

OPERATIONAL SUPPORT

Analysis plan for the survey of carbapenem-resistant Enterobacterales 2025 (CRE25 survey)

Introduction

The survey of carbapenem-resistant Enterobacterales 2025 (CRE25 survey) is the third genomic survey of CRE following the European survey of carbapenemase-producing *Enterobacteriaceae* (EuSCAPE) in 2013–2014 and the survey of carbapenem- and/or colistin-resistant Enterobacterales (CCRE survey) in 2019. National reference laboratories (NRLs) from the 37 countries that are members of the European Antimicrobial Resistance Genes Surveillance Network (EURGen-Net) are invited to participate in the CRE25 survey, including all European Union (EU) and European Economic Area (EEA) countries, the Western Balkan countries (Albania, Bosnia and Herzegovina, Kosovo¹, Montenegro, North Macedonia, Serbia) and Türkiye.

This analysis plan outlines the interim and final analysis for the CRE25 survey. It describes the baseline analysis to be conducted by ECDC which does not exclude additional and more in-depths analysis of specific findings of interest. The analysis plan is based on the previous CCRE survey analysis plan and takes into account the experience and lessons learned from the analyses of the EuSCAPE and CCRE survey data sets [1-4]. Inclusion criteria, definitions and variables are described in the CRE25 survey protocol [5], as well as the data and isolate collection process for the CRE25 survey. The survey isolate collection period is from 1 October 2025 to 31 December 2025. Epidemiological and whole genome sequencing (WGS) data will be submitted by nominated country users via EpiPulse Cases using the AMRISO and AMRISO\$AST data set, as described in the protocol.

Planned analysis

1. Overview of submitted isolates

For the CRE25 survey main collection, the participating countries are invited to submit *Klebsiella pneumoniae* species complex (SC) and *Escherichia coli* isolates that are in the categories 'resistant' (R) or 'susceptible increased exposure' (I) for any carbapenem in accordance with the European Committee for Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints. Countries are also invited to voluntarily submit carbapenemase-suspected *K. pneumoniae* SC and *E. coli* isolates based on EUCAST screening breakpoints. As a starting point, an overview of submitted *K. pneumoniae* SC isolates and submitted *E. coli* isolates will be provided for the CRE25 main and voluntary collections.

¹ 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.

Example Table 1. Number of carbapenem-R/I *Klebsiella pneumoniae* species complex isolates and carbapenemase gene families involved, by country

Country	Isolates carrying							Total submitted isolates n (%)
	<i>bla</i> _{KPC} (n, %)	<i>bla</i> _{NDM} (n, %)	<i>bla</i> _{OXA-48-like} (n, %)	<i>bla</i> _{VIM} (n, %)	Other carbapenemase genes (n, %)	Multiple carbapenemase genes (n, %)	No. detected carbapenemase genes n (%)	
Country 1								
Country 2								
Country 3								
etc.								

Example Table 2. Number of carbapenem-R/I *Escherichia coli* isolates and carbapenemase gene families involved, by country

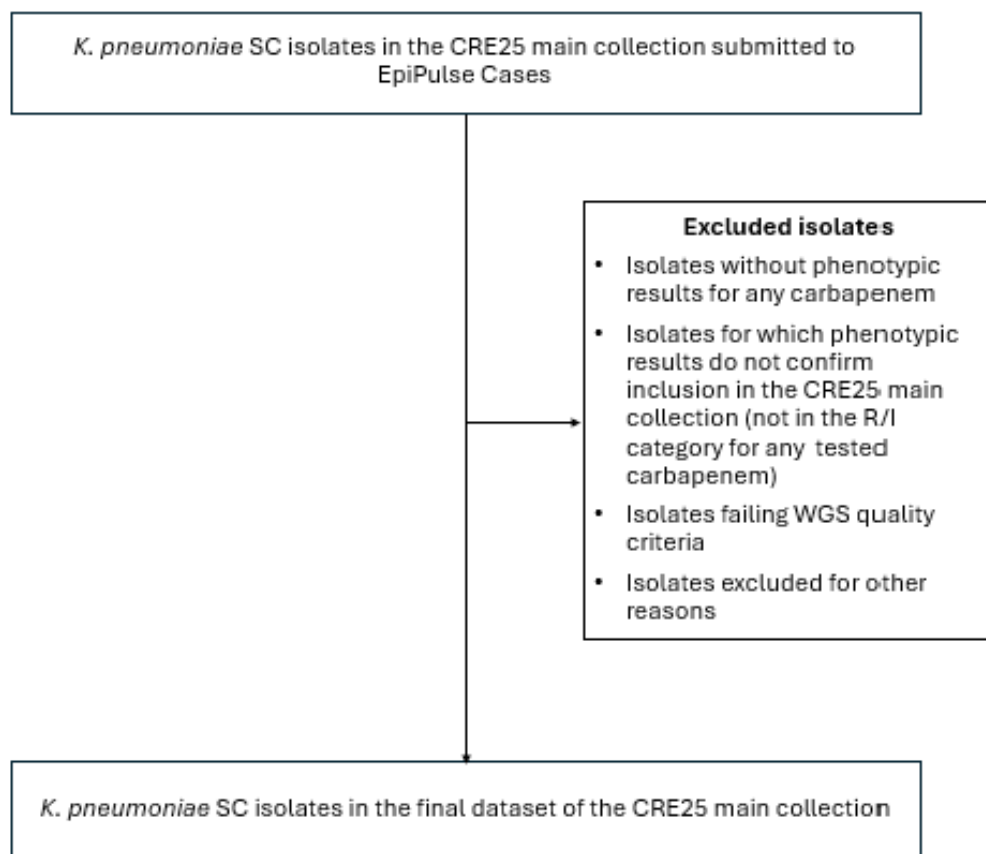
Country	Isolates carrying							Total submitted isolates n (%)
	<i>bla</i> _{KPC} (n, %)	<i>bla</i> _{NDM} (n, %)	<i>bla</i> _{OXA-48-like} (n, %)	<i>bla</i> _{VIM} (n, %)	Other carbapenemase genes (n, %)	Multiple carbapenemase genes (n, %)	No. detected carbapenemase genes n (%)	
Country 1								
Country 2								
Country 3								
etc.								

Similar tables will be prepared for carbapenemase-suspected *K. pneumoniae* SC and carbapenemase-suspected *E. coli* isolates collected in the CRE25 voluntary collection. For a more detailed description of carbapenemase variants, please see Section 7.3.1.

2. Analysis of data completeness

For rapid genomic analysis and interim reports, WGS data will be accepted with the minimum metadata (submitting country, sampling date) for upload to EpiPulse Cases. All submitted isolates will be included in interim analysis and reports, regardless of metadata completeness. For the final report, attempts will be made to obtain complete metadata for all variables, as far as possible, taking into account differences in legal and data protection regulations in various countries. For the final report, isolates that do not have any phenotypic antimicrobial susceptibility testing (AST) results available for at least one carbapenem (ertapenem, imipenem, meropenem) to validate their inclusion in the mandatory or voluntary CRE25 collection will be excluded. Isolates that are registered for the mandatory or voluntary collection but have carbapenem testing results that do not conform with the inclusion criteria will also be excluded (for example isolates that are registered for the main collection but are not in the R/I category according to EUCAST clinical breakpoints for any reported carbapenem) [6]. Isolate inclusion and exclusion will be presented in a flow chart (Example Figure 1) and a list of excluded isolates by species, country and carbapenemase gene variant will be provided. For all other variables, including epidemiological, microbiological variables and AST results other than for carbapenems, the percentage of data completeness will be presented in the final report, but missing data will not lead to exclusion of isolates.

Example Figure 1. Flowchart of isolates for those included as *Klebsiella pneumoniae* species complex in the CRE25 main collection



A similar flowchart will be prepared for the carbapenem-R/I *E. coli* isolates in the main collection and carbapenemase-suspected *K. pneumoniae* and *E. coli* isolates in the voluntary collection.

3. Analysis of epidemiological variables

An overview of epidemiological variables with confidence intervals associated with *K. pneumoniae* SC and *E. coli* isolates for the main and voluntary collections will be provided in Example Table 3.

