



Review

Frequency distribution, genotypes and prevalent sequence types of New Delhi metallo- β -lactamase-producing *Escherichia coli* among clinical isolates around the world: A review

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ABSTRACT

Objectives: New Delhi metallo- β -lactamase (NDM)-producing *Escherichia coli* is perceived as one of the primary multidrug-resistant bacteria causing infections in hospitals and clinics. In this review, we present the frequency distribution, genotypes and most prevalent sequence types (STs) of NDM-producing *E. coli* among clinical isolates worldwide.

Methods: Several international databases, including Medline, Embase, Scopus and Web of Science, were searched from 2008 to 2018 to identify studies addressing the prevalence of NDM-producing *E. coli* around the world.

Results: Of 974 records identified from the databases, 110 studies fulfilled the eligibility criteria and were included in this analysis. The prevalence of NDM-producing *E. coli* was 82.6%, 12.9%, 1.5%, 1.0% and 2.0% in Asia, Europe, America, Africa and Oceania, respectively. The most common reported STs among NDM-producing *E. coli* were ST101, ST167, ST131, ST405, ST410 and ST648.

Conclusion: The spread of NDM variants among *E. coli* strains is a serious threat to global public health. In addition, the most prevalent *E. coli* clonal groups, such as ST101 and ST167, are one of the main causes of *E. coli* infection in different countries.

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1. Introduction

Nowadays, antimicrobial resistance is a serious threat to public health all around the globe [1]. Researchers are trying to overcome this challenge by identifying and producing new and more effective antibiotics. Bacteria producing β -lactamase enzymes are able to resist β -lactam antibiotics. Carbapenem antibiotics were developed to tackle β -lactamase-producing bacteria [2]. Unfortunately, following widespread use of carbapenems, various members of the family Enterobacteriaceae as well as other Gram-negative bacteria have become resistant to this group of antibiotics by acquiring new genes encoding carbapenem-hydrolysing enzymes called carbapenemases [3,4]. Moreover, transferable resistance plasmids play an important role in the spread of extended-spectrum β -lactamases (ESBLs) around the world [5,6].

In 2009, New Delhi metallo- β -lactamase (NDM) was detected for the first time in a *Klebsiella pneumoniae* isolate from a Swedish patient who had been hospitalised in New Delhi, India [7]. Thereafter, detection of carbapenemase-producing Gram-negative bacteria was reported from numerous countries worldwide, creating a serious problem for controlling bacterial infections, especially in hospitals [8–11]. Among Gram-negative bacteria, NDM enzymes are more commonly found in *Escherichia coli* and *K. pneumoniae* [12,13]. Several NDM enzyme variants have been identified in different species of Enterobacteriaceae and other Gram-negative bacilli such as *Pseudomonas* and *Acinetobacter* spp. [14,15]. Amino acid substitution is the main factor behind genetic variations between NDM variants [16].

The highest distribution of NDM-producing bacteria has been observed in Asian countries, especially China and India [8,17,18]. Brazil and Algeria are a major reservoir of NDM-1-producing bacteria in the American and African continents, respectively. In Europe, the highest rates of NDM-1 spread have been observed in Bulgaria, Italy, Turkey, Germany, Greece, Romania, Poland, France, Serbia, the UK and Ukraine. Moreover, NDM-5 and NDM-7 are abundant in Denmark and Finland, whilst NDM-4 is prevalent in Italy [8,19,20].

The frequency of NDM-producing bacteria of different sequence types (STs) was reported in most studies [21,22]. Various STs have been reported in NDM-producing *E. coli* isolates in different continents and countries, therefore it seems that knowing the most prevalent STs is important for discriminating outbreak strains and for infection control policies around the world.

The aim of the present study was to investigate the frequency distribution, genotypes and most prevalent STs of NDM-producing *E. coli* among clinical isolates worldwide.

2. Methods

2.1. Search strategy and selection criteria

A systematic search on the prevalence of NDM-producing *E. coli* around the world was conducted by searching the Medline (via PubMed), Embase, Scopus and Web of Science databases from 2008 to 2018. Scientific search terms were '*Escherichia coli*' or '*E. coli*' and 'New Delhi metallo- β -lactamase' or 'NDM' or '*bla*_{NDM}'. The search was restricted to original articles published in English that indicated the epidemiology of NDM variants in *E. coli* strains

isolated from human samples in different geographic regions. The bibliographies of each retrieved article were also searched to identify further relevant studies.

2.2. Eligibility

2.2.1. Inclusion criteria

All original papers presenting cross-sectional studies on the prevalence of NDM-producing *E. coli* were selected. The title, abstract and full-text of selected studies were independently evaluated and assessed for eligibility. All of the included articles were evaluated according to the following criteria: (i) original articles that provided sufficient data on the prevalence of NDM variants in *E. coli* isolated from human clinical samples; and (ii) studies used valid molecular methods for detecting NDM and presented data regarding the number of enrolled patients.

2.2.2. Exclusion criteria

Studies on non-human subjects, studies that considered NDM-producing bacteria other than *E. coli*, and studies that reviewed other types of carbapenemase as well as review articles, systematic reviews, meta-analyses and duplicate publications for the same investigation were excluded from the study.

