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DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Public Health, Cancer and Health security
Health Security

Opinion of the Health Security Committee on rapidly increasing incidence of carbapenem-resistant Enterobacterales (CRE) in healthcare settings

13 MAY 2025

1. BACKGROUND

Pathogens resistant to last-line antimicrobials such as carbapenem-resistant Enterobacterales (CRE), notably carbapenem-resistant *Klebsiella pneumoniae* and carbapenem-resistant *Escherichia coli*, pose a significant threat to patients and healthcare systems in European Union/European Economic Area (EU/EEA) countries.

Since 2019, the number of cases of carbapenem-resistant *K. pneumoniae* bloodstream infections and related estimated incidence has been rapidly increasing in the EU and in most Member States ([1]) *(see Annex)*. The European Centre for Disease Prevention and Control (ECDC) estimated that carbapenem-resistant *K. pneumoniae* infections alone resulted in about 4,000 deaths directly attributable to the infections in the EU/EEA in 2020 ([2]).

In 2023, the Council issued a recommendation ([3]) aiming to limit the spread of key resistant pathogens in the EU and set a target to reduce the incidence of bloodstream infections of carbapenem-resistant *K. pneumoniae* by 5% for the EU as a whole and by 0%-12% for individual Member States by 2030, in comparison to the baseline year 2019. The monitoring of progress on this target ([4]) in 2023 and 2024 so far shows that incidence is not only not decreasing, but that instead, there are alarming levels of increase of close to 60% for the EU as a whole ([5]) and very high (triple digit percentage) increases for certain individual Member States.

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[1] https://www.ecdc.europa.eu/sites/default/files/documents/risk-assessment-carbapenem-resistant-enterobacterales-third-update-february-2025_0.pdf

[2] https://www.ecdc.europa.eu/en/publications-data/health-burden-infections-antibiotic-resistant-bacteria-2016-2020. More recent estimates of the health burden of carbapenem-resistant *K. pneumoniae* are not available and these estimates do not include CRE other than carbapenem-resistant *K. pneumoniae*.

[3] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32023H0622(01)

[4] ECDC, https://www.ecdc.europa.eu/en/news-events/reducing-antimicrobial-resistance-accelerated-efforts-are-needed-meet-eu-targets

[5] Excluding France that did not report case-based data on *Klebsiella pneumoniae* to EARS-Net for 2023 due to recent changes in reporting from the French surveillance system (see Annex).

In their latest Rapid Risk Assessment of 3 February 2025 ([6]), ECDC stressed that compared to the previous ECDC rapid risk assessment in 2019 ([7]), the CRE epidemiological situation in the EU/EEA continued to deteriorate. ECDC assessed the probability of further spread of CRE in the EU/EEA as **high**. When considering probability and impact of further spread of CRE together, ECDC assessed the public health risk represented by CRE for the EU/EEA as **high to very high**.

The high level of attributable mortality of carbapenem-resistant *K. pneumoniae* and other CRE infections is primarily due to delays in administration of effective antimicrobial therapy as well as to the limited number of alternative and easily available treatment options ([8]), despite the existence of newly approved antimicrobials with activity against CRE. The latter are indicated for the treatment of infections in patients with limited treatment options ([9]) ([10]) ([11]) ([12]) ([13]), but their activity against CRE varies depending on the type of carbapenemase produced or other mechanisms of resistance. To optimise their use against specific CRE and ensure appropriate use, prior susceptibility testing is required. Carbapenemase detection may also aid treatment decisions. Consumption of colistin, an antimicrobial with activity against CRE but with significant nephrotoxicity, in the EU/EEA is much higher than that of newly approved antimicrobials with activity on CRE, which suggests that some clinicians and hospitals in the EU/EEA may be experiencing difficulties in using these newly approved antimicrobials due to a number of possible reasons (insufficient access, higher price, lack of clinical practice, etc.).

In addition to increased mortality, CRE infections have been associated with prolonged hospital stays ([14]). CRE are therefore likely to result in a financial burden for healthcare systems. CRE outbreaks have also been found to be highly costly. For all infections with antimicrobial resistant pathogens and after adjusting for purchasing power parity (PPP), the Organisation for Economic Co-operation and Development (OECD) estimated that, each year in the EU/EEA, the costs amounted to nearly EUR 11.7 billion PPP (or almost EUR 24 per capita), due to extra health expenditures as well as reduced participation in the workforce and reduced productivity gains. OECD also estimated, after reviewing the cost-effectiveness of various policies and control measures, that every euro invested in a mixed policy package, starting with improved compliance with infection prevention and control (IPC) measures and antimicrobial stewardship, would return nearly EUR 3 PPP in economic benefits, although this return varies between EU/EEA countries ([15]).

