RAPID RISK ASSESSMENT

Regional outbreak of New Delhi metallo-beta-lactamase-producing carbapenem-resistant Enterobacteriaceae, Italy, 2018–2019

4 June 2019

Summary

A large outbreak of New Delhi metallo-beta-lactamase (NDM)-producing carbapenem-resistant Enterobacteriaceae (CRE) has been reported from the Tuscany region in Italy. Between November 2018 and May 2019, seven Tuscan hospitals notified a total of 350 cases. Due to its size and the resulting change in the epidemiology of CRE, the reported outbreak is a significant event, despite previous endemicity of *Klebsiella pneumoniae* carbapenamase (KPC)-producing CRE in this geographic area. The change in the type of carbapenemase further reduces treatment options because NDM-producing CRE are not susceptible to some of the new beta-lactam/beta-lactamase inhibitor combinations such as ceftazidime-avibactam and meropenem-vaborbactam.

Numerous reported outbreaks and examples of cross-border transmission of NDM-producing CRE in the European Union/European Economic Area (EU/EEA) demonstrate the transmission potential of NDM-producing CRE in European healthcare systems. Outbreaks such as the one in Tuscany present a risk for cross-border transmission and further spread to other EU/EEA countries, especially since the affected area is a major tourist destination. Given the previous rapid establishment of KPC-producing CRE in Italy (which resulted in an endemic situation), the risk for further spread of NDM-producing CRE from the current outbreak is considered to be high for Italy and moderate for cross-border spread to other EU/EEA countries.

Sporadic cases of community acquisition of NDM-producing CRE have also been described for other European countries. However, the introduction and dissemination of these bacteria have mainly been associated with healthcare settings. Therefore, the risk of acquisition of NDM-producing CRE related to this outbreak is likely restricted to persons with recent healthcare contact.

Event background

Italy reported an outbreak of NDM-producing CRE affecting seven hospitals in the northwestern area of Tuscany, with 350 cases reported between November 2018 and 23 May 2019. Among these cases, there were 50 with bloodstream infection, 43 with isolation in the urine, 15 with isolation in respiratory tract samples and 242 with gastrointestinal tract carriage. The isolates are resistant to aminoglycosides but retain susceptibility to fosfomycin and colistin. The presence of NDM has been confirmed by molecular testing. Preliminary results of pulsed-field gel electrophoresis show that the involved NDM-producing *K. pneumoniae* isolates are mostly clonal. The source of the outbreak remains to be determined. In the same geographic area, KPC-producing CRE have been endemic since

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early 2010, while metallo-beta-lactamase (MBL)-producing CRE such as VIM- or NDM-producing CRE had remained sporadic. Data from the Italian surveillance system for bloodstream infections due to carbapenemase-producing Enterobacteriaceae indicate an increase of NDM-producing *K. pneumoniae* bloodstream infection cases in Italy between November 2018 and May 2019. Cases are mainly clustered in Tuscany (19 cases) while sporadic cases were reported in four other regions: Liguria (two cases), Emilia Romagna, Lazio and Piedmont (one case each). It is unknown whether these cases are related to those reported from Tuscany. However, these results should be interpreted with caution, since genotypic information is only available for 35% of isolates.

Measures taken for the control of this outbreak include further epidemiological analysis of reported cases, a survey of the practices of active surveillance for CRE carriage at the Tuscan hospitals, and a meeting with the hospital directors of the Tuscany region to convey information about the outbreak and reinforce infection control measures. Additional measures included further analyses of collected strains to confirm the resistance mechanism, clonal lineage profiling, and antimicrobial susceptibility testing for potentially active antibiotics.

Disease background

Disease characteristics

NDM is a metallo-beta-lactamase able to hydrolyse almost all beta-lactams, including carbapenems. Since its first description in 2008 from a *Klebsiella 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; 24 NDM variants have been identified in various bacterial species responsible for healthcare-associated infections from the *Enterobacteriaceae* family and from *Acinetobacter* spp. and *Pseudomonas* spp. [1].

Risk factors for acquisition of carbapenemase-producing CRE, including those producing NDM, include recent admissions to healthcare facilities, especially in regions with a high CRE prevalence, residence in long-term care facilities, surgical procedures and indwelling devices, as well as intensive care therapy and long duration of hospitalisation [2,3].

