RAPID RISK ASSESSMENT

Carbapenem-resistant Enterobacterales – third update

3 February 2025

Summary

Epidemiological situation

Carbapenem resistance in Enterobacterales, such as *Klebsiella pneumoniae* and *Escherichia coli*, poses a significant threat to patients and healthcare systems in European Union/European Economic Area (EU/EEA) countries. Since the last update of ECDC's rapid risk assessment on carbapenem-resistant Enterobacterales (CRE) was published in 2019, there have been various signs that the epidemiological situation in the EU/EEA is continuing to deteriorate. These signs include (a) an 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; (b) convergence of virulence and resistance in *K. pneumoniae,* including healthcare-associated spread of hypervirulent *K. pneumoniae* ST23 carrying carbapenemase genes; (c) newly emerging Enterobacterales species carrying carbapenemase genes; (d) plasmid-mediated spread of carbapenemase genes causing outbreaks within hospitals and across healthcare networks, and (e) increasing detection of isolates (including isolated cases and clusters) of high-risk lineages of *E. coli* carrying carbapenemase genes with a risk of spread in the community.

Risk assessment

Based on the deteriorating epidemiological situation, the probability of further spread of CRE in the EU/EEA is high. CRE bloodstream infections are associated with a high level of attributable mortality, primarily due to delays in administration of effective antimicrobial therapy, and the limited number of alternative and easily available treatment options, despite the existence of newly approved antimicrobials. Consistent application of infection prevention and control (IPC) measures and antimicrobial stewardship can reduce the spread of CRE, but their implementation in many hospitals is sub-optimal and has been insufficient to achieve sustained control of high-risk lineages of carbapenem-resistant *K. pneumoniae* and other Enterobacterales. If spread of CRE continues at the current rate, the impact is expected to be high. If strong, consistent EU/EEA-wide national control efforts are implemented to slow down the spread of CRE, the impact will be moderate. When considered together, probability and impact result in a high-to-very-high risk of further spread of CRE in the EU/EEA.

Recommendations

Enhanced efforts are required to control and reduce harm related to the spread of CRE in the EU/EEA, as follows:

- Strengthen national coordination of control measures between hospitals and regions and support to hospitals in the implementation of control measures. If not already in existence, a dedicated multidisciplinary national management team should be set up at the appropriate national level.

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- Develop a CRE management plan (as part of the National Action Plan on antimicrobial resistance, an action plan on multidrug-resistant organisms (MDROs), or as a stand-alone document) outlining actions and budget, with regular public reporting on progress. Clear targets should be established with defined timelines.
- Implement enhanced IPC measures in hospitals to interrupt transmission of carbapenem-resistant *K. pneumoniae* and other CRE. This also includes pre-emptive isolation and screening for asymptomatic CRE carriage on hospital admission for patients who have been hospitalised in a country or hospital with a known or suspected high prevalence of CRE in the preceding 12 months. Detailed IPC measures are outlined in the Recommendations section.
- Apply antimicrobial stewardship to decrease selection pressure and preserve the effectiveness of the carbapenems and the newly approved antimicrobials. This includes national treatment guidelines for CRE infections and audits of their implementation.
- Strengthen genomic surveillance, including whole-genome sequencing in near real time, accompanied by systematic metadata to guide IPC measures by identifying sources of CRE outbreaks and delineating transmission chains. Genomic surveillance is also required for *E. coli* carrying carbapenemase genes for early identification of community-associated spread.
- Provide adequate laboratory capacity for rapid detection and characterisation of CRE, including phenotypic antimicrobial susceptibility testing and identification of carbapenemase genes to enable targeted use of newly approved antimicrobials.
- Strengthen innovation and access to antimicrobials indicated against CRE infections.

Infections with MDROs, including CRE, result in a substantial human and economic burden for EU/EEA countries. Nevertheless, according to a study from the Organisation for Economic Co-operation and Development, investment in implementing a mixed policy package, including improving IPC and antimicrobial stewardship, would be not only cost-effective, but would also result in savings for EU/EEA countries.

Epidemiological situation

Phenotypic surveillance of carbapenem-resistant Enterobacterales

For *Klebsiella pneumoniae*, data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) for 2023 show large variability in the national percentages of carbapenem (imipenem or meropenem) resistance in isolates from invasive infections (mostly bloodstream infections), ranging from 0% to 69.7% [1]. The population-weighted mean percentage for the EU/EEA showed a significantly increasing trend from 10.4% in 2019 to 13.3% in 2023 [1]. Significantly increasing national trends in carbapenem resistance percentages were observed in invasive isolates of *K. pneumoniae* during the period 2019−2023 for Belgium, Bulgaria, Croatia, Cyprus, Czechia, Estonia, Germany, Hungary, Latvia, Poland, Romania, Slovakia, Slovenia and Sweden [2].

In 2023, the estimated incidence of bloodstream infections (BSIs) of carbapenem-resistant *K. pneumoniae* for the EU/EEA increased from 2.52 in 2019 to 3.97 per 100 000 population, which corresponds to an increase of 57.5% [1]. This increasing incidence runs contrary to the EU target laid out in the Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach, which invites Member States to take appropriate national measures to ensure that, by 2030, the total incidence of BSIs with carbapenem-resistant *K. pneumoniae* is reduced by 5% in the EU, compared to 2019 (baseline year) [3]. On the basis of data from 2023, to date only three EU Member States have reported a decreasing incidence of carbapenem-resistant *K. pneumoniae* BSI and already reached their national reduction target. All other Member States reported an increase between 2019 and 2023, moving away from their national targets (Table 1). It is worth noting that the overall incidence of *K. pneumoniae* BSIs (i.e. including both carbapenem-resistant and carbapenem-susceptible cases) also increased by 18% (from 20.5 to 24.2 per 100 000 population) during 2019−2023, but the increase for carbapenem-resistant *K. pneumoniae* BSIs (57.5%) was much steeper than for carbapenem-susceptible *K. pneumoniae* BSI (12.5%).

