



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 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

Implementation of and strict adherence to infection control measures - including hand hygiene, contact precautions, environmental cleaning, proper reprocessing of medical devices, adequate microbiological laboratory capacity and sufficient capacity for contact isolation - are the basis for preventing 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 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

Patients who have recently been hospitalised in a country or region known as having a high CRE prevalence – or who have been transferred from an individual hospital with a high CRE prevalence – should be considered at high risk of CRE carriage in their digestive tract. Screening these patients for digestive tract CRE carriage 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 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.

Risk factors that could be helpful in identifying patients at increased risk of 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. Based on the local epidemiology, additional at-risk populations could be defined.

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 the environmental reservoir of epidemic CRE strains and/or carbapenemase-encoding plasmids should be investigated 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 (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 antimicrobial usage in animal production within the EU in accordance with prudent use guidelines is also of high priority [2]. In addition, 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. 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' [3].

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

Measures related to enhanced CRE surveillance and pre-emptive isolation and screening of patients transferred from hospitals and other healthcare settings in high-CRE-prevalence countries represent an immediate means of reducing transmission in healthcare and preventing outbreaks of imported CRE. Documentation and inter-facility communication of known CRE carriage or infection 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 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 Early Warning and Response System (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.

Only concerted worldwide measures, such as regulating antimicrobial use, improving infection control in hospitals, and improving 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. Patients should be tested for faecal carriage of CRE upon hospital admission, in accordance with the relevant national guidelines for

testing persons at risk of carrying CRE and other multidrug-resistant gram-negative bacteria. However, the presence of such infection or colonisation should not preclude the transfer or inhibit the care of patients.

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 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 regarding 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 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* [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 to be 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 as a result of various mechanisms. These are frequently carbapenemase enzymes, but combinations of other different mechanisms may also cause carbapenem resistance.

Carbapenemases are a heterogeneous 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

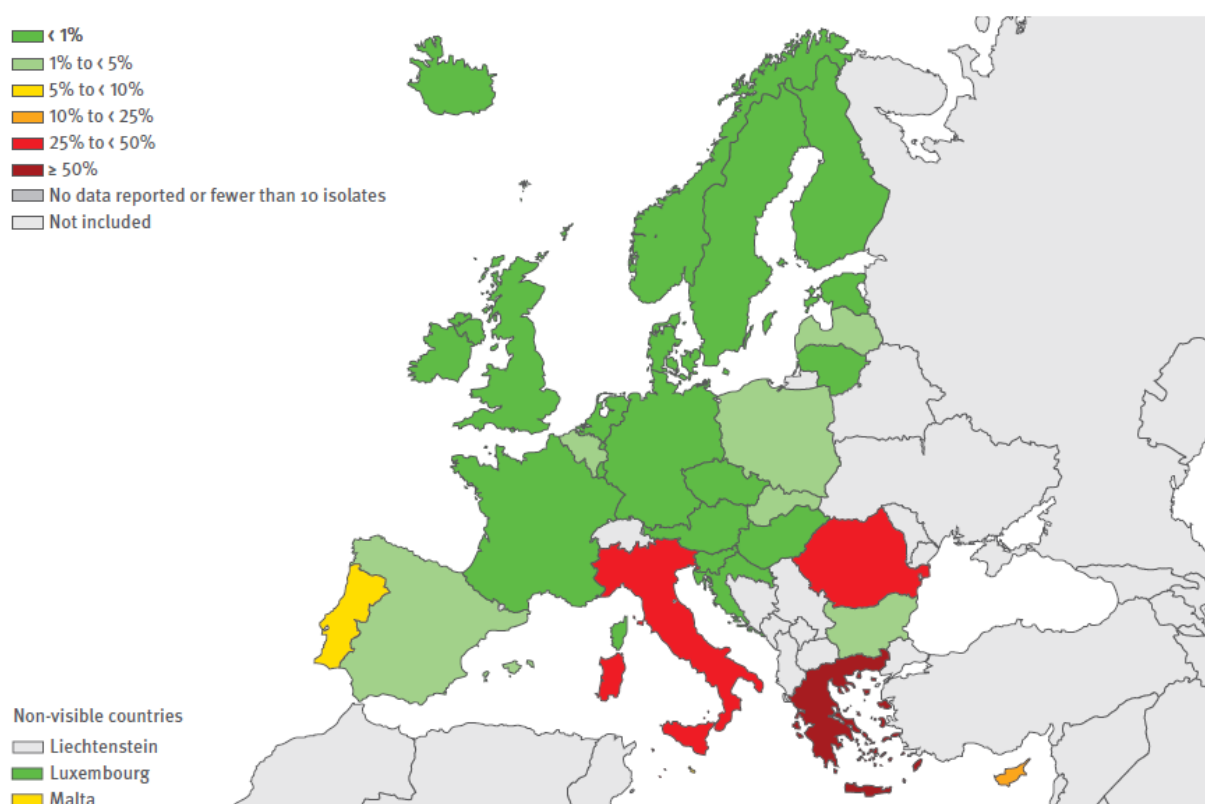
Current situation of CRE in EU/EEA countries

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, <https://ecdc.europa.eu/en/about-us/networks/disease-networks-and-laboratory-networks/ears-net-about>) 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 in 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].

