ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

SURVEILLANCE REPORT

Increase in *Escherichia coli* isolates carrying bla_{NDM-5} in the European Union/European Economic Area, 2012–2022

May 2023

www.ecdc.europa.eu

ECDC SURVEILLANCE REPORT

Increase in *Escherichia coli* isolates carrying *bla*$_{\text{NDM-5}}$ in the European Union/European Economic Area, 2012–2022

This report of the European Centre for Disease Prevention and Control (ECDC) was coordinated by Anke Kohlenberg and Marius Linkevicius.

Contributing authors (in alphabetical order):
Erik Alm, Anke Kohlenberg, Marius Linkevicius, Dominique L. Monnet, Daniel Palm, Olov Svartström.

Consulted external experts (in alphabetical order):
- Petra Apfalter (Austrian National Reference Centre for Antimicrobial Resistance, Linz, Austria);
- Rémy A. Bonnin (French National Reference Centre for Antimicrobial Resistance, Paris, France);
- Lilla Buzgó (National Public Health Centre, Budapest, Hungary);
- Manuela Caniça (National Reference Laboratory of Antibiotic Resistances and Healthcare Associated Infections, Department of Infectious Diseases, National Institute of Health Dr. Ricardo Jorge, Lisbon, Portugal);
- Martin Cormican (University of Galway, Galway, Ireland);
- Niall De Lappe (University of Galway, Galway, Ireland);
- Laurent Dortet (French National Reference Centre for Antimicrobial Resistance, Paris, France);
- Maria Giufrè (Department of Infectious Diseases, Istituto Superiore di Sanità – ISS, Rome, Italy);
- Jörg B. Hans (National Reference Centre for multidrug-resistant Gram-negative bacteria, Ruhr University Bochum, Bochum, Germany);
- Rainer Hartl (Austrian National Reference Centre for Antimicrobial Resistance, Linz, Austria);
- Henrik Hasman (Department of Bacteria, Parasites and Fungi, Statens Serum Institut – SSI, Copenhagen, Denmark);
- Antoni P.A. Hendrickx (Centre for Infectious Disease Control (CIb), National Institute for Public Health and the Environment – RIVM, Bilthoven, the Netherlands);
- Vera Manageiro (National Reference Laboratory of Antibiotic Resistances and Healthcare Associated Infections, Department of Infectious Diseases, National Institute of Health Dr. Ricardo Jorge, Lisbon, Portugal);
- Barbro Mäkitalo (Public Health Agency of Sweden, Stockholm, Sweden);
- Monica Monaco (Department of Infectious Diseases, Istituto Superiore di Sanità – ISS, Rome, Italy);
- Jesús Oteo-Iglesias (Laboratorio de Referencia e Investigación en Resistencia a Antibióticos del Centro Nacional de Microbiología and CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain);
- María Pérez-Vázquez (Laboratorio de Referencia e Investigación en Resistencia a Antibióticos del Centro Nacional de Microbiología and CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain);
- Niels Pfennigwerth (National Reference Centre for multidrug-resistant Gram-negative bacteria, Ruhr University Bochum, Bochum, Germany);
- Anna K. Pöntinen (Norwegian National Advisory Unit on Detection of Antimicrobial Resistance, University Hospital of North Norway, Tromsø, Norway);
- Kati Räisänen (Department of Health Security, Finnish Institute for Health and Welfare – THL, Helsinki, Finland);
- Louise Roer (Department of Bacteria, Parasites and Fungi, Statens Serum Institut – SSI, Copenhagen, Denmark);
- Ørjan Samuelsen (Norwegian National Advisory Unit on Detection of Antimicrobial Resistance, University Hospital of North Norway, Tromsø, Norway);
- Ákos Tóth (National Public Health Centre, Budapest, Hungary);
- Karin Westmo (Public Health Agency of Sweden, Stockholm, Sweden).

Suggested citation: European Centre for Disease Prevention and Control. Increase in Escherichia coli isolates carrying *bla*$_{NDM-5}$ in the European Union/European Economic Area, 2012–2022. Stockholm: ECDC; 2023.

Stockholm, May 2023

ISBN 978-92-9498-627-6
doi: 10.2900/72700
Catalogue number TQ-03-23-096-EN-N

Contents

Figures

Tables

Abbreviations

AST	Antimicrobial susceptibility testing
CCRE-survey	Survey of carbapenem- and/or colistin-resistant Enterobacterales
cgMLST	core genome multilocus sequence typing
EEA	European Economic Area
EU	European Union
EuSCAPE	European survey of carbapenemase-producing Enterobacterales
ESBL	Extended-spectrum β-lactamase
KPC	*Klebsiella pneumoniae* carbapenemase
NDM	New Delhi metallo-β-lactamase
OXA	Oxacillinase
ST	Sequence type

Executive summary

Unpublished preliminary results of the survey of carbapenem- and/or colistin-resistant Enterobacterales (CCRE-survey) conducted in 36 European countries in 2019 had shown that NDM-5 had become the most frequently reported carbapenemase in *Escherichia coli*. The aim of this study was to determine the extent of the spread of *E. coli* isolates carrying *bla*$_{NDM-5}$ in the European Union/European Economic Area (EU/EEA). Analysis of whole genome sequencing and epidemiological data of 874 *E. coli* isolates from the national collections of 13 countries confirmed the increase of *E. coli* isolates carrying *bla*$_{NDM-5}$ which was previously detected in the CCRE survey.

While the *bla*$_{NDM-5}$ gene was detected in 83 different *E. coli* sequence types (STs) from national collections, there was a strong predominance of a few STs, mainly ST167, ST405, ST410, ST361, and ST648. The high number and the large size of multi-country clusters in the dataset, including recent isolates from 2022, suggest an ongoing rapid global expansion of these dominant *E. coli* STs carrying *bla*$_{NDM-5}$, including the EU/EEA.

Despite limited data completeness, about 84.2% of the *E. coli* isolates carrying *bla*$_{NDM-5}$ with available information on travel and/or hospitalisation within the six months before sampling were linked to a country outside of the EU/EEA, mainly countries in Africa and Asia. This suggests that travel-related acquisition may still be the most likely origin of these isolates. Additionally, about 30% of the *E. coli* isolates carrying *bla*$_{NDM-5}$ were documented as related to infections, emphasising the clinical relevance and need for early detection. Furthermore, a high proportion of the isolates carrying *bla*$_{NDM-5}$ also co-harboured resistance markers to aminoglycosides, fluoroquinolones, and trimethoprim-sulfamethoxazole, indicating multidrug resistance with limited options left for the treatment of patients.

Further spread of *E. coli* isolates carrying *bla*$_{NDM-5}$ within and between the EU/EEA countries, particularly in healthcare facilities, as well as introductions from outside of the EU/EEA have the potential to increase dissemination, with severe consequences on the health-related and economic burden caused by these infections. Due to resistance to carbapenems as well as other antibiotics, such a scenario would leave limited options for the treatment of *E. coli* infections, both in healthcare and community.

1 Background

New Delhi metallo-β-lactamase (NDM) is a metallo-β-lactamase capable of hydrolysing penicillin, cephalosporins and carbapenems, but not monobactams such as aztreonam. NDM is not inhibited by the β-lactamase inhibitors, avibactam, relebactam, vaborbactam, clavulanate, sulbactam, and tazobactam [1]. According to the Beta-Lactamase DataBase (BLDB), 48 NDM-variants have been detected as of the beginning of 2023 [2] in more than 60 bacterial species [1]. While NDM-1 is most frequently reported in *Klebsiella pneumoniae, Enterobacter* and *Acinetobacter* species, NDM-5 is most commonly detected in *Escherichia coli* [1]. NDM-5 was first described in 2011 in an *E. coli* ST648 isolate, from a patient in the United Kingdom (UK) who had been repatriated after hospitalisation in India [3]. Subsequently, it has been described throughout the world [4].

