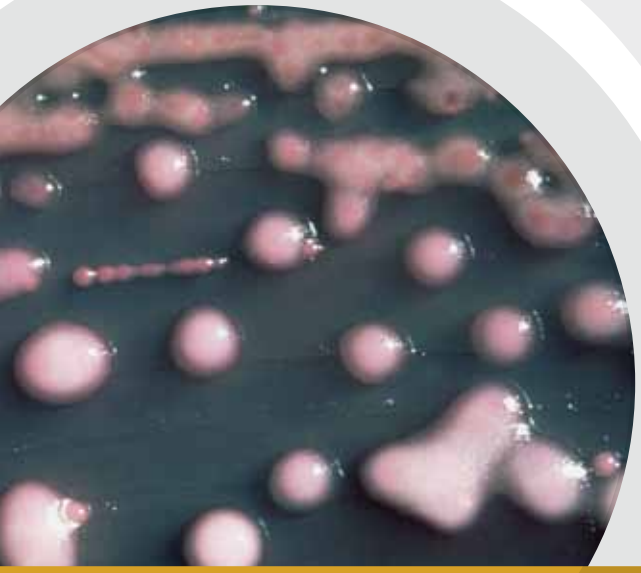

TECHNICAL REPORT

Updated ECDC risk assessment on the spread of New Delhi metallo-β-lactamase and its variants within Europe

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ECDC TECHNICAL REPORT

Updated ECDC risk assessment on the spread of New Delhi metallo-β-lactamase (NDM) and its variants within Europe

This risk assessment was produced by:
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Acknowledgments are given to the participants of the ECDC survey, who provided the data for this risk assessment. (See Annex 1).

Note: This risk assessment specifically addresses the spread of NDM-producing Enterobacteriaceae in Europe. It updates a previous threat assessment on the same topic produced by ECDC on 25 August 2010 and published by the European Commission on the Early Warning and Response System (EWRS) on 26 August 2010, and complements the "Risk assessment on the spread of carbapenemase-producing Enterobacteriaceae (CPE) through patient transfer between healthcare facilities, with special emphasis on cross-border transfer" published by ECDC on 13 September 2011: http://ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=740

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Public health issue

Emergence and spread of human cases of infection and colonisation with highly antibiotic-resistant, New Delhi metallo-β-lactamase (NDM)-producing Enterobacteriaceae.

Methods

We performed a systematic search of the medical literature for articles published up to and including 29 July 2011. The search strategy was outlined in PubMed as ((("ndm 1"[All Fields]) OR "ndm 2"[All Fields])) OR ("new delhi metallo beta lactamase"[All Fields] OR "new delhi metallo beta lactamase 1"[All Fields]), indexed as of 28 June 2011.

Survey of EU Member States and two EEA countries (Iceland and Norway)

To optimise the search for information beyond the published literature, on 17 May 2011 a questionnaire was sent by e-mail to the ECDC National Antimicrobial Resistance Focal Points from all EU Member States, Iceland and Norway. The purpose of this survey was to register all cases of colonisation or infection with NDM-producing Enterobacteriaceae by country and to collect as much data as possible on patient characteristics and epidemiological histories. An NDM-case was defined as a patient from whom one or more Enterobacteriaceae producing an NDM enzyme (e.g. NDM-1 or NDM-2) had been isolated and confirmed by an expert laboratory.

The survey also collected the following clinical, epidemiological and microbiological data: bacterial species producing the variants of the NDM enzyme (e.g., NDM-1 or NDM-2), date of detection, whether the case represented colonisation or infection, the body site sampled and the type of infection (if any), the patient's sex and age, the patient's clinical status at hospital discharge or at the last follow-up, travel history and/or contact with healthcare facilities abroad (during the 30 days preceding detection of NDM-producing *Enterobacteriaceae*) including information about the country visited, and any local transmission events involving known contact with a travel-associated case of NDM-producing Enterobacteriaceae.

Executive summary

The data currently available from scientific publications and enhanced surveillance established by some EU Member States indicate that there is an increase in the spread of not only NDM-producing Enterobacteriaceae, but of all carbapenemase-producing Enterobacteriaceae (CPE) in Europe. It is evident from these reports and surveillance results that even though carbapenemases such as *Klebsiella pneumoniae* carbapenemase (KPC) and Verona integron-encoded metallo-β-lactamase (VIM) are the most prevalent in Europe, others such as NDM and OXA-48 are on the increase, with recent reports of travel-related cases, autochthonous cases and outbreaks.

One of the major barriers to our understanding of the magnitude of risk that these highly antibiotic-resistant bacteria represent for Europe is that EU Member States lack systematic surveillance systems and policies to detect carriage or infection with NDM-producing Enterobacteriaceae and CPE generally. It is important that all EU Member States implement such systems to ensure the collection of reliable surveillance data, the prompt notification of the public health authorities, the surveillance of secondary transmission following travel-associated cases in the EU and the timely implementation of infection control measures.

Patient mobility is a risk factor for the transmission of NDM-producing Enterobacteriaceae and CPE. Since the reservoir of such resistance determinants in Europe and globally is unknown, any patient transferred from any country is considered to be at risk of carrying these highly antibiotic-resistant bacteria. A recent ECDC risk assessment suggests that active surveillance through rectal screening of any patient transferred across borders could be an effective way to detect carriage of CPE and therefore prevent its introduction into healthcare settings in the EU.

Public health preparedness should be enhanced by developing the necessary infrastructure to prevent further spread of all CPE in EU Member States. Structures and measures to put in place include the development and dissemination of national guidelines, active surveillance of high-risk patients and ensuring that clinical and reference microbiological laboratories have adequate resources for the detection and prompt reporting of imported or indigenous cases to surveillance systems and public health authorities.

EU-wide surveillance could be strengthened by linking national reference laboratories and public health institutes through current antimicrobial resistance surveillance networks such as EARS-Net, to enable monitoring of CPE and other highly antibiotic-resistant bacteria. National generic reporting and early warning systems should be compared to identify elements of appropriate practice. These elements could then be harnessed for rapid information exchange at EU level via the Epidemic Intelligence Information System (EPIS) or the Early Warning and Response System (EWRS).