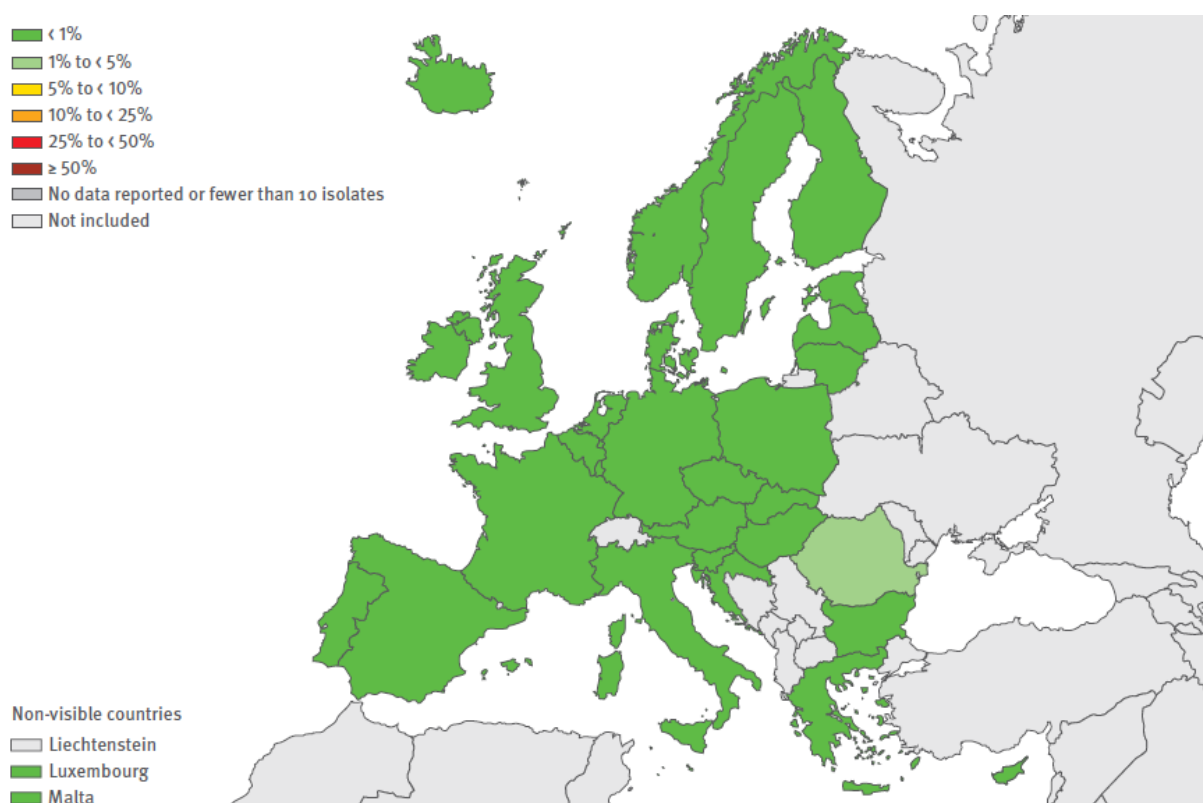
Figure 1. Percentage of invasive *K. pneumoniae* isolates with resistance to carbapenems, EU/EEA, 2016 [9]



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-resistance 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. Regions and countries identified as having a high prevalence are the Indian subcontinent (NDM CRE), USA, Israel, Greece and Italy (KPC CRE), Turkey, the Middle East and North Africa (OXA-48 CRE) [13,14].

Indirect evidence for the prevalence of CRE in different regions is also provided through CRE carriage detected in patients transferred from hospitals [15] and travellers returning from high-prevalence regions to Europe [16].

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 [17]. 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 has resulted in frequent resistance to all penicillins and cephalosporins, with the consequence of an increase in carbapenem consumption [18], 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 about, and 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 [19]. Combination therapy with two or more active agents, showed a survival benefit among patients with a high probability of death [20]. 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. Colistin resistance among CRE isolates can develop rapidly in hospitals and countries with increasing use of colistin [21-24]. 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 [25]. Since 2015, the discovery of transferable plasmid-mediated colistin resistance genes (*mcr 1-5*) that can transmit colistin resistance more easily between bacteria has further increased the risk of colistin resistance spreading [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. pan-drug-resistant CRE [27-31].