Five *E. coli* sequence types (STs) including ST131, ST167, ST405, ST410, and ST1284 were previously identified as associated with the global spread of carbapenemases [4]. Links between these STs and carbapenemases have been established as follows: ST131 and *Klebsiella pneumoniae* carbapenemases (KPCs), ST167 and NDM-5, ST405 and various carbapenemases, ST410 and NDM-5, as well as ST1284 and oxacillinase-181 (OXA-181) [4]. In European countries, the emergence of *E. coli* isolates of sequence types ST167, ST361, ST405, ST410, and ST1284 carrying the *bla*$_{NDM-5}$ gene has been recently described [5-8]. The structured survey of carbapenem- and/or colistin-resistant Enterobacterales (CCRE) [9] conducted in 2019 in 36 European countries showed a considerable increase of *E. coli* isolates carrying *bla*$_{NDM-5.}$ This was the reason for the initiation of this investigation.

1.1 Preliminary CCRE survey results on *Escherichia coli* isolates carrying *bla*$_{NDM-5}$

As described in a post on the European surveillance portal for infectious diseases (EpiPulse) [10] dated 1 June 2022, preliminary results of the CCRE survey show that NDM-5 has become the most frequently reported carbapenemase in *E. coli* isolates. The *bla*$_{NDM-5}$ gene was detected in 62 (30.8%) of 201 carbapenemase-producing *E. coli* isolates collected in 2019. This is a considerable increase compared to the *E. coli* dataset from the European survey of carbapenemase-producing Enterobacterales (EuSCAPE) project [11], which included only two (5.3%) *E. coli* isolates carrying *bla*$_{NDM-5}$ among a total of 38 carbapenemase-producing *E. coli* isolates which were collected in 2013. In 2019, the 62 *E. coli* isolates carrying *bla*$_{NDM-5}$ from the CCRE survey were detected in 15 countries (Czechia, Denmark, Estonia, Finland, France, Germany, Iceland, Italy, Luxembourg, the Netherlands, Norway, Slovenia, Sweden, Türkiye, and the UK[i]). The *bla*$_{NDM-5}$ gene was present in isolates belonging to 17 different *E. coli* STs, some of which (such as, ST167, ST405, ST410 and ST648) have been described as high-risk STs for extraintestinal infections. Forty-nine of the *E. coli* isolates carrying *bla*$_{NDM-5}$ were part of 14 clusters, 12 of which involved more than one country. The *bla*$_{NDM-5}$ gene occurred frequently in combination with either *bla*$_{CTX-M-15}$ or *bla*$_{CMY-42}$, which are capable of hydrolysing aztreonam.

Based on available phenotypic antimicrobial susceptibility testing (AST) results, the *E. coli* isolates carrying *bla*$_{NDM-5}$ showed 'resistant' or 'susceptible, increased exposure' to penicillins, cephalosporins, and carbapenems, as defined in the CCRE survey consensus protocol [12]. They also showed high percentages of resistance to aztreonam (31/37 tested isolates; 83.8%), trimethoprim-sulfamethoxazole (34/37; 91.9%), ciprofloxacin (49/51; 96.1%), and tobramycin (20/35; 57.1%). The percentages of 'resistant' or 'susceptible, increased exposure' were lower for tigecycline (3/43; 7.0%), fosfomycin (3/21; 14.3%), and colistin (2/55; 3.6%). *E. coli* isolates carrying *bla*$_{NDM-5}$ were isolated from samples that were recorded as clinical samples in 25/62 (40.3%) of the cases, with urine being the most frequent type of sample, and 20/57 (35.1%) cases with available information being classified as infections. Availability of data on travel and/or hospitalisation was very limited due to missing information. However, 13 patients had a reported link to another country (either direct hospital transfer, previous hospitalisation, or travel) within the six months prior to the detection of *E. coli* carrying *bla*$_{NDM-5}$. The countries mentioned at least once as links were, Cambodia, Egypt, India, Iran, Iraq, Russia, Syria, Somalia, and Thailand.

1.2 Data collection and molecular analysis

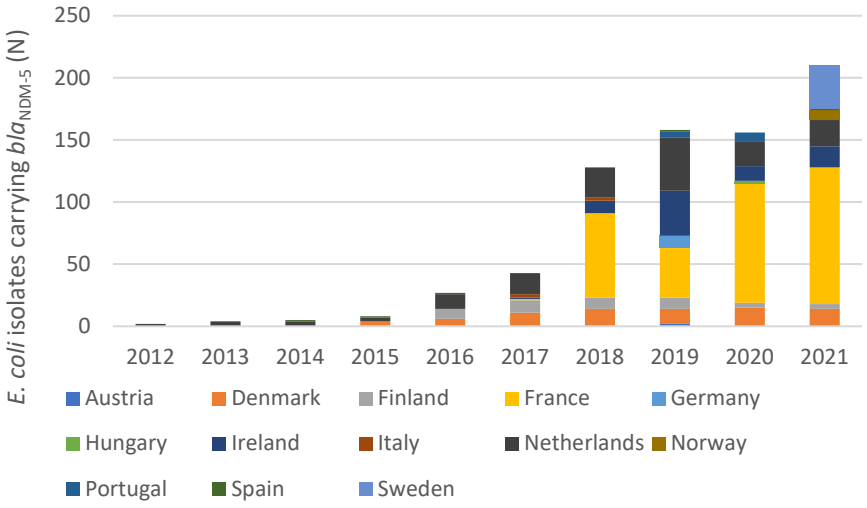
After posting the above information on EpiPulse on 1 June 2022, along with a request for data, ECDC received whole genome sequences of 905 *E. coli* isolates selected from the national collections in 13 European Union (EU) / European Economic Area (EEA) countries, of which 874 were included in further analyses. Twenty-nine isolates did not fit the quality criteria (assembled genome size 3.7–6.4 megabase pairs (Mbp) with ≥90% of covered core genome loci using the EnteroBase core genome multilocus sequence typing (cgMLST) scheme). Two isolates did not carry the *bla*$_{NDM-5}$ gene. Table 1 shows the number of included isolates by country and the period covered. Figure 1 shows the number of isolates by country and year.

[i]The United Kingdom (UK) is a former Member State of the European Union (EU). The UK withdrew from the EU on 31 January 2020.

Table 1. Number of *Escherichia coli* isolates carrying *bla*$_{NDM-5}$ submitted for analysis by country, 2012–2022 (n=874)

Country	Number of isolates	Period covered (First to last isolate)
Austria	4	2019–2022
Denmark	82	2015–2022
Finland	45	2016–2022
France	403	2017–2022
Germany	10	2019
Hungary	2	2020
Ireland	80	2017–2022
Italy	6	2017–2018
Netherlands	158	2012–2022
Norway	12	2021–2022
Portugal	13	2017–2020
Spain	5	2014–2021
Sweden	54	2021–2022
Total	**874**	**2012–2022**

Figure 1. Number of *Escherichia coli* isolates carrying *bla*$_{NDM-5}$ by country from national collections, 2012–2021* (n=741)



**The isolates for 2022 (n=133) are not displayed in this figure, as data for 2022 were incomplete at time of analysis.*

Whole genome sequences from ECDC surveys were added to the dataset for a part of the analysis (clustering), i.e. 62 *E. coli* isolates carrying *bla*$_{NDM-5}$ from the CCRE survey (2019), and two isolates from EuSCAPE (2013).

Whole genome sequences were also downloaded from the National Center for Biotechnology Information (NCBI) Pathogen Detection system on 20 July 2022, and 2 561 *E. coli* isolates carrying *bla*$_{NDM-5}$ were included after quality control. The countries of origin of the 2 561 sequences from the public domain are listed in Table 2. Of note, the availability/non-availability of sequences in the public domain is dependent on national systems for laboratory surveillance and reporting. This is not a reliable indicator of the prevalence of *E. coli* carrying *bla*$_{NDM-5}$.

