



RAPID RISK ASSESSMENT

Carbapenem-resistant *Enterobacteriaceae* (CRE)

08 April 2016

Main conclusions and options for response

Carbapenem-resistant *Enterobacteriaceae* (CRE) pose a significant threat for patients as well as healthcare systems in EU/EEA Member States. CRE infections are associated with high mortality, primarily due to delays in administration of effective treatment and the limited availability of effective treatment options. New antibiotics capable of replacing carbapenems in respect of their main indications for use are not likely to be 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 are likely to benefit from consultations from infectious diseases or clinical microbiology experts to achieve the best possible outcome with the limited treatment options available.

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

Good standard infection control, including environmental cleaning and adequate reprocessing of medical devices, and adequate capacity of microbiological laboratories are the basis for prevention of transmission of multidrug-resistant bacteria such as CRE. Prompt notification of the clinical team and of the infection prevention and control/hospital hygiene team is essential.

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Suggested citation: European Centre for Disease Prevention and Control. Rapid risk assessment: Carbapenem-resistant *Enterobacteriaceae* – 08 April 2016, Stockholm, 2016.

Targeting patients at high risk for carriage of CRE

Patients transferred from or who had recently been hospitalised in a country/region/hospital (including hospitals in another or in the same country) known as having a high CRE prevalence should be considered at high risk of digestive tract carriage of CRE. Screening of these patients to confirm digestive tract carriage of CRE, and implementation of pre-emptive contact precautions and pre-emptive isolation should be considered. Hospitals could also consider pre-emptive isolation and screening for CRE carriage according to national guidance for patients who recently travelled to countries/regions known for their high CRE prevalence, even if they were not in contact with healthcare.

Preventing transmission from CRE-positive patients

For patients who are CRE-positive, i.e. confirmed with digestive tract carriage of or infection with CRE, hospitals should consider use of enhanced control measures such as contact precautions, isolation or cohorting, and dedicated nursing staff.

Preventing spread of CRE in specific wards/units

In wards/units where patients are at high risk of infection (e.g. ICU and haematology wards), pre-emptive isolation and active surveillance ("screening") for CRE by rectal swab at admission should be considered, depending on the risk for CRE colonisation and the local prevalence of CRE.

Antimicrobial stewardship

Antimicrobial stewardship refers to coordinated programmes that implement interventions to ensure appropriate antimicrobial prescribing. They aim to improve clinical efficacy of antimicrobial treatment and limit antimicrobial resistance through reducing selective pressure for the development of resistance to currently effective antibiotics.

Although evidence for a specific beneficial effect of antimicrobial stewardship on the emergence and spread of CRE are limited, the previous use of broad-spectrum antimicrobials from various classes, and in particular carbapenems, is a known risk factor for colonisation by CRE. Therefore, implementation of comprehensive antimicrobial stewardship programmes is recommended to prevent and control the emergence and spread of CRE.

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

Although available information is still limited, it may be important to avoid the potential transmission of CRE via contaminated food. Close cooperation between veterinary medicine and human medicine as well as the regular monitoring for CRE of locally produced and imported food items are needed to prevent CRE-contaminated food from reaching the market. In addition, conditions of animal husbandry such as overcrowding and antimicrobial use that promote the occurrence and spread of multidrug-resistant bacteria, including CRE, should be addressed.

In households, standard rules of personal hygiene and good food handling practices should be applied.

4. Actions related to cross-border aspects

Measures related to enhanced CRE surveillance and pre-emptive isolation and screening of patients being 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 of known colonisation 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.

Finally, only measures taken to improve public health in all countries of the World, such as regulating antimicrobial use, improving infection control in hospitals and improving water and sanitation infrastructure, can provide a definitive solution. Until and unless this threat is eliminated, the capacity for resistance detection and surveillance in low-resource countries needs to be improved to have more reliable data on worldwide distribution of CRE as a first step to global control.

Testing for faecal carriage of CRE upon admission should be considered for persons requiring hospitalisation and who have recently been in countries/regions with high prevalence of CRE, and this even if they had no contact with healthcare services. This, however, should be done in accordance with the relevant national guidelines for testing persons at risk of carrying CRE and other multidrug-resistant Gram-negative bacteria. An Expert Opinion on the "Risks from digestive tract colonisation with multidrug-resistant *Enterobacteriaceae* after international travel and implications for surveillance, infection control and patient management" is currently under preparation at ECDC.

5. Actions related to risks for functioning of health care 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 their spread 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. The example of Italy shows that carbapenem resistance rates in *K. pneumoniae* can increase abruptly and rapidly, from 1-2% during the period of 2006-2009 to 33% in 2014. The same rapid resistance development might happen in other countries if no action is taken.

Source and date of request

Request from the European Commission to ECDC on 9 March 2016

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 document assesses the risk for patients and health-care systems in EU/EEA Member States due to global spread of CRE.

Consulted experts

Internal experts consulted (in alphabetical order) Anke Kohlenberg, Dominique L. Monnet, Diamantis Plachouras, Emmanuel Robesyn.

External experts consulted: Elisabeth Prestler (University Hospital Vienna), Jesús Rodríguez-Baño (H.Virgen de Macarena, Sevilla), Gunnar Skov Simonsen (University Hospital North Norway, Tromsø).

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* [1].

