RAPID RISK ASSESSMENT

Outbreak of carbapenemase-producing (NDM-1 and OXA-48) and colistin-resistant *Klebsiella pneumoniae* ST307, north-east Germany, 2019

28 October 2019

Summary

Germany has reported an outbreak of carbapenemase-producing (NDM-1 and OXA-48) and colistin-resistant *Klebsiella pneumoniae* sequence type (ST) 307. As of 21 October 2019, 17 patients in three hospitals and one rehabilitation clinic in Mecklenburg-West Pomerania in north-east Germany have been affected. Six of the 17 cases presented with clinical symptoms of infection, while 11 were identified as be carriers.

This is the first reported outbreak in Germany of *K. pneumoniae* that produce both NDM-1 and OXA-48 while also involving the emerging clone ST307. The outbreak strain is closely related to a *K. pneumoniae* ST307 isolate producing the same carbapenemases detected earlier in Finland from a patient previously hospitalised in Russia, yet there is no epidemiological link between the Finnish case and the outbreak in Germany.

K. pneumoniae ST307 is a high-risk clone expanding globally, including in the EU/EEA. The specific German outbreak strain carries virulence markers associated with increased ability to cause disease. Genetic characteristics related to a potential survival advantage in the environment have also been described for *K. pneumoniae* ST307. The combination of extensive antimicrobial resistance, increased virulence and capacity to persist in the environment result in a high risk for dissemination and future healthcare-associated outbreaks of this *K. pneumoniae* ST307 outbreak strain in hospitals and other healthcare settings. By contrast, the risk of transmission for individuals outside healthcare settings is low. Enhanced control measures have been implemented in the involved German hospitals, and no further cases have been detected since the end of September 2019.

The highly virulent and resistant *K. pneumoniae* strain of this outbreak was introduced to the EU/EEA in at least two countries in 2019: Germany and in Finland. As not all EU/EEA countries have an effective screening system for carbapenemase-producing Enterobacteriaceae (CPE) in high-risk patients and may also lack the capacity to perform whole genome sequencing (WGS) – or do not routinely employ WGS on all carbapenem-resistant *K. pneumoniae* isolates collected at the national level – the number of such imported events may be considerably underestimated. In addition, several other high-risk clones of carbapenemase-producing *K. pneumoniae* have been spreading in hospitals and other healthcare settings in the EU/EEA in recent years. Hospital admissions of patients with previous hospitalisations, including prior hospitalisation in another country, are a daily occurrence in the EU/EEA, and the risk for further introduction of such high-risk clones of *K. pneumoniae* to hospitals in the EU/EEA, possibly resulting in other hospital outbreaks, is therefore high.

This outbreak also highlights the concomitant increase in virulence, transmissibility and antimicrobial resistance among certain *K. pneumoniae* strains, which are posing a considerably higher risk to human health than has

Suggested citation: European Centre for Disease Prevention and Control. Outbreak of carbapenemase-producing (NDM-1 and OXA-48) and colistin-resistant *Klebsiella pneumoniae* ST307, north-east Germany, 2019. 28 October 2019. ECDC: Stockholm; 2019.

previously been the case with the broader *K. pneumoniae* population. Early detection of such strains and close cooperation between clinicians and public health services are crucial to avoid spread into the EU patient population. There is a need for increased capacity in the EU/EEA to support outbreak investigations and surveillance with real-time WGS to identify high-risk clones and to implement enhanced control measures in order to avoid further spread.

Event background

Outbreak investigation in Germany

Germany has reported an outbreak of NDM-1- and OXA-48-co-producing *K. pneumoniae* with additional resistance to colistin and belonging to lineage ST307. Three hospitals and one rehabilitation clinic in Mecklenburg-Western Pomerania in the north-east of Germany were affected. Between June and September 2019, 17 cases were reported to the German mandatory notification system for carbapenem-resistant Enterobacteriaceae (CRE). Six of the 17 cases presented with clinical symptoms of infection (sepsis, pneumonia, urinary tract infection), while 11 were determined to be carriers. The first three cases, reported at the end of June 2019, were hospitalised in the intensive care unit (ICU) of a university hospital. All but one of the following cases were hospitalised at the same university hospital, with a link in place and time (overlapping stays in the same ward). The only reported case without admission to the university hospital had contact – at another hospital – with a patient who had previously been admitted to the same university hospital. Environmental and epidemiological investigations suggest that one of the cases may also be explicable by endoscopy with a contaminated device in which the outbreak strain was also detected (preliminary results). Apart from that, the outbreak clone could not be detected in the environment, despite extensive sampling. Thus, the most likely primary mode of transmission is considered to be patient-to-patient transmission. The mode of introduction of the outbreak strain to the university hospital has not yet been determined. Epidemiologic investigations are ongoing.

The *K. pneumoniae* outbreak strain was resistant to penicillins (piperacillin-tazobactam, temocillin), cephalosporins including combinations with beta-lactamase inhibitors (cefotaxime, ceftazidime, ceftazidime-avibactam, ceftolozane-tazobactam and cefepime), carbapenems (imipenem, meropenem, ertapenem, doripenem), aztreonam, fluoroquinolones (ciprofloxacin and levofloxacin), aminoglycosides (amikacin, gentamicin and tobramycin), fosfomycin, trimethoprim-sulfamethoxazole and colistin. It was only susceptible to chloramphenicol, tigecycline and cefiderocol; the latter is not yet approved for use in the EU/EEA. Pulsed-field gel electrophoresis (PFGE) and WGS results indicate clonal relatedness of the isolates collected from the cases.