Disease background information

The Enterobacteriaceae is a large family of bacteria, many members of which are a normal part of the gut flora and frequently cause urinary tract, bloodstream and intra-abdominal community-acquired and healthcare-associated infections. β-lactamases are enzymes produced by some of these bacteria that, depending on the type of enzyme, can make them resistant to various classes of β-lactam antibiotics, the main treatment for these infections. In the mid-1980s, a new group of these enzymes was detected, the extended-spectrum β-lactamases (ESBLs), which confer resistance to expanded-spectrum cephalosporins but not to carbapenems. Carbapenems are primarily used for treating infections due to ESBL-producing Enterobacteriaceae.

Over the past decade carbapenemases, a group of clinically important β-lactamases have emerged and spread among Enterobacteriaceae (1). Carbapenemases are enzymes that can efficiently hydrolyse most β-lactams, including carbapenems (2, 3). Some prevalent and emerging types of carbapenemases are *Klebsiella pneumoniae* carbapenemase (KPC), Verona integron-encoded metallo-β-lactamase (VIM), OXA-48, an OXA-type β-lactamase, and recently New Delhi metallo-β-lactamase (NDM).

Many carbapenemase-producing Enterobacteriaceae (CPE) strains frequently carry additional resistance determinants to other non-β-lactam antibiotics, making them highly antibiotic-resistant (4–6). The most common are colistin (in general, the polymyxins), tigecycline (although less consistently) (5, 7, 8) and fosfomycin (9, 10).

In patients infected with CPE there are increasing reports of clinical failures (11) and emerging resistance to tigecycline, colistin and fosfomycin (5, 12–16). For these reasons, but also because of toxicity, limited indications and variable serum concentrations, tigecycline, colistin and fosfomycin are not always an optimum therapeutic choice. Furthermore, the antimicrobials in question do not have proven clinical efficacy against these strains.

The emergence and spread of CPE is a public health threat. Recent studies from Europe and the USA on CPE (17–19) and on carbapenem-non-susceptible Enterobacteriaceae (CNSE) (20, 21) show that infection or colonisation with these bacteria is associated with higher in-hospital mortality and healthcare costs. The already small

therapeutic arsenal available for the treatment of infected patients is even smaller because of the limited number of new antimicrobial agents that are in the developmental pipeline (22, 23).

Types of carbapenemases

One of the milestones in the emergence of carbapenemases in Enterobacteriaceae was the detection of a novel carbapenemase, *Klebsiella pneumoniae* carbapenemase (KPC) in a *Klebsiella pneumoniae* isolate in North Carolina, USA which later spread throughout the world (24). Since then, most acquired carbapenemases have been found and reported in CPE globally (25, 26). Interspecies spread has also been reported, demonstrating the facility with which the genetic elements can disseminate (27–31).

Although the most widespread types of carbapenemases found in Enterobacteriaceae have so far been KPC, VIM and IMP, other carbapenemases like NDM and OXA-48 have also emerged (8, 26, 32-35). The first report of OXA-48 in Enterobacteriaceae was from Turkey (36, 37). Since then, it has been isolated from Enterobacteriaceae in other countries in the Mediterranean basin, including Israel (38), Tunisia (39), Morocco (40) and Spain (34). There are two disturbing aspects linked to the emergence of OXA-48. Firstly, OXA-48- producing Enterobacteriaceae can spread into healthcare facilities in destination countries, e.g. France (32, 33), from patients who are transferred from foreign countries, strongly suggesting that patient and population mobility are risk factors (32, 33, 37, 41). Secondly, autochthonous cases (42, 43), as well as outbreaks (44) of OXA-48-producing Enterobacteriaceae, are being reported in Europe.

New Delhi metallo-β-lactamase (NDM)

In 2008, a novel MBL carbapenemase, the New Delhi metallo-β-lactamase (NDM) (4, 7), was first detected in a *K. pneumoniae* isolate from a patient repatriated to Sweden after being treated in a hospital in New Delhi, India, hence its name (7). Variants of this carbapenemase, such as NDM-2, have recently been reported from the north of Africa. (45). Hereafter, New Delhi metallo-β-lactamase and its variants will be referred to as 'NDM'.

The term 'carbapenemase-producing Enterobacteriaceae', and the corresponding acronym CPE, used in this risk assessment both include NDM-producing Enterobacteriaceae.

Epidemiology of CPE

In Europe, antimicrobial susceptibility testing data and trends for *K. pneumoniae* resistance to carbapenem antimicrobials have been reported annually since 2005 through the European Antimicrobial Resistance Surveillance Network (EARS-Net, formerly EARSS) (available from http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/Database.aspx). EARS-Net data from 2009 showed that, whereas in most countries in Europe percentages of carbapenem-resistance in invasive *K. pneumoniae* isolates from blood and cerebrospinal fluid were below 1%, Greece, Cyprus and Italy reported resistance percentages of 43.5%, 17.0% and 1.3%, respectively. This represented a rise in the rates since 2005. Similar rates have also been indicated in national reports from these countries (30, 46).

Epidemiology of NDM-producing Enterobacteriaceae

After the first NDM-producing *K. pneumoniae* isolate was reported from a Swedish patient who had travelled to India (7), there were several other reports of importation of NDM-producing Enterobacteriaceae due to cross-border transfer of patients (5, 7, 47, 48).

Although local and global surveillance data on the prevalence of NDM-producing Enterobacteriaceae are scarce, a few recent studies provide interesting information on their presence in the community and in healthcare settings on the Indian subcontinent. One study reported the prevalence of community-acquired Enterobacteriaceae isolates from two regions in India. In the region of Chennai, 1% of all the Enterobacteriaceae analysed were NDM-positive, predominantly *E. coli* and *K. pneumoniae*, and in Haryana 13% of all *K. pneumoniae* were NDM-positive (5). Another study looking at the prevalence of these organisms in the healthcare system from 2006–2007, two years before the first case was reported in Europe, found that 38.5% of all carbapenem-resistant Enterobacteriaceae isolates from 14 hospitals across India produced NDM (49). Lastly, a study looking at the prevalence of NDM in seepage and tap water samples from New Delhi, India found that NDM was generally present, not only in key species of Enterobacteriaceae but also in non-fermentative Gram-negative bacteria (47). These data show just how widely the gene encoding NDM is disseminated.