Table 2. Public domain: Number of downloaded sequences of *Escherichia coli* isolates carrying *bla*$_{NDM-5}$ (n=2 561)* by the countries of origin

Country	Number of isolates
China	934
United States	557
United Kingdom	168
Australia	164
Thailand	128
Israel	100
India	97
Myanmar/Burma	70
Pakistan	57
Switzerland	57
Qatar	33
Germany	30
Other countries**	166
Total	**2 561**

** The period covered cannot be determined as sampling dates are not available for all isolates.*
*** Less than 20 sequences per country were included, by decreasing number of isolates. The sequences were from: Singapore (n=17), Bangladesh (n=15), Canada (n=15), Chile (n=12), Nepal (n=11), Kenya (n=11), Egypt (n=10), Italy (n=10), Lebanon (n=9), South Korea (n=8), Spain (n=7), France (n=6), Japan (n=6), Nigeria (n=5), the Netherlands (n=3), Tanzania (n=3), Taiwan (n=3), Vietnam (n=3), Malawi (n=2), Niger (n=2), Laos (n=2), Argentina (n=1), Cambodia (n=1), Czechia (n=1), Denmark (n=1), Ireland (n=1), and Norway (n=1).*

STs were determined by the MLST 2.0 tool developed by the Technical University of Denmark (DTU) [13] (version 2.0.9, database version 26 July 2022, using Achtman's MLST scheme for *E. coli* [14]). Resistance and virulence genes were determined using the *E. coli* analysis plugin of BioNumerics 7.6.3 with standard settings (thresholds with minimum 90% gene sequence identity and minimum 60% sequence length for gene coverage). Fluoroquinolone resistance point mutations were detected using the PointFinder tool developed by DTU [15] (reference sequences collected on 29 September 2022).

2 Results

2.1 Sequence types of *Escherichia coli* isolates carrying *bla*$_{NDM-5}$

The overall dataset included 3 435 *E. coli* isolates carrying *bla*$_{NDM-5}$ belonging to 267 STs. Of these, 237 STs were present in the 2 561 isolates from the public domain dataset, and 83 STs in the 874 isolates from the dataset combining sequences from national collections. A few *E. coli* STs were predominant in the dataset from the national collections as well as in the public domain dataset. Based on the distribution in the overall dataset as shown in the last column of Table 3, the most frequently identified ST was ST167, followed by ST410 and ST405. The ten most frequently identified STs accounted for 65.6% of isolates in the public domain dataset (1 681/2 561), and 72.9% of isolates in the dataset from national collections (637/874) (Table 3, Figure 2).

Table 3. The ten most frequent sequence types of *Escherichia coli* isolates carrying *bla*$_{NDM-5}$ in the overall dataset

E. coli sequence type	Isolates from the public domain		Isolates from national collections		Total
	N	%	N	%	N
ST167	559	21.8	200	22.9	**759**
ST410	350	13.7	96	11.0	**446**
ST405	244	9.5	115	13.2	**359**
ST361	118	4.6	70	8.0	**188**
ST648	99	3.9	65	7.4	**164**
ST617	106	4.1	31	3.5	**137**
ST156	56	2.2	23	2.6	**79**
ST10	62	2.4	9	1.0	**71**
ST46	31	1.2	28	3.2	**59**
ST48	56	2.2	0	0	**56**

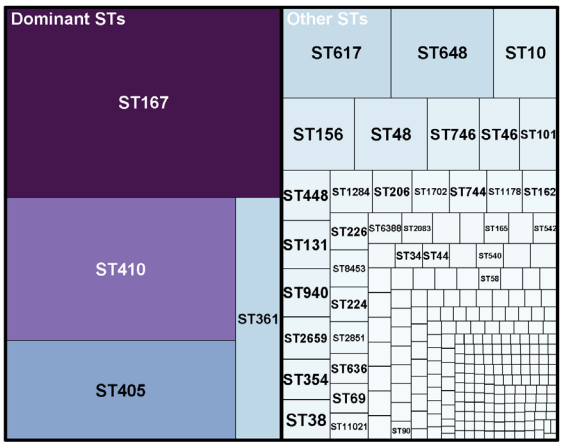
ST: sequence type

Eight *E. coli* STs (ST167, ST410, ST405, ST361, ST648, ST617, ST156, and ST46) were the same among the ten most frequent STs in both the public domain and national collections datasets. Two STs differed, i.e. ST1284 and ST2851 in the dataset from national collections, and ST10 and ST48 in the public domain dataset. The distribution of STs in both datasets is displayed in Figure 2.

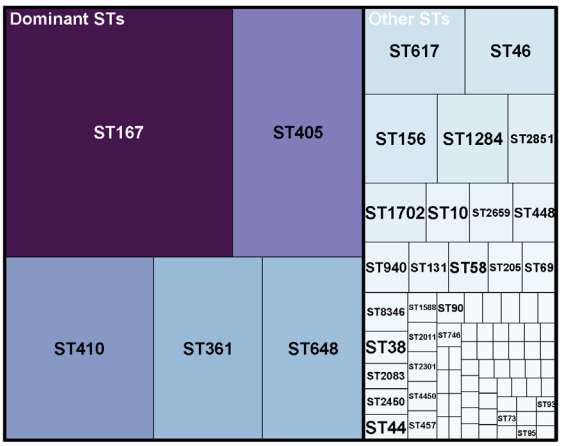
In line with the definitions used in published studies [4], major STs were defined as representing >10%, and minor STs as representing 5–10% of STs of the *E. coli* isolates carrying *bla*$_{NDM-5}$ in the dataset from national collections. Following these definitions, ST167, ST405, and ST410 were classified as major STs, and ST361 and ST648 as minor STs. These major and minor STs were then grouped together as dominant STs for the following analyses described in in the subsequent sections.

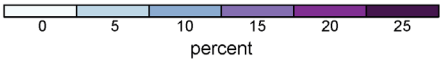
Figure 2. Distribution of sequence types of *Escherichia coli* isolates carrying *bla*$_{NDM-5}$ from two datasets: a) public domain, and b) national collections. Isolates without a specified sequence type were excluded.