According to national antimicrobial resistance surveillance data for 2018, resistance to carbapenems in *K. pneumoniae* is rare in Germany, and only 0.4% of *K. pneumoniae* isolates were reported as non-susceptible to meropenem. The antimicrobial resistance data reported from north-east Germany show even lower levels of resistance, with 0.2% of isolates non-susceptible to meropenem [1]. This is the first outbreak of *K. pneumoniae* harbouring both NDM-1 and OXA-48 carbapenemases, and the first outbreak with the emerging high-risk clone ST307 reported in Germany.

The measures implemented for control of the outbreak included systematic rectal screening programmes to identify carriers, enhanced barrier precautions such as patient cohorting, contact precautions and reduction of bed occupancy. The systematic rectal screening programme with both culture- and PCR-based methods included a) screening of all patients (at least once) on all wards of the affected institutions, and b) regular screenings (at least once per week) of patients on wards where a case had been detected. Local public health authorities, and state/national authorities are working together with hospital staff to control the outbreak. Local hospitals and the public were informed by a press release and a publication in the national epidemiological bulletin of the Robert Koch Institute [2]. No additional case has been detected since the end of September 2019.

Molecular investigation

The genome of the outbreak strain was compared with the genomes of other *K. pneumoniae* isolates containing both NDM-1 and OXA-48 carbapenemases in order to characterise the outbreak strain, investigate possible cross-border transmission, and narrow down the origin of the outbreak strain. This comparison included 23 genomes available in the public domain and 78 genomes positive for the genes encoding for NDM-1 and OXA-48, shared from their national collections by Belgium, Denmark, Finland, France, Ireland, Norway, the Netherlands, Slovenia, Spain, Sweden and the UK. The outbreak strain reported from Germany belonged to ST307 and contained the virulence genes encoding for aerobactin and yersiniabactin, resulting in a virulence score of 4/5; it also contained both allele variants for the regulator of the mucoid phenotype (*rmpA/rmpA2*) [3]. Mobile colistin resistance (*mcr*) genes have not been detected in the outbreak strain. The outbreak strain clustered with an isolate from the Finnish collection, with 0 allelic differences based on the Institut Pasteur core gene scheme. The Finnish ST307 isolate also contained the same virulence genes and was isolated in 2019 from a patient with prior hospitalisation in Saint Petersburg, Russia. Another *K. pneumoniae* isolate from Marseille, France, containing the genes encoding NDM-1

and OXA-48, which was publicly available, also belonged to ST307. However, this isolate was not closely related to the German outbreak strain based on virulence gene content and core genome MLST.

Disease background

Disease characteristics

For information on carbapenem-resistant Enterobacteriaceae (CRE) in general, please refer to the ECDC Rapid Risk Assessment on Carbapenem-resistant Enterobacteriaceae – second update [4]. The specific characteristics of the German *K. pneumoniae* outbreak strain, i.e. production of the two carbapenemases NDM-1 and OXA-48, additional resistance to colistin, and belonging to ST307, are described below.

NDM is a metallo-beta-lactamase (MBL) able to hydrolyse almost all beta-lactams, including carbapenems, and not inhibited by approved beta-lactamase inhibitors. NDM does not hydrolyse aztreonam. Since its first description in 2008 from a *K. pneumoniae* strain isolated from a patient repatriated to Sweden after hospitalisation in New Delhi, India, NDM-positive strains have been causing healthcare-associated outbreaks worldwide. So far, more than twenty NDM variants have been identified in various bacterial species responsible for healthcare-associated infections and primarily from the Enterobacteriaceae family, *Acinetobacter* spp. and *Pseudomonas* spp. [5,6].

Oxacillinase-48 (OXA-48) is a serine-beta-lactamase with hydrolytic activity against carbapenems and penicillins, but low or negligible activity against extended-spectrum cephalosporins. It was first identified in Turkey in 2001 [7]. In the 2015 *European survey of carbapenemase-producing Enterobacteriaceae* (EuSCAPE), four countries reported regional spread (Croatia, Germany, Ireland and Italy), four countries reported interregional spread (Belgium, France, Romania and Spain), and two countries (Malta and Turkey) reported an endemic situation of OXA-48 producing Enterobacteriaceae [8]. Both, NDM-1 and OXA-48, are often associated with the presence of other beta-lactamases such as extended-spectrum beta-lactamases (ESBL) or AmpC beta-lactamases.

Colistin is a polymyxin antibiotic interacting with lipopolysaccharides in the outer cell membrane. It is used as a last-line option for the treatment of CRE, but mutations within chromosomal genes leading to resistance to colistin may develop during treatment with this antibiotic. The recently described plasmid-mediated colistin resistance genes (*mcr*) may transmit colistin resistance between bacteria and increase the risk of spread of colistin resistance. However, chromosomal mutations predominate in colistin-resistant *K. pneumoniae*. Greece, Italy, Portugal and Spain are the EU/EEA countries with the highest consumption of polymyxins, including colistin in the hospital sector [9]. Resistance to polymyxins is increasingly common in parts of the EU/EEA. The EuSCAPE survey showed that in 2013–2014, 43% of the included carbapenemase-producing *K. pneumoniae* isolates from Italy were resistant to colistin [10]. In Greece, a substantial increase of colistin resistance in carbapenemase-producing *K. pneumoniae* was reported: from 0% colistin resistance in 2002 to 26.9% in 2016 [11].