For *Escherichia coli*, EARS-Net data for 2023 show a lower overall EU/EEA population-weighted mean percentage (0.3%) of carbapenem resistance in invasive isolates, with national percentages ranging from 0% to 1.8% [2]. Between 2019 and 2023, a slightly decreasing trend was observed for the EU/EEA population-weighted mean of national percentages from 0.4% to 0.3%, and the incidence of carbapenem-resistant *E. coli* BSIs decreased from 0.2 to 0.14 per 100 000 population (30% decrease) [1].

Table 1. Estimated incidence of bloodstream infections with carbapenem resistance and trend 2019–2023, as well as the percentage change 2019–2023, EU/EEA, 2023 [1,2]

Country	Estimated incidence[a] of *K. pneumoniae* isolates from bloodstream infections with carbapenem resistance (n per 100 000 population)			
	2019	2023	Trend[b] 2019-2023	Change (%)[c] 2019-2023
Austria	0.20	0.29	-	+45.0
Belgium	0.27#	0.47#	↑	+74.1
Bulgaria	2.24#	7.75#	↑	+246.0
Croatia	1.2#	4.53	↑	+277.5
Cyprus	2.61	9.80	↑	+275.5
Czechia	0.09^	0.26^	↑	+188.9
Denmark	0.07	0.08	-	+14.3
Estonia	0.00^	0.44^	↑	NA
Finland	0.06	0.02	↓	-66.7
France	0.22	0.13 (2022)*	NA*	NA*
Germany	0.20#	0.25#	-	+25.0
Greece	13.05#	21.44	↑	+64.3
Hungary	0.09	0.76	↑	+744.4
Iceland	ND	0.00	NA	NA
Ireland	0.11	0.04	-	-63.6
Italy	8.43	9.29	-	+10.2
Latvia	0.00#	0.89#	↑	NA
Liechtenstein	ND	0.00#	NA	NA
Lithuania	0.54	0.73	-	+35.2
Luxembourg	0.16#	0.30	-	+87.5
Malta	2.13	0.97	-	-54.5
Netherlands	0.02	0.04	-	+100.0
Norway	0.04	0.08	-	+100.0
Poland	1.38#	3.69#	↑	+167.4
Portugal	2.93	4.19	↑	+43.0
Romania	7.12#	20.02#	↑	+181.2
Slovakia	0.52	1.33	-	+155.8
Slovenia	0.05	0.62	↑	+1 140
Spain	0.76#	0.96#	↑	+26.3
Sweden	0.03	0.12	↑	+300.0
EU[d]	**2.52**	**3.97**	↑	**+57.5**

NA: not applicable.
[a] Incidence was estimated using the EARS-Net data reported to EpiPulse. Each de-duplicated isolate from a blood sample (>99% data) or cerebrospinal fluid sample (<1% data) was considered a proxy for bloodstream infection.
[b] ↑ and ↓ indicate statistically significant increasing and decreasing trends, respectively;–indicates no statistically significant trend.
[c] The 'Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach' (2023/C 220/01) includes 2030 EU targets, with 2019 as the baseline year: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOC_2023_220_R_0001
[d] Excluding France (see footnote).*
^ The antimicrobial group/agent was tested for <90% of isolates. The results should be interpreted with caution.
 # One or more of the three representativeness indicators (geographical, hospital and/or isolate representativeness) were not reported as 'High'. The results should 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.*

Genomic surveillance of carbapenem-resistant Enterobacterales

Genomic surveillance showed that the spread of carbapenem-resistant *K. pneumoniae* in European countries is primarily caused by the spread of high-risk lineages of *K. pneumoniae* carrying carbapenemase genes within and between acute care hospitals [4]. These high-risk lineages include *K. pneumoniae* sequence type (ST)11, ST15, ST101 and ST258/512 [4] and more recently ST147 and ST307 [5,6]. Frequent transmission events within hospitals are driving the repeated emergence and rapid spread of new high-risk lineages throughout healthcare systems [7,8]. Among 1 566 carbapenem-resistant *K. pneumoniae* isolates collected in 36 European countries for the carbapenem- and/or colistin-resistant Enterobacterales (CCRE) survey in 2019, the most frequently detected carbapenemase genes were *bla*$_{KPC}$ in 38.3% of isolates, *bla*$_{OXA-48}$-like in 28.9% and *bla*$_{NDM}$ in 15.3% (ECDC, unpublished data). However, this European-level summary conceals major differences in the national epidemiology, with different predominant carbapenemase genes in individual EU/EEA countries. Furthermore, the carbapenemase gene distribution has probably changed since 2019. In particular, there have been several reports about increasing detection of metallo-beta-lactamase (MBL) genes [9-14] and of isolates carrying two carbapenemase genes, such as *bla*$_{OXA-48}$ and *bla*$_{NDM}$, in European countries [15-18].

Convergence of multidrug resistance (including carbapenem resistance) and increased virulence in *K. pneumoniae* poses an additional threat for patients [19]. There are examples of healthcare-adapted carbapenem-resistant high-risk lineages of *K. pneumoniae* acquiring virulence genes [20-24], as well as known community-associated hypervirulent *K. pneumoniae* (hvKp) lineages acquiring carbapenemase genes [20,25,26]. Both examples have been reported in the EU/EEA. Mosaic plasmids that carry both carbapenemase genes and virulence genes have been detected. While previously hvKp were only rarely observed in the EU/EEA, sustained healthcare-associated spread of hvKp ST23 carrying carbapenemase genes has now been reported in Ireland [26]. For more details please refer to ECDC's rapid risk assessment 'Emergence of hypervirulent *Klebsiella pneumoniae* ST23 carrying carbapenemase genes in EU/EEA countries, first update' [26].