In June 2016, ceftazidime-avibactam, a new antibiotic combination against CRE infections (except for infections with CRE producing metallo-beta-lactamases, such as NDM or VIM), was approved by the European Medicines Agency 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 [32]. Limited evidence shows promising results, although there are concerns about the development of resistance [33]. Progress in developing new drugs has been slow [34]; however, there are new compounds or combinations in development such as meropenem-vaborbactam, imipenem-relebactam, plazomicin, cefiderocol, eravacycline and aztreonam-avibactam [33]. There is an urgent need for research and clinical development of antimicrobials to keep up with the evolution of bacterial resistance [34].

High mortality

High mortality rates, ranging from 30% to 75%, have been reported for patients with severe CRE infections [35]. Mortality above 50% has been reported in patients with CRE bloodstream infection [36], and a study has shown an excess mortality of 27% in patients with pneumonia or bloodstream infection caused by carbapenem-resistant *K. pneumoniae* [37]. The high mortality associated with CRE is probably 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. Czech Republic, France, Germany, Greece, Italy, Spain and the UK [39-44]. 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 [45,46]. 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 [47]. Long-term care facilities have also been shown to be a reservoir for CRE in some settings [48,49].

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 [43], 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 [46]. 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 [50].

Colonisation - i.e. digestive tract carriage - with CRE has been associated with high rates (up to 89%) of subsequent infection, most frequently pneumonia, followed by urinary tract infections, primary bloodstream infections, skin and soft tissue infections, and surgical site infections [35]. Eradication of CRE from the intestinal flora is difficult. Rates of spontaneous clearance vary between studies [51,52], and continuous carriage beyond two years has been reported [52]. Eradication 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 [51].

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. A systematic review of molecular epidemiological 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. [53]. 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 infecting Enterobacteriaceae [54-56]. 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 and 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 [58]. A systematic literature review, with the addition of an 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 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 [59]. Based on local epidemiology, additional risk groups have been proposed, such as hematopoietic stem cell transplant recipients or new-borns, especially if they had previously received carbapenem treatment [60,61].

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 through 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 emphasises 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 [63]. 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 on the local prevalence of CRE, travel patterns of the local population, 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 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 [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 [66]. 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. 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 [43]. 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 CRE transfer 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 chain 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 standard antimicrobial therapy failing 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 such 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 in relation to chicken or poultry meat in Austria, Germany, the Netherlands, Italy and Spain [70-74], and for vegetables in the Netherlands [75]. 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 [76]. 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 [77-80], and carbapenemase production has also been reported in the foodborne pathogen *Salmonella enterica* [81]. 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 [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 [9,83]. 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 [11,31,84].

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 and overcrowding), has resulted in high rates of antimicrobial resistance in gram-negative bacteria in emerging economies [85]. Through travel and migration, populations around the world are subsequently exposed to antimicrobial resistance arising in these areas [85]. 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 [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 [86].

A high rate of digestive tract carriage of multidrug-resistant Enterobacteriaceae has also been described in travellers returning to the EU from tropical regions [16]. 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 [87,88].

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 WHO's 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) Report 2016 presenting data from 30 EU/EEA countries. According to this report, seven countries were performing carbapenemase identification using EUCAST guidance at the request of 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 the testing of colistin, which is frequently used for treatment of CRE, guidance for susceptibility testing, 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 who 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 currently being prepared.

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 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 [45,91]. Bloodstream infection with CRE was also a predictor of death in liver transplant patients, and infection-related mortality was high, with 64% in allogeneic stem cell transplant recipients in Italy [92]. Mortality rates associated with CRE infections were high in patients with haematological malignancies [93]. Low-birthweight neonates have also been affected by CRE septicaemia [94]. In addition, CRE outbreaks have been related to frequently-performed invasive medical procedures – e.g. in outbreaks related to bronchoscopy and endoscopy in Germany [42,95] and France [96].

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 [35]. 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 Enterobacteriaceae were EUR 642 104. This included the costs related to restricted activities in the affected units, additional working hours and screening samples [97].

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 [99]. Israel experienced a clonal outbreak of carbapenem-resistant *Klebsiella pneumoniae* that affected 27 hospitals. As a result it 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 [100]. In France, after the occurrence of several outbreaks of carbapenemase-producing Enterobacteriaceae, the Assistance Publique-Hôpitaux de Paris, a multi-hospital institution consisting of 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 [63,101].

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 853/2004 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 with their respective advantages and disadvantages. 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 countries. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency.

