0023232-01/08/2018-DGPRE-DGPRE-P

Ministero della Salute

DIREZIONE GENERALE DELLA PREVENZIONE SANITARIA

UFFICIO 5 PREVENZIONE DELLE MALATTIE TRASMISSIBILI E PROFILASSI INTERNAZIONALE

A

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Istituto nazionale per la promozione della salute delle popolazioni migranti e per il contrasto delle malattie della povertà (INMP)

OGGETTO: ***Rapid Risk Assessment dell'ECDC: Enterobatteri resistenti ai Carbapenemi –primo aggiornamento del 4 giugno 2018***

I batteri della famiglia delle *Enterobacteriaceae* (enterobatteri), come *Escherichia coli* e *Klebsiella pneumoniae*, sono parte della normale flora batterica intestinale. Tuttavia, sono spesso responsabili di infezioni acquisite in comunità o correlate all'assistenza sanitaria. Questi batteri sono inclini ad acquisire geni di resistenza agli antibiotici, in particolare penicilline e cefalosporine, in seguito alla diffusione globale delle beta-lattamasi ad ampio spettro (ESBL), ovvero il meccanismo di resistenza nei confronti degli antibiotici beta-lattamici che ha interessato prima *Klebsiella pneumoniae* e altre *Klebsiella* species, e successivamente *E. coli*.
I carbapenemi sono tra gli antibiotici beta-lattamici in grado di contrastare sia batteri gram-positivi (come gli enterobatteri) che gram-negativi e sono attivi anche verso Enterobatteri produttori di ESBL, nel trattamento delle cui infezioni in pazienti ospedalizzati vengono, spesso, considerati come la migliore opzione terapeutica. Tuttavia, a partire dagli anni '90, sempre più frequentemente vengono riportati casi di resistenza anche ai carbapenemi. Gli enterobatteri carbapenemi-resistenti

(Carbapenem-resistant *Enterobacteriaceae* - CRE) riescono a sviluppare la loro resistenza attraverso diversi meccanismi, per lo più mediante enzimi (carbapenemasi) in grado di idrolizzare l'anello beta-lattamico.

I CRE rappresentano una importante minaccia per i pazienti e per i sistemi sanitari in tutta Europa e nel mondo, essendo associati ad alta mortalità, principalmente dovuta a un ritardo nella somministrazione di trattamenti efficaci e a una limitata disponibilità di opzioni terapeutiche. Inoltre, i CRE sono in grado di diffondersi in setting assistenziale così come in comunità, e misure di controllo dovrebbero interessare entrambi i contesti.
Il problema dei CRE è diffuso globalmente: in base ai dati contenuti nel report dell'OMS sulla sulla sorveglianza globale dell'AMR (2014), solo il 37% dei Paesi membri sono in grado di fornire dati relativi a *K. Pneumoniae* carbapenemi-resistente. Le Regioni e i Paesi con la più alta prevalenza sono: il Subcontinente Indiano, gli Stati Uniti d'America, Israele, Grecia, Italia, Turchia, Medio Oriente e Nord Africa.
Per quanto riguarda *K. Pneumoniae*, secondo i dati ECDC 2016, le percentuali di microrganismi resistenti ai carbapenemi isolati da infezioni invasive sono molto variabili tra le diverse nazioni (range 0%-67%). Si osserva, in particolare, un trend in aumento in Grecia e Portogallo, nel periodo 2013-2016, mentre una diminuzione è stata registrata in Repubblica Ceca, Estonia e Ungheria.
Relativamente a *E. coli*, la percentuale di batteri carbapenemi-resistenti isolati nello stesso periodo risulta essere inferiore con un trend in diminuzione.
K. pneumoniae ed *E. coli* sono spesso causa di polmoniti associate all'utilizzo di respiratori e infezioni ematiche nei setting assistenziali; inoltre, *E. coli* è il più frequente agente eziologico di infezioni del tratto urinario sia in comunità che in ambito assistenziale. Lo sviluppo e la frequenza di AMR in questi batteri ha un forte impatto sulla scelta terapeutica e sugli esiti. Infatti, esiste un circolo vizioso responsabile dell'incremento di AMR tra gli Entorobatteri: l'aumentata resistenza a penicilline e cefalosporine induce al consumo di carbapenemi, con aumento della pressione selettiva per lo sviluppo di resistenza anche nei loro confronti. Perciò la scelta terapeutica per i CRE è limitata.
Ne consegue che il tasso di mortalità in pazienti con infezioni severe da CRE è molto alto, compreso tra il 30% e il 75%.
Purtroppo, nuovi antibiotici in grado di sostituire i carbapenemi per le loro principali indicazioni non saranno disponibili nel prossimo futuro.
Antibiotici che spesso mostrano *in vitro* attività nei confronti dei CRE sono colistina, tigeciclina e fosfomicina. Tuttavia, la scarsità dei dati disponibili sulla loro reale efficacia, l'alta frequenza di effetti avversi e il rapido sviluppo di resistenza, durante la terapia ma anche globalmente, inducono ad essere cauti riguardo al loro impiego su larga scala. Inoltre, studi osservazionali (i cui risultati devono, quindi, essere verificati) mostrano un miglioramento dell'esito, in termini di sopravvivenza, in pazienti con alta probabilità di decesso, solo in caso di uso di questi antibiotici in combinazione, mentre la mono-terapia non comporterebbe alcun beneficio.
Una nuova combinazione di antibiotici, ceftazidime-avibactam, è stata recentemente approvata dall'EMA (European Medicines Agency) per il trattamento delle infezioni da CRE non produttori di metallo-beta-lattamasi, responsabili di infezioni intra-addominali complicate, infezioni complicate del tratto urinario, polmoniti acquisite in ospedale e infezioni dovute a batteri aerobi gram-negativi con limitate opzioni terapeutiche.

