RAPID RISK ASSESSMENT

Combined clonal and plasmid-mediated outbreak of carbapenemase-producing Enterobacterales, Lithuania, 2019–2020

3 February 2020

Summary

Lithuania reported an outbreak of carbapenem-resistant, and for some cases, colistin-resistant Enterobacterales, including 223 cases detected between 1 February 2019 and 7 January 2020. The majority of cases (208 cases) occurred in one single hospital (Hospital 1). Most of the carbapenem-resistant Enterobacterales (CRE) isolates detected from cases were *Klebsiella pneumoniae* (199 cases, 89%), followed by *Escherichia coli* (21 cases, 9%). Whole genome sequencing (WGS) of 97 isolates revealed one major strain of *K. pneumoniae* ST392 responsible for the outbreak in Hospital 1 and detected in five additional hospitals. This *K. pneumoniae* ST392 outbreak strain carried a plasmid containing the bla_{KPC-2} gene. The same plasmid was also found in isolates of carbapenem-resistant *K. pneumoniae* of different sequence types and in *E. coli* and *Citrobacter* spp., thus indicating plasmid-mediated spread of carbapenem resistance in addition to clonal expansion of one single CRE strain. The number of CRE cases reported here represents a large increase compared with the total number of CRE cases for the whole country in previous years (five and 12 cases in 2017 and 2018, respectively).

The risk of further spread of CRE in the most-affected hospital appears to persist as new cases continue to be detected at the time of this risk assessment update, despite the implementation of enhanced infection control measures. The risk of further spread in the Lithuanian healthcare system is also likely to be high as WGS data indicated that the outbreak strain had been detected in five hospitals in addition to Hospital 1. By contrast, the risk of transmission for individuals outside healthcare settings is low. There is also no evidence, so far, for cross-border transmission related to transfer of patients with CRE from the hospitals affected by the outbreak, to healthcare facilities in other countries.

This outbreak highlights the high transmissibility of CRE, and in particular KPC-producing *K. pneumoniae* in healthcare settings. The outbreak is further complicated by parallel clonal expansion and plasmid spread including to other species. Early detection of outbreaks and close cooperation between healthcare units, clinicians and public health services are crucial to control the spread of CRE in the hospitalised patient population. Moreover, this outbreak highlights the importance of early detection of CRE in countries and settings with low incidence. To improve early detection and the control of CRE high-risk clones, and to better target control measures in healthcare facilities, there is a need for increased laboratory capacity in the European Union (EU)/European Economic Area (EEA) to support outbreak investigations and surveillance with real-time WGS in order to avoid further spread.

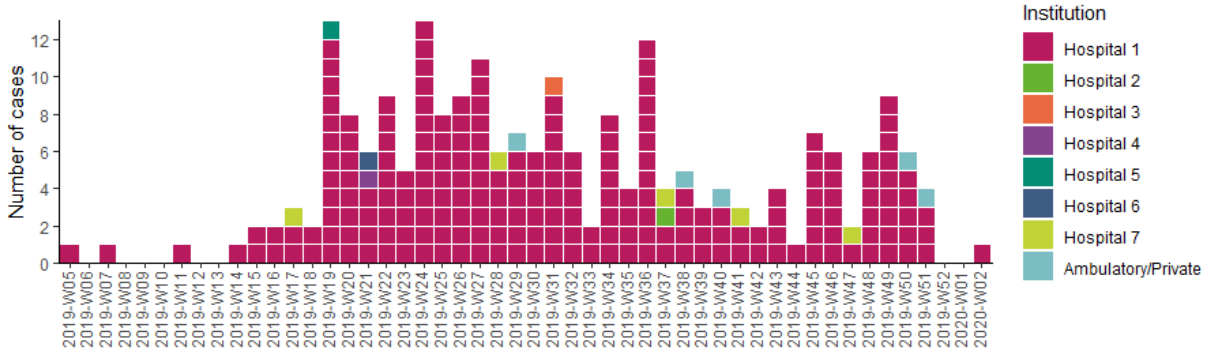
Available options for response are in the relevant section below.

Suggested citation: European Centre for Disease Prevention and Control. Combined clonal and plasmid-mediated outbreak of carbapenemase-producing Enterobacterales in Lithuania, 2019-2020 – 3 February 2020. ECDC: Stockholm; 2020.