2.3. Data extraction and definitions

The following information was extracted from included studies: first author's name; year of study; publication year; country;

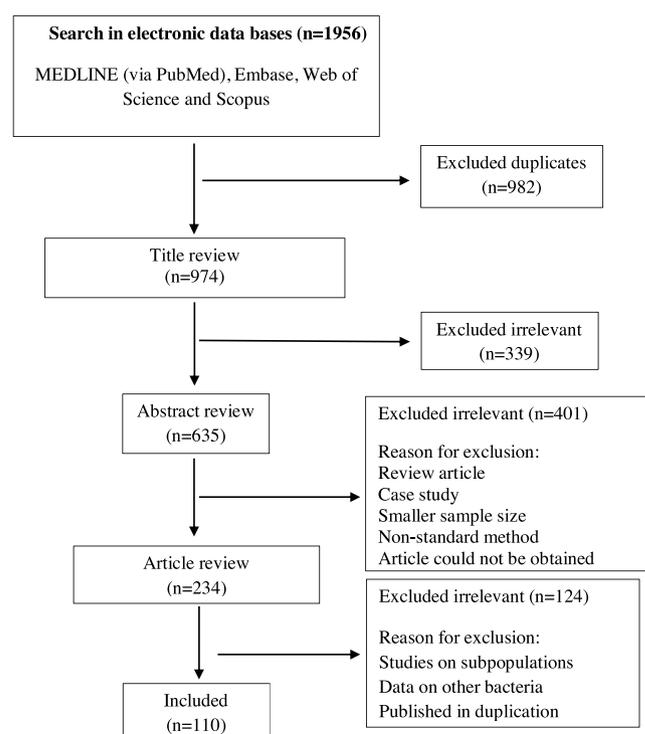


Fig. 1. Flow chart of study selection for inclusion in the systematic review.

numbers of *E. coli* and NDM-producing *E. coli*; type of NDM variants in *E. coli* isolates; ST of isolates; NDM detection methods; and source of isolates. The prevalence of NDM-producing *E. coli* isolates was extracted; concurrently, for accuracy in data extraction, two reviewers recorded the data independently from all included articles without any bias. Contradiction among the reviewers was discussed to reach a consensus.

3. Results

3.1. Characteristics of included studies

A total of 1956 articles were identified through the initial searching of electronic databases, of which 982 duplicate articles were removed, leaving 974 unique articles. Of the 974 articles, 740 articles were excluded based on evaluation of the title and abstract. Of the remaining 234 studies, 124 were excluded based on a full-text search, thus 110 articles fulfilled the eligibility criteria for the final statistical analysis. Of the 110 included studies, 80 reported results from Asia, 29 from Europe, 8 from America, 4 from Africa and 5 from Oceania. Some studies included results of NDM-producing *E. coli* outbreaks in several countries. The reasons for excluding studies based on the title, abstract and full-text are presented in Fig. 1. The main characteristics of the 110 included articles are summarised in Supplementary Table S1.

Based on the data in Supplementary Table S1, the majority of articles included in the present study were performed in China (26 articles), followed by India (23 articles). Prior to 2010, there were no studies reported NDM-producing *E. coli*. More than 50% of the studies included in this review were published from 2014–2018. The distribution of NDM-producing *E. coli*, including NDM-1, -3, -4, -5, -6, -7, -8, -9, -11, -12 and -13, among different continents is shown in Table 1 and Fig. 2. As shown in Fig. 2, the five most prevalent NDM variants among *E. coli* strains isolated from human samples were NDM-1, -5, -7, -4 and -6. Four studies reported NDM-3, two studies each reported NDM-9, -12 and -13, and only one study reported NDM-11. There were no data regarding the prevalence of NDM-2 and NDM-10 in the evaluated studies.

The distribution of STs of NDM-producing *E. coli* in various parts of the world is shown in Table 2. All included studies were conducted on clinical samples. Urine was the most common sample (60) evaluated in the included studies, followed by blood (37), pus (34), respiratory tract (23), rectal (14) and sputum (12) (Supplementary Table S1). In all included studies, NDM-producing *E. coli* strains were identified by PCR or whole-genome sequencing (Supplementary Table S1). The antimicrobial susceptibility of NDM-producing *E. coli* in the different continents is shown in Supplementary Table S2. Tigecycline, colistin and fosfomycin were the three most effective antibiotics against NDM-producing *E. coli* (Supplementary Table S2).

3.2. NDM variants among *E. coli* strains isolated from human clinical samples in different continents

The prevalence of NDM-producing *E. coli* in Asia, Europe, America, Africa and Oceania was 82.6%, 12.9%, 1.5%, 1.0% and 2.0%, respectively (Table 1). The number of reported NDM-producing *E. coli* isolates along with the distribution of NDM variants in various geographical locations of the continents of Asia, Europe, America, Australia and Oceania are shown in Tables 3–5.

All of the mentioned NDM variants were reported only in Asia. Among the Asian countries, India (50.3%; 251/499), China (21.4%; 107/499), Pakistan (7.4%; 37/499) and Nepal (6.8%; 34/499) had the highest prevalence of NDM-producing *E. coli*. According to the results of studies conducted in Asia, NDM-1, -5 and -7 with prevalence rates of 73.7% (368/499), 15.6% (78/499) and 3.6% (18/499), respectively, had the greatest distribution among the NDM variants in Asian countries. In addition to the outbreak of NDM-1 in all countries of Asia except Saudi Arabia, the following NDM variants were reported: NDM-4, -5, -6, -7, -8 and -11 in India; NDM-3, -4, -5, -6, -7, -9 and -13 in China; NDM-3, -4, -5, -7, -8, -12 and -13 in Nepal; NDM-4 and -5 in Vietnam; NDM-4, -5 and -7 in Myanmar; NDM-3 and -5 in Japan; and NDM-5 in Kuwait (Table 3). In contrast, NDM-9, -11 and -12 have also been reported only in China, India and Nepal, respectively (Table 3).

In Europe and America, NDM-1, -5 and -7 (the three most common variants) have been reported as common variants (Tables 4 and 5). Among the European countries, Turkey (39.7%; 31/78), the UK (14.1%; 11/78), Norway (9.0%; 7/78), Spain (7.7%; 6/78) and Italy (6.4%; 5/78) had the largest number of reports of NDM variants (Table 4). In the American continent, NDM-1 was reported in the USA (11.1%; 1/9), Canada (33.3%; 3/9) and Mexico (22.2%; 2/9). NDM-5 (11.1%; 1/9) and NDM-7 (22.2%; 2/9) were only identified in the USA and Canada, respectively (Table 5).

According to included articles related to Africa, there is no report of NDM-1 in this continent. In Africa, NDM-5 was reported in three studies, from Egypt (16.7%; 1/6), South Africa (16.7%; 1/6) and Algeria (50.0%; 3/6). NDM-4 was only reported in Cameroon (16.7%; 1/6) (Table 5).