Cases of colonisation or infection with NDM-producing Enterobacteriaceae in Europe and worldwide are reported either as imported cases in patients with a travel history to, or contact with healthcare systems on the Indian subcontinent, as cases of within-country secondary transmission or as autochthonous cases. Such cases have now

been reported from all over the world, e.g. Australia (50, 51) Canada (52-54), China (55), Japan (56), Kenya (57), Oman (58) and the USA (59).

In Europe, NDM- producing Enterobacteriaceae have been detected and reported, with incremental spread initially from Sweden (7) and the United Kingdom (4, 5) but also from Austria (60), Belgium (61), France (62), Germany (63), Switzerland (64), the Netherlands (65), Norway (66), and recently from countries in the Balkan region (4, 67-70).

Until now, NDM was predominantly found in Enterobacteriaceae and mostly in *K. pneumoniae* and *E. coli* isolates. Cases of non-fermentative Gram-negative bacteria such as *Acinetobacter* spp. that produce NDM have also been reported from Germany (n=1) and the UK (n=9) (4) in the last few years. More recent publications continue to report cases not only of *Acinetobacter* spp. but also *Pseudomonas* spp. that produce NDM. These reports have been from Europe, more specifically from Germany and Serbia (70, 71), but also from countries outside Europe such as China and Egypt (55, 72, 73).

Clonal spread and outbreaks

Enterobacteriaceae that produce either VIM, OXA-48 or KPC carbapenemases have been the cause of local outbreaks and country-wide epidemics of healthcare-associated infections in several European countries, in Israel and in the USA (8, 30, 44, 74). To date only scant reports of such outbreaks exist for NDM-producing Enterobacteriaceae (5).

In response to the growing threat, guidelines have been published recommending the implementation of multimodal infection control interventions to prevent the spread of CPE, including NDM-producing Enterobacteriaceae, in acute healthcare facilities in the United States and in Europe (59, 75, 76). ECDC recently published its "Risk assessment on the spread of carbapenemase-producing Enterobacteriaceae (CPE) through patient transfer between healthcare facilities, with special emphasis on cross-border transfer" which covers NDM-producing Enterobaceriaceae and includes expert guidance for prevention and control of their spread in Europe (1). Moreover, many countries in Europe have addressed the spread of CPE by creating new or modifying existing guidelines and strategies for other multidrug-resistant organisms, or by creating national task forces (77) and developing local or national strategies to tackle this public health threat (Table 2).

Results of the survey to all EU Member States plus Iceland and Norway

All questionnaires were completed and returned by e-mail. The clinical and epidemiological data requested were included for most, but not all cases reported from the countries. The questionnaire had requested data for NDM-producing Enterobacteriaceae and, although most of the responses contained data for these organisms, Germany and the UK also reported updated data on cases of NDM-producing *Acinetobacter* spp.

The United Kingdom reported its results as aggregated data by year and species, reporting some clinical and epidemiological data in aggregated format for a number of cases. The results are presented in Tables 1 and 2 and Figures 1 and 2 and, where relevant, they are reported separately for the UK and the other EU/EEA countries.

Reported cases of NDM-producing bacteria

Summary

Within the EU/EEA, 13 countries reported a total of 106 cases (plus one bacterial isolate from an endoscope not counted as a case) of NDM-producing Enterobacteriaceae up to 31 March 2011.

This is an increase on the total 77 cases reported to ECDC by the same 13 countries on 4 October 2010 (4). This means that 29 additional cases of NDM-producing Enterobacteriaceae were reported in the EU/EEA during this period, more specifically from the UK (n=17 cases), France (n=5), Germany (n=3), Sweden (n=2), Netherlands (n=1) and Slovenia (n=1). No new EU/EEA country reported cases. Overall, the majority of cases were reported from the UK (n=68).

Klebsiella pneumoniae was the predominant NDM-producing bacterial species (n=84 isolates), followed by 34 isolates of *E. coli* and 10 of *Enterobacter* spp. In total, seven deaths were reported from four countries: one patient of unclear aetiology, five (three of these were *Acinetobacter* spp.) due to other causes and one patient, a 51 year-old diabetic man, whose death was attributed to septic shock from a necrotic leg wound infected with NDM-1-producing *E. coli*.

Aside from the reported cases of Enterobacteriaceae, there were six new cases of NDM-producing *Acinetobacter* spp., one from the UK and five from Germany (one case from Germany with a travel history to Egypt was the first report of NDM-2).

NDM-producing Enterobacteriaceae, UK

Ninety-six isolates of NDM-producing Enterobacteriaceae belonging to 68 cases, were reported from the UK between 2008 and 31 March 2011 (one additional isolate, not counted as a case, was cultured from an endoscope, bringing the total number of isolates to 97). Complete clinical and epidemiological data were not available for all 68 cases and no distinction was made as to whether they represented colonisation or infection. The NDM-producing bacterial isolates were distributed among six species which were *K. pneumoniae* (n=63), *E. coli* (n=20), *Enterobacter* spp. (n=10), *Citrobacter freundii* (n=2), *Morganella morganii* (n=1), *Proteus mirabilis* (n=1).

A relevant travel history was provided for only 40 of the 68 cases of NDM-producing Enterobacteriaceae. Twenty-five cases had travelled to or had been hospitalised in India (20) or Pakistan (5) and one had travelled to Spain. Fourteen cases had no history of recent overseas travel. Travel history was unknown for the remaining 29 cases.

NDM-producing Enterobacteriaceae, EU/EEA countries other than UK

Thirty-nine isolates of NDM-producing Enterobacteriaceae belonging to 38 cases were reported from 12 countries in the EU/EEA, other than the UK. Fifteen of these cases represented infection, 22 represented colonisation, and two were not specified. The patient age range was 21 months–86 years (age was not reported for five cases) and the male-to-female ratio was 25:12 (in two cases, gender was not reported). The NDM-producing bacterial isolates were distributed among five species, which were *K. pneumoniae* (n=21), *E. coli* (n=15), *M. morganii* (n=1), *C. freundii* (n=1) and *P. mirabilis* (n=1).

