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UFFICIO 5 PREVENZIONE DELLE MALATTIE TRASMISSIBILI E PROFILASSI INTERNAZIONALE

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**OGGETTO: *Rapid Risk Assessment dell'ECDC: Enterobatteri Resistenti ai carbapenemi (CRE)*
– 26 settembre 2019.**

Lo scorso 26 settembre, il Centro Europeo per la Prevenzione e il Controllo delle Malattie (ECDC) di Stoccolma ha pubblicato il Rapid Risk Assessment (RRA)¹ in oggetto, che si fornisce in allegato, per aggiornare il rischio di diffusione degli Enterobatteri resistenti ai carbapenemi (CRE) nell'Unione Europea (UE) e nell'Area Economica Europea (AEE), rispetto al precedente RRA dello scorso anno². Pertanto, la presente nota vuole fornire un aggiornamento rispetto alla precedente³ pubblicata dallo scrivente Ministero.

La resistenza ai carbapenemi nei batteri appartenenti alla famiglia delle *Enterobacteriaceae*, come *Klebsiella pneumoniae* ed *Escherichia coli*, rappresenta una minaccia significativa per i

¹ European Centre for Disease Prevention and Control. Carbapenem-resistant Enterobacteriaceae, second update – 26 September 2019. ECDC: Stockholm; 2019. <https://www.ecdc.europa.eu/en/publications-data/carbapenem-resistant-enterobacteriaceae-second-update>

² European Centre for Disease Prevention and Control. Rapid risk assessment: Carbapenem-resistant Enterobacteriaceae - first update 4 June 2018. Stockholm: ECDC; 2018. <https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-carbapenem-resistant-enterobacteriaceae-first-update>

³ Circolare ministeriale 1 agosto 2018 - Rapid Risk Assessment ECDC: Enterobatteri resistenti ai Carbapenemi - primo aggiornamento del 4 giugno 2018. <http://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2018&codLeg=65182&parte=1%20&serie=null>

cittadini, i pazienti e i sistemi sanitari in tutti i paesi dell'Unione Europea/Spazio economico europeo (UE/SEE). Le infezioni da CRE sono associate ad alta mortalità, con tassi dal 30% al 75%⁴, soprattutto in pazienti con infezioni del flusso sanguigno⁵, principalmente a causa dei ritardi nella somministrazione di un trattamento efficace e della disponibilità limitata di opzioni terapeutiche efficaci. Inoltre, sono stati segnalati ceppi di *K. pneumoniae* resistenti ai carbapenemi particolarmente virulenti, con un potenziale di diffusione globale. Sebbene la resistenza antimicrobica sia rara nei ceppi di *K. pneumoniae* ipervirulenti, sono stati descritti isolati che combinano resistenza ai carbapenemi, elevata trasmissibilità e ipervirulenza, finora principalmente in Asia^{6,7}, con mortalità complessiva estremamente elevata (84%)⁸. I ceppi ipervirulenti di *K. pneumoniae* si stanno diffondendo nella comunità, causando gravi infezioni in individui giovani sani senza comorbidità⁹.

I recenti eventi di importazione transfrontaliera dopo il trasferimento di pazienti, insieme ai grandi focolai regionali, nonché il peggioramento della situazione epidemiologica dei CRE nell'UE/SEE, evidenziano l'elevato rischio di ulteriore diffusione e la necessità di maggiori sforzi di controllo, descritte nelle sezioni seguenti di questo documento.

Per quanto riguarda la situazione epidemiologica dei CRE nei paesi UE/SEE, si rimanda alla recente pubblicazione del rapporto della Rete europea di sorveglianza della resistenza antimicrobica (EARS-Net, che raccoglie i dati degli isolati invasivi provenienti da sangue e liquido cerebrospinale nei paesi UE/SEE) per il 2018¹⁰. In generale, permane il gradiente nelle percentuali di resistenza, con quelle inferiori segnalate dai paesi del nord e le più elevate nel sud e nell'est dell'Europa, con oltre la metà degli isolati di *E. coli* e oltre un terzo degli isolati di *K. pneumoniae* resistenti ad almeno un gruppo antimicrobico sotto sorveglianza e con frequente resistenza combinata a diversi gruppi antimicrobici. La diffusione dei CRE produttori di carbapenemasi nell'UE/SEE è spesso legata, in particolare per *K. pneumoniae*, a specifici lignaggi clonali, come *K. pneumoniae* tipi 11, 15, 101, 258/512 e i loro derivati¹¹.

Nel mondo, le regioni e i paesi con la più alta prevalenza di CRE sono il subcontinente indiano (NDM CRE), Stati Uniti, Israele, Grecia e Italia (KPC CRE), Turchia, Medio Oriente e Nord Africa (OXA-48 CRE)^{12,13,14}. Per il Sud-est asiatico, sono state stimate percentuali di resistenza ai carbapenemi > 5% per *K. pneumoniae* in Vietnam, Filippine, Indonesia e Thailandia e per *E. coli* in Myanmar e Indonesia¹⁵. Prove indirette circa la prevalenza di CRE in diverse regioni sono fornite anche dallo stato di portatore di CRE in pazienti trasferiti da ospedali in altre regioni del mondo¹⁶ e in viaggiatori di ritorno in Europa da altre regioni¹⁷.

⁴ Tischendorf J, de Avila RA, Safdar N. Risk of infection following colonization with carbapenem-resistant Enterobacteriaceae: A systematic review. *Am J Infect Control*. 2016 May 1;44(5):539-43.

⁵ Neuner EA, Yeh JY, Hall GS, Sekeres J, Endimiani A, Bonomo RA, et al. Treatment and outcomes in carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections. *Diagn Microbiol Infect Dis*. 2011 Apr;69(4):357-62.

⁶ Gu D, Dong N, Zheng Z, Lin D, Huang M, Wang L, et al. A fatal outbreak of ST11 carbapenem-resistant hypervirulent *Klebsiella pneumoniae* in a Chinese hospital: a molecular epidemiological study. *Lancet Infect Dis*. 2018 Jan;18(1):37-46.

⁷ Lee CR, Lee JH, Park KS, Jeon JH, Kim YB, Cha CJ, et al. Antimicrobial Resistance of Hypervirulent *Klebsiella pneumoniae*: Epidemiology, Hypervirulence-Associated Determinants, and Resistance Mechanisms. *Frontiers in cellular and infection microbiology*. 2017;7:483.

⁸ Shankar C, Nabarro LE, Anandan S, Ravi R, Babu P, Munusamy E, et al. Extremely High Mortality Rates in Patients with Carbapenem-resistant, Hypermucoviscous *Klebsiella pneumoniae* Blood Stream Infections. *J Assoc Physicians India*. 2018 Dec;66(12):13-6.

⁹ Lee CR, Lee JH, Park KS, Jeon JH, Kim YB, Cha CJ, et al. Antimicrobial Resistance of Hypervirulent *Klebsiella pneumoniae*: Epidemiology, Hypervirulence-Associated Determinants, and Resistance Mechanisms. *Frontiers in cellular and infection microbiology*. 2017;7:483.

¹⁰ European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe 2018. Stockholm: ECDC; 2019. <https://www.ecdc.europa.eu/sites/default/files/documents/surveillance-antimicrobial-resistance-Europe-2018.pdf>

¹¹ David S, Reuter S, Harris SR, Glasner C, Feltwell T, Argimon S, et al. Epidemic of carbapenem-resistant *Klebsiella pneumoniae* in Europe is driven by nosocomial spread. *Nature microbiology*. 2019 Jul 29.

¹² El-Herte RI, Kanj SS, Matar GM, Araj GF. The threat of carbapenem-resistant Enterobacteriaceae in Lebanon: an update on the regional and local epidemiology. *Journal of infection and public health*. 2012 Jun;5(3):233-43.