Carbapenems are beta-lactam antibiotics with a broad spectrum of activity against Gram-negative (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 multidrug-resistant (including ESBL-producing) infections by *Enterobacteriaceae*.

Resistance to carbapenems has been reported with increasing frequency and geographical spread since the beginning of the 1990s [2,3]. 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 heterogeneous group of enzymes that can hydrolyse most beta-lactams including carbapenems [4]. In the literature, CRE 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).

Event background information

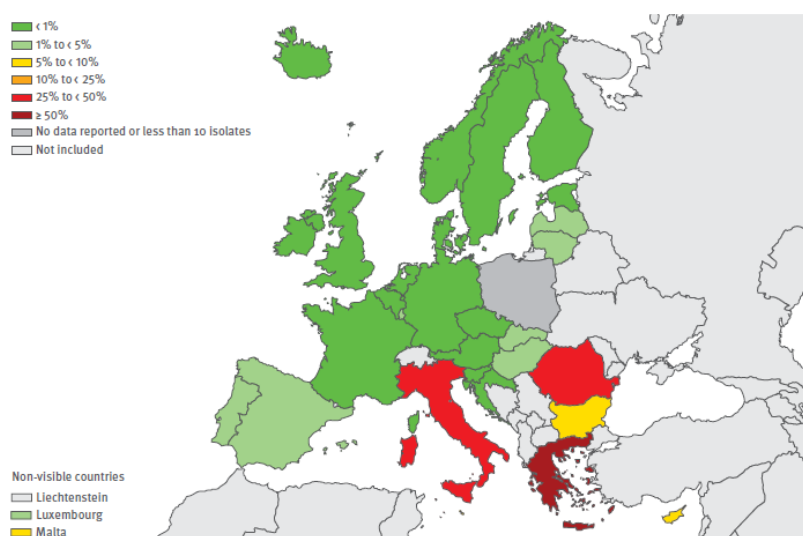
Current situation of CRE in EU/EEA Member States

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

For *K. pneumoniae*, data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) for 2014 show large differences in the national percentages of carbapenem resistance in invasive (i.e. mostly from bloodstream infections) isolates ranging from 0% to 62.3%, depending on the Member State (Figure 1).

The population-weighted mean percentage for the EU/EEA showed a significantly increasing trend from 6% (2011) to 7.3% (2014) and increasing trends for the period 2011-2014 were observed for seven Member States: Bulgaria, Croatia, France, Germany, Italy, Portugal and Spain [5].

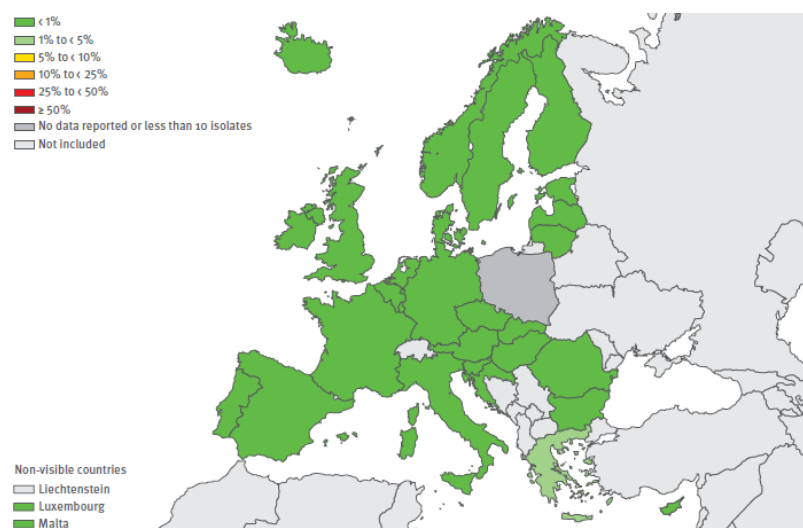
Figure 1 Percentage (%) of invasive *K. pneumoniae* isolates with resistance to carbapenems, EU/EEA Member States, 2014 [5]



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 2014 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 1.2% (Figure 2). No significant trend was observed for the EU/EEA population-weighted mean or national percentages [5].

Figure 2 Percentage of invasive *E. coli* isolates with resistance to carbapenems, EU/EEA Member States, 2014 [5]



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.

Epidemiological stage of spread of carbapenemase-producing *Enterobacteriaceae* (*K. pneumoniae* and *E. coli*) as assessed by national experts

A recent assessment by national experts that participated in the EuSCAPE project of the occurrence and spread of carbapenemase-producing *Enterobacteriaceae* (i.e. CRE that are resistant to carbapenems via production of a carbapenemase) in European countries showed that the epidemiological situation had worsened since 2013, with 13 of 38 countries reporting inter-regional spread of carbapenemase-producing *Enterobacteriaceae* or an endemic situation

[6]. Changes in the level of spread of carbapenemase-producing *Enterobacteriaceae* since 2010 is presented in Table 1. The situation as of May 2015 is presented in Figure 3.