Twenty-five of the 38 cases had a recent (within one month) history of hospitalisation abroad: India (n=13 cases), Pakistan (n=3), Serbia (n=1), Kosovo (UNSCR 1244) (n=1), Serbia and Kosovo (UNSCR 1244) (n=1, this case had been to both countries), Montenegro (n=1), Bosnia-Herzegovina (n=2), Iraq (n=2), and one case with a history of having lived in India in the past. Two cases had a travel history that was not reported, one case was acquired secondarily, two cases were autochthonous and one case was reported as possibly autochthonous.

NDM-producing *Acinetobacter* spp., Germany and UK

Even though the questionnaire had requested data solely for NDM-producing Enterobacteriaceae, two countries, Germany and the UK, provided additional data for cases of NDM-producing *Acinetobacter* spp. These data are included in a separate section and presented in Figure 2.

Between 2008 and 31 March 2011, ten cases of NDM-producing *Acinetobacter* spp. were reported from the UK and six from Germany. Of the ten UK cases, only one was reported since the previous survey ended on 4 October 2010 (4). The other cases were one case from 2008, five cases that were part of a cluster of colonised patients from 2009 and three cases from 2010. No other clinical or travel information was available for these cases.

Of the six cases of *Acinetobacter* spp. reported from Germany, five were additional cases reported since the previous survey ended on 4 October 2010 (4). All these *Acinetobacter* spp. isolates produced NDM-1 except for one, isolated from a patient with a recent hospitalisation in Egypt, that produced NDM-2. These cases had an age range

from 4–57 years (age of one of the cases was not reported), the male-to-female ratio was 5:1 and all six cases represented an infection. Three of these cases survived hospitalisation and three died, but due to other causes. One of the cases had a recent travel history to Egypt (NDM-2-producing isolate), another to Serbia and the other four cases had no relevant travel history and were considered autochthonous.

Available national guidance documents

Guidance documents for the management of carbapenemase- or NDM-producing Enterobacteriaceae were available or in development in 17 European countries, in the form of online, peer-reviewed publications, interim or national guidance (Table 2). Of these 17 countries, thirteen had national guidance documents. Among the remaining countries without national guidance documents, Hungary reported that national guidance documents were in preparation; the Netherlands reported that it was preparing national guidance, although two peer-reviewed documents were already available and in use as guidance (78, 79); Ireland had interim guidance available and national guidelines in preparation, and Austria had infection control guidelines available at hospital level and national guidelines in preparation.

Among the 16 countries that had national (final or interim) or hospital guidance documents, the following components were present: detection and surveillance methods in all 16 countries: referral to a reference laboratory in 15 countries, mandatory notification of health authorities in 12 countries and infection control measures in 13 countries. Hungary, whose national guidance is expected soon, has made notification to public health authorities mandatory since 2004.

Epidemiological characteristics of NDM-producing Enterobacteriaceae infections

Risk factors for colonisation and infection

To date, there have been no case-control or cohort studies looking at risk factors linked to colonisation or infection of humans with NDM-producing Enterobacteriaceae. Evidence from initial reports on NDM-producing Enterobacteriaceae in Europe (7), the series of consecutive clinical isolates of Enterobacteriaceae from three Indian hospitals (5), and the increasing number of reports of patients carrying NDM-producing Enterobacteriaceae who are transferred from the Indian subcontinent strongly suggest that contact with healthcare systems on the Indian subcontinent (5, 48) is a risk factor for acquisition of NDM-producing Enterobacteriaceae.

Recent reports from countries in Europe, however, show that NDM-producing Enterobacteriaceae have also been found in patients who were transferred from the Balkan region, e.g. Bosnia-Herzegovina, Kosovo (UNSCR 1244), Montenegro and Serbia (4, 61) to other European countries. Many of these patients had previous epidemiological links with the Indian subcontinent (4, 60, 61, 69). It is evident that since some of these reported cases are considered autochthonous, there is an existing, unknown reservoir of NDM. The significance of this is that any patient who has a history of hospitalisation abroad or foreign travel, even within Europe, could be considered at risk of acquiring NDM-producing Enterobacteriaceae (4, 5, 7, 51, 53, 59, 61, 69, 80, 81).

Similar to the results of a recent risk assessment on CPE (1), there is strong evidence from descriptive clinical and epidemiological data in the published cases of NDM-producing Enterobacteriaceae that cross-border transfer of patients poses a clear risk for the transmission of CPE. This is particularly relevant when: a) patients are transferred from areas with high rates of CPE to healthcare facilities in another country and b) patients have received medical care abroad in areas with high rates of CPE.

Clinical severity of infection

According to published series and case reports and the results of our survey, the clinical spectrum of disease presentation and severity of illness of patients with NDM-producing Enterobacteriaceae appears similar to that described for infections with other types of CPE in this patient population. Asymptomatic cases of colonisation were detected by culturing wounds or urine and by rectal or throat swab screening. Patients infected with NDM-producing Enterobacteriaceae were diagnosed with, amongst others, urinary tract, surgical site, bloodstream, skin and soft tissue and deep wound infections, as well as peritonitis and ventilator-associated pneumonia. Although the full clinical profile was not available for all patients reported in the questionnaires, it is known that many of them had significant co-morbidities or immunosuppressive states (e.g. diabetes, cancer or chronic renal failure on haemodialysis), were on chronic immunosuppressive therapy or had undergone recent invasive procedures (4, 5, 61).

Not all patients, however, had previously been ill. Some were young and healthy and had become colonised or infected with these organisms after hospitalisation in a foreign country while travelling (4, 60, 62, 73).

The exact cause of death in those patients with invasive infections was difficult to ascertain, due to the complexity of their medical diagnoses and co-morbidities.