[6] https://www.ecdc.europa.eu/sites/default/files/documents/risk-assessment-carbapenem-resistant-enterobacterales-third-update-february-2025_0.pdf

[7] https://www.ecdc.europa.eu/sites/default/files/documents/carbapenem-resistant-enterobacteriaceae-risk-assessment-rev-2.pdf

[8] https://pubmed.ncbi.nlm.nih.gov/38267096/

[9] https://www.ema.europa.eu/en/medicines/human/EPAR/zavicefta

[10] https://www.ema.europa.eu/en/medicines/human/EPAR/vaborem

[11] https://www.ema.europa.eu/en/medicines/human/EPAR/recarbrio#authorisation-details

[12] https://www.ema.europa.eu/en/medicines/human/EPAR/fetcroja#authorisation-details

[13] https://www.ema.europa.eu/en/medicines/human/EPAR/emblaveo#authorisation-details

[14] https://www.ncbi.nlm.nih.gov/pubmed/26899297

[15] https://www.oecd.org/content/dam/oecd/en/publications/reports/2023/11/fighting-antimicrobial-resistance-in-eu-and-eea-countries_aa49a732/fdb1629f-en.pdf

2. RATIONALE FOR THE OPINION

The most recent Rapid Risk Assessment from ECDC, pointing to a deteriorating situation, is based on evidence across several elements including:

- An important increase in the incidence of carbapenem-resistant *K. pneumoniae* bloodstream infections in 23 EU Member States due to continued transmission of high-risk lineages of carbapenem-resistant *K. pneumoniae* in hospitals;
- convergence of virulence and resistance in *K. pneumoniae*, including rising healthcare-associated spread of hypervirulent *K. pneumoniae* ST23 carrying carbapenemase genes;
- newly emerging Enterobacterales species carrying carbapenemase genes;
- plasmid-mediated spread of carbapenemase genes causing outbreaks within hospitals and across healthcare networks; and
- increasing detection of isolates (including sporadic cases and clusters) of high-risk lineages of *E. coli* carrying carbapenemase genes with a risk of spread in the community.

The **spread of CRE** is a **cross-border** health threat, as indicated by many examples of **cross-border spread of CRE** to and within the EU/EEA ([16]) ([17]) ([18]) ([19]) ([20]). The rapid increase in CRE across the EU/EEA has most likely been driven by initial undetected cross-border spread, followed by transmission events in receiving hospitals and inter-hospital and inter-regional spread through hospital networks when the necessary IPC measures were not adequately implemented or not sufficiently complied with. The COVID-19 pandemic may have hastened the emergence and transmission of CRE and other Gram-negative multidrug-resistant organisms (MDROs) in healthcare settings due to increased use of third-generation cephalosporins and carbapenems in hospitals, and suboptimal infection control ([21]). Furthermore, since 2022, cases of CRE carriage and infection have been reported among war casualties and other patients transferred from Ukraine to hospitals in the EU/EEA ([22]). The increasing emergence and spread of CRE and other MDROs globally and the cross-border movement of patients and people mean that there will be increasing pressure on healthcare systems in EU/EEA countries, from multiple introductions of CRE and other MDROs.

Although the consistent application of IPC measures and antimicrobial stewardship can reduce the spread of CRE, their implementation in many hospitals is sub-optimal and has so far been insufficient to achieve sustained control of high-risk lineages of carbapenem-resistant *K. pneumoniae* and other CREs. **ECDC thus assessed the expected impact of CRE as high if spread of CRE continues at the current rate, but moderate if strong consistent EU/EEA-wide national control efforts are implemented to slow down the spread of CRE ([23]).**

[16] https://www.eurosurveillance.org/content/10.2807/ese.15.46.19716-en

[17] https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-carbapenemase-producing-oxa-48-klebsiella-pneumoniae-st392

[18] https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2022.27.50.2200926

[19] https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.20.2000627

[20] https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2023.28.19.2300209

[21] https://pmc.ncbi.nlm.nih.gov/articles/PMC9733301/

[22] https://doi.org/10.1128/spectrum.01142-24

[23] https://www.ecdc.europa.eu/sites/default/files/documents/risk-assessment-carbapenem-resistant-enterobacterales-third-update-february-2025_0.pdf

Given the high to very high risk posed by these highly resistant pathogens to public health in the EU, especially in healthcare settings, and the evidence for increased cross-border spread, as assessed in the third update of ECDC's rapid risk assessment on CRE, it is important to strengthen coordinated and concerted efforts to curb the rapid rise of CRE in human health in the EU through reinforced targeted measures in Member States, adapted to national contexts. In addition, the evidence for inter-hospital spread of these highly resistant pathogens poses a threat to EU preparedness to withstand possible future health emergencies that may lead to and necessitate a rise in hospitalisations, including in the events of future pandemics or large-scale mass casualty events.