In Oceania, just one study in New Zealand reported NDM-6 (8.3%; 1/12). In this continent, NDM-1 was reported in Australia (25.0%; 3/12) and New Zealand (16.7%; 2/12) (Table 5). NDM-3, -4 and -5 and NDM-6 were reported in Australia and New Zealand, respectively (Table 5).

3.3. Most prevalent sequence types among NDM-producing *E. coli* strains in different continents

Based on the results of the included articles, 53 exclusive STs have been reported among NDM-producing *E. coli* isolated from clinical samples in different countries. The number of reported STs in these studies was 147 in Asia, 38 in Europe, 9 in America, 6 in Africa and 11 in Oceania. The most common reported STs among

Table 1
Prevalence of New Delhi metallo- β -lactamase (NDM)-producing *Escherichia coli* isolated from clinical samples in different continents.

Continent	NDM type [n (%)]	Total N ^a
Asia	NDM-1 (368, 73.7), NDM-3 (3, 0.6), NDM-4 (14, 2.8), NDM-5 (78, 15.6), NDM-6 (8, 1.6), NDM-7 (18, 3.6), NDM-8 (3, 0.6), NDM-9 (2, 0.4), NDM-11 (1, 0.2), NDM-12 (2, 0.4), NDM-13 (2, 0.4)	499
Europe	NDM-1 (65, 83.3), NDM-4 (2, 2.6), NDM-5 (6, 7.7), NDM-7 (5, 6.4)	78
America	NDM-1 (6, 66.7), NDM-5 (1, 11.1), NDM-7 (2, 22.2)	9
Africa	NDM-4 (1, 16.7), NDM-5 (5, 83.3)	6
Oceania	NDM-1 (5, 41.7), NDM-3 (1, 8.3), NDM-4 (3, 25.0), NDM-5 (2, 16.7), NDM-6 (1, 8.3)	12
All continents	NDM-1, 443 (73.3); NDM-3, 4 (0.7); NDM-4, 20 (3.3); NDM-5, 93 (15.4); NDM-6, 9 (1.5); NDM-7, 25 (4.1); NDM-8, 3 (0.5); NDM-9, 2 (0.3); NDM-11, 1 (0.2); NDM-12, 2 (0.3); NDM-13, 2 (0.3)	604

^a N = number of NDM-producing *E. coli*.

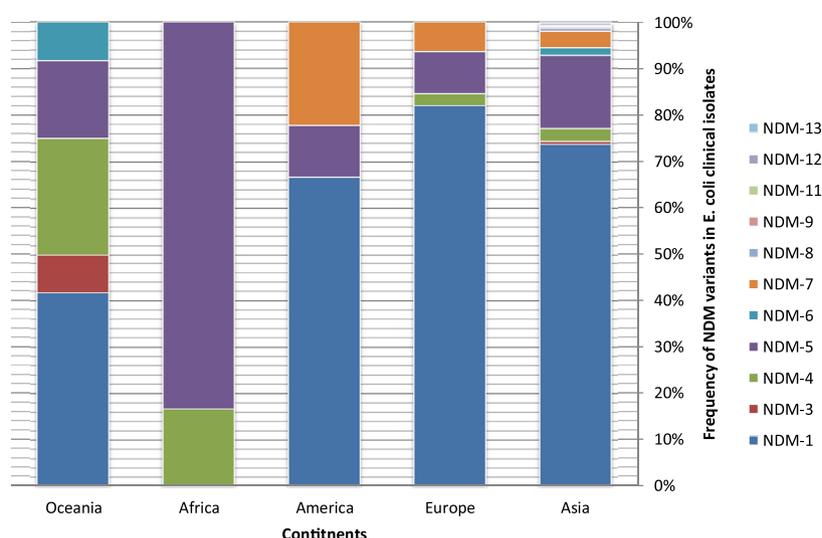


Fig. 2. Distribution of New Delhi metallo- β -lactamase (NDM)-producing *Escherichia coli* isolated from clinical samples among continents.

Table 2

Distribution of sequence types (STs) among various New Delhi metallo- β -lactamase (NDM) variants in different continents.^a

Continent	NDM-1 (N)	NDM-3 (N)	NDM-4 (N)	NDM-5 (N)			
Asia	ST101 (17), ST131 (16), ST167 (8), ST2 (5), ST2083 (1), ST2206 (1), ST224 (1), ST2373 (1), ST2513 (1), ST2659 (1), ST267 (1), ST354 (1), ST361 (1), ST38 (3), ST3835 (1), ST405 (4), ST43 (1), ST448 (1), ST471 (1), ST501 (1), ST5703 (1), ST5838 (1), ST594 (1), ST617 (2), ST648 (3), ST69 (1), ST744 (2), ST90 (1), ST94 (1)	ST38 (1), ST88 (1)	ST101 (2), ST131 (1), ST405 (2), ST410 (1), ST5838 (1), ST648 (1)	ST101 (1), ST131 (2), ST156 (1), ST167 (15), ST354 (2), ST361 (2), ST405 (5), ST410 (1), ST448 (2), ST533 (1), ST5703 (2), ST617 (1), ST648 (1)			
	NDM-7 (N) ST101 (1), ST131 (2), ST167 (1), ST405 (1), ST410 (1), ST4108 (1), ST648 (3), ST650 (3)	NDM-8 (N) ST101 (1), ST131 (1)	NDM-9 (N) ST5836 (1), ST617 (1)	NDM-11 (N) ST131 (1)	NDM-12 (N) ST448 (1)	NDM-13 (N) ST101 (1), ST5138 (1)	
Europe	NDM-1 (N) ST101 (6), ST782 (1), ST410 (6), ST744 (1), ST10 (1), ST31 (1), ST5123 (1), ST156 (2), ST617 (1), ST681 (1), ST405 (3), ST648 (1), ST131 (1)	NDM-4 (N) ST405 (2)	NDM-5 (N) ST405 (2), ST448 (1), ST43 (1), ST648 (1), ST636 (1)	NDM-7 (N) ST599 (1), ST399 (1), ST679 (1), ST101 (1), ST167 (1)			
America	NDM-1 (N) ST405 (1), ST101 (1), ST1193 (1), ST617 (1), ST10 (1), ST131 (1)	NDM-5 (N) ST167 (1)		NDM-7 (N) ST44 (1), ST91 (1)			
Africa	NDM-4 (N) ST405 (1)			NDM-5 (N) ST410 (1), ST2659 (3), ST167 (1)			
Oceania	NDM-1 (N) ST101 (1), ST410 (2), ST361 (1), ST2488 (1)	NDM-4 (N) ST167 (1), ST4450 (1), ST101 (1)		NDM-5 (N) ST648 (1), ST147 (1)	NDM-6 (N) ST101 (1)		

^a N = number of NDM-producing *E. coli*.