Example Table 3. Epidemiological characteristics associated with *Klebsiella pneumoniae* SC and *Escherichia coli* isolates from the CRE25 main and voluntary collections

Variables	<i>K. pneumoniae</i> SC main collection n (%)	<i>K. pneumoniae</i> SC voluntary collection n (%)	All <i>K. pneumoniae</i> SC n (%)	<i>E. coli</i> main collection n(%)	<i>E. coli</i> voluntary collection n (%)	All <i>E. coli</i> n (%)	All isolates n
Gender							
Male							
Female							
Unknown							
Age							
0–19 years							
20–39 years							
40–59 years							
60–79 years							
≥80 years							
Missing							
Hospitalisation status							
Outpatient							
Inpatient							
Missing							
Type of ward							
Medical							
Intensive care							
Surgical							
Other							
Missing							
Clinical significance							
Colonisation							
Infection							
Undetermined/Unknown							
Missing							
Organ system /location of infection/colonisation							
Urinary tract							
Lower respiratory tract							
Intra-abdominal							
Blood stream							
Skin/soft tissue							
Other							
Missing							
Type of sample							
Clinical sample							
Screening sample							
Missing							
Origin of sample							
Urine							
Blood							
Lower respiratory tract							
Wound							
Aspirates							
Soft tissue samples							
Skin							
Catheter exit site							
Reproductive tract samples							
Bone marrow							
Cerebrospinal fluid							
Faeces							
Gastrointestinal tract							
Other							
Missing							
Hospital/community acquisition							
Community-onset							
Hospital-acquired							
Missing							
Hospital admission within previous six months							
Yes							
No							
Missing							
Residence in a long-term/elderly care facility within previous six months							
Yes							
No							
Missing							
Travel within previous six months							
Yes							
No							
Missing							

4. Analysis of antimicrobial susceptibility testing results

The phenotypic testing results are reported by the participating NRLs as minimum inhibitory concentrations (MIC) in mg/L or disk diffusion zone diameters (DDZD) in mm. AST is performed at national level based on EUCAST methodology [6]. Results generated with methods differing from EUCAST methodology should not be reported. ECDC will interpret the received MICs and DDZDs according to EUCAST breakpoints version 15, 2025 [6]. Results with confidence intervals are displayed in Example Tables 4 and 5. AST results within the area of technical uncertainty will be reported as tested with a warning message in line with EUCAST guidance [7].

Example Table 4. Antimicrobial susceptibility testing results for carbapenem-R/I *Klebsiella pneumoniae* SC isolates in the main collection

Antimicrobial agent	Carbapenem-R/I <i>K. pneumoniae</i> SC				Carbapenem-R/I <i>K. pneumoniae</i> SC carrying carbapenemase genes			
	n tested	% R	% I	%S	n tested	% R	% I	% S
Cefotaxime (CTX)								
Ceftazidime (CAZ)								
Cefiderocol (FDC)			NA				NA	
Aztreonam (ATM)								
Piperacillin-tazobactam (TZP)			NA				NA	
Ceftazidime-avibactam (CZA)			NA				NA	
Ceftolozane-tazobactam (CZT)			NA				NA	
Imipenem-relebactam (IMR)			NA				NA	
Meropenem-vaborbactam (MEV)			NA				NA	
Aztreonam-avibactam (AZA)			NA				NA	
Amikacin (AMK)			NA				NA	
Tobramycin (TOB)			NA				NA	
Gentamicin (GEN)			NA				NA	
Ciprofloxacin (CIP)								
Levofloxacin (LVX)								
Colistin (COL)			NA				NA	
Trimethoprim-sulfamethoxazole (SXT)								

Example Table 5. Antimicrobial susceptibility testing results for carbapenem-R/I *Escherichia coli* isolates in the main collection

Antimicrobial agent	Carbapenem-R/I <i>E. coli</i>				Carbapenem-R/I <i>E. coli</i> carrying carbapenemase genes			
	n tested	% R	% I	%S	n tested	% R	% I	% S
Cefotaxime (CTX)								
Ceftazidime (CAZ)								
Cefiderocol (FDC)			NA				NA	
Aztreonam (ATM)								
Piperacillin-tazobactam (TZP)			NA				NA	
Ceftazidime-avibactam (CZA)			NA				NA	
Ceftolozane-tazobactam (CZT)			NA				NA	
Imipenem-relebactam (IMR)			NA				NA	
Meropenem-vaborbactam (MEV)			NA				NA	
Aztreonam-avibactam (AZA)			NA				NA	
Amikacin (AMK)			NA				NA	
Tobramycin (TOB)			NA				NA	
Gentamicin (GEN)			NA				NA	
Ciprofloxacin (CIP)								
Levofloxacin (LVX)								
Colistin (COL)			NA				NA	
Trimethoprim-sulfamethoxazole (SXT)								
Tigecycline (TGC)			NA				NA	
Fosfomycin (FOS)			NA				NA	

Tables for the AST results of *K. pneumoniae* SC and *E. coli* isolates collected in the CRE25 survey voluntary collections will be prepared in the same way as in Example Tables 4 and 5 above. Phenotypic results will also be analysed by carbapenemase gene family if sufficient data are available.

5. Genomic analysis

The genomic analyses for the CRE25 survey are part of the standard pipeline implemented at ECDC, which is applied to all WGS data received by the Centre. Calculations are performed in Azure batch, with calculation resources managed by Nextstrain. Raw data are stored in a cloud storage solution (currently Amazon Web Services S3) while all epidemiological data and analysis results are stored on ECDC's premises. All software will use the versions currently employed by the standard pipeline. The databases used by the tools listed will be upgraded to their latest version prior to the final analysis.

- Sequence data will be trimmed and quality controlled using fastp [8] and reads will be reduced to 150x theoretical coverage using Rasusa [9].
- Long reads will be assembled using Flye [10] while short-read data will be assembled using SPAdes [11]. If FASTQ files for both short- and long-read technologies are submitted, the long-read sequences will be used for analysis. Genomes fulfilling the following genome size criteria will be further analysed: 4.3-5.9 Mbp for *E. coli* and 4.87-6.5 Mbp for *K. pneumoniae* SC. Depth of coverage, contig N50 and number of contigs will be calculated, but not used as inclusion criteria.
- Species identification for *K. pneumoniae* SC will be performed using the species module integrated into Kleborate. No formal tool will be employed for *E. coli* species identification, but instead passing the ≥90% core genome loci coverage cut-off will indirectly confirm the species as *E. coli*.
- Core-genome multilocus sequence typing (cgMLST) profiles will be determined using ChewBBACA [12] with the Enterobase scheme [13] for *E. coli* and the Ridom scheme [14] for *K. pneumoniae* SC. Genomes with ≥90% core genome loci covered will be further analysed. Genomes with ≥90%, but <95% core genome loci covered will be included with a low coverage warning.
- Genomes outside of the genome size and core genome loci cut-offs will be excluded from further analyses and the respective NRLs will be informed that the isolates have been excluded.
- Full resolution neighbour-joining trees will be calculated based on the cgMLST profiles (pairwise ignore missing values). Single locus polymorphism based phylogenetic analysis will be performed for selected most frequent lineages.

- Clusters based on 10 allelic differences (AD) [15] single-linkage hierarchical clustering will be calculated, including data from previous surveys and previous investigations.
- Five-level hierarchical cluster addresses will be calculated based on single-linkage clustering at 100 AD, 25 AD, 10 AD, 5 AD and 2 AD [16].
- PlasmidFinder [17] will be used to detect and annotate plasmid replicons. For information about the markers included in the database, refer to the [PlasmidFinder database](#).
- For *E. coli*, ResFinder [18] will be used to detect and annotate resistance genes and mutations and VirulenceFinder [19] will be used to detect and annotate virulence markers. FimTyper [20] will be used to assign type 1 fimbriae adhesin *fimH* alleles. For information on the genes included in the databases, refer to the [ResFinder database](#), the [VirulenceFinder database](#), and the [FimTyper database](#). Molecular serotyping to assign O-antigen and H-antigen types will be performed using *E. coli* analysis plugin for BioNumerics v7.6.3 (Applied Maths NV/bioMérieux).
- AMRFinderPlus [21] integration into ECDC genomic pipeline is planned for 2026. After integration and for the final analysis of the CRE25 survey, the tool and its reference database will be used for antimicrobial resistance gene annotation in parallel to the ResFinder database, as well as the CARD database [22], a curated version of which is used by Kleborate. For information on the markers included in the AMRFinderPlus database, refer to the [AMRFinderPlus documentation](#).
- MLST v2 [23] will be used to determine sequence types based on 7-gene MLST scheme by Achtman [24] for *E. coli*.
- For *K. pneumoniae* SC, Kleborate [25] with integrated Kaptive [26] module will be used to detect species, sequence type using Institut Pasteur 7-gene MLST scheme [27], capsule type [28], O-antigen type [29], virulence markers [30,31] and resistance markers [22]. For information on the analyses and markers included in Kleborate, refer to the [Kleborate documentation](#).
- For long-read data, plasmid replicons, resistance genes and virulence genes will be combined into an in-house mobile genetic element analysis, which provides visualisations of annotated genetic elements.
- Descriptive statistical analysis will be performed on the results derived from the WGS data.
- In-depth analysis of specific parts of the dataset using additional tools may be performed, as deemed necessary.