In *E. coli*, phenotypic carbapenem resistance has remained low [1]. However, investigations by the European Antimicrobial Resistance Genes Surveillance Network (EURGen-Net) have documented an increase in the detection of *E. coli*-carrying carbapenemase genes in the EU/EEA involving various combinations of high-risk STs and carbapenemase genes, including *E. coli* ST167, ST361, ST405, ST410 and ST648 carrying *bla*$_{NDM-5}$ [27] and *E. coli* ST38 carrying *bla*$_{OXA-244}$ [28]. In addition, whole-genome sequencing (WGS) and epidemiological data from 17 national reference laboratories participating in EURGen-Net has shown that *E. coli* ST131 has now acquired a variety of carbapenemase genes, most frequently *bla*$_{OXA-244}$ and *bla*$_{OXA-48}$ [29]. For the 211 carbapenem-resistant *E. coli* isolates collected in the CCRE survey, the most frequently detected carbapenemase genes were *bla*$_{NDM}$ in 38%, followed by *bla*$_{OXA-48}$-like in 32% and *bla*$_{KPC}$ in 10% (ECDC, unpublished data).

Import of various multidrug-resistant organisms (MDROs) including carbapenem-resistant Enterobacterales (CRE) into EU/EEA countries (e.g. Denmark, Germany, the Netherlands, Norway, Poland, Spain, Sweden) was documented in relation to patients from Ukraine after the start of the war in 2022 [16-18,30-32]. However, high-risk lineages of carbapenemase-producing *K. pneumoniae* had been spreading in hospitals in the EU/EEA before the war, as documented by EuSCAPE in 2013−2014 [4] and the CCRE survey in 2019. In addition, cross-border transfer of patients with CRE occurs frequently between EU/EEA countries and from non-EU/EEA countries other than Ukraine [15]. An example is *Providencia stuartii* carrying *bla*$_{NDM}$ genes that recently received attention due to cross-border spread related to medical transfers from Ukraine [33]. However, further investigation provided evidence of a wider dissemination of *P. stuartii* carrying *bla*$_{NDM}$ or *bla*$_{VIM}$ genes in Eastern Europe and the Balkan region, including Bulgaria, Greece, Hungary, North Macedonia, Romania and Serbia, that was not related to medical transfers from Ukraine [34].

In addition to the increasing spread of the above-mentioned species of CRE (i.e. carbapenem-resistant *K. pneumoniae*, *E. coli* and *P. stuartii*), an unpublished ECDC survey from 2023 and other studies have shown that other species of CRE are being detected in the EU/EEA countries, including carbapenem-resistant *Citrobacter freundii* complex [35,36], carbapenem-resistant *Enterobacter cloacae* complex [37], carbapenem-resistant *Klebsiella oxytoca*, carbapenem-resistant *Proteus* spp., and carbapenem-resistant *Serratia marcescens*. In addition, carbapenemase genes on plasmids disseminate through horizontal transfer between different Enterobacterales species and strains [38]. Plasmid outbreaks and transmission events involving different CRE species have been described in European countries [39-43]. Moreover, it should be noted that not all Enterobacterales isolates carrying carbapenemase genes show carbapenem resistance in phenotypic susceptibility tests, thereby resulting in undetected spread of these isolates and of these genes among Enterobacterales. For example, this is the case for isolates carrying *bla*$_{OXA-48}$-like genes [44].

Treatment options for CRE including newly approved antimicrobials

Most carbapenemase enzymes are active against penicillins, cephalosporins and carbapenems and the presence of carbapenemase genes and carbapenemase production therefore results in reduced susceptibility, or even resistance to these agents. In addition, carbapenemase genes are often present together with genes that confer resistance to other antimicrobials, including aminoglycosides, quinolones and trimethoprim-sulfamethoxazole, resulting in resistance to multiple classes of antimicrobials that might otherwise be used as alternatives to penicillins, cephalosporins and carbapenems [27,45]. Historically, the antimicrobials that showed generally consistent *in vitro* activity against most CRE include colistin, fosfomycin and tigecycline. There are, however, concerns about their effectiveness, frequent adverse effects, rapid development of resistance during treatment and increasing resistance globally [46-48]. According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), colistin should only be used in combination with another active antimicrobial [49]. There is a particular concern regarding colistin therapy and nephrotoxicity [46,50,51]. Testing for susceptibility to fosfomycin is discouraged, except for urinary tract infections caused by *E. coli* [52]. For tigecycline, EUCAST provides interpretative breakpoints for *E. coli* and *Citrobacter koseri* [53] and tigecycline has significant limitations for treatment of BSIs.

Since 2016, several new antimicrobials active against CRE have received marketing authorisation for use in the EU, including ceftazidime-avibactam (2016) [54], eravacycline (2018) [55], meropenem-vaborbactam (2018) [56], imipenem-relebactam (2020) [57], cefiderocol (2020) [58], cefepime-enmetazobactam (2024) [59], and aztreonam-avibactam (2024) [60] (Table A1 in the Annex). Of these, eravacycline has EUCAST breakpoints only for *E. coli* (and not for other Enterobacterales) and it is not recommended for the treatment of CRE infections due to insufficient evidence that it works. [61]. In addition, the role of cefepime-enmetazobactam for the treatment of CRE infections has not yet been determined [62]. These antimicrobials are therefore not discussed further in this assessment.