¹³ Nordmann P, Poirel L. The difficult-to-control spread of carbapenemase producers among Enterobacteriaceae worldwide. *Clin Microbiol Infect*. 2014 Sep;20(9):821-30.

¹⁴ Mitgang EA, Hartley DM, Malchione MD, Koch M, Goodman JL. Review and mapping of carbapenem-resistant Enterobacteriaceae in Africa: Using diverse data to inform surveillance gaps. *Int J Antimicrob Agents*. 2018 Sep;52(3):372-84.

¹⁵ Malchione MD, Torres LM, Hartley DM, Koch M, Goodman JL. Carbapenem and colistin resistance in Enterobacteriaceae in Southeast Asia: Review and mapping of emerging and overlapping challenges. *Int J Antimicrob Agents*. 2019 Jul 29.

¹⁶ Kalpoe JS, Al Naiemi N, Poirel L, Nordmann P. Detection of an Ambler class D OXA-48-type beta-lactamase in a *Klebsiella pneumoniae* strain in The Netherlands. *J Med Microbiol*. 2011 May;60(Pt 5):677-8.

¹⁷ Ruppe E, Armand-Lefevre L, Estellat C, Consigny PH, El Mniai A, Boussadia Y, et al. High rate of acquisition but short duration of carriage of multidrug-resistant Enterobacteriaceae after travel to the Tropics. *Clin Infect Dis*. 2015 Aug 15;61(4):593-600.

La terapia di combinazione con due o più agenti attivi ha mostrato un beneficio in termini di sopravvivenza tra i pazienti con un'alta probabilità di morte¹⁸. Nel giugno 2016, è stata approvata dalla Commissione Europea la ceftazidima-avibactam, una nuova combinazione di antibiotici con attività contro le infezioni da CRE (ad eccezione delle infezioni da metallo-beta-lattamasi che producono CRE, come NDM o VIM), da utilizzare nell'UE per il trattamento di infezioni complicate addominali, del tratto urinario, polmonite acquisita in ospedale (inclusa la polmonite associata a ventilazione) e le infezioni dovute a batteri Gram-negativi aerobici in cui le opzioni terapeutiche sono limitate¹⁹. Alcuni risultati sono promettenti, sebbene vi siano preoccupazioni per lo sviluppo di resistenza²⁰. Anche la combinazione meropenem-vaborbactam è stata autorizzata nell'UE per le stesse indicazioni del ceftazidime-avibactam²¹ e ci sono ulteriori nuovi composti o combinazioni in sviluppo come imipenem-relebactam, plazomycin, cefiderocol, eravacycline e aztreonam-avibactam²².

Rischio di trasmissione dei CRE e focolai in ambito sanitario

I CRE hanno un elevato potenziale di provocare focolai in ambito sanitario. Tali focolai sono stati segnalati da diversi Stati Membri dell'UE, ad es. Repubblica ceca, Francia, Germania, Grecia, Spagna, Paesi Bassi e Regno Unito, incluso il nostro paese²³. Nel 2019, un focolaio esteso di CRE con produzione di NDM in Toscana è stato segnalato tramite l'Early Warning and Response System (EWRS)²⁴. I fattori di rischio per l'acquisizione di CRE in contesti sanitari sono simili a quelli segnalati per l'acquisizione di altri batteri multiresistenti. Questi includono l'ammissione e/o la lunga degenza in un'unità di terapia intensiva (UTI), una malattia grave, l'utilizzo di dispositivi invasivi e una precedente terapia antimicrobica, soprattutto se con carbapenemi^{25,26}.

L'eradicazione della resistenza ai carbapenemi dalla flora intestinale è difficile. Le percentuali di clearance spontanea variano tra gli studi²⁷ e sono stati riportati casi di trasporto continuo oltre i due anni²⁸. L'eradicazione del trasporto di CRE è stata anche tentata mediante trapianto di microbiota fecale^{29,30,31,32}.

È stato documentato il ruolo come serbatoio e fonte di CRE dell'ambiente ospedaliero, inclusi impianti idraulici per acque reflue mal progettati e lavandini, che richiedono un trattamento speciale

¹⁸ Gutierrez-Gutierrez B, Salamanca E, de Cueto M, Hsueh PR, Viale P, Pano-Pardo JR, et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. *Lancet Infect Dis.* 2017 Jul;17(7):726-34.

¹⁹ European Medicines Agency. Zavicefta - ceftazidime / avibactam. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004027/human_med_001993.jsp&mid=WC0b01ac058001d124.

²⁰ European Centre for Disease Prevention and Control. Emergence of resistance to ceftazidime-avibactam in carbapenem-resistant Enterobacteriaceae. Stockholm: ECDC; 2018. Available from: <https://ecdc.europa.eu/sites/portal/files/documents/RRA-Emergence-of-resistance-to%20CAZ-AVI-in-CRE-Enterobacteriaceae.pdf>.

²¹ European Medicines Agency. Vaborem -meropenem / vaborbactam. Amsterdam: EMA; 2018. <https://www.ema.europa.eu/en/medicines/human/EPAR/vaborem>.

²² Rodriguez-Bano J, Gutierrez-Gutierrez B, Machuca I, Pascual A. Treatment of Infections Caused by Extended-Spectrum-Beta-Lactamase-, AmpC-, and Carbapenemase-Producing Enterobacteriaceae. *Clin Microbiol Rev.* 2018 Apr;31(2).

²³ Gaibani P, Colombo R, Arghittu M, Cariani L, Ambretti S, Bua G, et al. Successful containment and infection control of a Carbapenem-resistant *Klebsiella pneumoniae* outbreak in an Italian hospital. *New Microbiol.* 2014 Jan;37(1):87-90.

²⁴ European Centre for Disease Prevention and Control. Rapid risk assessment: Regional outbreak of New Delhi metallo-beta-lactamase-producing carbapenem-resistant Enterobacteriaceae, Italy, 2018-2019. Stockholm ECDC; 2019. <https://ecdc.europa.eu/sites/portal/files/documents/04-Jun-2019-RRA-Carbapenems%2C%20Enterobacteriaceae-Italy.pdf>.

²⁵ Brizendine KD, Richter SS, Cober ED, van Duin D. Carbapenem-resistant *Klebsiella pneumoniae* urinary tract infection following solid organ transplantation. *Antimicrob Agents Chemother.* 2015 Jan;59(1):553-7.

²⁶ Savard P, Perl TM. Combating the spread of carbapenemases in Enterobacteriaceae: a battle that infection prevention should not lose. *Clin Microbiol Infect.* 2014 Sep;20(9):854-61.

²⁷ Oren I, Sprecher H, Finkelstein R, Hadad S, Neuberger A, Hussein K, et al. Eradication of carbapenem-resistant Enterobacteriaceae gastrointestinal colonization with nonabsorbable oral antibiotic treatment: A prospective controlled trial. *Am J Infect Control.* 2013 Dec;41(12):1167-72.

²⁸ Lubbert C, Lippmann N, Busch T, Kaisers UX, Ducombe T, Eckmanns T, et al. Long-term carriage of *Klebsiella pneumoniae* carbapenemase-2-producing *K pneumoniae* after a large single-center outbreak in Germany. *Am J Infect Control.* 2014 Apr;42(4):376-80.

²⁹ Saidani N, Lagier JC, Cassir N, Million M, Baron S, Dubourg G, et al. Faecal microbiota transplantation shortens the colonisation period and allows re-entry of patients carrying carbapenemase-producing bacteria into medical care facilities. *Int J Antimicrob Agents.* 2019 Apr;53(4):355-61.

³⁰ Dinh A, Fessi H, Duran C, Batista R, Michelon H, Bouchand F, et al. Clearance of carbapenem-resistant Enterobacteriaceae vs vancomycin-resistant enterococci carriage after faecal microbiota transplant: a prospective comparative study. *J Hosp Infect.* 2018 Aug;99(4):481-6.