6. Access to raw data and initial results

According to the CRE25 planning survey, about 80% of the WGS data will be generated by NRLs and submitted to EpiPulse Cases. For the WGS data supported by ECDC and conducted by the contractor Eurofins Genomics, raw sequence data will be delivered to participating countries as soon as it has passed quality control performed by the contractor. Eurofins Genomics will provide the NRLs with two types of FASTQ files (unprocessed and trimmed raw reads). Countries will then be required to upload the untrimmed data together with the metadata to EpiPulse Cases. Initial results will be provided through the EpiPulse Molecular Typing Tool (MTT) within the Microreact visualisation [32] as they become available (usually within one working day of data upload). For this initial analysis, WGS data will be accepted with minimal metadata (sampling date and submitting country), as stated in the CRE25 survey protocol.

7. Specific analyses

7.1 Species distribution (*Klebsiella pneumoniae* SC only)

Species distribution within the *K. pneumoniae* SC will be determined and displayed in Example Table 6.

Example Table 6. Species distribution within *Klebsiella pneumoniae* SC

<i>Klebsiella pneumoniae</i> species complex	Isolates n (%)
<i>Klebsiella pneumoniae</i>	
<i>Klebsiella quasipneumoniae</i> subsp. <i>quasipneumoniae</i>	
<i>Klebsiella quasipneumoniae</i> subsp. <i>similipneumoniae</i>	
<i>Klebsiella variicola</i> subsp. <i>variicola</i>	
<i>Klebsiella variicola</i> subsp. <i>tropica</i>	
<i>Klebsiella quasivariicola</i>	
<i>Klebsiella africana</i>	
Total	

7.2 Distribution of sequence types

The total number of sequence types (STs) for *K. pneumoniae* SC and *E. coli* within the CRE25 survey main and voluntary collections will be outlined. When necessary, new STs will be defined through submission to BIGSDB-Pasteur (*K. pneumoniae* SC) and EnteroBase (*E. coli*). A more detailed description of country and Nomenclature of Territorial Units for Statistics level 2 (NUTS-2) distribution will be provided for dominant STs that represent $\geq 5\%$ of the total *K. pneumoniae* SC and *E. coli* STs in the CRE25 survey data set. Sequence types that were dominant for *K. pneumoniae* SC or *E. coli* in the CCRE survey will also be described, even if they are no longer dominant in the CRE25 survey. The geographical distribution and the main carbapenemase genes by ST will be displayed as outlined in Example Table 7. This table will be prepared for *K. pneumoniae* ST and *E. coli* separately. ST distribution by country will be visualised in a stacked bar plot.

Example Table 7. Geographical distribution of dominant STs and major carbapenemase genes of carbapenem-R/I and carbapenemase-suspected isolates of *Klebsiella pneumoniae* SC*

Sequence type	Isolates (n, %)	Carbapenem-R/I isolates [^] (n, %)	Carbapenemase-suspected isolates [§] (n, %)	Countries (n isolates, %)	Countries with > 10% of isolates (n isolates, %)	NUTS-2 (n)	Carbapenemase gene variants found in $\geq 10\%$ of isolates of this ST (n)
ST #1							
ST #2							
etc.							

*The same table will be prepared for *E. coli* isolates.

[^]Isolates collected in CRE25 survey main collection.

[§]Isolates collected in CRE25 survey voluntary collection.

7.3 Distribution of carbapenemase gene variants and other resistance genes

7.3.1 Carbapenemase genes

Outputs from the antimicrobial resistance analysis tools (see Section 5) will be used to describe the main findings. In-depth analyses will focus on the most frequent carbapenemase genes in the dataset and for the following gene families: KPC-like, NDM-like, VIM-like, OXA-48-like and IMP-like. Distribution of carbapenemase gene variants will be displayed in an UpSet plot for *K. pneumoniae* SC and *E. coli* as well as CRE25 main and voluntary collections. Geographic distribution of carbapenemase gene variants by ST will be summarised as outlined in Example Table 8. Separate tables will be provided for *K. pneumoniae* SC and *E. coli*.

Example Table 8. Geographical distribution and major sequence types among the most common carbapenemase gene variants across all *Klebsiella pneumoniae* SC isolates

Carbapenemase gene variant	Isolates	Carbapenem-R/I isolates [*]	Carbapenemase-suspected isolates [§]	STs [†] (all isolates)	STs with $\geq 10\%$ of isolates	Countries (all isolates)	Countries with $\geq 10\%$ of isolates
	n	n (%)	n (%)	n	(n)	n	(n)
<i>bla</i> _{gene variant 1}							
<i>bla</i> _{gene variant 2}							
Relevant combination of variants							
etc.							

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

*Isolates collected in CRE25 survey main collection.

[§]Isolates collected in CRE25 survey voluntary collection.

[†]Isolates with no fully designated ST were excluded from the ST counts.

Country distribution of carbapenemase gene variants will also be presented in a stacked bar plot for *K. pneumoniae* SC and *E. coli* isolates and the CRE25 survey main and voluntary collections.

7.3.2 Other resistance genes

Other beta-lactam resistance genes (ESBL, AmpC genes) will be investigated during the analysis of the AMR tool outputs mentioned in Section 5. Outer membrane porin gene (*ompK35*, *ompK36*) loss or truncation will be described for *K. pneumoniae* SC. Relevant and/or frequent (>5% in the *K. pneumoniae* SC and *E. coli* datasets) genetic determinants for colistin (e.g. *mgrB*, *pmrB*, *mcr*), aminoglycosides (e.g. *armA*, *rmt*, frequent and relevant *aac*, *ant* and *aph* genes), fluoroquinolones (e.g. *gyrA*, *parC*, *parE*, *qnr* genes, *qep* genes), trimethoprim-sulfamethoxazole (e.g. *dhfr* genes, *sul* genes) will also be reported. Combinations of carbapenemase gene variants with other relevant resistance genes will be visualised using UpSet plots for *K. pneumoniae* SC and *E. coli*.

7.4 Distribution of virulence markers (*Klebsiella pneumoniae* only)

Five key virulence loci prevalent in hypervirulent lineages will be reported:

- siderophores:
 - yersiniabactin (*ybt*)
 - aerobactin (*iuc*)
 - salmochelin (*iro*)
- genotoxin colibactin (*clb*)
- hypermucoidy locus *rmpABC*, as well as an alternative hypermucoidy gene *rmpA2*.

Distribution of the five virulence loci identified will be summarised in a table (Example Table 9) and frequency of the loci combinations will be displayed in an UpSet plot.

Example Table 9. Summary of virulence loci identified among *Klebsiella pneumoniae* SC isolates

Virulence locus	Isolates	Carbapenem-R/I isolates*	Carbapenemase-suspected isolates [§]	Major STs with ≥10% of isolates
	n (%)	n (%)	n (%)	(n)
Yersiniabactin				
Aerobactin				
Salmochelin				
Colibactin				
<i>rmpABC</i>				
<i>rmpA2</i>				

*Isolates collected in CRE25 survey main collection. [§]Isolates collected in CRE25 survey voluntary collection.

Bar plots visualising the distribution of virulence scores will be generated and supplemented, with the table (Example Table 10) summarising the findings per CRE25 main and voluntary collection.

Example Table 10. Summary of virulence scores among *Klebsiella pneumoniae* SC isolates

Virulence score	Isolates	Carbapenem-R/I isolates*	Carbapenemase-suspected isolates [§]	Major STs with ≥10% of isolates
	n (%)	n (%)	n (%)	(n)
0				
1				
2				
3				
4				
5				

*Isolates collected in CRE25 survey main collection.

[§]Isolates collected in CRE25 survey voluntary collection.

7.5 Molecular serotyping of surface antigens

Distribution of the most frequent capsular polysaccharide (K-antigen) and outer component of lipopolysaccharide (O-antigen) types in *K. pneumoniae* SC will be visualised in respective bar plots. Similar plots will also be drawn for the most frequent O-polysaccharide (O-antigen) and flagellin (H-antigen) types for the *E. coli* isolates. Furthermore, stacked bar plots will be generated to display the distribution of surface antigen types within high-risk lineages of *K. pneumoniae* and *E. coli*.

7.6 Plasmid replicons

The most frequent plasmid replicons will be reported. The distribution of the most frequent carbapenemase gene variants and plasmid replicons will be summarised in tables (Example Table 11) for *K. pneumoniae* SC and *E. coli*.

Example Table 11. Proportion of *Klebsiella pneumoniae* SC genomes with and without particular carbapenemase gene variant carrying individual plasmid replicons

Plasmid replicon	No. of isolates	Carbapenemase gene							
		<i>bla</i> _{gene variant 1}		<i>bla</i> _{gene variant 2}		<i>bla</i> _{gene variant 3}		<i>bla</i> _{gene variant 4}	
		Yes	No	Yes	No	Yes	No	Yes	No
Inc #1									
Inc #2									
Inc #3									
etc.									

