

# New Delhi Metallo- $\beta$ -Lactamase-Mediated Carbapenem Resistance: Origin, Diagnosis, Treatment and Public Health Concern

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## Abstract

**Objective:** To review the origin, diagnosis, treatment and public health concern of New Delhi metallo- $\beta$ -lactamase (NDM)-producing bacteria.

**Data Sources:** We searched database for studies published in English. The database of PubMed from 2007 to 2015 was used to conduct a search using the keyword term “NDM and *Acinetobacter* or *Enterobacteriaceae* or *Pseudomonas aeruginosa*.”

**Study Selection:** We collected data including the relevant articles on international transmission, testing methods and treatment strategies of NDM-positive bacteria. Worldwide NDM cases were reviewed based on 22 case reports.

**Results:** The first documented case of infection caused by bacteria producing NDM-1 occurred in India, in 2008. Since then, 13 *bla*NDM variants have been reported. The rise of NDM is not only due to its high rate of genetic transfer among unrelated bacterial species, but also to human factors such as travel, sanitation and food production and preparation. With limited treatment options, scientists try to improve available therapies and create new ones.

**Conclusions:** In order to slow down the spread of these NDM-positive bacteria, a series of measures must be implemented. The creation and transmission of *bla*NDM are potentially global health issues, which are not issues for one country or one medical community, but for global priorities in general and for individual wound care practitioners specifically.

**Key words:** Bacterial; Carbapenem Resistance; Drug Resistance; New Delhi Metallo- $\beta$ -Lactamase

## INTRODUCTION

The history of antimicrobial resistance dates back to antimicrobial discovery and parallels its use.<sup>[1,2]</sup> Gram-negative bacteria have developed resistance to many antibiotics including the last line  $\beta$ -lactams, carbapenems. There are various mechanisms leading to an increase in multi-drug resistance in bacteria.<sup>[3-7]</sup> Among all these factors, the most important mechanism is the production of carbapenemases.<sup>[8,9]</sup>

Broadly carbapenemases are categorized into three groups: Class A (penicillinases), Class B (metallo- $\beta$ -lactamases [MBL]), and Class D (Oxacillinases).<sup>[6]</sup> The New Delhi metallo- $\beta$ -lactamase (NDM) is one of the class B metallo- $\beta$ -lactamases. They are present largely in

*Enterobacteriaceae*, but also in nonfermenters (*Acinetobacter* spp.) and Vibrionaceae (*Vibrio cholerae*).<sup>[10-12]</sup> Till now, both hospital- and community-acquired infections, such as wound, respiratory, bloodstream, and urinary tract infections (UTIs), caused by *bla*NDM harboring bacteria, have been reported.

Studies have proved the inactivation of these carbapenems (meropenem, imipenem [IPM], doripenem, ertapenem) by a number of MBL which pose extended spectrum activity against all  $\beta$ -lactam antibiotics.<sup>[7,13,14]</sup> The epidemiology of NDM is compounded by interspecies dispersion and recognized implications for patient care, public health, antimicrobial surveillance programs, and drug development.<sup>[14]</sup> As the antibiotic pipeline offers little in the short-term, our most important tools against the spread of antibiotic resistant organisms are intensified infection control, surveillance and antimicrobial stewardship.<sup>[15]</sup>

Access this article online

Quick Response Code:



Website:  
www.cmj.org

DOI:  
10.4103/0366-6999.160566

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## Origin and international transmission of New Delhi metallo-β-lactamase

In 2007, a clinical isolate *Klebsiella pneumoniae* was derived from a urinary culture of a 59-year-old male patient, who was hospitalized in Ludhiana and New Delhi. Testing of this isolate suggested that the carbapenem resistance was due to the production of a novel MBL, designated NDM-1, as the authors of the report believed the resistance originated from India.<sup>[2,16]</sup> The following year NDM-1 was identified in 29 patients in the UK. The same year, *bla*NDM was identified in 143 patients from multiple sites in the Indian subcontinent.<sup>[15]</sup>