Epidemiology of NDM-producing CRE in the EU/EEA and Italy

After the initial report of NDM-1 from Sweden in 2008, Public Health England, concerned with the rapid increase in the number of human cases with NDM-1-producing CRE in hospitals across the UK, issued a national alert in July 2009 [4]. By November 2010, a survey distributed among 29 European countries showed that 13 had already identified and reported NDM-producing CRE cases [5,6]. The first reported outbreak in Europe occurred in a hospital in Bologna in northern Italy in 2011 [7]. In 2012, a large interregional outbreak of NDM-producing *K. pneumoniae* was reported in Poland [8], only a few months after a first case of NDM-1-producing *K. pneumoniae* was detected in a patient with previous travel history to Africa [9]. Most of the early cases with known travel history were shown to be associated with previous hospitalisation in the Indian subcontinent or in the Balkans [10-12].

In 2015, EuSCAPE (the European survey on carbapenem-producing Enterobacteriaceae) confirmed that NDM-producing CRE were spreading in the Balkan region, with large numbers of isolates collected in Montenegro, Serbia, and Greece [13]. In 2015, NDM was the third most frequent carbapenemase detected in the EU/EEA [13]. A national expert assessment indicated that a number of EU countries were facing outbreaks of NDM-producing CRE in hospitals located either in the same or different regions, suggesting autochthonous interinstitutional transmission [13,14].

After 2010, CRE became a major issue in Italy when KPC-producing *K. pneumoniae* became endemic due to rapid countrywide dissemination mostly caused by strains of clonal complex 258 [14,15]. Since 2010, the increase in the proportion of carbapenem resistance in invasive *K. pneumoniae* isolates has been documented by EARS-Net, the European Antimicrobial Resistance Surveillance Network. The latest EARS-Net data show that 29.7% of *K. pneumoniae* invasive isolates were carbapenem-resistant in 2017 [16]. There were also reports of NDM-producing CRE from Italy but their dissemination was still limited, and cases were mostly acquired abroad [14,17]. Even before the outbreak in Tuscany, this situation seemed to have changed, with reports of cases of NDM-producing Enterobacteraceae strains isolated from patients without travel history and with increasing numbers of NDM-positive strains [18,19].

Risk assessment questions

What is the EU/EEA risk for interregional and cross-border spread of NDM-producing CRE from the outbreak in Tuscany?

ECDC risk assessment for the EU/EEA

Due to its size and the resulting change in the epidemiology of CRE, the described outbreak with regional interinstitutional spread of NDM-producing CRE is a significant event, despite the previous endemicity of KPC-producing CRE in this geographic area. While international spread of KPC-producing *K. pneumoniae* has often been linked to *K. pneumoniae* clonal complex 258 (including sequence type (ST) 258, ST11, and closely related STs), the spread of NDM is generally less clonal than other carbapenemases and often mediated by plasmids [1,20]. This might complicate outbreak investigations and the tracing of further cases as isolates of different species and different STs within species might be part of the outbreak [21].

The type of carbapenemase (KPC vs NDM) is also relevant for treatment because NDM- and other MBL-producing CRE are not susceptible to some of the new beta-lactam/beta-lactamase inhibitor combinations such as ceftazidime-avibactam (CAZ-AVI) [22]. This leads to a further reduction of treatment choices for infected patients, and diagnostic and treatment protocols may have to be adapted accordingly. In addition, treatment with CAZ-AVI might lead to the replacement of CAZ-AVI-susceptible CRE strains such as KPC-producing CRE with CAZ-AVI-resistant strains, including NDM-producing CRE, as has been observed in other settings with high prevalence of VIM-producing CRE [23]. CRE infections have been shown to be associated with increased mortality in high-risk patients, such as stem cell transplant recipients in Italy [24]. While infections with carbapenem-resistant *K. pneumoniae* are typically also associated with high mortality in other patient populations [25-27], more specific data on NDM-producing *K. pneumoniae* are insufficient [1].

Multiple outbreaks of NDM-producing CRE that were difficult to control have recently been reported from other EU/EEA countries. The largest reported outbreak occurred in Greece and affected several hospitals and over 300 patients [28]. This outbreak was linked to the widespread dissemination of an ST11 NDM-1-producing *K. pneumoniae* clonal strain from the Balkan region [29,30]. Another example is an outbreak in Slovenia that involved 40 cases, two types of carbapenemase (NDM and OXA-48), and multiple Enterobacteriaceae species (mainly *K. pneumoniae* of two different STs, but also *E. coli* and other Enterobacteriaceae species) [21]. An outbreak of NDM-1-producing *K. pneumoniae* in Belgium affected 29 patients in two hospitals, with transmission between the hospitals linked to outpatient contact [31]. In the Netherlands, an outbreak of NDM-1-producing *K. pneumoniae* affected 26 patients [32]. In addition, 16 isolates of five other Enterobacteriaceae species harbouring the same plasmid were detected and considered as related to this outbreak [32].