a) Public domain



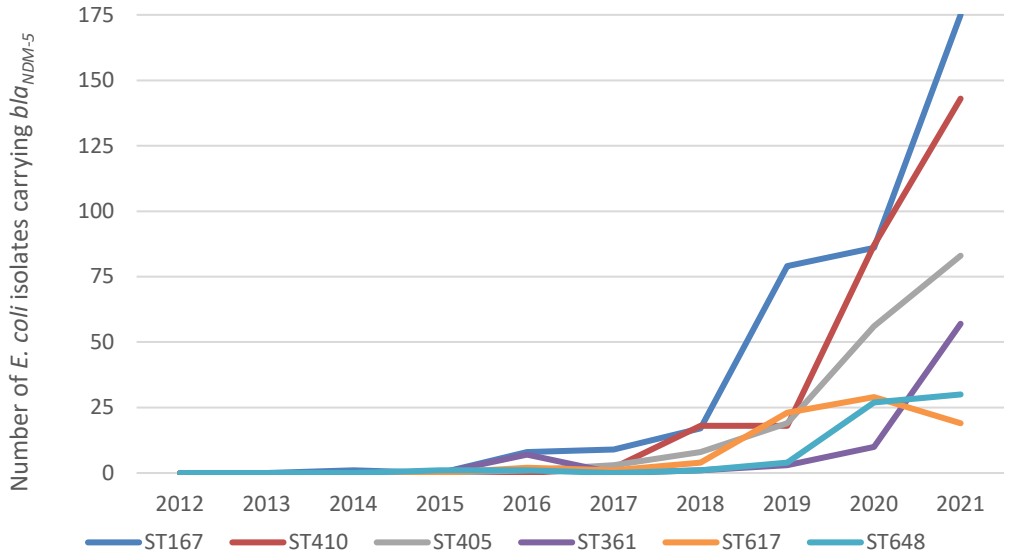
b) National collections





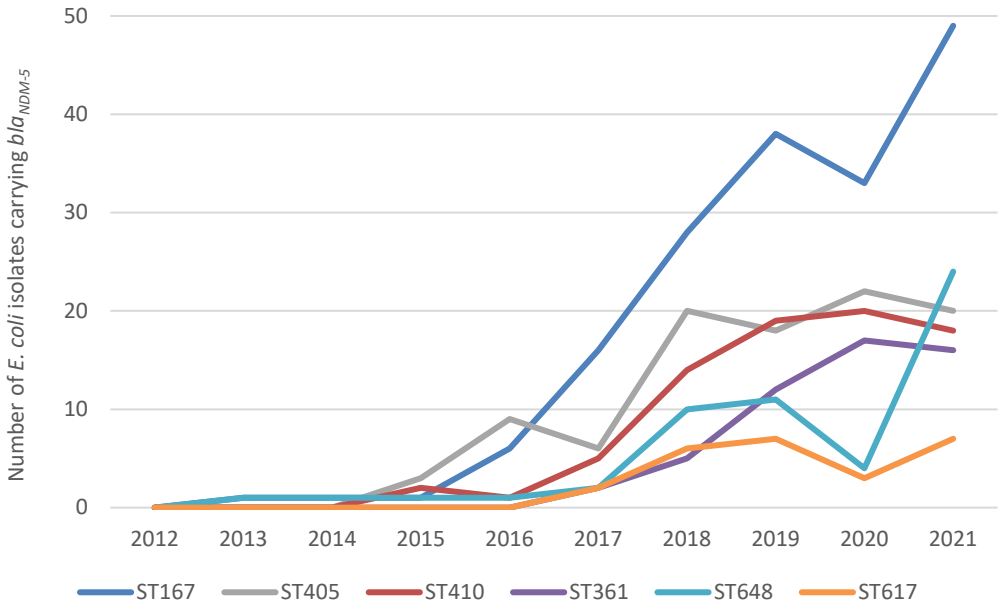
A trend of increasing frequency of detection over time was observed since 2013, especially for the most frequent STs, in the public domain and national collections datasets (Figures 3 and 4). However, this finding should be interpreted with caution due to likely detection and reporting biases.

Figure 3. Frequency of detection of the six most frequent sequence types of *Escherichia coli* isolates carrying *bla*$_{NDM-5}$, by year of uploading to public database in the public domain dataset* (n=1 033), 2012–2021



**The time distribution illustrated above should not be interpreted as an epidemic curve, as year-to-year variation is likely affected by detection and reporting biases and may not reflect true temporal trends in incidence. Isolates of the same STs from 2022 (n=443) are not displayed in this figure, as data for this year were incomplete at the time of analysis.*

Figure 4. Frequency of detection of the six most frequent sequence types of *Escherichia coli* isolates carrying *bla*$_{NDM-5}$ over time, by year of sampling in the dataset from national collections* (n=482), 2012–2021



**The time distribution illustrated above should not be interpreted as an epidemic curve, as year-to-year variation is likely affected by detection and reporting biases and may not reflect true temporal trends in incidence. Isolates of the same STs from 2022 (n=95) are not displayed in this figure, as data for this year were incomplete at the time of analysis.*

Table 4 lists the *E. coli* isolates carrying *bla*$_{NDM-5}$ submitted from national collections by country with a focus on the dominant STs. The five dominant STs of *E. coli* isolates carrying *bla*$_{NDM-5}$ (ST167, ST405, ST410, ST361, and ST648) were detected in all the six countries which submitted more than 20 isolates for analysis (i.e. Denmark, Finland, France, Ireland, the Netherlands, and Sweden).

Table 4. Isolates of the dominant sequence types of *Escherichia coli* isolates carrying *bla*$_{NDM-5}$ submitted from national collections (n=874), by country

E. coli sequence type	No. of isolates by country													
	AT	DE	DK	ES	FI	FR	HU	IE	IT	NL	NO	PT	SE	Total
ST167	0	2	23	1	5	95	0	8	4	42	3	6	11	200
ST405	0	2	8	2	8	49	0	15	0	24	0	0	7	115
ST410	0	2	7	0	3	54	1	8	2	13	0	1	5	96
ST361	0	1	9	0	3	42	0	5	0	6	2	0	2	70
ST648	0	1	5	0	6	18	0	11	0	12	1	0	11	65
Other STs	4	2	30	2	20	145	1	33	0	61	6	6	18	328
Total	**4**	**10**	**82**	**5**	**45**	**403**	**2**	**80**	**6**	**158**	**12**	**13**	**54**	**874**

AT: Austria; DE: Germany; DK: Denmark; ES: Spain; FI: Finland; FR: France; HU: Hungary; IE: Ireland; IT: Italy; NL: the Netherlands; NO: Norway; PT: Portugal; SE: Sweden.

2.2. Antimicrobial resistance determinants

2.2.1 β-lactam resistance

Out of 3 435 *E. coli* isolates carrying *bla*$_{NDM-5}$ included in the combined dataset from national collections and the public domain, several isolates (n=180) harboured additional carbapenemase genes, with 68.3% of these additional carbapenemase genes being detected in the dominant STs (Table 5). *bla*$_{OXA-181}$ was the most common carbapenemase gene (110/180, 61.1%) in addition to *bla*$_{NDM-5}$.

The combination of these genes was most frequent among ST410 *E. coli* isolates. Among the most frequent STs, 15.5% of ST410 isolates carried two carbapenemase genes, which was higher than for the other dominant STs (Table 5).

Table 5. *Escherichia coli* isolates carrying *bla*$_{NDM-5}$ with additional carbapenemase genes, by sequence types (n=180)

E. coli sequence type	No. of *bla*$_{NDM-5}$-positive *E. coli* isolates, by additional carbapenemase gene										
	bla$_{OXA-181}$	*bla*$_{OXA-244}$	*bla*$_{OXA-232}$	*bla*$_{OXA-48}$	*bla*$_{OXA-484}$	*bla*$_{OXA-347}$	*bla*$_{KPC-2}$	*bla*$_{KPC-3}$	*bla*$_{IMP-70}$	*bla*$_{OXA-181}$ + *bla*$_{IMP-4}$	Total (%)
ST167	11	6	1	5	1	0	1	0	0	1	26/759 (3.4)
ST405	5	1	3	1	1	0	0	0	0	0	11/359 (3.1)
ST410	52	0	3	3	0	0	11	0	0	0	69/446 (15.5)
ST361	3	6	1	1	1	0	0	2	0	0	14/188 (7.4)
ST648	2	0	1	0	0	0	0	0	0	0	3/164 (1.8)
Other STs	37	2	7	1	2	1	3	3	1	0	57/1 519 (3.8)
Total	**110**	**15**	**16**	**11**	**5**	**1**	**15**	**5**	**1**	**1**	**180/3 435 (5.2)**

ST: sequence type

Most *E. coli* isolates carrying *bla*$_{NDM-5}$ (2 129/3 435; 62.0%) also carried at least one extended-spectrum β-lactamase (ESBL) gene, with 62.3% of isolates of the dominant STs carrying an ESBL gene (Table 6). Among the five most frequent STs, the highest prevalence of ESBL genes was in ST405 (74.9%), followed by ST167 (73.6%) and ST410 (69.5%).

CTX-M family enzyme genes were the most common co-carried ESBL genes (2 096/2 129; 98.4%) with most isolates being positive for *bla*$_{CTX-M-15}$ (1 464/2 129; 68.8%) as a single ESBL gene. Out of 91 *E. coli* isolates carrying *bla*$_{NDM-5}$ and co-carrying a combination of two or three ESBL genes, the combination of *bla*$_{CTX-M-14}$-*bla*$_{TEM-126}$ was the most common (13/91; 14.3%). *bla*$_{CTX-M-14}$ (40/91; 44.0%) and *bla*$_{CTX-M-55}$ (39/91; 42.9%) were the most frequent ESBL determinants found in *bla*$_{NDM-5}$ *E. coli* isolates harbouring more than one ESBL gene. Additionally, one *bla*$_{NDM-5}$ *E. coli* isolate carried a combination of three ESBL genes: *bla*$_{CTX-M-15}$-*bla*$_{CTX-M-14b}$-*bla*$_{SHV-12}$.

