RAPID RISK ASSESSMENT

Outbreak of carbapenemase-producing Enterobacterales in Lithuania, 2019

18 December 2019

Summary

Lithuania reported an outbreak of carbapenem-resistant, and for some cases, colistin-resistant, Enterobacterales in November 2019. Between 1 February and 26 November 2019, 199 cases were detected, including cases with infection as well as carriage. The majority of cases (186 cases) occurred in one single hospital (Hospital 1). Most of the carbapenem-resistant Enterobacterales (CRE) isolates were *Klebsiella pneumoniae* (93%), followed by *Escherichia coli*. In all isolates, carbapenem resistance was mediated by a *Klebsiella pneumoniae* carbapenemase (KPC) enzyme. In the majority of cases, the KPC-producing carbapenem-resistant Enterobacterales (KPC-CRE) were detected from screening samples (126 cases, 63.3%) while the remaining 73 (36.7%) isolates were from various clinical samples. However, some of these patients with KPC-CRE isolates from clinical samples did not receive treatment for CRE infections and were therefore considered to be carriers. The number of cases represents a large increase compared with the total number of cases for the whole country in previous years (five and 12 cases of CRE in Lithuania in 2017 and 2018, respectively). Whole genome sequencing results are not yet available.

The risk of further spread of CRE in the most-affected hospital is high, as a large number of cases have been identified from multiple wards and new cases continue to be detected at the time of this risk assessment. While enhanced infection control measures have been implemented, the outbreak appears not yet to have been controlled. The risk of further spread in the Lithuanian healthcare system is also high, as screening for carriage of CRE was not in place in Lithuanian hospitals before December 2019, except for the hospital mostly affected by the outbreak. Six additional Lithuanian hospitals have reported the detection of KPC-producing CRE, however, it is currently unclear how many of these cases are related to cases in Hospital 1. By contrast, the risk of transmission for individuals outside healthcare settings is low. In addition, there is no evidence, so far, for cross-border transmission related to transfer of patients with CRE from the hospital affected by the outbreak to healthcare facilities in other countries. Further epidemiological investigations are ongoing and molecular typing is planned with ECDC support.

This outbreak highlights the high transmissibility of CRE, and in particular KPC-producing *K. pneumoniae* in healthcare settings. Early detection of outbreaks and close cooperation between healthcare units, clinicians and public health services are crucial to control the spread 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 whole genome sequencing (WGS) in order to avoid further spread.

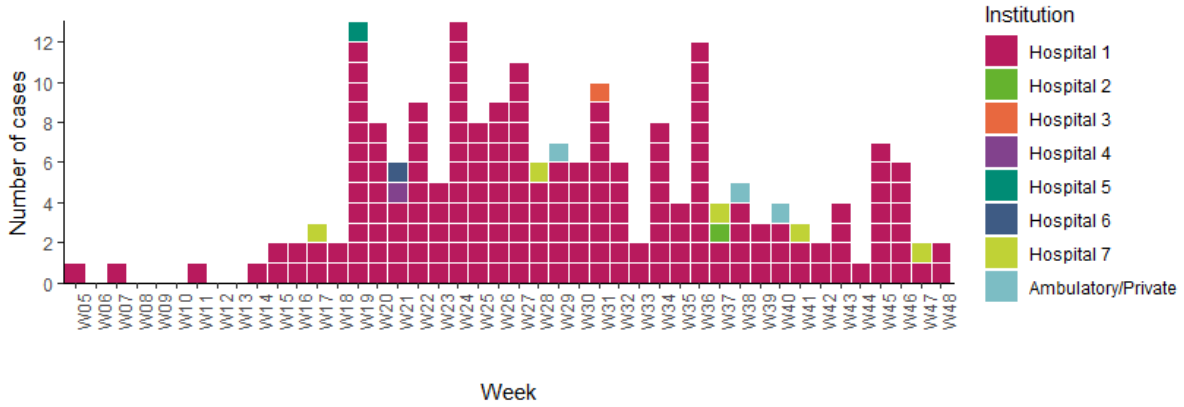
For available options for response, please refer to the 'Options for response' section below.