Event background

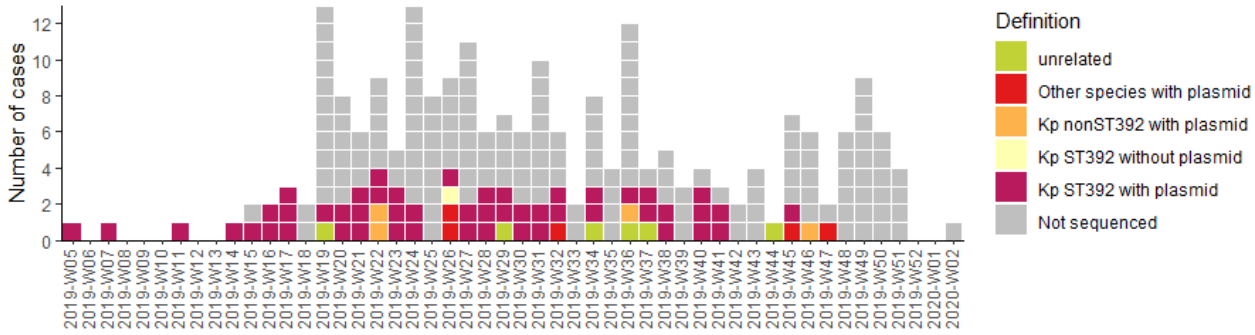
Between 1 February 2019 and 7 January 2020, 223 cases of *Klebsiella pneumoniae* carbapenemase (KPC)-producing, carbapenem-resistant Enterobacterales (KPC-CRE) were detected in Lithuania, including cases with infections as well as carriage. This is a large increase in CRE cases in Lithuania compared with previous years: only 12 cases of CRE (two cases with KPC-producing, two cases with VIM-producing and eight cases with NDM-producing CRE) were detected in 2017, and five cases of CRE (one case with KPC-producing, two cases with OXA-48-producing and two NDM-producing CRE) in 2018. The first detected case of the current outbreak was a patient with a surgical site infection admitted to the intensive care unit (ICU) of Hospital 1 in January 2019. Following this case, KPC-CRE were isolated from clinical samples of additional patients treated in the same ICU. The outbreak was identified in April 2019, when the information about the resistance mechanism (KPC) of the CRE isolates was obtained from the National Reference Laboratory (NRL), as initially only phenotypic resistance testing was performed at the local clinical microbiology laboratory. The epidemic curve is presented below: 208 KPC-CRE cases occurred in the most-affected hospital, Hospital 1. However, cases were also detected in six other hospitals (Hospital 2, one case; Hospital 3, one case; Hospital 4, one case, Hospital 5, one case, Hospital 6, one case; and Hospital 7, five cases; and in ambulatory care, five cases). One patient was transferred to another hospital (Hospital 8) and a subsequent sample of this patient was positive for the outbreak strain (not shown in epidemic curve).

Figure 1. Epidemic curve of the outbreak of KPC-producing carbapenem-resistant Enterobacterales (KPC-CRE), Lithuania, 1 February 2019–7 January 2020



Cases are presented per week of sampling. Only the first isolate per case was included.

Figure 2. Epidemic curve of KPC-CRE cases with isolates analysed by WGS, by species, ST and plasmid containing *bla*$_{KPC}$, Lithuania, 1 February 2019–7 January 2020.



Cases are presented per week of sampling. Only the first isolate per case was included.

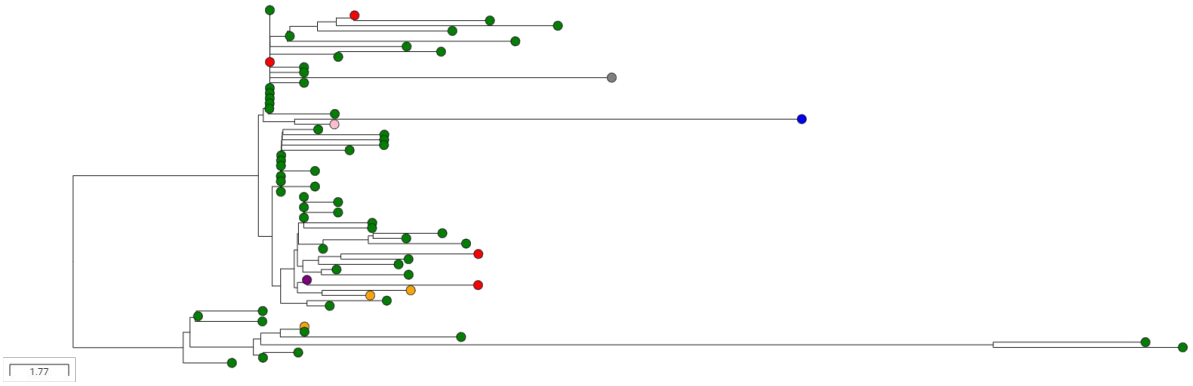
Unrelated isolates included contaminated samples (n=2) and samples where the phenotypic species identification did not match genotypic identification (n=4).

