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REVIEW

NDM Metallo-β-Lactamases and Their Bacterial Producers in Health Care Settings

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(continued)

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SUMMARY New Delhi metallo-β-lactamase (NDM) is a metallo-β-lactamase able to hydrolyze almost all β-lactams. Twenty-four NDM variants have been identified in >60 species of 11 bacterial families, and several variants have enhanced carbapenemase activity. *Klebsiella pneumoniae* and *Escherichia coli* are the predominant carriers of bla_{NDM}, with certain sequence types (STs) (for *K. pneumoniae*, ST11, ST14, ST15, or ST147; for *E. coli*, ST167, ST410, or ST617) being the most prevalent. NDM-positive strains have been identified worldwide, with the highest prevalence in the Indian subcontinent, the Middle East, and the Balkans. Most bla_{NDM}-carrying plasmids belong to limited replicon types (IncX3, IncFII, or IncC). Commonly used phenotypic tests cannot specifically identify NDM. Lateral flow immunoassays specifically detect NDM, and molecular approaches remain the reference methods for detecting bla_{NDM}. Polymyxins combined with other agents remain the mainstream options of antimicrobial treatment. Compounds able to inhibit NDM have been found, but none have been approved for clinical use. Outbreaks caused by NDM-positive strains have been reported worldwide, attributable to sources such as contaminated devices. Evidence-based guidelines on prevention and control of carbapenem-resistant Gram-negative bacteria are available, although none are specific for NDM-positive strains. NDM will remain a severe challenge in health care settings, and more studies on appropriate countermeasures are required.

KEYWORDS *Acinetobacter*, *Enterobacteriaceae*, NDM, carbapenem resistance, carbapenemase, metalloenzymes

INTRODUCTION

New Delhi metallo-β-lactamase (NDM) is a type of metallo-β-lactamase (MBL) able to hydrolyze most β-lactams (including carbapenems) but not monobactams (1, 2). NDM has poor activity against amdinocillin, an extended-spectrum penicillin antibiotic of the amidinopenicillin family (3). Carbapenems are the mainstay antimicrobial agents of choice for treating severe infections caused by many Gram-negative bacteria (4, 5). The hydrolysis of β-lactams by NDM enzymes cannot be prevented by clinically available β-lactamase inhibitors, including avibactam, clavulanate, sulbactam, and tazobactam. NDM-1 was first identified in a *Klebsiella pneumoniae* strain isolated from a Swedish patient who had been hospitalized in New Delhi, India, in 2008 (2). Since then, NDM-1 has been found in various species of the *Enterobacteriaceae*, *Acinetobacter*, and *Pseudomonas*, and 24 variants of NDM have been identified. NDM-positive strains are usually resistant to most antimicrobial agents in addition to β-lactams due to the coexistence of other resistance mechanisms (1). NDM-positive strains cause a variety of infections that have been reported to be associated with high mortality rates (6). NDM-positive strains have been found worldwide, representing a significant challenge for clinical management and public health (7, 8).

NDM, A SUBCLASS B1 MBL

β-Lactamases are divided into the A, B, C, and D classes based on amino acid sequence identity (9–11). Class A, C, and D enzymes contain a serine residue at the active site of the β-lactamase, while class B enzymes contain one or two zinc ions and are therefore termed MBLs. MBLs have been further subdivided into three subclasses (B1, B2, and B3) based on amino acid sequence identities (12, 13). The subclass B1 and B3 enzymes have two zinc ions at the active site and exhibit a broad-spectrum substrate profile, including penicillins, cephalosporins, and carbapenems (9, 12, 14). In contrast, subclass B2 enzymes have one active zinc ion, while the binding of the second zinc ion inhibits their catalysis activity (15). The subclass B2 enzymes exhibit a narrow-spectrum substrate profile, including carbapenems but not penicillins and cephalosporins (15, 16). A few MBLs belong to subclass B2, including CphA from *Aeromonas hydrophila*, Sfh-1 from *Serratia fonticola*, and ImiS from *Aeromonas veronii*. Similarly, a few subclass B3 MBLs have been identified, such as L1 from *Stenotrophomonas maltophilia*, AIM-1 from *Pseudomonas aeruginosa*, and GOB-1 from *Elizabethkingia meningoseptica* (formerly *Chryseobacterium septicum*). The majority of MBLs that have been identified so far belong to subclass B1 (9, 17). The three most common MBLs seen in clinical isolates, IMP (imipenemase), VIM (Verona integron-encoded metallo-β-lactamase), and NDM, are subclass B1 enzymes (17). Genes encoding IMP, VIM, and NDM are largely plasmid borne and can be transferred between bacterial strains, meaning that they are of particular significance in health care settings. NDM enzymes have low amino acid sequence identity with the other subclass B1 MBLs; for instance, the amino acid identity between NDM-1 and IMP-1 or VIM-2 is only 34% or 35%. It has been proposed that subclass B1 be further divided into two clades (B1a and B1b), with NDM belonging to clade B1b and the remaining subclass B1 enzymes belonging to clade B1a (9). Zinc ions play the key role in the function of NDM-1 (18, 19). The interaction between NDM-1 and the substrate is through zinc ions bound in the active site (20). The zinc ions also activate a water molecule, which donates a proton to generate a new active hydroxide for the hydrolysis of the β-lactam ring by attacking the carbon atom of the β-lactam carbonyl group (20, 21).

Of note, the cellular localization of NDM is different from that of all other MBLs. NDM is a lipoprotein that anchors to the outer membrane in Gram-negative bacteria, which has been attributed to the presence of a canonical lipidation amino acid sequence, LSGC (lipobox), at end of the signal peptide of NDM (22, 23). In contrast, all other MBLs are soluble periplasmic proteins (24). Membrane anchoring significantly enhances the stability of NDM under conditions of zinc deprivation, which occurs at the infection site as large amounts of the metal-chelating protein calprotectin are released as a response of host immunity. The resulting zinc deprivation can interfere with the function of MBLs such as NDM. Membrane anchoring also facilitates the secretion of this enzyme in outer membrane vesicles (OMVs) (23, 25). OMVs containing NDM can protect neighboring bacterial populations from the action of β-lactams, and OMVs can carry both NDM and bla_{NDM} (23, 25). As a result, membrane anchoring, an important feature of NDM, may therefore contribute to the wide distribution of NDM-positive strains in health care settings.

NDM VARIANTS

NDM enzymes are composed of 270 amino acids, containing two zinc ions at the active site, where the hydrolysis of β-lactams takes place. The secondary structure of NDM enzymes contains 9 α-helices, 17 β-strands, and 3 turns (Fig. 1). Substitutions have been observed at 17 of the 270 amino acids, resulting in 24 distinct NDM variants. The M154L substitution is the most common and is observed in 10 of the 24 distinct NDM variants. NDM variants commonly contain between 1 and 5 amino acid substitutions compared to NDM-1. NDM-18 is an exception in that it is identical to NDM-1, with the exception of a tandem repeat of 5 amino acids (QRFGD, amino acid positions 44 to 48 of NDM-1). None of the amino acid substitutions observed in NDM variants occur within the active site (Fig. 1), but some variants have been reported to exhibit altered activities

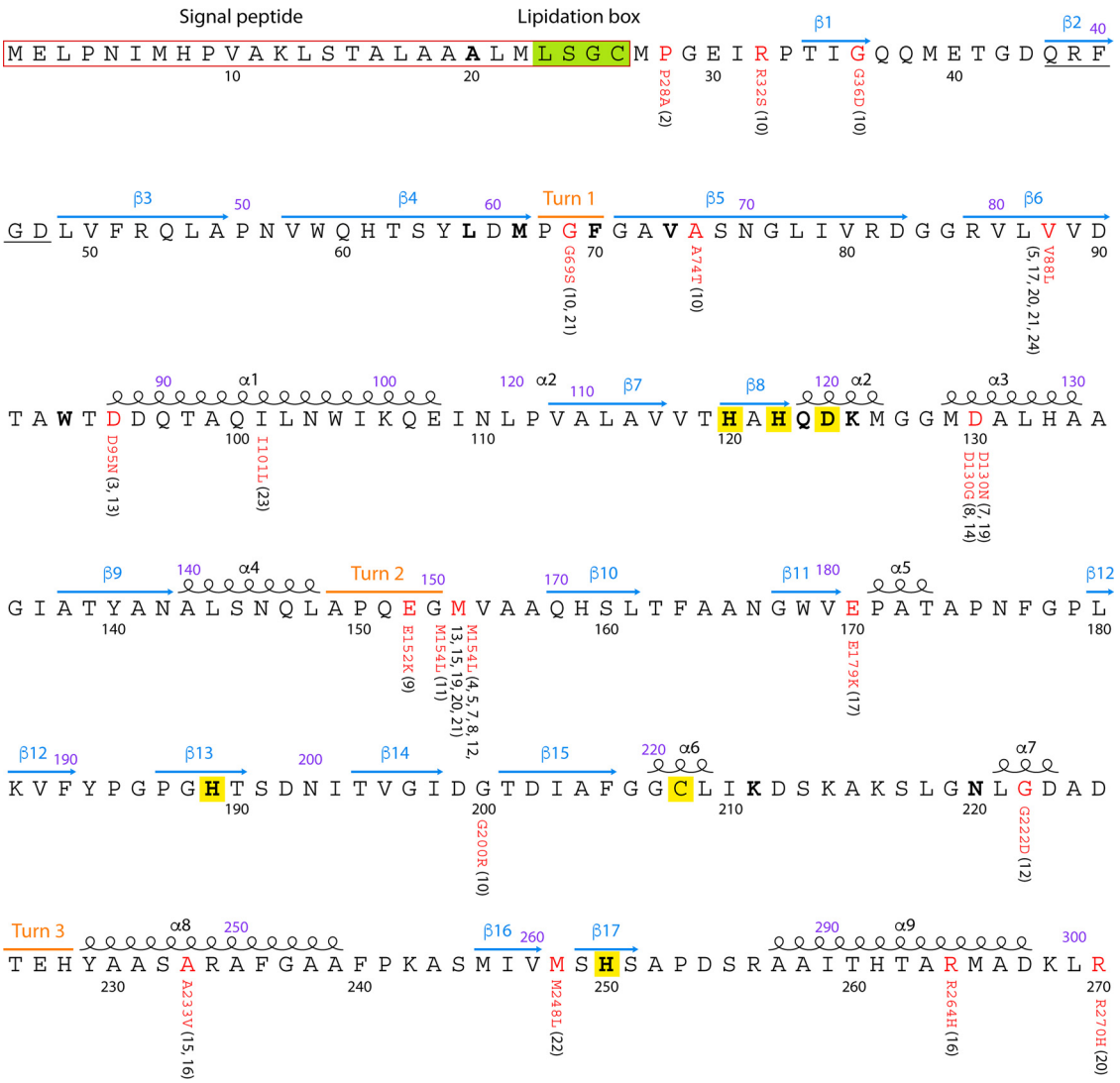

FIG 1 NDM-1 amino acid sequence and NDM variants. The annotation of the NDM amino acid sequence is adopted from data reported under UniProt accession no. C7C422. Signal peptides of NDM-1 are framed with red lines. α-Helices, β-strands, and turns are indicated as black spirals and blue and orange lines, respectively. Amino acids at active sites of NDM-1 are highlighted in boldface type, and the zinc binding residues are highlighted in yellow. The lipidation box is highlighted in green. Two numbering systems for the amino acids are shown: numbering according to the standard number scheme of MBLs is shown in purple above the amino acid sequence, while numbering from the translation of NDM enzymes is shown in black below the sequence. Amino acid substitutions compared with NDM-1 are labeled in red, with the variant names shown in parentheses. NDM-18 has a tandem repeat of 5 amino acids (QRFGD), which is underlined.

against β-lactams (see Table S1 in the supplemental material). Caution is required when interpreting the impact of amino acid substitutions on the carbapenemase activity of NDM variants due to the inconsistency of phenotypic susceptibility results, heterogeneity in experiment methodologies (e.g., the use of different promoters, cloning vectors, and strains), and the fact that different parameters (e.g., MICs or kinetics) have been used for comparing the activities of NDM variants across different studies. Nonetheless, variants containing the V88L substitution (NDM-5, -17, -20, and -21) (Table S1) have repeatedly been reported to exhibit enhanced carbapenemase activity (26–29). MICs of ertapenem against strains producing NDM-5 or NDM-20 are 4- or 8-fold higher than those against strains producing NDM-1 (26, 28), while NDM-17 and NDM-21 have the same carbapenemase activity as NDM-5 (27, 29). This suggests that such a substitution may have a significant impact on enzyme activity despite not being located at the active site, and the mechanism of action of enhanced activity remains

unclear. Variants containing V88L also have other substitutions, and a recent study, using the natural promoter of bla_{NDM-1} for cloning, failed to report any difference in carbapenem MICs between strains producing NDM-5 or NDM-17 (V88L-containing variants) and a strain producing NDM-1 (30). A variant exists which contains solely the V88L substitution, NDM-24, and the true ability of this substitution to enhance activity will be known when the phenotypic characteristics of this variant are reported. M154L (NDM-4) and D130G (NDM-14) substitutions have also been reported to result in enhanced carbapenemase activity (31, 32). However, MICs of carbapenems against *Escherichia coli* TOP10 strains harboring the recombinant plasmid pNDM-4 or pNDM-1, expressing NDM-4 and NDM-1, respectively, have no significant changes in MIC (31). NDM-8, which contains both M154L and D130G, does not exhibit increased carbapenemase activity (31). Of note, the media used in these experiments, such as Mueller-Hinton (MH) broth and LB, are rich in zinc. However, under conditions of zinc deprivation, the M154L (NDM-4), A233V (NDM-6), and E152K (NDM-9) substitutions in NDM enzymes enhance resistance to cefotaxime by improving metal affinity (M154L) or by improving the stability of NDM enzymes (A233V and E152K) (25). The D95N (NDM-3) and D130G (NDM-14) substitutions also enhance resistance to cefotaxime under conditions of zinc starvation, but their mechanisms remain unclear (25). In contrast, R264H (NDM-16), M154V (NDM-11), and P28A (NDM-2) have no significant impact on NDM function under zinc-restricting conditions (25). The stress imposed by zinc deprivation has therefore been proposed to be a major driver of the evolution of NDM enzymes (25). Unfortunately, MICs of carbapenems against strains producing different NDM variants have not been determined under conditions of zinc deprivation. The carbapenemase activity of new NDM variants is required to be characterized by a standardized assay under both zinc-rich and zinc-restricting conditions to fully elucidate the phenotypic importance of the emergence and evolution of novel substitutions.

EPIDEMIOLOGY OF NDM-POSITIVE STRAINS

Distribution and Prevalence of NDM-Positive Strains in Health Care Settings

After the initial discovery of NDM-1, a follow-up study revealed the widespread existence of bla_{NDM-1} in the Indian subcontinent, including India, Pakistan, and Bangladesh (33). Since then, NDM-positive strains have been shown to be globally distributed, with virtually all countries conducting epidemiological searches detecting NDM-positive strains (Fig. 2; a complete list of countries with documented NDM-positive strains is available in Appendix S1 in the supplemental material).