Suggested citation: European Centre for Disease Prevention and Control. Outbreak of carbapenemase-producing Enterobacterales in Lithuania – 18 December 2019. ECDC: Stockholm; 2019.

Event background

Between 1 February and 26 November 2019, 199 cases of *Klebsiella pneumoniae* carbapenemase (KPC)-producing carbapenem-resistant Enterobacterales (KPC-CRE) were detected in Lithuania, including cases with infections as well as carriage. The first detected case was a patient with a surgical site infection admitted to the intensive care unit (ICU) of Hospital 1. Following this case, there were additional patients treated in the same ICU, from whom KPC-CRE were isolated from clinical samples. 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: 186 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 (three cases). It is currently unclear how many of these cases are related to cases in Hospital 1.

Figure 1. Epidemic curve of the outbreak of KPC-producing carbapenem-resistant Enterobacterales (KPC-CRE) in Lithuania



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

In the majority of cases, the first KPC-CRE isolate detected was *K. pneumoniae* (186 cases, 93%) followed by *Escherichia coli* (16 cases, 8%), *Citrobacter freundii* (two cases) and *Enterobacter aerogenes* (one case). Of these isolates, 126 (63.3%) were detected in faeces samples, thus were most likely the result of screening for carriage, while the remaining 73 (36.7%) isolates were from various clinical samples including urine, wound, aspirates/drainage fluid, blood or respiratory tract samples. However, some of these patients with KPC-CRE isolation 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 of 52 isolates of KPC-CRE in which antimicrobial susceptibility testing for colistin was performed. Initially, all isolates were reported to be susceptible to ceftazidime-avibactam, but resistance to ceftazidime-avibactam developed in at least two cases. Many isolates were susceptible to amikacin.

The Lithuanian NRL detects the genes encoding for carbapenemases using PCR. In addition to the above described KPC-CRE isolates, four CRE isolates producing oxacillinase-48 (OXA-48) and one isolate producing a New Delhi metallo-beta-lactamase (NDM) were submitted to the NRL in 2019 to date. Due to the current outbreak, there is a large increase in CRE cases in Lithuania compared with previous years: only a total of 12 cases of CRE (two KPC-producing, two VIM-producing and eight NDM-producing) were detected in 2017 and five cases of CRE (one KPC-producing, two OXA-48-producing and two NDM-producing) in 2018.

The control measures implemented in Hospital 1 to date include: active screening for CRE carriage, contact precautions including isolation or cohorting of CRE-positive patients, and enhanced hand hygiene measures. Although patients with CRE are cohorted, there has been no possibility to have dedicated staff to care for KPC-CRE positive patients. Environmental samples were taken to control the efficiency of environmental disinfection and no persistent contamination was detected. In Hospital 1, screening for CRE carriage is performed for all patients who have been hospitalised in other countries, as well as immunocompromised patients and patients with previous admission in the same hospital. Patients with a planned stay of more than 48 hours in the ICU and patients in other high-risk wards are screened for CRE carriage on admission and once weekly thereafter. Systematic screening for CRE carriage was not performed in other Lithuanian hospitals before December 2019, and there is no information on the spread of the outbreak to other hospitals in the country beyond the information provided in the epidemic curve. Nevertheless, several patients with KPC-CRE were transferred from Hospital 1 to other hospitals in Lithuania with information on the KPC-CRE infection/carriage status of the patient in the patient record.