The infection caused by NDM-producing bacteria is now recognized as endemic throughout India and Pakistan. It has spread worldwide due to travel, “medical tourism” and the ability of the genetic element to transfer between bacteria.<sup>[17]</sup> Antimicrobial use while traveling was an independent risk for acquisition and prolonged carriage of such organisms.<sup>[4]</sup> The NDM-1 was found in many species of bacteria, predominantly *K. pneumoniae* and *Escherichia coli*, collected in an extended survey in the UK, India, Pakistan and Bangladesh in 2008–2009.<sup>[10,18]</sup> Recent reports have indicated the spread of NDM-1 and its variants in many different countries [Table 1] including the United States, Austria, Australia, Norway, Belgium, Canada, Denmark, France, Germany, Kenya, The Netherlands, the Sultanate of Oman, China, Hong Kong, Taiwan, Singapore, Sweden, Egypt, Japan, Switzerland, Morocco, Kuwait, Italy, South Korea, Ireland, Czech Republic, Guatemala, New Zealand, Israel, Iran, Russia, Colombia, Malaysia, Sri Lanka, Algeria, Mexico, Tunisia, reunion island, Nepal, Mauritius and Honduras.<sup>[11,19-53]</sup> In addition, the Balkans region such as Montenegro, Serbia, Bosnia–Herzegovina and Kosovo, and the Middle East (Oman and Iraq), may constitute an additional reservoir for NDM-1 producers, which may or may not initially have reached these countries from the Indian subcontinent.<sup>[10,18]</sup> In view of this situation, we believe that an immediate response to the emergence of NDM-producing bacteria should be an urgent priority

worldwide. At a local level, patients with a history of travel to or originating from high-risk countries or areas should be screened for NDM-producing bacteria.<sup>[48]</sup>

## Environmental distribution of New Delhi metallo-β-lactamase

The problem of NDM-1 was not confined to hospital strains of bacteria but was widespread in the community environment in India.<sup>[54-58]</sup> Given that NDM-positive bacteria are common in the environment that many infections in India are community acquired, and that these bacteria can colonize the gastrointestinal tract, it is likely that fecal-oral transmission plays a major role in transmission occurring through contaminated food, water, and hands.<sup>[59-72]</sup> Besides, Wang *et al.*<sup>[73]</sup> detected NDM-1 carbapenemase-producing *Acinetobacter calcoaceticus* and *Acinetobacter junii* in environmental samples from livestock farms in China. These findings highlighted the need for improvements in sanitary conditions as a key public health intervention.

Recently, a novel bleomycin resistance protein has been characterized, which was associated with the *bla*NDM-1 gene as part of the same operon. Walsh and colleagues hypothesized that bleomycin or bleomycin-like molecules exert a selective pressure on the large spread of the *bla*NDM-1 gene in the environment.<sup>[66]</sup> It is possible that bleomycin-like molecules contribute to selective pressure, leading to the further spread of NDM producers in the environment.<sup>[68]</sup>

## Diagnosis

Rapid detection of MBL-producing strains, including NDM producers, is necessary to prevent their dissemination and associated nosocomial infections. Laboratory detection of NDM involves the following four aspects.

### Identification of the microorganism

Bacteria isolated from patients were identified via the Phoenix automated phenotypic identification criteria (Becton Dickinson, Oxford, UK) or with API 20E strips (bioMérieux, Basingstoke, UK).<sup>[60]</sup>

**Table 1: Initial reports of the NDM-1 and its variants**

Genotyping	Organism	Country	Travel and healthcare history	Reference
NDM-1	<i>K. pneumoniae</i> , <i>E. coli</i>	India	Traveled to India and hospitalized in Ludhiana, Punjab and New Delhi	[16]
NDM-2	<i>A. baumannii</i>	Egypt	Transferred from a hospital in Egypt to Germany	[22]
NDM-3	<i>E. coli</i>	Australia	The patient returned from travel to India a few days earlier	[4]
NDM-4	<i>E. coli</i>	India	Previously hospitalized in India	[49]
NDM-5	<i>E. coli</i>	UK	A recent history of hospitalization in India	[50]
NDM-6	<i>E. coli</i>	New Zealand	NZ resident hospitalized in New Delhi With pneumonia	[32]
NDM-7	<i>E. coli</i>	Germany	Had initially been hospitalized in Three different facilities in Mumbai, India	[18]
NDM-8	<i>E. coli</i>	Nepal	–	[51]
NDM-9	<i>K. pneumoniae</i>	China	The child and his family members had no history of travel to an endemic area	[52]
NDM-14	<i>A. lwoffii</i>	China	–	[53]
NDM-10 <sup>†</sup> , NDM-11 <sup>*†</sup> , NDM-12 <sup>†</sup> , NDM-13 <sup>†</sup>	–	–	–	–