7.7 Development over time

Comparison of STs, carbapenemase and virulence genes with previous surveys (CCRE survey, EuSCAPE) will be performed for carbapenem-R/I isolates by NUTS-2 unit as the CRE25 survey no longer collects hospital-based data. For this purpose, the NUTS-2 units recorded for EuSCAPE and the CCRE survey have been compared and harmonised with the latest 2024 NUTS-2 classification [33]. The frequency of relevant high-risk lineages in the datasets, including carbapenem-R/I isolates of the three surveys, will be prepared and displayed in the bar plot and a table, such as Example Table 12.

Example Table 12. Carbapenem R/I *Klebsiella pneumoniae* SC high-risk lineages over time

High-risk lineage	EuSCAPE (2013-2014)		CCRE survey (2019)		CRE25 survey (2025)	
	Isolates, n (%)	Change, confidence interval	Isolates, n (%)	Change, confidence interval	Isolates, n (%)	Change, confidence interval
Lineage #1		Reference				
Lineage #2		Reference				
Lineage #3		Reference				
etc.		Reference				

Similar tables and bar plots will be produced to depict the change of relevant carbapenemase gene variants and virulence loci over time for *K. pneumoniae* SC and *E. coli*.

7.8 Cluster analysis

Isolates with genetic relatedness of 10 AD (default threshold) using single linkage algorithm will be considered as forming a cluster. Such clusters will be described in a tabular format (Example Table 13) compiled for *K. pneumoniae* SC and *E. coli*. Genomes close to the cut-off will be inspected to validate the clusters.

Example Table 13. Summary of *Klebsiella pneumoniae* clusters

Cluster	Sequence type	Carbapenemase gene(s)	No. of CRE25 isolates	No. of non-CRE25 isolates	No. of CRE25 countries	No. of involved NUTS-2 regions	Virulence score
Cluster #1							
Cluster #2							
Cluster #3							
etc.							

8. Visualisation in molecular typing tool

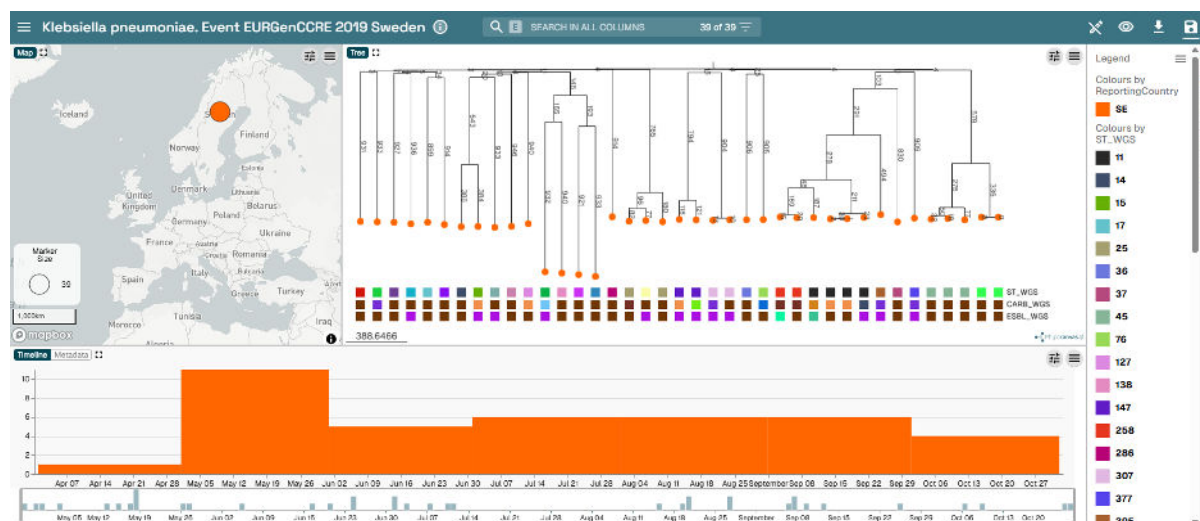
The interactive overview of the CRE25 survey dataset for *K. pneumoniae* SC and *E. coli* will generally be available in the molecular typing tool (MTT) on the following working day after data submission. The MTT can be accessed by following these steps:

- Log in to the [EpiPulse platform](#) with ECDC credentials available for the nominated operational contact points
- Navigate to the **Molecular Typing** tab at the top of the EpiPulse landing page
- Select the pathogen of interest in the **Pathogen** drop down menu:
 - *Klebsiella pneumoniae* or
 - *E. coli/Shigella*
- Fill out fields in the **Search & Refine Selection** menu:
 - **Events** field: 2025-ARH-00006
 - **Countries** field: choose the country
- Clicking on **Search** button to open the visualisation in Microreact.

The generated visualisation (Example Figure 2) will be divided into sections containing:

- Map
- Dendrogram
- Timeline/Metadata
- Legend.

Example Figure 2. Interactive view of the CCRE survey *Klebsiella pneumoniae* isolates from Sweden



9. Reporting and publication of data and results

9.1 Interim reports

Interim reports will be generated based on predefined thresholds and shared with EURGen-Net operational contact points (OCPs) via the EpiPulse event 2025-ARH-00006. All isolates submitted will be included in the interim analysis, regardless of metadata completeness at the time of the interim analysis. At the EURGen-Net network meeting 2025, national contact points preferred an interim analysis based on isolate thresholds over analysis at predetermined points in time (32 votes, 44% of votes for interim analysis based on isolate thresholds, 31% for interim analysis based on predetermined points in time, 25% not sure). While flexibility will still be required based on initial findings, the following interim analysis thresholds are proposed, based on WGS data received:

- WGS data received for the initial 250 isolates followed by interim analysis for
- any further addition of 250 isolates or data from at least two countries.

A total of 22 (79%) of the 28 national contact points voting on the respective questions at the EURGen-Net meeting 2025 expressed an interest in participating in teleconferences to discuss interim results. These teleconferences will be scheduled as soon as results of the interim reports based on the above thresholds become available, up to a maximum of one teleconference per month. An example of the automated analysis presented in the interim report (using CCRE survey results as example) is displayed in the Annex.

9.2 Final report

Preparation of the final report will start as soon as all participating countries have confirmed that no further WGS data or isolates for central WGS are to be expected. At the EURGen-Net meeting 2025 a strong majority 81% of votes of 31 national contact points were in favour of a 'research-quality' manuscript as a final output, rather than just an ECDC final report. A requirement for a final manuscript will be the release of the national WGS data submitted for the CRE25 survey into the public domain. ECDC will confirm with EURGen-Net OCPs at the start of the preparations for the final report whether there are any objections to uploading the national WGS data into the public domain. Unless the respective NRL prefers to upload the data themselves, ECDC will upload raw sequence data and minimum metadata (country, year, type of sample) to the European Nucleotide Archive. WGS data generated from ECDC central sequencing support will be released into the public domain with the same metadata by default.

A final ECDC report will be prepared first, including detailed results of the analysis above. The most relevant results will then be selected for additional presentation in a manuscript, or potentially two manuscripts with separate analysis for the two species, similar to the CCRE survey reporting. The main responsibility for preparation of the draft final report lies with ECDC. Authorship will be allocated according to the ECDC authorship policy. EURGen-Net OCPs will be welcome to join a writing group for the manuscript (maximum one writing group member per country and ten in total on a first-come, first-served basis). All writing group authors will be offered authorship for the manuscript. All other EURGen OCPs of countries that have contributed isolates will receive the report and manuscript for validation and authorisation and will be offered the possibility of being part of a group authorship, up to a maximum of two group authors by country.

10. Trigger of further EURGen-Net investigations

The findings below will result in consultation with participating countries and further analysis, potentially involving national WGS data:

- newly detected cross-border clusters of *K. pneumoniae* or *E. coli* isolates;
- newly dominant ST (>5% of STs of carbapenem-R/I *K. pneumoniae* or *E. coli* isolates) compared to the CCRE survey. This means any ST other than ST11, ST15, ST101, ST147, ST258/512 and ST307 for *K. pneumoniae* and ST131, ST167, ST38, ST410 and ST648 for *E. coli* which were the dominant STs in the CCRE survey;
- expanding clades in the phylogenetic analysis;
- increase in carbapenemase variant or other resistance mechanisms of concern among carbapenem-R/I *K. pneumoniae* or carbapenem-R/I *E. coli* isolates compared to the CCRE survey;
- increase in specific virulence markers (yersiniabactin or colibactin or aerobactin) as determined by Kleborate among dominant STs or in potentially hypervirulent isolates, as indicated by a Kleborate virulence score of 5 or of *K. pneumoniae* STs known to be associated with hypervirulence in carbapenem-R/I *K. pneumoniae* compared to the CCRE survey.