K. pneumoniae ST307 is an internationally emerging high-risk clone in healthcare-associated outbreaks. Carbapenem resistance in ST307 in previous studies was mostly mediated by KPC-2 and KPC-3 [12]. Most isolates also carried the ESBL CTX-M-15 [13]. A gene cluster for glycogen synthesis and increased resistance to complement-mediated killing in *K. pneumoniae* ST307 is considered to possibly enhance its survival outside the host and in the environment conferring a survival advantage compared to other *K. pneumoniae* lineages [12,14].

The genome of the outbreak strain contains the two virulence genes yersiniabactin and aerobactin. In the animal model, yersiniabactin promotes respiratory tract infections with *K. pneumoniae* [15]. In *K. pneumoniae* strain collections from humans, the presence of yersiniabactin was significantly associated with isolates recovered from invasive infections such as liver abscess and bloodstream infection [16]. Yersiniabactin has also been shown to be associated with mobile genetic elements that are highly transmissible in the *K. pneumoniae* population [16]. Insertion of these yersiniabactin-containing mobile genetic elements has frequently been detected in multidrug-resistant isolates of *K. pneumoniae* ST258 and other high-risk clones that are already adapted to hospitals [16]. This finding highlights the substantial risk for further convergence of virulence and resistance and the emergence of *K. pneumoniae* clones of higher risk to human health than the broader *K. pneumoniae* population [16]. The outbreak strain received a score of 4/5 regarding virulence genes that contribute to hypervirulence in *K. pneumoniae* [3].

Risk assessment questions

What is the risk for interregional and cross-border spread of the carbapenemase-producing (NDM-1 and OXA-48) and colistin-resistant *K. pneumoniae* ST307 outbreak strain in the EU/EEA?

ECDC risk assessment for the EU/EEA

Frequency of occurrence

K. pneumoniae is one of the most common pathogens responsible for healthcare-associated infections. According to ECDC surveillance data, *K. pneumoniae* was the third most common pathogen in pneumonia, bloodstream infections and urinary tract infections acquired in European ICUs [17]. In the EU/EEA, the percentage of carbapenem-resistant isolates varies among countries, but is generally increasing [4]. Carbapenem-resistant *K. pneumoniae* isolates are rare in Germany and even rarer in the north-eastern part of the country. Outbreaks of NDM-1- and OXA-48-co-producing *K. pneumoniae* have not previously been reported from Germany.

The *K. pneumoniae* strain of the current outbreak is characterised by a rare combination of several high-risk factors. Firstly, ST307 is an internationally emerging high-risk clone that has previously been reported from several European countries including France, Hungary, Italy, the Netherlands, Norway, Serbia, Spain and the United Kingdom [12,13,18-22], but so far without the combination of resistance mechanisms (NDM-1 and OXA-48 carbapenemases combined with colistin resistance) as seen in the current outbreak. This is the first outbreak of *K. pneumoniae* ST307 reported from Germany.

Secondly, only a few cases of *K. pneumoniae* producing both NDM-1 and OXA-48 carbapenemases have been previously reported in the EU/EEA. Several unrelated lineages have been implicated in these cases. Outbreaks or single cases of such NDM-1- and OXA-48-co-producing *K. pneumoniae* have been reported from Greece (ST11) [23], Italy (ST3366 and ST3367) [24,25], Slovenia (NDM subtype not reported; ST437) [26], Spain (ST147, SLV_ST15, DLV_ST437) [27-29] and the United Kingdom (ST11) [30]. A case from Switzerland (ST11) was reported as imported from Serbia [31]. Additional resistance to colistin in an NDM-1- and OXA-48-co-producing *K. pneumoniae* ST147 has been documented in a hospital outbreak in Barcelona, Spain [28,29]. Another hospital outbreak with a comparable resistance pattern and high associated mortality recently occurred in Turkey [32]. In September 2019, a case of a patient with osteitis caused by a NDM-1- and OXA-48-co-producing *K. pneumoniae* ST307 isolate was reported from Marseille, France [33]. The involved strain was susceptible to colistin, and the patient was successfully treated with a combination of colistin, fosfomycin and doxycycline. This was the first published case with the combination of ST307, NDM-1 and OXA-48 in the EU/EEA. Another ST307 isolate co-producing NDM-1 and OXA-48 was reported from China [34].

NDM-1- and OXA-48-co-producing *K. pneumoniae* isolates of other sequence types were also documented from Egypt (ST not reported) [35], India (ST not available) [36], Iran (ST11, ST893) [37], Jordan (ST101) [38], Morocco (ST not available) [39], Saudi Arabia (ST152, ST199 and ST348) [40-42], Tunisia (ST11) [43-45], Turkey (ST11) [32,46-49], the United Arab Emirates (ST14, ST1318) [41,50-52] and Yemen (ST309) [53].

Risk for transmission and outbreaks in healthcare settings

Hospital outbreaks with NDM-1- and OXA-48-co-producing *K. pneumoniae* involving 18 patients in Slovenia [26] and more than 81 patients in Barcelona, Spain, have been reported [28,29]. Transmission within and between healthcare institutions has frequently been reported for carbapenemase-producing Enterobacteriaceae (CPE) and is not limited to any specific type of carbapenemase [4]. Patient-to-patient transmission of NDM-1- and OXA-48-co-producing *K. pneumoniae* was reported from Barcelona, Spain [28], and was also the most likely mode of transmission in the Slovenian outbreak [26]. ICU stays were identified as the main sources of outbreaks in Iran [37] and Turkey [32].