\*NDM-11 is assigned without any information in GenBank; <sup>†</sup>The articles about NDM-10, NDM-11, NDM-12 and NDM-13 remain unpublished.  
*E. coli*: *Escherichia coli*; *K. pneumoniae*: *Klebsiella pneumoniae*; *A. baumannii*: *Acinetobacter baumannii*; *A. lwoffii*: *Acinetobacter lwoffii*.

## Detection of carbapenemase minimum inhibitory concentrations

The first cause for suspicion that a carbapenemase is involved in a clinical infection is an elevated carbapenem minimum inhibitory concentration (MIC). However, elevated carbapenem MICs are generally predictive of carbapenemase production in the *Enterobacteriaceae*, full clinical resistance is not always seen.<sup>[59]</sup> MICs and carbapenem resistance were established by microbroth dilution (Phoenix), British Society for Antimicrobial Chemotherapy agar dilution or disc diffusion and interpreted according to Clinical and Laboratory Standards Institute (CLSI) guidelines.<sup>[60]</sup> Carbapenem resistant bacteria detected by MIC method should be further explored for carbapenemase production by phenotypical methods.<sup>[6]</sup>

## Phenotype detection

Several phenotypic methods to detect MBL production have been developed, including the modified Hodge test (MHT), the double-disk synergy tests (DDSTs), combined disk tests and E-test.<sup>[65]</sup>

The MHT is the only CLSI-recommended carbapenemase-screening method and has been widely used because of the direct analysis of the carbapenemase activity.<sup>[61,62]</sup> The advantage of this method is that even the weak carbapenemase activity enzyme can be detected.<sup>[6]</sup> However, it shows a low sensitivity of 11% when NDM carbapenemase is tested by the MHT according to CLSI. And many NDM-positive bacteria give negative results in particularly in *Acinetobacter baumannii*, whereas strains with high levels of AmpC can give false positives, confusing interpretation.<sup>[10]</sup>

Other tests are based on the synergy between MBL inhibitors and carbapenems. MBL inhibitors used in these methods include the metal-chelating agent ethylenediaminetetraacetic acid (EDTA), thiol compounds (mercaptopyropionic acid or sodium mercaptoacetic acid), and dipicolinic acid. The different formats include the DDSTs using 2-mercaptoacetic acid or EDTA, combined disk tests with dipicolinic acid or EDTA, and IPM/IPM-EDTA E-test strips.<sup>[61,65]</sup>

In laboratories, where molecular methods are not available, the DDSTs would serve as a useful screening technique.<sup>[67]</sup> The DDST using  $\beta$ -lactamase and  $\beta$ -lactamase-inhibitor disks is a convenient method of detecting extended spectrum  $\beta$ -lactamase (ESBL)-producing Gram-negative bacilli. EDTA inhibition of  $\beta$ -lactamase activity is used to differentiate a MBL to other  $\beta$ -lactamase. The E-test MBL strip is one of the recommended tests for detection of NDM based on inhibition of MBL activity by EDTA. This E-test method showed good sensitivity for the detection of NDM production.<sup>[62]</sup> However, false-negative results had been reported for the E-test when an isolate had an IPM MIC of  $\leq 4$   $\mu\text{g/ml}$ . EDTA alone has inhibitory action against some bacteria and can lead to false-positive results.<sup>[59]</sup> The E-test MBL may be used in labs that do not screen for MBL producers on a daily basis, or in those which perform

susceptibility testing using liquid medium techniques and rarely use disk diffusion susceptibility techniques. In addition, the combined disk test is also based on inhibition of MBL activity by EDTA. NDM-1 producers are positively detected by this technique, which is reliable for detecting MBL producers on a daily basis.<sup>[46]</sup>