Il Centro Europeo per la prevenzione ed il Controllo delle Malattie (ECDC) di Stoccolma nel Rapid Risk Assessment (RRA) pubblicato il 4 giugno 2018 (Allegato 1), evidenzia che procedure mediche avanzate, come la terapia intensiva, i trapianti, la chemioterapia antitumorale, l'assistenza neonatale, le procedure invasive, aumentano il rischio di sviluppare infezioni a causa di una immunodepressione o per un indebolimento delle barriere naturali come quella cutanea. In assenza di profilassi e trattamento antibiotico efficace, queste procedure si associano a un alto rischio di sviluppare infezioni sostenute da CRE. Inoltre, in molti Paesi si sono verificati focolai di CRE in

terapia intensiva e in altri reparti in cui erano ricoverati pazienti ad alto rischio (es. pazienti sottoposti a trapianto, a broncoscopia, a endoscopia, terapia intensiva neonatale).

Oltre all'alta mortalità e morbosità, le infezioni sostenute da CRE hanno un forte impatto economico sui sistemi sanitari, e non solo perché associate a prolungamento delle ospedalizzazioni. Le misure di controllo sono time-consuming e richiedono una formazione specifica e personale dedicato in numero adeguato; infatti, il rapporto tra un basso livello di assistenza e le infezioni correlate all'assistenza è ben noto.
l'ECDC sottolinea che solo azioni combinate, come uso consapevole degli antibiotici, controllo delle infezioni ospedaliere e igiene degli impianti idrici delle strutture, possono portare a risultati a lungo termine.
Nel citato RRA vengono presentate schematicamente le misure che sarebbe opportuno attuare a livello locale per il contenimento del rischio di diffusione dei CRE:

INTERVENTI PER LA RIDUZIONE DEL RISCHIO

1. Azioni correlate alle limitate opzioni terapeutiche e all'alta mortalità

Diagnosi laboratoristiche tempestive e appropriate, così come la segnalazione dei casi, sono essenziali nel velocizzare l'inizio di un trattamento terapeutico efficace, migliorando le probabilità di successo terapeutico attraverso una diminuzione di morbosità e mortalità. Pazienti infettati da CRE potrebbero trarre benefici, in termini di miglioramento dell'esito, da un consulto con uno specialista in malattie infettive o un microbiologo clinico, pur tenendo conto delle limitate opzioni terapeutiche.

2. Azioni per la prevenzione della trasmissione dei CRE nei setting assistenziali

Il miglioramento delle misure di controllo quali l'igiene delle mani, l'applicazione delle precauzioni da contatto, la pulizia dell'ambiente, l'appropriato trattamento dei dispositivi medici, adeguate capacità diagnostiche dei laboratori di microbiologia, così come la capacità delle strutture di isolare i contatti, costituiscono le basi per la prevenzione della trasmissione di batteri multi-resistenti come i CRE, in pazienti sia infetti che colonizzati. La tempestiva segnalazione dei casi all'interno della struttura è essenziale per la corretta implementazione delle appropriate misure di controllo.

a. Gestione dei pazienti ad alto rischio di essere portatori di CRE

Pazienti che sono stati recentemente ricoverati in Paesi o Regioni note per l'elevata prevalenza dei CRE, devono essere considerati ad alto rischio di essere portatori di CRE nel tratto intestinale. In queste circostanze è importante considerare forme di screening dei portatori e isolamento preventivo. Gli ospedali potrebbero valutare l'applicazione di queste misure anche nei confronti di pazienti che hanno recentemente viaggiato in Paesi o Regioni a rischio anche senza essere venuti a contatto con le strutture sanitarie.
Fattori in grado di migliorare l'identificazione dei soggetti ad alto rischio per infezione da CRE sono: storia di ricovero con pernottamento in un setting assistenziale negli ultimi 12 mesi, dialisi o chemioterapia antitumorale negli ultimi 12 mesi, anamnesi positiva per portatore di CRE negli ultimi 12 mesi, link epidemiologico con un portatore noto di CRE. Sulla base dell'epidemiologia locale potrebbero essere identificate altre condizioni di rischio.

b. Prevenzione della trasmissione da pazienti positivi ai CRE

I CRE sono responsabili di focolai in ambito assistenziale, e i fattori di rischio associati sono gli stessi di altri microrganismi multi-resistenti. Pertanto, al fine di prevenire, in ambiente ospedaliero, la trasmissione dei CRE è necessario potenziare i sistemi di controllo come le precauzioni da contatto, l'isolamento o il cohorting (raggruppamento) dei pazienti positivi (colonizzati o infetti), il

personale infermieristico dedicato. Lo screening dei contatti consente la rapida identificazione dei portatori e la consequenziale applicazione delle idonee misure di controllo.