NDM-producing *E. coli* were ST101 (34 isolates), ST167 (28 isolates), ST131 (25 isolates), ST405 (21 isolates), ST410 (12 isolates) and ST648 (11 isolates). All of these STs have been reported in Asia and Europe, whilst ST410 and ST648 have not been reported in America, ST101, ST131 and ST648 have not been

reported in Africa, and ST131 and ST405 have not been reported in Oceania. Table 6 shows the presence of the reported STs in different countries. The results of the included studies show that China has reported the most diverse range of STs (24 types), followed by Nepal (11 types), India, Norway and Australia (6 types each), the

Table 3Distribution of New Delhi metallo- β -lactamase (NDM)-producing *Escherichia coli* isolated from clinical samples in different countries of Asia.

Country	NDM type (n, %)	Total N ^a
India	NDM-1 (218, 86.9), NDM-4 (7, 2.8), NDM-5 (12, 4.8), NDM-6 (5, 2.0), NDM-7 (6, 2.4), NDM-8 (2, 0.8), NDM-11 (1, 0.4)	251
China	NDM-1 (44, 41.1), NDM-3 (1, 0.9), NDM-4 (2, 1.9), NDM-5 (49, 45.8), NDM-6 (3, 2.8), NDM-7 (5, 4.7), NDM-9 (2, 1.9), NDM-13 (1, 0.9)	107
Nepal	NDM-1 (15, 44.10), NDM-3 (1, 2.9), NDM-4 (1, 2.9), NDM-5 (7, 20.6), NDM-7 (6, 17.6), NDM-8 (1, 2.9), NDM-12 (2, 5.9), NDM-13 (1, 2.9)	34
Pakistan	NDM-1 (37, 100)	37
Vietnam	NDM-1 (25, 89.3), NDM-4 (1, 3.6), NDM-5 (2, 7.1)	28
Myanmar	NDM-1 (1, 11.1), NDM-4 (3, 33.3), NDM-5 (4, 44.4), NDM-7 (1, 11.1)	9
Kuwait	NDM-1 (4, 66.7), NDM-5 (2, 33.3)	6
Singapore	NDM-1 (5, 100)	5
Philippines	NDM-1 (3, 100)	3
Thailand	NDM-1 (3, 100)	3
Iran	NDM-1 (2, 100)	2
Iraq	NDM-1 (2, 100)	2
Japan	NDM-1 (1, 33.3), NDM-3 (1, 33.3), NDM-5 (1, 33.3)	3
Bangladesh	NDM-1 (2, 100)	2
Taiwan	NDM-1 (2, 100)	2
UAE	NDM-1 (2, 100)	2
Korea	NDM-1 (1, 100)	1
Malaysia	NDM-1 (1, 100)	1
Saudi Arabia	NDM-5 (1, 100)	1
Total	NDM-1 (368, 73.7), NDM-3 (3, 0.6), NDM-4 (14, 2.8), NDM-5 (78, 15.6), NDM-6 (8, 1.6), NDM-7 (18, 3.6), NDM-8 (3, 0.6), NDM-9 (2, 0.4), NDM-11 (1, 0.2), NDM-12 (2, 0.4), NDM-13 (2, 0.4)	499

UAE, United Arab Emirates.

^a N = number of NDM-producing *E. coli*.**Table 4**Distribution of New Delhi metallo- β -lactamase (NDM)-producing *Escherichia coli* isolated from clinical samples in different countries of Europe.

Country	NDM type (n, %)	Total N ^a
Norway	NDM-1 (5, 71.4), NDM-5 (1, 14.3), NDM-7 (1, 14.3)	7
Spain	NDM-1 (2, 33.3), NDM-5 (2, 33.3), NDM-7 (2, 33.3)	6
Italy	NDM-1 (1, 20.0), NDM-4 (2, 40.0), NDM-5 (2, 40.0)	5
Belgium	NDM-1 (3, 100)	3
Germany	NDM-1 (1, 50.0), NDM-7 (1, 50.0)	2
Poland	NDM-1 (4, 100)	4
Serbia	NDM-1 (2, 100)	2
Turkey	NDM-1 (31, 100)	31
Austria	NDM-1 (1, 100)	1
Switzerland	NDM-1 (1, 100)	1
Denmark	NDM-1 (1, 100)	1
Romania	NDM-1 (1, 100)	1
UK	NDM-1 (10, 90.9), NDM-5 (1, 9.1)	11
Sweden	NDM-1 (2, 100)	2
France	NDM-7 (1, 100)	1
Total	NDM-1 (65, 83.3), NDM-4 (2, 2.6), NDM-5 (6, 7.7), NDM-7 (5, 6.4)	78

^a N = number of NDM-producing *E. coli*.**Table 5**Distribution of New Delhi metallo- β -lactamase (NDM)-producing *Escherichia coli* isolated from clinical samples in different countries of America, Africa and Oceania.