Table 6. *Escherichia coli* isolates carrying *bla*$_{NDM-5}$ and co-carrying ESBL genes, by sequence types (n=2 129)

E. coli sequence type	No. of *bla*$_{NDM-5}$-positive *E. coli* isolates, by ESBL gene								
	One ESBL gene							Two or three ESBL genes	Total (%)
	bla$_{CTX-M-15}$	*bla*$_{CTX-M-55}$	*bla*$_{CTX-M-14}$	*bla*$_{CTX-M-65}$	*bla*$_{CTX-M-199}$	*bla*$_{SHV-12}$	Other ESBL genes*		
ST167	407	45	21	15	27	1	14	29	559/759 (73.6)
ST405	260	3	1	0	0	1	0	4	269/359 (74.9)
ST410	256	23	8	2	0	3	11	7	310/446 (69.5)
ST361	61	4	0	2	0	0	0	8	75/188 (39.9)
ST648	99	1	4	4	0	2	1	2	113/164 (68.9)
Other STs	381	142	111	68	4	13	43	41	803/1 519 (52.9)
Total	**1 464**	**218**	**145**	**91**	**31**	**20**	**69**	**91**	**2 129/3 435 (62.0)**

*ESBL: extended-spectrum β-lactamase; ST: sequence type; *ESBL genes found in <20 isolates*

Plasmid-mediated AmpC β-lactamases were also prevalent in *E. coli* carrying *bla*$_{NDM-5}$ (1 027/3 435; 29.9%) with 67.7% of *bla*$_{CMY}$ genes detected among the dominant STs. *bla*$_{CMY-42}$ (490/1 027; 47.7%) and *bla*$_{CMY-2}$ (406/1 027; 39.5%) were the most frequently detected plasmid-mediated AmpC β-lactamase genes with more than 50% of co-carriers being the dominant STs (78.8% for *bla*$_{CMY-2}$ and 54.7% for *bla*$_{CMY-42}$). Of note, while less than 20% of isolates of each dominant ST were positive for the *bla*$_{CMY-42}$ gene, a higher proportion of *E. coli* ST410 (266/406; 65.5%) compared to other dominant STs (each less than 11%) was harbouring *bla*$_{CMY-2}$. Additionally, other β-lactamase genes, such as *bla*$_{TEM-1B}$ and *bla*$_{OXA-1}$ were also commonly detected in the overall collection of *E. coli* carrying *bla*$_{NDM-5}$ isolates.

2.2.2 Predicted resistance to other antibiotics

Out of the *E. coli* isolates carrying *bla*$_{NDM-5}$ included in the overall dataset analysis (n=3 435), 94.2% were carrying aminoglycoside resistance genes. Among the five most frequent STs, aminoglycoside resistance was the most prevalent in ST405 (356/359; 99.2%) followed by ST361 (186/188; 98.9%), ST410 (440/446; 98.7%), ST648 (159/164; 97.0%), and ST167 (735/759; 96.8%). The most common determinants each harboured by more than 20% of isolates with predicted aminoglycoside resistance were: *aadA2* (2 424/3 236; 74.9%), *aac(6')-Ib-cr* (1 274/3 236; 39.4%), *aadA5* (1 125/3 236; 34.8%), and *rmtB* (796/3 236; 24.6%). All these genes encode enzymes that lead to high-level aminoglycoside resistance. However, *rmtB* is particularly worrisome due to its known resistance to next-generation aminoglycoside plazomicin and association with mobile genetic elements co-carrying *bla*$_{NDM-5}$ [16-18].

Chromosomal point mutations in DNA gyrase and topoisomerase IV enzymes associated with fluoroquinolone resistance were present in 93.0% of *E. coli* isolates carrying *bla*$_{NDM-5}$ and almost all isolates (99–100%) belonging to the five most frequent STs. The most prevalent set of mutations carried by 70.4% of the isolates with mutations in DNA replication enzymes (n=3 195) was S83L and D87N amino acid substitutions in DNA gyrase subunit A (encoded by *gyrA*), combined with S80I amino acid change in DNA topoisomerase IV subunit A (encoded by *parC*) and S458A mutation in subunit B (encoded by *parE*). Plasmid-mediated quinolone resistance genes were much less frequent (751/3 435; 21.9%), with *qnrS1* being the most prevalent gene (526/751; 70.0%).

Overall, very high proportions of trimethoprim (3 185/3 435; 92.7%) and sulfamethoxazole (3 223/3 435; 93.8%) resistance were predicted in the *E. coli* isolates carrying *bla*$_{NDM-5}$. Among the five most frequent STs, the highest proportion of trimethoprim resistance genes was detected in ST361 (185/188; 98.4%), followed by ST410 (433/446; 97.1%), ST405 (346/359; 96.4%), ST167 (731/759; 96.3%), and ST648 (141/164; 86.0%). A similar trend was observed for sulfamethoxazole resistance determinants in ST361 (186/188; 98.9%), ST410 (436/446; 97.8%), ST405 (351/359; 97.8%), ST167 (737/759; 97.1%), and ST648 (145/164; 88.4%). Most of the *E. coli* carrying *bla*$_{NDM-5}$ with predicted trimethoprim resistance harboured the *dfrA12* (2 281/3 185; 71.6%) and *dfrA17* (1 156/3 185; 36.3%) genes.

Among the *E. coli* carrying *bla*$_{NDM-5}$ with predicted sulfamethoxazole resistance, *sul1* (2 776/3 223; 86.1%) and *sul2* (1 483/3 223; 46.0%) genes were the most prevalent. Trimethoprim and sulfamethoxazole resistance genes mostly complemented each other in various combinations.

Among the *E. coli* carrying *bla*$_{NDM-5}$, resistance to colistin was predicted to be 5.1% (n=176) and tigecycline to be 0.3% (n=10) based on the *mcr-1.1* and *tet*(X) genes respectively.

2.3 Epidemiological and clinical information

Description of the epidemiological and clinical information is restricted to the 874 isolates included from national collections, due to the absence of standardised epidemiological information for sequences in the public domain.

2.3.1 Infection or carriage

Data on the infection/carriage status was available for 618 (70.7%) of the 874 *E. coli* isolates carrying *bla*$_{NDM-5}$ from national collections. Of those, 189 (30.6%) were associated with infection, and 425 (68.8%) with carriage. The infection/carriage status was undetermined for 4 (0.6%) isolates. The numbers and percentages of infection and carriage for the dominant STs are shown in Table 7. Of the 189 reported *E. coli* isolates carrying *bla*$_{NDM-5}$ associated with infections, 125 (66.1%) belonged to the five most frequent STs (Table 7).

Table 7. Frequency of infection and carriage for isolates of the dominant sequence types of *Escherichia coli* isolates carrying *bla*$_{NDM-5}$ (n=546)

E. coli sequence type	Infection N (%)	Carriage N (%)	Undetermined N (%)	Information not available N (%)	Total
ST167	33 (16.5)	121 (60.5)	1 (0.5)	45 (22.5)	200
ST405	42 (36.5)	38 (33.0)	1 (0.9)	34 (29.6)	115
ST410	24 (25.0)	50 (52.1)	0 (0)	22 (22.9)	96
ST361	19 (27.1)	37 (52.9)	0 (0)	14 (20.0)	70
ST648	7 (10.8)	28 (43.1)	1 (1.5)	29 (44.6)	65

ST: sequence type

2.3.2 Type and site of sample

For 766 (87.6%) of the 874 *E. coli* isolates carrying *bla*$_{NDM-5}$, information was available regarding the detection of these isolates from a clinical sample, or a sample related to screening activities. Of these, 234 (30.5%) *E. coli* isolates carrying *bla*$_{NDM-5}$ originated from clinical samples, and 532 (69.5%) from screening samples. Among the isolates from clinical samples, the most frequent specimen type was urine (n=178; 76.1%). Isolation from other sites such as blood (n=23; 9.8%) and the respiratory tract (n=6; 2.6%) was less frequent. Of the 234 isolates from clinical samples, 150 (64.1%) belonged to the five most frequent STs of *E. coli* isolates carrying *bla*$_{NDM-5}$ (Table 8).