The risk of transmission and spread between healthcare institutions is especially high if patient carriage of the strain remains undetected. No further transmission outside the initially affected hospital was documented in Slovenia [26]. But in the German outbreak described in this Rapid Risk Assessment, the strain spread within one month of detection of the first case via patient transfers to three other healthcare institutions, leading to increased challenges for outbreak control. As carbapenemases including NDM-1 and OXA-48 are usually plasmid-encoded, the genes encoding for these resistance mechanisms are transferable between bacteria, including the bacteria present in the human microbiome. Thus, there is a high risk of dissemination and future healthcare-associated outbreaks of Enterobacteriaceae with these resistance mechanisms. So far, there is a low risk of transmission for individuals outside of healthcare settings.

Risk for cross-border spread

This particular highly virulent and resistant outbreak strain has been detected in the EU/EEA at least twice in 2019, once in Germany and once in Finland. As not all EU/EEA countries have an effective screening system for CPE in high-risk patients and may also lack the capacity to perform WGS – or do not routinely employ WGS on all carbapenem-resistant *K. pneumoniae* isolates collected at the national level – the number of events may be considerably underestimated.

The Finnish isolate was recovered from a patient with previous hospitalisation in Russia. No evidence for cross-border transmission was noted in the outbreak of NDM-1- and OXA-48-co-producing *K. pneumoniae* reported from Barcelona [28], but the Romanian patient with NDM-1- and OXA-48-co-producing *K. pneumoniae* ST307 who was treated in Marseille, France, had previously been hospitalised in Bulgaria. Further, importation of NDM-1- and OXA-48-co-producing *K. pneumoniae* from Serbia to Switzerland has previously been reported, and a patient previously hospitalised in Serbia was suspected to be the index case in the Slovenian outbreak [26,31]. Thus, the introduction of NDM-1- and OXA-48-co-producing, colistin-resistant *K. pneumoniae* may occur from any EU/EEA or other country.

The risk for infection is probably higher for individuals who were hospitalised in countries that report high prevalence of NDM-1-producing, OXA-48-producing or colistin-resistant *K. pneumoniae*, especially countries that have previously reported outbreaks of NDM-1- and OXA-48-co-producing *K. pneumoniae*. As strains of *K. pneumoniae* producing both NDM-1 and OXA-48 seem to be diverse, WGS may be useful in supporting other evidence of cross-border spread.

K. pneumoniae ST307 carries genes that have been reported to provide a survival advantage in the environment, such as those encoding for glycogen synthesis. *K. pneumoniae* ST307 is spreading globally and has been reported to spread rapidly once introduced to a hospital [12,13,54]. In addition, extensive drug resistance as seen in the outbreak strain reported from Germany likely provides an additional survival advantage in a hospital with an overall high level of consumption of antibiotics, in particular carbapenems and colistin. Thus, the risk of other introductions of the same strain in hospitals in the EU/EEA is high, and, in the absence of appropriate screening or other mitigation measures, likely to cause additional hospital outbreaks.

Limited treatment options and mortality

Carbapenems are a first-line treatment for infections with ESBL-producing *K. pneumoniae*. However, the widespread use of carbapenems has led to selection pressure and facilitated the spread of carbapenem-resistant strains, for which colistin is one of the last treatment options. Additional colistin resistance in carbapenem-resistant *K. pneumoniae*, such as the outbreak strain reported from Germany, leaves few remaining treatment options, among them tigecycline and fosfomycin [55,56].

However, suboptimal treatment outcomes [57,58] or the risk of rapid emergence of resistance [59] make these two remaining options suboptimal choices for treatment. In a Spanish study, a patient survival benefit was noted for combination therapy compared with monotherapy in patients receiving combinations of fosfomycin, gentamicin and/or tigecycline against carbapenem- and colistin-resistant KPC-producing isolates [60]. Combinations of a beta-lactam with a new beta-lactamase inhibitor such as ceftazidime-avibactam [61] or meropenem-vaborbactam [62] may be suitable options for the treatment of infections with Enterobacteriaceae producing certain carbapenemases such as KPC or, in the case of ceftazidime-avibactam, OXA-48, but they are not effective for *K. pneumoniae* or other Enterobacteriaceae producing MBLs such as NDM-1. However, MBLs such as NDM-1 usually do not hydrolyze aztreonam, a monobactam. Unfortunately, MBL production is usually associated with a range of other mechanisms that confer resistance to beta-lactams, including to aztreonam. The use of beta-lactamase inhibitors, such as avibactam or vaborbactam, may re-establish susceptibility to aztreonam [63]. The combination of aztreonam and amoxicillin-clavulanic acid may also restore aztreonam susceptibility in MBL-producing Enterobacteriaceae [64]. However, fixed combinations of aztreonam and avibactam (or other beta-lactamase-inhibitors) are currently not approved for use in the EU/EEA or in the USA.

There are only a few clinical reports providing specific data on the treatment of infections with colistin-resistant NDM-1- and OXA-48-co-producing *K. pneumoniae*. In Turkey, mortality of patients infected with NDM-1- and OXA-48-co-producing *K. pneumoniae* who were treated with colistin and meropenem was 100% [32]. In an outbreak of NDM-1- and OXA-48-co-producing *K. pneumoniae* in Barcelona, Spain, successful therapy with a combination of ceftazidime-avibactam plus aztreonam was reported in 6 out 10 patients [29]. In vitro studies also suggest the effectiveness of ceftazidime-avibactam or amoxicillin-clavulanic acid combined with aztreonam for the treatment of NDM- and OXA-48-co-producing Enterobacteriaceae infections [64-68].

The activity of cefiderocol against OXA-48-like-positive isolates and against most NDM-positive isolates has been shown *in vitro* [69]. The strain of the current outbreak was reported to be susceptible to cefiderocol (MIC 2mg/L). Phase III clinical trials of cefiderocol for the treatment of carbapenem-resistant gram-negative infections (EudraCT: 2015-004703-23; ClinicalTrials.gov: NCT02714595) have been completed, but the results are not yet published.

