

OPERATIONAL SUPPORT

Protocol for the carbapenem-resistant *Enterobacter cloacae* complex (CRECC) pilot survey

1 Introduction

Carbapenem-resistant Enterobacterales (CRE) pose a significant threat to patients and healthcare systems in European Union/European Economic Area (EU/EEA) countries as outlined in the third update of ECDC's rapid risk assessment on carbapenem-resistant Enterobacterales [1]. Since the survey of carbapenem- and/or colistin-resistant Enterobacterales (CCRE survey) conducted in 2019, the following developments show that the epidemiological situation in the EU/EEA continues to deteriorate:

- an increase in the incidence of carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections;
- convergence of virulence and resistance in *K. pneumoniae*;
- newly emerging Enterobacterales species carrying carbapenemase genes;
- plasmid-mediated spread of carbapenemase genes;
- increasing detection of isolates of high-risk lineages of *Escherichia coli* carrying carbapenemase genes with a risk of community spread [1].

Previous European genomic surveys of CRE, including EuSCAPE, the CCRE survey 2019, and the CRE25 survey have focused on carbapenem-resistant *K. pneumoniae* species complex (SC) and carbapenem-resistant *E. coli* as the most frequent CRE. However, carbapenem-resistant *Enterobacter cloacae* complex (CRECC) has also emerged globally and is associated with various carbapenemases. Potential high-risk CRECC clones carrying carbapenemase genes have been described [2], and several European countries have experienced increasing numbers of cases, outbreaks and dissemination of carbapenemase-producing *E. cloacae* complex (ECC) [3-7]. A recent investigation from the European Antimicrobial Resistance Genes Surveillance Network (EURGen-Net) traced a cross-border outbreak of *E. hormaechei* ST1344 carrying *bla*_{NDM-5} [8].

At the EURGen-Net network meeting in 2025, participants selected CRECC as the most relevant CRE for a pilot study on expanding European-level genomic surveillance of CRE. This document is intended as a protocol for such a EURGen-Net CRECC pilot survey in 2027.

1.1 Objectives of the CRECC pilot survey

The primary EU-level public health objective of the CRECC pilot survey is to determine the occurrence, geographical distribution and population dynamics of high-risk CRECC lineages, and related transmissible genetic elements of public health importance, within healthcare settings in Europe to improve risk assessment and control policies. A secondary objective is to support participating countries in developing the technical capability and proficiency for genomic-based surveillance and for conducting risk assessments of multidrug-resistant pathogens with epidemic potential.

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2 Protocol changes compared to the CRE25 survey

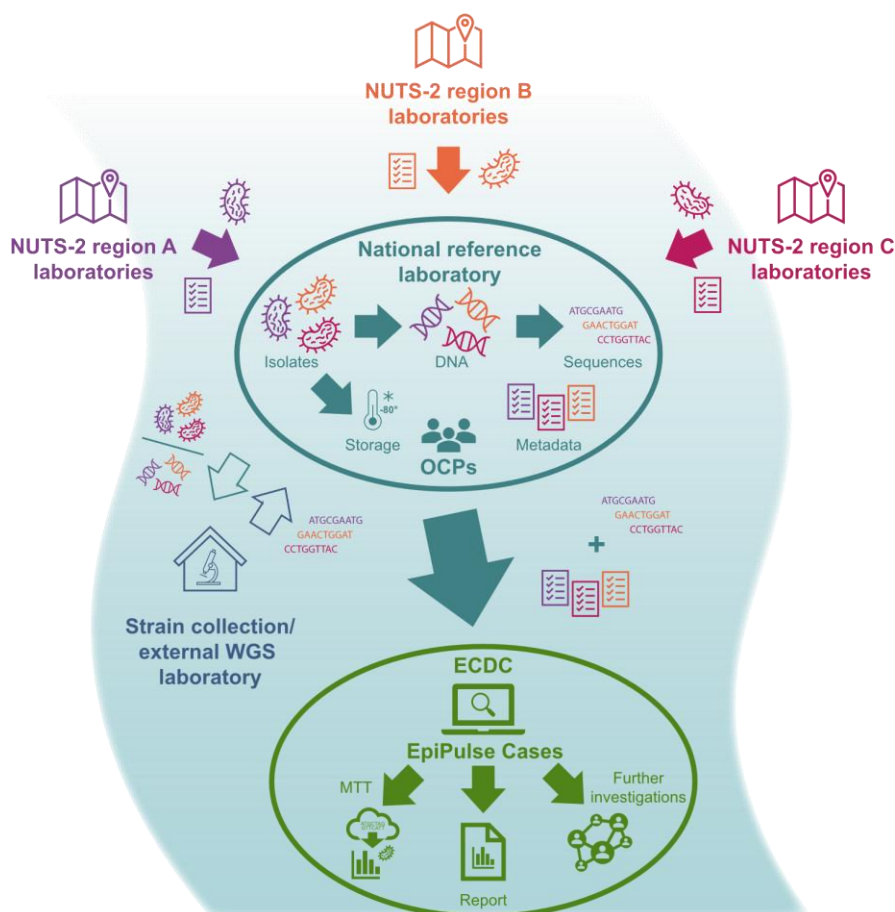
The CRECC pilot survey is based on the model of the CRE25 survey [9,10]. Modifications of the CRE25 survey protocol have been made related to the target bacterial species (*E. cloacae* complex instead of *K. pneumoniae* SC and *E. coli*), the number of isolates to be collected per nomenclature of territorial units for statistics (NUTS) level 2 region (five instead of ten isolates per NUTS-2 region), and the inclusion criteria based on carbapenem antimicrobial susceptibility testing (AST) due to an expected change in the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for carbapenems. Otherwise, the sampling design, definitions, the inclusion process and the metadata collection remain the same as outlined below.