In the majority of cases, the first KPC-CRE isolate detected by phenotypic species identification was *K. pneumoniae* (199 cases, 89%) followed by *Escherichia coli* (21 cases, 9%), *Citrobacter freundii* (two cases) and *Enterobacter aerogenes* (one case). Of these first KPC-CRE isolates, 141 (63.2%) were detected in faeces, the result of screening for carriage, while the remaining 82 (36.8%) isolates were recovered from various clinical samples including urine, wound, aspirates/drainage fluid, blood or respiratory tract samples. However, some of the patients with KPC-CRE isolates from clinical samples did not receive treatment for CRE infections and were therefore considered to be carriers. Additional resistance to colistin was detected in 26 (50%) of 52 KPC-CRE isolates for which colistin susceptibility testing was performed. Initially, all isolates were reported to be susceptible to ceftazidime-avibactam, but resistance to ceftazidime-avibactam developed in at least two KPC-CRE cases. Many isolates were susceptible to amikacin.

In total, 105 KPC-CRE isolates were submitted for whole genome sequencing (WGS). The raw reads were assembled using SPAdes 3.11.1 with the careful option enabled. The resulting assemblies were then submitted to PathogenWatch for analysis. Resistance genes were determined using Kleborate [1] for the *Klebsiella* sequences and Resfinder for the remaining species. All assembled contigs were matched against *bla*$_{KPC-2}$ (accession AY034847.1) using local BLASTn and matching contigs were aligned using mafft to compare the flanking regions of *bla*$_{KPC-2}$, the resulting alignment was inspected using CLC Genomics Workbench. Isolates with coverage below 20x, with assembled genomes larger than 6.5 Mbp or with species (determined by PathogenWatch) not matching the phenotypic determination were excluded from further analysis. A phylogenetic tree for *K. pneumoniae* genomes was created based on core genome single nucleotide polymorphisms (SNPs) using PathogenWatch.

Of the 105 samples submitted for WGS, 97 samples passed quality control. The epidemic curve including the WGS results for the first sample per patient is shown in Figure 2. One large cluster of 68 isolates of *K. pneumoniae* ST392, 30 core genome SNPs from root to tip, carrying a plasmid with the *bla*$_{KPC-2}$ gene was identified, shown in Figure 3. One isolate being part of the cluster had lost the plasmid. An additional 27 isolates carried the plasmid but did not belong to the *K. pneumoniae* ST392 cluster. Of these, 13 were *E. coli*, 11 *K. pneumoniae* of sequence types other than ST392 and three were *Citrobacter* spp. Thus, there was evidence of both clonal expansion of a *K. pneumoniae* strain and plasmid spread to other sequence types or species. The plasmids were an IncN plasmid with an identical 15 kbp region. The *bla*$_{KPC-2}$ gene was localised on a Tn4401 transposon and a type IV secretion system was identified on the same contig. Mobile colistin resistance (*mcr*) genes were not detected. Multiple other resistance genes mediating resistance against various classes of antibiotics were identified by WGS.

Figure 3. Neighbour joining tree showing the main *K. pneumoniae* ST392 cluster.



The tree is based on core genome SNPs; it was calculated using PathogenWatch v3.9.5. The isolates are coloured by hospital of origin (anonymised). The bottom-left scale gives an indication of the genetic distance measured as the number of core genome SNPs.

The control measures implemented in Hospital 1 to date include:

- active screening for CRE carriage in high-risk units;
- active screening of patients transferred from other hospitals,
- re-admissions with hospitalisations in the previous twelve months and immunocompromised patients;
- contact precautions including isolation or cohorting of CRE-positive patients;
- enhanced hand hygiene measures.

KPC-CRE colonised or infected patients are flagged in the electronic charts in Hospital 1, and contacts of KPC-CRE carriers are investigated. Although patients with CRE are cohorted, there has been no possibility to dedicate staff to care for KPC-CRE positive patients. Environmental samples were taken to verify the effect of environmental disinfection and no persistent KPC-CRE contamination was detected.