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References

1. European Commission. Commission implementing decision of 12 November 2013 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria. Official Journal of the European Union [Internet]. 2013. Available from: <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32013D0652>.
2. European Food Safety Authority Panel on Biological Hazards. Scientific Opinion on Carbapenem resistance in food animal ecosystems. EFSA Journal. 2013;11(2):3501.
3. European Medical Agency & European Food Safety Authority. 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 2017. Available from: <https://www.efsa.europa.eu/en/efsajournal/pub/4666>.
4. European Centre for Disease Prevention and Control. Rapid risk assessment: Carbapenem-resistant Enterobacteriaceae Stockholm: ECDC; 2016. Available from: <https://ecdc.europa.eu/en/publications-data/rapid-risk-assessment-carbapenem-resistant-enterobacteriaceae-14-april-2016>.
5. Woerther PL, Burdet C, Chachaty E, Andremonet A. Trends in human fecal carriage of extended-spectrum beta-lactamases in the community: toward the globalization of CTX-M. Clin Microbiol Rev. 2013 Oct;26(4):744-58.
6. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. Clin Infect Dis. 2011 Jul 1;53(1):60-7.
7. Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, Cormican M, et al. Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. Lancet Infect Dis. 2013 Sep;13(9):785-96.
8. Nordmann P, Naas T, Poirel L. Global spread of Carbapenemase-producing Enterobacteriaceae. Emerg Infect Dis. 2011 Oct;17(10):1791-8.
9. European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe 2016. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2017. Available from: <https://ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2016>.
10. European Centre for Disease Prevention and Control. ECDC study protocol for genomic-based surveillance of carbapenem-resistant and/or colistin-resistant Enterobacteriaceae at the EU level - version 1.1. Stockholm: ECDC; 2017. Available from: <https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/Protocol-genomic-surveillance-resistant-Enterobacteriaceae.pdf>.
11. World Health Organization. Antimicrobial Resistance Global Report on Surveillance. Geneva: WHO; 2014.
12. World Health Organization. Global antimicrobial resistance surveillance system (GLASS) Report - Early implementation 2016-2017. Geneva: WHO; 2018. Available from: <http://www.who.int/glass/resources/publications/early-implementation-report/en/>.
13. 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.
14. Nordmann P, Poirel L. The difficult-to-control spread of carbapenemase producers among Enterobacteriaceae worldwide. Clin Microbiol Infect. 2014 Sep;20(9):821-30.
15. 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.
16. 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.
17. Peleg AY, Hooper DC. Hospital-acquired infections due to gram-negative bacteria. N Engl J Med. 2010 May 13;362(19):1804-13.
18. Meyer E, Schwab F, Schroeren-Boersch B, Gastmeier P. Dramatic increase of third-generation cephalosporin-resistant *E. coli* in German intensive care units: secular trends in antibiotic drug use and bacterial resistance, 2001 to 2008. Crit Care. 2010;14(3):R113.
19. Tzouveleakis LS, Markogiannakis A, Piperaki E, Souli M, Daikos GL. Treating infections caused by carbapenemase-producing Enterobacteriaceae. Clin Microbiol Infect. 2014 Sep;20(9):862-72.
20. 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.