The numerous reported outbreaks and examples of cross-border transmission of NDM-producing CRE in the EU/EEA [21,28,31,32] highlight the transmission potential of NDM-producing CRE in European healthcare systems. Outbreaks such as the one in Tuscany therefore present a risk for cross-border transmission and further spread to other EU/EEA countries. This risk may be higher when tourist destinations are affected. Given the rapid establishment of KPC-producing CRE in Italy in previous years and the resulting endemic situation [14], the risk for further spread of NDM-producing CRE from the current outbreak is considered high for Italy and moderate for cross-border spread to other EU/EEA countries. While sporadic cases of community acquisition have also been described in Europe [28], introduction and dissemination of NDM-producing CRE in Europe has mainly been associated with hospitals and other healthcare settings [21,28,31,32]. Therefore, the risk of acquisition of NDM-producing CRE related to this outbreak is likely restricted to persons with recent healthcare contact.

Options for response

Actions to prevent cross-border spread

Hospitals in EU/EEA countries should consider taking a detailed history of travels and hospitalisations for every patient at hospital admission. They should also consider performing pre-emptive isolation and screening for carriage of CRE, including NDM- and KPC-producing *K. pneumoniae*, at least in patients who were directly transferred from or hospitalised in countries with known high prevalence in the 12 months before admission, or in patients who were hospitalised in their own country in the 12 months before admission, but in a region or hospital with known high prevalence of CRE. However, screening every patient who was hospitalised in a foreign country in the 12 months before admission might be a more suitable option, as prevalence of CRE is difficult to monitor in some regions, and national prevalence might not always reflect the regional or local situation. Repeated screening of these patients during admission could also be considered. In case of patient transfer, good inter-facility communication is a key element to ensure effective measures to limit the spread of CRE in the receiving hospital.

Moreover, gathering reliable epidemiological data, notifying cases to public health authorities, and exchanging information are important activities to enable informed and coordinated actions by public health authorities across the EU/EEA. Public health authorities should issue notifications on the Early Warning and Response System (EWRS) where relevant, as per Article 9 of Decision No 1082/2013/EU on serious cross-border threats to health. The use of the Epidemic Intelligence System (EPIS) is encouraged to ensure transparent and timely sharing of information among participating public health authorities in order to detect public health threats at an early stage.

Actions to prevent transmission in healthcare facilities

Appropriate hand hygiene compliance is considered fundamental to all good infection prevention and control (IPC) programmes and the control of cross-transmission of many pathogens, including CRE [33]. Contact precautions are also an important component of the IPC measures necessary to control HAI and other infections. Contact precautions include appropriate patient placement, use of personal protective equipment (including gloves and gowns), limitation of transport and movement of patients, use of disposable or dedicated patient care equipment, and prioritisation of cleaning and disinfection of patient rooms.

Preventing transmission from CRE-positive patients

Enhanced control measures (for example contact precautions, isolation or cohorting) and a dedicated nursing staff should be considered for hospitalised patients with confirmed digestive tract CRE carriage or confirmed CRE infection. In addition, screening of contacts will enable early identification of carriers and implementation of control measures.

Preventing spread of CRE in specific wards/units

In units/wards where patients are at high risk of infection (e.g. intensive care units and onco-haematology units), pre-emptive isolation and active surveillance (screening) for CRE by rectal swab on admission should be considered, depending on the risk of digestive tract CRE carriage and the local prevalence of CRE. Regular review of appropriate device use is an important infection prevention measure in high-risk settings. The role of the environmental reservoir of epidemic CRE strains and/or carbapenemase-encoding plasmids should be investigated, and relevant control measures should be implemented accordingly. Compliance with environmental cleaning protocols for the immediate surroundings ('patient zone') of patients colonised or infected with CRE should be ensured.

Further control measures are outlined in the updated ECDC rapid risk assessment on carbapenem-resistant Enterobacteriaceae [34] and an ECDC guidance document [35].

Source and date of request

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Experts from WHO reviewed the risk assessment, but the views expressed in this document do not necessarily represent the views of WHO.

