analysis to avoid calculation difficulties caused by small group sizes.
[D] Previous travel is a combined variable on all information on travel within 6 months, combining travel information entered concerning direct transfer, previous hospital admission and travel. For details see section on limitations and modifications above.
N, not available; Ref, reference.

Table A8h. Results of multilevel univariate and multilevel multivariate logistic regression analysis: *Klebsiella pneumoniae* ST147 *versus* non-epidemic STs of carbapenem-R/I *K. pneumoniae* SC

Variable	Overall n (%)	Epidemic carbapenem-R/I *K. pneumoniae* ST147 n (%)	Non-epidemic ST carbapenem-R/I *K. pneumoniae* SC n (%)	Unadjusted odds ratio	Unadjusted odds ratio 95% confidence interval	Unadjusted p-value	Adjusted odds ratio	Adjusted odds ratio 95% confidence interval	Adjusted p-value
n	677	95	582						
Gender									
Male	386 (57.0)	54 (56.8)	332 (57.0)	Ref					
Female	272 (40.2)	38 (40.0)	234 (40.2)	1.08	0.67-1.74	0.758	1.10	0.66-1.84	0.725
Missing	19 (2.8)	3 (3.2)	16 (2.7)	NA	NA	NA	NA	NA	NA
Age[A]									
0-19	43 (6.4)	2 (2.1)	41 (7.0)	Ref					
20-39	44 (6.5)	6 (6.3)	38 (6.5)	4.03	0.72-22.42	0.112			
40-59	127 (18.8)	22 (23.2)	105 (18.0)	4.07	0.88-18.88	0.073			
60-79	306 (45.2)	42 (44.2)	264 (45.4)	3.60	0.80-16.07	0.094			
≥80	137 (20.2)	20 (21.1)	117 (20.1)	3.39	0.72-15.94	0.123			
Missing	20 (3.0)	3 (3.2)	17 (2.9)	NA	NA	NA	NA	NA	NA
Children/adult									
Adult (>19)	614 (90.7)	90 (94.7)	524 (90.0)	Ref					
Children (0-19)	43 (6.4)	2 (2.1)	41 (7.0)	0.27	0.06-1.18	0.083	0.24	0.05-1.06	0.059
Missing	20 (3.0)	3 (3.2)	17 (2.9)	NA	NA	NA	NA	NA	NA
Type of ward									
Medical	273 (40.3)	36 (37.9)	237 (40.7)	Ref					
Intensive care	189 (27.9)	26 (27.4)	163 (28.0)	1.13	0.62-2.06	0.679	1.52	0.76-3.02	0.232
Surgical	87 (12.9)	12 (12.6)	75 (12.9)	0.93	0.44-1.97	0.849	1.03	0.46-2.33	0.938
Other	91 (13.4)	15 (15.8)	76 (13.1)	1.56	0.74-3.27	0.242	1.59	0.64-3.95	0.318
Missing	37 (5.5)	6 (6.3)	31 (5.3)	1.54	0.53-4.41	0.426	1.38	0.27-7.08	0.697
Hospitalisation status									
Outpatient	97 (14.3)	15 (15.8)	82 (14.1)	Ref					
Inpatient	553 (81.7)	75 (78.9)	478 (82.1)	0.90	0.47-1.75	0.764	1.54	0.58-4.07	0.383
Missing	27 (4.0)	5 (5.3)	22 (3.8)	1.70	0.47-6.09	0.415	4.28	0.55-33.62	0.167
Infection/colonisation status									
Colonisation	154 (22.7)	17 (17.9)	137 (23.5)	Ref					
Infection	448 (66.2)	71 (74.7)	377 (64.8)	1.53	0.80-2.95	0.201	1.59	0.74-3.43	0.237
Undetermined clinical significance	57 (8.4)	5 (5.3)	52 (8.9)	1.05	0.33-3.30	0.940	0.74	0.17-3.28	0.690
Missing	18 (2.7)	2 (2.1)	16 (2.7)	1.34	0.22-8.27	0.750	3.60	0.17-77.08	0.412
Organ/system or location of infection/colonisation									
Urinary tract	259 (38.3)	39 (41.1)	220 (37.8)	Ref					
Lower respiratory tract	73 (10.8)	12 (12.6)	61 (10.5)	1.04	0.49-2.21	0.926	0.96	0.41-2.26	0.934
Intra-abdominal	35 (5.2)	5 (5.3)	30 (5.2)	0.88	0.28-2.78	0.828	1.09	0.32-3.69	0.895
Bloodstream	75 (11.1)	10 (10.5)	65 (11.2)	0.67	0.30-1.50	0.333	0.59	0.24-1.48	0.259