Outcomes of infections

There is currently no study available examining whether there is a higher risk of complications or mortality in those patients infected with NDM-producing Enterobacteriaceae compared to those with non-NDM-producing, carbapenem-susceptible isolates of Enterobacteriaceae. However, it is possible to draw conclusions on the outcomes of patients infected with NDM-producing Enterobacteriaceae by looking at studies of other types of CPE that document a higher risk of complications and mortality in comparable patient populations of CPE-infected patients (19, 20).

Extent and geographic distribution of the epidemiological reservoir

At EU level, there is no dedicated molecular surveillance system to monitor the geographic distribution of CPE by incidence and resistance mechanisms, even though some countries have documented the frequency and incidence of infection with VIM, KPC and OXA-48 by using national molecular surveys and surveillance structures (8, 30, 41, 74). Overall, the data available from EU Member States' responses to the survey and published reports indicate that detection of NDM-producing Enterobacteriaceae is still rare in the EU.

Transmissibility of the genetic vector and bacterial clones harbouring *bla*$_{NDM}$ genes

Recent studies examined the genetic features of NDM-producing isolates (5, 7, 49). The bla$_{NDM}$ determinant in *E. coli* and *K. pneumoniae* isolates from the UK and India was generally located on plasmids ranging in size from 50 to over 500 kb (5, 49). Some isolates carried the gene on multiple plasmids. These plasmids belonged to type A/C or incompatibility type FI/FII or were non-typable (5). A truncated IS26 element was identified in the vicinity of bla$_{NDM}$ in the first characterised strain of NDM-producing *K. pneumoniae* (7). In a few isolates, the bla$_{NDM}$ resistance determinant was located on the bacterial chromosome, indicating intra-genomic recombination (5). In the first reported case, NDM was produced both by a *K. pneumoniae* isolate from urine and a faecal *E. coli* isolate, suggesting in vivo transfer by conjugation between these species (7). Experimental data from many studies have shown that the bla$_{NDM}$ resistance determinant is readily transferable by conjugation into *E. coli* and other genera of the Enterobacteriaceae family (5, 47). These data suggest that bla$_{NDM}$ plasmids have high transmissibility and genetic plasticity, conferring on them a potent capacity for horizontal dissemination among the commensal reservoir of Enterobacteriaceae, as further evidenced by detection of bla$_{NDM}$ in multiple genera of this family and in *Acinetobacter baumannii*.

Besides plasmid spread, the extent of strain transmission in the human population has been examined with genomic macrorestriction typing by PFGE in one study (5). The data indicated genotypic heterogeneity in the NDM-producing *E. coli* isolates and in the vast majority of *K. pneumoniae* isolates from both the UK and India. Notable exceptions are a *K. pneumoniae* clonal strain found in 26 cases from Haryana, India, and a small independent cluster of two to nine cases with isolates *of K. pneumoniae* linked to the same clonal type from UK hospitals (5). In a more recent report, clonality from different cities in India was documented in *K. pneumoniae* isolates with identical PFGE profiles (49), suggesting the clonal spread of NDM-producing *K. pneumoniae* strains.

Mode of transmission in the community and healthcare settings

Even though global data on this topic are not available, some insight into community and healthcare distribution of NDM-producing Enterobacteriaceae is given by the results of a large study from the Indian subcontinent and the UK. These results showed that most cases of NDM-producing Enterobacteriaceae in India were community-acquired, whereas those from the UK were healthcare-associated, acquired following hospital admissions in India, Pakistan and Bangladesh (5, 81).

Furthermore, another study from the Indian subcontinent showed that NDM is widely disseminated among key species of Enterobacteriaceae in the community, hospitals and the environment (most notably seepage and tap

water) (5, 47-49). It is likely that indirect faecal-oral inter-human transmission plays a major role via contaminated hands, food or water.

Reliability of routine antibiotic susceptibility testing methods for detection

Any Enterobacteriaceae isolate that exhibits carbapenem resistance, with a minimum inhibitory concentration (MIC) above the epidemiological cut-off or with clinical resistance to ertapenem, imipenem or meropenem should trigger further testing for the production of a carbapenemase.

Various methods used for the detection of carbapenem resistance and production of carbapenemase enzymes, including NDM, in Enterobacteriaceae have been reported and a few are mentioned below.

Carbapenemase activity has been screened by using recommended metallo-β-lactamase detection tests such as the modified Hodge test (20). Caution should be used, however, when interpreting the results of tests on NDM-producing Enterobacteriaceae using the modified Hodge test because false-negative results have been reported (49). Other tests are those that use carbapenemase inhibitors, e.g., the metallo-β-lactamase E-test, the double-disk synergy test using a carbapenem and EDTA (5, 7, 49, 59, 82, 83), and phenotypic tests such as disk diffusion synergy tests (5, 7, 35, 48, 82, 84).

Automated systems for susceptibility testing have been evaluated and shown good sensitivity but poor specificity for the detection of carbapenem resistance mediated by NDM and other carbapenemases (82, 85). To confirm the presence of the NDM enzyme requires molecular analysis. This can be done by either single or multiplex PCR or DNA sequencing, which are often only performed in reference laboratories (82, 86, 87). Diagnostic tests used for rapid screening of isolates are selective chromogenic agar media and DNA microarray and these have been shown to produce good results (35, 82, 88-90).

Effectiveness of control measures in acute care settings and the community

There has been no specific study evaluating the effectiveness of infection control interventions for the early detection and/or control of transmission for NDM-producing Enterobacteriaceae. Some countries, however, have created national alerts for healthcare practitioners, triggered by reports of cases of NDM-producing Enterobacteriaceae and other CPE from hospitals across Europe. One of the purposes of developing these alerts was to increase the awareness that multidrug-resistant bacteria can be transferred into countries by cross-border patient transfer, mostly from countries with higher rates of antimicrobial resistance.

For other multidrug-resistant bacteria such as meticillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant Gram-negative bacteria, infection control measures have been used and advocated for the active screening and subsequent management of patients who are considered at risk. Some examples are active screening, placing patients pre-emptively in single bed rooms with dedicated cohort nursing and use of additional barrier precautions pending results of microbiological screening. Similar measures have also been applied in many countries for NDM-producing Enterobacteriaceae.