Whereas in some Member States, the absolute number of cases remains low, this is not the case in many others. Even if some countries have very low incidence, the measures suggested in this Opinion will still be relevant to ensure that the situation remains under control and that CRE do not become a more significant health threat as evidenced elsewhere in the EU.

This Opinion, therefore, seeks to address through recommended targeted measures the public health challenge of rapidly rising CRE, especially in healthcare settings, notwithstanding and complementary to other existing and overarching initiatives on antimicrobial resistance (AMR) through a One Health approach.

3. WORK DONE BY THE HEALTH SECURITY COMMITTEE

The Health Security Committee (HSC) has been regularly kept abreast of developments regarding AMR in public health, given that AMR and healthcare-associated infections (HAI) fall in the remit of work of the Committee as they are an integral part of the scope of the Regulation on serious cross-border health threats ([24]).

At the Senior-Level HSC Plenary meeting on 14 November 2024, the HSC was presented with the latest ECDC surveillance data including progress of the EU and of Member States towards the recommended AMR reduction targets to be reached by 2030 ([25]). ECDC data showed that AMR levels remained high in the EU/EEA in 2023, and that the AMR situation reported by EU/EEA countries varied widely, depending on the bacterial species, antimicrobial group, and geographical region. The EU incidence of carbapenem-resistant *K. pneumoniae* bloodstream infections increased by almost 60%, thus going against the 5% reduction target, and increased in 23 individual Member States and Norway between 2019 and 2023 *(see Annex)*.

On 5 February 2025, the HSC discussed the third update of the ECDC rapid risk assessment on CRE ([2]) at its General Working Group meeting ([26]). Finland and Ireland – two Member States that showed positive progress regarding the carbapenem-resistant *K. pneumoniae* target – presented on the CRE situation in their country, sharing good practice in current surveillance, mandatory reporting as well as the implemented measures and their effectiveness to control spread of CRE. The European Medicines Agency (EMA) gave an overview of several new antimicrobials active against CRE that have received marketing authorisation for use in the EU, and Commission services (DG HERA and DG ECHO) provided information about actions to improve the availability and access to recently

[24] https://eur-lex.europa.eu/eli/reg/2022/2371/oj/eng

[25] https://health.ec.europa.eu/health-security-and-infectious-diseases/crisis-management/list-authorities-represented-health-security-committee/health-security-committee-reports_en#ref-2024

[26] https://health.ec.europa.eu/health-security-and-infectious-diseases/crisis-management/list-authorities-represented-health-security-committee/health-security-committee-reports_en#ref-2025

approved antibiotics. The HSC concluded that a HSC opinion should be drafted proposing concrete and coordinated public health measures to counter the spread of CRE in the EU/EEA.

4. COORDINATED APPROACH IN EUROPE – PROPOSED MEASURES

4.1. EU/EEA level action

Several initiatives at EU level to address AMR in public health already exist and should be further exploited to help curb the rapid rise of carbapenem resistance.

Most notably, the **EU joint action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI 2)** ([27]), started in 2024 and running to 2027, provides a major investment to complement national action to address AMR, including through concrete activities in infection prevention and control, antimicrobial stewardship, surveillance and awareness-raising. These efforts are expected to substantially contribute to curbing the incidence of AMR, including of critically resistant pathogens. Member States should actively explore all possibilities for stronger collaboration and mutual exchange of best practice through EU-JAMRAI 2.

The newly established **European Reference Laboratory on AMR in bacteria (EURL-PH-AMR)** will further support the national reference laboratories to promote good practice and alignment by Member States on a voluntary basis regarding diagnostics, testing methods, use of certain tests for the uniform surveillance, notification and reporting of serious cross-border health threats. The EURL-PH-AMR can provide support aiding the more rapid detection of CREs, including through support to carry out optimised Whole Genome Sequencing.

The 2023 Council Recommendation highlights the need for coordinated EU actions to reduce AMR, including action on infection prevention and control practices across Member States. The Commission, together with ECDC, is working on developing **EU guidelines on infection prevention and control in human health** and on the treatment of major common infections in humans. Work on these two sets of guidelines has started and the first set is expected to be published in 2026.