Table 1 Epidemiological stages of spread of carbapenemase-producing *Enterobacteriaceae* (*K. pneumoniae* and *E. coli*) as assessed by national experts, and changes in these epidemiological stages, 38 European countries, 2010, 2013 and 2014–2015 [6]

Country	Epidemiological stage for the spread of CPE			Change in epidemiological situation for CPE between 2013 and 2015
	2010 ^a	2013 ^b	2014–2015 ^c	
Albania	NA	2a	1	↓
Austria	0	2b	2b	→
Belgium	2b	3	4	↑
Bosnia and Herzegovina	1	1	0	↓
Bulgaria	0	2a	2a	→
Croatia	1	3	3	→
Cyprus	2a	2a	1	↓
Czech Republic	1	2b	2b	→
Denmark	1	2a ^d	4	↑
Estonia	0	2a	1	↓
Finland	1	2a	2a	→
France	3	3	4	↑
Germany	3	3	3	→
Greece	5	5	5	→
Hungary	3	4	4	→
Iceland	0	0	0	→
Ireland	1	4	3	↓
Israel	5	4	4	→
Italy	4	5	5	→
Kosovo*	NA	2b	0	↓
Latvia	1	1	1	→
Lithuania	1	1	1	→
Luxembourg	NA	1	1	→
Malta	1	5	5	→
Montenegro	NA	0	1	↑
The Netherlands	2a	2b	2a	↓
Norway	2a	2a	1	↓
Poland	4	3	4	↑
Portugal	1	1	2b	↑
Romania	1	1	4	↑
Serbia	1	1	2b	↑
Slovakia	NA	2a	4	↑
Slovenia	0	1	2a	↑
Spain	2b	3	4	↑
Sweden	2a	2b	2a	↓
The former Yugoslav Republic of Macedonia	NA	0	1	↑
Turkey	NA	2a	5	↑
United Kingdom	2b	3	3	→

CPE: carbapenemase-producing *Enterobacteriaceae*; NA: not available.

↑: increase in the epidemiological stage between 2013 and 2015; ↓: decrease in the epidemiological stage between 2013 and 2015; →: unchanged epidemiological stage between 2013 and 2015.

Grey: countries with no data available.

Dark green: no case reported (Stage 0).

Light green: sporadic occurrence (Stage 1).

Light yellow: single hospital outbreak (Stage 2a).

Dark yellow: sporadic hospital outbreaks (Stage 2b).

Orange: regional spread (Stage 3).

Red: inter-regional spread (Stage 4).

Brown: endemic situation (Stage 5).

^a The results were based on data obtained through a Europe-wide consultation during a workshop at the Dutch National Institute for Public Health and the Environment (RIVM) on 29–30 April 2010 [3].

^b The results were based on data obtained through a self-assessment questionnaire (February 2013) to the national experts who participated in the 'European survey of carbapenemase-producing *Enterobacteriaceae* (EuSCAPE)' project [1,2].

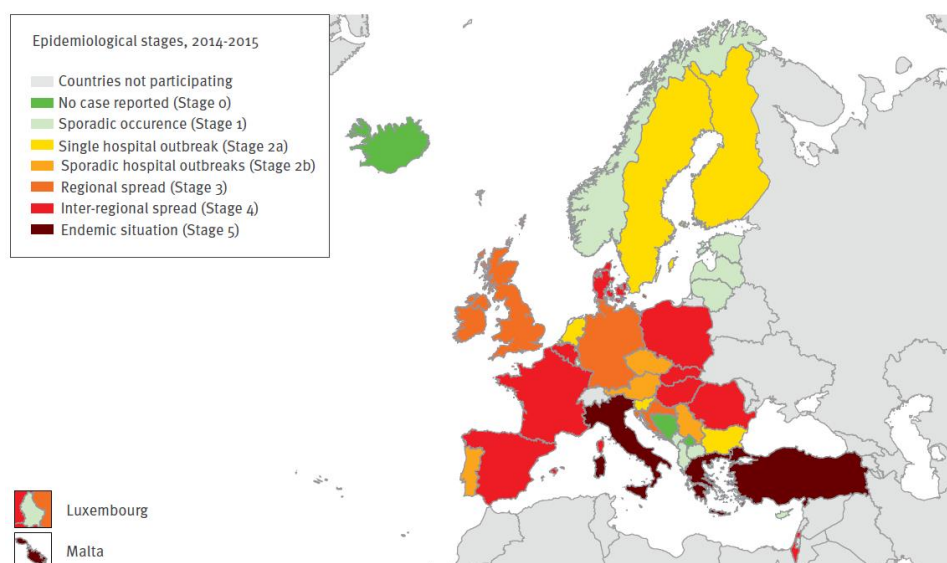
^c This online survey (March–May 2015).

^d Data provided in 2015.

*This designation is without prejudice to positions on status, and is in line with United Nations Security Council resolution 1244/99 and the International Court of Justice Opinion on the Kosovo declaration of independence.

The EuSCAPE surveys were based on non-validated self-assessments by national experts.