The activity of several newly approved antimicrobials depends on the type of CRE. The inhibitors avibactam, relebactam and vaborbactam do not inhibit MBLs such as New Delhi metallo-beta-lactamase (NDM), imipenemase (IMP) and Verona integron-encoded metallo-beta-lactamase (VIM), and therefore cannot protect their antimicrobial combination partner against the activity of these carbapenemases. However, aztreonam is not inactivated by MBLs, so the combination aztreonam-avibactam retains activity against MBLs when protected from other beta-lactamases by avibactam [63]. In addition, meropenem-vaborbactam and imipenem-relebactam have limited activity against CRE-carrying $bla_{\text{OXA-48}}$-like carbapenemase genes and are not suggested for treating infections with CRE-carrying $bla_{\text{OXA-48}}$-like carbapenemase genes, even if these isolates are susceptible *in vitro* [64]. Due to these differences in activity against specific carbapenemases, treatment decisions require early availability of antimicrobial susceptibility testing (AST) results and characterisation of the carbapenemase gene of the CRE isolate responsible for the infection [64], as well as the expertise to apply this information to treatment decisions.

Based on the distribution of carbapenemase genes from the 2019 CCRE survey, it is estimated that in Europe about a third of carbapenem-resistant *K. pneumoniae* can be treated with imipenem-relebactam and meropenem-vaborbactam, based on their carriage of bla_{KPC}, and about two-thirds can be treated with ceftazidime-avibactam, based on their carriage of bla_{KPC} or $bla_{\text{OXA-48}}$-like genes. However, the distribution of carbapenemase genes varies widely, by country and hospital, and this distribution may have changed considerably since 2019, especially with recent reports of the increasing prevalence of CRE-carrying MBL genes, against which ceftazidime-avibactam, imipenem-relebactam and meropenem-vaborbactam are not active.

EARS-Net does not monitor susceptibility to newly approved antimicrobials with activity against CRE and the corresponding resistance percentages in invasive *K. pneumoniae* and *E. coli* infections (mostly from BSIs) are therefore not available for the EU/EEA. In 2018, an ECDC rapid risk assessment signalled the emergence of CRE with resistance to ceftazidime-avibactam [65]. The CCRE survey performed in 2019 showed that 24.6% (277/1 126) of carbapenem-resistant *K. pneumoniae* and 37.4% (61/163) of carbapenem-resistant *E. coli* isolates were resistant to ceftazidime-avibactam, which was mainly explained by the presence of MBL genes in these isolates.

Aztreonam-avibactam and cefiderocol are substances with activity against a broader range of CRE, regardless of the type of carbapenemase. Aztreonam is not inactivated by MBLs, but is hydrolysed by many other clinically relevant beta-lactamases that are commonly carried in association with MBLs [63]. These other beta-lactamases can be inhibited by avibactam so that the combination aztreonam-avibactam retains broad activity against CRE carrying MBL genes. Susceptibility to aztreonam-avibactam has shown to be high when testing large strain collections [66], but various resistance mechanisms have already been described [67-69].

Cefiderocol is a siderophore cephalosporin that can bind to extracellular free iron and utilises iron transport channels to enter the bacterial cell [70]. Cefiderocol primarily targets penicillin-binding protein 3 (PBP3) and modifications of PBP3 may confer resistance to cefiderocol. Other reported cefiderocol resistance mechanisms (usually found in combination) include beta-lactamase variants, porin mutations, siderophore receptor mutations and efflux pumps [71]. In addition, cross-resistance between ceftazidime-avibactam and cefiderocol due to KPC variants has been reported [72]. Data currently available on cefiderocol resistance percentages vary widely because of the bias introduced when isolates are selected for testing and because cefiderocol poses several unsolved technical challenges related to phenotypic susceptibility testing. The highest cefiderocol resistance percentages are seen in NDM-producing CRE [73-76].

During the past few years (latest year available: 2023), the combined consumption of newly approved antimicrobials with activity against CRE (including ceftazidime-avibactam, imipenem-relebactam, meropenem-vaborbactam, cefiderocol, but excluding aztreonam-avibactam which was only approved for use in the EU in 2024) has increased in the EU/EEA. Data from the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) show that consumption of newly approved antimicrobials is at a much lower level than consumption of polymyxins – i.e. mainly colistin (Table 2). The high polymyxin consumption suggests lack of sufficient access to more effective and better tolerated antimicrobials, including the newly approved antimicrobials, for the treatment of infections with CRE and other carbapenem-resistant Gram-negative bacteria. Another potential factor contributing to the high polymyxin consumption may also be the unavailability of rapid tests for the identification of carbapenemase genes, which is required to guide treatment with newly approved antimicrobials.

The lack of access to newly approved antibiotics in the EU was illustrated by a study published in 2020 which showed that most new antibacterials approved since 1 January 2010 were not commercially available to patients in many high-income countries due to a combination of delayed marketing authorisation submission and approval, delayed commercial launch after marketing approval, and market withdrawals and delays due to bankruptcy. European marketing authorisation did not lead to automatic European access, as even though 14 of the antimicrobials had been approved by the European Medicines Agency, far fewer were commercially launched [77].

In 2024, the European Commission Health Emergency Preparedness and Response Authority (HERA) conducted a survey of EU/EEA countries in preparation for a pilot multi-country revenue guarantee initiative to improve the availability and access to new or recently authorised antibiotics. Twenty-four countries expressed an interest in participating in the pilot, confirming inadequate access to newly approved antibiotics for the treatment of CRE and other carbapenem-resistant Gram-negative bacteria in the EU/EEA (unpublished data).