Skin and soft tissue	52 (7.7)	10 (10.5)	42 (7.2)	1.16	0.49-2.74	0.733	1.16	0.45-2.97	0.754
Other	70 (10.3)	7 (7.4)	63 (10.8)	0.71	0.26-1.90	0.492	0.81	0.26-2.52	0.715
Missing	113 (16.7)	12 (12.6)	101 (17.4)	0.69	0.24-1.99	0.493	0.31	0.05-1.85	0.198
Hospital/community acquisition									
Community-onset	153 (22.6)	27 (28.4)	126 (21.6)	Ref					
Hospital-acquired	398 (58.8)	55 (57.9)	343 (58.9)	0.58	0.32-1.04	0.068	0.53	0.24-1.15	0.107
Missing	126 (18.6)	13 (13.7)	113 (19.4)	0.63	0.28-1.42	0.264	0.60	0.22-1.68	0.333
Direct hospital transfer[A]									
No hospital transfer	381 (56.3)	53 (55.8)	328 (56.4)	Ref					
Another hospital in the same country	65 (9.6)	10 (10.5)	55 (9.5)	1.44	0.60-3.46	0.418			
Hospital in an EU/EEA country[B]	6 (0.9)	0 (0.0)	6 (1.0)	NA	NA	NA	NA	NA	NA
Hospital in a non-EU/EEA country[B]	13 (1.9)	3 (3.2)	10 (1.7)	NA	NA	NA	NA	NA	NA
Hospital in another country (country not specified)[B]	2 (0.3)	0 (0.0)	2 (0.3)	NA	NA	NA	NA	NA	NA
Hospital in another country[B, C]	21 (3.1)	3 (3.2)	18 (3.1)	1.90	0.46-7.85	0.378			
Missing	210 (31.0)	29 (30.5)	181 (31.1)	2.02	1.01-4.02	0.046			
Previous hospital admission within six months									
No hospitalisation	156 (23.0)	22 (23.2)	134 (23.0)	Ref					
Same hospital	163 (24.1)	20 (21.1)	143 (24.6)	0.81	0.39-1.69	0.577	0.86	0.40-1.87	0.709
Another hospital in the same country	76 (11.2)	11 (11.6)	65 (11.2)	1.18	0.49-2.85	0.718	1.33	0.53-3.33	0.544
Hospital in an EU/EEA country[B]	6 (0.9)	0 (0.0)	6 (1.0)	NA	NA	NA	NA	NA	NA
Hospital in a non-EU/EEA country[B]	16 (2.4)	3 (3.2)	13 (2.2)	NA	NA	NA	NA	NA	NA
Hospital in another country (country not specified)[B]	14 (2.1)	5 (5.3)	9 (1.5)	NA	NA	NA	NA	NA	NA
Hospital in another country[B, C]	36 (5.3)	8 (8.4)	28 (4.8)	2.89	0.97-8.60	0.057	3.62	1.09-12.02	0.036
Unknown hospital	26 (3.8)	4 (4.2)	22 (3.8)	0.79	0.21-2.94	0.721	0.87	0.22-3.42	0.847
Missing	220 (32.5)	30 (31.6)	190 (32.6)	1.26	0.62-2.55	0.520	1.44	0.60-3.46	0.408
Previous residence in a long-term/elderly care facility									
No residence in care facility	304 (44.9)	43 (45.3)	261 (44.8)	Ref					
In the same country	45 (6.6)	9 (9.5)	36 (6.2)	1.92	0.74-5.02	0.182	1.83	0.65-5.14	0.254
In an EU/EEA country[B]	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	NA	NA
In a non-EU/EEA country[B]	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	NA	NA
Missing	328 (48.4)	43 (45.3)	285 (49.0)	1.27	0.67-2.41	0.459	0.91	0.41-2.04	0.818
Previous travel within 6 months[D]									
No reported travel or information not available	648 (95.7)	92 (96.8)	556 (95.5)	Ref					
To an EU/EEA country[B]	8 (1.2)	0 (0.0)	8 (1.4)	NA	NA	NA	NA	NA	NA
To a non-EU/EEA country[B]	21 (3.1)	3 (3.2)	18 (3.1)	NA	NA	NA	NA	NA	NA
To another country[B,C]	29 (4.3)	3 (3.2)	26 (4.5)	0.77	0.20-2.89	0.697	0.67	0.17-2.64	0.563

The multilevel multivariate logistic analysis was adjusted for random effect by country. Random effect std=1.4375, logLikelihood=-238, p-value=0.534.