c. Prevenzione della diffusione dei CRE in specifici reparti

Nei reparti che ospitano pazienti ad alto rischio di infezione (es. reparti di terapia intensiva e di onco-ematologia), l'isolamento preventivo e una sorveglianza attiva - con tampone rettale al momento del ricovero - dovrebbero essere presi in considerazione, in base anche all'epidemiologia locale. Un regolare controllo dell'uso appropriato dei dispositivi medici rappresenta un'altra importante misura di prevenzione nei setting ad alto rischio.

d. Antimicrobial stewardship

Programmi di Antimicrobial Stewardship devono essere implementati, al fine di assicurare una appropriata prescrizione antibiotica. Questi programmi devono mirare a migliorare l'efficacia clinica del trattamento antibiotico e a limitare lo sviluppo di AMR riducendo la pressione selettiva. Tuttavia, l'uso appropriato degli antibiotici, per quanto essenziale, non è in grado di bloccare o invertire completamente l'attuale trend dei CRE, o il trend dell'AMR in generale, per cui risulta fondamentale la ricerca di nuovi antibiotici.

3. Azioni per la prevenzione della diffusione dei CRE nella comunità

È importante prevenire la diffusione dei CRE in comunità, ad esempio attraverso la catena alimentare. Gli Stati Membri devono, pertanto, attenersi alle indicazioni fornite dalle istituzioni sovranazionali (Commissione Europea, EMA, EFSA, etc) in tema di produzione degli alimenti di origine animale, di monitoraggio dell'AMR nei sistemi di produzione, di uso degli antibiotici negli allevamenti. Inoltre, il miglioramento delle condizioni igieniche e di biosicurezza negli allevamenti e il potenziamento di misure alternative all'utilizzo di antibiotici, potrebbe ridurre il ricorso agli antibiotici stessi e lo sviluppo di AMR in campo veterinario.

4. Azioni per la prevenzione della diffusione transfrontaliera dei CRE

Misure in grado di migliorare la sorveglianza dei CRE, l'isolamento preventivo e lo screening dei pazienti trasferiti da ospedali o altri setting assistenziali in Paesi ad elevata prevalenza di CRE, rappresentano misure efficaci nel ridurre la diffusione e prevenire i focolai di CRE importati in ambito assistenziale. Per questo è importante che, durante il trasferimento transfrontaliero di pazienti, venga comunicato l'eventuale positività per CRE, che permette l'attivazione precoce di misure di prevenzione. A questo scopo, la notifica tempestiva alle autorità sanitarie e lo scambio di informazioni sono attività importanti in grado di avviare azioni coordinate.

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

Referente:
Dr.ssa Stefania Iannazzo

IL DIRETTORE DELL'UFFICIO 5
*** F.to Francesco Maraglino**

***"firma autografa sostituita a mezzo stampa, ai sensi dell'art. 3, comma 2, del d. Lgs. N. 39/1993"**

RAPID RISK ASSESSMENT

Carbapenem-resistant Enterobacteriaceae, first update

4 June 2018

Conclusions and options for response

Carbapenem-resistant Enterobacteriaceae (CRE) pose a significant threat to patients and healthcare systems in all EU/EEA countries. CRE infections are associated with high mortality, primarily due to delays in administration of effective treatment and the limited availability of treatment options. New antibiotics capable of replacing carbapenems for their main indications are not likely to become available in the near future. CRE are adapted to spread in healthcare settings as well as in the community, and measures should address both routes of transmission.

Options for actions to reduce identified risks

1. Actions related to limited treatment options and high mortality

Timely and appropriate laboratory investigation and reporting is essential 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 considering the limited treatment options.

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

Implementation of and strict adherence to infection control measures, including hand hygiene, contact precautions, environmental cleaning, adequate reprocessing of medical devices, adequate capacity of microbiological laboratories as well as sufficient capacity of healthcare facilities for contact isolation, are the basis for prevention of transmission of multidrug-resistant bacteria such as CRE for both infected and colonised patients. Prompt notification of the clinical team and of the infection prevention and control/hospital hygiene team is essential in order to implement infection control precautions in a timely manner. For healthcare settings other than acute care, the control measures implemented should be proportionate to the risk for CRE transmission to other patients.

Suggested citation: European Centre for Disease Prevention and Control. Rapid risk assessment: Carbapenem-resistant Enterobacteriaceae, first update – 4 June 2018. Stockholm: ECDC; 2018.

Targeting patients at high risk for carriage of CRE

Patients who had recently been hospitalised in a country or region known as having a high CRE prevalence – or who were transferred from an individual hospital with a high CRE prevalence – should be considered at high risk of digestive tract carriage of CRE. Screening these patients for digestive tract carriage of CRE and implementing pre-emptive contact precautions and pre-emptive isolation should be considered. Hospitals could also consider pre-emptive isolation and screening for digestive tract carriage of CRE in accordance with national guidance for patients who recently travelled to countries/regions known for their high CRE prevalence, even if they were not in contact with a healthcare institution/service.