All clinical microbiology laboratories were requested by the Ministry of Health to report to the National Reference Laboratory on isolates of CRE found until November 2019. However, systematic screening for CRE carriage was not performed in Lithuanian hospitals other than in Hospital 1 before December 2019. In December 2019, a letter from the Ministry of Health was sent to all healthcare institutions with information on the increase in KPC-CRE in the country, and a reminder on relevant infection prevention and control measures. In January 2020 the outbreak was still ongoing. A national recommendation for screening for CRE carriage, as well as for control measures was published for public consultation on 27 January 2020 [2] but has not yet been legally approved by the Ministry of Health.

Disease background

For information on carbapenem-resistant Enterobacterales (formerly known as Enterobacteriaceae) please refer to the ECDC Rapid Risk Assessment 'Carbapenem-resistant Enterobacteriaceae – second update' [3]. *Klebsiella pneumoniae* carbapenemase (KPC), which is encoded by *bla*$_{KPC}$ genes, was first described in a strain of *K. pneumoniae* isolated in a hospital in North Carolina, United States of America [4]. Besides carbapenems, KPC also hydrolyses monobactams and most cephalosporins. It may be inhibited by certain beta-lactamase inhibitors. Ceftazidime-avibactam was approved by the European Medicines Agency for therapeutic use in the EU in June 2016 and is a new option to treat patients infected with CRE as it is usually active against KPC-CRE. However, mutations of *bla*$_{KPC}$ genes, differences in susceptibility among KPC subtypes and other resistance mechanisms have led to the development of ceftazidime-avibactam-resistant KPC-CRE isolates [5]. Meropenem-vaborbactam has also recently been approved for therapeutic use in the EU and is usually active against KPC-CRE [6]. Prudent use of these new antimicrobial agents is recommended. Other last-line therapeutic options, such as colistin and tigecycline, are available but may be significantly more toxic or less effective. Additionally, resistance to these other last-line agents also occurs frequently, as was observed in the present outbreak.

The spread of carbapenem-resistant *K. pneumoniae* in the EU/EEA is most likely driven by direct or indirect patient-to-patient transmission in hospitals and other healthcare settings and clonal expansion of CRE strains [7]. ST392, the main clone of this outbreak, has been previously involved in healthcare associated outbreaks in several countries. A sample from Spain was among the first isolates, reported in 2013 [8]. *K. pneumoniae* ST392 was also found in Argentina [9], Colombia [10], Iran [11], Italy [12-14], Mexico [15], Tunisia [16], the United States [17]. *K. pneumoniae* ST392 carrying a plasmid with *bla*$_{KPC-2}$ has also previously been reported from China [18]. Cross-border transmission of carbapenem-resistant *K. pneumoniae* ST392 within the EU/EEA has previously been documented in patients previously hospitalised in Gran Canaria, Spain [19].

In addition, carbapenemase genes including *bla*$_{KPC}$ genes, may also spread by horizontal gene transfer, e.g. via plasmids, to other strains of the same species or other species [20]. The *bla*$_{KPC-2}$ gene is frequently carried on plasmids, i.e. circular, extrachromosomal DNA molecules frequently carrying antimicrobial resistance genes. Plasmids can be exchanged between bacteria, even between different species. Tn4401, the transposon including the sequence of the *bla*$_{KPC-2}$ gene in this outbreak, is carried by an IncN plasmid and has also been described previously in Brazil [21], Israel [22], Italy [23] and the United States [24].

Risk assessment questions

What is the risk for further spread of KPC-CRE within the Lithuanian healthcare system, including the most affected hospital, other hospitals and the community in Lithuania, and what is the risk for cross-border spread of KPC-CRE to other EU/EEA countries?

ECDC risk assessment for the EU/EEA

The risk of further spread in the most-affected hospital, Hospital 1, is high, as a large number of cases were identified from multiple wards, and new cases were detected until at least 07 January 2020. This means that, while enhanced infection control measures have been implemented, the outbreak was still ongoing at the time of this assessment. The outbreak is further complicated by concomitant clonal expansion and plasmid spread, including transfer to species of the normal gastrointestinal flora such as *E. coli*. All microbiology laboratories were requested by the Ministry of Health to provide updated information to the national reference laboratory on isolates of CRE until November 2019, resulting in the reporting of seven additional isolates not yet presented in the epidemic curve. However, the risk of further spread within the healthcare system is likely to be high, in the light of the known transfer of patients with the outbreak strain from Hospital 1. Screening for CRE carriage was not in place in Lithuanian hospitals before December 2019, except for Hospital 1, which started screening for CRE in May 2019. CRE carriage status is marked in the hospital information system and on discharge documents of Hospital 1, and Lithuanian healthcare institutions were informed about the increase of CRE in the country in 2019. Several isolates of KPC-CRE were reported from other Lithuanian healthcare institutions and were shown to be related to the outbreak by WGS for five hospitals in addition to Hospital 1. Due to the low number of samples sequenced, it is not possible to rule out that the outbreak may have also affected hospitals that were not confirmed by WGS as being part of the outbreak.