The worldwide distribution of NDM-positive strains appears to be heterogeneous with regard to prevalence. The SMART global surveillance program collected 103,960 isolates of *Enterobacteriaceae* in 55 countries from 2008 to 2014 and demonstrated that 290 strains (0.28% of all strains) were NDM positive, suggesting a relatively low prevalence (34). In the SMART program, the prevalence of NDM-positive strains varied significantly across countries: up to 5.01% in the United Arab Emirates (UAE), 6.15% in Egypt, 6.22% in India, and 6.26% in Serbia (34). This supports the observation that NDM-positive strains are more highly prevalent in South Asia, the Balkans, North Africa, and the Middle East. The high prevalence of NDM-positive strains in the Middle East has been proposed to be a result of population exchange with the Indian subcontinent (8). INFORM is another large-scale multinational study, which collected 38,266 *Enterobacteriaceae* isolates and 8,010 *P. aeruginosa* strains from 40 countries between 2012 and 2014 (35). The proportions of NDM-positive strains were 0.19% (72/38,266) in *Enterobacteriaceae* and 0.04% (3/8,010) in *P. aeruginosa* strains (35), consistent with the relatively low prevalence revealed by the SMART project. Unfortunately, the prevalence of NDM-positive strains in individual countries was not provided in that study (35). Other than the SMART and INFORM global surveillance programs, there are very few appropriately designed large-scale studies to determine the true prevalence of NDM carriage in given species or genera at a national level. In Pakistan, 18.5% of hospitalized patients at two military hospitals were found to carry NDM-positive *Enterobacteriaceae* (36). In China, a study of 1,162 clinical isolates of *Enterobacteriaceae* and *Acinetobacter*

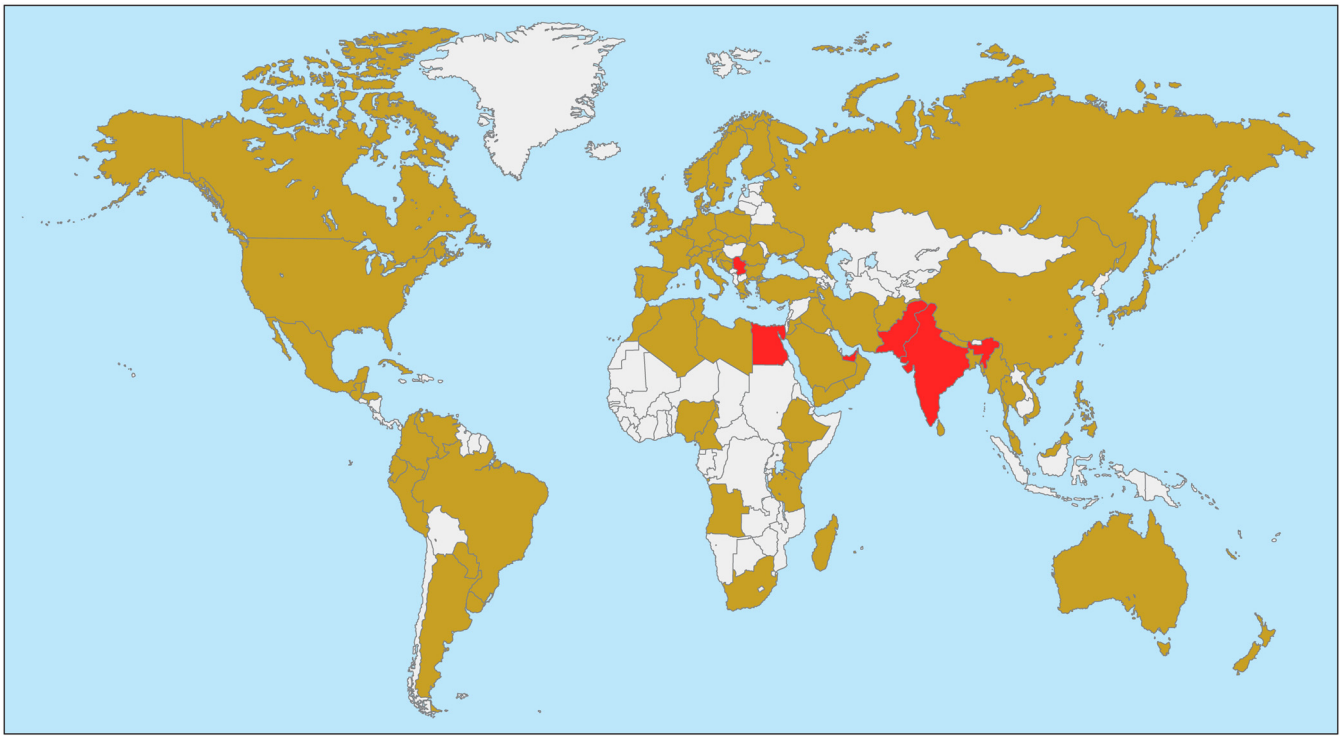

FIG 2 Worldwide distribution of NDM-positive strains of the *Enterobacteriaceae*. Countries (Egypt, India, Pakistan, Serbia, and UAE) with evidence showing a prevalence of NDM-positive strains among the *Enterobacteriaceae* of ≥5% are indicated in red, while countries with reports of NDM-positive strains but without evidence of a ≥5% prevalence are shown in light brown. Countries without reports or data on NDM-positive strains are indicated in white.

spp. collected at multiple sites reported that 3.9% were NDM positive, but the proportion of NDM-positive strains among the *Enterobacteriaceae* remains unclear, as the exact number of isolates of *Enterobacteriaceae* was not given (37). More large-scale surveillance studies, in particular on strains collected after 2014, are required to reveal changing trends and changes in the prevalence of NDM-positive strains.

In the SMART global surveillance program, bla_{NDM} was the third most common carbapenemase-encoding gene and accounted for 19.42% of carbapenemase positivity, after bla_{KPC} (53.18%) and the bla_{OXA-48}-like gene (20.09%) (34). In China, which was not included in the SMART program, 31% of 1,105 carbapenem-resistant *Enterobacteriaceae* (CRE) strains were NDM positive (38). The EuSCAPE survey across Europe revealed that 7.7% of carbapenem-resistant *K. pneumoniae* ($n = 1,203$) and 10.3% of carbapenem-resistant *E. coli* ($n = 194$) isolates were NDM positive (39).

In addition to clinical samples, bla_{NDM} genes have also been detected in hospital sewage in several countries, including China (40, 41), India (42), and Lebanon (43). Some NDM-positive strains recovered from hospital sewage belong to the *Enterobacteriaceae* (42, 43), which may reflect intestinal carriage of NDM-positive strains among the population within health care settings. However, NDM-positive strains of various *Acinetobacter* species have also been recovered from hospital sewage (40, 41). This suggests that sewage may be a reservoir of bla_{NDM}- and NDM-positive strains. The links between hospital sewage and the spread of bla_{NDM} are yet to be established and require more studies. Nonetheless, hospital sewage should be properly treated according to existing guidelines and regulations (44).

Spread of NDM-Positive Strains and International Travel

The rapid spread of NDM from its initial emergence in India to all continents is significantly associated with global travel (33). The initial discovery of bla_{NDM-1} in India, Pakistan, and the United Kingdom showed that almost all United Kingdom cases were associated with travel to the Indian subcontinent (33). Following the first report, the

incidence of NDM cases rose sharply, with countries in the Mediterranean region of Europe showing the largest increase (45). A detailed study of the first reported cases of NDM in Europe showed that 57% of all cases were associated with previous hospitalization in the Indian subcontinent or Balkans region (46). The first reported outbreak in Europe was in Italy in 2011. The bla_{NDM-1} gene was detected in both *Klebsiella* and *E. coli* strains isolated from clinical infections in a hospital in Bologna, Italy, with the index case being a patient initially treated for an infection due to NDM-positive bacteria in New Delhi, India, before traveling to Bologna, where further treatment was required (47). This initial seeding led to Italy having some of the highest rates of NDM cases in Europe by 2017 (39). By 2014, Greece was reporting sustained cases of hospital-associated infections caused by *K. pneumoniae* sequence type 11 (ST11) strains carrying bla_{NDM-1} (48), believed to be first introduced via travel from the eastern Balkans region. International travel has also been associated with the movement of NDM into North America, with direct patient transfer from India to Canada resulting in the introduction of bla_{NDM-1}-carrying *P. aeruginosa* ST654 (49) as well as cases of bla_{NDM-1}-carrying *E. coli* and *K. pneumoniae* (50). Direct travel from India and then Iran was also implicated in the first cases of NDM isolation in the United States (51–53).

While the role of travel in observed clinical cases of infection with bla_{NDM-1}-carrying bacteria is clear, less is known of the role that travel may play in introducing NDM into the wider community. A number of high-quality studies have been performed, showing that travel to regions of endemicity, such as India and Southeast Asia, leads to significant levels of intestinal colonization by bacteria carrying extended-spectrum β-lactamase (ESBL) genes (54–56). However, to date, there has been only one study examining the risk of asymptomatic colonization by bla_{NDM-1}-carrying bacteria during travel (57). This small study of French travelers to India identified intestinal colonization by a bla_{NDM-1}-carrying *E. coli* strain and reported that colonization lasted for only 1 month, compared to as long as 8 months for ESBL-carrying *E. coli* (55). This suggests that there may be intrinsic differences in the abilities of bla_{NDM}-carrying bacteria to successfully outcompete intestinal microbiota and colonize the human intestinal tract, an area that merits full and intensive study.

Host Species of NDM

To obtain a comprehensive picture of the distribution of NDM across bacteria, we retrieved all bacterial genome sequences containing bla_{NDM} from GenBank ($n = 766$; accessed on 8 January 2018) (see Data Set S1 in the supplemental material), in addition to reviewing the available literature. bla_{NDM} genes have been found in species belonging to 11 bacterial families (*Aeromonadaceae*, *Alcaligenaceae*, *Cardiobacteriaceae*, *Enterobacteriaceae*, *Moraxellaceae*, *Morganellaceae*, *Neisseriaceae*, *Pseudomonadaceae*, *Shewanellaceae*, *Vibrionaceae*, and *Xanthomonadaceae*) of the class *Gammaproteobacteria* (Table 1). A bla_{NDM} gene has also been identified in the genome sequence (GenBank accession no. JPNZ00000000) of a strain of *Bacillus subtilis*, which is a Gram-positive bacterium of the family *Bacillaceae*. This is very unusual, and resequencing of this strain would be advised to exclude any possibility of sequence read contamination. According to the literature, the *Enterobacteriaceae* are the major hosts of bla_{NDM}, among which *K. pneumoniae* is the most common species, accounting for just over half of all isolates, followed by *E. coli* and the *Enterobacter cloacae* complex (Table 2). The *Enterobacteriaceae* are able to cause a variety of community-onset or hospital-acquired infections, such as abscesses, bloodstream infection, intra-abdominal infection, meningitis, pneumonia, and urinary tract infection (58).

Acinetobacter spp. are also frequently identified as hosts of bla_{NDM} (41). *Acinetobacter* strains carrying bla_{NDM} have been found in at least 25 countries in Africa (Algeria, Libya, Morocco, Egypt, Ethiopia, Kenya, and Tunisia), the Americas (Argentina, Brazil, Cuba, Honduras, and Paraguay), Asia (Bangladesh, China, India, Israel, South Korea, Lebanon, Malaysia, Palestine, and Thailand), and Europe (Croatia, Denmark, Greece, and Slovenia). *Acinetobacter baumannii* is a notorious opportunistic pathogen associated with hospital-acquired infections and pneumonia in particular (59). Surprisingly, bla_{NDM}

TABLE 1 Bacterial species having NDM variants

Type	Family	Species	Reference(s)
NDM-1	*Enterobacteriaceae*	*Cedecea lapagei*, *Citrobacter braakii*,[a] *Citrobacter freundii*, *Citrobacter koseri*, *Citrobacter portucalensis*,[a] *Citrobacter sedlakii*, *Citrobacter werkmanii*,[a] *Enterobacter asburiae*,[a] *E. cloacae*, *E. hormaechei*, *Enterobacter kobei*,[a] *E. coli*, *Klebsiella aerogenes*, *Klebsiella michiganensis*, *Klebsiella oxytoca*, *K. pneumoniae*, *Klebsiella quasipneumoniae*,[a] *Klebsiella variicola*,[a] *Leclercia adecarboxylata*, *Lelliottia nimipressuralis*,[a] *Pantoea agglomerans*, *Pseudocitrobacter faecalis*,[a] *Raoultella ornithinolytica*, *Raoultella planticola*, *Salmonella enterica*, *Serratia marcescens*, *Shigella boydii*	2, 86, 102, 279, 320, 347–358
	Morganellaceae	*Morganella morganii*, *Providencia rettgeri*, *Providencia stuartii*	359–361
	Moraxellaceae	*A. baumannii*, *Acinetobacter baylyi*, *Acinetobacter beijerinckii*, *Acinetobacter bereziniae*, *Acinetobacter calcoaceticus*, *Acinetobacter defluvii*, *Acinetobacter dijkshoorniae*,[a] *Acinetobacter guillouiae*, *Acinetobacter haemolyticus*, *Acinetobacter johnsonii*, *Acinetobacter junii*, *Acinetobacter lwoffii*, *Acinetobacter nosocomialis*, *Acinetobacter pittii*, *Acinetobacter radioresistens*,[a] *Acinetobacter schindleri*, *Acinetobacter soli*, *Acinetobacter towneri*, *Acinetobacter variabilis*[a]	104, 107, 362–374
	Pseudomonadaceae	*P. aeruginosa*, *Pseudomonas oryzihabitans*, *Pseudomonas putida*, *Pseudomonas pseudoalcaligenes*	86, 375, 376
	Xanthomonadaceae	*Stenotrophomonas maltophilia*[b]	377
	Aeromonadaceae	*Aeromonas caviae*	86
	Vibrionaceae	*Vibrio parahaemolyticus*, *Vibrio fluvialis*, *V. cholerae*	256, 378, 379
	Cardiobacteriaceae	*Suttonella indologenes*	86
	Neisseriaceae	*Kingella denitrificans*	86
	Alcaligenaceae	*Achromobacter* spp.	86
	Shewanellaceae	*Shewanellaceae* spp.[a]	
	Bacillaceae	*Bacillus subtilis*[a,b]	
NDM-2	*Moraxellaceae*	*A. baumannii*	380
NDM-3	*Enterobacteriaceae*	*E. coli*	37
	Moraxellaceae	*A. baumannii*	381
NDM-4	*Enterobacteriaceae*	*E. cloacae*, *E. coli*, *K. pneumoniae*	95, 382, 383
NDM-5	*Enterobacteriaceae*	*C. freundii*, *Citrobacter europaeus*,[a] *E. coli*, *K. michiganensis*, *K. pneumoniae*, *K. quasipneumoniae*,[a] *S. enterica*	37, 355, 384, 385
	Morganellaceae	*P. mirabilis*	386
NDM-6	*Enterobacteriaceae*	*E. coli*, *K. aerogenes*[a]	387
NDM-7	*Enterobacteriaceae*	*C. freundii*, *K. pneumoniae*, *E. cloacae*, *E. hormaechei*, *E. coli*, *S. enterica*[a]	35, 95, 384
NDM-8	*Enterobacteriaceae*	*E. coli*	388
NDM-9	*Enterobacteriaceae*	*Cronobacter sakazakii*, *E. coli*, *K. pneumoniae*, *K. variicola*, *S. enterica*[a]	134, 389–391
NDM-10	*Enterobacteriaceae*	*K. pneumoniae*	392
NDM-11	*Enterobacteriaceae*	*E. coli*	393
NDM-12	*Enterobacteriaceae*	*E. coli*	384
NDM-13	*Enterobacteriaceae*	*E. coli*	135
NDM-14	*Moraxellaceae*	*A. lwoffii*	32
NDM-15	*Enterobacteriaceae*	*E. coli*[a]	
NDM-16	*Enterobacteriaceae*	*K. pneumoniae*	35
NDM-17	*Enterobacteriaceae*	*E. coli*	27
NDM-18	*Enterobacteriaceae*	*E. coli*[a]	
NDM-19	*Enterobacteriaceae*	*E. coli*,[a] *K. pneumoniae*[a]	