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

Disclaimer

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References

1. 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).
2. Janelle SJ, Kallen A, de Man T, Limbago B, Walters M, Halpin A, et al. Notes from the Field: New Delhi Metallo-beta-Lactamase-Producing Carbapenem-Resistant Enterobacteriaceae Identified in Patients Without Known Health Care Risk Factors - Colorado, 2014-2016. MMWR Morb Mortal Wkly Rep. 2016 Dec 16;65(49):1414-5.
3. de Jager P, Chirwa T, Naidoo S, Perovic O, Thomas J. Nosocomial Outbreak of New Delhi Metallo-beta-Lactamase-1-Producing Gram-Negative Bacteria in South Africa: A Case-Control Study. PLoS One. 2015;10(4):e0123337.
4. Health Protection Agency. Multi-resistant hospital bacteria linked to India and Pakistan. . London: Health Protection Agency; 2009. Available from: https://webarchive.nationalarchives.gov.uk/20140714084152/http:/www.hpa.org.uk/hpr/archives/2009/hpr2609.pdf.
5. European Centre for Disease Prevention and Control. Updated ECDC risk assessment on the spread of New Delhi metallo-beta-lactamase (NDM) and its variants within Europe. Stockholm: ECDC; 2011. Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/1111_TER_Risk-assessment-NDM.pdf.
6. Struelens MJ, Monnet DL, Magiorakos AP, Santos O'Connor F, Giesecke J. New Delhi metallo-beta-lactamase 1-producing Enterobacteriaceae: emergence and response in Europe. Euro Surveill. 2010 Nov 18;15(46).
7. Gaibani P, Ambretti S, Berlingeri A, Cordovana M, Farruggia P, Panico M, et al. Outbreak of NDM-1-producing Enterobacteriaceae in northern Italy, July to August 2011. Euro Surveill. 2011 Nov 24;16(47):20027.
8. Baraniak A, Izdebski R, Fiett J, Gawryszewska I, Bojarska K, Herda M, et al. NDM-producing Enterobacteriaceae in Poland, 2012-14: inter-regional outbreak of Klebsiella pneumoniae ST11 and sporadic cases. J Antimicrob Chemother. 2016 Jan;71(1):85-91.
9. Fiett J, Baraniak A, Izdebski R, Sitkiewicz I, Zabicka D, Meler A, et al. The first NDM metallo-beta-lactamase-producing Enterobacteriaceae isolate in Poland: evolution of IncFII-type plasmids carrying the bla(NDM-1) gene. Antimicrob Agents Chemother. 2014;58(2):1203-7.
10. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect Dis. 2010 Sep;10(9):597-602.
11. Mazzariol A, Bosnjak Z, Ballarini P, Budimir A, Bedenic B, Kalenic S, et al. NDM-1-producing Klebsiella pneumoniae, Croatia. Emerg Infect Dis. 2012 Mar;18(3):532-4.
12. Meletis G. Carbapenem resistance: overview of the problem and future perspectives. Therapeutic advances in infectious disease. 2016 Feb;3(1):15-21.
13. Grundmann H, Glasner C, Albiger B, Aanensen DM, Tomlinson CT, Andrasevic AT, et al. Occurrence of carbapenemase-producing Klebsiella pneumoniae and Escherichia coli in the European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study. Lancet Infect Dis. 2017 Feb;17(2):153-63.
14. 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.
15. Conte V, Monaco M, Giani T, D'Ancona F, Moro ML, Arena F, et al. Molecular epidemiology of KPC-producing Klebsiella pneumoniae from invasive infections in Italy: increasing diversity with predominance of the ST512 clade II sublineage. J Antimicrob Chemother. 2016 Dec;71(12):3386-91.
16. European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe - Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2017. Stockholm: ECDC; 2018. Available from: https://ecdc.europa.eu/sites/portal/files/documents/AMR-surveillance-EARS-Net-2017.pdf.
17. Principe L, Mauri C, Conte V, Pini B, Giani T, Rossolini GM, et al. First report of NDM-1-producing Klebsiella pneumoniae imported from Africa to Italy: Evidence of the need for continuous surveillance. Journal of global antimicrobial resistance. 2017 Mar;8:23-7.

18. Avolio M, Vignaroli C, Crapis M, Camporese A. Co-production of NDM-1 and OXA-232 by ST16 Klebsiella pneumoniae, Italy, 2016. Future Microbiol. 2017 Oct;12:1119-22.

19. Castagnola E, Tatarelli P, Mesini A, Baldelli I, La Masa D, Biassoni R, et al. Epidemiology of carbapenemase-producing Enterobacteriaceae in a pediatric hospital in a country with high endemicity. Journal of infection and public health. 2019 Mar - Apr;12(2):270-4.

20. Paskova V, Medvecky M, Skalova A, Chudejova K, Bitar I, Jakubu V, et al. Characterization of NDM-Encoding Plasmids From Enterobacteriaceae Recovered From Czech Hospitals. Front Microbiol. 2018;9:1549.

21. 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.