A recent ECDC risk assessment on CPE showed that evidence from the medical literature consistently supports the effectiveness of active surveillance (active screening of any patient transferred across borders upon admission to a hospital or other healthcare facility); use of additional precautions for CPE-positive patients (e.g. contact precautions, such as wearing of disposable gloves and gown, and isolation measures) and cohort nursing by a separate, dedicated team for all suspected and CPE- positive patients (1).

ECDC threat assessment for the European Union

Based on the rise in the number of published reports and the results of the survey reported from 13 EU/EEA countries, it is evident that the spread of travel-related, secondary or autochthonous cases of infection or colonisation with NDM-producing Enterobacteriaceae is increasing.

By 4 October 2010, seventy-seven cases had been reported and by 31 March 2011 this had increased to 106 cases reported from the same 13 countries. However, these cases were not limited to Enterobacteriaceae alone. Two countries, Germany and the UK, also reported an increase in the number of *Acinetobacter* spp. cases, from 10 to 16 during the same time period. It is also significant that one of the *Acinetobacter* spp. cases was the first reported variant of NDM-1, namely NDM-2.

From the data that we have accrued, it is not possible to estimate the rate at which NDM-producing Enterobacteriaceae is spreading within Europe. Firstly, this is because the number of reported cases largely depends on differences in the countries' awareness and capacity for detection and surveillance, which leads to detection and publication bias. Secondly, due to the lack of systematic surveillance of NDM-producing Enterobacteriaceae and other CPE in Europe, the true prevalence is unknown.

Some evidence supporting the spread potential of the bla_{NDM} gene is that it has been found in most genera of Enterobacteriaceae, and also in non-fermentative Gram-negative bacteria such as *Acinetobacter* spp. and *Pseudomonas* spp. This has been reported not only from endemic areas such as the Indian subcontinent, but also from Europe. Whereas until recently cases reported in Europe have mostly involved patients with a travel association to or hospitalisation in countries outside of Europe, cases are also now being reported as autochthonous or related to the cross-border transfer of patients within Europe.

It is therefore evident that foreign travel to or hospitalisation in any geographic area, including Europe, can be a risk factor for the acquisition of NDM-producing Enterobacteriaceae and this concurs with the conclusions of a recent ECDC risk assessment on CPE (1).

The extent of the risk, in terms of future incidence of human infections caused by NDM- producing Enterobacteriaceae across the EU, depends on the prevalence in the community, the healthcare setting and the environment. It also depends on the frequency with which travel-associated NDM-producing strains are introduced into the EU and transmitted between EU countries, and the likelihood of secondary transmission. The latter will depend on strain transmissibility, strain and plasmid fitness, the selective pressure from patient exposure to broad-spectrum antimicrobial agents, and the national, regional and local preparedness and capacity of healthcare facilities.

Despite the lack of studies addressing the risk posed by NDM-producing Enterobacteriaceae to the human population in Europe, the similarity of resistance mechanisms with other CPE enables us to infer that these NDM-producing Enterobacteriaceae may behave in a similar manner, rendering them a potential risk for public health in Europe.

Public health preparedness should be enhanced by developing the necessary infrastructure to prevent further spread of all CPE in EU Member States. Structures and measures to put in place include the development and dissemination of national guidelines, active surveillance of high-risk patients and ensuring that clinical and reference microbiological laboratories have adequate resources for the detection and prompt reporting of imported or indigenous cases to surveillance systems and public health authorities.

EU-wide surveillance could be strengthened by linking national reference laboratories and public health institutes through current antimicrobial resistance surveillance networks such as EARS-Net, to enable monitoring of CPE and other highly antibiotic-resistant bacteria. National generic reporting and early warning systems should be compared to identify elements of appropriate practice. These elements could then be harnessed for rapid information exchange at EU level via the Epidemic Intelligence Information System (EPIS) or the Early Warning Response System (EWRS).

Table 1. Demographic characteristics and travel history of patients colonised or infected with New Delhi metallo-beta-lactamase (NDM)-producing Enterobacteriaceae, EU/EEA countries, 2008–Q1 2011.