[A] Variables "age" and "direct hospital transfer from" were excluded from the multivariate analysis, due to collinearity with other variables. See section on limitations and modifications above for details.
[B] Hospitals in an EU/EEA country and a non-EU/EEA country refers to countries other than the country of sampling.
[C] Combined category used in logistic regression analysis to avoid calculation difficulties caused by small group sizes.
[D] Previous travel is a combined variable on all information on travel within 6 months, combining travel information entered concerning direct transfer, previous hospital admission and travel. For details see section on limitations and modifications above.
NA, not available. Ref, reference.

Table A8i. Results of multilevel univariate and multilevel multivariate logistic regression analysis: *Klebsiella pneumoniae* ST15 *versus* non-epidemic STs of carbapenem-R/I *K. pneumoniae* SC

Variable	Overall n (%)	Epidemic carbapenem-R/I *K. pneumoniae* ST15 n (%)	Non-epidemic STs carbapenem-R/I *K. pneumoniae* SC n (%)	Unadjusted odds ratio	Unadjusted odds ratio 95% confidence interval	Unadjusted p-value	Adjusted odds ratio	Adjusted odds ratio 95% confidence interval	Adjusted p-value
n	663	81	582						
Gender									
Male	374 (56.4)	42 (51.9)	332 (57.0)	Ref					
Female	270 (40.7)	36 (44.4)	234 (40.2)	1.20	0.70-2.05	0.505	1.21	0.66-2.23	0.529
Missing	19 (2.9)	3 (3.7)	16 (2.7)	NA	NA	NA	NA	NA	NA
Age[A]									
0-19	41 (6.2)	0 (0.0)	41 (7.0)	Ref					
20-39	43 (6.5)	5 (6.2)	38 (6.5)	1.18e+07	0.00-3.0e+138	0.916			
40-59	114 (17.2)	9 (11.1)	105 (18.0)	7.35e+06	0.00-1.9e+138	0.918			
60-79	304 (45.9)	40 (49.4)	264 (45.4)	1.27e+07	0.00-3.2e+138	0.916			
>=80	142 (21.4)	25 (30.9)	117 (20.1)	1.69e+07	0.00-4.3e+138	0.914			
Missing	19 (2.9)	2 (2.5)	17 (2.9)	NA	NA	NA	NA	NA	NA
Children/adult									
Adult (>19)	603 (91.0)	79 (97.5)	524 (90.0)	Ref					
Children (0-19)	41 (6.2)	0 (0.0)	41 (7.0)	0.00	0.00-1.0e+301	0.964	0.00	0.00-Inf	0.992
Missing	19 (2.9)	2 (2.5)	17 (2.9)	NA	NA	NA	NA	NA	NA
Type of ward									
Medical	268 (40.4)	31 (38.3)	237 (40.7)	Ref					
Intensive care	174 (26.2)	11 (13.6)	163 (28.0)	0.66	0.29-1.46	0.304	0.85	0.35-2.04	0.714
Surgical	82 (12.4)	7 (8.6)	75 (12.9)	0.78	0.31-1.99	0.610	0.88	0.31-2.46	0.804
Other	104 (15.7)	28 (34.6)	76 (13.1)	2.84	1.41-5.71	0.003	2.40	1.03-5.63	0.043
Missing	35 (5.3)	4 (4.9)	31 (5.3)	1.74	0.47-6.46	0.408	1.42	0.20-9.87	0.725
Hospitalisation status									
Outpatient	108 (16.3)	26 (32.1)	82 (14.1)	Ref					
Inpatient	529 (79.8)	51 (63.0)	478 (82.1)	0.51	0.27-0.95	0.035	1.00	0.39-2.57	0.999
Missing	26 (3.9)	4 (4.9)	22 (3.8)	2.29	0.53-9.83	0.267	5.70	0.72-45.00	0.099
Infection/colonisation status									
Colonisation	154 (23.2)	17 (21.0)	137 (23.5)	Ref					