Risk factors that could be helpful to identify patients at increased risk for CRE carriage are a history of an overnight stay in a healthcare setting in the last 12 months, dependency on dialysis or receiving 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. Based on the local epidemiology additional at-risk populations could be defined.

Preventing transmission from CRE-positive patients

Hospitals should consider enhanced control measures such as contact precautions, isolation or cohorting, and dedicated nursing staff for patients who are CRE-positive, i.e. patients confirmed with digestive tract carriage of CRE or confirmed infection with CRE. Screening of contacts will allow 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 at admission should be considered, depending on the risk of digestive tract carriage of CRE 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 the environmental reservoir of epidemic CRE strains and/or carbapenemase-encoding plasmids should be investigated and relevant control measures implemented accordingly.

Antimicrobial stewardship

Antimicrobial stewardship refers to coordinated programmes that implement interventions to ensure appropriate antimicrobial prescribing. These programmes aim to improve clinical efficacy of antimicrobial treatment and limit antimicrobial resistance through reducing the selective pressure for the development of resistance and have been shown to significantly reduce the incidence of infections with and carriage of antibiotic-resistant bacteria. 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 (antibiotics) 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 [1]. Continued prohibition of the use of carbapenems in food-producing animals would be a simple and effective option for intervention. 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 use of antimicrobials in animal production in the EU in accordance with prudent use guidelines is also of high priority [2]. In addition, the improvement of the conditions of animal husbandry (e.g. biosecurity, hygienic conditions) and the implementation of alternative measures to antimicrobials would reduce the need to use antimicrobials and the development of resistant bacteria in food-producing animals. A multifaceted integrated approach to minimise antimicrobial use is recommended and further options in this regard 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" [3].

In households and shared public environments, standard rules of personal hygiene should be applied to prevent person-to-person transmission as well as good food handling practices to prevent contamination of food by colonised handlers.

4. Actions with regard to cross-border aspects

Measures related to enhanced CRE surveillance and pre-emptive isolation and screening of patients who were transferred from hospitals and other healthcare settings in high-CRE-prevalence countries are an immediate measure to reduce transmission in healthcare and prevent outbreaks of imported CRE. Documentation and inter-facility communication of known carriage or infection by CRE during cross-border patient transfer would optimise the early and effective implementation of measures to prevent the spread of CRE. Moreover, gathering reliable epidemiological data through notification of cases to public health authorities and exchange of information through electronic early warning platforms, such as the Epidemic Intelligence System (EPIS) are important activities to allow informed and coordinated actions by public health authorities across the EU/EEA.

Only concerted worldwide measures, such as regulating antimicrobial use, improved infection control in hospitals, and an improved water and sanitation infrastructure, can offer a long-term solution. As a first step towards control, the capacity for resistance detection and surveillance in low-resource countries needs to be improved in order to collect more reliable data on the worldwide distribution of CRE. Testing for faecal carriage of CRE upon hospital admission should be performed in accordance with the relevant national guidelines for testing persons at risk of carrying CRE and other multidrug-resistant gram-negative bacteria. Nevertheless, the presence of such infection or colonisation should not preclude the transfer or inhibit the care of patients.

5. Actions with regard to risks for healthcare systems

Adequate 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. Currently, prevalence of CRE is 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. Once an endemic situation is reached, control efforts will be more costly and less likely to be effective.

Source and date of request

Request from the European Commission on 9 March 2016.
Updated request from the European Commission on 26 April 2018.

Public health issue

The global rise of carbapenem-resistant Enterobacteriaceae (CRE) is alarming and represents an increasing threat to healthcare delivery and patient safety. CRE have been associated with higher healthcare costs, prolonged hospital stays, treatment failures and mortality. This update of the 2016 ECDC Rapid Risk Assessment on CRE [4] evaluates the risk for patients and healthcare systems in EU/EEA countries due to the global spread of CRE.

Consulted experts

Internal experts consulted: (in alphabetical order) Anke Kohlenberg, Dominique L. Monnet, Diamantis Plachouras, Marc Struelens.

External experts consulted: Elisabeth Presterl (University Hospital Vienna, Austria) Jesús Rodríguez-Baño (Hospital Universitario Virgen Macarena, Spain), Gunnar Skov Simonsen (University Hospital North Norway, Tromsø, Norway), Sotirios Tsiodras (Hellenic Centre for Disease Control and Prevention and Athens University Medical School, Athens, Greece). Additional comments on the recommendations in section 3 related to actions to prevent the spread of CRE into the community were provided by Ernesto Liebana (European Food Safety Authority).

Disease background information

Bacteria of the family Enterobacteriaceae such as *Escherichia coli* and *Klebsiella 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 the past decades have seen a rapid increase of 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* [5].

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 considered as being the most reliable treatment 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 [6,7]. Carbapenem-resistant *Enterobacteriaceae* (CRE) can be resistant to carbapenems by various mechanisms. These are frequently carbapenemase enzymes, 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 [8]. In the literature, CRE producing carbapenemases are often named after the specific carbapenemases 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.