3 Survey protocol

3.1 Survey and surveillance design

The proposed surveillance design is a European multi-country molecular epidemiological pilot survey of the distribution of CRECC by genotype among patients seeking medical care. Isolates and data will be collected by NUTS-2 region and processed by National Reference Laboratories (NRLs) (Figure 1). Resulting whole genome sequencing (WGS), and epidemiological and microbiological metadata will be submitted to ECDC, while isolates remain in storage at the NRLs. Central support to WGS and isolate storage will be available to NRLs if required. The outcome will determine if CRECC will be included in future European genomic CRE surveillance and if so, at which frequency and sample size. This will be discussed with the EURGen-Net Operational Contact Points (OCPs) once CRECC pilot survey results are available.

Figure 1. Isolate and data collection and analysis workflow the CRECC pilot survey 2027



MTT: molecular typing tool; NUTS-2: nomenclature of territorial units for statistics level 2; OCP: Operational Contact Point; WGS: whole genome sequencing.

3.2 Inclusion criteria

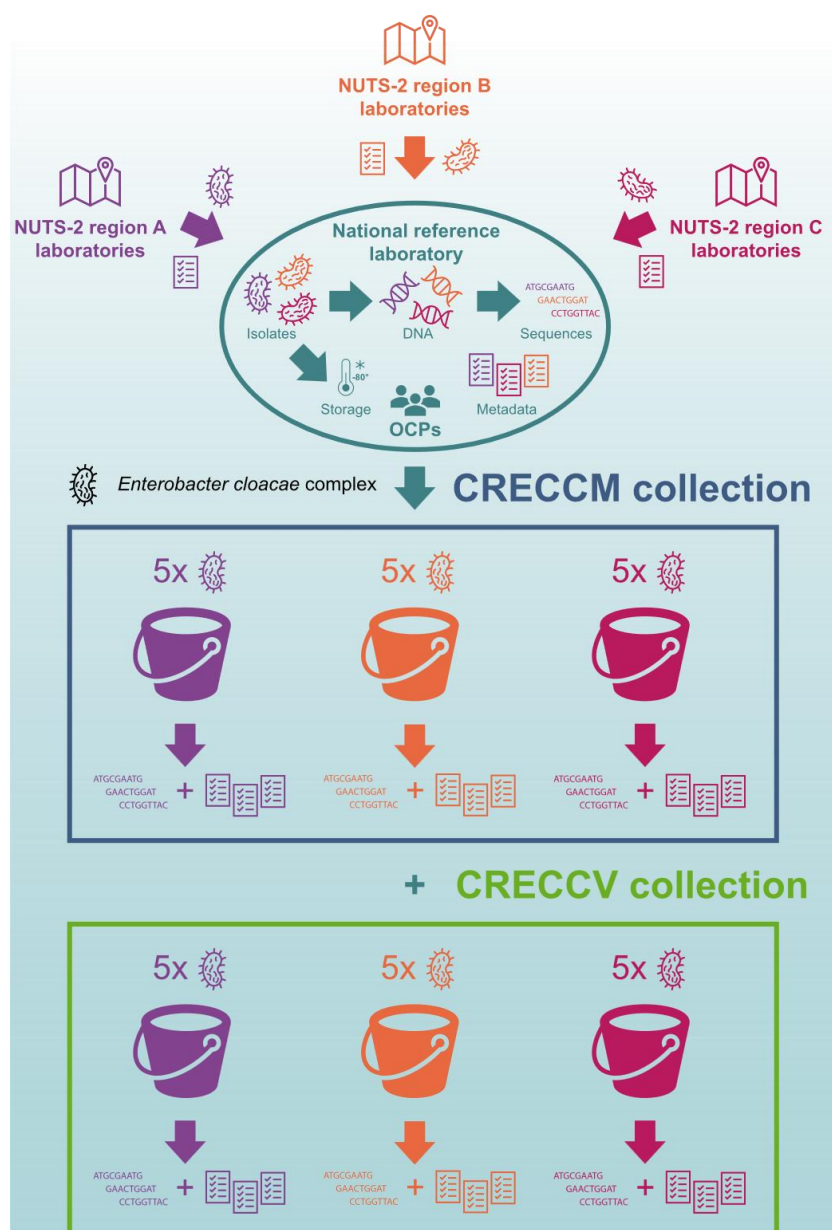
3.2.1 National reference/expert laboratory