11. Triggering of ECDC country consultations

The Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach invites Member States to take appropriate national measures to ensure that, by 2030, the total incidence of bloodstream infections (BSIs) with carbapenem-resistant *K. pneumoniae* is reduced by 5% in the EU, compared to 2019 (baseline year) [34]. However, the data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) showed an increase in the estimated incidence of BSIs of carbapenem-resistant *K. pneumoniae* for the EU/EEA from 2.52 in 2019 to 3.97 per 100 000 population between 2019 and 2023, which corresponds to an increase of 57.5%, running contrary to the goal stipulated in the Council Recommendation. One important reason for this increase is the continued transmission of high-risk lineages of carbapenem-resistant *K. pneumoniae* in European hospitals, as shown in the CCRE survey and other EURGen-Net investigations [3,35].

Clustering of *K. pneumoniae* isolates within the same or between different NUTS-2 regions can be used as a proxy of potential transmission within healthcare facilities, indicating the need for enhanced control. To promote and enable control, ECDC therefore intends to inform national public health authorities of any national *K. pneumoniae* clusters within the same NUTS-2 or in different NUTS-2 regions within the country detected in the CRE25 survey. For this purpose, a threshold of AD ≤ 5 will be used to determine a very likely recent transmission event and a threshold of ≤ 10 to determine a likely recent transmission event. A respective report with a list of transmission events will be shared with the EURGen-Net OCPs of every country for validation and agreement. Once agreed, the report will be sent to the NFPs for AMR and Healthcare-Associated Infections of the respective country, together with an offer for further consultation and support. It will be possible to opt out of this procedure if the EURGen-Net OCPs do not consider it useful for promoting control of CRE in their respective countries.

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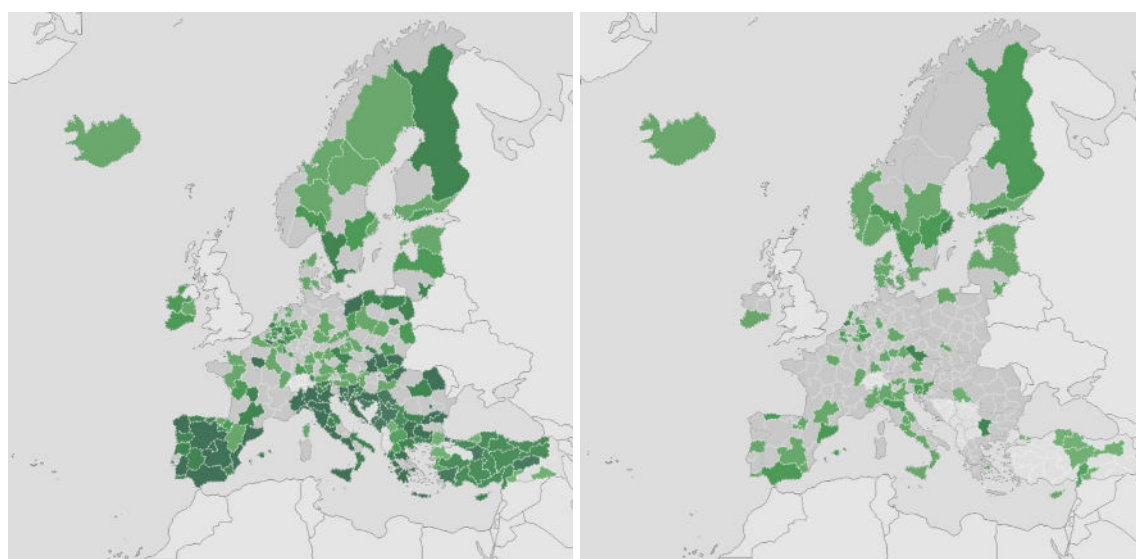
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Annex. Template for interim report

Data from the carbapenem-R/I dataset of the CCRE survey has been used to generate the example tables displayed in this annex. For the CRE25 survey, this interim report will be generated repeatedly throughout the survey once the predefined isolate thresholds are reached. Where relevant, separate tables and figures for the main and voluntary collections will be produced for the interim report.

Table 1. Overview of carbapenem R/I *Klebsiella pneumoniae* SC and carbapenem R/I *Escherichia coli* isolates submitted to the CCRE survey by country

Country	No <i>K. pneumoniae</i> isolates submitted	No <i>E. coli</i> isolates submitted
Austria	19	5
Belgium	51	10
Bosnia and Herzegovina	10	0
Bulgaria	84	7
Croatia	59	0
Cyprus	8	1
Czechia	27	10
Denmark	3	6
Estonia	2	2
Finland	11	10
France	40	7
Germany	33	14
Greece	128	2
Hungary	40	1
Iceland	1	1
Ireland	8	1
Italy	278	17
Kosovo	1	0
Latvia	3	1
Lithuania	8	2
Luxembourg	3	3
Malta	9	0
Montenegro	10	0
Netherlands	23	10
Norway	7	5
Poland	55	2
Portugal	52	3
Republic of North Macedonia	3	0
Romania	66	0
Serbia	69	1
Slovakia	30	0
Slovenia	24	7
Spain	176	16
Sweden	20	16
Turkey	138	12
United Kingdom	67	39
Total	1566	211

Figure 1. Carbapenem R/I isolates submitted to the CCRE survey by geographical region (NUTS-2)*Klebsiella pneumoniae* SC*Escherichia coli***Table 2. Carbapenem R/I *Klebsiella pneumoniae* SC isolates submitted to the CCRE survey**

Species	No isolates submitted
<i>Klebsiella pneumoniae</i>	1473
<i>Klebsiella quasipneumoniae</i> subsp. <i>quasipneumoniae</i>	4
<i>Klebsiella quasipneumoniae</i> subsp. <i>similipneumoniae</i>	8
<i>Klebsiella variicola</i> subsp. <i>variicola</i>	9
unknown	72
Total	1566

Table 3. Overview of carbapenem R/I *Klebsiella pneumoniae* SC and carbapenem R/I *Escherichia coli* isolates submitted to the CCRE survey by specimen type

Specimen	No <i>K. pneumoniae</i> isolates submitted	No <i>E. coli</i> isolates submitted
Not reported	30	17
Aspirates	41	5
Blood	270	15
Bone and joint specimens	8	0
Catheter exit site	35	4
Cerebrospinal fluid	1	0
Lower respiratory tract specimens	200	6
Other	195	73
Reproductive tract samples	1	1
Soft tissue samples	36	2
Urine	646	71
Wound swabs	103	17
Total	1566	211

Table 5. Overview of most common sequence types for carbapenem R/I *Escherichia coli* isolates submitted for the CCRE survey, and the country and NUTS-2 region of origin

Sequence Type	No <i>E. coli</i> isolates submitted	Country codes	NUTS2 regions
131	27	AT, BE, CY, CZ, EL, ES, FR, IT, PL, PT, RS, SI, UK	AT21, BE33, CY00, CZ01, CZ03, EL30, ES62, FR10, ITC1, ITF3, ITF6, ITG1, ITH1, ITH3, ITI2, ITI3, PL63, PT15, RS12, SI03
410	20	CZ, DE, DK, EL, ES, IT, SE, SI, TR, UK	CZ01, DE13, DE25, DEA1, DK02, DK04, EL30, ES51, ITH5, SE12, SE23, SI04, TR63, TR72, TRC1
38	19	AT, BE, DE, ES, FI, FR, LU, LV, NO, SE, SI, TR, UK	AT13, BE23, DE25, DEA2, ES22, FI18, FRJ2, LU00, LV00, NO08, SE12, SE22, SI04, TRA1
167	16	BG, CZ, DE, FR, IT, NL, NO, SE, UK	BG41, CZ08, DE11, DEG0, FRY4, ITF3, NL22, NL32, NL36, NO09, NO0A, SE11
648	14	DE, DK, ES, NL, SE, TR, UK	DEA1, DEA4, DK03, ESS3, NL42, SE11, SE22, SE23, SE31, TR63, TR82
405	8	IS, IT, NL, SE, UK	IS00, IT4, NL36, SE11
361	8	FI, IE, LU, NO, TR, UK	FI18, FI1C, IE05, LU00, NO08, TRA1
224	5	AT, ES, SI, UK	AT13, ES42, SI04
1284	4	FR, NO, UK	FRY4, NO08
88	4	BE, ES, SI	BE24, ES61, SI04
46	3	LT, SE, UK	LTD1, SE23
10	3	BE, FI, TR	BE32, FI18, TR83
155	3	FR, IT, UK	FRY4, ITH5
349	3	AT, ES, HU	AT31, ES12, HU11
354	3	BG, EE, ES	BG41, EE00, ES61
Other	71		
Total	211		

Figure 4. Distribution of carbapenem R/I *Klebsiella pneumoniae* SC isolates submitted for the CCRE survey by sequence type