21. Mezzatesta ML, Gona F, Caio C, Petrolito V, Sciortino D, Sciacca A, et al. Outbreak of KPC-3-producing, and colistin-resistant, *Klebsiella pneumoniae* infections in two Sicilian hospitals. Clin Microbiol Infect. 2011 Sep;17(9):1444-7.
22. Parisi SG, Bartolini A, Santacatterina E, Castellani E, Ghirardo R, Berto A, et al. Prevalence of *Klebsiella pneumoniae* strains producing carbapenemases and increase of resistance to colistin in an Italian teaching hospital from January 2012 To December 2014. BMC Infect Dis. 2015;15:244.
23. Monaco M, Giani T, Raffone M, Arena F, Garcia-Fernandez A, Pollini S, et al. Colistin resistance superimposed to endemic carbapenem-resistant *Klebsiella pneumoniae*: a rapidly evolving problem in Italy, November 2013 to April 2014. Euro Surveill [Internet]. 2014; 19(42):[pii=20939 p.]. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20939>.
24. Bathoorn E, Tsioutis C, da Silva Voorham JM, Scoulica EV, Ioannidou E, Zhou K, et al. Emergence of pan-resistance in KPC-2 carbapenemase-producing *Klebsiella pneumoniae* in Crete, Greece: a close call. J Antimicrob Chemother. Epub 2016 Jan 26.
25. Weterings V, Zhou K, Rossen JW, van Stenis D, Thewessen E, Kluytmans J, et al. An outbreak of colistin-resistant *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae* in the Netherlands (July to December 2013), with inter-institutional spread. Eur J Clin Microbiol Infect Dis. 2015 Aug;34(8):1647-55.
26. European Centre for Disease Prevention and Control. Rapid Risk Assessment: plasmid-mediated colistin resistance in Enterobacteriaceae. Stockholm: ECDC; 2016. Available from: <https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/enterobacteriaceae-risk-assessment-diseases-caused-by-antimicrobial-resistant-microorganisms-europe-june-2016.pdf>.
27. Giamarellou H, Galani L, Baziaka F, Karaikos I. Effectiveness of a double-carbapenem regimen for infections in humans due to carbapenemase-producing pandrug-resistant *Klebsiella pneumoniae*. Antimicrob Agents Chemother. 2013 May;57(5):2388-90.
28. Camargo JF, Simkins J, Beduschi T, Tekin A, Aragon L, Perez-Cardona A, et al. Successful treatment of Carbapenemase-producing pandrug-resistant *Klebsiella pneumoniae* bacteremia. Antimicrob Agents Chemother. 2015 Oct;59(10):5903-8.
29. Douka E, Perivolioti E, Kraniotaki E, Fountoulis K, Economidou F, Tsakris A, et al. Emergence of a pandrug-resistant VIM-1-producing *Providencia stuartii* clonal strain causing an outbreak in a Greek intensive care unit. Int J Antimicrob Agents. 2015 May;45(5):533-6.
30. Zowawi HM, Forde BM, Alfaresi M, Alzarouni A, Farahat Y, Chong TM, et al. Stepwise evolution of pandrug-resistance in *Klebsiella pneumoniae*. Sci Rep. 2015;5:15082.
31. Ghafur A VP, Murali A, Priyadarshini K, Thirunarayan MA. Emergence of Pan-drug resistance amongst gram negative bacterial! The First case series from India. J Microbiol Infect Dis. 2014;4(3):86-91.
32. European Medicines Agency. Zavicefta - ceftazidime / avibactam 2016. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004027/human_med_001993.jsp&mid=WC0b01ac058001d124.
33. 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).
34. Boucher HW, Talbot GH, Benjamin DK, Jr., Bradley J, Guidos RJ, Jones RN, et al. 10 x '20 Progress--development of new drugs active against gram-negative bacilli: an update from the Infectious Diseases Society of America. Clin Infect Dis. 2013 Jun;56(12):1685-94.
35. Tischendorf J, de Avila RA, Safdar N. Risk of infection following colonization with carbapenem-resistant Enterobacteriaceae: A systematic review. Am J Infect Control. Epub 2016 Feb 15.
36. 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.
37. Hauck C, Cober E, Richter SS, Perez F, Salata RA, Kalayjian RC, et al. Spectrum of excess mortality due to carbapenem-resistant *Klebsiella pneumoniae* infections. Clin Microbiol Infect. Epub 2016 Feb 3.
38. Burnham JP, Olsen MA, Stwalley D, Kwon JH, Babcock HM, Kollef MH. Infectious Diseases Consultation Reduces 30-Day and 1-Year All-Cause Mortality for Multidrug-Resistant Organism Infections. Open forum infectious diseases. 2018 Mar;5(3):ofy026.
39. Vergara-Lopez S, Dominguez MC, Conejo MC, Pascual A, Rodriguez-Bano J. Lessons from an outbreak of metallo-beta-lactamase-producing *Klebsiella oxytoca* in an intensive care unit: the importance of time at risk and combination therapy. J Hosp Infect. 2015 Feb;89(2):123-31.
40. Voulgari E, Gartzonika C, Vrioni G, Politi L, Priavali E, Levidiotou-Stefanou S, et al. The Balkan region: NDM-1-producing *Klebsiella pneumoniae* ST11 clonal strain causing outbreaks in Greece. J Antimicrob Chemother. 2014 Aug;69(8):2091-7.