Table 8. Number of *Escherichia coli* isolates of the dominant sequence types carrying *bla*$_{NDM-5}$ from clinical and screening samples (n=589)

E. coli sequence type	Screening sample N (%)	Clinical sample			Information not available N (%)	Total
		Urine N (%)	Blood N (%)	Other/NA N (%)		
ST167	134 (62.6)	29 (13.6)	6 (2.8)	8 (3.7)	37 (17.3)	214
ST405	57 (47.1)	35 (28.9)	5 (4.1)	8 (6.6)	16 (13.2)	121
ST410	60 (58.3)	20 (19.4)	4 (3.9)	4 (3.9)	15 (14.6)	103
ST361	44 (57.1)	19 (24.7)	0 (0)	3 (3.9)	11 (14.3)	77
ST648	43 (58.1)	7 (9.5)	0 (0)	2 (2.7)	22 (29.7)	74

2.3.3 Healthcare or community acquisition

Information on the classification of cases as healthcare-associated or community-acquired was available for 252 (28.8%) of the 874 *E. coli* isolates carrying *bla*$_{NDM-5}$. Of these, 135 (53.6%) were classified as healthcare-associated and 117 (46.4%) isolates as community-acquired.

2.3.4 Age and sex distribution

Information on the age of the patients with the included *E. coli* isolates carrying *bla*$_{NDM-5}$ was available for 781 (89.4%) of the 874 isolates. The median age was 61 years (25th–75th percentile: 45–73 years; range: 0–99 years). Information on sex was available for 756 (86.5%) of the 874 isolates, with 452 (59.8%) male and 304 (40.2%) female cases. This is different from a previous analysis for the risk assessment of OXA-244-producing *E. coli* in 2021, which showed a younger age (median 54 years), and a predominance of female cases with 145 (69.7%) out of 208 cases for which information on sex was available [19].

2.3.5 Links to countries outside of the EU/EEA

Out of 341 *E. coli* isolates carrying *bla*$_{NDM-5}$ with available information on prior travel and/or hospitalisation within the past six months before sampling, links to countries outside of the EU/EEA were reported for 287 (84.2%) isolates, mostly countries in Asia (158/341; 46.3% isolates) or Africa (125/341; 36.7% isolates). The most frequent countries mentioned as a link to the *E. coli* isolates carrying *bla*$_{NDM-5}$ were: India (n=68), Egypt (n=28), Pakistan (n=18), Mali (n=11), Iraq (n=10), Congo (n=9), Senegal (n=9), Thailand (n=9), Madagascar (n=8), Afghanistan (n=7), Türkiye (n=6), Vietnam (n=6), Cameroon (n=5), Guinea (n=5), and Somalia (n=5). Countries mentioned at least twice (but less than five times) were (in a descending order): the Comoros, Ethiopia, Gabon, Kuwait, Lebanon, Nepal, Sri Lanka, Sudan, Syria, Algeria, Cambodia, Central African Republic, Côte d'Ivoire, Morocco, Myanmar/Burma, Tunisia, Bangladesh, China, the Democratic Republic of the Congo, Mauritius, Mayotte, and Tanzania. The links to countries outside of the EU/EEA for the dominant STs are listed in Table 9.

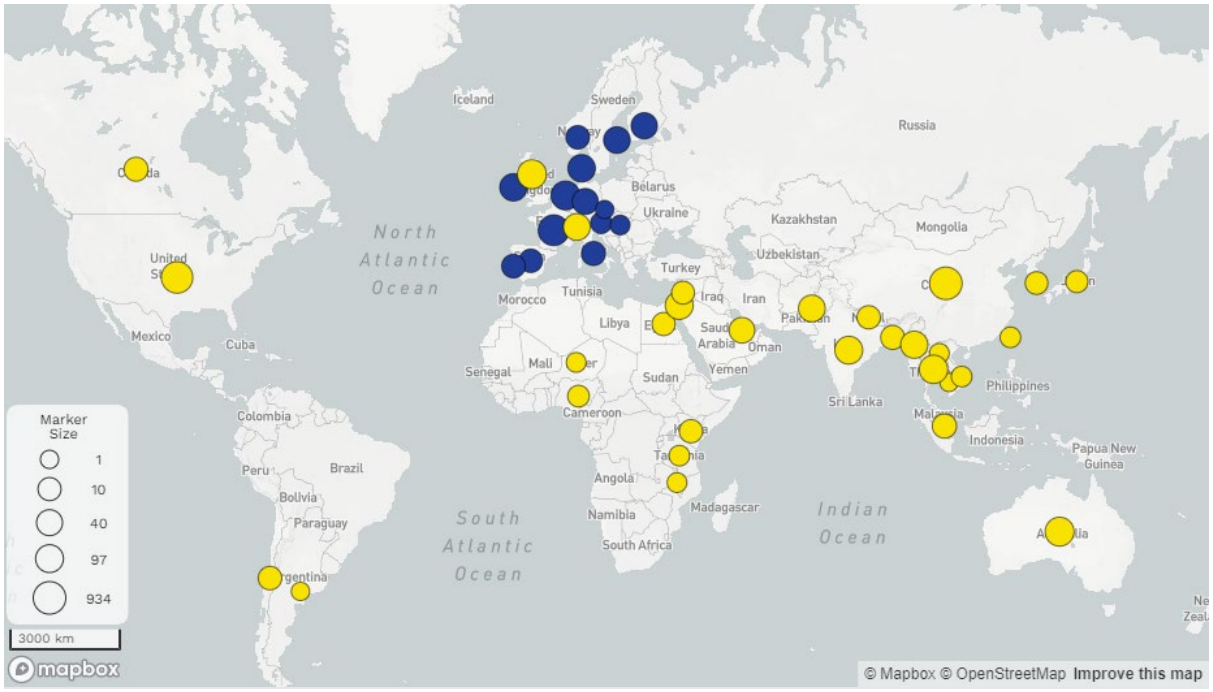
Table 9. Reported links to countries outside of the EU/EEA based on prior travel and/or prior hospitalisation within six months prior to detection, for the dominant sequence types of *Escherichia coli* isolates carrying *bla*$_{NDM-5}$

E. coli sequence type	No. of isolates		Links to countries outside of the EU/EEA mentioned at least twice
	Total submitted from national collections	With information about prior travel and/or prior hospitalisation	
ST167	214	86	India (n=22), Egypt (n=11), Madagascar (n=6), Senegal (n=5), Mali (n=4), Pakistan (n=4), Ethiopia (n=3), Iraq (n=3), Congo (n=3), Afghanistan (n=2), Cameroon (n=2), Guinea (n=2), Myanmar/Burma (n=2), Nepal (n=2), Somalia (n=2)
ST405	121	25	India (n=9), Egypt (n=4), Sri Lanka (n=3)
ST410	103	32	India (n=4), Mali (n=4), Vietnam (n=4), Cambodia (n=3), Egypt (n=3), Thailand (n=3)
ST361	77	25	Egypt (n=5), India (n=5), Pakistan (n=4), Algeria (n=3)
ST648	74	25	India (n=6), Iraq (n=4), Bangladesh (n=2), Somalia (n=2), Türkiye (n=2)

ST: sequence type

The following three maps show the country distribution of the whole genome sequence data of *E. coli* isolates carrying *bla*$_{NDM-5}$ for the overall dataset (n=3 435 isolates; Figure 5), as compared to the travel destinations (n=248; Figure 6), and countries of hospitalisation (n=42; Figure 7) outside of the EU/EEA associated with *E. coli* isolates carrying *bla*$_{NDM-5}$ in the dataset from national collections. While Figure 6 shows the travel destinations throughout Africa and Asia, there were much less whole genome sequence data available from African countries than Asian countries (Figure 5).