Effectiveness of control measures

The Slovenian outbreak of NDM-1- and OXA-48-co-producing *K. pneumoniae* was successfully controlled by cohorting of CPE carriers, systematic rectal screening of contact patients, pre-emptive isolation until screening results were available, assignment of dedicated healthcare workers, tagging of patients and contacts in the hospital's information system, restricted transfers of patients to other wards, a strict cleaning protocol for patients' rooms after discharge of CPE-positive cases, and education campaigns on infection control practices [26]. For further details on the general effectiveness of control measures for CRE, please refer to the ECDC Rapid Risk Assessment on Carbapenem-resistant Enterobacteriaceae – second update, 26 September 2019 [4] and the WHO Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in healthcare facilities [70].

Options for response

For options for response, please refer to the ECDC Rapid Risk Assessment on Carbapenem-resistant Enterobacteriaceae – second update, 26 September 2019 [4].

Source and date of request

ECDC round-table decision, 8 October 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.

References

1. Robert Koch Institut. Datenbank Resistenzübersicht 2018. Berlin: RKI; 2019 [Internet; cited 14 Oct 2019]. Available from: https://ars.rki.de/Content/Database/ResistanceOverview.aspx.
2. Robert Koch Institut. Information zum Auftreten von *Klebsiella pneumoniae* mit OXA-48 und NDM-1 Carbapenemasen und Colistinresistenz in Mecklenburg-Vorpommern. Epidemiologisches Bulletin. 2019 2019(40).
3. Kleborate. Available from: https://github.com/katholt/Kleborate#virulence-loci.
4. European Centre for Disease Prevention and Control. Carbapenem-resistant Enterobacteriaceae – second update. Stockholm: ECDC; 2019. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/carbapenem-resistant-enterobacteriaceae-risk-assessment-rev-2.pdf.
5. Wu W, Feng Y, Tang G, Qiao F, McNally A, Zong Z. NDM Metallo-beta-Lactamases and Their Bacterial Producers in Health Care Settings. Clin Microbiol Rev. 2019 Mar 20;32(2).
6. U.S. National Library of Medicine. Bacterial Antimicrobial Resistence Reference Gene Database [23/10/2019]. Available from: https://www.ncbi.nlm.nih.gov/pathogens/isolates#/refgene/NDM.
7. Poirel L, Heritier C, Tolun V, Nordmann P. Emergence of oxacillinase-mediated resistance to imipenem in Klebsiella pneumoniae. Antimicrob Agents Chemother. 2004 Jan;48(1):15-22.
8. Albiger B, Glasner C, Struelens MJ, Grundmann H, Monnet DL. Carbapenemase-producing Enterobacteriaceae in Europe: assessment by national experts from 38 countries, May 2015. Euro Surveill [Internet]. 2015 Nov 12; 20(45):[pii=30062 p.]. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21300.
9. European Centre for Disease Prevention and Control. Antimicrobial Consumption Database. Available from: https://www.ecdc.europa.eu/en/antimicrobial-consumption/surveillance-and-disease-data/database.
10. Monaco M, Giani T, Raffone M, Arena F, Garcia-Fernandez A, Pollini S, et al. Colistin resistance superimposed to endemic carbapenem-resistant Klebsiella pneumoniae: a rapidly evolving problem in Italy, November 2013 to April 2014. Euro Surveill. 2014 Oct 23;19(42).
11. Tansarli GS, Papaparaskevas J, Balaska M, Samarkos M, Pantazatou A, Markogiannakis A, et al. Colistin resistance in carbapenemase-producing Klebsiella pneumoniae bloodstream isolates: Evolution over 15 years and temporal association with colistin use by time series analysis. Int J Antimicrob Agents. 2018 Sep;52(3):397-403.
12. Villa L, Feudi C, Fortini D, Brisse S, Passet V, Bonura C, et al. Diversity, virulence, and antimicrobial resistance of the KPC-producing Klebsiella pneumoniae ST307 clone. Microbial genomics. 2017 Apr;3(4):e000110.
13. Wyres KL, Hawkey J, Hetland MAK, Fostervold A, Wick RR, Judd LM, et al. Emergence and rapid global dissemination of CTX-M-15-associated Klebsiella pneumoniae strain ST307. J Antimicrob Chemother. 2019 Mar 1;74(3):577-81.
14. Somorin Y, Abram F, Brennan F, O'Byrne C. The General Stress Response Is Conserved in Long-Term Soil-Persistent Strains of Escherichia coli. Appl Environ Microbiol. 2016 Aug 1;82(15):4628-40.
15. Bachman MA, Oyler JE, Burns SH, Caza M, Lepine F, Dozois CM, et al. Klebsiella pneumoniae yersiniabactin promotes respiratory tract infection through evasion of lipocalin 2. Infect Immun. 2011 Aug;79(8):3309-16.
16. Lam MMC, Wick RR, Wyres KL, Gorrie CL, Judd LM, Jenney AWJ, et al. Genetic diversity, mobilisation and spread of the yersiniabactin-encoding mobile element ICEKp in Klebsiella pneumoniae populations. Microbial genomics. 2018 Sep;4(9).
17. European Centre for Disease Prevention and Control. Healthcare-associated infections acquired in intensive care units - Annual Epidemiological Report for 2017. 2019.
18. Hennequin C, Chlilek A, Beyrouthy R, Bonnet R, Robin F. Diversity of DHA-1-encoding plasmids in Klebsiella pneumoniae isolates from 16 French hospitals. J Antimicrob Chemother. 2018 Nov 1;73(11):2981-9.
19. Domokos J, Damjanova I, Kristof K, Ligeti B, Kocsis B, Szabo D. Multiple Benefits of Plasmid-Mediated Quinolone Resistance Determinants in Klebsiella pneumoniae ST11 High-Risk Clone and Recently Emerging ST307 Clone. Front Microbiol. 2019;10:157.
20. Ruiz-Garbajosa P, Hernandez-Garcia M, Beatobe L, Tato M, Mendez MI, Grandal M, et al. A single-day point-prevalence study of faecal carriers in long-term care hospitals in Madrid (Spain) depicts a complex clonal and polyclonal dissemination of carbapenemase-producing Enterobacteriaceae. J Antimicrob Chemother. 2016 Feb;71(2):348-52.
21. Sanchez-Lopez J, Canton R. Current status of ESKAPE microorganisms in Spain: Epidemiology and resistance phenotypes. Rev Esp Quimioter. 2019 Sep;32 Suppl 2:27-31.
22. Novovic K, Trudic A, Brkic S, Vasiljevic Z, Kojic M, Medic D, et al. Molecular Epidemiology of Colistin-Resistant, Carbapenemase-Producing Klebsiella pneumoniae in Serbia from 2013 to 2016. Antimicrob Agents Chemother. 2017 May;61(5).