³¹ Davido B, Batista R, Michelon H, Lepointeur M, Bouchand F, Lepeule R, et al. Is faecal microbiota transplantation an option to eradicate highly drug-resistant enteric bacteria carriage? *J Hosp Infect.* 2017 Apr;95(4):433-7.

³² Mahieu R, Cassisa V, Sanderink D, Chenouard R, Pailhories H, Kempf M, et al. Iterative Fecal Microbiota Transplantations for Eradicating Digestive Colonization With Carbapenemase-Producing Enterobacteriaceae: Is It Worth It? *Infect Control Hosp Epidemiol.* 2017 Oct;38(10):1265-6.

dell'acqua o misure di disinfezione per un controllo efficaci^{33,34}. Recenti studi hanno rivelato che serbatoi ambientali ospedalieri hanno permesso la diffusione di plasmidi che conferiscono resistenza ai carbapenemi a diverse specie e ceppi clonali di *Enterobacteriaceae*^{33,34,35,36}. Ciò evidenzia il valore della sorveglianza genomica avanzata per rilevare le epidemie, nonché la necessità di progettare in sicurezza l'ambiente del paziente in ospedale e dei dispositivi medici per evitare contaminazioni e/o consentire un'adeguata pulizia e disinfezione.

Rischio di diffusione dei CRE in comunità

Mentre i ceppi di *K. pneumoniae* resistenti ai carbapenemi attualmente sono più frequenti e hanno maggiori probabilità di causare focolai in ambito assistenziale, quelli di *E. coli* resistente ai carbapenemi presentano un rischio maggiore di diffusione nella comunità. Vi sono prove crescenti che l'*E. coli* patogeno extra-intestinale possa essere trasmesso all'uomo da una fonte animale alimentare^{37,38}. La produzione di carbapenemasi è stata riportata anche nell'agente patogeno di origine alimentare *Salmonella enterica*³⁹. La trasmissione oro-fecale e attraverso la catena alimentare hanno il potenziale di diffondere questa resistenza in comunità, anche tra la popolazione sana e giovane. I dati sulla prevalenza dell'infezione da CRE acquisita in comunità sono scarsi. Una revisione del 2017⁴⁰ ha descritto che una quota dallo 0,04% al 29,5% delle infezioni da CRE sarebbero state acquisite o avrebbero avuto esordio in comunità. Tuttavia, recentemente nell'UE sono stati segnalati casi di infezione da CRE a insorgenza comunitaria in soggetti che non avevano ricevuto assistenza sanitaria nei tre mesi precedenti⁴¹.

Recentemente, la presenza di CRE è stata documentata anche nell'ambiente - campioni provenienti da un sito di balneazione in Irlanda, un ecosistema fluviale spagnolo e acque reflue nel Regno Unito^{42,43,44} -, che costituisce una potenziale fonte di infezione e diffusione ulteriore.

Rischio di diffusione dei CRE in altri Paesi

Focolai di CRE dovuti a viaggiatori o al trasferimento oltre confine di pazienti infettati o colonizzati sono già stati descritti per molti Paesi in Europa^{10,45} e nel mondo⁴⁶.

Rischio per il funzionamento dei sistemi sanitari

Oltre alla elevata morbosità e mortalità, le infezioni da CRE causano un sovraccarico dei sistemi sanitari per le prolungate ospedalizzazioni, le ulteriori ore di lavoro del personale di

³³ Decraene V, Phan HTT, George R, Wyllie DH, Akinremi O, Aiken Z, et al. A Large, Refractory Nosocomial Outbreak of *Klebsiella pneumoniae* Carbapenemase-Producing *Escherichia coli* Demonstrates Carbapenemase Gene Outbreaks Involving Sink Sites Require Novel Approaches to Infection Control. *Antimicrob Agents Chemother.* 2018 Dec;62(12).

³⁴ Tofteland S, Naseer U, Lislevand JH, Sundsfjord A, Samuelsen O. A long-term low-frequency hospital outbreak of KPC-producing *Klebsiella pneumoniae* involving Intergenous plasmid diffusion and a persisting environmental reservoir. *PLoS One.* 2013;8(3):e59015.

³⁵ Weingarten RA, Johnson RC, Conlan S, Ramsburg AM, Dekker JP, Lau AF, et al. Genomic Analysis of Hospital Plumbing Reveals Diverse Reservoir of Bacterial Plasmids Conferring Carbapenem Resistance. *mBio.* 2018 Feb 6;9(1).

³⁶ Conlan S, Thomas PJ, Deming C, Park M, Lau AF, Dekker JP, et al. Single-molecule sequencing to track plasmid diversity of hospital-associated carbapenemase-producing *Enterobacteriaceae*. *Sci Transl Med.* 2014 Sep 17;6(254):254ra126.

³⁷ Manges AR, Johnson JR. Food-borne origins of *Escherichia coli* causing extraintestinal infections. *Clin Infect Dis.* 2012 Sep;55(5):712-9.

³⁸ Lazarus B, Paterson DL, Mollinger JL, Rogers BA. Do human extraintestinal *Escherichia coli* infections resistant to expanded-spectrum cephalosporins originate from food-producing animals? A systematic review. *Clin Infect Dis.* 2015 Feb 1;60(3):439-52.

³⁹ Le Hello S, Harrois D, Bouchrif B, Sontag L, Elhani D, Guibert V, et al. Highly drug-resistant *Salmonella enterica* serotype Kentucky ST198-X1: a microbiological study. *Lancet Infect Dis.* 2013 Aug;13(8):672-9.

⁴⁰ Kelly AM, Mathema B, Larson EL. Carbapenem-resistant *Enterobacteriaceae* in the community: a scoping review. *Int J Antimicrob Agents.* 2017 Aug;50(2):127-34.

⁴¹ Politi L, Gartzonika K, Spanakis N, Zarkotou O, Poulou A, Skoura L, et al. Emergence of NDM-1-producing *Klebsiella pneumoniae* in Greece: evidence of a widespread clonal outbreak. *J Antimicrob Chemother.* 2019 May 7.

⁴² Mahon BM, Brehony C, Cahill N, McGrath E, O'Connor L, Varley A, et al. Detection of OXA-48-like-producing *Enterobacteriales* in Irish recreational water. *Sci Total Environ.* 2019 Nov 10;690:1-6.

⁴³ Piedra-Carrasco N, Fabrega A, Calero-Caceres W, Cornejo-Sanchez T, Brown-Jaque M, Mir-Cros A, et al. Carbapenemase-producing *enterobacteriaceae* recovered from a Spanish river ecosystem. *PLoS One.* 2017;12(4):e0175246.

⁴⁴ Ludden C, Reuter S, Judge K, Gouliouris T, Blane B, Coll F, et al. Sharing of carbapenemase-encoding plasmids between *Enterobacteriaceae* in UK sewage uncovered by MinION sequencing. *Microbial genomics.* 2017 Jul;3(7):e000114.

⁴⁵ European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe - Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2017. Stockholm: ECDC; 2018. <https://ecdc.europa.eu/sites/portal/files/documents/AMR-surveillance-EARS-Net-2017.pdf>

⁴⁶ World Health Organization Regional Office for Europe. Central Asian and Eastern European Surveillance of Antimicrobial Resistance, Annual Report for 2017. Copenhagen: WHO; 2017. Available from: http://www.euro.who.int/_data/assets/pdf_file/0005/354434/WHO_CAESAR_AnnualReport_2017.pdf

assistenza e cura, i ripetuti test diagnostici necessari, gli interventi di controllo da attuare, e quindi il costo complessivo molto maggiorato per paziente.