Figure 3 Occurrence of carbapenemase-producing *Enterobacteriaceae* (*K. pneumoniae* and *E. coli*) as assessed by national experts, 38 European countries, May 2015 [6]

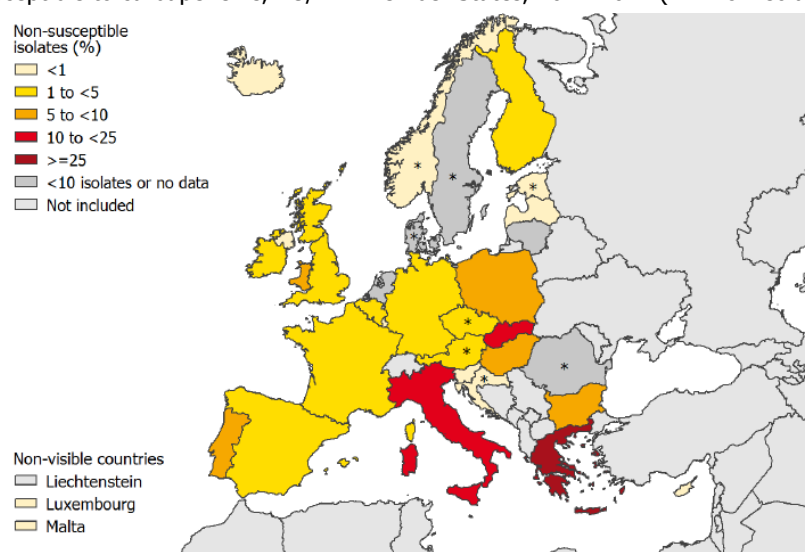


This EuSCAPE survey was based on non-validated self-assessments by national experts.

Prevalence of carbapenem non-susceptible *Enterobacteriaceae* among healthcare-associated infections in European acute care hospitals

In the ECDC point prevalence survey (PPS) of healthcare-associated infections and antimicrobial use in European acute care hospitals 2011-2012, data from 947 hospitals with 231 459 patients and 1500 reported healthcare-associated infections were analysed. Antimicrobial resistance was determined for pathogens associated with healthcare-associated infections including carbapenem non-susceptibility (i.e. resistance or intermediate resistance) for *Enterobacteriaceae*. Ten of 28 countries did not report any *Enterobacteriaceae* that were not susceptible to carbapenems. Three countries reported more than 20% *Enterobacteriaceae* isolates non-susceptible to carbapenems with the highest percentage (39.9%) being reported by Greece (Figure 4) [7].

Figure 4 Percentage of *Enterobacteriaceae* isolates from healthcare-associated infections that were not susceptible to carbapenems, EU/EEA Member States, 2011-2012 (n=2787 isolates) [7]



Countries with <10 isolates with known antimicrobial susceptibility results not shown. The Netherlands: only resistant isolates reported (n of carbapenem-R isolates: 0/142 *Enterobacteriaceae* isolates); Lithuania was excluded because no carbapenem susceptibility data provided for *Enterobacteriaceae* other than *K. pneumoniae*.

*PPS data representativeness was poor in Austria, Croatia, Czech Republic, Estonia, Norway and Romania and very poor in Denmark and Sweden.

Analyses of the epidemiological situation of CRE in Europe are limited by the absence of a dedicated surveillance system for CRE. The EARS-Net data are based on invasive isolates from blood and cerebrospinal fluid only and bacteria isolated from other sites of infection or colonisation are not included. The EuSCAPE surveys were based on non-validated self-assessments by national experts. The ECDC PPS is only performed every five years (the 2nd ECDC PPS is taking place in 2016-2017).

Current situation of CRE in third countries

From the WHO Global report on antimicrobial resistance surveillance, only 71 (37%) of WHO Member States were able to provide data on carbapenem resistance in *K. pneumoniae* [8]. Carbapenem-resistant *K. pneumoniae* were reported from all WHO regions with reports of carbapenem resistance in two regions exceeding 50% of *K. pneumoniae* [8].

CRE with different carbapenemase genes show variation in their geographic spread. Identified regions and countries with a high prevalence are the Indian subcontinent for NDM CRE, the USA, Israel, Greece and Italy for KPC CRE, and Turkey and North Africa for OXA-48 CRE [9].

Indirect evidence for the prevalence of CRE in different regions is also provided through CRE carriage detected in patients transferred from hospitals [10] and travellers returning from these regions to Europe [11].

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 [12]. Resistance in these bacteria will therefore have an impact on choices of antibiotic therapy as well as treatment outcomes of these frequent infections.

Limited treatment options

For the *Enterobacteriaceae*, there has been a vicious cycle of increasing resistance. Global spread of ESBLs resulted in frequent resistance to all penicillins and cephalosporins with the consequence of increasing carbapenem consumption [13], 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 or insufficient data about their effectiveness, less clinical experience with their use, more adverse effects, rapid development of resistance during treatment and increasing resistance globally. In addition, a review of available data on treatment regimens with the above mentioned antibiotics came to the conclusion 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. Only combination therapy with two or more active agents, and especially carbapenem-containing combinations, showed a survival benefit [14]. However, these data should be taken with caution as they come from retrospective 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 [15-18].

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 [19].

The consequence of failing to control CRE is the development of colistin-resistant CRE strains that, in addition, are resistant to almost all other antibiotics or possibly all antibiotics, i.e. pandrug-resistant CRE [20-24].

Although ceftazidime-avibactam, a new antibiotic combination with activity against CRE infections (except for infections with metallo-beta-lactamase-producing CRE such as NDM CRE or VIM CRE), was recently approved by the US Food and Drug Administration (FDA) for complicated intra-abdominal infections and complicated urinary tract infections [25], progress of new drug development has been slow [26]. There is an urgent need for research and clinical development of antimicrobials to keep up with the evolution of bacterial resistance [26].