Table 2. Comparison of consumption of newly approved antimicrobials with activity against carbapenem-resistant Enterobacterales, polymyxins and carbapenems, EU/EEA, 2023

Name	EU/EEA consumption volume (number DDD)	EU/EEA consumption rate**** (DDD per 1 000 inhabitants per day)
Newly approved antimicrobials with activity against CRE*	652 808	0.00405
Polymyxins**	4 113 729	0.02576
Carbapenems***	11 317 105	0.07031

DDD – defined daily doses; EEA – European Economic Area; EU – European Union.
** Newly approved antimicrobials included in the calculation for this table are ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam and cefiderocol. For more details, please refer to Table A1 in the Technical Annex.*
*** Polymyxins include colistin (oral, inhaled, and parenteral) and polymyxin B (oral and parenteral).*
**** Carbapenems included all carbapenems in ATC group J01DH, with the exception of the newly approved combinations meropenem-vaborbactam and imipenem-relebactam, which are included with newly approved antimicrobials.*
***** Population-weighted mean rate among EU/EEA countries that reported data to ESAC-Net for 2023. Population coverage data for hospital sector consumption from ESAC-Net was used to calculate consumption rates.*

ECDC risk assessment for the EU/EEA

Carbapenem-resistant Enterobacterales (CRE) pose a significant threat to patients and healthcare systems in the EU/EEA. Since the publication of the second update of ECDC's rapid risk assessment on CRE in 2019, there have been various signs of increasing spread of CRE in the EU/EEA:

- increasing incidence of carbapenem-resistant *K. pneumoniae* BSI in 23 EU/EEA countries (Table 1);
- additional genomic evidence of continued transmission and outbreaks of high-risk lineages of carbapenemase-producing *K. pneumoniae* in hospitals in the EU/EEA [7];
- examples of convergence of virulence and resistance in *K. pneumoniae* including healthcare-associated spread of hvKp ST23 in the EU/EEA [26];
- newly emerging Enterobacterales species carrying carbapenemase genes [34];
- increasing evidence of plasmid-mediated spread of major carbapenemase genes, through intra- and inter-species horizontal gene transfer, causing outbreaks within hospitals and across healthcare networks [78];
- increasing detection of high-risk lineages of *E. coli* carrying carbapenemase genes in the EU/EEA, with a risk for transmission in the community [27,29].

Based on these findings, the probability of further spread is considered to be high.

CRE infections are associated with a high level of attributable mortality, primarily due to delays in administration of effective antimicrobial therapy and the limited number of alternative treatment options [79]. Novel antimicrobials or combinations have recently been approved for use in the EU. These have varying activity against CRE, depending on the type of carbapenemase produced or other mechanisms of resistance. These newly approved antimicrobials therefore require prior AST, as well as carbapenemase identification to optimise their use against specific CRE and ensure appropriate use. In addition, the high consumption of colistin, an antimicrobial that has a significant nephrotoxicity, suggests that many hospitals in the EU/EEA experience difficulties in accessing these newly approved antimicrobials.

The impact of CRE infections on patients can be mitigated by appropriate awareness, early laboratory detection and characterisation and timely expert advice on infection management. Consistently applied infection prevention and control (IPC) measures, as well as antimicrobial stewardship can be effective to reduce the spread of CRE. However, the increasing spread of high-risk lineages of carbapenem-resistant *K. pneumoniae* shows that in many EU/EEA hospitals the implementation of IPC measures is currently insufficient to achieve control. If spread of CRE continues at the current rate, the impact is expected to be high. If strong and consistent EU/EEA-wide national control efforts are implemented to slow down the spread of CRE, the impact will be moderate. When considered together, probability and impact result in a high-to-very-high risk of further CRE spread in the EU/EEA.

ECDC recommendations

1. National coordination and response

CRE national management team

The inter-hospital and inter-regional spread of CRE requires a national response to coordinate control measures between hospitals and regions and support hospitals in the implementation of control measures. If not already in existence, 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 generate, collate and analyse surveillance data; 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. In addition, such teams could report on challenges in availability (beyond shortages) of these antimicrobials according to processes agreed with the European Commission services and EU agencies, and support EU-wide initiatives to identify and address gaps in access and availability [80,81].

CRE management plan

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

2. Measures to prevent transmission of CRE in healthcare settings

The IPC measures should be applied through 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 [82].

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 at all times since many patients colonised with CRE or 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 (1) appropriate patient placement; (2) appropriate use of personal protective equipment, including gloves and gowns; (3) limiting transport and movement of patients; (4) appropriate use of disposable or dedicated patient-care equipment; and (5) prioritisation of cleaning and disinfection of patient rooms [83].
- 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 and medical equipment.
- Communication in advance in the case of patient transport or transfer of a CRE-positive patient (asymptomatic carriage of infected) and flagging the CRE status in patient administration systems and/or medical charts.
- Upon hospital admission, implementation of active surveillance of patients at high risk of asymptomatic CRE carriage, through rectal/faecal screening for CRE carriage and tailored to the local epidemiology. Risk factors 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 [84]. 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-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 facility with a known CRE outbreak or high CRE prevalence in the same country. Depending on the epidemiological situation, screening of 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* BSIs and urinary tract infections from various countries and regions of the world are available from the Global Antimicrobial Resistance and Use Surveillance System (GLASS) dashboard ('Global AMR data', 'Resistance to antibiotics in the selected calendar year') [85].
- 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 (typically sinks, toilets, showers or drains), environmental cultures followed by removal (where possible) or management of the identified environmental reservoirs of CRE.
- Training of staff on IPC, including the above-listed measures.
- 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 CRE when in a hospital).
- Monitoring of 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.

3. Laboratory capacity and surveillance

For Enterobacterales isolated from diagnostic samples, standardised quality-assured AST is required to detect carbapenem resistance. Timely reporting of AST results is important to inform treatment decisions. In addition, control of CRE in EU/EEA countries requires active surveillance to detect asymptomatic carriers of CRE. 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 indicates that meropenem provides the optimal balance between sensitivity and specificity for detecting CRE that produce carbapenemases using the screening cut-off values (MIC >0.125 mg/L or zone diameter <28 mm) [86].

After detecting reduced susceptibility to carbapenems, it is important to determine whether the organism produces a carbapenemase, and if so the family of carbapenemase produced. This 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 in molecular testing and detection and analyses of relevant virulence genes, in addition to carbapenemase and other resistance genes. WGS enables the relatedness of CRE isolates to be determined and transmission events and outbreaks to be detected. It is particularly valuable in tracking the emergence and spread of high-risk clonal groups of CRE and associated plasmids within and between 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 [87]. Genomic surveillance is also required to detect virulence genes that are becoming increasingly important due to hvKp and other high-risk *K. pneumoniae* lineages. While carbapenem-resistant *K. pneumoniae* and carbapenem-resistant *E. coli* remain the main public health threat in the EU/EEA, other carbapenem-resistant Enterobacterales species, as well as the tracking of epidemic plasmids carrying carbapenemase genes will require enhanced surveillance in the coming years.