Patients infected with CRE are at risk of receiving inappropriate empiric antimicrobial therapy, which is associated with higher mortality [25]. In 2015 in the EU/EEA, 2 118 deaths and 11.5 DALYs per 100 000 population were attributed to carbapenem-resistant *K. pneumoniae* [26]. Patient populations that were especially vulnerable were those with haematologic malignancies and those undergoing solid organ or bone marrow transplantation. In Italy, survival of patients with haematologic malignancies was lower if they were colonised with carbapenem-resistant Gram-negative bacteria than if they were not colonised [27]. Gut colonisation with multidrug-resistant bacteria such as CRE also increases the risk of bloodstream infections after stem-cell transplantation [28].

In neutropenic patients, carbapenem resistance of the microorganism responsible for infection was found to be directly associated with mortality [29].

The risk for persons in Lithuania to acquire KPC-CRE related to this outbreak outside of the healthcare system is low. Spread of carbapenem-resistant *K. pneumoniae* in the EU/EEA is usually associated with healthcare [7]. For this specific outbreak, the risk for spread to other countries is also considered low, based on the currently available information and assuming that information on carrier status is shared between healthcare providers. So far, there is no evidence of cross-border patient transfers or cross-border transmission of KPC-CRE related to this outbreak. However, evidence of the presence of both *K. pneumoniae* ST392 and the involved plasmid in various other countries, the large number of other recent events of cross-border importation after patient transfer, large outbreaks in different countries as well as the worsening epidemiologic situation of carbapenemase-producing CRE, highlight the high risk for further spread of CRE in the EU/EEA in general and the need for enhanced control efforts [19,30-32].

Options for response

For control measures for carbapenem-resistant Enterobacterales (CRE) in general, please refer to the ECDC Rapid Risk Assessment 'Carbapenem-resistant Enterobacteriaceae – second update' [3]. The following range of control measures should be considered for an enhanced response to this specific outbreak.

Targeting patients at high risk of CRE carriage

Screening of patients at high risk for digestive tract carriage of CRE due to healthcare contact in the preceding 12 months as well as the immediate implementation of pre-emptive contact precautions and isolation of such high-risk patients should be considered. This should be done both in hospitals known to have an ongoing outbreak and in other hospitals, especially those receiving direct patient transfers from hospitals with known ongoing outbreaks. In the particular case of this outbreak, the highest risk of further spread is linked to the patients who had previously been hospitalised in Hospital 1, especially in the wards of Hospital 1 affected by the outbreak, when (a) they are transferred to another ward within Hospital 1 and (b) they are transferred to other hospitals as well as (c) when they are readmitted to Hospital 1. Screening of the above high-risk patients for CRE carriage should be considered a priority.

Preventing transmission from CRE-positive patients

Enhanced control measures, such as contact precautions, isolation or cohorting, as already implemented in Hospital 1, remain important. Monitoring of the appropriate application of these control measures by observing procedures and the adherence of healthcare staff to hand hygiene and contact precautions is important. Furthermore, dedicated nursing staff in dedicated wards could be considered for hospitalised patients with confirmed digestive tract carriage of CRE or confirmed CRE infection to limit transmission within hospitals with ongoing outbreaks (including Hospital 1). Hospital-wide point prevalence screening for CRE could be considered if new cases continue to appear. In addition, screening of contacts, i.e. patients who were in contact with a CRE-positive patient, will enable early identification of CRE carriers and implementation of control measures, both in hospitals with ongoing outbreaks (such as Hospital 1) and in other hospitals in case of patient transfers or readmissions. Similar to CRE-positive patients, contact patients need to be flagged on their medical records to facilitate their identification.