National isolate and data collection for the CRECC pilot survey will be coordinated by the NRLs and OCPs participating in EURGen-Net. Designation of additional National Technical Coordinators is not required. The OCPs will be responsible for managing the national workflow and supervising national sample and data collection.

3.2.2 Hospitals and regional laboratories

Isolates of ECC (see section 3.2.4 for list of species) routinely arriving at the NRLs for reference testing during the collection period will be included into two collections – a main collection based on EUCAST clinical breakpoints and a voluntary collection based on EUCAST screening breakpoints (case definitions section 3.2.5 and 3.2.6). A maximum of five isolates fulfilling the inclusion criteria by NUTS-2 region can be included in each collection (Figure 2).

Figure 2. Isolate recruitment workflow using the nomenclature of territorial units for statistics level 2 (NUTS-2)



CRECCM: main collection of the carbapenem-resistant *Enterobacter cloacae* complex (CRECC) pilot survey; CRECCV: voluntary collection of the CRECC pilot survey; NUTS-2: nomenclature of territorial units for statistics level 2; OCP: Operational Contact Point.

The isolates can originate from all types of healthcare facilities including acute care, specialised hospitals and community healthcare services. Isolates can be included from one or more healthcare facility within each NUTS-2 region. If the NRL does not receive a sufficient number of isolates from healthcare facilities in a particular NUTS-2 region through routine surveillance procedures, additional isolates may be actively requested from healthcare facilities in that region. However, there is no requirement to recruit specific hospitals for participation prior to the start of the survey. The NUTS 2024 classification should be used. Information on NUTS-2 regions can be found at <https://ec.europa.eu/eurostat/web/nuts>.

3.2.3 Patient population

The patient populations that should be recruited at the healthcare facility level are:

- outpatients: patients not hospitalised or hospitalised but not staying overnight in the hospital at the time of sampling (day care);
- inpatients: patients hospitalised and staying overnight in a hospital at the time of sampling.

3.2.4 Bacterial species

For this pilot survey, CRECC isolates are eligible for inclusion. ECC should be defined as isolates identified by routine laboratory methods as belonging to the *Enterobacter cloacae* complex, including but not limited to clinically significant species such as *E. cloacae* and *E. hormaechei*, as well as other recognised ECC members [2,11]. Isolates reported as '*Enterobacter cloacae* complex' without species-level assignment are also eligible.

3.2.5 Case definition for the main CRECC pilot survey collection

A case of carbapenem-resistant (R) or carbapenem-susceptible, increased exposure (I) ECC for the main CRECC pilot survey collection is an individual patient with an infection or with colonisation with an isolate of carbapenem-R/I *E. cloacae* complex according to EUCAST clinical breakpoints valid at the time of collection (v 17.0, valid from 2027-01-01) with:

- a minimum inhibitory concentration (MIC) >0.25 mg/L or a disk diffusion zone <25 mm for ertapenem OR;
- an MIC >2 mg/L or a disk diffusion zone <22 mm for imipenem OR;
- an MIC >1 mg/L or a disk diffusion zone of <22 mm for meropenem.