High mortality

High mortality rates, ranging from 30 to 75%, have been reported for patients with severe CRE infections [27]. Mortality above 50% has been reported in patients with CRE bloodstream infection [28] and a study has also shown an excess mortality of 27% in patients with pneumonia or bloodstream infection caused by carbapenem-resistant *K. pneumoniae* [29]. The high mortality that has been associated with CRE is likely attributable to the lack of appropriate treatment options.

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 and such outbreaks have been reported from several EU Member States, e.g. the Czech Republic, France, Germany, Greece, Italy, Spain and the UK [30-35]. 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 device use and prior antimicrobial therapy [36,37]. 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 [38].

Carbapenemase genes are often located on plasmids that can be exchanged between *Enterobacteriaceae* and other Gram-negative bacteria [4]. They are also often transmitted "in a package" together with other resistance genes resulting in multidrug-resistant bacteria. While carbapenem consumption has been shown to be associated with increases in CRE [34], this association of carbapenem resistance with other resistance genes means that treatment with antibiotics other than carbapenems can also select for CRE, as has been reported for cephalosporins and fluoroquinolones [37].

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 [27]. With CRE residing in the normal intestinal flora, eradication is difficult. Rates of spontaneous clearance vary between studies [39,40], and continuous carriage beyond two years has been reported [40]. 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 [39].

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 induced by the production of carbapenemases is heterogeneous, and because carbapenem resistance can be the result of various mechanisms without any single test being suitable for all situations [41]. There is also a need to define the circumstances under which screening for carriage should be conducted and to determine which methods should be used, as the best method will depend on multiple factors such as local CRE prevalence, type of hospital, capabilities of the laboratory and available resources [42].

A systematic review of the effectiveness of infection control measures to prevent the spread of CRE conducted by ECDC in 2011 and updated in 2014 identified the following measures 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 [43].

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 [34].

The above mentioned measures have been effective in studies, but their implementation needs the support of national policy. 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 for national CRE control [44].

Risk for transfer of CRE into the community

While carbapenem-resistant *K. pneumoniae* are currently more frequent and more prone to cause healthcare-associated outbreaks, carbapenem-resistant *E. coli* pose a greater risk for spread in the community [4]. There is growing evidence that extra-intestinal pathogenic *E. coli* may be transmitted to humans via the food supply from a food animal source [45]. 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 CRE carrier needs antimicrobial treatment or hospital care, there is a risk of failure of standard antimicrobial therapy in case of CRE infection, overgrowth of CRE and onward transmission to other patients.

The rapid spread of ESBL-producing *Enterobacteriaceae*, mainly *E. coli*, in the community during the last decade is an example of how rapidly these bacteria can spread in that setting [4]. ESBL-producing *Enterobacteriaceae* can serve as a model for the spread of CRE as the same bacterial species are involved and the resistance genes are plasmid-carried. Contamination of food items with antimicrobial-resistant *Enterobacteriaceae* have been described from several EU/EEA Member States, for example for chicken or poultry meat in Austria, Germany, the Netherlands, Italy and Spain [46-50] and vegetables in the Netherlands [51]. There is now evidence that a proportion of human extra-intestinal infections with *E. coli* resistant to third- and fourth-generation cephalosporins originates from food-producing animals, especially poultry [52]. Carbapenemases are already increasingly being detected in bacteria from environmental and animal sources [53-55] and carbapenemase production has also been reported in the foodborne pathogen *Salmonella enterica* [56]. Given the risks of CRE for human health, there have been calls for a zero-tolerance approach and international ban on the sale of food items that contain CRE [57].

Cross-border aspects

EU/EEA Member States

The maps from EARS-Net and EuSCAPE show that EU/EEA Member States are at very different stages of spread of CRE with, for *K. pneumoniae*, percentages of carbapenem resistance ranging from 0% to more than 60%, and epidemiologic stages of spread ranging from sporadic cases to an endemic situation [5,6]. 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 resistance. Cross-border transfer followed by outbreaks of CRE has been described in several EU/EEA Member States [32]. Introduction of CRE into low-prevalence countries can occur from EU Member States with high level of CRE, such as Greece and Italy as well as from other countries or regions with reported high level of CRE such as countries in the Eastern Mediterranean region, the Indian subcontinent and South-East Asia [8,24,58].

Third countries

High mobility and global trade play an important role in the transmission of antimicrobial resistance. A high level of antimicrobial use in medicine and agriculture combined with poor public health infrastructure (sewage, drinking water, overcrowding) has resulted in high rates of antimicrobial resistance in Gram-negative bacteria in emerging economies [59]. Through travel and migration, populations around the world are subsequently exposed to antimicrobial resistance arising in these areas [59]. Much of this dissemination happens unrecognized in the intestinal flora of healthy carriers and is only detected when microbiological tests are carried out in case of infection or active screening for digestive tract carriage. The epidemiology of ESBL-producing *E.coli* with high carriage rates in Southeast Asia, Western Pacific and Eastern Mediterranean regions and Africa also suggests a considerable role of poor access to drinking water, poverty and high population density as driving forces for dissemination in local communities and spread via international travel to regions with lower carriage rates such as Europe and America [1]. For CRE, a frequently cited example are NDM CRE for which a high proportion of cases diagnosed in the UK could be linked to prior travel and/or hospital care in India or Pakistan [60].