(Continued on next page)

TABLE 1 (Continued)

Type	Family	Species	Reference(s)
NDM-20	*Enterobacteriaceae*	*E. coli*	28
NDM-21	*Enterobacteriaceae*	*E. coli*	29
NDM-22	*Enterobacteriaceae*	*E. cloacae*[a]	
NDM-23	*Enterobacteriaceae*	*K. pneumoniae*[a]	
NDM-24	*Morganellaceae*	*P. stuartii*[a]	

[a]NDM-positive strains of the species have not been reported in literature but have genomes available in GenBank (see Data Set S1 in the supplemental material).
[b]This is unusual and needs to be verified to exclude contamination.

is also found in at least 18 other *Acinetobacter* species, most of which have been recovered from sewage and are rarely associated with human diseases (Table 1). This suggests that *Acinetobacter* may play a vital role in the dissemination of NDM-encoding genes and raises the question of whether *Acinetobacter* species could be the origin of bla_{NDM}. This wide species distribution may also be due to multiple mechanisms facilitating the transfer of bla_{NDM} across bacterial populations. In addition to conjugation, which is the major mode of horizontal transfer of bla_{NDM} in the *Enterobacteriaceae*, it has been found that OMVs of *A. baumannii* are able to mediate the intra- and interspecies transfer of bla_{NDM} plasmids at high transformation frequencies (10^{-5} to 10^{-6} transformants in the total cell count [CFU per milliliter]) (23, 60). General transduction facilitated by prophages present in the chromosome can also mediate the horizontal transfer of bla_{NDM} between *A. baumannii* strains (61). More studies are required on this remarkable diversity of *Acinetobacter* strains carrying bla_{NDM} and its relevance to the successful emergence of NDM across Gram-negative bacteria.

Among the 24 NDM variants, NDM-1 has the widest host spectrum identified so far and has been found in a number of species belonging to 11 bacterial families. Publicly available genome sequences also reveal that most NDM-positive *Acinetobacter* species, *Enterobacter* species, and *K. pneumoniae* isolates have NDM-1, while NDM-5 is most common in *E. coli*. NDM is rare in *P. aeruginosa*, with VIM being the most common MBL in this species (35).

Clonal Background of NDM-Positive Strains

There is a limited number of large-scale studies that have examined the clonal background of NDM-producing strains. These include one study involving multiple nations (62), one study across three countries (63), three studies conducted at a national level (38, 64, 65), and two municipal-level studies (66, 67) (see Table S2 in the supplemental material). While studying genomes deposited in GenBank can result in inherent bias, it is also the most comprehensive approach available to provide additional insights into the clonal background of NDM-positive strains. Among the 766

TABLE 2 Species distribution of NDM-positive *Enterobacteriaceae* strains[b]

Location	Yr(s)	NDM-positive strain	No. of isolates				Reference
			E. coli	*K. pneumoniae*	*E. cloacae*	Other	
South Africa	2012–2015	469	11	325	31	102	394
China	2014–2015	343	81	121	81	60	38
UK	2008–2013	326	80	180	31	35	64
Global ($n = 55$)[a]	2008–2014	290	57	169	40	24	34
South Korea	2010–2015	146	34	69	27	16	89
India (Mumbai)	2012	106	30	43	29	4	395
Total		1,680	293	907	239	241	

[a]The SMART Global Surveillance Program collected strains of the *Enterobacteriaceae* only in 55 countries.
[b]Studies with at least 100 strains are included.

NDM-positive bacterial genomes available in GenBank, *E. coli* ($n = 305$), *K. pneumoniae* ($n = 214$), *Acinetobacter* spp. ($n = 84$), and *Enterobacter* spp. ($n = 67$) are the most common (Data Set S1). NDM-positive *E. coli* and *K. pneumoniae* strains are distributed across more than 40 STs for each species. NDM-positive *Enterobacter* and *Acinetobacter* strains are also distributed across various species and multiple STs (Data Set S1). This suggests heterogeneous clonal backgrounds of NDM-positive strains and multiple acquisitions of bla_{NDM} genes across bacterial species. Despite this heterogeneity, a small number of STs of the *Enterobacteriaceae* and *A. baumannii* have been identified to be the most common carriers of bla_{NDM} (see below). These STs warrant further investigation to identify high-risk clones mediating the international spread of bla_{NDM} genes as well as determine underpinning factors that may make a clone more likely to emerge as a successful multidrug-resistant (MDR) pathogen.

NDM-positive *E. coli* strains belong to a variety of STs, and there are no predominant STs. NDM has been found in strains of *E. coli* ST131 (68–70), the pandemic clone mediating the global spread of the ESBL gene $bla_{CTX\text{-}M\text{-}15}$ (71, 72). However, NDM-positive ST131 strains remain uncommon (Table S2 and Data Set S1). In contrast, ST167 is relatively common among NDM-positive *E. coli* strains (Table S2 and Data Set S1) and accounted for 14.4% (44/305) of the 305 NDM-positive *E. coli* genomes available (Data Set S1). ST167 has been detected in multiple countries (India, Niger, South Africa, South Korea, Switzerland, and the United States) and throughout China and has been predominantly recovered from humans (Data Set S1). ST617 and ST410 are two other types of *E. coli* strains seen in multiple countries, although they are less common than ST167 (Data Set S1), and both types have sequenced isolates recovered from animals in addition to humans. In a multiple-site study in China, ST167 was the most common type of NDM-positive *E. coli* strain, followed by ST410 (38). Our previous study also suggested that *E. coli* ST167 and ST617 appear to be two major types of globally disseminated, NDM-positive *E. coli* strains (73). More studies are required to investigate whether ST167, ST410, and ST617 are international epidemic clones of NDM-positive *E. coli*.

NDM-positive *K. pneumoniae* strains are also distributed across a large number of STs, with no predominant lineages, suggesting that there are no obvious high-risk clones of NDM-positive *K. pneumoniae*. This is in contrast to KPC-positive *K. pneumoniae*, whose global spread is largely due to clonal complex 258 comprising ST258 and ST11 (74, 75). ST11, ST14, ST15, and ST147 strains are relatively common NDM-positive *K. pneumoniae* lineages and have been found in multiple countries across several continents, almost all of which were isolated from humans (Data Set S1). In the literature, ST14 is repeatedly reported as one of the most common types of NDM-positive *K. pneumoniae* strains (63–65). ST11 is another common type in multiple studies (38, 63–65). Of note, ST11 is the predominant ST of carbapenem-resistant *K. pneumoniae* in China but mainly carries KPC-2 rather than NDM (76). Although the currently available evidence is insufficient to demonstrate that ST11, ST14, ST15, and ST147 are truly epidemic clones mediating the international spread of bla_{NDM}, their distribution in multiple countries warrants further study. A multiple-site study reported that ST23 is the most common type of NDM-positive *K. pneumoniae* strain in China (38). However, ST23 is rarely seen in other countries, and there is only one ST23 genome in GenBank, isolated in China. This suggests that ST23 may be largely restricted to China (38). The well-known international epidemic carbapenem-resistant *K. pneumoniae* ST258, which carries $bla_{KPC\text{-}2}$ or $bla_{KPC\text{-}3}$, has not yet been found to carry bla_{NDM} (77).

Most NDM-positive strains of *Enterobacter* spp. are either *Enterobacter xiangfangensis* or *Enterobacter hormaechei* strains (Data Set S1). ST78 and ST171 have been reported as two emerging lineages of carbapenem-resistant *Enterobacter* spp., but strains of these lineages usually produce KPC rather than NDM (78). There are only three NDM-positive ST78 (belonging to *E. hormaechei*) and three NDM-positive ST171 (belonging to *E. xiangfangensis*) genomes in GenBank (Data Set S1). ST114 (belonging to *E. hormaechei*) strains have been found in multiple countries (Data Set S1). A study on an international collection of carbapenem-resistant *Enterobacter* strains demonstrated

TABLE 3 Replicon types of bla_{NDM}-carrying plasmids in the *Enterobacteriaceae*

Type	Replicon type(s)[b]	Reference(s)
NDM-1	**A/C**, ColE,[a] **FIA**, **FIB**, **FII**, HI1, HI3, HIB, L/M, N2, P, R, T,[a] X1,[a] **X3**, Y[a]	33, 82, 85–104, 396
NDM-3	A/C[a]	
NDM-4	FII, HI2, X3	95, 397
NDM-5	B/O/K/Z,[a] FUA,[a] FIB,[a] FIC,[a] FII, **X3**, X4,[a] Y[a]	82, 89, 385, 398–400
NDM-6	A/C, FIB, FII, R,[a] X3[a]	387, 399
NDM-7	A/C, FIC, FII, **X3**	89, 133, 399, 401, 402
NDM-8	FII	393
NDM-9	B/O/K/Z, FIA,[a] FII, HI2, N,[a] R[a]	134, 389, 390
NDM-10	FII	392
NDM-11	FII	393
NDM-12	F	403
NDM-13	X3	135
NDM-17	X3	27
NDM-19	X3[a]	
NDM-20	X3	28
NDM-21	X3	29

[a]Replicon types have not been reported in the literature but have plasmid sequences available in GenBank (see Data Set S2 in the supplemental material).
[b]Common replicon types (≥10 plasmid sequences in GenBank) are highlighted in boldface type.

that ST114 is the most common type of NDM-positive *Enterobacter* strain, although it accounts for only a minority of all strains due to the very diverse clonal background of NDM-positive *Enterobacter* strains (62). Therefore, no obvious international epidemic clones of NDM-positive *Enterobacter* strains have been identified at present.

NDM-positive *A. baumannii* strains are very genetically diverse with respect to ST lineage (67), with ST85 being the most commonly isolated (11 genomes in GenBank) (Data Set S1) across several countries. NDM has also been found in *P. aeruginosa* in multiple countries (35, 49, 79, 80). Whole-genome sequences exist for a small number of *P. aeruginosa* strains from lineage ST308, all isolated in Singapore (Data Set S1). NDM-positive ST308 *P. aeruginosa* has also been detected in neighboring Malaysia (81), suggesting that this type of NDM-positive *P. aeruginosa* strain may be circulating in the region.

Plasmids Carrying bla_{NDM}

Although bla_{NDM} has been found on bacterial chromosomes (82–84), the vast majority of carriage occurs on plasmids, which play a vital role in dissemination. bla_{NDM} has been reported to be carried on plasmids with a variety of replicon types (33, 82, 85–104). There are a total of 355 bla_{NDM}-carrying plasmids with complete sequences available in GenBank (accessed on 8 January 2018) (see Data Set S2 in the supplemental material). We determined their replicon types using PlasmidFinder (https://cge.cbs.dtu.dk/services/PlasmidFinder/). There are 20 replicon types of bla_{NDM}-carrying plasmids in the *Enterobacteriaceae*, including IncC, IncB/O/K/Z, IncFIA, IncFIB, IncFIC, IncFIII, IncHI1, IncHI2, IncHI3, IncN, IncN2, IncL/M, IncP, IncR, IncT, IncX1, IncX3, IncX4, IncY, and ColE10 (Table 3) (e.g., see references 33, 82, and 85–104). This suggests multiple acquisitions of bla_{NDM} by various plasmids and also highlights that the horizontal transfer of bla_{NDM} is mediated by multiple plasmids. The global distribution of the replicon types of bla_{NDM}-carrying plasmids is shown in Fig. 3.