3.2.6 Case definition for the additional voluntary CRECC pilot survey collection

A case of carbapenemase-suspected ECC for the voluntary CRECC pilot survey collection is a patient with an infection or with colonisation with an isolate of ECC suspected to produce carbapenemase according to the EUCAST screening breakpoint for meropenem valid at the time of collection [12]:

- an MIC >0.125 mg/L or a disk diffusion zone of <28 mm for meropenem AND;
- not eligible as carbapenem-R/I ECC for the main CRECC pilot survey collection due to MICs or disk diffusion zone diameters being in the susceptible (S) range according to EUCAST clinical breakpoints for ALL tested carbapenems.

It is possible to participate in the voluntary collection even if isolates are further selected by an additional confirmatory step for carbapenemase production or carriage of carbapenemase genes before WGS.

3.3 Sample design

3.3.1 Sampling period

The sampling period is a maximum of three months from 1 January to 31 March 2027. If sample collection cannot begin on the 1 January 2027, isolates collected between 1 February and 30 April 2027 will also be eligible for inclusion.

3.3.2 Biological samples

Non-duplicate consecutive bacterial isolates from individuals meeting the case definition are accepted. Preferably, isolates from clinical specimens collected for diagnostic purposes (e.g. blood, urine, sputum, wound secretion, etc.) should be included. However, isolates from rectal or faecal samples for CRE screening can also be included, but need to be marked as screening samples so that they can be analysed separately from clinical diagnostic samples.

3.3.3 Sample size

- **Main CRECC pilot survey collection:** the first five non-duplicate consecutive isolates of ECC categorised as I or R to one or several of the carbapenems per NUTS-2 region.
- **Additional voluntary CRECC pilot survey collection:** the first five non-duplicate consecutive isolates of ECC suspected to be carbapenemase-producing based on the EUCAST screening breakpoint for meropenem [12], but not categorised as carbapenem-R/I to one or several of the carbapenems per NUTS-2 region.

The maximum resulting sample size is 10 isolates per NUTS-2 region, including five carbapenem-R/I ECC isolates for the main collection and five carbapenemase-suspected ECC isolates for the additional voluntary collection.

3.3.4 Metadata collection

Each collected isolate is accompanied by the respective microbiological, clinical, epidemiological and WGS data as further outlined below.

3.4 Sample flow

Step 1. Species identification and antimicrobial susceptibility testing

Consecutive presumptive cases are passively identified through routine clinical microbiology procedures and referred to the NRL for reference testing. After identification of ECC and confirmation of isolates at the NRL as carbapenem-R/I according to the EUCAST clinical breakpoints for the main collection, or as carbapenemase-suspected according to the EUCAST screening breakpoint for meropenem for the voluntary collection, isolates will be registered with a unique identifier for the CRECC pilot survey (see 3.5.1 and 3.5.2). All registered isolates must be stored using an appropriate method to preserve their viability until conclusion of the analysis of the CRECC pilot survey.

Step 2. Whole genome sequencing

Performance of WGS of all isolates registered for the CRECC pilot survey will preferably be conducted at the NRL according to the established routine methodology. If national capacity is not sufficient, ECDC can provide central WGS services via a contractor. To ensure quality and comparability of data, all NRLs performing phenotypic and genotypic characterisation are encouraged to participate in the phenotypic external quality assessment and genomic proficiency testing exercises conducted by the EURL-PH-AMR in 2026 and 2027.