41. Hrabak J, Papagiannitsis CC, Studentova V, Jakubu V, Fridrichova M, Zemlickova H. Carbapenemase-producing *Klebsiella pneumoniae* in the Czech Republic in 2011. Euro Surveill [Internet]. 2013; 18(45):[pii=20626 p.]. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20626>.
42. Zweigner J, Gastmeier P, Kola A, Klefisch FR, Schweizer C, Hummel M. A carbapenem-resistant *Klebsiella pneumoniae* outbreak following bronchoscopy. Am J Infect Control. 2014 Aug;42(8):936-7.
43. Gharbi M, Moore LS, Gilchrist M, Thomas CP, Bamford K, Brannigan ET, et al. Forecasting carbapenem resistance from antimicrobial consumption surveillance: Lessons learnt from an OXA-48-producing *Klebsiella pneumoniae* outbreak in a West London renal unit. Int J Antimicrob Agents. 2015 Aug;46(2):150-6.
44. 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.
45. 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.
46. 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.
47. van Loon K, Voor In 't Holt AF, Vos MC. A Systematic Review and Meta-analyses of the Clinical Epidemiology of Carbapenem-Resistant Enterobacteriaceae. Antimicrob Agents Chemother. 2018 Jan;62(1).
48. Ben-David D, Masarwa S, Navon-Venezia S, Mishali H, Fridental I, Rubinovitch B, et al. Carbapenem-resistant *Klebsiella pneumoniae* in post-acute-care facilities in Israel. Infect Control Hosp Epidemiol. 2011 Sep;32(9):845-53.
49. Nucleo E, Caltagirone M, Marchetti VM, D'Angelo R, Fogato E, Confalonieri M, et al. Colonization of long-term care facility residents in three Italian Provinces by multidrug-resistant bacteria. Antimicrob Resist Infect Control. 2018;7:33.
50. Mathers AJ, Peirano G, Pitout JD. The role of epidemic resistance plasmids and international high-risk clones in the spread of multidrug-resistant Enterobacteriaceae. Clin Microbiol Rev. 2015 Jul;28(3):565-91.
51. 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.
52. Lubbert C, Lippmann N, Busch T, Kaisers UX, Ducomble 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.
53. Kizny Gordon AE, Mathers AJ, Cheong EYL, Gottlieb T, Kotay S, Walker AS, et al. The Hospital Water Environment as a Reservoir for Carbapenem-Resistant Organisms Causing Hospital-Acquired Infections-A Systematic Review of the Literature. Clin Infect Dis. 2017 May 15;64(10):1435-44.
54. 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.
55. 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).
56. 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.
57. Lutgring JD, Limbago BM. The Problem of Carbapenemase-producing-carbapenem-resistant-Enterobacteriaceae detection. J Clin Microbiol. 2016 Mar;54(3):529-34.
58. Viau R, Frank KM, Jacobs MR, Wilson B, Kaye K, Donskey CJ, et al. Intestinal carriage of Carbapenemase-producing organisms: current status of surveillance methods. Clin Microbiol Rev. 2016 Jan;29(1):1-27.
59. Magiorakos AP, Burns K, Rodriguez Bano J, Borg M, Daikos G, Dumpis U, et al. Infection prevention and control measures and tools for the prevention of entry of carbapenem-resistant Enterobacteriaceae into healthcare settings: guidance from the European Centre for Disease Prevention and Control. Antimicrob Resist Infect Control. 2017;6:113.
60. Averbuch D, Tridello G, Hoek J, Mikulska M, Akan H, Yanez San Segundo L, et al. Antimicrobial Resistance in Gram-Negative Rods Causing Bacteremia in Hematopoietic Stem Cell Transplant Recipients: Intercontinental Prospective Study of the Infectious Diseases Working Party of the European Bone Marrow Transplantation Group. Clin Infect Dis. 2017 Nov 13;65(11):1819-28.
61. Nour I, Eldegl HE, Nasef N, Shouman B, Abdel-Hady H, Shabaan AE. Risk factors and clinical outcomes for carbapenem-resistant Gram-negative late-onset sepsis in a neonatal intensive care unit. J Hosp Infect. 2017 Sep;97(1):52-8.
62. European Centre for Disease Prevention and Control. Systematic review of the effectiveness of infection control measures to prevent the transmission of carbapenemase-producing Enterobacteriaceae through cross-border transfer of patients. Stockholm: ECDC; 2014.