IncX3 appears to be the most common type of plasmid carrying bla_{NDM}. Among the 355 bla_{NDM}-carrying plasmids available in GenBank, 117 (about one-third) had the IncX3 replicon, including 112 plasmids with IncX3 alone and 5 with IncX3 plus other replicons. IncX3 plasmids are narrow-host-range plasmids and have so far been seen only in the *Enterobacteriaceae*. Most of the IncX3 plasmids in GenBank (67/117; 57.3%) were present in *E. coli*, followed by *K. pneumoniae* (20/117; 17.1%). Although bla_{NDM}-carrying IncX3 plasmids have been found in Europe and North America, most of the plasmids deposited in GenBank (80/117; 68.4%) have been recovered in China and neighboring countries, such as South Korea ($n = 7$), Vietnam ($n = 2$), and Myanmar

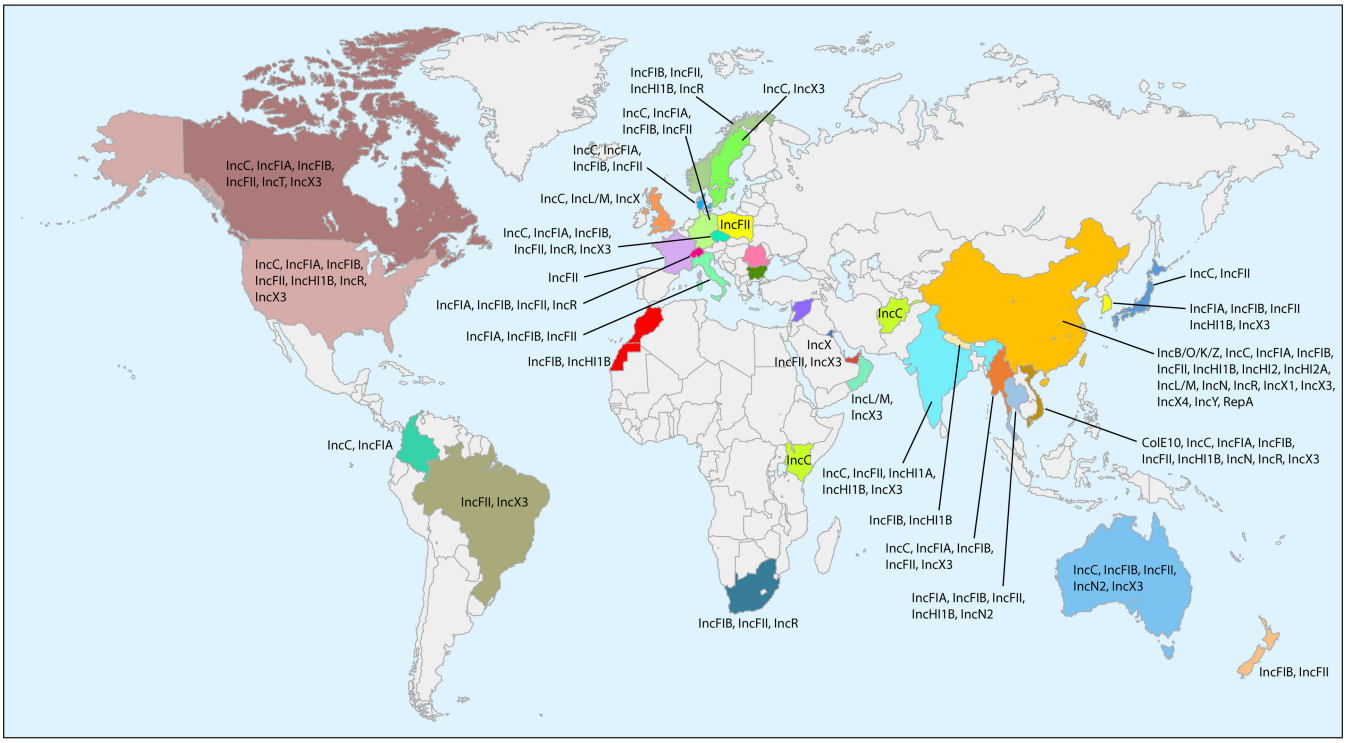

FIG 3 Worldwide distribution of the replicon types of *bla*$_{NDM}$-carrying plasmids in *Enterobacteriaceae*. Detailed information about the distribution of the replicon types of *bla*$_{NDM}$-carrying plasmids is available in Table 3 and Data Set S2 in the supplemental material.

($n = 3$). This suggests that IncX3 plasmids may be a major vehicle in mediating the dissemination of *bla*$_{NDM}$ in East Asia, particularly in China. Variants of *bla*$_{NDM,}$ including *bla*$_{NDM-1}$, *bla*$_{NDM-4}$, *bla*$_{NDM-5}$, *bla*$_{NDM-6}$, *bla*$_{NDM-7}$, *bla*$_{NDM-13}$, *bla*$_{NDM-17}$, *bla*$_{NDM-19}$, *bla*$_{NDM-20}$, and *bla*$_{NDM-21}$, have also been found on IncX3 plasmids (Table 3). This highlights that IncX3 plasmids may serve as one of the major platforms on which *bla*$_{NDM}$ genes are evolving with the generation of new NDM variants.

There are 99 *bla*$_{NDM}$-carrying plasmids containing an IncFII replicon, alone or in combination with other types of replicons, commonly IncFIB in GenBank. A replicon sequence typing (RST) scheme is available for IncF plasmids (105). We performed RST for these plasmids using the pMLST tool (https://cge.cbs.dtu.dk/services/pMLST/). It is evident that IncFII plasmids of the FIA$^-$:FIB36:FIIY4 allele type ($n = 27$) or the FIA$^-$:FIB$^-$:FII2 type ($n = 21$) are particularly common and have been found in various species of the *Enterobacteriaceae* from multiple countries in several continents (Data Set S2). These two IncFII plasmids have mainly been found in strains from human samples (Data Set S2).

Another common type of *bla*$_{NDM}$-carrying plasmid (53/355; 14.9%) is IncC (also incorrectly known as IncA/C2) (106). IncC plasmids carrying *bla*$_{NDM}$ have a worldwide distribution and are found on all continents except Antarctica (Data Set S2). IncA/C has a broad host range, and IncC plasmids carrying *bla*$_{NDM}$ have been found in the *Morganellaceae* and the *Vibrionaceae* in addition to the *Enterobacteriaceae*. A plasmid multilocus sequence typing (pMLST) scheme exists for IncA/C plasmids (https://pubmlst.org/plasmid/). Almost all IncC plasmids carrying *bla*$_{NDM}$ belong to either ST1 (39/53) or ST3 (12/53) (Data Set S2). However, there are only 13 STs of IncA/C plasmids in the database, suggesting low diversity of these plasmids or low resolution of the scheme for typing such plasmids. A core genome pMLST (cgPMLST) scheme also exists for IncA/C plasmids (https://pubmlst.org/plasmid/). IncC plasmids of cgST1.2 are particularly common ($n = 17$) (Data Set S2) and have been found in several species of the *Enterobacteriaceae* and *Morganellaceae* from all continents except Antarctica. Plasmids of the above-mentioned IncX3 type, FIA$^-$:FIB36:FIIY4 and FIA$^-$:FIB$^-$:FII2 types, and

cgST1.2 of IncC warrant further investigation to understand their epidemiology, their true contribution to the NDM problem, and the mechanisms mediating their wide spread.

Plasmids carrying bla_{NDM} have been well documented in *Acinetobacter* (e.g., see references 107–110). A replicon typing scheme for plasmids of *A. baumannii* has been developed (111), but the replicon types of bla_{NDM}-carrying plasmids in *Acinetobacter* have rarely been reported, and the scheme has not been incorporated into PlasmidFinder or any other commonly used plasmid typing tools. Therefore, the replicon types of bla_{NDM}-carrying plasmids in *Acinetobacter* remain largely unknown. These plasmids vary significantly in size from 1,634 bp to 354,308 bp (Data Set S2), suggesting that multiple plasmids are involved in the spread of bla_{NDM} in *Acinetobacter*.

Genetic Contexts of bla_{NDM}

Mobile genetic elements, such as insertion sequences, transposons, and integrons, can mobilize antimicrobial resistance genes. This mobilization can be between different plasmids as well as between plasmids and the chromosome. bla_{NDM} has been found in a variety of genetic contexts, which suggests that multiple mechanisms have been involved in the mobilization of bla_{NDM}. The genetic contexts of bla_{NDM} share two common features. The insertion sequence IS*Aba125* (intact or truncated) is always upstream of bla_{NDM}, while a bleomycin resistance gene, ble_{MBL}, is always downstream. Further downstream of ble_{MBL}, there is usually a complete or remnant form of a set of several genes, including *trpF* (encoding a phosphoribosylanthranilate isomerase), *dsbC* (also called *tat*, encoding a twin-arginine translocation pathway signal sequence domain protein), *cutA1* (also called *dct*, encoding a periplasmic divalent cation tolerance protein), and *groES-groEL* (encoding chaperonin), and the insertion sequence IS*CR27*. IS*Aba125* provides the −35 region of a promoter for the expression of bla_{NDM-1} (112, 113). Another IS*Aba125* element has been found downstream of IS*CR27* in *Acinetobacter*, and the two IS*Aba125* elements form a composite transposon carrying bla_{NDM-1}, termed Tn*125* (Fig. 4A). It appears that the genetic components within Tn*125* have different origins, as the *groES-groEL*-IS*CR27* section may originate from *Xanthomonas* spp. (114, 115). The exact origin of bla_{NDM-1} remains unknown. Careful examination of the genetic context and sequence of bla_{NDM-1} reveals that bla_{NDM-1} is a chimeric gene. The first 19 bp of nucleotide sequence (encoding the first 6 amino acids of NDM-1) originate from an aminoglycoside resistance gene, *aphA6*. The remaining nucleotide sequence originates from a yet-to-be-identified preexisting MBL gene (116). As IS*Aba125* and *aphA6* are widespread in *Acinetobacter* spp. (117, 118), it is very likely that the fusion of genes to form bla_{NDM-1} occurred in *Acinetobacter* (116). IS*CR* elements are known to acquire and accumulate genetic components via a rolling-circle mechanism (119, 120). As an IS*CR* element, IS*CR27* may have initially acquired the progenitor gene of bla_{NDM-1} (115, 116, 121) and mobilized the gene together with ble_{MBL}, *trpF*, *dsbC*, *cutA1*, and *groES-groEL* into *aphA6* (downstream of a copy of IS*Aba125*), allowing fusion and the formation of bla_{NDM-1} (115, 116). The second copy of IS*Aba125* then inserted downstream of IS*CR27* to form the IS*Aba125*-based composite transposon Tn*125* (116).

Acinetobacter spp. serve as the intermediate source for the mobilization of bla_{NDM} into the *Enterobacteriaceae* (116, 122). The bla_{NDM-1}-carrying element Tn*125* has been interrupted or truncated in *Enterobacteriaceae*, to generate a variety of complex genetic contexts for bla_{NDM}. This interruption is largely due to the insertion of many other mobile genetic elements (e.g., IS*1*, IS*5*, IS*26*, IS*903*, IS*Ec33*, and IS*Kpn14*, etc.) and recombination. The flanking sequences of various remnants of Tn*125* have also formed mechanisms involved in the mobilization of bla_{NDM-1}. These mechanisms included a number of composite transposons formed by two copies of the same insertion sequence, such as IS*26* (123) (Fig. 4B), IS*903* (124) (Fig. 4C), and IS*3000* (termed Tn*3000*) (Fig. 4F) (125). The duplication of bla_{NDM} on the same plasmid is due to the action of an IS*26*-formed composite transposon (94). The mobilization of bla_{NDM} may be asso-

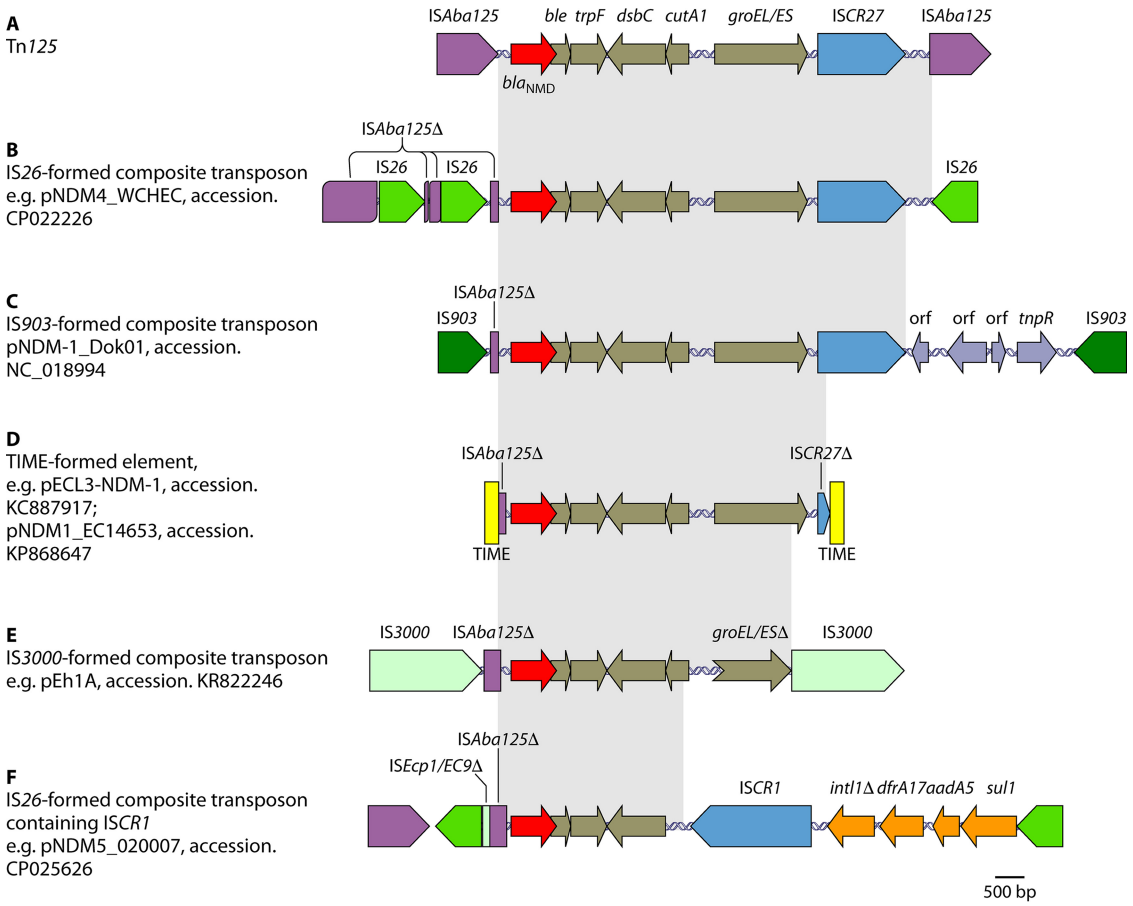

FIG 4 Examples of genetic contexts and mobilization mechanisms of bla_{NDM}. (A) Tn*125* formed by two copies of IS*Aba125*. (B) Composite transposon formed by two copies of IS*26*. (C) Composite transposon formed by two copies of IS*903*. orf, open reading frame. (D) Element formed by two copies of the TIME. (E) Composite transposon formed by two copies of IS*3000*. (F) Genetic contexts containing IS*CR1*. This element is also flanked by two copies of IS*26*. The plasmid names and GenBank accession numbers are shown. Δ represents truncated genes or elements.

ciated with IS*CR* element, IS*CR1* (Fig. 4E) (95, 126). Two tandem copies of bla_{NDM-1} genes have been found on the chromosomes of both an ST167 *E. coli* strain in China (127) and a *P. aeruginosa* strain in Serbia (128). In both cases, the tandem copies of bla_{NDM-1} are associated with IS*CR1*, which uses a rolling-circle mechanism of transposition and may generate a tandem duplication of its mobilized sequence via homologous recombination (119). Tn*3*-derived inverted-repeat transposable elements (TIMEs), which were previously described as miniature inverted-repeat transposable elements (MITEs) (94, 129), have also been found to mobilize bla_{NDM} (Fig. 4D) (95). TIMEs are a type of mobile genetic element bounded by 38-bp inverted repeats characteristic of the Tn*3* family but lacking the transposase gene *tnpA* and, usually, the resolvase gene *tnpR* (130). Two copies of the TIME can form a composite transposon-like element, which is able to mobilize the intervening genetic components in the presence of the external Tn*3*-like transposase (94, 129).

Genetic contexts similar to those of bla_{NDM-1} are shared in other bla_{NDM} variants, which are commonly associated with IS*Aba125* (intact or truncated) upstream and ble_{MBL} downstream (29, 95, 123, 131–135). This suggests that other bla_{NDM} variants emerged from bla_{NDM-1} via nucleotide mutations. Due to the highly mobile nature of bla_{NDM}, the gene can also be lost by bacterial cells. Loss can be due to the deletion of DNA fragments as a result of insertion sequence and transposon activity, such as recombination (136, 137), or the complete loss of the bla_{NDM}-carrying plasmids (138).