Event background information

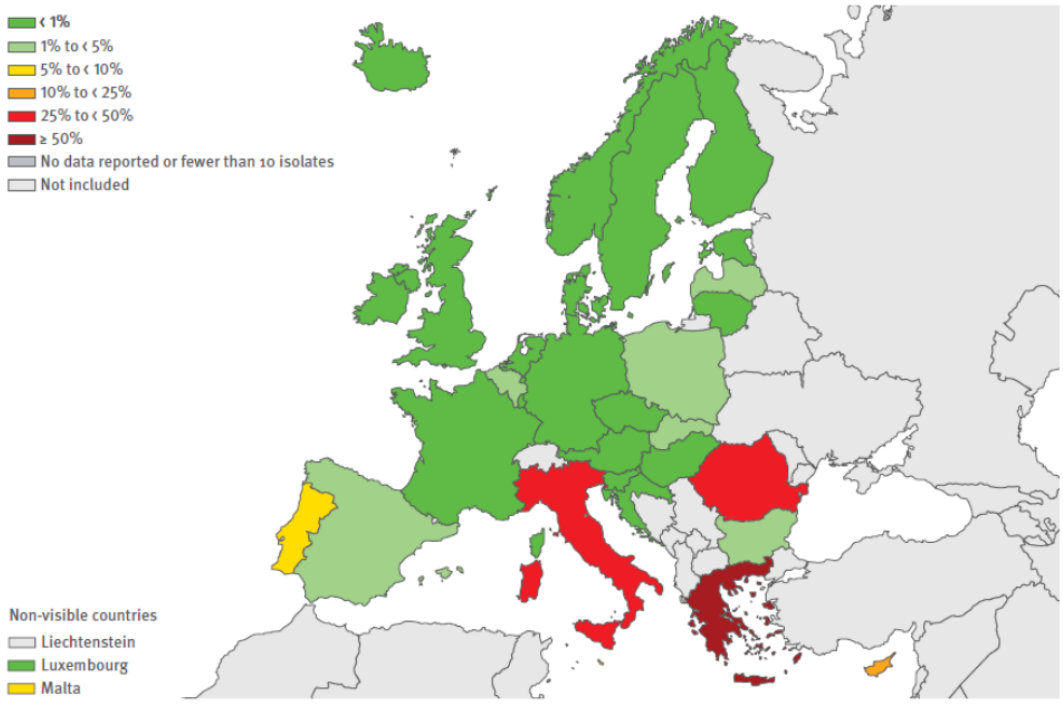
Current situation of CRE in EU/EEA countries

Percentage of invasive isolates of Enterobacteriaceae (*K. pneumoniae* and *E. coli*) resistant to carbapenems

For *K. pneumoniae*, data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) for 2016 show large differences in the national percentages of carbapenem resistance in invasive (i.e. mostly from bloodstream infections) isolates, ranging from 0% to 66.9%, depending on the country (Figure 1).

The population-weighted mean percentage for the EU/EEA fluctuated between 8.2% (2013) and 6.1% (2016) (no statistically significant trend). Increasing trends of carbapenem resistance in *K. pneumoniae* for the period 2013–2016 were observed for Greece and Portugal, while there was a decreasing trend in the Czech Republic, Estonia and Hungary [9].

Figure 1. Percentage of invasive *K. pneumoniae* isolates with resistance to carbapenems, EU/EEA, 2016 [9]



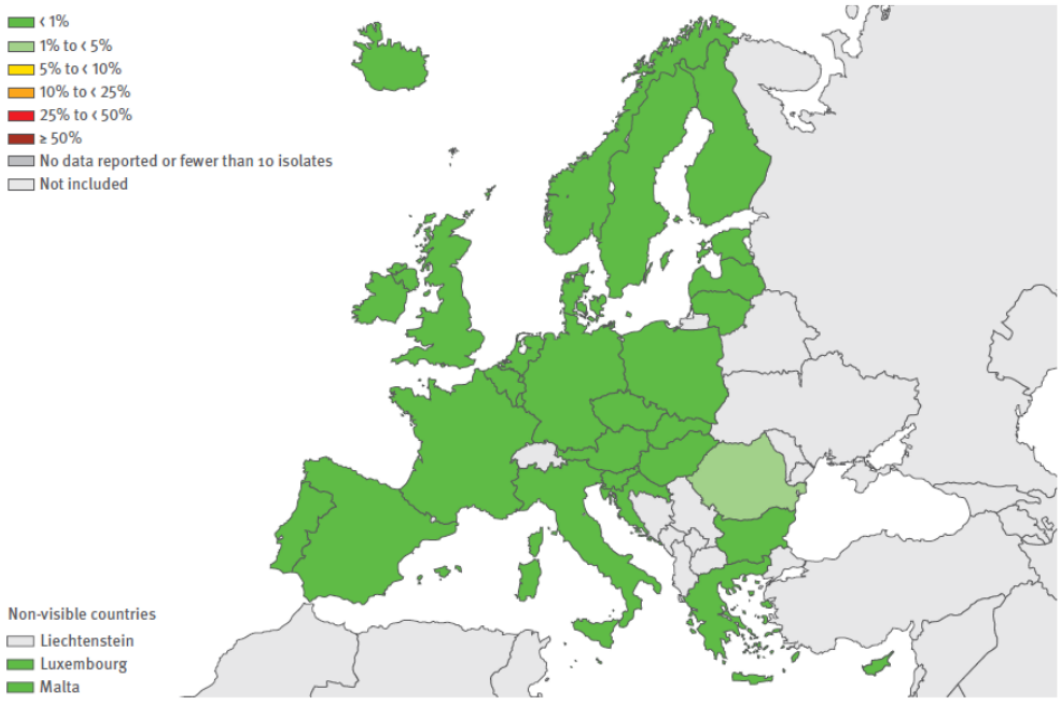
Note: EARS-Net data are based on invasive isolates from blood and cerebrospinal fluid only. Bacteria isolated from other sites of infection or colonisation are not included.