Interventi per la riduzione del rischio

Per le indicazioni relative ai seguenti interventi:

1. Azioni correlate alle limitate opzioni terapeutiche e all'alta mortalità
2. Azioni per la prevenzione della trasmissione dei CRE nei setting assistenziali
3. Azioni per la prevenzione della diffusione dei CRE nella comunità
4. Azioni per la prevenzione della diffusione transfrontaliera dei CRE

si rimanda alla precedente³ circolare ministeriale. Nel nuovo RRA, l'ECDC raccomanda:

5. Azioni volte alla riduzione dei rischi per i sistemi sanitari

Sono raccomandati: un numero adeguato di personale di assistenza e cura; addetti al controllo delle infezioni; finanziamenti adeguati per gli ospedali al fine di assicurare lo svolgimento delle corrette misure di controllo delle infezioni. Nella maggior parte dei Paesi europei, la prevalenza dei CRE è bassa. Tuttavia, quando i CRE diventano endemici, gli sforzi per il controllo richiedono investimenti economici maggiori e risultano, comunque, meno efficaci. La Direzione della struttura dovrebbe opportunamente valutare la messa a disposizione di materiale informativo e di supporto amministrativo e organizzativo, tramite l'allocazione di fondi dedicati e adeguati, per il piano di prevenzione e controllo delle infezioni.

6. Azioni ulteriori Le linee guida OMS per il controllo della diffusione dei CRE raccomandano ulteriori interventi per l'implementazione delle strategie di prevenzione e controllo delle infezioni da CRE:

- aderenza alla corretta igiene delle mani
- sorveglianza delle infezioni
- screening per i portatori di CRE
- attuazione delle precauzioni da contatto
- procedure di isolamento del paziente
- pulizia dell'ambiente del paziente, inclusa la definizione delle priorità
- campionamento ambientale per la sorveglianza
- monitoraggio mediante campioni biologici e ambientali
- audit e feedback.

Si sottolinea che la tempestiva segnalazione dei casi all'interno della struttura è essenziale per la corretta implementazione delle appropriate misure di controllo.

Si prega di dare la massima diffusione alla presente nota e al documento allegato presso le strutture sanitarie, inclusi presidi ed aziende ospedaliere, medici di medicina generale e pediatri di libera scelta.

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RAPID RISK ASSESSMENT

Carbapenem-resistant Enterobacteriaceae – second update

26 September 2019

Summary

Carbapenem resistance in Enterobacteriaceae such as *Klebsiella pneumoniae* and *Escherichia coli* poses a significant threat to patients and healthcare systems in all European Union / European Economic Area (EU/EEA) countries. Carbapenem-resistant Enterobacteriaceae (CRE) infections are associated with high mortality, primarily due to delays in administration of effective treatment and the limited availability of treatment options. Hypervirulent carbapenem-resistant *K. pneumoniae* strains have been reported presenting an additional threat with a potential for global dissemination. The spread of high risk clones and plasmids carrying carbapenemases in healthcare settings is a major cause of the spread of CRE in EU/EEA countries. Recent events of cross-border importation after patient transfer and large regional outbreaks as well as the worsening epidemiologic situation of carbapenemase-producing CRE in the EU/EEA highlight the high risk for further spread of CRE and the need for enhanced control efforts. Options for control are outlined in the respective section below.

Event background

Current situation of CRE in EU/EEA countries

For *K. pneumoniae*, data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) for 2017 show large variability in the national percentages of carbapenem resistance in isolates from invasive infections, ranging from 0% to 64.7% (Figure 1). The population-weighted mean percentage for the EU/EEA overall fluctuated without a statistically significant trend between 2014 and 2017, and was 7.3% in 2014 and 7.2% in 2017. Increasing national trends in carbapenem resistance in *K. pneumoniae* for the period 2014–2017 were observed in Slovakia, Poland and Portugal, while there was a decreasing trend in Croatia, Slovenia and Italy [1].

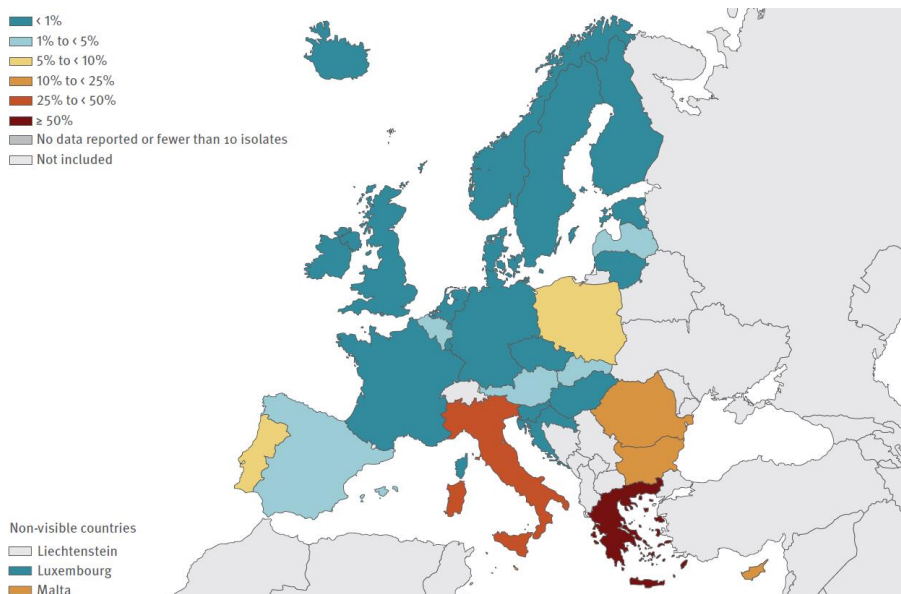
For *E. coli*, EARS-Net data for 2017 show a lower overall EU/EEA population-weighted mean percentage (0.1%) of carbapenem resistance in invasive isolates, with national percentages ranging from 0% to 1.6% (2017). Between 2014 and 2017, a slightly decreasing trend was observed for the EU/EEA population-weighted mean of national percentages [1].

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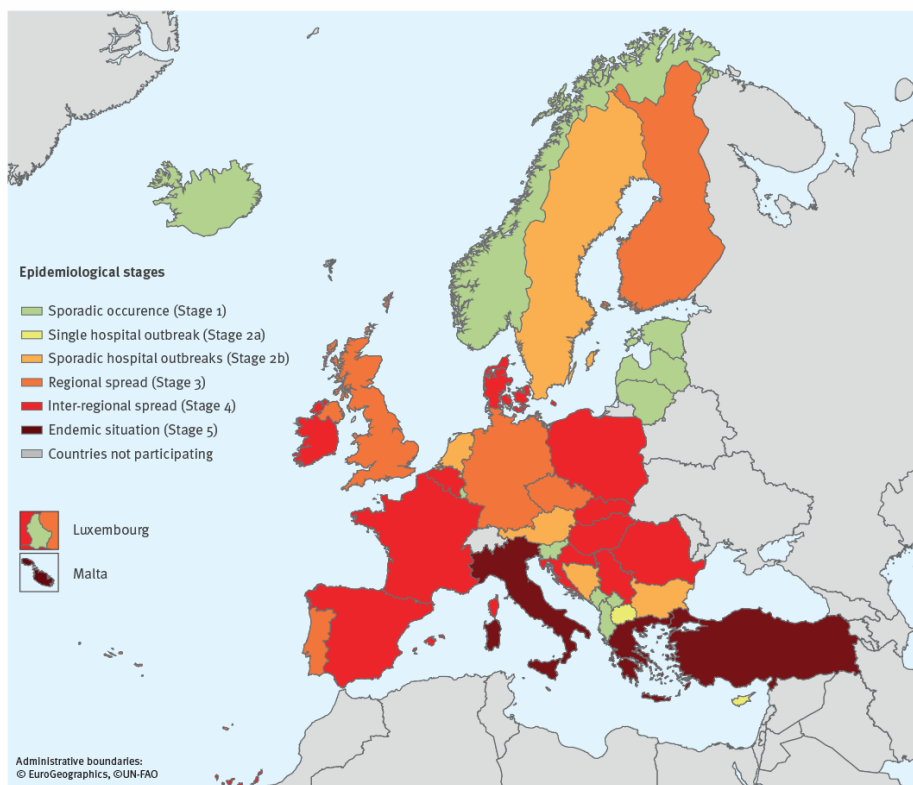
Figure 1. Percentage of invasive *K. pneumoniae* isolates with resistance to carbapenems, EU/EEA, 2017 [1]



Note: EARS-Net data are based on invasive isolates from blood and cerebrospinal fluid only. Bacteria isolated from other sites of infection or colonisation are not included.