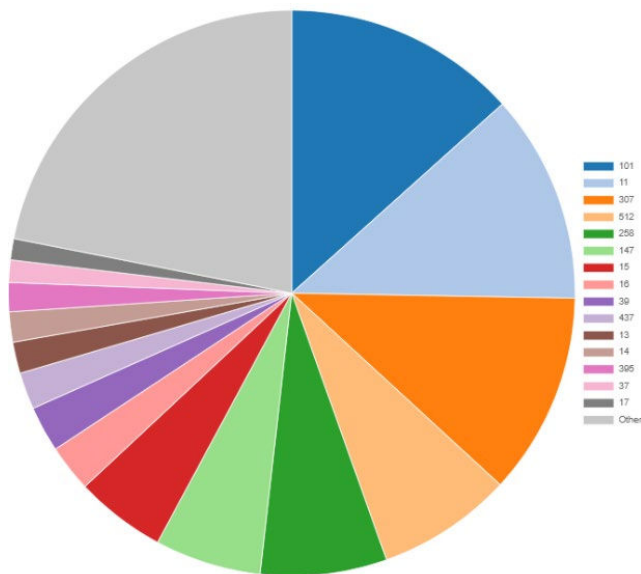


Figure 5. Distribution of carbapenem R/I *Escherichia coli* isolates submitted for the CCRE survey by sequence type

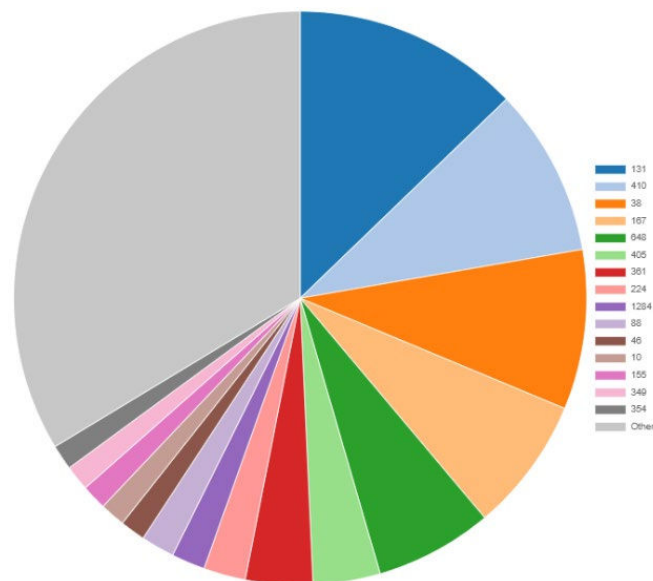
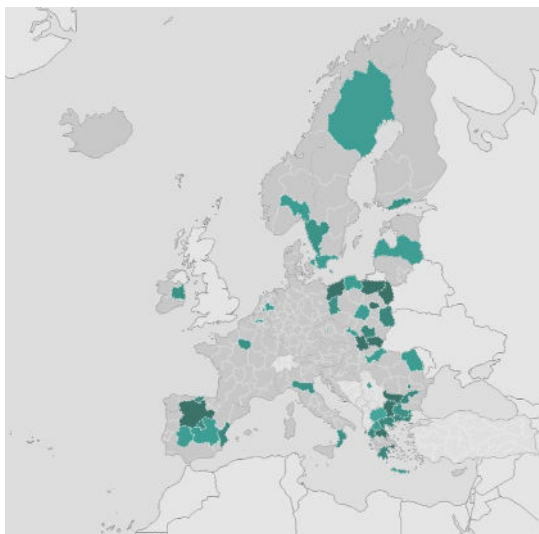
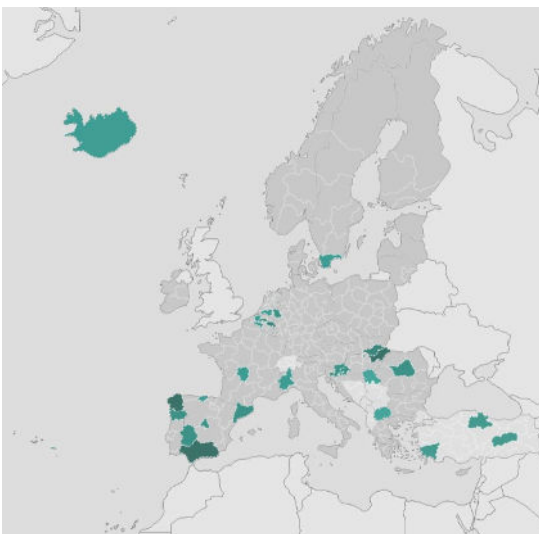


Figure 6. Geographical distribution of the dominant sequence types for the carbapenem R/I *Klebsiella pneumoniae* SC isolates of the CCRE survey by NUTS-2 regions

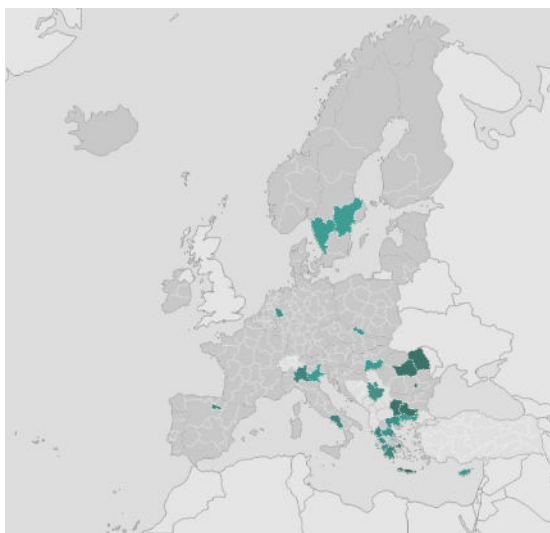
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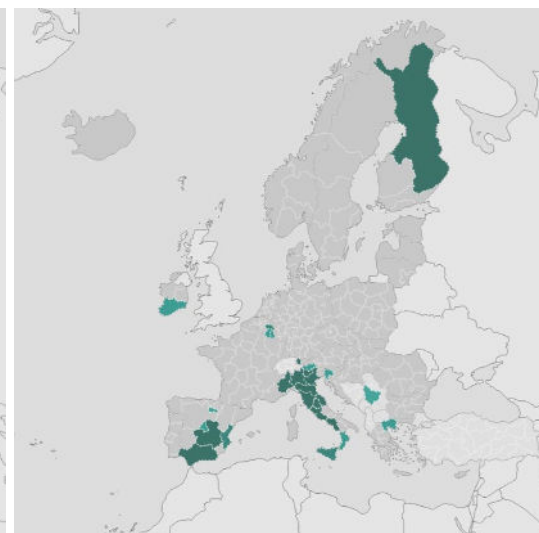
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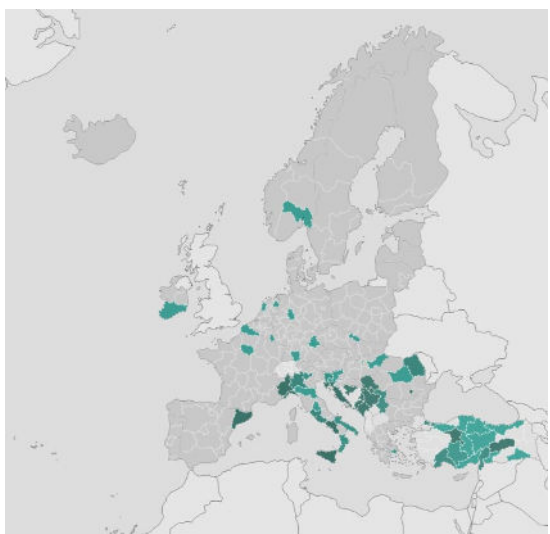
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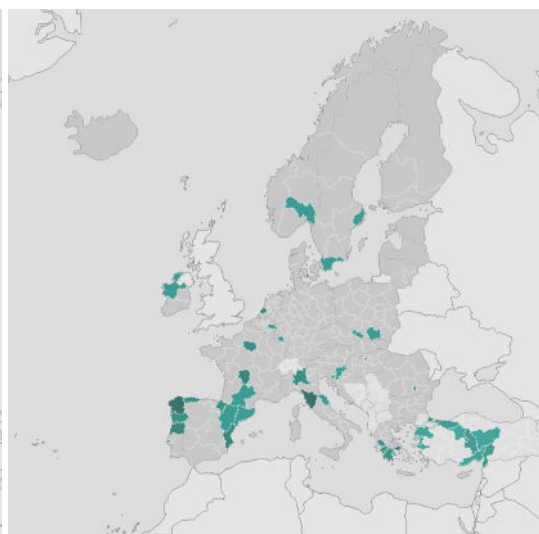
ST512