For *E. coli*, EARS-Net data for 2016 show a different epidemiological situation with a much lower EU/EEA population-weighted mean percentage (0.1%) of carbapenem resistance in invasive isolates, and national

percentages ranging from 0% to 1% (Figure 2). Between 2013 and 2016, a slightly decreasing trend from 0.2% to 0.1% was observed for the EU/EEA population-weighted mean of national percentages [9].

An estimate of the burden caused by CRE and other multidrug-resistant organisms in the EU/EEA based on data from EARS-Net and the ECDC point prevalence surveys is under development. An ECDC network for genomic-based surveillance of multidrug-resistant bacteria has been established (European Antimicrobial Resistance Genes Surveillance Network - EURGen-Net) and a survey of the prevalence and distribution of carbapenem- and/or colistin-resistant Enterobacteriaceae is planned for 37 EU/EEA and enlargement countries in 2019 including whole-genome sequencing of collected isolates [10].

Figure 2. Percentage of invasive *E. coli* isolates with resistance to carbapenems, EU/EEA, 2016 [9]



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.

Current situation of CRE in third countries

For the WHO Global report on antimicrobial resistance surveillance, only 71 (37%) WHO Member States were able to provide data on carbapenem resistance in *K. pneumoniae* [11]. Carbapenem-resistace in *K. pneumoniae* was reported from all WHO regions, exceeding 50% in two regions [11]. For the 2016-2017 Global Antimicrobial Resistance Surveillance System (GLASS) Report, only 22 countries provided AMR data [12], and a worldwide overview of carbapenem resistance in *K. pneumoniae* and *E. coli* is therefore difficult to establish from this report.

CRE with different carbapenemase genes show variation in their geographic spread. Identified regions and countries with a high prevalence are the Indian subcontinent (NDM CRE), the USA, Israel, Greece and Italy (KPC CRE), Turkey, the Middle East and North Africa (OXA-48 CRE) [12,13].

Indirect evidence for the prevalence of CRE in different regions is also provided through CRE carriage detected in patients transferred from hospitals [14] and travellers returning from high-prevalence regions to Europe [15].

ECDC threat assessment for the EU

Current and possible future risks for human health

Impact on human health

Frequency of occurrence

E. coli is the most common cause of community- and healthcare-associated urinary tract infections. *K. pneumoniae* and *E. coli* are also frequently associated with ventilator-associated pneumonia and bloodstream infections in healthcare settings [16]. Resistance in these bacteria will therefore have 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 resulted in frequent resistance to all penicillins and cephalosporins, with the consequence of increasing carbapenem consumption [17], which in turn 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 about, or insufficient data on, 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 [18]. Combination therapy with two or more active agents showed a survival benefit among patients with a high probability of death [19]. However, these data should be interpreted with caution as they come from observational studies.

Colistin is frequently being used to treat CRE infections, but colistin resistance may develop in CRE-infected patients treated with colistin. The percentage of colistin resistance among CRE isolates can increase rapidly in hospitals and countries with increasing use of colistin [20-23]. 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 [24]. The discovery of transferable plasmid-mediated colistin resistance genes (*mcr 1-5*) since 2015 that can transmit colistin resistance more easily between bacteria has further increased the risk for spread of colistin resistance [26]. The consequence of failing to control CRE is 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 [26-30].

In June 2016, ceftazidime-avibactam, a new antibiotic combination against CRE infections (except for infections with CRE producing metallo-beta-lactamases, like NDM or VIM), was recently approved by the European Medicines Agency for use in the EU for the treatment of 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 [32]. Limited evidence shows promising results, although there are concerns about the development of resistance [32]. Progress in developing new drugs has been slow [33]; however, there are new compounds or combinations in development such as meropenem-vaborbactam, imipenem-relebactam, plazomycin, cefiderocol, eravacycline and aztreonam-avibactam [32]. There is an urgent need for research and clinical development of antimicrobials to keep up with the evolution of bacterial resistance [33].

High mortality

High mortality rates, ranging from 30% to 75%, have been reported for patients with severe CRE infections [34]. Mortality above 50% has been reported in patients with CRE bloodstream infection [35], and a study has shown an excess mortality of 27% in patients with pneumonia or bloodstream infection caused by carbapenem-resistant *K. pneumoniae* [36]. The high mortality that has been associated with CRE is likely attributable to the lack of appropriate treatment options and the delayed institution of effective therapy. Infectious disease consultation has been shown to reduce all-cause mortality for multidrug-resistant organism infections [38].