Infection	438 (66.1)	61 (75.3)	377 (64.8)	1.45	0.72-2.93	0.302	1.15	0.48-2.77	0.756
Undetermined clinical significance	53 (8.0)	1 (1.2)	52 (8.9)	0.18	0.02-1.51	0.115	0.10	0.01-1.13	0.063
Missing	18 (2.7)	2 (2.5)	16 (2.7)	2.93	0.42-20.35	0.278	0.00	0.00-Inf	0.997
Organ/system or location of infection/colonisation									
Urinary tract	257 (38.8)	37 (45.7)	220 (37.8)	Ref					
Lower respiratory tract	67 (10.1)	6 (7.4)	61 (10.5)	0.53	0.19-1.48	0.226	0.67	0.22-2.00	0.469
Intra-abdominal	32 (4.8)	2 (2.5)	30 (5.2)	0.50	0.10-2.58	0.407	0.83	0.14-5.00	0.839
Bloodstream	71 (10.7)	6 (7.4)	65 (11.2)	0.59	0.21-1.62	0.304	0.65	0.20-2.17	0.488
Skin and soft tissue	50 (7.5)	8 (9.9)	42 (7.2)	1.03	0.38-2.74	0.958	1.60	0.52-4.95	0.416
Other	69 (10.4)	6 (7.4)	63 (10.8)	0.55	0.18-1.66	0.286	0.76	0.20-2.90	0.690
Missing	117 (17.6)	16 (19.8)	101 (17.4)	1.27	0.37-4.35	0.705	1.74	0.33-9.30	0.516
Hospital/community acquisition									
Community-onset	159 (24.0)	33 (40.7)	126 (21.6)	Ref					
Hospital-acquired	381 (57.5)	38 (46.9)	343 (58.9)	0.49	0.27-0.90	0.021	0.79	0.34-1.83	0.585
Missing	123 (18.6)	10 (12.3)	113 (19.4)	0.58	0.24-1.43	0.235	0.75	0.25-2.27	0.610
Direct hospital transfer[A]									
No hospital transfer	382 (57.6)	54 (66.7)	328 (56.4)	Ref					
Another hospital in the same country	59 (8.9)	4 (4.9)	55 (9.5)	0.45	0.14-1.51	0.198			
Hospital in an EU/EEA country[B]	7 (1.1)	1 (1.2)	6 (1.0)	NA	NA	NA	NA	NA	NA
Hospital in a non-EU/EEA country[B]	10 (1.5)	0 (0.0)	10 (1.7)	NA	NA	NA	NA	NA	NA
Hospital in another country (country not specified)[B]	3 (0.5)	1 (1.2)	2 (0.3)	NA	NA	NA	NA	NA	NA
Hospital in another country[B, C]	20 (3.0)	2 (2.5)	18 (3.1)	1.07	0.19-6.02	0.937			
Missing	202 (30.5)	21 (25.9)	181 (31.1)	1.20	0.56-2.57	0.638			
Previous hospital admission within six months									
No hospitalisation	151 (22.8)	17 (21.0)	134 (23.0)	Ref					
Same hospital	164 (24.7)	21 (25.9)	143 (24.6)	0.71	0.32-1.56	0.394	0.66	0.28-1.57	0.348
Another hospital in the same country	74 (11.2)	9 (11.1)	65 (11.2)	0.95	0.35-2.56	0.913	0.85	0.29-2.51	0.769
Hospital in an EU/EEA country[B]	9 (1.4)	3 (3.7)	6 (1.0)	NA	NA	NA	NA	NA	NA
Hospital in a non-EU/EEA country[B]	14 (2.1)	1 (1.2)	13 (2.2)	NA	NA	NA	NA	NA	NA
Hospital in another country (country not specified)[B]	10 (1.5)	1 (1.2)	9 (1.5)	NA	NA	NA	NA	NA	NA
Hospital in another country[B, C]	33 (5.0)	5 (6.2)	28 (4.8)	1.50	0.42-5.35	0.531	1.98	0.48-8.17	0.343
Unknown hospital	24 (3.6)	2 (2.5)	22 (3.8)	1.17	0.21-6.52	0.862	1.42	0.24-8.45	0.697
Missing	217 (32.7)	27 (33.3)	190 (32.6)	0.99	0.45-2.17	0.973	0.70	0.25-1.95	0.500
Previous residence in a long-term/elderly care facility									
No residence in care facility	296 (44.6)	35 (43.2)	261 (44.8)	Ref					