22. Rodriguez-Bano J, Gutierrez-Gutierrez B, Machuca I, Pascual A. Treatment of Infections Caused by Extended-Spectrum-Beta-Lactamase-, AmpC-, and Carbapenemase-Producing Enterobacteriaceae. Clin Microbiol Rev. 2018 Apr;31(2).

23. Papadimitriou-Olivgeris M, Bartzavali C, Lambropoulou A, Solomou A, Tsiata E, Anastassiou ED, et al. Reversal of carbapenemase-producing Klebsiella pneumoniae epidemiology from blaKPC- to blaVIM-harbouring isolates in a Greek ICU after introduction of ceftazidime/avibactam. J Antimicrob Chemother. 2019 Apr 19.

24. Girmenia C, Rossolini GM, Piciocchi A, Bertaina A, Pisapia G, Pastore D, et al. Infections by carbapenem-resistant Klebsiella pneumoniae in SCT recipients: a nationwide retrospective survey from Italy. Bone Marrow Transplant. 2015 Feb;50(2):282-8.

25. Tischendorf J, de Avila RA, Safdar N. Risk of infection following colonization with carbapenem-resistant Enterobactericeae: A systematic review. Am J Infect Control. 2016 May 1;44(5):539-43.

26. Neuner EA, Yeh JY, Hall GS, Sekeres J, Endimiani A, Bonomo RA, et al. Treatment and outcomes in carbapenem-resistant Klebsiella pneumoniae bloodstream infections. Diagn Microbiol Infect Dis. 2011 Apr;69(4):357-62.

27. Hauck C, Cober E, Richter SS, Perez F, Salata RA, Kalayjian RC, et al. Spectrum of excess mortality due to carbapenem-resistant Klebsiella pneumoniae infections. Clin Microbiol Infect. 2016 Jun;22(6):513-9.

28. Politi L, Gartzonika K, Spanakis N, Zarkotou O, Poulou A, Skoura L, et al. Emergence of NDM-1-producing Klebsiella pneumoniae in Greece: evidence of a widespread clonal outbreak. J Antimicrob Chemother. 2019 May 7.

29. Voulgari E, Gartzonika C, Vrioni G, Politi L, Priavali E, Levidiotou-Stefanou S, et al. The Balkan region: NDM-1-producing Klebsiella pneumoniae ST11 clonal strain causing outbreaks in Greece. J Antimicrob Chemother. 2014 Aug;69(8):2091-7.

30. Savov E, Politi L, Spanakis N, Trifonova A, Kioseva E, Tsakris A. NDM-1 Hazard in the Balkan States: Evidence of the First Outbreak of NDM-1-Producing Klebsiella pneumoniae in Bulgaria. Microbial drug resistance (Larchmont, NY). 2018 Apr;24(3):253-9.

31. Heinrichs A, Argudin MA, De Mendonca R, Deplano A, Roisin S, Dodemont M, et al. An Outpatient Clinic as a Potential Site of Transmission for an Outbreak of New Delhi Metallo-beta-Lactamase-producing Klebsiella pneumoniae Sequence Type 716: A Study Using Whole-genome Sequencing. Clin Infect Dis. 2019 Mar 5;68(6):993-1000.

32. Bosch T, Lutgens SPM, Hermans MHA, Wever PC, Schneeberger PM, Renders NHM, et al. Outbreak of NDM-1-Producing Klebsiella pneumoniae in a Dutch Hospital, with Interspecies Transfer of the Resistance Plasmid and Unexpected Occurrence in Unrelated Health Care Centers. J Clin Microbiol. 2017 Aug;55(8):2380-90.

33. World Health Organization. WHO guideliens on hand hygiene in health care. Geneva: WHO; 2009. Available from: https://apps.who.int/iris/bitstream/handle/10665/44102/9789241597906_eng.pdf;jsessionid=B99AAA3026F2BFE264616908939D5D7B?sequence=1.

34. European Centre for Disease Prevention and Control. Rapid risk assessment: carbapenem-resistant Enterobacteriacae, first update. Stockholm: ECDC; 2018. Available from: https://ecdc.europa.eu/sites/portal/files/documents/RRA-Enterobacteriaceae-Carbapenems-European-Union-countries.pdf.

35. Magiorakos AP, Burns K, Rodriguez Bano J, Borg M, Daikos G, Dumpis U, et al. Infection prevention and control measures and tools for the prevention of entry of carbapenem-resistant Enterobacteriaceae into healthcare settings: guidance from the European Centre for Disease Prevention and Control. Antimicrob Resist Infect Control. 2017;6:113.