Strengthening **AMR and Healthcare-associated infections (HAI) prevention, preparedness and response capacities** of Member States is part of the implementation of Regulation (EU) 2022/2371. Experience and knowledge gained through, for example, the Public Health Emergency Preparedness Assessment (PHEPA) visits in Member States conducted during 2024-2026 ([28]) will be used by ECDC to identify priorities and, upon their request, provide support to Member States. Based on the results of the ECDC assessments, the Commission may issue targeted recommendations for further action and will report in 2026 to the European Parliament and to the Council on the state of play and progress on prevention, preparedness and response planning at Union level, including on AMR and HAI.

ECDC will continue to actively monitor progress of the EU/EEA and of individual Member States towards the 2030 targets, including for the incidence of carbapenem-

[27] https://eu-jamrai.eu/

[28] https://www.ecdc.europa.eu/en/about-ecdc/what-we-do/public-health-emergency-preparedness-assessments

resistant *K. pneumoniae* bloodstream infections. ECDC will continue working on guidance on relevant topics.

ECDC will continue working with Member States to improve AMR surveillance, towards encompassing not only bloodstream and cerebrospinal fluid isolates (invasive isolates), but also all other isolates from clinical microbiology laboratories ([29]). ECDC will continue its genomic surveillance activities of CRE within the European Antimicrobial Resistance Genes Surveillance Network (EURGen-Net), expand and further integrate genomic surveillance as part of AMR surveillance, continue providing a platform for secure sharing of genomic information and visualisation of results to support detection of multi-country outbreaks (EpiPulse) and will produce related rapid risk assessment where relevant.

In accordance with the Council recommendation to step up the fight against AMR, and in particular provisions under point G., the Commission is supporting **research and development efforts and implementing incentives for innovation and access to antimicrobials and other AMR medical countermeasures (e.g. diagnostics)**. Moreover, additional measures to incentivise the development of innovative antimicrobials are proposed in the pharmaceutical reform. As the lack of treatment options is a main impediment to reversing the increasing morbidity and mortality caused by CRE, efforts need to be continued to ensure access to newly approved antibiotics as well as to develop novel antibiotics through EU and national initiatives.

4.2. EU/EEA country level actions

The measures suggested below aim to be comprehensive and encompassing but they may need to be adapted to national contexts, especially taking into account the levels of incidence, which vary across countries (see also Annex).

4.2.1. National coordination and response

CRE national management team. The current cross-border spread as well as inter-regional and inter-hospital spread of CRE requires national responses to coordinate control measures between hospitals and regions and support hospitals in the implementation of control measures. If it does not already exist, a dedicated national multidisciplinary management team with a focus on CRE and potentially other relevant MDROs should be set up at the appropriate level (Ministry of Health or National Public Health Institute). This team should be composed of members with expertise in laboratory detection and characterisation, phenotypic and genomic surveillance, IPC, clinical management and antimicrobial stewardship; and include experts from both public and private sector healthcare.

The team should be mandated and resourced to access, analyse and give guidance regarding relevant surveillance data, including to identify and address gaps in surveillance systems; coordinate outbreak investigations; provide national guidance on laboratory detection, IPC and clinical management and audit their implementation in hospitals, and to monitor the availability of newly approved antimicrobials to treat patients with CRE infections. Such teams need to be empowered to convene with other competent authorities at national level, including those responsible for surveillance, hospital management and

[29] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=oj:JOC_2023_220_R_0001

availability of antimicrobials, including those representing the country at EU-level structures, to be able to ensure appropriate follow-up and coordination, where relevant.

The various functions of a CRE national management team can be executed through coordination of existing organisational structures depending on the country context.

CRE management plan. A specific CRE management plan should be put in place (as part of the National Action Plan on AMR, an action plan on MDROs, or as a stand-alone document) outlining national actions to reduce CRE. The plan should specify related targets, indicators, responsibilities and timelines, and have a dedicated budget to ensure implementation. Progress should be reported publicly on an annual basis, as a minimum, to maintain transparency and accountability. The national CRE management team should plan, coordinate and oversee actions, and monitor implementation of the plan.

4.2.2. Measures to prevent and mitigate the impact of cross-border spread of CRE

Upon hospital admission, hospitals in EU/EEA countries should consider, for each admitted patient, taking a detailed history of travel and hospitalisations.

For patients directly transferred from a hospital in another country, hospitals should consider performing immediate pre-emptive isolation, contact precautions (in addition to standard precautions) and screening for carriage of CRE *(see 4.2.3 for details)*.