## Molecular tests

The gold standard for the identification of carbapenemase producers and for specific detection of *blaNDM* is molecular techniques, mostly based on PCR, ideally followed by sequencing. When the presence of a carbapenemase is suspected, PCR is the fastest way to detect *blaNDM* genes. Other molecular techniques, including real-time PCR and commercial DNA arrays (Check-Points), are useful alternatives.<sup>[10]</sup> While these assays for rapid, sensitive, and specific detection appear to be promising, PCR requires specialized high-cost instruments and consumables.<sup>[64]</sup>

Some laboratories have used colony blot hybridizations to efficiently screen large numbers of clinical isolates for carbapenemase genes.<sup>[59]</sup> And a novel nucleic acid amplification method, designated loop-mediated isothermal amplification (LAMP), had been well established and documented.<sup>[63]</sup> The LAMP method is demonstrated to be a potentially valuable means for the detection of *blaNDM* and rapid clinical diagnosis, being fast, simple, and low in cost.<sup>[64]</sup>

## Treatment and clinical outcomes

In infection due to highly resistant pathogens such as NDM-positive bacteria, antimicrobial choice is limited and requires a considered analysis of risk and benefit of available agents.<sup>[4]</sup> NDM-producing organisms frequently carry other resistance enzymes including ESBL and AmpC  $\beta$ -lactamases, rendering most available antibiotics inactive. Nevertheless, these organisms are usually susceptible to polymyxin (including colistin and polymyxin B) and tigecycline.<sup>[49,72-75]</sup> The clinically used polymyxin is effective against NDM-positive organisms. However, colistin has uncertain efficacy in pulmonary infections, and its use has always been hampered by the occurrence of renal toxicity, and to a lesser extent, neurological adverse effects.<sup>[49,50,72,74-78]</sup> More importantly, carbapenem resistant bacteria such as *blaNDM-1 E. coli* and *blaNDM-1 K. pneumoniae* have become resistant to colistin.<sup>[77]</sup> Tigecycline is a glycylycylone with a wide spectrum of activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria.<sup>[79]</sup> Though it is useful in tissue infections, it is less useful in systemic infections.<sup>[77]</sup> In addition, tigecycline is probably not appropriate in urinary infections owing to largely biliary excretion and low urinary levels.<sup>[72]</sup> To the best of our knowledge, colistin and tigecycline act on bacterial cells by different mechanisms. Albur's research indicated that adding tigecycline to colistin does not produce increased bacterial killing.<sup>[74]</sup> Instead, it may cause antagonism at lower concentrations. Based on these issues, development of molecular strategies that can rehabilitate the "old antibiotics" and halt the antibiotic resistance is a promising approach to target them. Uppu *et al.*<sup>[77]</sup> reported that membrane-active



macromolecules restore the antibacterial efficacy of tetracycline antibiotics toward blaNDM-1 *K. pneumoniae* and blaNDM-1 *E. coli* clinical isolates. These findings have potentially important therapeutic implications in the management of patients with infections caused by NDM-producing pathogen.<sup>[74]</sup>

Recently, susceptibility of NDM-harboring *Enterobacteriaceae* to fosfomycin has been reported. However, it is not included in all reports of blaNDM-harboring isolates.<sup>[4]</sup> Fosfomycin might be useful as a last-resort option as part of combination regimens. It is mainly used in the treatment of UTIs, particularly those caused by *E. coli* and *Enterococcus faecalis*. Intravenous fosfomycin has been administered in critically ill patients with sepsis or nosocomial-acquired infections due to carbapenem-resistant *K. pneumoniae*, in combination with other antibiotics, due to its unique mechanism of action and its protective effect against nephrotoxicity induced by aminoglycosides or colistin.<sup>[78-80]</sup>

Aztreonam is not appreciably hydrolyzed by NDM enzymes. Some research suggested that aztreonam was more effective than the carbapenems. Many MBLs-producing *Enterobacteriaceae* additionally carry ESBLs or other resistant determinants that confer resistance to aztreonam. There are no published clinical data as yet to support the use of aztreonam for the treatment of infections with MBL-producing *Enterobacteriaceae*.<sup>[81-85]</sup> However, the combination of aztreonam and avibactam, a non- $\beta$ -lactam  $\beta$ -lactamase inhibitor, may provide a much-needed therapeutic alternative. But a four-amino-acid insertion in penicillin-binding protein 3 had reduced susceptibility to aztreonam/avibactam according to Alm *et al.*'s report.<sup>[86]</sup>