Despite the still low percentages, in many European countries, of carbapenem resistance in *K. pneumoniae* and *E. coli* in invasive isolates from blood and cerebrospinal fluid, a national self-assessment of epidemiologic stages conducted in 2018, that considered all types of infection as well as carriage documented an evolving pattern of spread of carbapenemase-producing CRE, or CPE, in Europe (Figure 2) [2]. Sixteen (43%) of 37 participating countries reported regional or interregional spread of CPE and four countries reported an endemic situation. In comparison to a previous assessment in 2015, 11 countries reported a higher epidemiological stage of CPE indicating increasing spread between 2015 and 2018 [2]. The number of cases of infections for the EU/EEA in 2015 has been estimated as 15947 (range 13473-18478) infections with carbapenem-resistant *K. pneumoniae* and 2619 (range 2269 – 2961) infections with carbapenem-resistant *E. coli* [3].

Figure 2. Epidemiological situation of carbapenemase-producing Enterobacteriaceae, assessment by national experts in European countries, July 2018 (n=37) [2]



Current situation of CRE in third countries

Only 71 WHO Member States were able to provide data on carbapenem resistance in *K. pneumoniae* for the WHO global report on antimicrobial resistance surveillance (data from various years prior to 2014) [4]. Carbapenem resistance in *K. pneumoniae* was reported from all WHO regions and exceeded 50% of isolates in two regions [4]. For the 2017–2018 Global Antimicrobial Resistance Surveillance System (GLASS) Report, AMR frequency rates for countries and regions were not yet available due to limited representativeness and data quality and a worldwide overview of carbapenem resistance in *K. pneumoniae* and *E. coli* is therefore difficult to establish [5]. However, data available from the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) 2017 report shows that some countries immediately adjacent to the EU/EEA had high carbapenem resistance percentages in *K. pneumoniae* in 2017 [6].

CRE with different carbapenemase genes show variation in their geographic spread. Regions and countries considered as having the highest prevalence of the various carbapenemase-producing CRE are the Indian subcontinent (NDM CRE), United States, Israel, Greece and Italy (KPC CRE), Turkey, the Middle East and North Africa (OXA-48 CRE) [7,8]. For South-East Asia, carbapenem resistance percentages >5% were estimated for *K. pneumoniae* for Vietnam, the Philippines, Indonesia and Thailand and for *E. coli* for Myanmar and Indonesia [9]. Despite sparse data, attempts to estimate antimicrobial resistance percentages in Africa, based on a literature review, resulted in two countries (Uganda and Madagascar) having estimated percentages of carbapenem resistance in *K. pneumoniae* >5% [10]. Indirect evidence for the prevalence of CRE in different regions is also provided through CRE carriage detected in patients transferred from hospitals in other regions of the world [11] and in travellers returning from high-prevalence regions to Europe [12].

Disease background

Bacteria of the family Enterobacteriaceae such as *Escherichia coli* and *K. pneumoniae* are part of the normal human intestinal flora, but are also often responsible for community- 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* [13].

Carbapenems are beta-lactam antibiotics with a broad spectrum of activity against Gram-negative bacteria (including Enterobacteriaceae) and Gram-positive bacteria. Carbapenems are active against ESBL-producing Enterobacteriaceae. In hospitalised patients, carbapenems are therefore often the treatment of choice for infections with multidrug-resistant (including ESBL-producing) Enterobacteriaceae. Resistance to carbapenems has been reported with increasing frequency and geographical spread since the beginning of the 1990s [14,15]. Carbapenem-resistant Enterobacteriaceae (CRE) can be resistant to carbapenems as a result of various mechanisms, including the acquisition of carbapenemase enzymes which is most frequent, but combinations of other different mechanisms may also cause carbapenem resistance.

Carbapenemases are a heterogenous group of enzymes that can hydrolyse most beta-lactams including carbapenems [16]. In the literature, carbapenemase-producing CRE are often named after the specific carbapenemase that they produce, such as *Klebsiella pneumoniae* carbapenemase (KPC)-producing CRE (KPC CRE), oxacillinase 48 (OXA-48)-producing CRE (OXA-48 CRE), and CRE that produce metallo-beta-lactamases such as the New Delhi metallo-beta-lactamase (NDM)-producing CRE (NDM CRE), Verona integron-encoded metallo-beta-lactamase (VIM)-producing CRE (VIM CRE), and IMP-type metallo-beta-lactamase-producing CRE (IMP CRE), among others. The spread of carbapenemase-producing CRE in the EU/EEA is frequently linked, in particular for *K. pneumoniae*, to specific clonal lineages such as *K. pneumoniae* sequence types 11, 15, 101, 258/512 and their derivatives [17].

Risk assessment questions

This update of the 2018 ECDC Rapid Risk Assessment on CRE [18] evaluates the risk for patients and healthcare systems in EU/EEA countries due to the global spread of CRE.

ECDC risk assessment for the EU/EEA

Impact of CRE on human health

Frequency of occurrence

E. coli is the most common cause of community- and healthcare-associated urinary tract infections. *E. coli* and other Enterobacteriaceae such as *K. pneumoniae* are also frequently associated with ventilator-associated

pneumonia and bloodstream infections in healthcare settings [19]. Resistance in these bacteria has an impact on the choice of antibiotic therapy as well as treatment outcomes.

Limited treatment options

There has been a vicious cycle of increasing resistance in Enterobacteriaceae. Global spread of ESBLs has resulted in frequent resistance to all penicillins and cephalosporins, with the consequence of an increase in carbapenem consumption [20], which in turn has increased the selection pressure and facilitated the spread of CRE. Treatment options for CRE infections are limited. Antibiotics which more frequently show *in vitro* activity against CRE include colistin, tigecycline and fosfomycin, but there are concerns regarding their effectiveness, limited clinical experience with their use, more frequent adverse effects, rapid development of resistance during treatment, and increasing resistance globally. In addition, a review of available data on treatment regimens that include the above-mentioned antibiotics concluded that mortality rates in patients treated with a single antibiotic that was shown to be active *in vitro* were not significantly different from mortality rates in patients with no active therapy [21]. Combination therapy with two or more active agents, showed a survival benefit among patients with a high probability of death [22]. However, these data should be interpreted with caution as they come from observational studies.

Colistin is frequently being used to treat CRE infections, but resistance may develop in CRE-infected patients treated with colistin. Colistin resistance among CRE isolates can develop rapidly in hospitals and countries with increasing use of colistin [23-26]. Colistin-resistant CRE have been responsible for hospital outbreaks following the introduction of such strains by an index patient transferred from a high-prevalence country [27]. Since 2015, the discovery of transferable plasmid-mediated colistin resistance genes that can transmit colistin resistance more easily between bacteria has further increased the risk of colistin resistance spreading [28]. The development of colistin-resistant strains of CRE that are also resistant to almost all other antibiotics, or possibly all antibiotics - i.e. pandrug-resistant CRE [29-33], is now occurring as a consequence of failing to control CRE.