Otherwise, hospitals should implement active surveillance upon admission of patients with risk factors for asymptomatic CRE carriage, through rectal/faecal screening for CRE carriage and tailored to the local epidemiology *(see 4.2.3 for details).*

In the event of direct patient transfer from a hospital in another country, good inter-facility communication, including flagging the CRE-positive status (asymptomatic carriage or infection) of the patient in the letter of discharge, is a key element to ensure that effective measures are rapidly put in place to limit the spread of CRE in the receiving hospital.

Depending on the epidemiological situation, hospitals could consider screening for asymptomatic CRE carriage for patients who recently travelled (but without healthcare contact) to a region of the world with known or suspected high prevalence of CRE *(see 4.2.3).*

Moreover, it is important to ensure that reliable epidemiological data are gathered by notifying cases to public health authorities and exchanging information. This enables public health authorities to take informed and coordinated action across EU/EEA countries.

Public health authorities should report to EU and international systems such as the Early Warning and Response System (EWRS) and the GLASS Emerging Antimicrobial Resistance Reporting (GLASS-EAR), where relevant. Use of the European surveillance portal for infectious diseases (EpiPulse) including sharing of sequencing data in EpiPulse and public repositories is encouraged to ensure transparent and timely information sharing at an early stage.

4.2.3. Measures to prevent transmission of CRE, with a focus on healthcare settings

Effective IPC measures are pivotal to prevent transmission. IPC measures should be applied through the implementation of multi-modal strategies supported by the hospital

leadership to ensure the availability of the necessary human, material and financial resources, involving all relevant stakeholders in a multidisciplinary approach with clear accountability structures ([30]). Economic analysis by OECD ([31]) on some of the measures proposed below (e.g. hand-hygiene, environmental cleaning, etc.) also shows that they are largely cost-effective and can contribute significantly to reducing morbidity and mortality and reduce the economic burden of AMR through savings in health expenditure and improved workforce productivity.

Effective IPC measures to prevent the spread of CRE in hospitals include:

• Hand hygiene and monitoring of related compliance. Standard precautions, including hand hygiene, for all patients and at all times, since many patients who are asymptomatic carriers of CRE or of other antimicrobial-resistant organisms are not easily identified.

• Transmission-based (contact) precautions for in-patients in acute care hospitals who are carrying or infected with CRE including (a) appropriate patient placement; (b) appropriate use of personal protective equipment, including gloves and gowns; (c) limiting transport and movement of patients; (d) appropriate use of disposable or dedicated patient-care equipment; and (e) prioritisation of cleaning and disinfection of patient rooms ([32]).

• In acute-care hospitals, isolation of patients carrying or infected with CRE in a single room (preferably with their own toilet facilities) when available. When single-patient rooms are in short supply, cohorting of patients in the same room(s) or in a dedicated cohorting ward, and allocation of dedicated staff (cohort nursing) and medical equipment. CRE carriage should be flagged in the patient administration systems and/or medical charts to ensure that the information is available to the clinical teams during the current admission and potential readmissions or transfers.

• In case of patient transport or transfer of a CRE-positive patient (asymptomatic carriage or infected), communication in advance before transport or transfer, of the CRE status to relevant transport personnel and to the receiving hospital or facility.

• Upon hospital admission, implementation of active surveillance of patients with risk factors for asymptomatic CRE carriage, through rectal/faecal screening for CRE carriage and tailored to the local epidemiology. Such risk factors can include a) a history of an overnight stay in a healthcare setting in the last 12 months, b) dialysis-dependent or cancer chemotherapy in the last 12 months, c) known previous carriage of CRE in the last 12 months, and d) epidemiological linkage to a known carrier of a CRE ([33]). Active surveillance can also be implemented for all patients admitted to specific high-risk wards/units, such as intensive care units. Regular active surveillance for asymptomatic CRE carriage should ideally also be implemented in endemic situations, at least in the form of repeated point-

[30] https://apps.who.int/iris/handle/10665/312226

[31] https://www.oecd.org/en/publications/fighting-antimicrobial-resistance-in-eu-and-eea-countries_fdb1629f-en.html

[32] https://apps.who.int/iris/handle/10665/259462

[33] https://pubmed.ncbi.nlm.nih.gov/29163939/

prevalence studies, and/or targeted surveillance in high-risk or affected wards, depending on risk assessment.