Potential for spread

High potential for 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 and the UK [38-43]. Risk factors for acquisition of CRE in healthcare settings are similar to those reported for acquisition of other multidrug-resistant bacteria. These include, for example, admission to an intensive care unit (ICU), long ICU stay, critical illness, invasive devices and prior antimicrobial

therapy [44,45]. A recent meta-analysis found that "use of medical devices" and "carbapenem use" were the most significant risk factors for CRE acquisition by hospitalised patients [46]. Long-term care facilities have also been shown to be a reservoir for CRE in some settings [47,48].

Carbapenemase genes are often located on plasmids that can be exchanged between Enterobacteriaceae and other gram-negative bacteria [8]. They are also often transmitted together with other resistance genes, which results in multidrug-resistant bacteria. While carbapenem consumption has been shown to be associated with increases in CRE [42], 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 [45]. International high-risk bacterial clones such as the KPC-producing *K. pneumoniae* ST258 have emerged. These clones are very efficient at colonising human hosts and highly successful at transmission in hospital settings [49].

Colonisation, i.e. digestive tract carriage, with CRE has been associated with high rates (up to 89%) of subsequent infections, most frequently pneumonia, followed by urinary tract infections, primary bloodstream infections, skin and soft tissue infections, and surgical site infections [34]. Eradication of CRE from the intestinal flora is difficult. Rates of spontaneous clearance vary between studies [50,51], and continuous carriage beyond two years has been reported [51]. Eradication has been attempted with oral non-absorbable antibiotic treatment. The success of this latter approach has been limited due to failure of eradication, relapse, development of antibiotic resistance during treatment, and patient refusal [50].

The role of the hospital environment, including ill-designed waste water plumbing, handwashing basins and sinks, as 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. A systematic review of molecular epidemiologic studies using pre-whole genome sequencing (WGS) typing methods to trace the source of infection identified 32 waterborne hospital outbreaks of carbapenem-resistant bacteria including a variety of Enterobacteriaceae, *Pseudomonas* spp. and *Acinetobacter* spp [52]. Recent outbreak studies using advanced genomic epidemiologic methods, including WGS, have revealed hospital environmental reservoir of diverse bacteria with plasmids conferring carbapenem resistance that transferred to diverse species and clonal strains of infecting Enterobacteriaceae [53-55]. This raises the issue of the need for 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 or reprocessing.

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 [57]. There is also a need to define the circumstances under which screening for faecal carriage 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 [57]. A systematic literature review with addition of expert opinion conducted by ECDC identified the following risk factors for CRE carriage: a history of an overnight stay in a healthcare setting in the last 12 months, dependency on dialysis or receiving 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 [58]. Based on local epidemiology, additional risk groups have been proposed, such as hematopoietic stem cell transplant recipients or newborns, especially if they had received prior carbapenem treatment [59,60].

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. The following measures were identified as effective:

- Early implementation of active surveillance by rectal screening for CRE carriage on hospital admission, admission to specific wards/units, and during outbreaks;
- 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 [62].

A recently published study conducted in 38 French hospitals in the Paris area emphasizes the importance of a comprehensive control programme, including pre-emptive isolation and screening of every single patient with a history of hospital stay in a foreign country within the past year, contact precautions for every carrier, screening of contact patients and, if at least one secondary case was identified, cohorting of patients in distinct areas according to carriage/contact status [62]. However, there is limited generalisability even of successful programmes to healthcare settings in other countries. Every control programme needs to be adapted to the local setting depending, for example, on the local prevalence of CRE, travel patterns of the local population and the percentage of CRE cases imported from foreign countries, and the availability of local resources for laboratory testing and infection control.

The World Health Organization has published guidelines for the prevention and control of CRE, carbapenem-resistant *Acinetobacter baumannii* and carbapenem-resistant *Pseudomonas aeruginosa* in health care 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, as well as monitoring, auditing and feedback [64]. There is also facility guidance for control of CRE from the US Centers for Disease Control and Prevention [65], as well as guidelines for the management of infection control measures to reduce transmission of multidrug-resistant gram-negative bacteria in hospitalised patients from the European Society of Clinical Microbiology and Infectious Diseases [65]. In addition, 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 [67].

In addition to infection control measures, prudent antimicrobial use will reduce the selection pressure for CRE, and reduction of carbapenem use through an antimicrobial stewardship programme has been shown to be beneficial for CRE control [42]. The above-mentioned measures have been effective in studies, but their implementation 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 [68].

Risk of transfer of CRE into 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 [8]. There is growing evidence that extra-intestinal pathogenic *E. coli* may be transmitted to humans via the food supply from a food animal source [69]. 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 failure of standard antimicrobial therapy in the case of CRE infection, overgrowth of CRE, and onward transmission to other patients.

The spread of ESBL-producing Enterobacteriaceae, mainly *E. coli*, in the community during the last decade demonstrates how rapidly these bacteria can disseminate in this setting [8]. 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 plasmid-mediated. The contamination of food items with antimicrobial-resistant Enterobacteriaceae has been described in several EU/EEA countries, for example for chicken or poultry meat in Austria, Germany, the Netherlands, Italy and Spain [69-73], and for vegetables in the Netherlands [74]. There is now evidence that a proportion of human extra-intestinal infections with *E. coli* resistant to third- and fourth-generation cephalosporins originated from food-producing animals, especially poultry [75]. 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 [76-79], and carbapenemase production has also been reported in the foodborne pathogen *Salmonella enterica* [80]. The occurrence of CRE in multiple non-human sources is of concern and, given the risks of CRE for human health, there have been calls for a zero-tolerance approach and an international ban on the sale of food items that contain CRE [82].