DETECTION METHODS

Detection of NDM is essential for informing therapeutic decisions. Detection of NDM also provides critical information in investigating outbreaks, guiding infection control, and tracking the global and local epidemiology of NDM-positive strains.

Detection of Carbapenemase Activity

New methods and tools are continuously being introduced for the detection of carbapenemase activity. A number of phenotypic methods to detect carbapenemase activity have been developed. These include the modified Hodge test (MHT) (139), the Carba NP (CNP) test (140) and its variants, the β-Carba test (141, 142), the carbapenem inactivation method (CIM) (143), the modified carbapenem inactivation method (mCIM) (144), matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (145), isothermal titration calorimetry (ITC) (146), and UV spectrophotometry (147). The MHT, CNP, and mCIM have been extensively evaluated, and the latter two are currently recommended by the CLSI for detecting carbapenemases in carbapenemase-producing *Enterobacteriaceae* (CPE) and carbapenemase-producing *P. aeruginosa* (148). The MHT had been recommended by the CLSI for epidemiological or infection control purposes since 2009 (149), but the recommendation was removed in 2018 due to the availability of newer tests (CNP and mCIM) with higher accuracy (148). None of these phenotypic tests are specific for NDM, as they are designed to detect all carbapenemases, including class A (e.g., KPC) and class D (e.g., OXA-48) carbapenemases and other MBLs (e.g., IMP and VIM). We do not review these methods in detail here but refer the reader to the latest review on phenotypic methods for detecting carbapenemases (150).

CNP. The CNP test is based on the *in vitro* hydrolysis of imipenem and has been extensively evaluated for detecting carbapenemases in *Enterobacteriaceae* (140) and *Pseudomonas* (151). The test has both excellent specificity (84% to 100%) and sensitivity (93.3% to 100%) for detecting carbapenemases, including NDM in *Enterobacteriaceae* (152–154) and *P. aeruginosa* (155). However, CNP is relatively labor-intensive, as reagents need to be prepared in-house, and some have short shelf lives (e.g., 72 h) (156). It has also been reported that CNP may miss some mucoid NDM-positive *Enterobacteriaceae* strains (157). Many variants of CNP have been developed with minor modifications or are based on the same principle but with simplified procedures. A modified CNP test has been developed, with a short turnaround time (<2 h) from the isolation of single colonies (144). This test has 84.9% to 100% sensitivity and 100% specificity for detecting carbapenemases in *Enterobacteriaceae* (152–154, 158). The BYG (Bogaerts-Yunus-Glupczynski) Carba test uses an electrochemical method to detect enzymatic hydrolysis of carbapenems (159), while GoldNano Carb employs gold nanoparticles to visualize carbapenemase activity (160). The detection of carbapenemases in *Acinetobacter* by CNP is more challenging due to its intrinsic low permeability (161). The CarbAcineto NP test is a modified CNP protocol, using modified lysis conditions and an increased bacterial inoculum to detect all types of carbapenemases, with 88.9% to 94.7% sensitivity and 100% specificity for *Acinetobacter* (162, 163). Several variants of CNP with simplified procedures have become commercially available, including Rapidec Carba NP (bioMérieux) (141, 164, 165), Neo-Rapid Carb (Rosco Diagnostica) (153, 164), Rapid Blue Carb (Rosco Diagnostica) (166), and β-Carba (Bio-Rad) (141, 142). Rapidec Carba NP and Neo-Rapid Carb have overall comparable sensitivity and specificity compared with CNP (141, 153, 164, 165), while it has been reported that Rapid Blue Carb (166) and β-Carba (141, 142) may be slightly less sensitive.

CIM and mCIM. The CIM is based on the enzymatic hydrolysis of meropenem (143). The pooled sensitivity and specificity of this test are 85.7% to 95.1% and 94.4% to 95.7%, respectively, for detecting carbapenemases in *Enterobacteriaceae* (157, 167, 168). CIM is less expensive than CNP (<$1 per test compared to $2 to $16) (143, 150). An mCIM with a longer incubation period (4 h rather than 2 h) has been developed and demonstrated increases in both sensitivity and specificity to 100% for detecting carbapenemases in *Enterobacteriaceae* (144, 169–171). The mCIM has been included in

CLSI guidelines for detecting carbapenemases in *Enterobacteriaceae* for epidemiological or infection control purposes since 2017 (172). A rapid carbapenem inactivation method (rCIM) for detecting carbapenemases within 3 h has recently been developed and has exhibited excellent sensitivity (99%) and specificity (100%) (173). A multisite evaluation found that the mCIM is accurate for detection of carbapenemases in *P. aeruginosa*, with 86.7% to 100% sensitivity and 93.3% to 100% specificity. Detection of carbapenemase-producing *Acinetobacter* with this method is more problematic, with 36.3% to 95.7% sensitivity and 28.6% to 100% specificity (155). Another study has shown mCIM to have low sensitivity (45.1%) for the detection of carbapenemases in *Acinetobacter* and *Pseudomonas* (174). A new method, termed CIMTris, has been developed to detect carbapenemases in *Acinetobacter* and *Pseudomonas*. The method is modified by extracting carbapenemases from bacteria with 0.5 M Tris hydrochloride and has 97.6% sensitivity and 92.6% specificity (174).

MALDI-TOF MS. MALDI-TOF MS platforms are well established for genus or species identification for bacterial strains. MALDI-TOF MS has the potential to detect carbapenemases, as the method can detect carbapenem degradation products when bacterial protein extracts are incubated with carbapenems. MALDI-TOF MS has 77% to 100% sensitivity and 94% to 100% specificity when tested for detecting carbapenemases (145, 150, 175–177). MALDI-TOF MS works well to detect carbapenemases in *Acinetobacter* (178). MALDI-TOF MS has an objective endpoint for result interpretation (179), but no standardized in-house protocol for carbapenemase detection is available (150, 176, 180). A commercially available MBT Star-Carba IVD kit (Bruker) was introduced very recently and was evaluated with 96.1% to 100% sensitivity and 89.0% to 99.9% specificity (181).

ITC. ITC is an approach to measure heat change during binding between ligands and their targets (182) and has been developed to study kinetics and inhibition of β-lactamases (146). It can also be used to readily detect ($<$10 min) the activity of carbapenemases by monitoring the change in thermal power after the exposure of bacterial cells to carbapenems (146). Although the sensitivity and specificity of ITC for detecting carbapenemases have not been established, it has the potential to be used for screening the production of carbapenemases in bacterial strains.

Detection of MBLs

Disc- or strip-based inhibition methods. A number of tests have been developed for detecting MBLs in bacterial strains, mainly based on the combination of MBL inhibitors and carbapenems. The combined disc test (CDT), the double-disc synergy test (DDST), and the modified Etest have been widely used for detecting MBLs, including NDM (183, 184). Although the Etest MBL test is simple, it is costly, lacks the sensitivity to detect weak MBL activities (185), and can generate false-positive results in the presence of certain OXA-type enzymes (e.g., OXA-23) (186). The CDT compares the inhibition zones of carbapenem discs with or without MBL inhibitors (commonly EDTA), while the DDST is based on the difference of the inhibition zones of a β-lactam (commonly a carbapenem) disc in the presence of a disc containing MBL inhibitors (EDTA, dipicolinic acid, or 2-mercaptopropionic acid). Both the CDT and DDST are inexpensive, simple, and convenient and have good sensitivity and specificity for the detection of MBLs in *Enterobacteriaceae*. One study found that the imipenem-EDTA CDT correctly detected all 27 tested NDM-positive *Enterobacteriaceae* strains (187). Another study shows that the sensitivity and specificity of DDSTs using EDTA magnesium disodium salt tetrahydrate for 75 MBL producers (including 2 NDM producers) and 25 non-MBL producers were 96.0% and 100%, respectively (188). CDTs and DDSTs incorporating MBL inhibitors are unable to detect carbapenemases other than MBLs. MAST-Carba plus (MAST group) is a variant of the CDT containing multiple CDT discs and has been developed to detect major types of carbapenemases, including MBLs. It correctly detected all NDM-positive *Enterobacteriaceae* in small bacterial collections (189, 190). EDTA is a commonly used MBL inhibitor and may generate nonspecific (false-positive) results for nonfermenting bacteria, in particular *Acinetobacter*, as it increases the

permeability of the bacterial outer cell membrane (147, 191). It has also been reported that some other MBL inhibitors, such as sodium mercaptoacetic acid (SAM), may provide poor performance in DDSTs (190).

MBL-targeted mCIM. The mCIM alone is unable to differentiate MBLs from other carbapenemases, but the addition of MBL inhibitors can be used to specifically detect MBLs following a positive result with the mCIM. The combination of SAM and the mCIM (SAM-mCIM) has demonstrated 100% sensitivity and specificity for detecting MBLs in a small collection of CRE strains ($n = 55$) (169). The EDTA-modified mCIM (eCIM) was recommended by the CLSI in 2018 for detecting MBLs in CRE for epidemiological or infection control purposes as a tandem test following a positive mCIM result (148). The eCIM combined with the mCIM have a >95% sensitivity and a >92% specificity (148). Strains with a coexistence of MBLs and non-MBL carbapenemases (e.g., KPC and OXA-48) have been increasingly reported (51, 94, 192). In such cases, the eCIM and SAM-mCIM may generate false-negative results.

Carb NP test II. Carb NP test II is a derivate of CNP which incorporates tazobactam for detection of KPC and EDTA for detection of MBLs. It has been reported to exhibit 100% sensitivity and specificity (193). However, in a study on a small collection of isolates, Carb NP test II failed to detect three (*Providencia* or *Proteus*) out of four NDM-positive strains (194). More studies are clearly required to validate Carb NP test II.

Modified MALDI-TOF MS. Protocols for MALDI-TOF MS have been modified by the addition of carbapenemase inhibitors for detecting MBLs. The addition of phenylboronic acid (an inhibitor of class A carbapenemases) or dipicolinic acid (an MBL inhibitor) with ertapenem allows differentiation between MBLs and class A carbapenemases (195).

ITC with MBL inhibitors. In addition to detecting carbapenemases, ITC has also been used to detect the activity of MBLs by comparing the change in thermal power after the exposure of bacterial cells to carbapenems in the absence and presence of MBL inhibitors such as EDTA (146, 196). However, the sensitivity and specificity of ITC need to be established.

Detection of NDM Enzymes

Lateral flow immunoassays. The lateral flow immunoassay (LFIA) is an antibody-based method developed to detect different types of carbapenemases, which has been validated. It allows the specific detection of NDM enzymes in singleplex (for NDM only) (197) or multiplex (for NDM and other major types of carbapenemases) (198, 199) assays by using specific antibodies. These assays are easy to perform and have a short turnaround time, as they yield results from cultured colonies within 15 min. These tests have also been shown to have 100% sensitivity and specificity (197, 200). A multiplex LFIA has also been developed for the rapid detection of NDM, KPC, and OXA-48 carbapenemases directly from positive blood cultures (201). The LFIA has been shown to detect NDM-1, -2, -3, -4, -5, -6, -7, and -9 (199, 202), but any amino acid substitutions occurring in the epitope that is used to generate antibodies for detecting NDM may generate false-negative results. However, the limited diversity of amino acid sequences within the NDM family allows universal antibodies to be designed to detect all known NDM variants. Several commercially available multiplex LFIAs have been developed and evaluated. These assays include Resist-3 O.K.N. (OXA-48-like, KPC, and NDM; Coris BioConcept) (203), the O.K.N. K-SeT assay (OXA-48-like, KPC, and NDM; Coris BioConcept) (200), the O.K.N.V. K-Set assay (OXA-48-like, KPC, NDM, and VIM; Coris BioConcept) (204), and the NG-Test Carba 5 assay (OXA-48-like, KPC, NDM, VIM, and IMP; NG Biotech) (199, 202). These assays exhibit nearly 100% sensitivities and specificities for detection of NDM.

Detection of NDM-Encoding Genes

Molecular techniques are the reference methods for detecting carbapenemase genes, including bla_{NDM}, due to their excellent sensitivity and specificity and robust performance (187, 205). Molecular techniques are mostly based on PCR, but whole-

genome sequencing (WGS) is being increasingly used. The main limitations of molecular technologies are the high costs and the requirement for trained technicians (184, 206).

PCR. PCR can be singleplex, multiplex, or real time, and validated protocols are available to allow convenient and robust detection of bla_{NDM} (184). Many in-house singleplex and multiplex conventional and real-time PCR assays for detecting bla_{NDM} have been developed (e.g., see references 2 and 207–213). Commercially available real-time PCR approaches for detecting multiple carbapenemase genes, including bla_{NDM}, also exist. These include Xpert Carba-R (Cepheid), Check-Direct CPE (Check-Points Health), and an antibiotic resistance TaqMan assay (ThermoFisher Scientific). Xpert Carba-R is a fully automated and integrated system for sample preparation, DNA extraction, amplification, and qualitative detection of target genes using multiplex real-time PCR assays with a $<$1-h turnaround time (214). The method can be used directly on swab specimens and has 96.6% sensitivity and 98.6% specificity (215). In the Check-Direct CPE kit, bla_{NDM} and bla_{VIM} are detected using the same fluorochrome, and it is not possible to differentiate these two genes on certain real-time PCR platforms, such as ABI 7500, but they can be differentiated using other platforms, such as the BD Max platform (216). The Check-Direct CPE kit has been evaluated for detection of carbapenemase genes, including bla_{NDM}, in *Enterobacteriaceae* and *P. aeruginosa* (212, 216), with 100% sensitivity and specificity. The ePlex blood culture identification kit (GenMark) is a highly multiplexed, fully automated, one-step, single-use cartridge assay system that was announced recently. The kit incorporates bla_{NDM} detection, but validation has not been reported in the literature (217).

The hyplex SuperBug ID test system (AmplexDiagnostics) and the AID carbapenemase line probe assay (Autoimmun Diagnostika) are two commercially available PCR assays for detecting multiple carbapenemase genes, including bla_{NDM}. These assays use reverse hybridizations following multiplex PCR. Both assays have 100% sensitivity and specificity for detecting bla_{NDM} (218–220). A locked nucleic acid (LNA)-based quantitative real-time PCR assay has been developed to simultaneously detect multiple antimicrobial resistance genes, including bla_{NDM}, directly from positive blood cultures but has been tested only on several NDM-positive strains (221). A long-fragment real-time quantitative PCR–combined *in vitro* protein expression (PCR-P) method has been developed for detection of bla_{NDM-1}. PCR-P is able to detect bla_{NDM-1} variants that have led to changes of function by measuring rates of degradation of imipenem (222).