• Countries with evidence that acquisition of CRE is uncommon in the country should consider pre-emptive implementation of transmission-based (contact) precautions followed by screening for asymptomatic CRE carriage, based on specified risk criteria such as healthcare contact within the previous 12 months in another country with a high CRE prevalence, or in a hospital or facility with a known CRE outbreak or high CRE prevalence in the same country. Depending on the epidemiological situation, screening for asymptomatic CRE carriage for patients who recently travelled (but without healthcare contact) to a region of the world with known or suspected high prevalence of CRE could also be considered. Data on carbapenem resistance percentages in *K. pneumoniae* and *E. coli* bloodstream infections and urinary tract infections from various countries and regions of the world are available from the Global Antimicrobial Resistance and Use Surveillance System (GLASS) ([34]).

• Frequent routine cleaning and disinfection of the immediate surrounding area (the 'patient zone') and thorough cleaning of the whole patient room after patient discharge.

• If there is reason to suspect a persistent environmental reservoir of CRE in the healthcare facility (typically sinks, toilets, showers or drains), environmental cultures followed by mitigation measures (such as, enhancing cleaning and disinfection, decreasing the use of sinks near the patient, installing filters on taps, or even removing sinks from patient areas if possible) to manage the identified environmental reservoirs of CRE.

• Training of staff on IPC, including on the above-listed measures, and incorporating, where available, interventions addressing the behavioural aspects of Infection Prevention and Control, and practice implementation barriers.

• Appropriate accessible information on CRE for patients, families and friends (i.e. what it means for them and how they can contribute to reducing their risk of acquiring and possibly transmitting CRE when in a hospital).

• Monitoring compliance with and effectiveness of the implemented IPC interventions, as well as adjustment of and feedback on these interventions. In residential care settings, including long-term care facilities, all reasonable IPC measures and antimicrobial stewardship activities should be implemented to reduce the risk of CRE spread, taking into consideration the entirety of residents' care needs and the harm to residents associated with extended periods of single room isolation.

In the community, e.g. in households and shared public environments, standard personal hygiene rules should be applied to prevent person-to-person transmission of CRE, as well as ensuring implementation of existing advice for safe food handling to prevent food contamination from handlers who are asymptomatic carriers of CRE.

[34] https://worldhealthorg.shinyapps.io/glass-dashboard/_w_50b8c98a/#!/amr

4.2.4. Laboratory capacity and surveillance

For Enterobacterales isolated from diagnostic samples, standardised quality-assured AST is required to detect carbapenem resistance, i.e. CRE. Timely reporting of AST results is important to inform treatment decisions.

In addition, active surveillance to detect asymptomatic carriers of CRE is required to effectively control CRE in EU/EEA countries. National guidance should be provided on the screening of hospitalised patients for CRE carriage, accompanied with sufficient funding and laboratory capacity for implementation.

EUCAST guidance defines screening cut-off values to optimise the balance between sensitivity and specificity for detecting CRE that produce carbapenemases by identifying reduced susceptibility to carbapenems ([35]).

Carbapenemase detection, characterisation and monitoring are important for public health purposes, given the association of carbapenemase genes with high-risk lineages, the potential for horizontal gene transfer and the fact that some isolates that produce carbapenemases are not classified as resistant based on current clinical breakpoints. Carbapenemase detection and characterisation can be done with supplementary phenotypic or molecular testing. Several commercial products suitable for use in routine diagnostic laboratories are available for this purpose. Differentiation between the most commonly identified carbapenemase families (i.e. NDM, VIM, IMP, KPC and OXA-48-like) is necessary, both for surveillance and to inform treatment decisions. The use of rapid tests can significantly improve the timely detection of both symptomatic and asymptomatic CRE carriers.

Countries should reinforce the central role of the national reference laboratories for the detection and analyses of carbapenemase and other antimicrobial resistance genes, as well as the detection and analyses of relevant virulence genes. Whole genome sequencing (WGS) enables the determination of the relatedness of CRE isolates and the detection of transmission events and outbreaks. WGS is particularly valuable for tracking the emergence and spread of high-risk lineages of CRE and associated plasmids between and within countries. Guidance on WGS-based genome analysis methods and standard protocols for national CRE surveillance and integrated investigations of CRE outbreaks is available from the EURGen-RefLabCap project ([36]). Genomic surveillance is also required to detect virulence genes that are becoming increasingly important considering carbapenem-resistant hypervirulent *K. pneumoniae* (hvKp) and other high-risk lineages of *K. pneumoniae*.

Where needed (see Annex), countries should work towards increasing the geographical, hospital and/or isolate representativeness of the AMR data reported to the European Antimicrobial Resistance Surveillance Network (EARS-Net), including for carbapenem-resistant *K. pneumoniae* bloodstream infections.

While carbapenem-resistant *K. pneumoniae* and carbapenem-resistant *E. coli* remain the main public health threat in the EU/EEA, other CRE species, as well as the tracking of epidemic plasmids carrying carbapenemase genes will require enhanced surveillance in the coming years.