Figure 5. *Escherichia coli* isolates carrying *bla*$_{NDM-5}$ from the overall dataset (n=3 435), by country of detection



EU/EEA countries (blue) and countries outside of the EU/EEA (yellow). The size of the marker corresponds to the number of reported isolates per country.

Figure 6. *Escherichia coli* isolates carrying *bla*$_{NDM-5}$ from national collections, with reported links to prior travel to countries outside of the EU/EEA (n=248)

The size of the marker corresponds to the number of reported isolates per travel destination.

Figure 7. *Escherichia coli* isolates carrying *bla*$_{NDM-5}$ from national collections with reported links to prior hospitalisation in countries outside of the EU/EEA (n=42)

The size of the marker corresponds to the number of reported isolates per country of hospitalisation.

2.4 Clusters

Based on a threshold of 10 allelic differences using the EnteroBase cgMLST scheme [20], 428 clusters were identified in the overall dataset including 3 499 isolates (this is inclusive of 64 isolates from ECDC surveys), with a range in size from 2–106 isolates. In total, 2 143 isolates were part of the clusters. This included 1 597 isolates from the public domain dataset and 546 isolates from the national collections and ECDC surveys, while 1 356 isolates were not part of any cluster. The 546 isolates from the national collections and ECDC surveys were part of 166 (38.8%) out of 428 clusters.

Clusters were associated with 93 STs of *E. coli* isolates carrying *bla*$_{NDM-5}$. However, the highest number of clusters occurred for the dominant STs: ST167 (n=83 clusters), ST405 (n=52 clusters), ST410 (n=39 clusters), ST361 (n=24 clusters), and ST648 (n=23 clusters). The 10 largest clusters are listed in Table 10. All these clusters included isolates from the national collections and the ECDC survey dataset, as well as the public domain dataset. Further details of the clusters are available in the molecular typing tool in EpiPulse.

Table 10. The 10 largest clusters of *Escherichia coli* isolates carrying *bla*$_{NDM-5}$ based on a threshold of 10 allelic differences using the EnteroBase cgMLST scheme

Cluster name	*E. coli* sequence type	Total isolates in cluster N	Isolates from the national collections or ECDC survey in cluster N	Countries reporting isolates	Period
2022-07.ECOLI.03.ST167	ST167	106	32	US (72), FR (20), NL (6), DK (2), CH (1), ES (1), IE (1), NO (1), PK (1) UK (1)	2018–2022
2022-07.ECOLI.12.ST167	ST167	104	8	US (72), CN (16), UK (6), IT (4), DE (2), NL (2), FR (1), IE (1)	2017–2022
2022-07.ECOLI.05.ST410	ST410	78	18	TH (40), FR (11), AU (5), MM (5), CN (4), IE (3), KR (3), VN (2), CH (1), DK (1), FI (1), NL (1), SE (1)	2016–2022
2022-08.ECOLI.07.ST410	ST410	65	1	IL (61), UK (3), DE (1)	2018–2022

Cluster name	*E. coli* sequence type	Total isolates in cluster N	Isolates from the national collections or ECDC survey in cluster N	Countries reporting isolates	Period
2022-07.ECOLI.23.ST167	ST167	48	7	UK (6), CN (6), MM (5), PK (5), KE (4), DK (3), AU (2), CH (2), NL (2), TH (2), TZ (2), US (2), DE (1), FI (1) IE (1), IL (1), IN (1), LB (1), SG (1)	2017–2022
2022-07.ECOLI.19.ST410	ST410	46	11	UK (9), EG (8), CN (7), DK (5), FR (3), IN (2), IT (2), NL (2), AU (1), CH (1), DE (1), KR (1), MM (1), QA (1), SG (1), US (1)	2015–2022
2022-07.ECOLI.34.ST410	ST410	44	9	TH (34), FR (7), HU (1), NL (1), US (1)	2017–2022
2022-07.ECOLI.28.ST156	ST156	41	21	UK (10), FR (9), US (7), FI (3), NL (4), SE (3), AU (2), DK (2), PK (1)	2016–2022
2022-07.ECOLI.02.ST648	ST648	38	14	US (14), SE (5), AU (4), IN (4), FR (3), UK (3), FI (2), DE (1), IE (1), KE (1)	2017–2022
2022-07.ECOLI.36.ST405	ST405	36	9	UK (12), AU (6), NL (3), CN (2), FR (2), LB (2), US (2), DK (1), FI (1), IN (1), IS (1), QA (1), PK (1), SE (1)	2015–2022

AU: Australia; CH: Switzerland; CN: China; DE: Germany; DK: Denmark; EG: Egypt; ES: Spain; FI: Finland; FR: France; HU: Hungary; IE: Ireland; IL: Israel; IN: India; IS: Iceland; IT: Italy; KE: Kenya; KR: South Korea; LB: Lebanon; MM: Myanmar/Burma; NL: The Netherlands; NO: Norway; PK: Pakistan; QA: Qatar; SE: Sweden; SG: Singapore; TH: Thailand; TZ: Tanzania; UK: The United Kingdom; US: The United States; VN: Vietnam; cgMLST: core genome multilocus sequence typing; ST: sequence type.

The seven largest clusters comprised isolates from only two *E. coli* STs, namely ST167 and ST410. All the large clusters which have been listed include recent isolates from 2022, isolates from various countries, and (in some cases) different continents, indicating the ongoing global dissemination of *E. coli* carrying *bla*$_{NDM-5}$ including the EU/EEA.

3 Conclusions

The increase of *E. coli* isolates carrying *bla*$_{NDM-5}$ in the EU/EEA detected in the carbapenem- and/or colistin-resistant Enterobacterales (CCRE) survey was confirmed by data from the national collections. While the *bla*$_{NDM-5}$ gene was detected in 83 different STs of *E. coli* submitted from the national collections, there was a strong predominance of a few *E. coli* STs, mainly ST167, ST405, ST410, ST361, and ST648. Based on the sequences in the public domain, these dominant STs of *E. coli* isolates carrying *bla*$_{NDM-5}$ have a global distribution. The high number and the large size of multi-country clusters, including recent isolates from 2022, suggest rapid and ongoing global expansion of these dominant STs of *E. coli* carrying *bla*$_{NDM-5}$, including the EU/EEA.

Despite limited data completeness, about 84.2% of the *E. coli* isolates carrying *bla*$_{NDM-5}$ detected in EU/EEA countries with available information on prior travel/hospitalisation were linked to a country outside of the EU/EEA suggesting that acquisition outside of the EU/EEA may still be the most likely origin of these isolates. The main countries outside of the EU/EEA linked to *E. coli* isolates carrying *bla*$_{NDM-5}$ detected in the EU/EEA were countries in Africa and Asia. However, there are a few examples of clusters of closely related isolates that could potentially be related to transmission within some EU/EEA countries. These need further investigation.

About 30% of the *E. coli* isolates carrying *bla*$_{NDM-5}$ were documented as related to infections emphasising the clinical relevance and need for early detection. A high proportion of these isolates also carry ESBLs (62.0%) associated with resistance to aztreonam. This is significant because monobactams are a class of β-lactam antibiotics which are not inactivated by NDM enzymes. A high proportion of these isolates showed markers of resistance to aminoglycosides, fluoroquinolones, and trimethoprim-sulfamethoxazole, indicating multidrug resistance with limited options left for the treatment of patients.

Carbapenem resistance in *E. coli* in EU/EEA countries has so far been very low with only 0.2% in invasive isolates, according to a report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) [21]. However, the results from this study indicate that *E. coli* carrying *bla*$_{NDM-5}$ is already established as a significant concern in EU/EEA countries. Further spread within and between EU/EEA countries, particularly in healthcare facilities, as well as introductions from outside the EU/EEA have the potential to increase dissemination, with severe consequences on the health-related and economic burden caused by these infections. Due to resistance to various antibiotics, including the carbapenems, such a scenario would leave limited options for the treatment of *E. coli* infections, both in healthcare and the community. The large number of clusters with isolates from various countries indicate that the spread of *E. coli* isolates carrying *bla*$_{NDM-5}$ is occurring rapidly and on a large geographic scale with a considerable risk for rapidly increasing carbapenem resistance in *E. coli* in the EU/EEA.