23. Protonotariou E, Meletis G, Chatzopoulou F, Malousi A, Chatzidimitriou D, Skoura L. Emergence of Klebsiella pneumoniae ST11 co-producing NDM-1 and OXA-48 carbapenemases in Greece. Journal of global antimicrobial resistance. 2019 Sep 4;19:81-2.
24. Gona F, Bongiorno D, Aprile A, Corazza E, Pasqua B, Scuderi MG, et al. Emergence of two novel sequence types (3366 and 3367) NDM-1- and OXA-48-co-producing K. pneumoniae in Italy. Eur J Clin Microbiol Infect Dis. 2019 Sep;38(9):1687-91.
25. Monaco F, Mento GD, Cuscino N, Conaldi PG, Douradinha B. Infant colonisation with Escherichia coli and Klebsiella pneumoniae strains co-harbouring blaOXA-48 and blaNDM-1 carbapenemases genes: a case report. Int J Antimicrob Agents. 2018 Jul;52(1):121-2.
26. Pirs M, Cerar Kisek T, Krizan Hergouth V, Seme K, Mueller Premru M, Jeverica S, et al. Successful control of the first OXA-48 and/or NDM carbapenemase-producing Klebsiella pneumoniae outbreak in Slovenia 2014-2016. J Hosp Infect. 2019 Feb;101(2):142-9.
27. Perez-Vazquez M, Sola Campoy PJ, Ortega A, Bautista V, Monzon S, Ruiz-Carrascoso G, et al. Emergence of NDM-producing Klebsiella pneumoniae and Escherichia coli in Spain: phylogeny, resistome, virulence and plasmids encoding blaNDM-like genes as determined by WGS. J Antimicrob Chemother. 2019 Sep 3.
28. Càmara JS, E.; Cubero, M.; Tubau, F.; Gavaldà, L.; Ardanuy, C.;, Pujol, M.; Domínguez, M.A. Outbreak due to an extensively drug-resistant Klebsiella pneumoniae harbouring blaNDM-1 and/or blaOXA-48 in Barcelona, Spain. European Congress of Clinical Microbiology and Infectious Diseases; Vienna: ESCMID; 2017.
29. Shaw E, Rombauts A, Tubau F, Padulles A, Camara J, Lozano T, et al. Clinical outcomes after combination treatment with ceftazidime/avibactam and aztreonam for NDM-1/OXA-48/CTX-M-15-producing Klebsiella pneumoniae infection. J Antimicrob Chemother. 2018 Apr 1;73(4):1104-6.
30. Findlay J, Hopkins KL, Alvarez-Buylla A, Meunier D, Mustafa N, Hill R, et al. Characterization of carbapenemase-producing Enterobacteriaceae in the West Midlands region of England: 2007-14. J Antimicrob Chemother. 2017 Apr 1;72(4):1054-62.
31. Seiffert SN, Marschall J, Perreten V, Carattoli A, Furrer H, Endimiani A. Emergence of Klebsiella pneumoniae co-producing NDM-1, OXA-48, CTX-M-15, CMY-16, QnrA and ArmA in Switzerland. Int J Antimicrob Agents. 2014 Sep;44(3):260-2.
32. Guducuoglu H, Gursoy NC, Yakupogullari Y, Parlak M, Karasin G, Sunnetcioglu M, et al. Hospital Outbreak of a Colistin-Resistant, NDM-1- and OXA-48-Producing Klebsiella pneumoniae: High Mortality from Pandrug Resistance. Microbial drug resistance (Larchmont, NY). 2018 Sep;24(7):966-72.
33. Baron SA, Cassir N, Mekideche T, Mlaga KD, Brouqui P, Rolain JM. Successful treatment and digestive decolonisation of a patient with osteitis caused by a carbapenemase-producing Klebsiella pneumoniae isolate harbouring both NDM-1 and OXA-48 enzymes. Journal of global antimicrobial resistance. 2019 Sep;18:225-9.
34. Xie L, Dou Y, Zhou K, Chen Y, Han L, Guo X, et al. Coexistence of blaOXA-48 and Truncated blaNDM-1 on Different Plasmids in a Klebsiella pneumoniae Isolate in China. Front Microbiol. 2017;8:133.
35. Khalifa HO, Soliman AM, Ahmed AM, Shimamoto T, Hara T, Ikeda M, et al. High Carbapenem Resistance in Clinical Gram-Negative Pathogens Isolated in Egypt. Microbial drug resistance (Larchmont, NY). 2017 Oct;23(7):838-44.
36. Jaggi N, Chatterjee N, Singh V, Giri SK, Dwivedi P, Panwar R, et al. Carbapenem resistance in Escherichia coli and Klebsiella pneumoniae among Indian and international patients in North India. Acta Microbiol Immunol Hung. 2019 Sep 1;66(3):367-76.
37. Solgi H, Badmasti F, Giske CG, Aghamohammad S, Shahcheraghi F. Molecular epidemiology of NDM-1- and OXA-48-producing Klebsiella pneumoniae in an Iranian hospital: clonal dissemination of ST11 and ST893. J Antimicrob Chemother. 2018 Jun 1;73(6):1517-24.
38. Aqel AA, Findlay J, Al-Maayteh M, Al-Kaabneh A, Hopkins KL, Alzoubi H, et al. Characterization of Carbapenemase-Producing Enterobacteriaceae from Patients in Amman, Jordan. Microbial drug resistance (Larchmont, NY). 2018 Oct;24(8):1121-7.
39. Barguigua A, El Otmani F, Lakbakbi El Yaagoubi F, Talmi M, Zerouali K, Timinouni M. First report of a Klebsiella pneumoniae strain coproducing NDM-1, VIM-1 and OXA-48 carbapenemases isolated in Morocco. APMIS. 2013 Jul;121(7):675-7.
40. Zaman TU, Alrodayyan M, Albladi M, Aldrees M, Siddique MI, Aljohani S, et al. Clonal diversity and genetic profiling of antibiotic resistance among multidrug/carbapenem-resistant Klebsiella pneumoniae isolates from a tertiary care hospital in Saudi Arabia. BMC Infect Dis. 2018 May 3;18(1):205.
41. Al-Baloushi AE, Pal T, Ghazawi A, Sonnevend A. Genetic support of carbapenemases in double carbapenemase producer Klebsiella pneumoniae isolated in the Arabian Peninsula. Acta Microbiol Immunol Hung. 2018 Jun 1;65(2):135-50.
42. Zowawi HM, Sartor AL, Balkhy HH, Walsh TR, Al Johani SM, AlJindan RY, et al. Molecular characterization of carbapenemase-producing Escherichia coli and Klebsiella pneumoniae in the countries of the Gulf cooperation council: dominance of OXA-48 and NDM producers. Antimicrob Agents Chemother. 2014 Jun;58(6):3085-90.