Another finding is Api88, which is a novel, highly promising, 18-residue peptide lead compound with favorable *in vitro* and *in vivo* properties including a promising safety margin. Starting from the antibacterial peptide apidaecin 1b, we can treat systemic infections with the most threatening human pathogens, such as *E. coli*, *K. pneumoniae*, *Pseudomonas aeruginosa*, and *A. baumannii*.<sup>[85]</sup>

New carbapenemases such as NDM-1 enzyme are surfacing, resulting in almost total resistance to  $\beta$ -lactam antibiotics. Table 2 shows 22 cases related to the infection caused by NDM-producing bacteria. Facing with this serious situation, we are in urgent need of new therapeutic options.<sup>[87]</sup> One approach to combat this growing problem is the use of combination drug antibiotic adjuvant therapy. Antibiotic adjuvants include not only antibiotics but also other bioactive molecules according to the study of Lindsay and Gerard. It was reported that aspergillomarasmine A (AMA), a naturally occurring fungal product, is a rapid and potent inhibitor of NDM-1 enzyme and another clinically relevant MBL, VIM-2.<sup>[88]</sup> AMA also fully restored the activity of meropenem against *Enterobacteriaceae*, *Acinetobacter* spp. and *Pseudomonas* spp. Another promising strategy to target NDM-positive bacteria is using combination of two antibiotics. Combination therapy has

two desired outcomes: (1) Improved treatment efficacy, and (2) reduction in the rate of mutations that result in resistance.<sup>[84]</sup> MacVane *et al.*<sup>[89]</sup> reported *in vivo* activity using ceftazidime and ceftazidime-avibactam combination against NDM-producing isolates. In a case reported by Honore *et al.*,<sup>[71]</sup> wound cultures of a patient grew several types of bacteria including blaNDM-1 *E. coli*. Antibiotic regimen consisted of meropenem, vancomycin, colistin and tigecycline were used. But acute respiratory muscle weakness and apnea in the critically ill patient was induced by colistin neurotoxicity.

With limited treatment options available, slowing and preventing the spread of blaNDM is essential. Risk factors are associated with case status according to Pieter's research.<sup>[90]</sup> They reported that risk factors for hospital-associated infection include presence of co-morbid disease, mechanical ventilation and antibiotic exposure. In conclusion, we think that all necessary measures should be taken to reduce risks.

### Public health concern

NDM producers bring several factors that are deeply disconcerting for public health worldwide. First, the blaNDM gene has been identified in not a single species but in unrelated species (including *Acinetobacter* spp.). Second, it is present not only in *K. pneumoniae*, but also in *E. coli*, which is also a major community-acquired pathogen. Third, *E. coli* is also the number one cause of diarrhea in children in India and Pakistan. The risk of resistant strains being released into the environment is increasing.<sup>[56]</sup> The blaNDM gene spreading in *Enterobacteriaceae* is an alarming risk because these novel multidrug-resistant bacteria could disseminate worldwide very quickly. In addition, the NDM-1 encoding gene is located on different large plasmids (a 180-kb plasmid for *K. pneumoniae* and a 140-kb plasmid for *E. coli*) that are easily transferable to susceptible *E. coli* J53 at a high frequency. These plasmids are also harbor genes conferring resistance to almost all antibiotics. The rapid dissemination of NDM-1 in clinically relevant bacteria has become a serious threat for therapy.<sup>[88]</sup> A recent report indicated that in healthcare settings with source patients infected or colonized with NDM-producing bacteria, infection prevention control strategies and attention to colonization pressure will be key factors in minimizing the spread of blaNDM-1 plasmids in defined geographic units.<sup>[14]</sup>

The current diffusion of carbapenemase genes (especially blaNDM gene) in Gram-negative rods is now a serious public health issue, and in the near future, could lead back to the preantibiotic era.<sup>[89]</sup> So it is time to return to the basic tenets of combating antibiotic resistance. The major cause of the development of drug resistance is widespread antibiotic usage, which may provide a selection force for antibiotic-resistant. In many developing countries such as India, antibiotic prescriptions are not properly followed by patients, either due to a lack of awareness about the side effects of incomplete treatment or to low socioeconomic status.<sup>[91]</sup>