A high rate of digestive tract carriage of multidrug-resistant *Enterobacteriaceae* has also been described in travellers returning to the EU from tropical regions [11]. Although much less frequent than digestive tract carriage of ESBL-producing *Enterobacteriaceae*, digestive tract carriage of CRE has been reported in travellers returning from high CRE prevalence regions [61,62].

Antimicrobial resistance, including CRE, is a global problem and antimicrobial resistance generated by antimicrobial use and lack of public health infrastructure in one region of the world will eventually also affect other regions even if they have implemented measures for 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 the asymptomatic carriage in the human intestinal flora. The fact that countries from regions with high CRE prevalence were not able to provide data on CRE for the WHO global surveillance report is of concern [8].

Level of preparedness of EU/EEA Member States

National capacity for containment of carbapenemase-producing *Enterobacteriaceae* as assessed by national experts

The national capacity of EU/EEA Member States, EU enlargement countries and Israel was assessed by national experts that participated in the EuSCAPE project [6]. The results of this assessment are presented in Table 2. Of 38 participating European countries, 25 countries reported having a dedicated national surveillance system for carbapenemase-producing *Enterobacteriaceae*, 34 countries reported having an officially nominated 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*.

Table 2 National capacity for surveillance and containment of carbapenemase-producing *Enterobacteriaceae* as assessed by national experts, 38 European countries, May 2015 [6]

Country	National system for surveillance	Officially nominated national reference laboratory, or expert laboratory	National recommendation or obligation for reporting (notification) to health authorities	National plan for containment of (or preparedness to contain) CPE	National recommendation or guideline on infection control measures	Reference or URL for recommendation or guideline on infection control measures
Albania	..a, b	..a		..a		
Austria	• ^c	•	• ^d		•	http://www.analyse.eu/content/inhalte/nationales_referenzzentrum/station%C3%A4re_patienten_mit_auslandsanamnese/index.html
Belgium	• ^e	•	• ^f	•	•	http://www.health.belgium.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/19074512.pdf http://www.sante.belgique.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/19074512_nl.pdf
Bosnia and Herzegovina	..a, b		..a	..a		
Bulgaria	•	•	•	..a	•	
Croatia	• ^e	•	• ^f	•	•	
Cyprus	..a, g	• ^h				
Czech Republic	• ^e	•	• ^f	•	•	http://www.mzcr.cz/Legislativa/dokumenty/vestnik-c8/2012_6865_2510_11.html http://www.szu.cz/narodni-referencni-laborator-pro-antibiotika
Denmark	• ^c	•				
Estonia	..a		• ^d			
Finland	• ^e	•	• ^f		•	http://urn.fi/URN:ISBN:978-952-302-260-7
France	• ^e	•	• ^f	•	•	http://www.sante.gouv.fr/fichiers/bo/2014/14-02/ste_20140002_0000_0064.pdf
Germany	• ^c	•	..a		•	http://edoc.rki.de/documents/rki_ab/resuFmoGFF7o/PDF/210bND4dxM.pdf
Greece	• ^e	• ^h	• ^f	•	•	http://www.keelpno.gr/el-gr/vosmata-thematouyias/polyantheftikipaseogovasoanvooookomeia.aspx
Hungary	• ^e	• ^h	• ⁱ	..a	•	http://www.oek.hu/oek.web?nid=1067&pid=1&to=&lang=hun
Iceland	• ^e	•	• ^f	•	•	
Ireland	• ^e	•	• ^d		•	http://www.hpsc.ie/hpsc/A-Z/MicrobiologyAntimicrobialResistance/InfectionControlandHAI/Guidelines/File,12922,en.pdf
Israel	• ^e	•	• ^f	•	•	
Italy	• ^c	• ^h	• ^d	..a	•	http://www.trovanorme.salute.gov.it/renderNormsanPdf?anno=0&codLeg=45499&parte=1%20&serie=
Kosovo*	..a, b	• ^h			..a	
Latvia	• ^e	• ^h	• ^f	..a		
Lithuania	• ^e	•				
Luxembourg	• ^c	• ^h	• ^d		•	
Malta	• ^e	• ^h		..a	•	
Montenegro	..a, b	..a	• ^f			
The Netherlands	• ^c	• ^h		..a	•	http://www.rivm.nl/dsresource?objectid=rivm:46410&type=org&disposition=inline&ns_nc=1

CPE: carbapenemase-resistant *Enterobacteriaceae*.

In the table cells, a dot signifies 'in place' and the absence of dot signifies 'absent'. Black colour indicates that the system or document was already in place in 2013. Blue colour indicates a change reported in 2015, as compared with 2013.

^a In preparation.

^b No national system for surveillance, but country reports carbapenem-resistant Invasive Isolates (*Klebsiella pneumoniae* and *Escherichia coli*) to the Central Asian and Eastern European Surveillance on Antimicrobial Resistance (CAESAR).

^c Voluntary participation of the laboratories.

^d Voluntary notification to health authorities.

^e Mandatory participation of the laboratories (for the United Kingdom, only mandatory for Scotland).

^f Mandatory notification to health authorities (for the United Kingdom, only mandatory for Scotland).

^g No national system for surveillance, but country reports carbapenem-resistant Invasive Isolates (*K. pneumoniae* and *E. coli*) to the European Antimicrobial Resistance Surveillance Network (EARS-Net).