[35] https://www.eucast.org/clinical_breakpoints

[36] https://www.eurgen-reflabcap.eu/-/media/sites/eurgen-reflabcap/ny-eurgen-reflabcap-common-wgsprotocol-for-cre-and-ccre.pdf

4.2.5. Antimicrobial stewardship programmes

The implementation of comprehensive antimicrobial stewardship programmes is essential to prevent and control the emergence and spread of CRE and of other MDROs. Rational use of antimicrobials should be promoted using the AWaRe classification ([37]).

The recently approved antimicrobials with activity against CRE should be used judiciously to mitigate the development and spread of resistance. Antimicrobial stewardship programmes should oversee their use ensuring that they are prescribed after consultation with an infectious diseases specialist or clinical microbiologist and in patients with either microbiologically confirmed infection by carbapenem-resistant microorganisms or with suspected infection known to be colonised by such organisms susceptible to the specific antimicrobial. In the latter case, microbiological confirmation with susceptibility testing should be ensured to guide further treatment.

Increased awareness among clinicians of the challenge of detecting and treating CRE infections, and access to timely expert advice on infection management, including from the suggested CRE national management team, where relevant, are also important, in addition to the timely access to the antimicrobials listed in national clinical guidance National guidelines for the treatment of severe CRE infections should be developed considering the epidemiological situation of CRE and predominant carbapenemase genes in the country. They should also specify indications for the most appropriate newly approved antimicrobials.

National authorities need to ensure timely access to the antimicrobials listed in the national guidance, including newly approved antimicrobials; monitor and audit their use in accordance with the national guidance, and perform surveillance of resistance to newly approved antimicrobials.

Antimicrobial stewardship programmes need to be informed by behavioural and implementation science that goes beyond the simple publication of treatment guidelines and applies interventions that are tailored to the barriers and facilitators identified ([38]).

General good practice recommendations for the treatment of CRE infections include optimal dosing schemes with attention to adverse effects; optimisation of dosing and administration by pathogen and indication; use of recommended dosing according to the approved posology, source control, and follow-up cultures in case of treatment failure ([39]).

For ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, cefiderocol and aztreonam-avibactam, the EU Summary of Product Characteristic (SmPC) that describes the properties and the officially approved conditions of use in the EU specifies that these newly approved antimicrobials should be used to treat infections in patients ‘with limited treatment options’ and ‘only after consultation with a physician with appropriate experience in the management of infectious diseases’ ([40]) ([41]) ([42]) ([43]) ([44]).

[37] https://www.who.int/publications/i/item/9789240062382

[38] https://pubmed.ncbi.nlm.nih.gov/37973498/

[39] https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00679-0/fulltext

[40] https://www.ema.europa.eu/en/medicines/human/EPAR/zavicefta

[41] https://www.ema.europa.eu/en/medicines/human/EPAR/vaborem

[42] https://www.ema.europa.eu/en/medicines/human/EPAR/recarbrio#authorisation-details

[43] https://www.ema.europa.eu/en/medicines/human/EPAR/fetcroja#authorisation-details

[44] https://www.ema.europa.eu/en/medicines/human/EPAR/emblaveo#authorisation-details

5. ANNEX

Table. Carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections, EU/EEA countries, 2019 and 2023: number of cases reported to EARS-Net, estimated total number of cases and estimated incidence.