43. Dziri R, Ayari I, Barguellil F, Ouzari HI, El Asli MS, Klibi N. First Report of NDM and VIM Coproducing Klebsiella pneumoniae in Tunisia and Emergence of Novel Clones. Microbial drug resistance (Larchmont, NY). 2019 Jul 30.
44. Ben Helal R, Dziri R, Chedly M, Klibi N, Barguellil F, El Asli MS, et al. Occurrence and Characterization of Carbapenemase-Producing Enterobacteriaceae in a Tunisian Hospital. Microbial drug resistance (Larchmont, NY). 2018 Nov;24(9):1361-7.
45. Ben Nasr A, Decre D, Compain F, Genel N, Barguellil F, Arlet G. Emergence of NDM-1 in association with OXA-48 in Klebsiella pneumoniae from Tunisia. Antimicrob Agents Chemother. 2013 Aug;57(8):4089-90.
46. Cizmeci Z, Aktas E, Otlu B, Acikgoz O, Ordekci S. Molecular characterization of carbapenem- resistant Enterobacteriaceae yields increasing rates of NDM-1 carbapenemases and colistin resistance in an OXA-48-endemic area. J Chemother. 2017 Dec;29(6):344-50.
47. Karabay O, Altindis M, Koroglu M, Karatuna O, Aydemir OA, Erdem AF. The carbapenem-resistant Enterobacteriaceae threat is growing: NDM-1 epidemic at a training hospital in Turkey. Ann Clin Microbiol Antimicrob. 2016 Feb 9;15:6.
48. Kilic A, Baysallar M. The First Klebsiella pneumoniae Isolate Co-Producing OXA-48 and NDM-1 in Turkey. Ann Lab Med. 2015 May;35(3):382-3.
49. Alp E, Percin D, Colakoglu S, Durmaz S, Kurkcu CA, Ekincioglu P, et al. Molecular characterization of carbapenem-resistant Klebsiella pneumoniae in a tertiary university hospital in Turkey. J Hosp Infect. 2013 Jun;84(2):178-80.
50. Moubareck CA, Mouftah SF, Pal T, Ghazawi A, Halat DH, Nabi A, et al. Clonal emergence of Klebsiella pneumoniae ST14 co-producing OXA-48-type and NDM carbapenemases with high rate of colistin resistance in Dubai, United Arab Emirates. Int J Antimicrob Agents. 2018 Jul;52(1):90-5.
51. Dash N, Panigrahi D, Zarouni MA, Darwish D, Ghazawi A, Sonnevend A, et al. High incidence of New Delhi metallo-beta-lactamase-producing Klebsiella pneumoniae isolates in Sharjah, United Arab Emirates. Microbial drug resistance (Larchmont, NY). 2014 Feb;20(1):52-6.
52. Sonnevend A, Ghazawi A, Darwish D, AlDeesi Z, Kadhum AF, Pal T. Characterization of KPC-type carbapenemase-producing Klebsiella pneumoniae strains isolated in the Arabian Peninsula. J Antimicrob Chemother. 2015 May;70(5):1592-3.
53. Alsharapy SA, Gharout-Sait A, Muggeo A, Guillard T, Cholley P, Brasme L, et al. Characterization of Carbapenem-Resistant Enterobacteriaceae Clinical Isolates in Al Thawra University Hospital, Sana'a, Yemen. Microbial drug resistance (Larchmont, NY). 2019 Aug 9.
54. Castanheira M, Farrell SE, Wanger A, Rolston KV, Jones RN, Mendes RE. Rapid expansion of KPC-2-producing Klebsiella pneumoniae isolates in two Texas hospitals due to clonal spread of ST258 and ST307 lineages. Microbial drug resistance (Larchmont, NY). 2013 Aug;19(4):295-7.
55. Pontikis K, Karaiskos I, Bastani S, Dimopoulos G, Kalogirou M, Katsiari M, et al. Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria. Int J Antimicrob Agents. 2014 Jan;43(1):52-9.
56. Michalopoulos A, Virtzili S, Rafailidis P, Chalevelakis G, Damala M, Falagas ME. Intravenous fosfomycin for the treatment of nosocomial infections caused by carbapenem-resistant Klebsiella pneumoniae in critically ill patients: a prospective evaluation. Clin Microbiol Infect. 2010 Feb;16(2):184-6.
57. Shen F, Han Q, Xie D, Fang M, Zeng H, Deng Y. Efficacy and safety of tigecycline for the treatment of severe infectious diseases: an updated meta-analysis of RCTs. Int J Infect Dis. 2015 Oct;39:25-33.
58. Tasina E, Haidich AB, Kokkali S, Arvanitidou M. Efficacy and safety of tigecycline for the treatment of infectious diseases: a meta-analysis. Lancet Infect Dis. 2011 Nov;11(11):834-44.
59. Falagas ME, Athanasaki F, Voulgaris GL, Triarides NA, Vardakas KZ. Resistance to fosfomycin: Mechanisms, Frequency and Clinical Consequences. Int J Antimicrob Agents. 2019 Jan;53(1):22-8.
60. Machuca I, Gutierrez-Gutierrez B, Gracia-Ahufinger I, Rivera Espinar F, Cano A, Guzman-Puche J, et al. Mortality Associated with Bacteremia Due to Colistin-Resistant Klebsiella pneumoniae with High-Level Meropenem Resistance: Importance of Combination Therapy without Colistin and Carbapenems. Antimicrob Agents Chemother. 2017 Aug;61(8).
61. European Medicines Agency. Zavicefta - ceftazidime / avibactam2016. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004027/human_med_001993.jsp&mid=WC0b01ac058001d124.
62. European Medicines Agency. Vaborem -meropenem / vaborbactam. Amsterdam: EMA; 2018. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/vaborem.
63. Biagi M, Wu T, Lee M, Patel S, Butler D, Wenzler E. Searching for the Optimal Treatment for Metallo- and Serine-beta-Lactamase Producing Enterobacteriaceae: Aztreonam in Combination with Ceftazidime-avibactam or Meropenem-vaborbactam. Antimicrob Agents Chemother. 2019 Sep 30.
64. Emeraud C, Escaut L, Boucly A, Fortineau N, Bonnin RA, Naas T, et al. Aztreonam plus Clavulanate, Tazobactam, or Avibactam for Treatment of Infections Caused by Metallo-beta-Lactamase-Producing Gram-Negative Bacteria. Antimicrob Agents Chemother. 2019 May;63(5).