Loop-mediated isothermal amplification. Loop-mediated isothermal amplification (LAMP) has been used for the rapid and sensitive detection of bla_{NDM} (223, 224). LAMP does not require expensive thermocyclers, is quicker to perform than conventional PCR, and has been shown to exhibit higher sensitivity for detecting bla_{NDM} (223–225). In addition, LAMP does not require gel electrophoresis, making it convenient in clinical laboratories. A commercially available LAMP system called Eazyplex (AmplexDiagnostics) has been evaluated for detecting carbapenemase genes in *Acinetobacter* (226, 227), *Enterobacteriaceae* (216, 227, 228), and *P. aeruginosa* (216, 227, 228), with 100% sensitivity and specificity for bla_{NDM}. LAMP has been evaluated only for detecting bla_{NDM-1}, and since only 4 or 6 primers can be used in LAMP, it may not be able to detect all bla_{NDM} variants due to the possibility of nucleotide mutations occurring in primer binding regions. Due to the extremely high amplification efficiency of LAMP, extra care should also be taken to avoid contamination (223).

DNA microarray. DNA microarrays can simultaneously detect a vast number of genes. DNA microarrays for detecting antimicrobial resistance genes, including bla_{NDM}, have been developed (229) but may not be appropriate for specifically detecting bla_{NDM} alone, as PCR and LAMP are less expensive and simpler molecular methods. In addition, detection of DNA hybridization with electrochemical impedance spectroscopy (EIS) has also been developed to specially detect bla_{NDM} (196). DNA microarrays including bla_{NDM} in the target panel have become commercially available, including the Verigene Gram-negative blood culture nucleic acid test (BC-GN; Nanosphere), Check-MDR CT102 and Check-MDR CT103 assays (Check-Points Health), and the Carb-

Detect AS-1 kit and CarbDetect AS-2 kit (Alere Technologies). BC-GN and Check-MDR CT102 detect genes encoding ESBLs and major types of carbapenemases (IMP, KPC, VIM, NDM, and OXA-48), while Check-MDR CT103 also targets genes encoding plasmid-mediated AmpC cephalosporinases on the basis of CT102. CarbDetect kits also target genes mediating resistance to aminoglycosides, quinolones, macrolides, sulfonamides, and trimethoprim. Both CT102 and CT103 have been evaluated using collections including NDM-positive strains and exhibit 100% sensitivity and specificity (230, 231). BC-GN has 96.2% sensitivity for detecting bla_{NDM} and gives false-negative results for several NDM-positive strains (232). DNA microarrays have limitations, including high costs, long turnaround times, and inflexibility with respect to adding new targets once an array is established (233).

Whole-genome sequencing. WGS is being increasingly used in health care settings. It can be used for many purposes, including detecting genes encoding antimicrobial resistance. The cost of next-generation WGS, commonly the MiSeq and HiSeq platforms (Illumina), has significantly dropped to typically $74 per bacterial genome in 2018. Several databases of antimicrobial resistance are available for detecting known antimicrobial resistance genes. The most-used examples are ResFinder (https://cge.cbs.dtu.dk/services/ResFinder/) (234), ARDB (Antibiotic Resistance Genes Database) (https://ardb.cbcb.umd.edu/) (which is not maintained at present) (235), and CARD (Comprehensive Antibiotic Resistance Database) (https://card.mcmaster.ca/) (236). By querying the databases, next-generation WGS can be used to detect all known antimicrobial resistance genes and any new variants of a certain gene, such as bla_{NDM}, which could be missed by many other commonly used molecular methods such as real-time PCR and DNA microarrays. Genome sequences generated by WGS also allow precise species identification and strain typing for surveillance and tracking of the transmission of certain strains, critical for epidemiology and infection control (108, 237–239). The complete sequence of plasmids carrying certain antimicrobial resistance genes, such as bla_{NDM}, can be further obtained using long-read sequencing platforms such as PacBio (Pacific Biosciences) and MinION (Nanopore). These platforms can provide complementary information on the transmission of antimicrobial resistance in addition to strain typing. MinION is portable and is particularly useful in health care settings, but the cost is still relatively high at present. Metagenomic sequencing has also been developed for sequencing total DNA directly from clinical samples. This can also detect antimicrobial resistance genes such as bla_{NDM}. However, metagenomic sequencing needs much higher sequencing depth (costlier), and the analysis of metagenomic data is much more complex than WGS for single isolates (237). WGS is promising, but several major aspects, such as the cost, bioinformatics pipelines, and turnaround time, need to be improved before it can be used routinely for diagnosis and detection in health care settings (237).

TREATMENT OPTIONS AGAINST NDM-POSITIVE STRAINS

Treatment for CRE infections has been reviewed extensively (240–244). However, CRE strains included in previous studies are commonly KPC producers, or their type of carbapenemase has not been specified. In this review, we focus on treatment for NDM-positive strains rather than CRE as a whole.

Aztreonam-Avibactam or Aztreonam Combined with Ceftazidime-Avibactam

Although aztreonam is stable against MBLs, NDM-producing strains usually have ESBLs and/or AmpC enzymes that are able to hydrolyze aztreonam. Aztreonam alone therefore has limited clinical utility against NDM-producing strains. Avibactam is a non-β-lactam β-lactamase inhibitor with the ability to inhibit most serine β-lactamases, such as class A (e.g., KPC, CTX-M, TEM, and SHV), class C (AmpC), and some class D (e.g., OXA-48) enzymes. However, avibactam has no ability to inhibit MBLs, including NDM, and cannot effectively protect β-lactams from the hydrolysis of MBLs (245). The combination of avibactam with aztreonam can protect the latter from the hydrolysis of ESBLs and AmpC and therefore can expand the spectrum of aztreonam. The combi-

nation of aztreonam and avibactam has demonstrated potent *in vitro* activity against NDM-positive ESBL-producing *Enterobacteriaceae* (246). Aztreonam-avibactam is currently in clinical development and is not available for clinical use. Ceftazidime-avibactam has been approved for clinical use and is highly effective against KPC-positive CRE but has no activity against NDM-positive strains. *In vitro* studies have demonstrated synergistic activity and a bactericidal effect of the combination of ceftazidime-avibactam and aztreonam against CRE (247, 248). A small case series of 10 patients revealed that 7 of the patients survived after receiving the combination of aztreonam and ceftazidime-avibactam. The other three patients died as a result of other underlying conditions and therefore should not be considered a failure of the combination treatment (249). Several case reports have also demonstrated that the combination of aztreonam and ceftazidime-avibactam can successfully treat infections with NDM-positive CRE strains (247, 250). This combination could be considered if there are no alternative therapeutic options, and its efficacy warrants further, large-scale studies.

Polymyxins (Colistin and Polymyxin B) Alone and in Combination

Polymyxins are the current mainstay choice of antimicrobial agents against CRE and carbapenem-resistant *A. baumannii*, including NDM-positive strains. The treatment of infections due to multidrug-resistant organisms (MDRO) with polymyxins has been reviewed previously (251–253), and there are many studies on the efficacy of colistin against CRE, most of which have KPC rather than NDM (254, 255). In this review, we focus on treatment against NDM-positive strains only.

Polymyxin E (colistin) and polymyxin B have been evaluated for the treatment of infections caused by NDM-positive strains. NDM-positive strains are usually susceptible to polymyxins. There is a case report that colistin alone has been used successfully for treatment of a patient with a polymicrobial infection, including an NDM-positive *Vibrio cholerae* strain, with an increased dose (from 1 million units [MU] to 2 MU three times a day) and monitoring serum concentrations (256). However, an *in vitro* time-kill assay revealed that although initial killing of bacterial cells could be achieved by colistin alone, considerable regrowth occurs at 24 h, and resistant subpopulations are frequently detected after exposure to colistin alone (257). A murine infection model demonstrated that unlike in combination with amikacin, colistin alone is unable to achieve 1.5- to 2.8-$\log_{10}$ killing after 24 h of therapy (258). Another study using murine models revealed that colistin alone was inappropriate for treating pneumonia due to NDM-positive *K. pneumoniae*, although the strain was susceptible to colistin *in vitro* (259). The use of colistin has also been hampered by the occurrence of renal toxicity (260, 261) and, to a lesser extent, neurological adverse effects (262). Many NDM-positive *Enterobacteriaceae* strains have become resistant to colistin by acquiring plasmid-borne *mcr* genes or have mutations/interruptions of chromosomal genes such as *phoP-phoQ* (encoding a two-component system) and *mgrB* (a regulator of *phoP-phoQ*) (263–265).

Evidence suggests that treatment with colistin-based combinations may offer a benefit compared to colistin alone. Colistin is usually recommended in combination with other agents for treatment (266). Although various colistin-based combinations have been examined *in vitro* and occasionally *in vivo*, it remains unclear what the best combination is, as studies are usually done with small sample sizes or single case reports, are heterogeneous in methodology, and have generated inconsistent findings.

A patient with complicated health care-associated cystitis due to an NDM-positive *E. coli* strain recovered after receiving colistin and rifampin (267). The combination of colistin, rifampin, and meropenem was successfully used to treat pyoderma caused by multiple microorganisms, including an NDM-positive *E. coli* strain, in a 49-year-old male patient (268). A patient with acute pyelonephritis due to NDM-positive *P. aeruginosa* recovered when treated with colistin combined with aztreonam (269). Polymyxin B in combination with aztreonam and meropenem rescued a 65-year-old patient with acute myeloid leukemia from bloodstream infection caused by an NDM-positive *K. pneumoniae* strain (270).

The colistin-tigecycline combination was not bactericidal against two NDM-positive colistin-susceptible *K. pneumoniae* strains in a 24-h time-kill assay (271). Another study revealed that the addition of tigecycline to colistin did not produce increased bacterial killing. Instead, it may cause antagonism at lower concentrations (263). In a study including 28 NDM-positive *Enterobacteriaceae* strains, *in vitro* synergistic activity was observed with colistin plus tigecycline in very rare cases (272).

The combination of colistin and fosfomycin achieved increased bacterial killing and decreased the chance of emergence of resistance compared to either agent alone in 6 NDM-positive *Enterobacteriaceae* strains (273). Synergistic or bactericidal activity is present for fosfomycin and colistin in a 24-h time-kill assay (271). However, in another study including 28 NDM-positive *Enterobacteriaceae* strains, *in vitro* synergistic activity was observed for colistin plus fosfomycin only in very rare cases (272).

A time-kill assay revealed that the addition of amikacin is able to restore the susceptibility of four NDM-positive and *mcr*-positive *E. coli* strains to colistin (258). However, another time-kill assay demonstrated that the combination of amikacin and polymyxin B failed to eradicate NDM-positive and *mcr*-positive *E. coli* strains but that the addition of aztreonam with amikacin and polymyxin achieved eradication (274).

Tigecycline

The susceptibility of NDM-positive *Enterobacteriaceae* strains to tigecycline varies significantly. Some studies report that these strains are mostly susceptible to tigecycline *in vitro* (275, 276), while a multicenter study in China found that most NDM-positive strains were nonsusceptible to tigecycline (38). Nonetheless, tigecycline does not have desirable pharmacokinetic properties and is a bacteriostatic agent. There are concerns that *in vitro* susceptibility to tigecycline may not be translated to *in vivo* efficacy (277). A previous study demonstrated that treatment with tigecycline was associated with high mortality rates (40.1%) when used for treatment of infections due to CRE (most of which are likely to have KPC rather than NDM), whereas the mortality rate for inactive therapy was 46.1% (278). Both *in vivo* and clinical studies on tigecycline against NDM-positive strains are scarce. In an *in vivo* study using a murine infection model, a high-dose tigecycline scheme was effective for treating pneumonia due to NDM-positive *E. coli* and *K. pneumoniae* and was more active than colistin (259). The combination of tigecycline and levofloxacin was used to successfully treat a patient with hospital-acquired pneumonia caused by NDM-positive *Raoultella planticola* (279). However, during treatment against NDM-positive strains, high-level tigecycline resistance can emerge rapidly (280). Nonetheless, these limited data fail to provide a convincing argument for or against the use of tigecycline for treating infections due to NDM-positive strains, and further studies are therefore required.

Eravacycline

Eravacycline is a novel synthetic fluorotetracycline with potency that is 2- to 4-fold higher than that of tigecycline in NDM-positive strains. In an *in vitro* analysis of 2,644 Gram-negative pathogens, eravacycline demonstrated excellent activity against 18 *E. coli* strains that had carbapenem resistance associated with OXA and NDM (281). Eravacycline was approved for treating adults with complicated intra-abdominal infections by the FDA in August 2018. Eravacycline is also currently being tested against complicated urinary tract infections in a clinical trial (ClinicalTrials.gov registration no. NCT01978938).

Dual Carbapenems

The rationale for using two carbapenems together is to provide a competitive substrate for the β-lactamase. These studies are mainly aimed at CRE as a whole, most of which have serine-based β-lactamases, such as KPC and OXA-48, rather than NDM.

Carbapenem MICs for carbapenemase-producing *K. pneumoniae* isolates may vary within a broad range of values, from 0.12 to $>$256 mg/liter. This variation depends on the clonal background of the bacterial isolates and the type of carbapenemase pro-

duced. Isolates producing NDM usually have high carbapenem MICs (≥32 mg/liter) (33, 282). This has made dual-carbapenem-based treatment more challenging for NDM-positive strains.

Twenty carbapenem-resistant *K. pneumoniae* (CRKP) clinical strains, 6 of which were NDM positive, were tested with dual-carbapenem (any two of doripenem, ertapenem, imipenem, and meropenem) combinations. The data strongly support the hypothesis that dual-carbapenem combinations might be effective against KPC and OXA-48, but no synergy was observed for any of the NDM-positive strains (283), which might be due to the different action mechanism of MBLs compared to those of serine-based carbapenemases (15). NDM-positive *Enterobacteriaceae* were tested in immunocompetent and neutropenic murine thigh infection models using humanized regimens of standard (500 mg given every 8 h) and high-dose, prolonged infusion (2 g given every 8 h; 4-h infusion) of doripenem and 1 g of ertapenem given intravenously every 24 h. Doripenem and ertapenem demonstrated efficacy against several NDM-positive strains, especially using high-dose and prolonged infusion (284). The findings in this *in vivo* study are inconsistent with those of the *in vitro* study (283). Dual carbapenems (meropenem and ertapenem) plus fosfomycin were used to successfully treat urinary tract infections caused by NDM-positive *Enterobacteriaceae* in two patients (285). In general, there are very few studies of dual carbapenems against NDM-positive strains, and the current evidence is contradictory. More studies are therefore required.

Aminoglycosides

Susceptibility to aminoglycosides may be unpredictable and can vary according to the strain type. Aminoglycosides may be considered a viable option for combination therapy against NDM-positive strains. Plazomicin is a synthetic derivative of sisomicin that evades many aminoglycoside-modifying enzymes but is not active against bacterial strains having 16S rRNA methyltransferases (286). However, NDM-positive strains are usually resistant to plazomicin (MIC ≥ 64 mg/liter) (287). Apramycin is of the 4-monosubstituted deoxystreptamine (DOS) subclass and is active against ribosomes modified by all 16S rRNA methyltransferases except NpmA (288), which is not common in the *Enterobacteriaceae*. An *in vitro* study demonstrated that almost 90% of NDM-positive strains are susceptible to apramycin (289). However, apramycin is a veterinary agent and has not been approved for clinical use, likely due to its narrow therapeutic index (287). Apramycin therefore warrants further investigations as a repurposed agent against CRE, including NDM-positive strains.