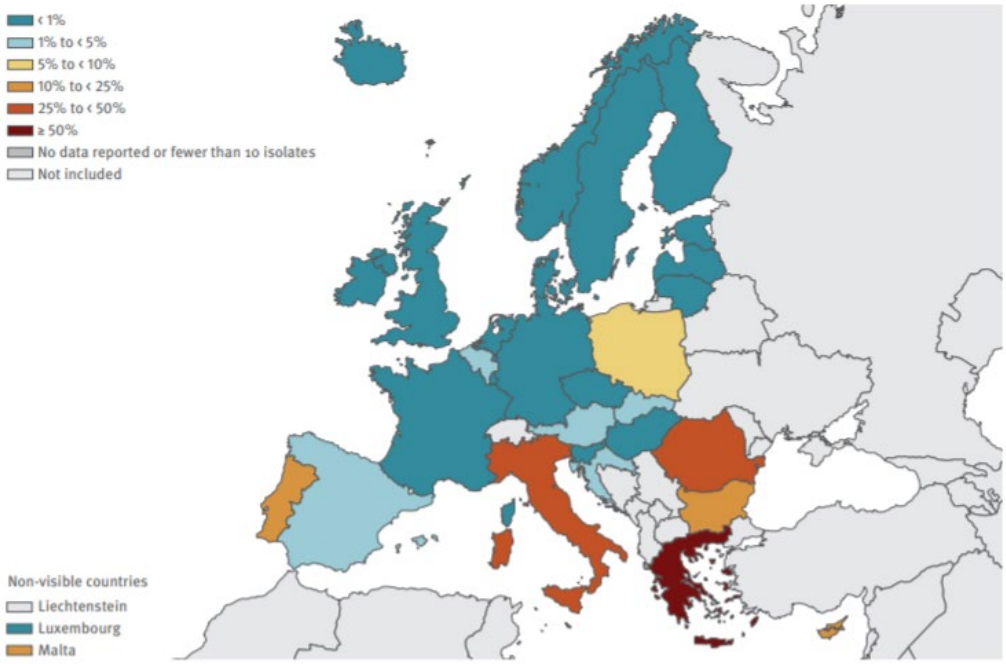
As of 11 December 2019, the outbreak was still ongoing. An epidemiological investigation is currently being carried out. A national recommendation for screening for CRE, as well as for control measures has been developed and is about to be distributed to all hospitals in Lithuania. So far, no further molecular investigation e.g. whole-genome sequencing (WGS), of the outbreak isolates has been performed. The sequence type of the isolates, the subtype of carbapenemase and a possible genetic link to other outbreaks have thus not yet been determined.

Disease background

For information on carbapenem-resistant Enterobacterales (formerly Enterobacteriaceae)please refer to the ECDC Rapid Risk Assessment 'Carbapenem-resistant Enterobacteriaceae – second update' [1]. *Klebsiella pneumoniae* carbapenemase, 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 [2]. Besides carbapenems, KPC also hydrolyses monobactams and most cephalosporins, but it may be inhibited by beta-lactamase inhibitors. Ceftazidime-avibactam was approved by the European Medicines Agency for use in the EU in June 2016 and is a newer 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 [3]. Also, meropenem-vaborbactam is usually active against KPC-CRE [4] and has been recently approved. Prudent use of these new drugs 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.

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, with most isolates belonging to the sequence types (ST) 11, 15, 101, and 258 with its derivative 512 [5]. The latter is disseminating globally and has become endemic in Greece, Israel and Italy [6-9], most probably after a single introduction and subsequent spread [5]. In addition, carbapenemase genes, including *bla*$_{KPC}$ genes, may not only spread by clonal expansion of KPC-CRE strains, but also by horizontal gene transfer, e.g. via plasmids [10].

Figure 2. Percentage of invasive *K. pneumoniae* isolates with resistance to carbapenems, EU/EEA, 2018 [11]



EARS-Net data for 2018 showed a very low proportion of carbapenem resistance among invasive *K. pneumoniae* isolates in the Baltic region, including in Lithuania (0.3%) [11]. In Poland, the reported proportion of carbapenem resistance among invasive *K. pneumoniae* isolates was more than 5% [11]. Additionally, KPC-CRE were identified in Poland [12] in the European Survey of Carbapenemase-producing Enterobacteriaceae (EuSCAPE) 2013–2014,. In the most recent self-assessment, carbapenemase-producing CRE were reported to have spread between regions in Poland [13]. Furthermore, in 2017, Belarus reported that over 70% of invasive *K. pneumoniae* isolates were resistant to carbapenems [14]. In the EU, KPC-CRE are endemic in Greece and Italy, and had been reported in most Member States by 2015 [5].