^h An expert laboratory fulfils a similar role to that of a national reference laboratory.

ⁱ This designation is without prejudice to positions on status, and is in line with United Nations Security Council Resolution 1244/99 and the Internal Court of Justice Opinion on the Kosovo declaration of Independence.

Table 2 (continued) National capacity for surveillance and containment of carbapenemase-producing *Enterobacteriaceae* as assessed by national experts, 38 European countries, May 2015 [6]

Country	National system for surveillance	Officially nominated national reference laboratory, or expert laboratory	National recommendation or obligation for reporting (notification) to health authorities	National plan for containment of (or preparedness to contain) CPE	National recommendation or guideline on infection control measures	Reference or URL for recommendation or guideline on infection control measures
Norway	• ^a	•	• ^f	.. ^a	•	http://www.fhi.no/dokumenter/96331178b9.pdf http://www.fhi.no/eway/default.aspx?pid=239&trg=List_6212&Main_6157=6263:0:25,6493&MainContent_6263=6464:0:25,6513&List_6212=6453:0:25,6499:1:0:0:0:0
Poland	• ^a	•	• ^f		•	http://www.antybiotyki.edu.pl/pdf/kpc-20120713.pdf
Portugal	• ^a	•	• ^f	•	.. ^a	
Romania	• ^c	• ^b			.. ^a	http://www.srm.ro
Serbia	• ^c	•				
Slovakia	• ^a	• ^b	• ^f	•	•	http://www.ruvzt.sk/OU%20MZ%20SR.pdf
Slovenia	.. ^{a, k}	• ^b	.. ^a		•	http://www.mz.gov.si/fileadmin/mz.gov.si/pageuploads/mz_dokumenti/delovna_podrocja/zdravstveno_varstvo/zdravstveno_varstvo_v_posebnih/NAKOBO_oktober_2010/PRIPOROCILA_ESBL_26.10.10.pdf
Spain	• ^c	• ^b	• ^d	.. ^a	•	http://www.aemps.gob.es/publicaciones/publica/docs/plan-estrategico-antibioticos.pdf http://www.madrid.org/cs/Satellite?blobcol=urldata&blobheader=application%2Fpdf&blobheadername1=Content-disposition&blobheadername2=cadena&blobheadervalue1=filename%3DPLAN+PREVENCION%2F93N+Y+CONTROL+EPC+CM_v1_sept+2013.pdf&blobheadervalue2=language%3Des%26site%3DPortalSalud&blobkey=id&blobtable=MungoBlobs&blobwhere=1352838664739&ssbinary=true http://safh.org/wp-content/uploads/2014/10/Programa-para-el-control-de-las-EPC_SSPA.pdf
Sweden	• ^a	•	• ^f	•	•	http://www.folkhalsomyndigheten.se/page-files/17838/ESBL-producerande%20tarmbakterier.pdf
The former Yugoslav Republic of Macedonia	• ^a	• ^b	• ^f			
Turkey	•	• ^b	• ^d			
United Kingdom	• ^{c, e}	•	• ^{d, f}	•	•	https://www.gov.uk/government/publications/carbapenemase-producing-enterobacteriaceae-early-detection-management-and-control-toolkit-for-acute-trusts http://www.documents.hps.scot.nhs.uk/hai/amr/cpe-guidance.pdf

CPE: carbapenemase-resistant *Enterobacteriaceae*.

In the table cells, a dot signifies 'In place' and the absence of dot signifies 'absent'. Black colour indicates that the system or document was already in place in 2013. Blue colour indicates a change reported in 2015, as compared with 2013.

^a In preparation.^b No national system for surveillance, but country reports carbapenem-resistant Invasive Isolates (*Klebsiella pneumoniae* and *Escherichia coli*) to the Central Asian and Eastern European Surveillance on Antimicrobial Resistance (CAESAR).^c Voluntary participation of the laboratories.^d Voluntary notification to health authorities.^e Mandatory participation of the laboratories (for the United Kingdom, only mandatory for Scotland).^f Mandatory notification to health authorities (for the United Kingdom, only mandatory for Scotland).^g No national system for surveillance, but country reports carbapenem-resistant Invasive Isolates (*K. pneumoniae* and *E. coli*) to the European Antimicrobial Resistance Surveillance Network (EARS-Net).^h An expert laboratory fulfils a similar role to that of a national reference laboratory.^{*} This designation is without prejudice to positions on status, and is in line with United Nations Security Council Resolution 1244/99 and the Internal Court of Justice Opinion on the Kosovo declaration of Independence.

Israel experienced a clonal outbreak of carbapenem-resistant *Klebsiella pneumoniae* that affected 1275 patients in 27 hospitals and implemented a nationwide and centrally controlled intervention with mandatory reporting, mandatory isolation and dedicated staffing, and a specific national taskforce that was effective in containing the outbreak [63]. 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 [64].

Risks for 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 treatment are available, these procedures will be associated with a higher risk of CRE infection for patients.

ICU patients have been affected by CRE outbreaks in many countries. Urinary tract infections with CRE in kidney/solid organ transplant recipients have been associated with antimicrobial failure and mortality [36,65]. 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 [66]. Mortality rates associated with CRE infections were high in patients with hematologic malignancies [67]. Low birthweight neonates have also been affected by CRE septicaemia [68]. In addition, CRE outbreaks have been related to frequently-performed invasive medical procedures as in two outbreaks related to bronchoscopy and duodenoscopy in Germany [33,69].