In the same country	47 (7.1)	11 (13.6)	36 (6.2)	4.51	1.65-12.32	0.003	3.71	1.18-11.64	0.024
In an EU/EEA country[B]	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	NA	NA
In a non-EU/EEA country[B]	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	NA	NA
Missing	320 (48.3)	35 (43.2)	285 (49.0)	1.38	0.72-2.65	0.326	1.23	0.54-2.81	0.627
Previous travel within 6 months[D]									
No reported travel or information not available	633 (95.5)	77 (95.1)	556 (95.5)	Ref					
To an EU/EEA country[B]	11 (1.7)	3 (3.7)	8 (1.4)	NA	NA	NA	NA	NA	NA
To a non-EU/EEA country[B]	19 (2.9)	1 (1.2)	18 (3.1)	NA	NA	NA	NA	NA	NA
To another country[C]	30 (4.5)	4 (4.9)	26 (4.5)	0.96	0.28-3.33	0.950	1.28	0.34-4.85	0.717

The multilevel multivariate logistic analysis was adjusted for random effect by country. Random effect std=1.4953, logLikelihood=-181, p-value=0.016.
[A] Variables "age" and "direct hospital transfer from" were excluded from the multivariate analysis, due to collinearity with other variables. See section on limitations and modifications above for details.
[B] Hospitals in an EU/EEA country and a non-EU/EEA country refers to countries other than the country of sampling.
[C] Combined category used in logistic regression analysis to avoid calculation difficulties caused by small group sizes.
[D] Previous travel is a combined variable on all information on travel within 6 months, combining travel information entered concerning direct transfer, previous hospital admission and travel. For details see section on limitations and modifications above.
N, not available. Ref, reference.

Table A9. *Klebsiella pneumoniae* SC isolates resistant to both colistin and ceftazidime-avibactam and classified as fully drug-resistant (n=26)

Isolate	Sequence type	Acquired carbapenemase gene	Acquired ESBL gene	Omp mutations	Colistin mutations	Country	Previous hospitalisation within 6 months	Hospital code	Type of clinical specimen	Colistin MIC (mg/L)	Ceftazidime-avibactam zone (mm)/ MIC (mg/L)
1	ST147	*bla*$_{VIM-1}$	*bla*$_{CTX-M-9}$	-	-	Spain	No hospitalisation	K	Lower respiratory tract specimens, Clinical sample	4	NA/ >16/4
2	ST392	*bla*$_{OXA-48}$	*bla*$_{CTX-M-15}$	OmpK35-8%; OmpK36-10%	-	Spain	Same hospital	A	Urine, Clinical sample	>8	NA/ >16/4
3	ST512	*bla*$_{KPC-3}$	-	OmpK35-25%; OmpK36GD	MgrB-79%	Spain	Same hospital	B	Blood, Clinical sample	4	NA/ >16/4
4	ST512	*bla*$_{KPC-3}$	-	OmpK35-25%; OmpK36GD	MgrB-79%	Spain	Another hospital in the same country	B	Lower respiratory tract specimens, Clinical sample	>8	NA/ 16/4
5	ST512	*bla*$_{KPC-3}$	-	OmpK35-25%; OmpK36GD	MgrB-79%	Spain	Same hospital	B	Blood, Clinical sample	8	NA/ >16/4
6	ST11	*bla*$_{NDM-1}$	-	-	MgrB-60%	Greece	No hospitalisation	D	Urine, Clinical sample	>8	6/ >16/4