63. Fournier S, Desenfant L, Monteil C, Nion-Huang M, Richard C, Jarlier V, et al. Efficiency of different control measures for preventing carbapenemase-producing enterobacteria and glycopeptide-resistant *Enterococcus faecium* outbreaks: a 6-year prospective study in a French multihospital institution, January 2010 to December 2015. *Euro Surveill.* 2018 Feb;23(8).
64. World Health Organization. Guidelines for the Prevention and Control of Carbapenem-Resistant Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in Health Care Facilities. Geneva: World Health Organization; 2017.
65. US Centers for Disease Control and Prevention. Facility guidance for control of carbapenem-resistant Enterobacteriaceae (CRE) - November 2015 Update CRE Toolkit: CDC; 2015. Available from: <https://ecdc.europa.eu/en/publications-data/directory-guidance-prevention-and-control/prevention-and-control-infections-1>.
66. Tacconelli E, Cataldo MA, Dancer SJ, De Angelis G, Falcone M, Frank U, et al. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. *Clin Microbiol Infect.* 2014 Jan;20 Suppl 1:1-55.
67. European Centre for Disease Prevention and Control. Directory of online resources for the prevention and control of antimicrobial resistance (AMR) and healthcare-associated infections (HAI) Stockholm: ECDC. Available from: <https://ecdc.europa.eu/en/publications-data/directory-online-resources-prevention-and-control-antimicrobial-resistance-amr>.
68. European Centre for Disease Prevention and Control. Update on the spread of carbapenemase-producing Enterobacteriaceae in Europe - Summary of the May 2015 expert assessment. Stockholm: ECDC; 2015.
69. Manges AR, Johnson JR. Food-borne origins of *Escherichia coli* causing extraintestinal infections. *Clin Infect Dis.* 2012 Sep;55(5):712-9.
70. Kluytmans JA, Overvest IT, Willemsen I, Kluytmans-van den Bergh MF, van der Zwaluw K, Heck M, et al. Extended-spectrum beta-lactamase-producing *Escherichia coli* from retail chicken meat and humans: comparison of strains, plasmids, resistance genes, and virulence factors. *Clin Infect Dis.* 2013 Feb;56(4):478-87.
71. Kola A, Kohler C, Pfeifer Y, Schwab F, Kuhn K, Schulz K, et al. High prevalence of extended-spectrum-beta-lactamase-producing Enterobacteriaceae in organic and conventional retail chicken meat, Germany. *J Antimicrob Chemother.* 2012 Nov;67(11):2631-4.
72. Zarfel G, Galler H, Luxner J, Petternel C, Reinthaler FF, Haas D, et al. Multiresistant bacteria isolated from chicken meat in Austria. *Int J Environ Res Public Health.* 2014 Dec;11(12):12582-93.
73. Ghodousi A, Bonura C, Di Noto AM, Mammina C. Extended-Spectrum ss-Lactamase, AmpC-Producing, and Fluoroquinolone-Resistant *Escherichia coli* in retail broiler chicken meat, Italy. *Foodborne Pathog Dis.* 2015 Jul;12(7):619-25.
74. Egea P, Lopez-Cerero L, Torres E, Gomez-Sanchez Mdel C, Serrano L, Navarro Sanchez-Ortiz MD, et al. Increased raw poultry meat colonization by extended spectrum beta-lactamase-producing *Escherichia coli* in the south of Spain. *Int J Food Microbiol.* 2012 Oct 1;159(2):69-73.
75. van Hoek AH, Veenman C, van Overbeek WM, Lynch G, de Roda Husman AM, Blaak H. Prevalence and characterization of ESBL- and AmpC-producing Enterobacteriaceae on retail vegetables. *Int J Food Microbiol.* 2015 Jul 2;204:1-8.
76. 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.
77. Woodford N, Wareham DW, Guerra B, Teale C. Carbapenemase-producing Enterobacteriaceae and non-Enterobacteriaceae from animals and the environment: an emerging public health risk of our own making? *J Antimicrob Chemother.* 2014 Feb;69(2):287-91.
78. Akiba M, Sekizuka T, Yamashita A, Kuroda M, Fujii Y, Murata M, et al. Distribution and relationships of antimicrobial resistance determinants among extended-spectrum cephalosporin or carbapenem-resistant *Escherichia coli* isolated from rivers and sewage treatment plants in India. *Antimicrob Agents Chemother.* Epub 2016 Mar 7.
79. Kieffer N, Poirel L, Bessa LJ, Barbosa-Vasconcelos A, da Costa PM, Nordmann P. VIM-1, VIM-34, and IMP-8 Carbapenemase-Producing *Escherichia coli* Strains Recovered from a Portuguese River. *Antimicrob Agents Chemother.* 2016 Apr;60(4):2585-6.
80. Kock R, Daniels-Haardt I, Becker K, Mellmann A, Friedrich AW, Mevius D, et al. Carbapenem-resistant Enterobacteriaceae in wildlife, food-producing and companion animals - a systematic review. *Clin Microbiol Infect.* 2018 Apr 11.
81. 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.
82. Kluytmans J, Price L, Grayson L, Gottlieb T, Mehtar S, Andreumont A, et al. Enterobacteria: Ban resistant strains from food chain. *Nature.* 2013 Sep 19;501(7467):316.