Country	NDM type (n, %)	Total N ^a	Country	NDM type (n, %)	Total N ^a	Country	NDM type (n, %)	Total N ^a			
America	Canada	NDM-1 (3, 60.0), NDM-7 (2, 40.0)	5	Africa	South Africa	NDM-5 (1, 100)	1	Oceania	Australia	NDM-1 (3, 33.3), NDM-3 (1, 11.1), NDM-4 (3, 33.3), NDM-5 (2, 22.2)	9
	Mexico	NDM-1 (2, 100)			Egypt	NDM-5 (1, 100)	1		New Zealand	NDM-1 (2, 66.7), NDM-6 (1, 33.3)	3
	USA	NDM-1 (1, 50.0), NDM-5 (1, 50.0)	2		Cameroon	NDM-4 (1, 100)	1				
		NDM-5 (1, 50.0)			Algeria	NDM-5 (3, 100)	3				
Total		NDM-1 (6, 66.7), NDM-5 (1, 11.1), NDM-7 (2, 22.2)	9	Total		NDM-4 (1, 16.7), NDM-5 (5, 83.3)	6	Total		NDM-1 (5, 41.7), NDM-3 (1, 8.3), NDM-4 (3, 25.0), NDM-5 (2, 16.7), NDM-6 (1, 8.3)	12

^a N = number of NDM-producing *E. coli*.

Table 6
Association of prevalent sequence types (STs) with different countries among continents.

Country	Prevalent STs (N)
Asia	
China	ST101 (2), ST131 (3), ST156 (1), ST167 (20), ST2 (5), ST224 (1), ST2373 (1), ST3835 (1), ST405 (1), ST410 (1), ST448 (1), ST5138 (1), ST533 (1), ST5703 (3), ST5836 (1), ST5837 (1), ST5838 (1), ST594 (1), ST617 (4), ST650 (3), ST69 (1), ST744 (2), ST354 (1), ST361 (1)
India	ST101 (6), ST131 (20), ST167 (2), ST405 (1), ST648 (1), ST90 (1)
Korea	ST101 (1)
Nepal	ST101 (7), ST167 (1), ST2083 (1), ST2659 (1), ST361 (2), ST38 (3), ST405 (8), ST4108 (1), ST448 (3), ST648 (5), ST94 (1)
UAE	ST2206 (1), ST2513 (1)
Singapore	ST267 (1), ST43 (1), ST471 (1), ST501 (1)
Myanmar	ST101 (2), ST167 (1), ST354 (2), ST405 (2), ST410 (2)
Japan	ST38 (1), ST88 (1)
Pakistan	ST101 (5), ST648 (2)
Europe	
Poland	ST10 (1), ST410 (2), ST744 (1)
Belgium	ST101 (1), ST782 (1)
Denmark	ST101 (1)
Norway	ST101 (1), ST131 (1), ST410 (2), ST617 (1), ST636 (1), ST681 (1)
Spain	ST156 (1), ST399 (1), ST43 (1), ST448 (1), ST679 (1)
Romania	ST31 (1)
Italy	ST405 (4)
Switzerland	ST410 (1)
Serbia	ST5123 (1)
Germany	ST599 (1)
UK	ST101 (4), ST648 (2), ST156 (1), ST405 (3), ST410 (1)
France	ST167 (1)
America	
USA	ST167 (1), ST131 (1)
Canada	ST405 (1), ST101 (1), ST1193 (1), ST44 (1), ST91 (1)
Mexico	ST617 (1), ST10 (1)
Africa	
Egypt	ST410 (1)
Cameroon	ST405 (1)
South Africa	ST167 (1)
Algeria	ST2659 (3)
Oceania	
Australia	ST101 (2), ST410 (2), ST167 (1), ST4450 (1), ST648 (1), ST147 (1)
New Zealand	ST361 (1), ST2488 (1), ST101 (1)

UAE, United Arab Emirates.

UK, Spain, Myanmar and Canada (5 types each), Singapore (4 types), Poland and New Zealand (3 types each), and United Arab Emirates, Japan, Pakistan, USA, Belgium and Mexico (2 types each).

The distribution of different STs reported in different countries is shown in Supplementary Table S3. ST101, ST167, ST131, ST405, ST410 and ST648 were the most frequent STs among the countries. ST101 was found in 13 countries and ST167, ST405 and ST410 were found in 8 countries. Other frequent STs were ST648 (in 5 countries), ST131 (4 countries), ST156, ST448, ST361 and ST617 (3 countries) and ST10, ST38, ST43, ST2659, ST354 and ST744 (each in two countries). Finally, 37 (71%) of 52 STs in different countries were only reported by one country. Figs. 3 and 4 show the distribution of various STs detected in NDM-producing *E. coli* isolated from clinical samples among continents and countries, respectively. Fig. 5 shows the most common ST in every country around the world.

4. Discussion

To the best of our knowledge, this study is the first report evaluating the prevalence and distribution of NDM-producing *E. coli* based on clinical samples, geographical location and STs around the world. The results indicate that there is a global increase in the prevalence of NDM-producing *E. coli* among clinical isolates.

In this review, 604 NDM-producing *E. coli* isolates were described from 43 countries all around the world between 2010 and 2018. Based on the analysed data, the majority of NDM-

producing *E. coli* isolates were from Asia (India, China and Pakistan). The number of reported NDM-producing *E. coli* isolated from clinical specimens may be less than the actual prevalence rate because, in most countries, systematic monitoring of infections due to highly resistant bacteria such as *E. coli* is not performed routinely. In addition, in some cases bacteria may colonise a patient without causing clinical signs. Moreover, failure to use guidelines for isolating and identifying antimicrobial-resistant bacteria leads to unrealistic results.

According to results of this study, Asia had the highest level of NDM-producing *E. coli* with a frequency of 82.6%, mostly in China and India. Fig. 6 shows the frequency of NDM variants around the world. In Europe, the frequency of NDM-producing *E. coli* was 12.9%, with the maximum spread of the NDM-1 variant in 14 countries. The frequency of NDM-producing *E. coli* in America was 1.5%, of which Canada had the highest rate of NDM-producing *E. coli*. Approximately 1.0% of NDM-producing *E. coli* were reported from Africa, with the highest rates distributing in Algeria, whereas South Africa, Cameroon and Egypt showed low rates of NDM-producing *E. coli*. Oceania carries 2.0% of NDM-producing *E. coli* distributed in Australia and New Zealand.