7	ST11	*bla*$_{NDM-1}$	*bla*$_{CTX-M-15}$	OmpK36-75%	-	Greece	NA	E	Blood, Clinical sample	>8	NA/ >16/4
8	ST11	*bla*$_{NDM-1}$	*bla*$_{CTX-M-15}$	-	-	Greece	Same hospital	L	Urine, Clinical sample	8	6/ >16/4
9	ST147	*bla*$_{KPC-2}$	*bla*$_{VEB-1}$	OmpK35-48%; OmpK36GD	MgrB-62%	Greece	Information not available	C	Urine, Clinical sample	>8	6/ >16/4
10	ST11	*bla*$_{NDM-1}$	*bla*$_{CTX-M-15}$	-	MgrB-60%	Greece	No hospitalisation	M	Urine, Clinical sample	>8	8/ >16/4
11	ST11	*bla*$_{NDM-1}$	*bla*$_{CTX-M-15}$	-	MgrB-60%	Greece	Another hospital in the same country	M	Urine, Clinical sample	>8	8/ >16/4
12	ST11	*bla*$_{NDM-1}$	*bla*$_{CTX-M-15}$	-	MgrB-60%	Greece	Information not available	N	Lower respiratory tract specimens, Clinical sample	>8	NA/ >16/4
13	ST39	*bla*$_{KPC-2}$	-	OmpK36GD	MgrB-51%	Greece	No hospitalisation	C	Catheter exit site, Clinical sample	>8	11/ >16/4
14	ST147	*bla*$_{KPC-2}$	*bla*$_{VEB-1}$	OmpK35-48%; OmpK36GD	MgrB-62%	Greece	No hospitalisation	C	Blood, Clinical sample	>8	10/ >16/4
15	ST258	*bla*$_{KPC-2}$	-	OmpK35-25%; OmpK36GD	MgrB-62%	Greece	Another hospital in the same country	E	Blood, Clinical sample	>8	NA/ >16/4
16	ST101	*bla*$_{KPC-2}$*	-	OmpK35-17%; OmpK36TD	MgrB-62%	Croatia	Another hospital in the same country	F	Wound swabs, Clinical sample	16	6 /NA
17	ST101	*bla*$_{NDM-1}$; *bla*$_{KPC-2}$	*bla*$_{CTX-M-15}$	OmpK35-17%; OmpK36GD	-	Romania	No hospitalisation	G	Blood, Clinical sample	32	6 /NA
18	ST101	*bla*$_{NDM-1}$; *bla*$_{OXA-48}$	*bla*$_{CTX-M-15}$; *bla*$_{SHV-12}$	OmpK35-17%	-	Romania	NA	H	Other, Screening sample	4	10 /NA
19	ST219	*bla*$_{NDM-1}$	*bla*$_{CTX-M-15}$	OmpK36-34%	-	Romania	Another hospital in the same country	O	Wound swabs, Clinical sample	32	6/ NA
20	ST258	*bla*$_{NDM-1}$; *bla*$_{KPC-33}$	*bla*$_{SHV-12}$	OmpK35-25%; OmpK36GD	MgrB-60%	Romania	NA	H	Blood, Clinical sample	4	6 /NA
21	ST11	*bla*$_{NDM-1}$	*bla*$_{CTX-M-15}$	OmpK36-11%	MgrB-60%	Slovakia	Same hospital	I	Urine, Clinical sample	>16	6 /NA
22	ST11	*bla*$_{NDM-1}$	*bla*$_{CTX-M-15}$	OmpK36-11%	MgrB-60%	Slovakia	No hospitalisation	I	Other, Screening sample	16	6 /NA
23	ST11	*bla*$_{NDM-1}$	*bla*$_{CTX-M-15}$	OmpK36-11%	MgrB-60%	Slovakia	Same hospital	I	Lower respiratory tract specimens, Clinical sample	16	6 /NA
24	ST11	*bla*$_{NDM-1}$	*bla*$_{CTX-M-15}$	-	MgrB-60%	Slovakia	Same hospital	I	Other, Screening sample	>16	6/ NA
25	ST11	*bla*$_{NDM-1}$	*bla*$_{CTX-M-15}$	-	-	Bulgaria	Another hospital in the same country	J	Catheter exit site, Clinical sample	4	10/ NA
26	ST11	*bla*$_{NDM-1}$	*bla*$_{CTX-M-15}$	-	-	Bulgaria	Same hospital	J	Catheter exit site, Clinical sample	4	9/ NA

ESBL, extended-spectrum beta-lactamase; MIC, minimum inhibitory concentration; NA, not applicable; ST, sequence type.

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