Fosfomycin

Fosfomycin is available as an oral agent in the United States and is also available for intravenous use in Europe and China. Few large-scale studies have addressed the susceptibility of NDM-positive *Enterobacteriaceae* to fosfomycin (267). Sufficient data are lacking to support the use of fosfomycin alone, but fosfomycin-containing combination therapy has demonstrated promising results, as mentioned above (273).

New Antimicrobial Agents in Development

Cefiderocol. Cefiderocol (S-649266) (the chemical structure is shown in Fig. S1 in the supplemental material) is a novel catechol siderophore cephalosporin and is usually stable against the hydrolysis of carbapenemases, including MBLs (290). When tested on 49 NDM-producing strains, MICs for most strains (44/49; 89.8%) were 2 to 4 mg/liter, but those for 5 strains were ≥16 mg/liter. Although breakpoints to define susceptibility have not been established, the high MICs suggest that the 5 strains were likely resistant to cefiderocol. Cefiderocol demonstrated bactericidal activity against an NDM-1-producing *K. pneumoniae* strain in a rat lung infection model (the cefiderocol MIC was 8 mg/liter) (291). A phase 2 randomized study demonstrated that cefiderocol was noninferior to imipenem for treating patients with complicated urinary tract infections caused by carbapenem-susceptible Gram-negative bacteria (292). Cefiderocol is currently being tested for the treatment of severe infections caused by carbapenem-

resistant Gram-negative bacteria and nosocomial pneumonia caused by Gram-negative bacteria in two clinical trials (ClinicalTrials.gov registration no. NCT02714595 and NCT03032380).

LYS228. LYS228 (Fig. S1) is a novel monobactam stable against the hydrolysis of MBLs and serine carbapenemases. *In vitro* studies revealed that it has potent activity against the majority of ESBL-producing *Enterobacteriaceae* and CRE strains tested, including NDM-positive ones (293). LYS228 is currently being tested for treating patients with complicated intra-abdominal infections in a clinical trial (ClinicalTrials.gov registration no. NCT03354754).

Odilorhabdins. Odilorhabdins are a new antibiotic class against both Gram-positive and Gram-negative pathogens, which act on ribosomes to inhibit bacterial translation (294). A compound of this class, named NOSO-502 (Fig. S1), has activity against CRE strains producing NDM, KPC, AmpC, or OXA enzymes (295), demonstrated using a murine systemic infection model (296).

Piscidins. Tilapia piscidin 3 (TP3) and tilapia piscidin 4 (TP4) are two antimicrobial peptides (Fig. S1) from fish that exhibit strong activity against NDM-positive *K. pneumoniae in vitro*. Administration of TP3 (150 μg/mouse) or TP4 (50 μg/mouse) is able to significantly increase survival in a murine sepsis model, and TP4 was more effective than tigecycline at reducing CFU counts in several organs. TP3 and TP4 were shown to be nontoxic and have the potential for use in combating NDM-positive strains (297).

Photoactivated 2,3-distyrylindoles. A compound based on the 2,3-distyrylindole scaffold has been found to exhibit activity against various MDR Gram-negative bacteria, including NDM-positive *Enterobacteriaceae* (298). The compound exhibited bactericidal properties at a concentration of 5 μM and in the presence of colistin at nonbactericidal concentration of 1.25 μg/ml. This resulted in a 7- to 9-log reduction in bacterial counts of NDM-positive *Enterobacteriaceae* via disruption of the bacterial cell membrane (298). The photoactivated 2,3-distyrylindole-based compounds may have the potential to be applied topically.

Broad-Spectrum β-Lactamase Inhibitors

VNRX-5133. VNRX-5133 (see Fig. S1 in the supplemental material) is a second-generation boronate in development with cefepime. It is a new broad-spectrum β-lactamase inhibitor with direct inhibitory activity against Ambler class A, B (including NDM and VIM but not IMP), C, and D β-lactamases. However, MICs of cefepime–VNRX-5133 (1:1 ratio) for some NDM-producing strains are around 8 mg/liter (299). VNRX-5133 is currently being tested for safety, pharmacokinetics, and drug-drug interactions in several clinical trials (ClinicalTrials.gov registration no. NCT03690362, NCT02955459, and NCT03332732).

Other Non-β-Lactam Serine β-Lactamase Inhibitors in Development

Relebactam (MK7655) (300) and nacubactam (RG6080 or OP0595) (301) are two non-β-lactam β-lactamase inhibitors (see Fig. S1 in the supplemental material), like avibactam, and can inhibit serine β-lactamases but cannot inhibit MBLs. Relebactam and nacubactam are being developed in combination with imipenem and meropenem, respectively, and imipenem-relebactam has successfully completed a phase 3 trial. Although relebactam and nacubactam have no activity against NDM-positive strains, their combination with aztreonam may have potential, like aztreonam-avibactam (see above), against NDM-positive strains.

MBL Inhibitors

An attractive strategy to combat NDM-positive bacteria is to develop MBL (including NDM) inhibitors. A number of NDM inhibitors of various classes have been identified and characterized, but none of the compounds have been approved for clinical use thus far. The inhibitors have been summarized in several excellent reviews (19, 302, 303). In this review, we summarize these inhibitors, including those that have been developed in the past 3 years, in Table 4.

TABLE 4 NDM inhibitors reported

Inhibitor(s)	Description	Reference(s)
Sulfur-containing inhibitors		
Bisthiazolidines	Penicillin analogs containing thiol	404
Captopril and various analogs	Angiotensin-converting enzyme inhibitor	405, 406
Thiorphan	Active metabolite of racecadotril, a peripherally acting enkephalinase inhibitor	407
Thiophenecarboxylic acid derivatives	Sulfur atom of the thiophene ring	408
Thioazoles and thiophene-containing amino acid thioesters		409, 410
Tryptophan-containing compound	Thiol-containing amides	411
Sulfonamides		412
Thiol-containing compounds		413
ANT431	Pyridine-2-carboxylic acid derivative	304
Metal-complexing agents		
1,4,7-Triazacyclononane-1,4,7-triacetic acid	Metal chelators	414
1,4,7,10-Tetraazacyclononane-1,4,7,10-tetraacetic acid	Metal chelators	414
Calcium disodium EDTA	Metal chelators	306, 415, 416
ME1071 (disodium 2,3-diethylmaleate)	Maleic acid derivative	287
Colloidal bismuth subcitrate and related Bi(III) compounds	Anti-*Helicobacter pylori* drug	417
Inhibitor 36	2,6-Dipicolinic acid derivative	418
Aspergillomarasmine A	Extract of a strain of the fungus *Aspergillus versicolor*	305
Chromenes		
Chromenone compound		419
Chromenone and chromeno[3,2-c]pyridine compound	2 polyketides isolated from *Penicillium* sp. from the rhizosphere soil of the plant *Picea asperata*	420
3-Formylchromone		421
3-Cyanochromone		421
Thiol-modifying agents		
p-Chloromer-curibenzoic acid and sodium nitroprusside [Na2Fe(CN)5NO·2H2O]	Thiol-modifying agents	422
Ebselen	Selenium-containing molecule	423
Covalent irreversible inhibition by β-lactams		
Supratherapeutic doses of β-lactams such as cephalothin and moxalactam	Key residue for interaction with the substrate	424
β-Phospholactam	Tetrahedral transition state analog	425
4-Chloroisoquinolinols		426
Aminoimidazoles		427
Synthetic nucleotide analogs		
Peptide-conjugated phosphorodiamidate morpholino oligomer		428

Many of the NDM inhibitors have been tested only *in vitro*. However, several, including ANT431 (304), aspergillomarasmine A (305), calcium disodium EDTA (306), and colloidal bismuth subcitrate (CBS) (an anti-*Helicobacter pylori* drug) (307), have also been studied using *in vivo* models and have been shown to be efficacious. None of the NDM inhibitors have been approved for clinical use yet.

Antimicrobial Adjuvants in Development

With limited treatment options available, we are in urgent need of new therapeutic options. One approach to combat this growing problem is the use of combinations containing adjuvants. Antimicrobial adjuvants include not only antimicrobial agents but also compounds from plants.

Organic acid. The antibacterial activity of organic acids and their combinations against NDM-positive *E. coli* was tested by a disc diffusion method. The MIC of colistin is reduced from 8 to 0.5 μg/ml in the presence of 320 μg/ml oxalic and succinic acids. The addition of oxalic and succinic acids may have the potential for reducing the dose of colistin (308).

Macromolecules. Membrane-active macromolecules (MAMs) have been found to enhance the uptake of tetracycline by bacterial cells and therefore are able to resensitize NDM-positive strains to tetracycline (309). The MAM-tetracycline combination was bactericidal, in contrast to the bacteriostatic effect of tetracycline alone (309).

Copper ions and coordination complexes. A study found that copper is able to directly inhibit the activity of NDM-1. Copper shows synergy with ertapenem and meropenem against NDM-positive *E. coli* in standard checkerboard assays. The synergy between copper and carbapenems has also been confirmed using a low concentration (10 μM) of copper with the FDA-approved copper-pyrithione coordination complex. Copper coordination complexes therefore have potential as novel carbapenemase adjuvants (307).

Zidebactam and WCK 5153. Zidebactam and WCK 5153 are novel β-lactam enhancers that are bicyclo-acyl hydrazides (BCHs), derivatives of the diazabicyclooctane (DBO) scaffold. They are targeted for the treatment of serious infections caused by MDR Gram-negative pathogens, including NDM-positive strains. Zidebactam and WCK 5153 exhibit specific penicillin binding protein 2 (PBP2) inhibition but do not inhibit MBLs. Time-kill assays and live-dead staining revealed the bactericidal activity of zidebactam and WCK 5153. Zidebactam and WCK 5153 restored susceptibility to β-lactams in *P. aeruginosa* mutant strains and represent a promising β-lactam "enhancer-based" approach to treat MDR *P. aeruginosa* infections, bypassing the need for MBL inhibition (310). The combination of cefepime and zidebactam showed potent activity against *Enterobacteriaceae* and *P. aeruginosa* strains producing various clinically relevant β-lactamases, including ESBLs, KPCs, AmpC, and MBLs (including NDM) (311).

Plant derivatives. In one particular study of note, ethanol extracts from the leaves of 240 medicinal plant species were screened for antibacterial activity (312). The extracts from *Combretum albidum* G. Don, *Hibiscus acetosella* Welw. ex Hiern, *Hibiscus cannabinus* L., *Hibiscus furcatus* Willd., *Punica granatum* L., and *Tamarindus indica* L. inhibited the NDM-1 enzyme *in vitro* and showed synergistic effects when combined with colistin (312). In another study, magnolol, from the bark of magnolia trees, significantly inhibited NDM-1 enzyme activity and was able to restore the activity of meropenem against NDM-positive *E. coli* (28). Molecular modeling and a mutational analysis demonstrated that magnolol binds directly to the catalytic pocket of NDM-1, thereby blocking the binding of the substrate to NDM-1 and leading to its inactivation (28).

Immunotherapeutic Agents

Nonantimicrobial immunotherapeutic agents represent a new, alternative way to treat infections due to NDM-positive strains. Two recombinant human cysteine proteinase inhibitors, cystatin 9 (rCST9) and cystatin C (rCSTC), have been tested using murine pneumonia models of infection with NDM-positive *K. pneumoniae* (313). That study demonstrated that the combination of rCST9 and rCSTC led to significantly improved survival compared to that of infected mice treated with one of the inhibitors or without treatment (313). This suggests that rCST9-rCSTC is a promising therapeutic candidate for treating bacterial pneumonia (313).

INFECTION PREVENTION AND CONTROL FOR NDM-POSITIVE STRAINS

Outbreaks

Many outbreaks caused by NDM-producing strains of *Enterobacteriaceae* and *A. baumannii* have been reported in the literature (Table 5). Many reports describe only the microbiological aspects of the outbreak and fail to provide full information regarding outbreak investigations. The source of outbreaks has often been identified as a

TABLE 5 Outbreaks of NDM-positive strains reported in the literature[a]

Yr(s)	Country	Unit(s) of isolation	Age group	Infection site and/or specimen type	Species	ST(s)	No. of cases	Source(s)	Control measure(s)	Reference(s)
2014–2015	Belgium	/	/	/	*K. pneumoniae*	ST716	29	/	/	429
2012	Bulgaria	ICU, hepatology	/	/	*E. coli*	ST101	12	/	/	430
2015–2016	Bulgaria	ICU, other wards	/	Abscess, BSI, pneumonia, UTI	*K. pneumoniae*	ST11	14	/	Frequent hand hygiene audits; educational session at the ward level; microbiological investigation of HCWs, equipment, and hospital environment; additional disinfection in affected units; and patient cohorting or isolation when available	316
2011	Canada	Respiratory	Adult	Blood, wound	*K. pneumoniae*	ST231	5	/	Standard control measures, including active screening	323
2011	Canada	/	/	BSI, UTI, colonization	*K. pneumoniae*	/	7	Environment contamination	Contact precautions, screening of contacts, and strengthening of environmental cleaning	314
2011–2012	China	/	Adult	VAP	*K. pneumoniae*	ST147	3	/	/	431
2012	China	Neonatal	Neonate	Blood, sputum	*K. pneumoniae*	ST17, ST20	18	Bed railing	/	432
2012–2013	China	Neonatal	Neonate	Pneumonia, sepsis	*K. pneumoniae*	ST17	7	/	/	433
2014	China	Hospital wide, mainly NICU and neonatal	Neonate	Sputum, urine, colonization	*K. pneumoniae*	ST37, ST76	22	/	Strengthening standard control measures	317
2014	China	Neonatal	Neonate	Pneumonia, sepsis	*K. pneumoniae*	ST1419	5	/	/	434
2014	China	NICU	Neonate	Blood, sputum, stool	*K. pneumoniae*	ST105	17	Incubator water	/	435
2015	China	Neonatal	Neonate	Aspiration catheter, BSI, UTI	*K. pneumoniae*	ST20	4	Radiant warmer and nurses' hands	Strengthening control measures, including monitoring hand hygiene compliance by video; placing patients in single rooms; extensive cleaning of shared equipment; and maximum use of disposable materials	318
2015	China	/	Adult	/	*E. cloacae* complex	ST88	4	/	/	436
2011–2012	Colombia	Neonatal	Neonate	BSI, necrotizing enterocolitis	*K. pneumoniae*	ST1043	6	/	Hand hygiene, patient isolation, contact precautions, supervised disinfection	324
2013	Denmark	Hematology	/	UTI, wound	*C. freundii*	ST18	7	/	Strengthening control measures, including isolation, contact precautions, screening for colonizers and contaminated environment, and cleaning	325
2013	France	SICU	Adult	BSI, pneumonia, colonization	*A. baumannii*	ST85	7	/	/	437
2010	Greece	Hematology	/	/	*K. pneumoniae*	ST11	4	/	/	48
2010	Greece	Hospital wide	/	Mainly blood or urine	*K. pneumoniae*	ST11	67	/	/	48
2009	India	Neonatal	Neonate	BSI	*E. coli*	/	4	/	/	438
2012	India	NICU	Neonate	Sepsis	*K. pneumoniae*	/	6	/	/	439
2015	Iran	ICU	/	/	*K. pneumoniae*	ST893	29	/	/	440
2014–2015	Ireland	Hemodialysis	Adult	UTI, colonization	*K. pneumoniae*	/	9	/	Measures including screening contacts, distributing information leaflets, using long-sleeved disposable gowns and gloves, single-room isolation, chlorhexidine bathing, flagging on the ICNet system, education for HCWs, hand hygiene audit, and enhanced cleaning (twice daily)	319)
2011	Italy	Neonatal	Neonate	Bile, sputum, urine	*K. pneumoniae*	/	6	/	/	47
2013	South Korea	Geratology	Elderly	Colonization	*E. coli*	ST101	4	Sharing room	Strengthening control measures, including contact precautions and rigorous cleaning	315
2016–2017	South Korea	SICU	/	CAUTI	*Providencia rettgeri*	/	8	/	Strengthening control measures, including isolation, contact precautions, and environmental cleaning	322
2014	Kuwait	/	Adult	Blood, CVC, tip tissue	*K. pneumoniae*	/	3	/	/	441
2012	Nepal	Nurseries, NICU, PICU	Child, neonate	Mainly blood	*K. pneumoniae*	ST15	31	/	Closing NICU and PICU	333
2012	Nepal	HDU	Child	Blood	*K. pneumoniae*	ST1559	10	/	/	333
2013	Mexico	ICU	Adult	/	*K. pneumoniae*	ST22	3	/	Using hydrogen peroxide-based disinfection	326
2014–2015	Mexico	/	/	/	*K. pneumoniae*	ST392	28	/	/	442