In June 2016, ceftazidime-avibactam, a new antibiotic combination with activity against CRE infections (except for infections with CRE producing metallo-beta-lactamases, such as NDM or VIM), was approved by the European Commission, after positive advice from the European Medicines Agency (EMA), for use in the EU to treat complicated intra-abdominal infections, complicated urinary tract infections, hospital-acquired pneumonia (including ventilator-associated pneumonia) and infections due to aerobic Gram-negative bacteria where treatment options are limited [34]. Limited evidence shows promising results, although there are concerns about the development of resistance [35]. Meropenem-vaborbactam has also recently been authorised for use in the EU for the same indications as ceftazidime-avibactam [36] and there are additional new compounds or combinations in development such as imipenem-relebactam, plazomycin, cefiderocol, eravacycline and aztreonam-avibactam [37]. However, progress in developing new drugs has been slow and there is an urgent need for research and clinical development of antimicrobials to keep up with the evolution of bacterial resistance [38].

High mortality

High mortality rates, ranging from 30% to 75%, have been reported for patients with severe CRE infections [39]. Mortality above 50% has been reported in patients with CRE bloodstream infections [40], and a study has shown an excess mortality of 27% in patients with pneumonia or bloodstream infections caused by carbapenem-resistant *K. pneumoniae* [41]. The number of deaths attributable to infections with carbapenem-resistant *K. pneumoniae* and carbapenem-resistant *E. coli* has been estimated as 2118 (range 1795 – 2473) and 141 (119 – 165) in the EU/EEA for 2015, respectively [3].

Hypervirulent *K. pneumoniae* strains with a hypermucoviscous phenotype are disseminating in the community causing severe infections in young healthy individuals without comorbidities [42]. Although antimicrobial resistance is rare in hypervirulent *K. pneumoniae* strains, strains combining carbapenem resistance, high transmissibility and hypervirulence have been described, so far mainly from Asia [42,43]. Extremely high overall mortality (84%) was associated with 86 *K. pneumoniae* bacteraemia isolates in India that exhibited hypervirulence (determined by a positive string test) and carbapenem resistance (determined by a meropenem minimum inhibitory (MIC) concentration of $\geq 16\mu\text{g/ml}$) [44].

Potential for spread

Risk for transmission and outbreaks in healthcare settings

CRE, especially carbapenem-resistant *K. pneumoniae*, have a high potential to cause outbreaks in healthcare settings. Such outbreaks have been reported from several EU Member States, e.g. the Czech Republic, France, Germany, Greece, Italy, Spain, the Netherlands and the UK [45-51]. Some of these countries report low overall carbapenem resistance percentages in *K. pneumoniae* as shown in Figure 1, thus indicating that outbreaks may occur independently of a country's overall CRE situation and all EU/EEA countries are at risk for CRE outbreaks. In 2019, a large outbreak of NDM-producing CRE in Tuscany was reported via the Early Warning and Response System (EWRS) [52]. Risk factors for acquisition of CRE in healthcare settings are similar to those reported for acquisition of other multidrug-resistant bacteria. These include admission to an intensive care unit (ICU), long ICU stay, critical illness, invasive devices and prior antimicrobial therapy [53,54]. A meta-analysis found that 'use of

medical devices' and 'carbapenem use' were the most significant risk factors for CRE acquisition by hospitalised patients [55]. Long-term care facilities have also been shown to be a reservoir for CRE in some settings, including in EU/EEA countries [56-59].

Carbapenemase genes are often located on plasmids that can be exchanged between Enterobacteriaceae and other Gram-negative bacteria [16]. They are also often transmitted together with other resistance genes, which results in multidrug-resistant strains. While carbapenem consumption has been shown to be associated with increases in CRE [49], this association of carbapenem resistance with other resistance genes means that treatment with antibiotics other than carbapenems can also increase the selection pressure for CRE, as has been reported for cephalosporins and fluoroquinolones [54]. International high-risk bacterial clones such as the KPC-producing *K. pneumoniae* ST258 have emerged. These clones are very efficient at colonising human hosts, adapting to the hospital environments and are responsible for outbreaks in hospital settings across Europe [60]. The presence of both virulence and AMR determinants on the same plasmid has been detected in two *K. pneumoniae* isolates from patients hospitalised in Norway, but with epidemiological and genomic links to Romania [61].

Colonisation - i.e. digestive tract carriage - with CRE has been associated with high rates (16.5% overall, range from 0% to 89% in high risk patients) of subsequent infection, most frequently pneumonia, followed by urinary tract infections, primary bloodstream infections, skin and soft tissue infections, and surgical site infections [39]. Eradication of CRE from the intestinal flora is difficult. Rates of spontaneous clearance vary between studies [62,63], and continuous carriage beyond two years has been reported [63]. Eradication of CRE carriage has been attempted with oral, non-absorbable antibiotic treatment. However, the success of this approach has been limited due to failure of eradication, relapse, development of antibiotic resistance during treatment, and patient refusal [62]. Eradication of CRE carriage has also been attempted by fecal microbiota transplantation [64-67].

The role of the hospital environment, including ill-designed waste water plumbing, hand wash basins and sinks, as a reservoir and source of CRE has been documented and found to be the source of some outbreaks requiring special water treatment or disinfection measures for effective control [68,69]. Recent outbreak studies using advanced genomic epidemiological methods, including WGS, have revealed hospital environmental reservoirs of a variety of bacteria, with plasmids conferring carbapenem resistance that transferred to diverse species and clonal strains of Enterobacteriaceae [68-71]. This emphasises the value of advanced genomic surveillance to detect and trace the plasmid epidemics, as well as the need for safe design of the close patient environment in the hospital and of medical devices to avoid contamination and/or permit adequate cleaning, disinfection and reprocessing.

Risk of CRE spread in the community

While carbapenem-resistant *K. pneumoniae* are currently more frequent and more likely to cause healthcare-associated outbreaks, carbapenem-resistant *E. coli* pose a greater risk for spread in the community [16]. There is growing evidence that extra-intestinal pathogenic *E. coli* may be transmitted to humans via the food chain from a food animal source [72]. Faecal-oral transmission and transmission via the food chain has the potential to spread carbapenem-resistant *E. coli* to a larger, healthier and younger population. After ingestion of food items contaminated with CRE bacteria or their resistance genes, CRE could become part of the intestinal flora of healthy persons who have not been exposed to healthcare or antimicrobials. If such a digestive tract carrier of CRE needs antimicrobial treatment or hospital care, there is a risk of standard antimicrobial therapy failing in the case of CRE infection, overgrowth of CRE, and onward transmission to other patients.

Data on the prevalence of community-acquired CRE infection is scarce. A 2017 review described proportions of 0 to 29.5% community-acquired or community-onset CRE infections (of all included CRE infections), but prior healthcare exposure had been recorded inconsistently [73]. However, cases of community-onset CRE infection in patients without healthcare contact in the preceding three months have also been reported in the EU recently [74]. The spread of ESBL-producing Enterobacteriaceae, mainly *E. coli*, in the community during the last decade demonstrates how rapidly such bacteria can disseminate in the community [16]. ESBL-producing Enterobacteriaceae 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. The contamination of food items with antimicrobial-resistant Enterobacteriaceae has been described in several EU/EEA countries, for example in relation to chicken or poultry meat in Austria, Germany, the Netherlands, Italy and Spain [75-79], and for vegetables in the Netherlands [80]. There is now evidence that a proportion of third- and fourth-generation cephalosporin-resistant *E. coli* isolates from extra-intestinal infections humans originated from food-producing animals, especially poultry [81].

Carbapenem-resistant bacteria or carbapenemases are increasingly being 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 [82-85], and carbapenemase production has also been reported in the foodborne pathogen *Salmonella enterica* [86]. The occurrence of CRE in multiple non-human sources is of concern and, given the risks of CRE to human health, there have been calls for a zero-tolerance approach and an international ban on the sale of food items that contain CRE [87]. CRE have also been detected in seawater samples from a bathing site in Ireland, a Spanish river ecosystem and wastewater in the UK [88-90] indicating potential environmental reservoirs for further dissemination.