The most distributed and prevalent NDM variant is NDM-1, followed by NDM-5, -7 and -4, which were more distributed in Asia followed by Europe, Oceania, America and Africa (Fig. 7). In Asia, most NDM-1, -4 and -7 distribution was observed in India, and NDM-5 was reported in China (Table 3). These four most prevalent NDM variants were more disseminated in Turkey, Belgium, Spain and Italy in Europe (Table 4). In America, NDM-1 had a greater

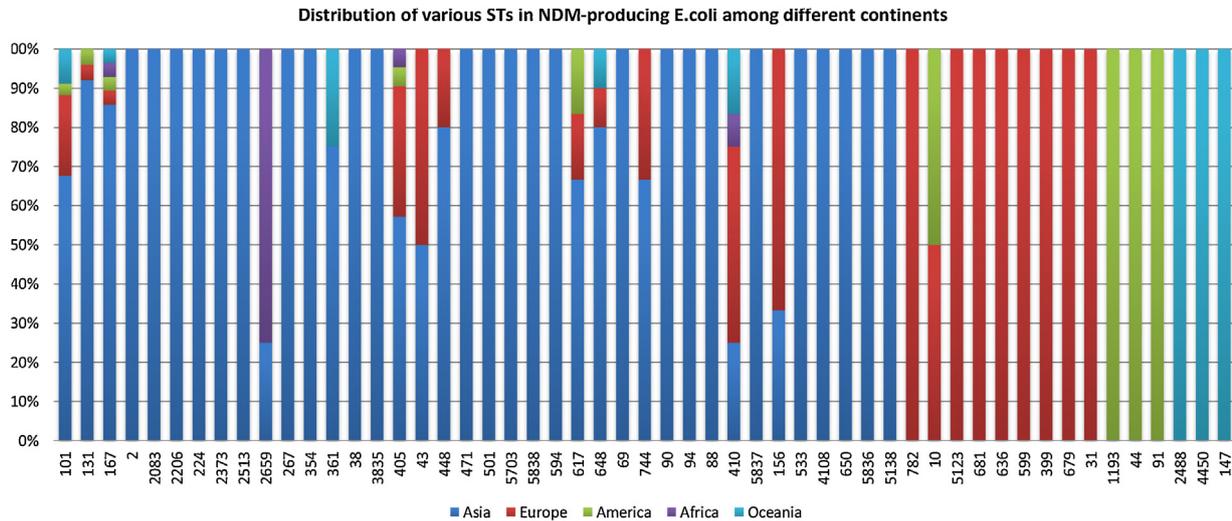


Fig. 3. Distribution of various sequence types (STs) detected in New Delhi metallo-β-lactamase (NDM)-producing *Escherichia coli* from clinical samples among continents.

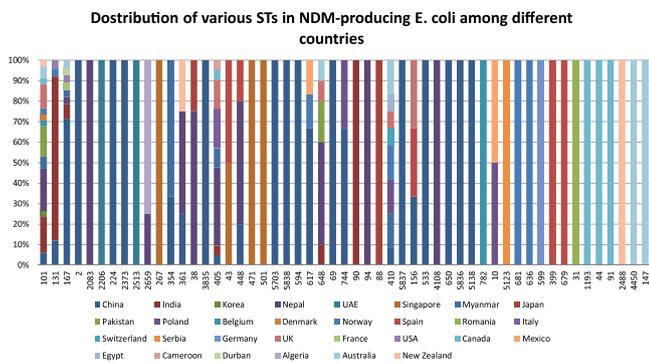


Fig. 4. Distribution of various sequence types (STs) in New Delhi metallo-β-lactamase (NDM)-producing *Escherichia coli* isolated from clinical samples among different countries.

distribution in Canada. On the other hand, NDM-5 and NDM-7 were only reported from the USA and Canada, respectively. NDM-4 was not reported in this continent. NDM-1 was not reported in Africa, but NDM-5 was reported from South Africa, Egypt and Algeria. NDM-4 was reported in Cameroon. Finally, in Oceania, NDM-1 was more prevalent in Australia. In addition, NDM-4 and NDM-5 were reported only in Australia. NDM-7, as one of the most common NDM variants, was not reported in Oceania. Data analysis showed that the NDM-8, -9, -11, -12 and -13 variants were reported only in Asia (India, China and Nepal). In addition, NDM-3 and NDM-6 were only reported from Asia (China, Nepal, India and Japan) and Oceania (Australia and New Zealand).

The present study reports the distribution of STs of NDM-producing *E. coli* among clinical isolates around the world. Based on published articles, ST101 was the most common ST among NDM-producing *E. coli* isolated from clinical samples. In Asia, ST101 was the most prevalent, which was detected in India, Nepal, Pakistan, China, Korea and Myanmar. The second most prevalent ST in Asia was ST131, which was predominantly found in India and China. ST101 and ST405 were the most abundant STs in Europe, with maximum distribution in the UK and Italy, respectively. ST410 was the next most widespread ST, which was distributed in four countries (Poland, Norway, Switzerland and the UK).

It should not be underestimated that a larger sample size could be proof of the validity of the acquired data. It should also be noted that in the present study a disparity in sample size among the different countries has caused deviation in the

report of the most prevalent STs in Europe. ST167, ST2659 and ST101 were reported as the most common STs in America, Africa and Oceania, respectively. Although ST2659 was more common in Africa, it was only reported from Algeria. In Oceania, ST410 was the second most prevalent ST, which was only reported from Australia. ST167 was reported from five continents. In total, ST101, ST167, ST131, ST405, ST410 and ST648 were the most abundant STs among NDM-producing *E. coli* isolated from clinical samples around the world. More than one-half of the STs have been reported from only one country (Supplementary Table S3). Interestingly, the most common STs have all been found in NDM-1-producing bacteria worldwide. It is worth noting that not all of the included articles in this study mentioned STs in NDM-producing *E. coli* isolated from clinical specimens. The frequency of STs among continents and countries may have changed if all of the included studies mentioned the abundance of STs in their investigation. Furthermore, the presence of similar STs in countries or continents may be due to migration between those countries or continents. In Asia and Europe, NDM-1, -4, -5 and -7 have the most association with frequent STs. In addition, ST101 and ST131 (as two of the most prevalent STs) were associated with NDM-8, -11 and -13 in Asia. NDM-1 and -5 in America, NDM-4 and -5 in Africa, and NDM-1, -4 and -6 in Oceania were most related with the most common STs. Fig. 8 shows the distribution of various STs among NDM-producing *E. coli* around the world. In the current study, antibiotics to which NDM-producing *E. coli* had full susceptibility were extracted from the included articles. The analysis revealed that NDM-producing *E. coli* are not very susceptible to most of the antibiotics. The majority of studies reported from different countries have shown that among the effective antibiotics, colistin, tigecycline and fosfomycin are the most common antibiotics against NDM-producing *E. coli* isolated from clinical samples (Supplementary Table S2).