4. 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 [88]. Increased awareness among clinicians of the challenge of detecting and treating CRE infections, and access to timely expert advice on infection management are also important.

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 [89].

General good practice recommendations include optimal dosing schemes with attention to adverse effects; optimisation of dosing and administration by pathogen and indication; use of EUCAST recommended dosing, source control and follow-up cultures [61]. 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' [54,56-58,60].

5. Measures to prevent spread of CRE into the community

It is important to avoid the potential transmission of CRE via the food chain. The harmonised monitoring programme for antimicrobial resistance in 'food-producing animals and food thereof' stipulates that CRE should be monitored in broilers, fattening turkeys, fattening pigs and bovine animals (less than one year of age), and in meat derived thereof every second year on a routine basis [90]. Continued prohibition of the use of carbapenems in food-producing animals is a simple and effective option for intervention [91]. As genes encoding carbapenemase production are mostly plasmid-mediated and co-resistance may be an important issue in the spread of such resistance mechanisms, decreasing the frequency of antimicrobial usage in animal production within the EU in accordance with prudent use guidelines is also a high priority [91].

A multifaceted, integrated approach to minimising antimicrobial use in food-producing animals is recommended and further options related to this are outlined in the 'EMA and EFSA Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety' [92]. Improving the conditions of animal husbandry (e.g. biosecurity, hygienic conditions) and implementing alternative measures to antimicrobials would reduce both the development of antimicrobial-resistant bacteria in food-producing animals and the need to use antimicrobials.

In households and shared public environments, standard personal hygiene rules should be applied to prevent person-to-person transmission, as well as good food handling practices to prevent food contamination from colonised handlers. In addition, antimicrobial-resistant bacteria, including CRE, can spread from humans to the animal population through a variety of routes (wastewater, human/animal contact, etc.). Measures addressing such transmission routes which would be able to minimise the potential spill-over of CRE from humans to food-producing animals, are therefore particularly important.

6. Measures to prevent cross-border spread

Upon hospital admission, hospitals in EU/EEA countries should consider taking a detailed history of travel and hospitalisations for every admitted patient. Hospitals should also consider performing immediate pre-emptive isolation and screening for carriage of CRE (see Section 2 for details). In the event of direct patient transfer, 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.

Moreover, it is important to ensure that reliable epidemiological data is 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 international systems such as the GLASS-Emerging Antimicrobial Resistance Reporting (GLASS-EAR) and in the Early Warning and Response System (EWRS) where relevant. Use of the European surveillance portal for infectious diseases (EpiPulse) is encouraged to ensure transparent and timely information sharing at an early stage.

Limitations

The field of antimicrobial resistance is evolving, and new evidence may become available at short notice. In particular, any information related to treatment options for CRE infections, indications for specific antimicrobials and their safety should be considered as a general indication of potential use at this time. Individual prescribing decisions should be made in the context of the current SmPC, the individual patient context and other relevant information. At the time of writing, information on newly approved antimicrobials and resistance to them was limited. In addition, antimicrobial resistance percentages varied between studies. It is therefore important to bear in mind that resistance percentages are always strongly influenced by the bacterial collection selected for testing. Expected resistance to the newly approved antimicrobials was estimated based on genomic data for carbapenemase gene distribution. However, the last large-scale survey (CCRE survey) in European countries was conducted in 2019 and carbapenemase gene distribution may have considerably changed since then. Furthermore, there is limited information on treatment outcomes and adverse effects for the newly approved antimicrobials.

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Disclaimer

ECDC issues this risk assessment document based on an internal decision and in accordance with Article 20 of Regulation (EU) 2022/2371 on serious cross-border threats to health, Article 7(1) and 8a of Regulation (EC) No 851/2004 establishing a European Centre for Disease Prevention and Control (ECDC). In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU Member States and EEA countries. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency. This report was written with the coordination and assistance of an internal response team at the ECDC. All data published in this risk assessment are correct to the best of our knowledge at the time of publication. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

Technical annex

Disease background

Bacteria of the order Enterobacterales, such as *Escherichia coli* and *Klebsiella pneumoniae,* are part of the normal human intestinal microbiota, but are also often responsible for community-acquired and healthcare-associated infections. These bacteria are prone to acquiring resistance genes, and recent decades have seen a rapid increase in resistance to penicillins and cephalosporins due to the global spread of extended-spectrum beta-lactamases (ESBLs), first in *K. pneumoniae* and other *Klebsiella* species, then in *E. coli* and other Enterobacterales [93].

Carbapenems are beta-lactam antibiotics with a broad spectrum of activity against Gram-negative bacteria (including Enterobacterales) and Gram-positive bacteria. Carbapenems are reserve antimicrobial agents; however, in hospitalised patients, they are the treatment of choice for infections with multidrug-resistant (including ESBL-producing) Enterobacterales. Resistance to carbapenems has been reported with increasing frequency and increasing geographical spread since the beginning of the 1990s [94,95]. Enterobacterales can acquire resistance to carbapenems as a result of various mechanisms, including the production of frequently plasmid-encoded carbapenemase enzymes, which is the most common mechanism. However, combinations of other resistance mechanisms, such as changes in outer membrane permeability and/or upregulation of efflux pumps alongside production of ESBLs or AmpC beta-lactamases, may also result in carbapenem resistance.