Besides morbidity and mortality, CRE are likely to result in a financial burden for healthcare systems; for example, CRE infections have been associated with prolonged hospital stay [27]. A retrospective study of the costs of patients carrying a 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 €642,104, including the costs related to a decrease in activity of the affected units, additional working hours and screening samples [70].

Infection control measures and especially contact precautions are time-consuming and a precondition for adherence is therefore sufficient human resources in healthcare institutions. The association between low healthcare staffing levels and healthcare-associated infections is well known [71]. Underfunded and understaffed healthcare institutions will not be able to comply with infection control measures, and will in contrast exacerbate resistance by becoming a reservoir for transmission of multidrug-resistant bacteria such as CRE.

Conclusions and options for response

CRE pose a significant threat for patients as well as healthcare systems in EU/EEA Member States. CRE infections are associated with high mortality, primarily due to delays in administration of effective treatment and the limited availability of effective treatment options. New antibiotics capable of replacing carbapenems in respect of their main indications for use are not likely to be 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 are likely to benefit from consultations from infectious diseases or clinical microbiology experts to achieve the best possible outcome with the limited treatment options available.

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

Good standard infection control, including environmental cleaning and adequate reprocessing of medical devices, and adequate capacity of microbiological laboratories are the basis for prevention of transmission of multidrug-resistant bacteria such as CRE. Prompt notification of the clinical team and of the infection prevention and control/hospital hygiene team is essential.

Targeting patients at high risk for carriage of CRE

Patients transferred from or who had recently been hospitalised in a country/region/hospital (including hospitals in another or in the same country) known as having a high CRE prevalence should be considered at high risk of digestive tract carriage of CRE. Screening of these patients to confirm digestive tract carriage of CRE, and implementation of pre-emptive contact precautions and pre-emptive isolation should be considered. Hospitals could also consider pre-emptive isolation and screening for CRE carriage according to national guidance for patients who recently travelled to countries/regions known for their high CRE prevalence even if they were not in contact with healthcare.

Preventing transmission from CRE-positive patients

For patients who are CRE-positive, i.e. confirmed with digestive carriage of or infection with CRE, hospitals should consider use of enhanced control measures such as contact precautions, isolation or cohorting, and dedicated nursing staff.

Preventing spread of CRE in specific wards/units

In wards/units where patients are at high risk of infection (e.g. ICU and haematology wards), pre-emptive isolation and active surveillance ("screening") for CRE by rectal swab at admission should be considered, depending on the risk for CRE colonisation and the local prevalence of CRE.

Antimicrobial stewardship

Antimicrobial stewardship refers to coordinated programmes that implement interventions to ensure appropriate antimicrobial prescribing. They aim to improve clinical efficacy of antimicrobial treatment and limit antimicrobial resistance through reducing selective pressure for the development of resistance to currently effective antibiotics.

Although evidence for a specific beneficial effect of antimicrobial stewardship on the emergence and spread of CRE are limited, the previous use of broad-spectrum antimicrobials from various classes, and in particular carbapenems, is a known risk factor for colonisation by CRE. Therefore,

implementation of comprehensive antimicrobial stewardship programmes is recommended to prevent and control the emergence and spread of CRE.

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

Although the available information is still limited, it may be important to avoid the potential transmission of CRE via contaminated food. Close cooperation between veterinary medicine and human medicine as well as the regular monitoring for CRE of locally produced and imported food items are needed to prevent CRE-contaminated food from reaching the market. In addition, conditions of animal husbandry such as overcrowding and antimicrobial use that promote the occurrence and spread of multidrug-resistant bacteria, including CRE, should be addressed. In households, standard rules of personal hygiene and good food handling practices should be applied.

4. Actions related to cross-border aspects

Measures related to enhanced CRE surveillance and pre-emptive isolation and screening of patients being 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 of known colonisation 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 EU/EEA.

Finally, only measures taken to improve public health in all countries of the World, such as regulating antimicrobial use, improving infection control in hospitals and improving water and sanitation infrastructure, can provide a definitive solution. Until and unless this threat is eliminated, the capacity for resistance detection and surveillance in low-resource countries needs to be improved to have more reliable data on worldwide distribution of CRE as a first step to global control.

Testing for faecal carriage of CRE upon admission should be considered for persons requiring hospitalisation and who have recently been in countries/regions with high prevalence of CRE, and this even if they had no contact with healthcare services. This, however, should be done in accordance with the relevant national guidelines for testing persons at risk of carrying CRE and other multidrug-resistant Gram-negative bacteria. An Expert Opinion on the "Risks from digestive tract colonisation with multidrug-resistant *Enterobacteriaceae* after international travel and implications for surveillance, infection control and patient management" is currently under preparation at ECDC.

5. Actions related to risks for functioning of health care 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 their spread could be controlled through proportionate investment into control measures in most countries. Once an endemic situation is reached, control efforts will be more costly and less likely to be effective. The example of Italy shows that carbapenem resistance rates in *K. pneumoniae* can increase abruptly and rapidly, from 1-2% during the period of 2006-2009 to 33% in 2014 [5,72]. The same rapid resistance development might happen in other countries if no action is taken.

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