As a matter of fact, such an alarming prevalence of NDM-producing *E. coli* strains in different countries around the world could be due to several notable issues. Along with indiscriminate use of antibiotics, insufficient implementation of prophylactic hygiene measures, inadequate staff training and lack of hospital infection control programmes are the main reasons for the significant increase of NDM-producing *E. coli* strains. Subsequently, insufficient NDM-producing *E. coli* management could lead to a wider spread of antimicrobial resistance genes in *E. coli* strains in clinics and hospitals in the world. Moreover, the association between a multidrug-resistant phenotype with NDM variants has

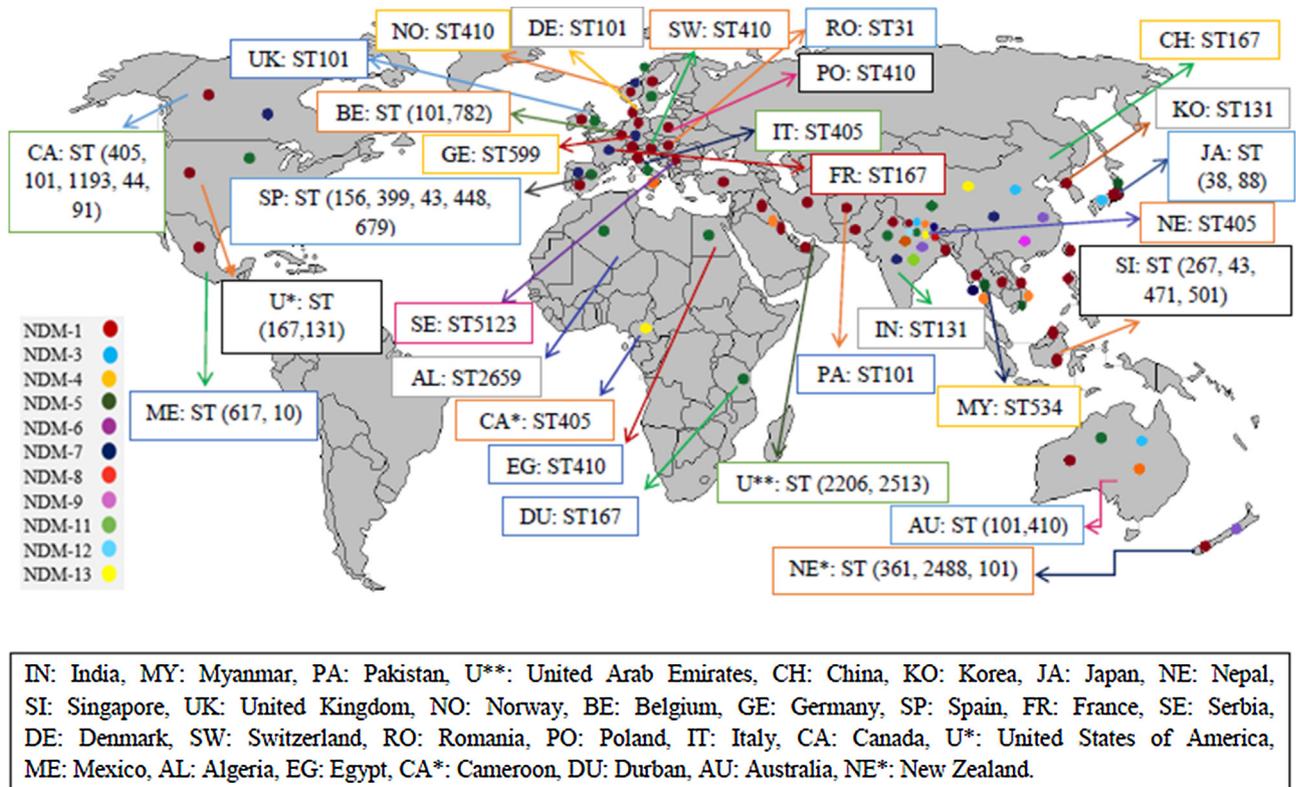


Fig. 5. Most common sequence types (STs) of New Delhi metallo-β-lactamase (NDM)-producing *Escherichia coli* isolated from clinical samples in each country.

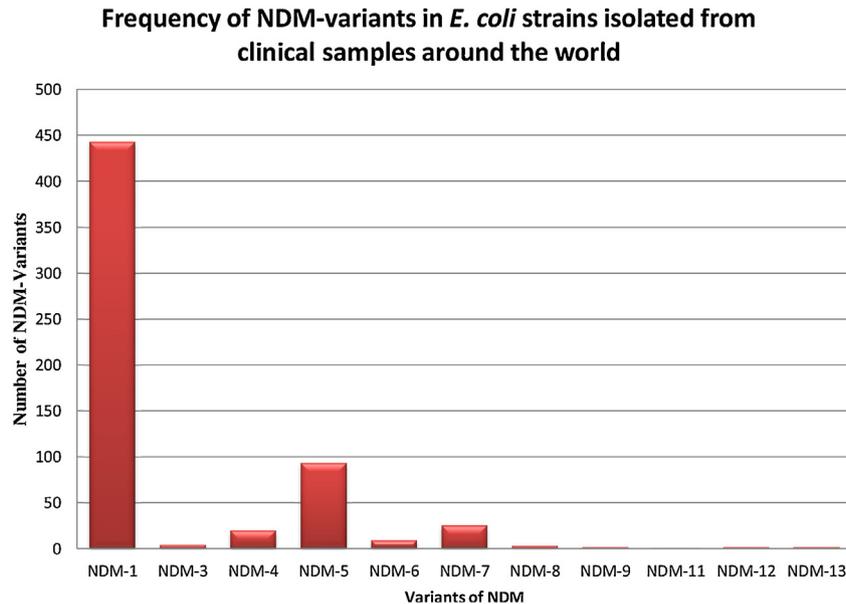


Fig. 6. Frequency of New Delhi metallo-β-lactamase (NDM) variants in *Escherichia coli* isolated from clinical samples around the world based on published papers.

further intensified the dilemma. Regular surveillance of hospital-associated infections, monitoring antimicrobial susceptibility patterns and formulation of definite antibiotic policies would certainly facilitate more accurate action regarding the prevention and control of antimicrobial resistance.