Carbapenemases are a heterogenous group of enzymes that can hydrolyse most beta-lactams including carbapenems [96]. In the literature, carbapenemase-producing carbapenem-resistant Enterobacterales (CRE) are often named after the specific carbapenemase that they produce, such as *Klebsiella pneumoniae* carbapenemase (KPC)-producing CRE, oxacillinase 48 (OXA-48)-producing CRE, and those producing metallo-beta-lactamases (MBLs) including New Delhi metallo-beta-lactamase (NDM)-producing CRE, Verona integron-encoded metallo-beta-lactamase (VIM)-producing CRE, and imipenemase (IMP)-type metallo-beta-lactamase-producing CRE, among others. In the EU/EEA, the spread of carbapenemase-producing CRE, particularly for *K. pneumoniae,* is frequently linked to specific clonal lineages such as *K. pneumoniae* sequence type (ST)11, ST15, ST101, ST147, ST258/512, ST307 [4-6]. In addition, carbapenemase-producing *E. coli* of the high-risk lineages ST131, ST167, ST361, ST38, ST405, ST410 and ST648 are being detected with increasing frequency [27-29]. Plasmid-encoded carbapenemase genes are rapidly disseminated among CRE, including the high-risk lineages [78,97,98].

Impact of carbapenem-resistant Enterobacterales on human health

Frequency of occurrence

E. coli is the most common cause of community-acquired and healthcare-associated urinary tract infections. Other Enterobacterales, such as *K. pneumoniae*, are frequently the cause of healthcare-associated infections such as ventilator-associated pneumonia and bloodstream infections (BSIs) in healthcare settings [99]. For these bacteria, antimicrobial resistance, including to carbapenems, affects the choice of antimicrobial therapy as well as treatment outcomes for severe infections in hospitalised patients. Information about incidence rates and trends is provided on pages 2–3 of the main text.

While *K. pneumoniae* is usually an opportunistic pathogen, typically affecting patients with comorbidities in healthcare facilities, hypervirulent *K. pneumoniae* (hvKp) strains can cause infections in healthy individuals [100]. In the Asian countries where it is endemic, hvKp has emerged as a frequent cause of pyogenic liver abscess, community-acquired pneumonia, and community-acquired meningitis, while these types of infections are rare for *K. pneumoniae* without hypervirulence [100].

Treatment options

There has been a vicious circle of increasing antimicrobial resistance in Enterobacterales: global spread of ESBLs has resulted in increasing resistance of Enterobacterales to penicillins and cephalosporins, which has led to an increase in carbapenem consumption to treat patients with ESBL-producing Enterobacterales infections [101]. This in turn has increased the selection pressure for CRE and facilitated their spread. In the ECDC point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2022–2023, an increasing percentage of patients receiving a carbapenem was associated with a higher prevalence of healthcare-associated CRE (ECDC, unpublished data).

Treatment options for CRE infections are limited (see the section entitled 'Treatment options for CRE including newly approved antimicrobials' in the main text). Further information on the consumption of newly marketed antimicrobials is presented in Table A1 below.

Table A1. Consumption of antimicrobials newly approved in the European Union with activity against carbapenem-resistant Enterobacterales, EU/EEA countries, 2023

Name (ATC code)	Marketing authorisation for use in the EU	EU/EEA countries that reported consumption (N=27*)	EU/EEA consumption volume (Number DDD)	EU/EEA consumption rate** (DDD per 1 000 inhabitants per day)
Ceftazidime-avibactam (J01DD52)	23/06/2016	27	452 441	0.00283
Meropenem-vaborbactam (J01DH52)	20/11/2018	12	103 076	0.00104
Imipenem-relebactam (J01DH56)	13/02/2020	15	25 360	0.00030
Cefiderocol (J01DI04)	23/04/2020	16	71 887	0.00055
Aztreonam-avibactam (J01DF51)	22/04/2024	0***	N/A	N/A

ATC– Anatomical Therapeutic Chemical classification system; DDD – defined daily doses; EEA – European Economic Area; EU – European Union.
** Cyprus, Liechtenstein, and Sweden did not report data to ESAC-Net for 2023.*
*** Population-weighted mean rate among EU/EEA countries that reported consumption of each newly marketed antimicrobial in 2023. Population coverage data for hospital sector consumption from ESAC-Net was used to calculate consumption rates.*
**** Not approved for use in the EU in 2023.*

Mortality

High mortality rates, ranging from 30% to 75%, have been reported for patients with severe CRE infections in general [79,102]. Hospital outbreaks of carbapenem-resistant hvKp have also been associated with very high mortality [103-105].

An ECDC study estimated that in the EU/EEA in 2019, a total of 36 517 (95% uncertainty interval (UI): 32 081 – 41 308) carbapenem-resistant *K. pneumoniae* infections resulted in 3 853 (95% UI: 3 363 – 4 347) attributable deaths [106]. More recent estimates are not available, but the large increase in incidence between 2019–2023 strongly suggests that the number of attributable deaths also largely increased during this period. The same ECDC study estimated that in 2019, 4 094 (95% UI: 3 452 – 4 833) carbapenem-resistant *E. coli* infections overall resulted in 324 (95% UI: 269 – 380) attributable deaths in the EU/EEA [106].

Potential for spread

Transmission and outbreaks in healthcare settings

CRE, especially carbapenemase-producing *K. pneumoniae*, have a high potential for causing outbreaks in healthcare settings. Such outbreaks have been reported for years from several European countries [107-113] and frequently affect intensive care units [114-116]. In addition, CRE outbreaks have been related to frequently performed invasive medical procedures (e.g. in outbreaks related to bronchoscopy and endoscopy procedures) [110,117]. Long-term care facilities have also been shown to be a reservoir for CRE, including in EU/EEA countries [118-121]. The European survey of carbapenemase-producing *Enterobacteriaceae* (EuSCAPE) showed that a few high-risk lineages of *K. pneumoniae* are responsible for most of the spread of carbapenemase-producing *K. pneumoniae* throughout European hospitals, with evidence of within-hospital transmission in more than half of the participating European hospitals [4].