Risk for cross border spread

EU/EEA countries

EU/EEA countries are at very different stages of CRE spread. For *K. pneumoniae*, percentages of carbapenem resistance in invasive isolates range from 0% to more than 60%, and epidemiological stages of spread range from only sporadic cases to endemicity [1,2]. Introduction of CRE via cross-border patient transfers or returning travellers might therefore significantly contribute to the spread of these bacteria into countries with a still low prevalence of CRE. A recent example is the import to Norway and Sweden of carbapenemase-producing *K. pneumoniae* ST392 by travellers who were hospitalised in Gran Canaria for acute medical conditions [91]. Outbreaks of CRE following cross-border transfer of a CRE infected/carrier index patient have been described in several EU/EEA countries. Introduction of CRE may result from any country with CRE, although the risks are higher for patients/individuals coming from EU Member States with a high prevalence of CRE or from other European countries or regions of the world with high reported prevalence of CRE [1,4,6].

Third countries

High mobility and global trade play an important role in the dissemination of antimicrobial resistance. A high level of antimicrobial use in humans, animals and agriculture, combined with poor public health infrastructure (inadequate sewage systems, poor-quality drinking water and overcrowding), has resulted in high prevalence of antimicrobial resistance in Gram-negative bacteria in emerging economies [92]. Through travel and migration, populations around the world are subsequently exposed to antimicrobial resistance arising in these areas [92]. Much of this dissemination is unrecognised as it takes place in the intestinal flora of healthy carriers and is only detected when microbiological tests are carried out in the case of infection or active screening for digestive tract carriage.

The epidemiology of ESBL-producing *E. coli* with high carriage rates in Africa, south-east Asia, and the western Pacific and eastern Mediterranean regions also suggests that poor access to drinking water, poverty, and high population density are driving forces behind the dissemination in local communities and the spread through international travel to regions with lower carriage rates, such as Europe and America [13]. A frequently cited example is NDM CRE, for which a high proportion of the cases diagnosed in the UK could be linked to prior travel, with or without hospital care, in India or Pakistan [93]. A high rate of digestive tract carriage of multidrug-resistant Enterobacteriaceae has also been described in travellers returning to the EU from tropical regions [12]. Although much less frequent than digestive tract carriage of ESBL-producing Enterobacteriaceae, digestive tract carriage of CRE has been reported in travellers returning from regions with high prevalence of CRE [94,95].

Risks to the functioning of health systems

Advanced medical procedures such as intensive care, transplantation, cancer chemotherapy, neonatal care and invasive procedures increase the risk to patients of developing infections by weakening the immune system or other barriers to infections, such as the skin barrier. If no effective antimicrobial prophylaxis and treatments are available, these procedures will be associated with a higher risk from CRE infection for patients. In many countries, ICU patients have been affected by CRE outbreaks. Urinary tract infections with CRE in kidney and other solid organ transplant recipients have been associated with antimicrobial failure and mortality [53,96]. Bloodstream infection with CRE was also a predictor of death in liver transplant patients, and infection-related mortality was high, with 64% in allogenic stem cell transplant recipients in Italy [97]. Mortality rates associated with CRE infections were high in patients with haematological malignancies [98]. Low-birthweight neonates have also been affected by CRE septicemia [99]. In addition, CRE outbreaks have been related to frequently-performed invasive medical procedures – e.g. in outbreaks related to bronchoscopy and endoscopy in Germany [48,100] and France [101].

Besides morbidity and mortality, CRE are likely to result in a financial burden for healthcare systems; CRE infections have been associated with prolonged hospital stays [39]. A retrospective study of the costs of patients carrying carbapenemase-producing Enterobacteriaceae admitted over a period of two years to a French hospital estimated that the attributable costs for 16 patients carrying a carbapenemase-producing CRE were EUR 642 104. This included the costs related to restricted activities in the affected units, additional working hours and screening samples [102]. Outbreaks of carbapenem-resistant gram-negative bacteria have also been found to be highly costly, for example, a cost evaluation of a CPE outbreak occurring across five hospitals in the United Kingdom estimated a cost of approximately 1.1 million Euro over 10 months [103].

Effectiveness of control measures

Implementation of enhanced CRE control measures in healthcare settings requires reliable identification of CRE by the microbiology laboratory. However, phenotypic detection is complicated by that fact that the level of carbapenem resistance resulting from the production of carbapenemase is heterogeneous, and because carbapenem resistance can be the result of various mechanisms without any single test being suitable for all situations [104]. There is also a need to define the circumstances under which screening for faecal carriage of CRE should be conducted and to determine which screening methods should be used, because multiple factors such as local CRE prevalence, type of hospital, capabilities of the laboratory and available resources need to be taken into account in order to identify the most appropriate method [105].

In 2011, ECDC conducted a systematic review of the effectiveness of infection control measures to prevent the spread of CRE, with an update in 2014. Measures identified as effective included early implementation of active

surveillance through rectal screening for CRE carriage on hospital admission, admission to specific wards/units, and during outbreaks as well as pre-emptive isolation on admission, contact precautions, hand hygiene, patient cohorting, patient isolation, dedicated nursing or other types of dedicated care by staff members, environmental cleaning, staff education, case notification/flagging, contact tracing and antibiotic restriction [106].

Prudent antimicrobial use will reduce the selection pressure for CRE. Antimicrobial stewardship refers to coordinated programmes that implement interventions to ensure appropriate antimicrobial prescription. These programmes aim to improve clinical efficacy of antimicrobial treatment and limit antimicrobial resistance and have been shown to significantly reduce the incidence of infections with and carriage of antibiotic-resistant bacteria. Reduction of carbapenem use through an antimicrobial stewardship programme has been shown to be beneficial for CRE control [49].

The above-mentioned measures have been effective in studies, but their broad implementation in the healthcare system needs to be supported by national policies. National guidelines, national surveillance systems, national reference laboratories, mandatory reporting of CRE and national campaigns to promote infection control and prudent antimicrobial use are the cornerstones of national CRE control [107]. Infection control measures – and especially contact precautions – are time-consuming and require training and an adequate number of staff in healthcare institutions. The association between low healthcare staffing levels and healthcare-associated infections is well known [108]. Underfunding and understaffing of healthcare institutions challenge the implementation of infection control measures and risks creating reservoirs of multidrug-resistant bacteria, such as CRE.

Consistently implemented infection control programmes have been shown to reduce the spread of CRE. Active surveillance and infection control measures including hand hygiene have led to reduction of CRE in an endemic setting in Greece [109]. To control a clonal outbreak of carbapenem-resistant *K. pneumoniae* in 27 hospitals, Israel implemented a nationwide and centrally controlled intervention with mandatory reporting, mandatory isolation and dedicated staffing, and a dedicated national taskforce that was effective in containing the outbreak [110]. In France, after the occurrence of several outbreaks of carbapenemase-producing CRE, 38 hospitals successfully implemented a programme for controlling CRE, consisting of screening and isolation of patients previously hospitalised abroad and a bundle of measures for control of cross-transmission, including barrier precautions, dedicated staff and screening of contact patients [111,112]. However, there is limited generalisability even of successful programmes to healthcare settings in other countries. Control programmes need to be adapted to the local prevalence of CRE, travel patterns of the local population, the percentage of CRE cases imported from foreign countries, and the availability of resources for laboratory testing and infection control.

Preparedness in EU/EEA countries

The national capacity of EU/EEA countries, EU enlargement countries and Israel was assessed in July 2018 by national experts who participated in the European Antimicrobial Resistance Genes Surveillance Network (EURGen-Net) [2]. Of 37 participating European countries, 27 (73%) countries reported having a dedicated national surveillance system for CRE; 33 (89%) countries reported having an officially appointed national reference laboratory or national expert laboratory for CRE; 21 (57%) countries were developing, or had implemented a national plan for containment or for preparedness to contain carbapenemase-producing CRE; and 24 (65%) countries reported having national recommendations or guidelines for infection prevention and control measures for confirmed cases of carbapenemase-producing CRE [2].