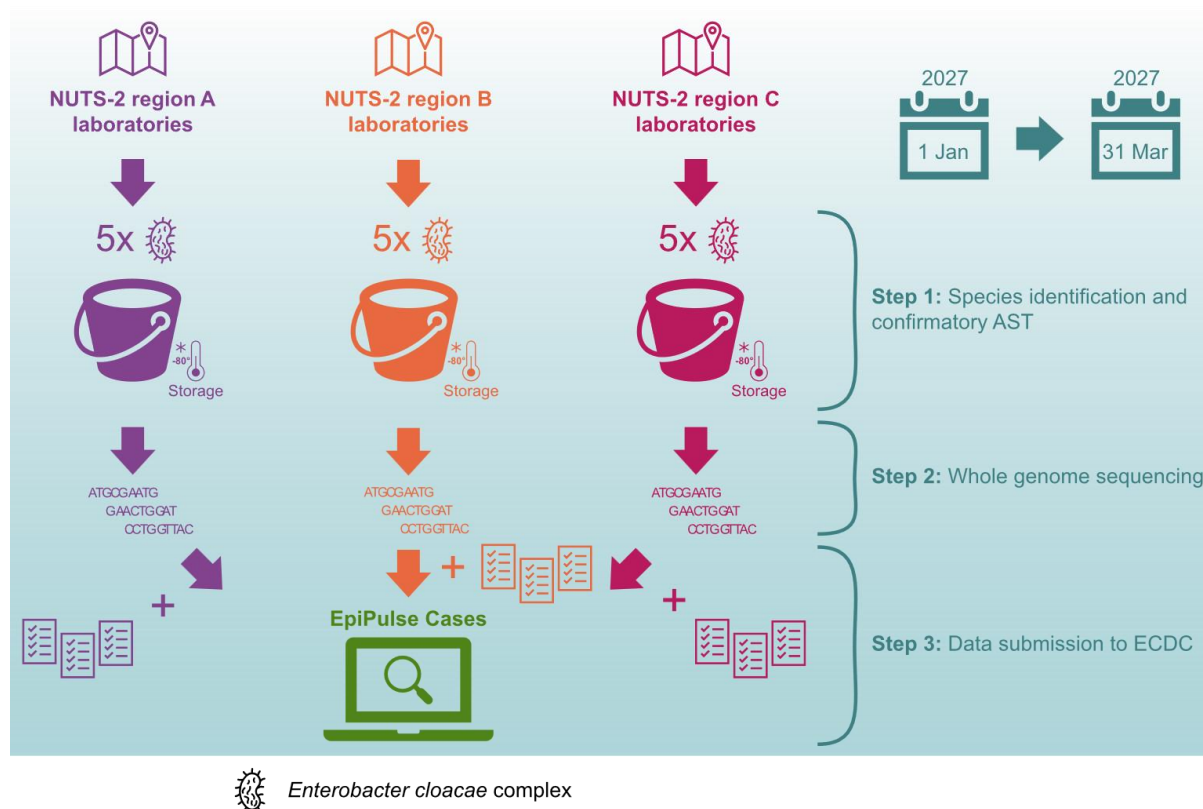
If high quality long-read data can be generated (Oxford Nanopore with base caller SUPv5.0.0 or later, or Pacific Biosciences HiFi reads), these are the preferred data to be submitted to ECDC. If only short reads are available (e.g. Illumina), these should be provided. Provision of hybrid data (both long reads and short reads) is not required.

Step 3. Submission of data to ECDC

Metadata in the AMRISO and AMRISO\$AST format together with WGS data should be submitted to ECDC via EpiPulse Cases. Data should be submitted as soon as available. Submitting batches of isolates for data submission or delaying of WGS data upload until epidemiological metadata are complete should be avoided. More instructions on how to use EpiPulse Cases for data submission can be found under the Help section of the EpiPulse landing page or at the following links:

- [EpiPulse Cases Guide](#)
- [EpiPulse Cases Visualised Guide](#)

Once data have been submitted, they will automatically be processed by the ECDC Bioinformatics system. The analysis can generally be expected to be finished on the following working day after submission. The progress of analysing uploaded data can be tracked through the [EpiPulse Molecular Typing Tool](#) (MTT) by first selecting the appropriate pathogen and then selecting the *My Isolates Data* tab. The details of the included analyses are described in the analysis plan (see separate document). The entirety of the CRECC pilot survey dataset analysed up to any given time can be displayed in the embedded Microreact tool. This can be done by searching for the appropriate *Event code* (2026-ARH-00019, see 3.5.1) in the search and refine section of MTT.

Figure 3. Sample flow for the CRECC pilot survey as described under steps 1-3 above

NUTS-2: nomenclature of territorial units for statistics level 2.

Note: if sample collection cannot begin on the 1 January 2027, isolates collected between 1 February and 30 April 2027 will also be eligible for inclusion.