ST101



ST147



ST307

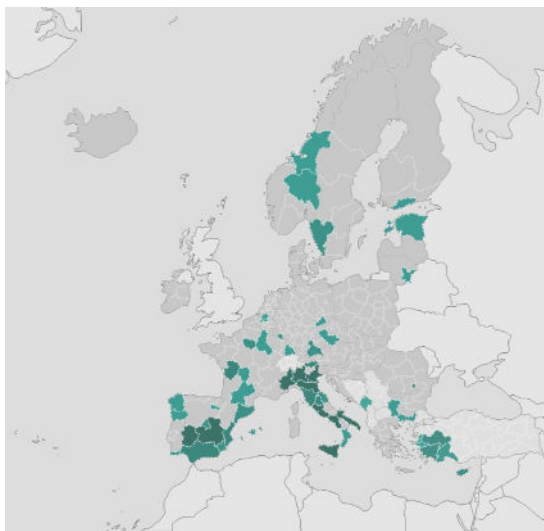
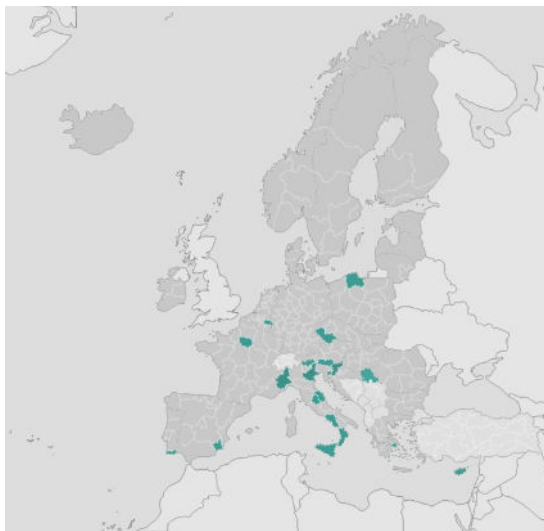
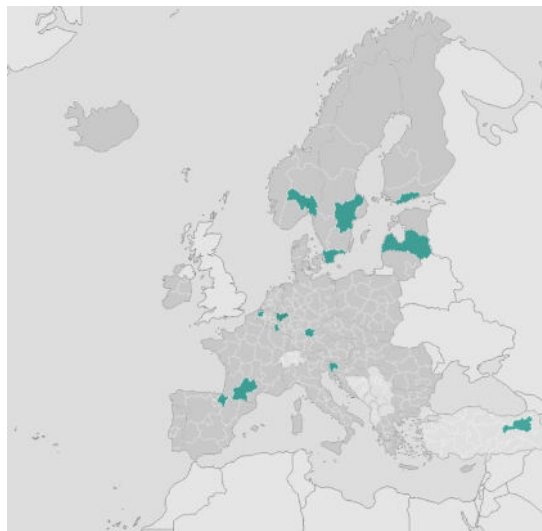


Figure 7. Geographical distribution of the dominant sequence types for carbapenem R/I *Escherichia coli* isolates from the CCRE survey by NUTS-2 regions

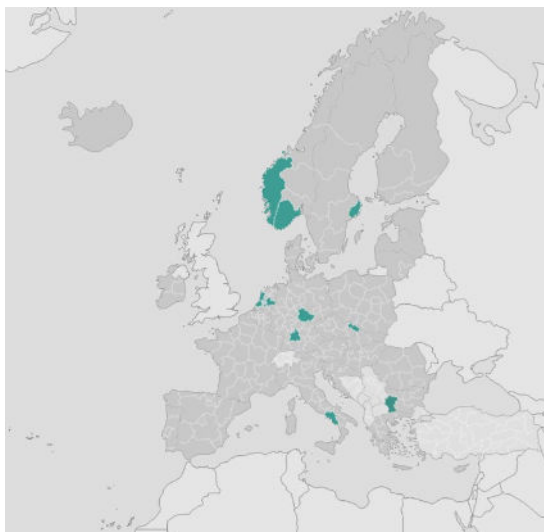
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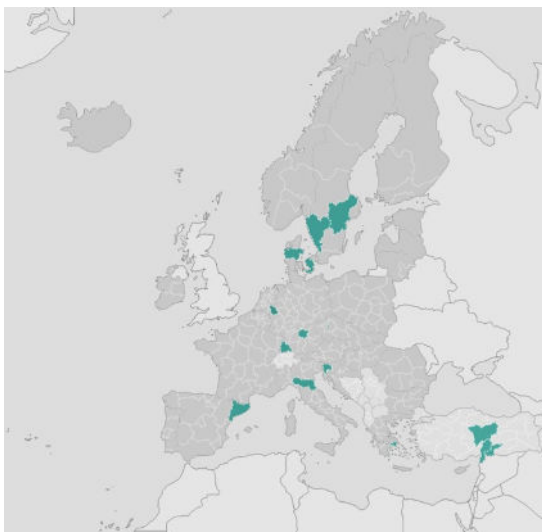
ST38



ST167



ST410



ST648

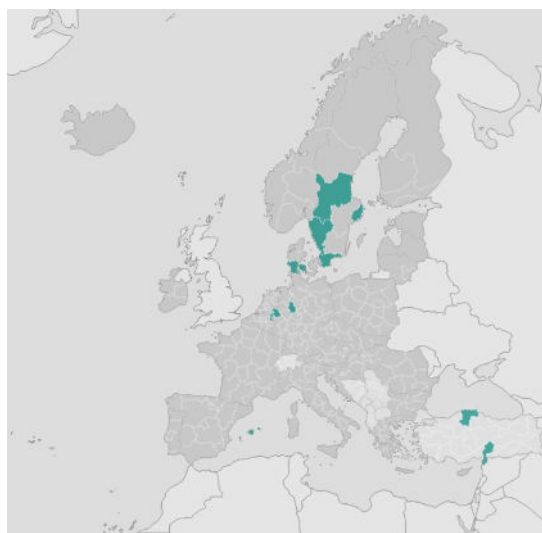


Table 6. Overview of carbapenemase gene variants for carbapenem R/I *Klebsiella pneumoniae* SC and carbapenem R/I *Escherichia coli* isolates submitted to the CCRE survey

Carbapenemase	No <i>K. pneumoniae</i> isolates submitted	No <i>E. coli</i> isolates submitted
blaOXA-48	405	40
blaKPC-3	347	14
blaKPC-2	245	7
blaNDM-1	228	14
-	171	29
blaVIM-1	34	7
blaNDM-1;blaOXA-48	27	0
blaOXA-232	19	3
blaOXA-181	19	11
blaVIM-4	16	0
blaNDM-5	9	59
blaOXA-244	5	12
blaKPC-2;blaVIM-1	5	0
blaNDM-4	4	7
blaOXA-245	4	0
blaNDM-7	3	1
blaNDM-1;blaOXA-232	3	1
blaNDM-1;blaOXA-181	2	0
blaKPC-2;blaNDM-1	2	0
blaNDM-5;blaOXA-181	2	1
blaNDM-5;blaOXA-232	2	0
blaNDM-5;blaOXA-48	2	0
blaOXA-162	1	2
blaOXA-48;blaVIM-1	1	0
blaVIM-19	1	0
blaKPC-3;blaOXA-181	1	0
blaKPC-3;blaOXA-48	1	0
blaKPC-34	1	0
blaKPC-58	1	0
blaKPC-99	1	0
blaIMP-4	1	0
blaKPC-23	1	0
blaNDM-1;blaVIM-19	1	0
blaNDM-20	1	0
blaNDM-5;blaOXA-244	0	2
blaNDM-1;blaVIM-1	0	1
Total	1566	211

- no carbapenemase gene detected

Figure 8. Distribution of carbapenemase gene variants for carbapenem R/I *Klebsiella pneumoniae* SC isolates submitted to the CCRE survey

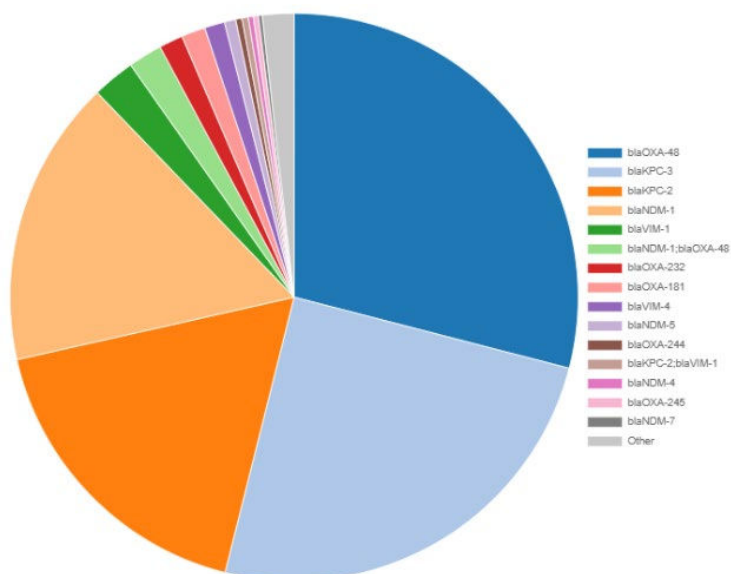


Figure 9. Distribution of carbapenemase gene variants for carbapenem R/I *Escherichia coli* isolates submitted to the CCRE survey by carbapenemase gene variant