Country	Total patients to 30/3/11	Year of detection	NDM type	NDM-producing bacterial species	Sex (M:F)	Age range (yrs)	Clinical presentation		No. of fatal cases	Recent travel to country (no. of cases)	Recent healthcare in country (no. of cases)	Autochthonous & secondary cases (no. of cases)
							Colonisation, no. of cases	Infection, type (no. of cases)				
Austria	3	2009–2010	NR	*E. coli* (1), *K. pneumoniae* (2)	3:0	14–56	1	Intra-abdominal sepsis (1), perianal necrotising fasciitis (1)	0	India (1), Kosovo[b] (1), Pakistan (1)	India (1), Kosovo[b] (1), Pakistan (1)	0
Belgium	3	2010	NDM-1 (3)	*E. coli* (2), *K. pneumoniae* (1), *Morganella morganii* (1)	2:0	46–53	2	Sepsis from necrotic wound (1)	1	Kosovo[b] and Serbia (1), Montenegro (1), Pakistan (1)	Kosovo[b] and Serbia (1), Montenegro (1), Pakistan (1)	0
Bulgaria	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cyprus	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Czech Republic	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Denmark	1	2010	NDM-1 (1)	*K. pneumoniae* (1)	0;1	57	1	NA	0	Bosnia and Herzegovina (1)	Bosnia and Herzegovina (1)	0
Estonia	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Finland	1	2010	NDM (1)	*K. pneumoniae* (1)	1:0	46	1	NA	0	India (1)	India (1)	0
France	9	2009–2011	NDM-1 (9)	*Citrobacter freundii* (1), *E. coli* (4), *K. pneumoniae* (3), *Proteus mirabilis* (1)	6:3	1–86 (1 unknown)	6	Skin and soft tissue infection (2), UTI (1)	0	India (5), Iraq (1), No travel (2), + India (1)	India (4), Iraq (1)	2 secondary
Germany	6[c]	2009–2011	NDM-1 (6)	*E. coli* (3), *K. pneumoniae* (3)	4:1 (1 unknown)	22–70	2	UTI (2), wound infection (2)	5 alive; 1 NR	India (2), Pakistan (1), Bosnia (1), No travel (2)	India (1) Pakistan (1), Bosnia and Herzegovina (1)	2 autochthonous
Greece	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hungary	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Iceland	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ireland	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Italy	2	2009	NDM-1 (2), NR (2)	*E. coli* (2)	2;0	NR	2	0	0	No travel (2)	0	2 secondary transmission
Latvia	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lithuania	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Luxembourg	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Malta	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nether-lands	3	2008–2011	NDM-1 (3)	*E. coli* (1), *K. pneumoniae* (2)	1:2	30–66	3	0	0	India (3)	India (1)	0
Norway	2	2010	NDM-1 (2)	*E. coli* (1), *K. pneumoniae* (1)	1:1	65–70	1	UTI and secondary bacteraemia (1)	0	India (1) + India (1)[d]	India (1) + India (1)[d]	0
Poland	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Portugal	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Romania	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Slovakia	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Slovenia	3	2009–2010	NDM-1 (2), NR (2)	*K. pneumoniae* (2)	1:1	59–79	0	Pneumonia (1) UTI (2)	1 (unclear cause of death)	Serbia (1), India (1), No travel (1)	Serbia (1)	0
Spain	1	2010	NA	*K. pneumoniae* (1)	1:0	36	0	Abdominal abscess (1)	0	India (1)	India (1)	0
Sweden	4	2008–2011	NDM-1 (3)	*E. coli* (1), *K. pneumoniae* (4)	2:2	26–72	3	UTI (1)	2 (death due to other causes)	India (3), Iraq (1)	India (3), Iraq (1)	0
United Kingdom	68[c]	2008–2011	NR	*Klebsiella* spp. (63), *E. coli* (20), *Enterobacter* spp. (10), *C. freundii* (2), *M. morganii* (1), *Providencia* spp. (1)	55:24	2–95	NR	NR[e]	5[f]	India (20), Pakistan (5), Spain (1), No travel (14), NR (39)	NR[g]	2[f]

NA: not applicable; NR: data not reported

[a] History of travel or contact with healthcare facilities in a foreign country within 30 days prior to detection of NDM-producing Enterobacteriaceae

[b] Under United Nations Security Council Resolution 1244

[c] Additional cases of Acinetobacter spp. with an NDM enzyme: Germany (n=6) and UK (n=10)

[d] Patient hospitalised in India 8–9 months before identification of NDM-1-producing E. coli

[e] Body sites from where specimens were obtained (including the 10 Acinetobacter spp. isolates): urine (n=50), wound (n=12), sputum (n=7), blood (n=10), other (n=25), unknown body site (n=3)

[f] These five fatal cases are from the first 29 cases in the UK, for which information on mortality was available. No data on mortality were reported for the remaining 39 cases from the UK.

[g] For n=17 cases of the first 29 cases from the UK, the link to foreign country was defined as having travelled to India or Pakistan up to one year before detection of NDM-producing Enterobacteriaceae, , or having been born in these countries.

[f] Two clusters, each comprising one index travel-associated case and one secondary case, that were both admitted to the same hospital ward during the same period.

Figure 1. Number of cases of NDM-producing Enterobacteriaceae per species in the UK and in other EU/EEA countries, 2008–Q1 to 2011.

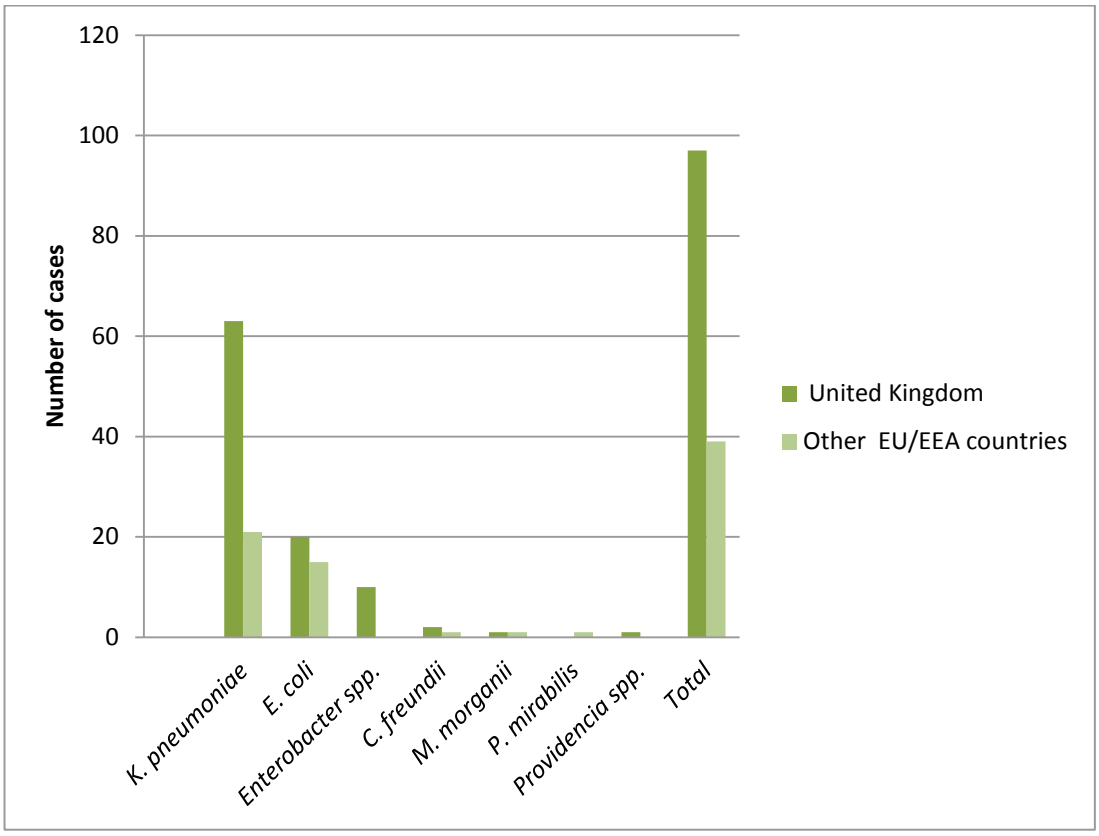
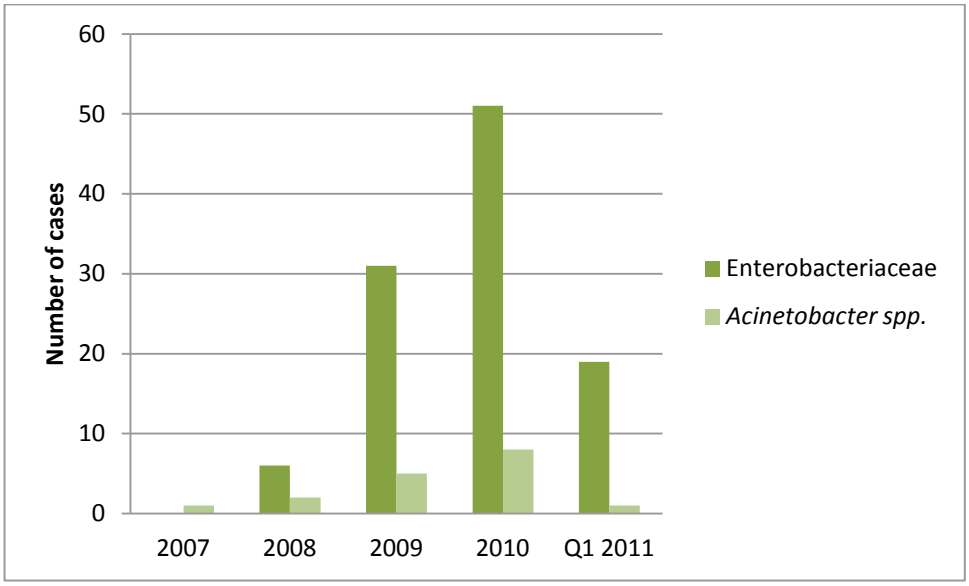