83. Albiger B, Glasner C, Struelens MJ, Grundmann H, Monnet DL. Carbapenemase-producing Enterobacteriaceae in Europe: assessment by national experts from 38 countries, May 2015. Euro Surveill [Internet]. 2015 Nov 12; 20(45):[pii=30062 p.]. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21300>.
84. Sheng WH, Badal RE, Hsueh PR. Distribution of extended-spectrum beta-lactamases, AmpC beta-lactamases, and carbapenemases among Enterobacteriaceae isolates causing intra-abdominal infections in the Asia-Pacific region: results of the study for Monitoring Antimicrobial Resistance Trends (SMART). Antimicrob Agents Chemother. 2013 Jul;57(7):2981-8.
85. Hawkey PM. Multidrug-resistant Gram-negative bacteria: a product of globalization. J Hosp Infect. 2015 Apr;89(4):241-7.
86. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect Dis. 2010 Sep;10(9):597-602.
87. Ruppe E, Armand-Lefevre L, Estellat C, El-Mniai A, Boussadia Y, Consigny PH, et al. Acquisition of carbapenemase-producing Enterobacteriaceae by healthy travellers to India, France, February 2012 to March 2013. Euro Surveill [Internet]. 2014; 19(14):[pii=20768 p.]. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20768>.
88. Penders J. Acquisition of ESBL-and carbapenemase-producing Enterobacteriaceae during travel: the carriage of multiresistant bacteria after travel (COMBAT) Study [Internet]. EU Regional Maastricht Symposium on Immune Compromised Traveller: Maastricht 2014 Available from: http://www.minc.eu/eumict/3rd%20EUMICT_11_Penders.pdf.
89. European Centre for Disease Prevention and Control. EU Laboratory Capability Monitoring System (EULabCap) - Report on 2016 survey of EU/EEA country capabilities and capacities. Stockholm: ECDC; 2018. Available from: <https://ecdc.europa.eu/en/publications-data/eu-laboratory-capability-monitoring-system-eulabcap-report-2016-survey-eueea>.
90. Revez J, Espinosa L, Albiger B, Leitmeyer KC, Struelens MJ. Survey on the Use of Whole-Genome Sequencing for Infectious Diseases Surveillance: Rapid Expansion of European National Capacities, 2015-2016. Frontiers in public health. 2017;5:347.
91. Pouch SM, Kubin CJ, Satlin MJ, Tsapepas DS, Lee JR, Dube G, et al. Epidemiology and outcomes of carbapenem-resistant *Klebsiella pneumoniae* bacteriuria in kidney transplant recipients. Transpl Infect Dis. 2015 Dec;17(6):800-9.
92. Girmenia C, Rossolini GM, Piciocchi A, Bertaina A, Pisapia G, Pastore D, et al. Infections by carbapenem-resistant *Klebsiella pneumoniae* in SCT recipients: a nationwide retrospective survey from Italy. Bone Marrow Transplant. 2015 Feb;50(2):282-8.
93. Satlin MJ, Jenkins SG, Walsh TJ. The global challenge of carbapenem-resistant Enterobacteriaceae in transplant recipients and patients with hematologic malignancies. Clin Infect Dis. 2014 May;58(9):1274-83.
94. Datta S, Roy S, Chatterjee S, Saha A, Sen B, Pal T, et al. A five-year experience of carbapenem resistance in Enterobacteriaceae causing neonatal septicaemia: predominance of NDM-1. PLoS One. 2014;9(11):e112101.
95. Kola A, Piening B, Pape UF, Veltke-Schlieker W, Kaase M, Geffers C, et al. An outbreak of carbapenem-resistant OXA-48 - producing *Klebsiella pneumonia* associated to duodenoscopy. Antimicrob Resist Infect Control. 2015;4:8.
96. Potron A, Bernabeu S, Cuzon G, Ponties V, Blanchard H, Seringe E, et al. Analysis of OXA-204 carbapenemase-producing Enterobacteriaceae reveals possible endoscopy-associated transmission, France, 2012 to 2014. Euro Surveill. 2017 Dec;22(49).
97. Daroukh A, Delaunay C, Bigot S, Ceci JM, Siddhoun N, Bukreyeva I, et al. Characteristics and costs of carbapenemase-producing enterobacteria carriers (2012/2013). Med Mal Infect. 2014 Jul;44(7):321-6.
98. Stone PW, Pogorzelska M, Kunches L, Hirschhorn LR. Hospital staffing and health care-associated infections: a systematic review of the literature. Clin Infect Dis. 2008 Oct 1;47(7):937-44.
99. Karampatakis T, Tsergouli K, Iosifidis E, Antachopoulos C, Karapanagiotou A, Karyoti A, et al. Impact of active surveillance and infection control measures on carbapenem-resistant Gram-negative bacterial colonization and infections in intensive care. J Hosp Infect. 2018 May 21.
100. Schwaber MJ, Lev B, Israeli A, Solter E, Smollan G, Rubinovitch B, et al. Containment of a country-wide outbreak of carbapenem-resistant *Klebsiella pneumoniae* in Israeli hospitals via a nationally implemented intervention. Clin Infect Dis. 2011 Apr 1;52(7):848-55.
101. Fournier S, Monteil C, Lepointeur M, Richard C, Brun-Buisson C, Jarlier V, et al. Long-term control of carbapenemase-producing Enterobacteriaceae at the scale of a large French multihospital institution: a nine-year experience, France, 2004 to 2012. Euro Surveill [Internet]. 2014; 19(19):[pii=20802 p.]. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20802>.