Country[a]	**2019**			**2023**			**2019 – 2023**				
	Cases reported to EARS-Net (n)	Estimated total cases[b]* (n)	**Estimated incidence[b] (n per 100 000 population)**	Cases reported to EARS-Net (n)	Estimated total cases[b]* (n)	**Estimated incidence[b] (n per 100 000 population)**	Change in cases reported to EARS-Net (n)	Change in estimated total cases (n)	Change in estimated incidence (n per 100 000 population)	Change in estimated incidence (%)	Trend[c]
Iceland	ND	ND	ND	0	0	**0.00**	NA	NA	NA	NA	NA
Liechtenstein	ND	ND	ND	0 †	0 †	**0.00** †	NA	NA	NA	NA	NA
Finland	3	3	**0.06**	1	1	**0.02**	–2	–2	–0.04 #	-66.7	-
Ireland	5	5	**0.11**	2	2	**0.04**	–3	–3	–0.07 #	-63.6	-
Netherlands	3	4	**0.02**	6	8	**0.04**	+3	+4	+0.02	+100.0	-
Denmark	4	4	**0.07**	5	5	**0.08**	+1	+1	+0.01	+14.3	-
Norway	2	2	**0.04**	4	4	**0.08**	+2	+2	+0.04	+100.0	-
Sweden	2	3	**0.03**	11	12	**0.12**	+9	+9	+0.09	+300.0	↑
France	30	150	**0.22**	48 (2022) §	87 (2022) §	**0.13** (2022) §	NA	NA	NA	NA	NA
Germany	44 †	163 †	**0.20** †	85 †	213 †	**0.25** †	+41	+50	+0.05	+25.0	-
Czechia	8 ‡	10 ‡	**0.09** ‡	20 ‡	29 ‡	**0.26** ‡	+12	+19	+0.17	+188.9	↑
Austria	16	18	**0.20**	24	27	**0.29**	+8	+9	+0.09	+45.0	-
Luxembourg	1 †	1 †	**0.16** †	2	2	**0.30**	+1	+1	+0.14	+87.5	-
Estonia	0 ‡	0 ‡	**0.00** ‡	6 ‡	6 ‡	**0.44** ‡	+6	+6	+0.44	NA	↑
Belgium	8 †	31 †	**0.27** †	23 †	55 †	**0.47** †	+15	+24	+0.20	+74.1	-
Slovenia	1	1	**0.05**	13	13	**0.62**	+12	+12	+0.57	+1 140	↑

Lithuania	15	15	**0.54**	21	21	**0.73**	+6	+6	+0.19	+35.2	-
Hungary	8	9	**0.09**	66	73	**0.76**	+58	+64	+0.67	+744.4	↑
Latvia	0 †	0 †	**0.00** †	15 †	17 †	**0.89** †	+15	+17	+0.89	NA	↑
Spain	114 †	356 †	**0.76** †	129 †	461 †	**0.96** †	+15	+105	+0.20	+26.3	↑
Malta	10	11	**2.13**	5	5	**0.97**	-5	–6	–1.16 #	-54.5	-
Slovakia	16	29	**0.52**	39	72	**1.33**	+23	+43	+0.81	+155.8	-
Poland	89 †	524 †	**1.38** †	285 †	1 357 †	**3.69** †	+196	+833	+2.31	+167.4	↑
Portugal	292	301	**2.93**	430	439	**4.19**	+138	+138	+1.26	+43.0	↑
Croatia	39 †	49 †	**1.20** †	157	174	**4.53**	+118	+125	+3.33	+277.5	↑
Bulgaria	72 †	157 †	**2.24** †	230 †	500 †	**7.75** †	+158	+343	+5.51	+246.0	↑
Italy	2 086	5 088	**8.43**	3 616	5 479	**9.29**	+1 530	+391	+0.86	+10.2	-
Cyprus	8	23	**2.61**	74	90	**9.80**	+66	+67	+7.19	+275.5	↑
Romania	152 †	1 382 †	**7.12** †	496 †	3 815 †	**20.02** †	+344	+2 433	+12.90	+181.2	↑
Greece	182 †	1 400 †	**13.05** †	1 518	2 232	**21.44**	+1 336	+832	+8.39	+64.3	↑
EU[d]	**3 178**	**9 587**	**2.52**	**7 279**	**15 108**	**3.97**	**+4 101**	**+5 521**	**+1.45**	**+57.5**	↑

ND, no data available; NA, not applicable.

[a] Countries are ranked by increasing estimated incidence of carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections in 2023.

[b] Total number of cases and incidence were estimated using the EARS-Net data, including data on population coverage, reported to EpiPulse and country population from Eurostat. Each de-duplicated isolate from a blood sample (>99% data) or cerebrospinal fluid sample (<1% data) was considered a proxy for bloodstream infection (for more information, see https://www.ecdc.europa.eu/en/publications-data/antimicrobial-resistance-amr-reporting-protocol-2024)

[c] ↑ indicates a statistically significant increasing trend; - indicates absence of a statistically significant trend.

[d] Excluding France (see footnote §)

* Estimated based on population coverage separately for each country and rounded to the nearest integer.

† One or several of the three representativeness indicators (geographical, hospital and/or isolate representativeness) were not reported as 'High'. The results must be interpreted with caution.

‡ Carbapenem susceptibility testing results were available for less than 90% of the reported *Klebsiella pneumoniae* cases. The results must be interpreted with caution.

§ France did not report case-based data on *Klebsiella pneumoniae* to EARS-Net for 2023 due to recent changes in reporting from the French surveillance system.

National reduction target already reached by 2023 (see Council recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach 2023/C 220/01. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=oj:JOC_2023_220_R_0001)