Figure 2. Trends in the annual number of cases of New Delhi metallo-β-lactamase (NDM)-producing Enterobacteriaceae and *Acinetobacter* spp. in EU/EEA countries, 2007–Q1 to 2011–Q1.



Note: Only Germany and UK reported data on NDM-producing Acinetobacter spp.

Table 2. Guidance documents (updated and available) on New Delhi metallo-β-lactamase (NDM)-producing, or more generally, carbapenemase-producing Enterobacteriaceae, detection and surveillance methods, referral to reference laboratory, notification to health authorities and infection control measures reported in 16 European countries (as of June 2011).

Country	National guidance on NDM-producing, or more generally carbapenemase-producing, Enterobacteriaceae				Comment	Reference or URL
	Detection and surveillance methods	Referral to reference laboratory	Notification to health authorities	Infection control measures		
Austria	•	•	•		Infection control guidelines at hospital level; national guidelines in preparation	http://www.referenzzentrum.at
Belgium	•	•	•	•		http://www.nsih.be/surv_carba/carbapenemase_fr.asp
Czech Republic	•	•	•			http://www.szu.cz/uploads/documents/CeM/Zpravy_EM/18_2009/3_brezen/100_betal.pdf
Estonia	•					http://www.elmy.ee/public/files/Enterobacteriaceae%20algoritmide%20selgitused%20ver1.0.doc
Finland	•	•	•	•		http://www.ktl.fi/portal/17160
France	•	•	•	•		http://www.hcsp.fr/explore.cgi/hcspr20101116_bmrimport.pdf
Germany	•	•		•		http://www.rki.de/cln_169/nn_205760/DE/Content/Infekt/Krankenhaushygiene/Erreger_ausgewaehlt/ESBL/ESBL_LIT_03,templateId=raw,property=publicationFile.pdf/ESBL_LIT_03.pdf
Greece	•	•	•	•		http://www.keelpno.gr/index.php?option=com_content&view=article&id=190%3A2010-12-01-05-45-22&catid=64%3A2010-08-04-08-56-37&Itemid=1
Hungary					National guidance in preparation	
Ireland	•		•	•	Interim guidance available; national guidelines in development	http://ndsc.newsweaver.ie/epiinsight/x3k8tfcgbkctx2boyfzyr4
Netherlands	•	•	•	•	National guidance in preparation	Please see references (78, 79)
Norway	•	•		•		http://www.unn.no/k-res/metoder-for-paavisning-av-karbapenemase-produserende-esbl-carba-enterobacteriaceae-article77546-21588.html http://www.fhi.no/dokumenter/96331178b9.pdf
Poland	•	•	•	•		http://www.antybiotyki.edu.pl http://www.korld.edu.pl
Portugal	•	•	•	•		http://www.dgs.pt/?f=3&id=16683 http://www.dgs.pt/upload/membro.id/ficheiros/i013491.pdf
Slovenia	•	•		•		http://www.mz.gov.si/fileadmin/mz.gov.si/pageuploads/mz_dokumenti/delovna_podrocja/zdravstveno_varstvo/zdravstveno_varstvo_v_posebnih/NAKOBO_oktober_2010/PRIPOROCILA_ESBL_18.10.2010.doc
Sweden	•	•	•	•		http://soapimg.icecube.snowfall.se/strama/ESBLdokument%20inkl%20bakgrund.pdf http://soapimg.icecube.snowfall.se/strama/supplement%202%20ESBL%20definition.pdf
United Kingdom	•	•	•	•		http://www.hpa.org.U.K./web/HPAwebFile/HPAweb_C/1248854046470 http://www.hpa.org.U.K./web/HPAwebFile/HPAweb_C/1248854045473

Adapted and updated with permission from "New Delhi metallo-beta-lactamase 1-producing Enterobacteriaceae: emergence and response in Europe" Struelens MJ, et al. Euro Surveill. 2010 Nov 18;15(46).

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