(Continued on next page)

TABLE 5 (Continued)

Yr(s)	Country	Unit(s) of isolation	Age group	Infection site and/or specimen type	Species	ST(s)	No. of cases	Source(s)	Control measure(s)	Reference(s)
2012–2013	Nepal	Neonatal	Neonate	Blood, urine	*E. cloacae* complex	/	19	Contaminated soap dispensers	/	443
2015	Netherlands	/	/	/	*K. pneumoniae*	/	29	/	/	330
2015	Netherlands	/	/	/	*K. pneumoniae*	ST873	26	/	/	90
2014	Singapore	General	Adult	UTI, colonization	*E. cloacae* complex	/	4	Via health care staff	Strengthening control measures, especially pertaining to hand hygiene and ward staffing	320
2014–2015	Tunisia	/	Adult, child	Blood, catheter, urine, wound	*K. pneumoniae*	ST147, ST307	19	/	/	444
2016	Turkey	ICU, NICU	Adult, neonate	BSI, empyema, tracheal aspirate, UTI	*K. pneumoniae*	ST11	6	/	/	6
2010	UK	/	Adult	UTI	*Klebsiella* spp.		12	Urology endoscopic camera head	Sterilization or use of single-use sterile disposable plastic camera sheaths	445
2014–2015	UK	/	/	/	*K. pneumoniae*	/	40	/	Enhanced screening (including renal outpatients), contact precautions, enhanced chlorine disinfection of the environment, labeling of electronic case notes for identification of readmission, regular teleconference calls internally and externally, and enhanced antimicrobial stewardship; later, hydrogen peroxide vapor and ward-based monitoring of hand and environmental hygiene were implemented	321
/	UK	/	Adult	/	*E. cloacae* complex	/	3	Ceramic sluice sink to dispose of waste material	Replacement of the whole sink unit in the sluice, control bundle	446
2012	USA	Burn/trauma ICU, SICU, cardiology, and rehabilitation	Adult	Pneumonia, colonization	*K. pneumoniae*	/	8		Timely surveillance cultures combined with targeted control measures	447
2013	USA	/	Adult	/	*E. coli*	/	48	Duodenoscopy	Change of the reprocessing procedure from automated high-level disinfection to gas sterilization with ethylene oxide	328, 329

[a]Abbreviations: BSI, bloodstream infection; CAUTI, catheter-associated urinary tract infection; CVC, central venous catheter; HCWs, health care workers; HDU, high-dependence unit; SICU, surgical intensive care unit; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; VAP, ventilator-associated pneumonia; UTI, urinary tract infection; /, no information provided.

contaminated near-patient environment or communal medical device (Table 5). Outbreaks have also been seen in patients sharing rooms with those infected or colonized by NDM-positive strains (314, 315).

Outbreaks are generally controlled by strengthening commonly used infection control measures, such as contact precautions, hand hygiene, environmental cleaning, isolation, and active surveillance, with or without implementing additional measures (314–325). It has been reported that outbreaks due to CRE have been effectively controlled by enhanced environmental disinfection using hydrogen peroxide (326). Particular efforts should be taken to investigate possible environmental reservoirs during outbreaks (327), and if the source is identified, targeted measures are required to control the outbreak. For instance, duodenoscopes have been identified as the contamination source for several outbreaks, which were subsequently controlled by enhanced cleaning and a change from high-level disinfection to gas sterilization (328, 329). A "search-and-destroy" approach has been successfully used to control outbreaks but can be costly (330). The sources of outbreaks may not be identified in many cases. In such cases, the entire environment of affected wards may become heavily contaminated, and temporary ward closures have been recommended for enhanced cleaning and limiting the further spread of the pathogen (327, 331–333). External audits of infection control measures and extensive health service-wide education have also been recommended (334). If outbreaks persist despite the implementation of measures, screening of health care workers for carriage of MDRO is advised (332, 334), but the true relative value of this exercise is yet to be proven.

Infection Prevention and Control

The reservoirs and the mode of transmission of MDRO, including NDM-positive strains, are largely underinvestigated (335). Based on outbreak investigations, the source of NDM-positive strains in health care settings has been suggested to be patients infected or colonized with the strains or contaminated environment or devices (Table 5) (336). Unlike bla_{KPC-2}, the spread of bla_{NDM} is largely due to horizontal transfer, which is mainly mediated by plasmids but can also be mediated by OMVs, at least in *Acinetobacter* (60). The transmission of NDM-positive strains in health care settings is believed to be due to close contact (331). Hospitalized patients are the most vulnerable populations for infection or colonization by NDM-positive strains. Healthy persons can also acquire NDM-positive strains, although colonization is usually for a short period of time (less than 1 month, shorter than the period seen for hospitalized patients [see below]) (57).

Several guidance documents are available to address the prevention and control of carbapenem-resistant Gram-negative bacteria in health care settings. The CDC's guidance for the control of CRE in health care facilities was published in 2012 and updated in 2015 (336). The European Centre for Disease Prevention and Control (ECDC) issued its guidance on prevention of the entry of CRE into health care settings in 2017 (337). The World Health Organization (WHO) also released global guidance on the prevention and control of carbapenem-resistant *Enterobacteriaceae*, *A. baumannii*, and *P. aeruginosa* in 2017 (331). The WHO guidance also identified research gaps and the need for further research. Measures (summarized in Appendix S2 in the supplemental material) recommended by these guidance documents are evidence based and are overall highly similar (Table 6), although the emphasized points and the terminology are slightly different. In addition to the guidance documents, the Society for Healthcare Epidemiology of America (SHEA) established a step-by-step strategic roadmap for CRE infection control based on evidence and expert opinion (327). This roadmap has six successional steps, including determining whether CRE have been isolated, determining affected wards and the occurrence of intrafacility transmission, implementing early CRE detection and CRE containment measures, enhancing existing infection control requirements, regional strategy, and investigating for community spread of CRE, which should be applied in different situations, such as sporadic cases, single-hospital outbreaks,

TABLE 6 Infection control measures for carbapenem-resistant *Enterobacteriaceae* and other Gram-negative bacteria[a]

Measure(s)	Recommendation in guidance by:		
	CDC 2015[b]	ECDC 2017[c]	WHO 2017[d]
Hand hygiene	+	+	+
Antimicrobial stewardship	+	+	−
Health care personnel education	+	−	−
Monitoring, auditing, and feedback	−	−	+
Minimization of use of invasive devices	+	−	−
Microbiological capacity	−	+	−
Notification from laboratory	+	−	−
Contact precautions	+	+	+
Patient isolation or cohorting	+	+	+
Nurse cohorting	+	+	−
Active surveillance for patients	+	+	+
Screening contacts	+	+	−
Surveillance cultures of the environment	−	−	+
Environmental cleaning	+	−	+
Communication at discharge and transfer	+	+	−
Chlorhexidine bathing	+	−	−

[a]CDC and ECDC guidance documents are only for CRE, while WHO guidance also covers carbapenem-resistant *A. baumannii* and *P. aeruginosa*. "−" does not mean its absence in the guidance but indicates that it has not been highlighted as an independent measure.
[b]See reference 336.
[c]See reference 337. ECDC guidance is only for the prevention of the entry of CRE and does not address the control measures for patients with CRE infection or colonization.
[d]See reference 331.

and settings of endemicity (327). However, as the WHO guidance has identified, the quality of the evidence for the recommended measures in guidance is usually very low or low (331). The efficacy of the recommended measures within the guidelines remains to be verified in health care settings. In resource-limited settings, such as health care institutions in the developing world, overcrowding, shortage of staffing, and poor hygiene may be the critical factors contributing to the spread of NDM-positive strains. Such factors may not be addressed by studies that have been performed in developed countries and have been included as evidence during guideline development.

There are several other major challenges to the prevention and control of colonization and infection due to NDM-positive strains in health care settings. One such challenge is long-term carriage (colonization) in human hosts. It is well known that CRE can colonize the human gut for extended periods of time (338, 339), with reports of colonization for more than 3 years (340). Although studies on the duration of colonization usually do not specifically target NDM-positive strains, prolonged colonization by an NDM-positive strain for months was previously reported (341). A study in South Korea reveals that NDM-positive strains are difficult to clear, as only 11.3% (12/106) of colonized patients had no such strains upon discharge from the hospital (342). These colonized patients could serve as cryptic sources of further transmission of NDM-positive strains. Another particular challenge for infection control is the implementation of recommended measures. Even within a single geographic area in developed countries, the infection control strategies and practices against CRE vary remarkably (343). As stated in the WHO guidance (331), compliance should be monitored and analyzed to identify barriers to the implementation of countermeasures. A strategic roadmap for the control of CRE based on the best available evidence and expert opinion has been developed to facilitate implementation (327), and the WHO guidance has also detailed ways to help implementation (331).

The WHO guidance states that the same infection control measures should apply to carbapenem-resistant organisms regardless of the resistance mechanisms (331). NDM- and KPC-positive strains have some important differences, however. Unlike the well-known international spread of KPC-positive strains of *K. pneumoniae* clonal complex

258 (including ST258, ST11, and a few closely related STs), the spread of NDM-positive strains is less clonal, as there is no sustained global spread of certain high-risk clones. The spread of bla_{NDM} is primarily mediated by plasmids. bla_{NDM} is mainly seen in the *Enterobacteriaceae*, which usually colonize the gut of warm-blooded animals, including humans. bla_{NDM} has been found in various species of the *Enterobacteriaceae*. This suggests that the human gut may serve as a hot spot for the spread of bla_{NDM} in health care settings. However, the predisposing factors of colonization by NDM-positive strains remain largely underinvestigated. The avoidance of disturbance of the gut microflora and selective decontamination may be effective measures against NDM-positive strains and warrant further investigation.

CONCLUDING REMARKS

NDM-positive strains are continuing to spread worldwide despite continuous efforts and remain a critical challenge for clinical treatment and a significant threat to public health. The wide dissemination of bla_{NDM} genes is largely mediated by certain plasmids, particularly those of the IncX3 type. NDM enzymes are continually evolving to generate new variants, some of which have obtained enhanced carbapenemase activity. No treatment targeting NDM has been approved for clinical use at present, although many new agents with various mechanisms of action are under investigation or in development. Polymyxins remain the mainstream choice to treat infections caused by NDM-positive strains at present, while aztreonam-avibactam is a promising alternative option. The ultimate success of the fight against NDM also relies on effective infection control practice in addition to the development of antimicrobial agents. Awareness toward infection control and compliance with control measures still need to be significantly enhanced in health care settings.

There are a few notable research gaps regarding NDM enzymes and NDM-positive strains. First, very few studies have addressed the epidemiology of NDM-positive strains worldwide. Ten years after their initial discovery, we are still not sure whether NDM-positive strains are continuing to increase in prevalence, have reached a plateau, or are decreasing. Second, beyond health care settings, the spread of NDM-positive strains in the community remains unclear, although there are several reports that NDM-positive strains have been detected in healthy individuals (344). Third, the exact origin of bla_{NDM} remains unknown. Is it from the chromosome of a bacterial species, like many other β-lactamase genes such as $bla_{CTX\text{-}M}$? If so, what is the species? Fourth, although it is well known that infections caused by CRE are associated with high mortality rates (345, 346), CRE mortality studies usually refer to KPC-positive strains, or the carbapenemase type has not been specified. It is surprising that studies on the impact of the presence of NDM on mortality are scarce, and such studies are much needed. Fifth, the optimal treatment of infections caused by NDM-positive strains remains to be determined. Although polymyxins remain the mainstream choice, there are intrinsic limitations, such as toxicities, the absence of optimal dosage schemes, and the presence of heterogeneous resistance. There are still no treatments specifically targeted toward NDM. Sixth, almost all recommended infection control measures against carbapenem-resistant Gram-negative bacteria are based on low- or very-low-quality studies. Therefore, more well-designed prospective studies are needed to establish more-targeted and effective measures. Finally, although several guidance documents have stated that CRE should be regarded as a whole in terms of infection control, NDM- and KPC-positive strains have significant differences. Whether targeted measures should be established to control NDM-positive strains and what these measures might be remain to be determined.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/CMR.00115-18.

SUPPLEMENTAL FILE 1, PDF file, 0.7 MB.

SUPPLEMENTAL FILE 2, XLSX file, 0.1 MB.
SUPPLEMENTAL FILE 3, XLSX file, 0.1 MB.

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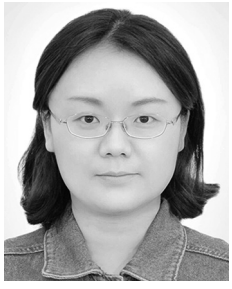

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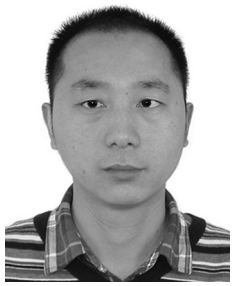

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