3.5 Data collection

The metadata collection includes variables at the isolate level (microbiological data) and the patient level (epidemiological and clinical data) as described in the AMRISO and AMRISO\$AST subject specifications. Data will be transferred to ECDC through the EpiPulse Cases platform, which is only accessible by nominated users such as the OCPs for AMRISO as well as ECDC. The specifications of the AMRISO and AMRISO\$AST subjects at the time of submission apply and can be found in the [EpiPulse Cases metadata set](#). A list of variables to be collected for the CRECC pilot survey and related definitions can also be found below.

The mandatory variables for a successful data submission to the EpiPulse Cases platform are highlighted in bold. In case of discrepancy, the AMRISO as well as AMRISO\$AST subject specifications apply. Hospital denominator should not be submitted for the CRECC survey. WGS data should be generated at the national level and FASTQ files should also be submitted:

- directly via the EpiPulse Cases platform, or
- indirectly by providing run identifiers from the public repositories such as European Nucleotide Archive (ENA) or Sequence Read Archive (SRA) (see 3.5.4).

It is possible to instead submit assembled genomes as FASTA files, but raw data are preferable to ensure that genomes are processed following the harmonised methodology. There is no need to provide FASTA files if FASTQ files are available.

3.5.1 Survey identifier

To be able to identify CRECC pilot survey isolates within the ECC datasets already in EpiPulse and to differentiate them from other ongoing investigations, it is important to allocate a unique CRECC survey code to these isolates. This code (2026-ARH-00019) should be included in an *ItemCode* variable in the AMRISO subject.

3.5.2 Unique isolate identifier

For the CRECC pilot survey, ECDC accepts only pseudonymised codes and not national record identifiers which could link to individual patient information. Such pseudonymised isolate codes should be inserted into the field of NationalRecordId variable in the AMRISO subject as well as ParentNationalRecordId variable in the AMRISO\$AST subject for AST results (see 3.5.4).

The unique identifier for each isolate submitted for the CRECC survey should include the following elements:

- Survey code CRECCM for the main collection or CRECCV for the voluntary additional collection;
- NUTS-2 code of the region of origin of the isolate;
- Running number (01-05) for a maximum of five isolates per NUTS-2 region.

Example codes:

- CRECCM_SE11_01 for the first carbapenem-resistant ECC isolate from Stockholm region included in the main collection;
- CRECCV_BE10_02 for the second carbapenemase-suspected ECC isolate from Brussels region included in the voluntary collection.

3.5.3 General subject data

The generic variables should be filled out as follows:

- Health topic (HealthTopic): the code of the health topic that is being reported should be set as AMRISO;
- Status (Status): the Status value is used to provide the functionality for a record within EpiPulse Cases database:
 - default value: NEW/UPDATE. If set to NEW/UPDATE, the record is inserted into the database;
 - if the same NationalRecordId already exists for the same data source and subject code, then the current submitted record updates (replaces) the existing one;
 - if set to DELETE, the record with the specified NationalRecordId is deleted (invalidated) from EpiPulse Cases database, if it exists.
- Data source (**DataSource**): the data source (surveillance system) that the record originates from; the DataSource value must be a special reference value from EpiPulse Cases metadata set and usually consists of two-letter country code followed by -AMRISO, e.g. SE-AMRISO for Sweden.
- Subject code (**SubjectCode**): this variable is a reporting model for a disease/health topic and identifies the reporting structure and format of a record (case based or aggregate reporting); for the CRECC pilot survey, in the appropriate [templates](#), subject code should be set to:
 - AMRISO for the metadata reporting in the AMRISO subject template (Template_AMRISO.csv);
 - AMRISO\$AST for the phenotypic AST data reporting in the AMRISO\$AST subject template (Template_AMRISO\$AST.csv).
- Reporting country (**ReportingCountry**): the country reporting the record (two-letter location code from the EpiPulse Cases metadata set).
- Isolate unique identifier (**NationalRecordId**): as described in 3.5.2, this variable will be populated by the CRECC pilot survey pseudonymised identifier, e.g. CRECCM_SE11_01.
- Date used for statistics (**DateUsedForStatistics**): the most epidemiologically relevant date for the isolate in the CRECC pilot survey is date of sampling if available; if not, use the date of receipt in the source laboratory, and if that is not available, the date of receipt in the NRL (yyyy-mm-dd).