Limitations of the present study ought to be taken into consideration. First, only published scientific studies were considered for inclusion in the present review. Second, due to

the large amount of data on NDM-producing *E. coli* isolated from clinical samples, we could not analyse the incidence of NDM-producing *E. coli* isolated from environmental samples in this study. Third, we could not fully represent the prevalence of NDM-producing *E. coli* since there were not sufficient data regarding this topic in many countries around the world. The extent of distribution of NDM variants is still gloomy in some countries around the world.

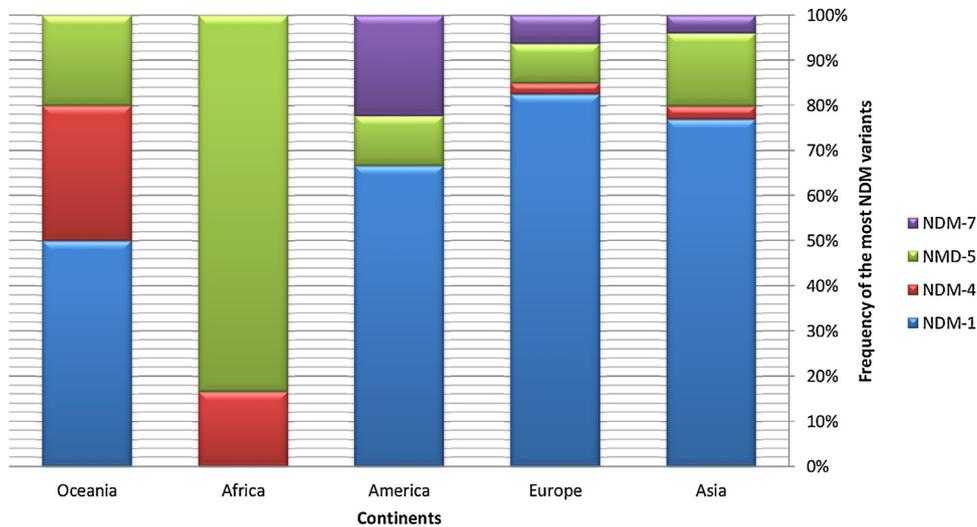


Fig. 7. Distribution of the most common New Delhi metallo-β-lactamase (NDM) variants in NDM-producing *Escherichia coli* isolated from clinical samples among different continents.

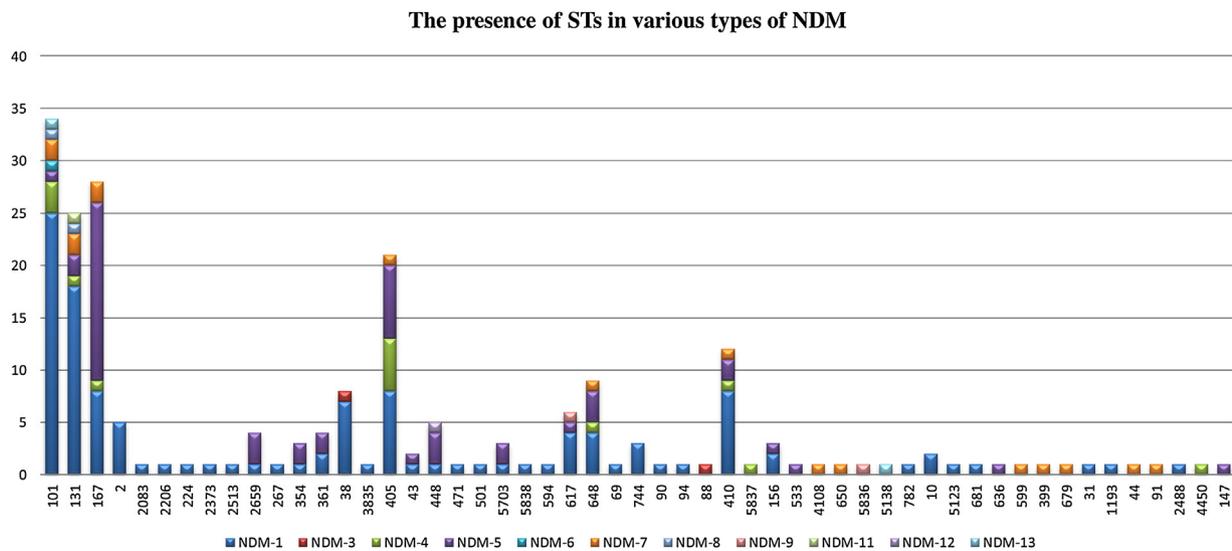


Fig. 8. Distribution of various sequence types (STs) in New Delhi metallo-β-lactamase (NDM)-producing *Escherichia coli* around the world.

5. Conclusion

It was ultimately concluded that the relatively high prevalence of NDM-producing *E. coli* strains, especially the most common *E. coli* clonal groups, in different countries around the world merits further attention by healthcare authorities, physicians and microbiologists. In particular, introduction of NDM-producing *E. coli* screening based on rapid and reliable diagnostic methods during admission of patients is important. Finally, it must be acknowledged that international co-operation is essential to overcome this medical threat to public health.

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Competing interests

None declared.

Ethical approval

Not required.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.jgar.2019.06.008>.

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