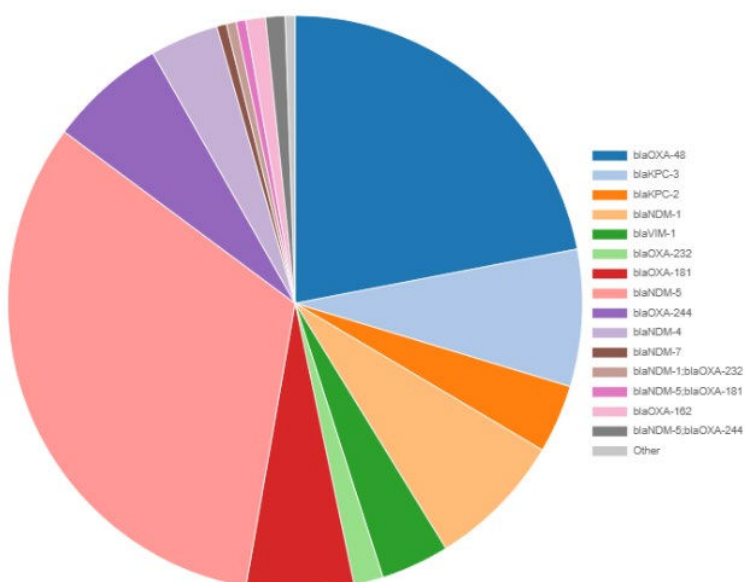


Table 7. Overview of virulence scores for carbapenem R/I *Klebsiella pneumoniae* SC isolates submitted to the CCRE survey

Virulence score	No isolates submitted
0	529
1	929
2	38
3	12
4	51
5	7
Total	1566

Table 8. Carbapenem R/I *Klebsiella pneumoniae* SC isolates submitted to the CCRE survey with Kleborate virulence score 5

key	Sequence type	Carbapenemase(s)	Country	NUTS2 code
SEQ-44A9B380-74B1-5408-9A8F-9FE2FA74A596	147	KPC-3	Turkey	TR31
SEQ-80157790-25CF-5362-BF61-F9999DC850B1	23	-	Germany	DEA4
SEQ-0FC869D9-7BFE-5792-A5DB-62E353116707	23	OXA-48	Croatia	HR05
SEQ-CF15DA65-67D6-596D-971B-EAC9C45590F2	23	OXA-48	Croatia	HR05
SEQ-8DA67CC1-AC38-5B85-A2D1-58F40AA0CCF8	380	OXA-48	Belgium	BE35
SEQ-B1230104-D041-5867-8AB8-0530024BAE76	65	-	Bulgaria	BG41
SEQ-C85AF011-6033-5EA7-93A4-B2A04B6220A6	65	KPC-3	Cyprus	CY00

Table 9. Overview of CCRE survey carbapenem R/I *Klebsiella pneumoniae* SC isolate clusters (10 AD)

Cluster	Sequence type	Carbapenemases	Isolates in study	Isolates not in study	Countries in study	Countries not in study
2025-01KLEB.26.ST101	ST101	KPC-2, KPC-3, KPC-58	52	20	Croatia, Czechia, Germany, Italy, Norway	Croatia, Italy, Republic of Moldova
2025-01KLEB.139.ST512	ST512	KPC-3, none	31	98	Belgium, Finland, Ireland, Italy, Luxembourg	Austria, Belgium, Ireland, Italy, Netherlands
2025-01KLEB.43.ST11	ST11	NDM-1	31	20	Greece, Norway, Poland	Greece, Netherlands, Poland, United Kingdom
2025-01KLEB.08.ST39	ST39	KPC-2, KPC-2+NDM-1, KPC-2+VIM-1, KPC-44, VIM-1, none	23	15	Bulgaria, Cyprus, Greece, Norway	Finland, Greece, Netherlands, Sweden
2025-01KLEB.84.ST11	ST11	OXA-48, VIM-1, none	23	0	Spain	
2025-01KLEB.113.ST13	ST13	KPC-3	19	2	Luxembourg, Portugal, United Kingdom	Netherlands
2025-01KLEB.28.ST258	ST258	KPC-2, none	17	1	Bulgaria, Greece	Netherlands
2025-01KLEB.35.ST258	ST258	KPC-2	17	11	Bulgaria, Greece, Serbia	Greece, United Kingdom
2025-01KLEB.81.ST512	ST512	KPC-3	16	1	Spain	
2025-01KLEB.372.ST258	ST258	KPC-2, KPC-99, NDM-1	14	0	Romania	
2025-01KLEB.141.ST101	ST101	OXA-48, none	13	0	Romania	
2025-01KLEB.15.ST147	ST147	KPC-3, NDM-1, NDM-1+OXA-48, NDM-9, OXA-48, none	13	62	Italy, Malta	Denmark, Italy, Malta, Netherlands, Sweden
2025-01KLEB.86.ST2096	ST2096	NDM-1+OXA-232+OXA-48, OXA-232, OXA-48, none	13	22	Turkey	Netherlands, Saudi Arabia, Tunisia, Turkey
2025-01KLEB.235.ST101	ST101	OXA-48, none	12	3	Serbia	Netherlands
2025-01KLEB.254.ST307	ST307	KPC-2, KPC-3, none	12	10	Italy	Italy, Netherlands
2025-01KLEB.04.ST11	ST11	KPC-3+NDM-1, NDM-1	11	2	Bulgaria, Denmark, Finland, Greece	Greece
2025-01KLEB.138.ST101	ST101	OXA-48	11	3	Croatia, Luxembourg, Slovenia	Sweden
2025-01KLEB.17.ST584	ST584	KPC-2	10	0	Slovakia	
2025-01KLEB.62.ST11	ST11	NDM-1	10	0	Bulgaria	
2025-01KLEB.83.ST147	ST147	NDM-1, NDM-1+OXA-48	10	2	Hungary, Turkey	Netherlands
2025-01KLEB.99.ST11	ST11	NDM-1	10	0	Slovakia	

Table 10. Overview of CCRE survey carbapenem R/I *Escherichia coli* isolate clusters (10 AD)

Cluster	Sequence type	Carbapenemases	Isolates in study	Isolates not in study	Countries in study	Countries not in study
2023-06FCO1.107.ST38	ST38	blaOXA-244	8	154	Belgium, Finland, Germany, Latvia, Luxembourg, Turkey, United Kingdom	Austria, Denmark, Finland, France, Germany, Ireland, Luxembourg, Netherlands, Norway, Sweden, United Kingdom
2022-07.FCO1.025.ST646	ST646	blaOXA-232, blaNDM-5	5	37	Denmark, Sweden, United Kingdom	Australia, Denmark, Finland, France, Germany, India, Ireland, Kenya, Sweden, United Kingdom, United States of America
2022-07.FCO1.045.ST187	ST187	blaOXA-48, blaNDM-1, blaNDM-5	4	112	France, Netherlands, Norway, United Kingdom	Australia, Canada, Denmark, France, Ireland, Netherlands, Norway, Pakistan, Spain, Switzerland, United States of America
2022-07.FCO1.195.ST430	ST430	blaOXA-181, blaNDM-5	3	45	Denmark, Germany, United Kingdom	Australia, China, Denmark, Egypt, France, India, Italy, Myanmar, Netherlands, Norway, Qatar, Republic of Korea, Singapore, Switzerland, United Kingdom, United States of America
2022-06.FCO1.191.ST1284	ST1284	blaNDM-5	3	7	France, United Kingdom	Australia, France, Germany, Ireland
2022-07.FCO1.145.ST187	ST187	blaNDM-21, blaNDM-5	2	107	Germany, Italy	China, France, Germany, Ireland, Italy, Netherlands, Portugal, Qatar, United Kingdom, United States of America
2022-07.FCO1.136.ST485	ST485	blaNDM-5	2	34	Iceland, Sweden	Australia, China, Denmark, Finland, France, India, Lebanon, Netherlands, Pakistan, Qatar, United Kingdom, United States of America
2022-07.FCO1.63.ST10643	ST10643	blaOXA-244, blaNDM-5	2	4	Denmark, Netherlands	Denmark, Ireland, Netherlands, Qatar