References

1. Wu W, Feng Y, Tang G, Qiao F, McNally A, Zong Z. NDM Metallo-β-Lactamases and Their Bacterial Producers in Health Care Settings. Clin Microbiol Rev. 2019 Mar 20;32(2):e00115-18. Available at: https://cmr.asm.org/content/cmr/32/2/e00115-18.full.pdf
2. Naas T, Oueslati S, Bonnin RA, Dabos ML, Zavala A, Dortet L, et al. Beta-lactamase database (BLDB) - structure and function. J Enzyme Inhib Med Chem. 2017 Dec;32(1):917-9. Available at: https://www.tandfonline.com/doi/full/10.1080/14756366.2017.1344235
3. Hornsey M, Phee L, Wareham DW. A novel variant, NDM-5, of the New Delhi metallo-β-lactamase in a multidrug-resistant *Escherichia coli* ST648 isolate recovered from a patient in the United Kingdom. Antimicrob Agents Chemother. 2011 Dec;55(12):5952-4. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3232805/pdf/zac5952.pdf
4. Peirano G, Chen L, Nobrega D, Finn TJ, Kreiswirth BN, DeVinney R, et al. Genomic Epidemiology of Global Carbapenemase-Producing *Escherichia coli,* 2015-2017. Emerg Infect Dis. 2022 May;28(5):924-31. Available at: https://wwwnc.cdc.gov/eid/article/28/5/pdfs/21-2535.pdf
5. Chakraborty T, Sadek M, Yao Y, Imirzalioglu C, Stephan R, Poirel L, et al. Cross-Border Emergence of *Escherichia coli* Producing the Carbapenemase NDM-5 in Switzerland and Germany. J Clin Microbiol. 2021 Feb 18;59(3):e02238-20. Available at: https://journals.asm.org/doi/10.1128/JCM.02238-20
6. Garcia-Fernandez A, Villa L, Bibbolino G, Bressan A, Trancassini M, Pietropaolo V, et al. Novel Insights and Features of the NDM-5-Producing *Escherichia coli* Sequence Type 167 High-Risk Clone. mSphere. 2020 Apr 29;5(2):e00269-20. Available at: https://journals.asm.org/doi/10.1128/mSphere.00269-20
7. Roer L, Overballe-Petersen S, Hansen F, Schønning K, Wang M, Røder BL, et al. *Escherichia coli* Sequence Type 410 Is Causing New International High-Risk Clones. mSphere. 2018 Jul 18;3(4):e00337-18. Available at: https://journals.asm.org/doi/10.1128/mSphere.00337-18
8. Bibbolino G, Di Lella FM, Oliva A, Lichtner M, Del Borgo C, Raponi G, et al. Molecular epidemiology of NDM-5-producing *Escherichia coli* high-risk clones identified in two Italian hospitals in 2017-2019. Diagn Microbiol Infect Dis. 2021 Aug;100(4):115399. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0732889321000924?via%3Dihub
9. European Centre for Disease Prevention and Control (ECDC). ECDC study protocol for genomic-based surveillance of carbapenem-resistant and/or colistin-resistant Enterobacteriaceae at the EU level. Version 2.0. Stockholm: ECDC; 2018. Available at: https://ecdc.europa.eu/en/publications-data/ecdc-study-protocol-genomic-based-surveillance-carbapenem-resistant-andor
10. European Centre for Disease Prevention and Control (ECDC). EpiPulse - the European surveillance portal for infectious diseases. Stockholm: ECDC; 2021. Available at: https://www.ecdc.europa.eu/en/publications-data/epipulse-european-surveillance-portal-infectious-diseases
11. Grundmann H, Glasner C, Albiger B, Aanensen DM, Tomlinson CT, Andrasević 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. Available at: https://www.sciencedirect.com/science/article/pii/S1473309916302572?via%3Dihub
12. European Centre for Disease Prevention and Control (ECDC). Expert consensus protocol on carbapenem resistance detection and characterisation for the survey of carbapenem- and/or colistin-resistant Enterobacteriaceae. Stockholm: ECDC; 2019. Available at: https://ecdc.europa.eu/en/publications-data/expert-consensus-protocol-carbapenem-resistance-detection-and-characterisation
13. Larsen MV, Cosentino S, Rasmussen S, Friis C, Hasman H, Marvig RL, et al. Multilocus sequence typing of total-genome-sequenced bacteria. J Clin Microbiol. 2012 Apr;50(4):1355-61. Available at: https://journals.asm.org/doi/10.1128/JCM.06094-11
14. Wirth T, Falush D, Lan R, Colles F, Mensa P, Wieler LH, et al. Sex and virulence in *Escherichia coli*: an evolutionary perspective. Mol Microbiol. 2006 Jun;60(5):1136-51. Available at: https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2958.2006.05172.x
15. Zankari E, Allesøe R, Joensen KG, Cavaco LM, Lund O, Aarestrup FM. PointFinder: a novel web tool for WGS-based detection of antimicrobial resistance associated with chromosomal point mutations in bacterial pathogens. J Antimicrob Chemother. 2017 Oct 1;72(10):2764-8. Available at: https://academic.oup.com/jac/article/72/10/2764/3979530
16. Cox G, Ejim L, Stogios PJ, Koteva K, Bordeleau E, Evdokimova E, et al. Plazomicin Retains Antibiotic Activity against Most Aminoglycoside Modifying Enzymes. ACS Infect Dis. 2018 Jun 8;4(6):980-7. Available at: https://pubs.acs.org/doi/10.1021/acsinfecdis.8b00001
17. Castanheira M, Deshpande LM, Woosley LN, Serio AW, Krause KM, Flamm RK. Activity of plazomicin compared with other aminoglycosides against isolates from European and adjacent countries, including Enterobacteriaceae molecularly characterized for aminoglycoside-modifying enzymes and other resistance mechanisms. J Antimicrob Chemother. 2018 Dec 1;73(12):3346-54. Available at: https://academic.oup.com/jac/article/73/12/3346/5096851

18. Turton JF, Pike R, Perry C, Jenkins C, Turton JA, Meunier D, et al. Wide distribution of *Escherichia coli* carrying IncF plasmids containing *bla*$_{NDM-5}$ and *rmtB* resistance genes from hospitalized patients in England. J Med Microbiol. 2022 Aug;71(8). Available at: https://www.microbiologyresearch.org/content/journal/jmm/10.1099/jmm.0.001569
19. European Centre for Disease Prevention and Control (ECDC). Rapid risk assessment: Increase in OXA-244-producing *Escherichia coli* in the European Union/European Economic Area and the UK since 2013, first update. Stockholm: ECDC; 2021. Available at: https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-increase-oxa-244-producing-escherichia-coli-eu-eea
20. Zhou Z, Alikhan NF, Mohamed K, Fan Y, Agama Study G, Achtman M. The EnteroBase user's guide, with case studies on *Salmonella* transmissions, *Yersinia pestis* phylogeny, and *Escherichia core* genomic diversity. Genome Res. 2020 Jan;30(1):138-52. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31809257
21. European Centre for Disease Prevention and Control (ECDC). Antimicrobial resistance in the EU/EEA (EARS-Net) - Annual epidemiological report for 2021. Stockholm: ECDC; 2022. Available at: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2021

European Centre for Disease Prevention and Control (ECDC)

Gustav III:s Boulevard 40, 16973 Solna, Sweden

Tel. +46 858601000
Fax +46 858601001
www.ecdc.europa.eu

An agency of the European Union
www.europa.eu

Subscribe to our publications
www.ecdc.europa.eu/en/publications

Contact us
publications@ecdc.europa.eu

Follow us on Twitter
@ECDC_EU

Like our Facebook page
www.facebook.com/ECDC.EU

Publications Office
of the European Union