In the published medical literature, data on CRE in Lithuania are scarce. In a survey published in 2014, carbapenemase-producing isolates of *K. pneumoniae* or *E. coli* were not detected in Lithuania or in neighbouring Latvia [15]. In a national self-assessment conducted in 2018, carbapenemase-producing CRE were reported to only occur sporadically on the national level in Lithuania [13]. Regarding preparedness, Lithuania had a NRL, a national surveillance system, and mandatory notification for CRE in place in 2018. However, there were also gaps in preparedness, with neither a related national plan for the containment, nor national recommendations or guidelines on infection control measures for carbapenemase-producing CRE [13]. The NRL is capable of identifying the most frequent resistance mechanisms by polymerase chain reaction (PCR), but does not have the capacity for molecular typing of isolates [13].

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 continue to be detected at the time of this risk assessment. While enhanced infection control measures have been implemented, it remains to be seen how fast the outbreak can be controlled. The current status of CRE in the Lithuanian healthcare system is not established, but the risk of further spread within the healthcare system is also likely to be high, in the light of the known transfer of patients with CRE 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. Although the CRE carriage status is marked in the hospital information system and on discharge documents, more proactive dissemination of information about the outbreak in Hospital 1 did not take place until recently. Several isolates of KPC-CRE were reported from other Lithuanian healthcare institutions, but it remains to be determined with WGS if these cases are related to the cases in Hospital 1.

Patients infected with CRE are at risk of receiving inappropriate empiric antimicrobial therapy, which translates into higher mortality [16]. In 2015 in the EU/EEA, 2 118 deaths and 11.5 DALYs per 100 000 population were attributed to carbapenem-resistant *K. pneumoniae* [17]. Patient populations that were especially vulnerable were those with haematologic malignancies and those undergoing solid organ or bone marrow transplantation. In Italy, survival was lower among patients with haematologic malignancies that were colonised with carbapenem-resistant Gram-negative bacteria compared with ones that were not colonised [18]. Gut colonisation with multidrug-resistant bacteria such as CRE also increases the risk of blood-stream infections after stem-cell transplantation [19]. In neutropenic patients, carbapenem resistance of the microorganism responsible for infection was found to be directly associated with mortality [20].

The risk for persons in Lithuania to acquire KPC-CRE related to this outbreak outside of the healthcare system is very low. Spread of carbapenem-resistant *K. pneumoniae* in the EU/EEA is usually associated with healthcare [5]. For this specific outbreak, the risk for spread to other countries is also considered low based on the currently available information. So far, there is no evidence on cross-border patient transfers or cross-border transmission related to this outbreak. However, the large number of other recent events of cross-border importation after patient transfer and 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 [13,21-23].

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' [1]. 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 and the implementation of pre-emptive contact precautions and isolation should be considered. This should be 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 hospitalised in Hospital 1, especially in the wards of Hospital 1 affected by the outbreak, when they are transferred within Hospital 1 and following transfers to other hospitals as well as readmissions to Hospital 1. Screening of the above patients 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 execution of measures by observing procedures and the adherence of healthcare staff to hand hygiene and contact precautions is also 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 the transmission within hospitals with ongoing outbreaks (including Hospital 1). A 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. To facilitate identification, contact patients need to be flagged on their medical records.

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 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.

Communication

Notification of the occurrence of each KPC-CRE to the public health authorities by all hospitals in Lithuania is pivotal to have an 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. Actively and timely collection and sharing of surveillance data can help the public health authorities to provide support in the facilities and areas with the most needs. 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. Flagged patients with CRE carriage should receive sufficient information on the carriage 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.

Molecular investigation

Molecular typing would provide important evidence and insight into the extent of the outbreak and the transmission chains within the country that can guide the adaption of control measures accordingly. ECDC will support Lithuania by providing WGS to determine the extent of this outbreak. There is a need for increased capacity in the EU/EEA to support outbreak investigations and surveillance with real-time WGS.

This is to identify high-risk clones as well as transmission chains [13], and to implement targeted control measures in order to avoid further spread, both within and between healthcare facilities. Until sufficient WGS capacity is available in all EU/EEA countries, ECDC can to a limited extent, provide support with these activities.

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' [1]. 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 [24]. There is also facility guidance for control of CRE from the US Centers for Disease Control and Prevention [25]. 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 [26,27]. 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 [28].

Source and date of request

ECDC internal decision, 25 November 2019.

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.

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

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