The hospital environment, including wastewater plumbing, hand wash basins and sinks, has been documented as a reservoir of CRE and found to be the source of CRE outbreaks, which required special water treatment or disinfection measures for effective control [122,123]. Investigations of outbreaks using whole genome sequencing (WGS) revealed hospital environmental reservoirs of a variety of bacteria, with plasmids carrying carbapenemase genes conferring carbapenem resistance, that transferred to diverse species and clonal strains of Enterobacterales [122-125]. Optimal design, installation and maintenance of essential sanitary ware and removal of those fittings that are not essential is expected to mitigate the associated risk.

Spread of carbapenem-resistant Enterobacterales in the community

While carbapenem-resistant *K. pneumoniae* is currently more frequent and more likely to cause healthcare-associated outbreaks, carbapenem-resistant *E. coli* poses a greater risk for community spread and a One Health perspective is important in managing risk associated with this species. Extraintestinal pathogenic *E. coli* have been identified in non-human reservoirs including food, food-producing animals, companion animals, sewage and other environmental sources [126] and can be transmitted via the faecal-oral, household, sexual or foodborne routes [127], making it difficult to control their spread in the human population. The spread of ESBL-producing Enterobacterales, mainly *E. coli*, in the community has demonstrated how rapidly such multidrug-resistant organisms (MDROs) can disseminate. ESBL-producing Enterobacterales can serve as a model for the spread of CRE because the same bacterial species are involved and the resistance genes are also carried on plasmids. In particular, *E. coli* ST131 is frequently resistant to several antimicrobial groups and has been a main driver of the global dissemination of the $bla_{\text{CTX-M-15}}$ ESBL gene [128]. There is a high risk that *E. coli* ST131 may play a similar role in disseminating carbapenemase genes in EU/EEA countries.

CRE have been detected from environmental, food and animal sources, including pigs, poultry, cattle, seafood, dogs, cats, horses, pet birds, swallows, wild boars, wild stork, gulls and black kites [129]. A few *E. coli* isolates harbouring carbapenemase genes ($bla_{\text{OXA-48}}$, $bla_{\text{OXA-181}}$, $bla_{\text{NDM-5}}$ and $bla_{\text{VIM-1}}$) were reported in fattening pigs, cattle under one year of age, poultry and meat thereof by a limited number of countries in harmonised antimicrobial resistance monitoring for 2021–2022 [130]. The European Food Safety Authority (EFSA) is currently working on a scientific opinion on CRE in the food chain in the EU/European Free Trade Association (EFTA) [131]. CRE have also been detected in seawater samples from a bathing site in Ireland, in a Spanish river ecosystem and in wastewater in the UK [132-134], thus indicating potential environmental reservoirs for further dissemination.

Consequences for health systems

By weakening the immune system or other barriers to infections, such as the skin barrier, advanced medical procedures such as intensive care, transplantation, cancer chemotherapy, neonatal care and invasive procedures increase the risk of patients developing healthcare-associated infections. If no effective antimicrobial prophylaxis and treatments are available, these procedures will be associated with a higher risk of morbidity and mortality for patients. Urinary tract infections with CRE in kidney and other solid organ transplant recipients have been associated with failure of antimicrobial therapy and fatal outcomes [135,136]. BSI with CRE was also a predictor of death in liver transplant patients, and CRE infection-related mortality was high (for example, 64% in allogenic stem cell transplant recipients in Italy) [137,138]. Mortality rates associated with CRE infections were high in patients with haematological malignancies [139] and low-birthweight neonates have also been affected by CRE BSI [140].

In addition to mortality, CRE infections have been associated with prolonged hospital stays [102]. CRE are therefore likely to result in a financial burden for healthcare systems. For example, in a French hospital over a period of two years, the costs of 16 patients with CRE was EUR 642 104 or, on average, more than EUR 40 000 per patient with CRE. These costs included losses due to decreased activity in the affected units, additional working hours and screening samples [141]. CRE outbreaks have also been found to be highly costly. For example, the cost of a CRE outbreak occurring across five hospitals in the UK was estimated to be EUR 1.1 million over 10 months [142].

For all infections with antimicrobial resistance (these include CRE infections) 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 (approximately EUR 6.6 billion PPP or 56% of total costs) as well as reduced participation in the workforce and reduced productivity gains [143]. OECD also estimated, after reviewing the cost-effectiveness of various policies and control measures, that investing EUR 3.4 PPP per capita per year in a mixed package of actions, starting with improved compliance with infection prevention and control (IPC) measures and antimicrobial stewardship, would save more than EUR 2.5 billion PPP in health expenditure and yield around EUR 2.3 billion PPP in productivity gains. In short, every euro invested in the mixed policy package would return nearly EUR 3 PPP in economic benefits, although this return varies between EU/EEA countries [143].

Guidance documents

For details on control measures for CRE and for the treatment of CRE infections, please refer to the following:

- ECDC's guidance on IPC measures and tools for the prevention of the entry of carbapenem-resistant *Enterobacteriaceae* into healthcare systems [84];
- WHO's guidelines for the prevention and control of carbapenem-resistant *Enterobacteriaceae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in healthcare facilities [83];
- WHO's implementation manual to prevent and control the spread of carbapenem-resistant organisms at the national and healthcare facility level [82];
- European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for treatment of infections caused by multidrug-resistant Gram-negative bacilli, for the management of infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalised patients and for the decolonisation of carriers of multidrug-resistant Gram-negative bacteria [61,144,145];
- WHO's guide to antimicrobial stewardship interventions [146] and the WHO AWaRe (Access, Watch, Reserve) antibiotic book [88];
- National guidelines of EU/EEA countries, as listed in the ECDC directory of online resources for the prevention and control of AMR and HAI [147].

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