Options for response

1. Actions related to limited treatment options and high mortality

Timely and appropriate laboratory investigation and reporting is essential in order to avoid a delay in appropriate treatment, which is associated with increased morbidity and mortality. Patients with CRE infections will benefit from consultations with specialists in infectious diseases or clinical microbiology, which would ensure the best possible outcome, given the limited treatment options.

2. Actions to prevent transmission of CRE in hospitals and other healthcare settings

Appropriate hand hygiene compliance is considered fundamental to all infection prevention and control programmes and for the control of cross-transmission of many pathogens, including CRE. Contact precautions are also an important component of the infection prevention and control measures necessary to control healthcare-associated infections and other infections. Contact precautions include appropriate patient placement, use of personal protective equipment (including gloves and gowns), limitation of transport and movement of patients, use of disposable or dedicated patient care equipment, and prioritisation of cleaning and disinfection of patient rooms. Prompt notification of the clinical team and of the infection prevention and control/hospital hygiene team is essential in order to implement timely infection control precautions. For healthcare settings other than acute care, the control measures implemented should be proportionate to the risk of CRE transmission to other patients.

Targeting patients at high risk of CRE carriage

Screening of patients at high risk for digestive tract CRE carriage and the implementation of pre-emptive contact precautions and isolation should be considered. Risk factors for CRE carriage are history of an overnight stay in a healthcare setting within the last 12 months, dependency on dialysis or having received cancer chemotherapy in the last 12 months, known previous carriage of CRE in the last 12 months, and epidemiological linkage to a known carrier of CRE [113]. Based on the local epidemiology, additional at-risk populations could be defined, for example hematopoietic stem cell transplant recipients or newborns, especially if they had previously received carbapenem treatment [114,115].

Preventing transmission from CRE-positive patients

Enhanced control measures, such as contact precautions, isolation or cohorting, and dedicated nursing staff can be considered for hospitalised patients with confirmed digestive tract CRE carriage or confirmed CRE infection. In addition, screening of contacts will enable early identification of carriers and implementation of control measures.

Preventing spread of CRE in specific wards/units

In units/wards where patients are at high risk of infection (e.g. intensive care units and onco-haematology units), pre-emptive isolation and active surveillance (screening) for CRE by rectal swab on admission should be considered, depending on the risk of digestive tract CRE carriage and the local prevalence of CRE. Regular review of appropriate device use is an important infection prevention measure in high-risk settings. The role of environmental reservoirs of epidemic CRE strains and/or carbapenemase-encoding plasmids should be investigated, especially when other infection control interventions have failed, and relevant control measures implemented accordingly.

Antimicrobial stewardship

The implementation of comprehensive antimicrobial stewardship programmes is recommended to prevent and control the emergence and spread of CRE and other multidrug-resistant bacteria. Nevertheless, targeted and appropriate use of antibiotics is not likely to fully reverse the current CRE trends, and antimicrobial resistance trends in general, and there is an urgent public health need for new antibacterial agents active against prevalent multidrug-resistant bacteria such as CRE.

3. Actions 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' requests the monitoring of CRE in broilers, turkeys, pigs and veal calves, and meat derived thereof every second year on a routine basis [116]. Continued prohibition of the use of carbapenems in food-producing animals would be a simple and effective option for intervention [117]. 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 of high priority [117].

A multifaceted integrated approach to minimising antimicrobial use 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' [118]. Improving the conditions of animal husbandry (e.g. biosecurity, hygienic conditions) and implementing alternative measures to antimicrobials would reduce both the need to use antimicrobials and the development of resistant bacteria in food-producing animals.

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.

4. Actions to prevent cross-border spread

Hospitals in EU/EEA countries should consider taking a detailed history of travels and hospitalisations for every patient at hospital admission. They should also consider performing pre-emptive isolation and screening for carriage of CRE at least in patients who were directly transferred from or hospitalised in countries with known high prevalence in the 12 months before admission, or in patients who were hospitalised in their own country in the 12 months before admission, but in a region or hospital with known high prevalence of CRE. However, screening every patient who was hospitalised in a foreign country in the 12 months before admission might be a more suitable option, as prevalence of CRE is difficult to monitor in some regions, and national prevalence might not always reflect the regional or local situation. Hospitals could also consider pre-emptive isolation and screening for digestive tract CRE carriage in accordance with national guidance for patients who may recently have travelled to countries/regions known for high CRE prevalence, even if they were not in contact with a healthcare institution/service.

In case of patient transfer, good inter-facility communication is a key element to ensure effective measures to limit the spread of CRE in the receiving hospital. Moreover, gathering reliable epidemiological data by notifying cases to public health authorities and exchanging information are important activities to enable informed and coordinated action by public health authorities across the EU/EEA. Public health authorities shall issue notifications on the EWRS where relevant, as per Article 9 of Decision 1082/2013/EU on serious cross-border threats to health. Use of

the Epidemic Intelligence System (EPIS) is encouraged to ensure transparent and timely information sharing among the participating public health authorities in order to detect public health threats at an early stage.

5. Actions to reduce risks for healthcare systems

Appropriate levels of healthcare staffing and infection control staffing as well as adequate funding for hospitals should be ensured to enable compliance with infection control measures. CRE prevalence is currently still low in many European countries, and it is likely that the spread of CRE could be controlled through proportionate investment in control measures in most countries. However, once the situation becomes endemic, control efforts might be more costly and less effective. Facility leadership can support the infection prevention and control programme aimed at preventing the spread of CRE by providing materials and organizational and administrative support through the allocation of a protected and dedicated budget, according to the infection prevention and control activity plan.

6. Additional guidance

Detailed further guidance has been published by international and national organisations. The World Health Organization has published guidelines for the prevention and control of CRE, carbapenem-resistant *Acinetobacter baumannii* and carbapenem-resistant *Pseudomonas aeruginosa* in healthcare facilities, with eight recommendations on the implementation of multimodal infection prevention and control strategies, the importance of hand hygiene compliance, surveillance of infection, screening for asymptomatic digestive tract carriage, contact precautions, patient isolation, environmental cleaning, environmental surveillance cultures, monitoring, auditing and feedback [119]. Implementing these recommendations may be complex in some health systems as it requires a multidisciplinary approach, including executive leadership, stakeholder commitment, coordination and possible modifications to workforce structure and process in some cases [120]. There is also facility guidance for control of CRE from the US Centers for Disease Control and Prevention [121]. The European Society of Clinical Microbiology and Infectious Diseases has published guidelines for the management of infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalised patients as well as for the decolonisation of carriers of multidrug-resistant Gram-negative bacteria [122,123]. A flowchart for assessment of CRE carriage in patients being admitted to healthcare settings and corresponding infection prevention and control measures to prevent the entry and further of CRE into hospitals and other healthcare settings is provided in the ECDC guidance [113]. The majority of EU/EEA countries have developed national guidelines. Links to these guidelines can be found in the ECDC directory of online resources for the prevention and control of antimicrobial resistance and healthcare-associated infections [124].

Source and date of request

ECDC internal decision, 17 September 2019.

Consulted experts

Internal experts consulted: Sergio Brusin, Anke Kohlenberg, Catherine Ludden, Daniel Palm, Dominique L. Monnet, Diamantis Plachouras, Marc Struelens.

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Experts from WHO reviewed the risk assessment, but the views expressed in this document do not necessarily represent the views of WHO.

All experts have submitted declarations of interest, and a review of these declarations did not reveal any conflict of interest.

Disclaimer

ECDC issues this risk assessment document based on an internal decision and in accordance with Article 10 of Decision No 1082/13/EC and Article 7(1) 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/EEA Member States. 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 European Centre for Disease Prevention and Control. 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.

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