3.5.4 Isolate data

Microbiological data

- Bacterial species (**Pathogen**): for CRECC the following reference values are expected: ENTCLC;
- Date of sampling (DateOfSampling): date the sample from which the isolate was derived was taken (yyyy-mm-dd);
- Date of receipt source laboratory (DateOfReceiptSourceLab): date of receipt in source laboratory, i.e. the laboratory the sample was first sent to (yyyy-mm-dd);
- Date of receipt reference laboratory (DateOfReceiptReferenceLab): if sample collection date is not available, date of receipt in NRL can be included (yyyy-mm-dd);
- Sample origin (SampleOrigin): source that the isolate was obtained from should always be set to human as non-human samples such as hospital environment samples are not collected for the CRECC pilot survey;
- Specimen source of human samples (SpecimenSource): clinical or screening sample;
- Type of human clinical specimen (Specimen): aspirate, blood, bone marrow, catheter exit site, cerebrospinal fluid, faeces, gastrointestinal tract, lower respiratory tract, reproductive tract, skin, soft tissue, urine, wound, other.

Antimicrobial susceptibility testing

- Antimicrobial susceptibility testing results and method(s) will be collected and interpreted based on EUCAST clinical breakpoints for the following antimicrobial agents (AntimicrobialAgent) using AMRISO\$AST subject:
 - Aminoglycosides: amikacin (AMK), tobramycin (TOB), gentamicin (GEN);
 - Beta-lactams/monobactams: aztreonam (ATM);
 - Beta-lactams/cephalosporins: cefiderocol (FDC);
 - Beta-lactams/carbapenems: ertapenem (ETP), imipenem (IPM), meropenem (MEM);
 - Beta-lactam - beta-lactamase inhibitor combinations: piperacillin-tazobactam (TZP), ceftazidime-avibactam (CZA), meropenem-vaborbactam (MEV), aztreonam-avibactam (AZA), imipenem-relebactam (IMR), ceftolozane-tazobactam (CZT);
 - Fluoroquinolones: ciprofloxacin (CIP), levofloxacin (LVX);
 - Polymyxins: colistin (COL);
 - Other: trimethoprim-sulfamethoxazole (SXT).

In case AST results cannot be provided for all antimicrobial agents listed above, the following prioritisation should be applied:

- Priority 1: meropenem (if not possible, imipenem or ertapenem). Isolates that do not have an AST result for at least one carbapenem confirming their inclusion into the CRECC main or voluntary collection will be excluded from the final analysis;
 - Priority 2: colistin, piperacillin-tazobactam, ciprofloxacin or levofloxacin, gentamicin (if not possible, the tobramycin and/or amikacin), ceftazidime-avibactam, meropenem-vaborbactam and aztreonam-avibactam, cefiderocol disk diffusion;
 - Priority 3: all other antibiotics listed above.
- AST record identifier (**NationalRecordId**): unique identifier for each antimicrobial susceptibility test selected and generated by the country reporting the record;
- Parent national record identifier (**ParentNationalRecordId**): the corresponding parent identifier for each record (i.e. CRECC pilot survey pseudonymised identifier described in 3.5.2 and corresponding to the specific isolate in AMRISO subject); a record with no corresponding parent identifier will not be added to EpiPulse Cases database.
- AST method used for the antimicrobial agent (ASTMethod): automated instrument method, broth microdilution, antimicrobial gradient, disc diffusion test;
- Minimum inhibitory concentration (MIC) sign (MICSusceptibilitySign):
 - < Less than
 - <= Less than or equal
 - = Equal
 - > Greater than
 - >= Greater than or equal.
- MIC value (MICValueAST): in mg/l; use '.' as decimal delimiter, e.g. 0.25;
- Disk diffusion zone diameter sign (DDZDSusceptibilitySign):
 - < Less than
 - <= Less than or equal
 - = Equal
 - > Greater than
 - >= Greater than or equal.
- disk diffusion zone diameter value (DDZDValueAST): in mm.