Preventing spread of CRE in specific wards/units and the healthcare system

In units/wards where patients are at high risk of infection (e.g. ICUs and other high-dependency units), pre-emptive isolation and active surveillance (screening) for CRE carriage by rectal swab on admission should be considered, especially in patients with previous admission to a hospital with an ongoing outbreak (such as Hospital 1). Regular review of appropriate device use is an important infection prevention measure in high-risk settings. The role of environmental reservoirs of epidemic CRE strains and/or carbapenemase-encoding plasmids should be investigated, especially when other infection control interventions have failed, and relevant control measures implemented accordingly. Environmental sampling should be performed with a clear understanding of the purpose of the sampling, for example mapping the extent of environmental contamination around positive cases or assessing the quality of cleaning. Even if environmental samples are negative, emphasis should be put on daily cleaning of patients' rooms, sinks and toilets, and especially terminal cleaning after the patient is discharged or moved to another room. Regular audits of cleaning and disinfection of the patient environment and medical devices are important. Commitment of the respective authorities and the hospital management, and their support to infection control (IC) teams, including IC nurses, and provision of training for healthcare staff, including cleaning staff, is crucial for the success of such measures.

Communication

Notification of the occurrence of each KPC-CRE case (infection or carriage) to the public health authorities by all hospitals in Lithuania is pivotal to ensuring an accurate overview of the extent of the problem within the country as a whole. Further communication between the healthcare facilities and public health authorities is likely to strengthen the organisation and implementation of targeted CRE screening of high-risk patients as well as pre-emptive control measures at admission. Active and timely collection and sharing of surveillance data can help the public health authorities to provide support in facilities and areas where it is most needed. The need for additional resources for hospitals affected by the outbreak should be kept under continual assessment at the national level.

In case of patient transfers, good inter-facility communication is a key element to ensure effective measures are in place to limit the spread of CRE in the receiving hospital(s). 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 within the country, and, where relevant between countries. The same applies for transfers or transport of CRE carriers or CRE-infected patients within healthcare institutions (e.g. when undergoing radiography, endoscopy, etc.), where the receiving units need to be informed about the CRE carriage or infection status of the patient. Flagging CRE-positive patients in health records may facilitate the flow of information. Patients flagged as CRE-positive should receive sufficient information on their carriage or infection status, and their community care providers should receive guidance on how to manage CRE carriers in outpatient and community care settings.

Antimicrobial stewardship

The implementation of comprehensive antimicrobial stewardship programmes, both in affected hospitals (such as Hospital 1) and in the healthcare system in general, is key to the prevention and control of the emergence and spread of CRE and other multidrug-resistant bacteria.

WGS-based investigation

ECDC supported Lithuania by providing access to WGS services for a limited number of isolates (105) to determine the extent of the outbreak and to provide more detailed information about its underlying mechanisms. The WGS analysis resulted in insights into the extent of the outbreak, transmissions chains within the country and detected the concomitant clonal expansion and plasmid spread as drivers of this outbreak. However, there is still is a need for increased capacity in the EU/EEA to support outbreak investigations and surveillance with real-time WGS. Until sufficient WGS capacity is available in all EU/EEA countries, ECDC is, to a limited extent, able to provide Member States with access to WGS services primarily for investigating potential multi-country outbreaks.

Additional guidance

Further information on measures to control carbapenem-resistant Enterobacterales can be found in the ECDC Rapid Risk Assessment 'Carbapenem-resistant Enterobacteriaceae – second update' [3]. Detailed further guidance has been published by international and national organisations. The World Health Organization published guidelines for the prevention and control of CRE, carbapenem-resistant *Acinetobacter baumannii* and carbapenem-resistant *Pseudomonas aeruginosa* in healthcare facilities [33]. There is also facility guidance for control of CRE from the US Centers for Disease Control and Prevention [34]. The European Society of Clinical Microbiology and Infectious Diseases published guidelines for the management of infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalised patients, as well as for the decolonisation of carriers of multidrug-resistant Gram-negative bacteria [35,36]. 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 [37].

Source and date of request for this update

ECDC internal decision, 23 January 2020.

Consulted experts

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

Disclaimer

ECDC issues this risk assessment document based on an internal decision and in accordance with Article 10 of Decision No 1082/13/EC and Article 7(1) of Regulation (EC) No 851/2004 establishing a European centre for disease prevention and control (ECDC). In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU/EEA Member States. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency.

This report was written with the coordination and assistance of an Internal Response Team at the European Centre for Disease Prevention and Control. All data published in this risk assessment are correct to the best of our knowledge at the time of publication. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

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