Cross-border aspects

EU/EEA countries

Maps by EARS-Net and the EuSCAPE project show that EU/EEA countries are at very different stages of CRE spread. For *K. pneumoniae*, percentages of carbapenem resistance range from 0% to more than 60%, and epidemiological stages of spread range from sporadic cases to endemicity [9,82]. 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 level of CRE. 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 into low-prevalence countries can occur from EU Member States with a high level of CRE, such as Greece and Italy, or from other countries or regions with high reported levels of CRE, e.g. countries in the eastern and southern Mediterranean regions, the Indian subcontinent and south-east Asia [10,30,83].

Third countries

High mobility and global trade play an important role in the transmission 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, overcrowding), has resulted in high rates of antimicrobial resistance in gram-negative bacteria in emerging economies [84]. Through travel and migration, populations around the world are subsequently exposed to antimicrobial resistance arising in these areas [84]. Much of this dissemination happens unrecognised 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 [5]. 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 and/or hospital care in India or Pakistan [85].

A high rate of digestive tract carriage of multidrug-resistant Enterobacteriaceae has also been described in travellers returning to the EU from tropical regions [15]. 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 [86,87].

Antimicrobial resistance, including CRE, is a global problem. Antimicrobial resistance caused by antimicrobial use and lack of public health infrastructure in one region of the world will eventually affect other regions, even if they have implemented measures for a more prudent antimicrobial use and a better public health infrastructure. It will be difficult for countries with low CRE prevalence to control CRE if there is continuous importation from high-prevalence regions because of asymptomatic digestive tract carriage in humans. The fact that countries from regions with high CRE prevalence were not able to provide data on CRE for the WHO global surveillance reports is of concern [11,12].

Preparedness in EU/EEA countries

Two indicators are relevant for CRE in the EU Laboratory Capability Monitoring System (EULabCap) 2016 report presenting data from 30 EU/EEA countries. According to this report seven countries were performing carbapenemase identification using EUCAST guidance upon request from diagnostic laboratories and 23 countries performed carbapenemase identification using EUCAST guidance as part of structured surveys for monitoring purposes (indicator 2.4.2, target 2.4 AMR monitoring) [89]. In addition, for testing of colistin, which is frequently used for treatment of CRE, guidance for susceptibility testing and confirmation and identification of resistance mechanisms issued by the National Antibiotic Committee or National Reference Laboratory was available in 14 of 30 countries (indicator 3.4.5, target 3.4 preparedness response) [89]. A survey of WGS-based typing in EU/EEA countries indicated that it was applied in nine countries in 2016 for national surveillance of CRE [90].

The national capacity of EU/EEA countries, EU enlargement countries and Israel was assessed in May 2015 by national experts that participated in the EuSCAPE project [83]. Of 38 participating European countries, 25 countries reported having a dedicated national surveillance system for carbapenemase-producing Enterobacteriaceae; 34 countries reported having an officially appointed national reference laboratory or national expert laboratory for carbapenemase-producing Enterobacteriaceae; 20 countries were developing, or had implemented, a national plan for containment or for preparedness to contain carbapenemase-producing Enterobacteriaceae; and 24 countries reported having national recommendations or guidelines for infection prevention and control measures for confirmed cases of carbapenemase-producing Enterobacteriaceae [83]. A repeat survey to update this information for 2018 is under preparation.

Risks for the functioning of health systems

Advanced medical procedures such as intensive care, transplantation, cancer chemotherapy, neonatal care and invasive procedures increase the risk for patients to develop 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 of 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 [44,90]. 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 [91]. Mortality rates associated with CRE infections were high in patients with haematologic malignancies [92]. Low-birthweight neonates have also been affected by CRE septicaemia [93]. In addition, CRE outbreaks have been related to frequently-performed invasive medical procedures, for example in outbreaks related to bronchoscopy and endoscopy in Germany [41,94] and France [95].

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 [34]. A retrospective study of the costs of patients carrying carbapenemase-producing Enterobacteriaceae admitted over a period of two years in a French hospital estimated that the attributable costs for 16 patients carrying a carbapenemase-producing Enterobacteriaceae were EUR 642 104. This included the costs related to restricted activities in the affected units, additional working hours and screening samples [95].

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 [98]. Underfunding and understaffing of healthcare institutions challenges the implementation of infection control measures and risks creating reservoirs of multidrug-resistant bacteria, such as CRE.

There is evidence that consistently implemented infection control programmes can reduce the spread of CRE. Active surveillance and infection control measures including hand hygiene have led to reduction of CRE in an endemic setting [98]. Israel experienced a clonal outbreak of carbapenem-resistant *Klebsiella pneumoniae* that affected 27 hospitals and 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 [97]. In France, after the occurrence of several outbreaks of carbapenemase-producing Enterobacteriaceae, the multi-hospital institution of 38 hospitals of the Assistance Publique-Hôpitaux de Paris 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 [62,98].

Disclaimer

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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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