Whole genome sequencing

It is expected that WGS data are collected from the NRLs or produced by an appointed central laboratory for a centralised WGS analysis approach. The following variables will be collected:

- protocol used for sequencing, limited to the sequencing technology used and the read length (WGSProtocol):
 - ILLUMINA: Illumina short-read sequencing (<1000 bp);
 - IONTORRENT: Ion Torrent short-read sequencing (<1000 bp);
 - MGI: MGI short-read sequencing (<1000 bp);
 - ONT: Oxford Nanopore long-read sequencing (>1000 bp);
 - PACBIO: Pacific Biosciences long-read sequencing (>1000 bp).
- WGS accession identifier (WgsAccession): ENA or SRA run identifier, based on which, the sequence read data can be retrieved from the public domain. Starts with ERR or SRR, i.e. not the sample or experiment which start with ERS/ERX or SRS/SRX.
- If assemblies are provided instead of raw reads (not recommended), the assembly software used should be reported in WgsAssembler.

If WGS data for CRECC isolates are provided to ECDC, it is not required to send any isolate to the strain collection. CRECC isolates must be stored at the NRL with a suitable method to preserve their viability until the end of the survey.

3.5.5 Patient data

Demographic data

- age (Age): age of patient in years at the date of sampling;
- gender (Gender): female, male or other;
- type of patient (PatientType): admission category of the patient, inpatient, outpatient or other (defined in section 3.2.3);
- type of unit/ward (HospitalUnitType): hospital department at sample collection: emergency department, intensive care unit (ICU), infectious diseases ward, inpatient ward, internal medicine, obstetrics/gynecology, haematology/oncology, paediatrics/neonatal, paediatrics/neonatal ICU, primary health care, surgery, urology ward, other;
- healthcare facility NUTS-2 level location (HealthcareFacilityLocation): NUTS-2 region of the healthcare facility where the respective isolate is originating from;
- date of hospitalisation (DateOfHospitalisation): date of hospitalisation or outpatient visit (yyyy-mm-dd).

Epidemiological and clinical data

- clinical significance (ClinicalSignificance): colonisation, infection, undetermined/unknown clinical significance;
- organ/system or location of infection/colonisation (SiteOfInfection): intra-abdominal, bloodstream, lower respiratory tract, skin or soft tissue, urinary tract, other;
- hospital-acquired or community-onset (HospitalAcquiredSample):
 - Yes: hospital-acquired colonisation/infection if the sample is collected from an inpatient later than 48 hours post-admission;
 - No: community-onset if the sample is collected from an outpatient or from a hospitalised patient earlier than 48 hours post-admission.

Healthcare exposure/referral history

- direct hospital transfer (HospitalTransfer): direct transfer of patient from another hospital to the current hospital where patient is admitted:
 - Yes, same country: another hospital in the same country (specify country in CountryOfHospitalTransfer);
 - Yes, other country: a hospital in another country (specify country in CountryOfHospitalTransfer);
 - No.
- previous hospitalisation within six months before sampling date (PriorHospitalisation):
 - Yes, same country: another hospital in the same country (specify country in CountryOfPriorHospitalisation);
 - Yes, other country: a hospital in another country (specify country in CountryOfPriorHospitalisation);
 - No.
- previous residence in a long-term/elderly care facility, direct transfer or within six months before sampling date (PriorResidenceInLTFCF):
 - Yes, same country (specify country in CountryOfPriorResidenceInLTFCF);
 - Yes, other country (specify country in CountryOfPriorResidenceInLTFCF);
 - No.

Travel history

- recent (past six months) travel history to another country prior to sample date (Travel):
 - Yes (specify country in TravelLocation);
 - No.

3.5.6 Data not collected for the CRECC pilot survey

The following variables will NOT be collected for the CRECC pilot survey:

- AMRISO subject:
 - hospital identifier (HospitalId);
 - date of onset of disease (DateOfOnset);
 - date of discharge (DateOfDischarge);
 - date of death (DateOfDeath);
 - outcome of hospital stay (OutcomeHospital);
 - prescribed antimicrobial agent (PrescribedAntimicrobial);
 - sample identifier (SampleId);
 - laboratory code (LaboratoryCode);
 - WGS assembled genome (WgsAssembly);
 - WGS raw sequence reads (WgsRawReads).
- AMRISO\$AST subject:
 - AST guideline (ReferenceGuidelinesSIR).

In addition, all variables of the AMRISODENOM subject are NOT collected for the CRECC pilot survey.

3.6 Data analysis

Data analysis will be described in the forthcoming analysis plan to be published later.

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