65. Pragasam AK, Veeraraghavan B, Shankar BA, Bakthavatchalam YD, Mathuram A, George B, et al. Will ceftazidime/avibactam plus aztreonam be effective for NDM and OXA-48-Like producing organisms: Lessons learnt from In vitro study. Indian J Med Microbiol. 2019 Jan-Mar;37(1):34-41.
66. Brennan-Krohn T, Kirby JE. Synergistic Combinations and Repurposed Antibiotics Active against the Pandrug-Resistant Klebsiella pneumoniae Nevada Strain. Antimicrob Agents Chemother. 2019 Sep;63(9).
67. Biedenbach DJ, Kazmierczak K, Bouchillon SK, Sahm DF, Bradford PA. In vitro activity of aztreonam-avibactam against a global collection of Gram-negative pathogens from 2012 and 2013. Antimicrob Agents Chemother. 2015 Jul;59(7):4239-48.
68. Karlowsky JA, Kazmierczak KM, de Jonge BLM, Hackel MA, Sahm DF, Bradford PA. In Vitro Activity of Aztreonam-Avibactam against Enterobacteriaceae and Pseudomonas aeruginosa Isolated by Clinical Laboratories in 40 Countries from 2012 to 2015. Antimicrob Agents Chemother. 2017 Sep;61(9).
69. Kazmierczak KM, Tsuji M, Wise MG, Hackel M, Yamano Y, Echols R, et al. In vitro activity of cefiderocol, a siderophore cephalosporin, against a recent collection of clinically relevant carbapenem-non-susceptible Gram-negative bacilli, including serine carbapenemase- and metallo-beta-lactamase-producing isolates (SIDERO-WT-2014 Study). Int J Antimicrob Agents. 2019 Feb;53(2):177-84.
70. Guidelines for the Prevention and Control of Carbapenem-Resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in Health Care Facilities. WHO Guidelines Approved by the Guidelines Review Committee. WHO: Geneva; 2017.