**Table 2: Worldwide reports of the NDM cases**

Genotyping	Related diseases	Antibiotic therapy	Clinical outcomes	Reference
NDM-1	Recurrent pyelonephritis	ATM, CL	Fever and abdominal pain resolved within 48 h after administration of antibiotics	[36]
NDM-1	Periappendicular abscess	CIP, MTZ, TZP	Good clinical response	[69]
NDM-1	Crush trauma	CIP, CC, MEN, VA, CL, TGC	He finally succumbed from refractory circulatory shock*	[71]
NDM-1	Persistent nonbloody diarrhea unspecified encephalitis	IMP, VA, MTZ, CL, CHL	Her condition worsened and she died <sup>†</sup>	[38]
NDM-3	Community-acquired uncomplicated cystitis	F/M	Resolve all clinical symptoms	[4]
NDM-1	Calciophylaxis	TZP, TGC, CIP, CL, MEM and TEC	Six months after initial presentation, the patient remains clinically stable	[58]
NDM-1	Extensive electrical burns	MEM, co-trimoxazole, CL, TEC	His fever defervesced, blood cultures became sterile. His wounds had healed and no MDR were detected	[8]

\*The critically ill patient got acute respiratory muscle weakness and apnea that were induced by colistin neurotoxicity; <sup>†</sup>The final diagnosis of this patient was toxic metabolic leukoencephalopathy, probably related to sepsis. TEC: Teicoplanin; TGC: Tigecycline; MEN: Meropenem; CIP: Ciprofloxacin; VA: Vancomycin; TZP: Piperacillin/tazobactam; ATM: Aztreonam; CL: Colistin; MTZ: Metronidazole; CHL: Chloramphenicol; F/M: Nitrofurantoin; CC: Clindamycin; IMP: Imipenem; Co-trimoxazole: Trimethoprim-sulfamethoxazole; NDM: New Delhi metallo- $\beta$ -lactamase.

Apart from this, antibiotic are used widely in food animals, aquaculture, and for some commercial plants. In 2001, the World Health Organization (WHO) launched a strategy to curb antibiotic resistance. The recommendations included banning the use of nonprescribed antibiotics, initiating prudent antibiotic formularies in hospitals, implementing stringent infection control policies, establishing national surveillance programs, and collaborating with international groups for better understanding of antibiotic resistance.<sup>[12,92,93]</sup> In addition, a recent WHO report also recommends reducing antimicrobial use in animal husbandry.<sup>[38,77]</sup> Thus, antibiotic stewardship activities should be undertaken in order to reduce inappropriate use of cephalosporins, fluoroquinolones,  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations, aminoglycosides, fosfomycin, tigecycline and polymyxins. Measurement of the use of these antibiotics should be performed as well.<sup>[7]</sup> In consideration of the serious situation currently, the focus must be on the following 4 aspects in the near term: (1) Providing clean water and basic sanitation in the areas where the environment is already contaminated or at high risk for becoming contaminated with NDM-producing bacteria; (2) identifying those who carry these bacteria; (3) controlling widespread, indiscriminate use of antibiotics; (4) preventing spread through the basic approaches of infection control.<sup>[52,53,94]</sup> We should adherence to the standard precautions including hand hygiene, environmental cleaning and disinfecting to prevent transmission of this newest “superbug.”<sup>[12]</sup> Indeed, many countries around the world have adopted some important measures according to the above principles. For example, enhanced environmental cleaning, and active surveillance of high-risk patients with electronic tagging of colonized patient’s medical records was introduced in Singapore, with isolation and cohorting of identified patients.<sup>[38]</sup> But the lack of basic hygiene facilities in many countries has substantially exacerbated this problem.<sup>[93]</sup>

To avoid the risk of hospital acquired and patient to patient spread of these pathogens, proper hygiene

should be implemented. Regular training of nursing staff should be practiced so the spread of pathogens can be decreased.<sup>[92]</sup> Strict infection-control measures were effective in controlling the potential spread of this resistance at a local level. Patients with a history of travel to high-risk areas and carriage of these bacteria should be sought in all hospital admissions and renal clinic attendees. At the international level, the response to the growing multidrug resistance in Gram-negative bacteria should be based on implementing a worldwide surveillance network to discover and report emerging resistance traits, whether to carbapenems or to other drugs.<sup>[10]</sup>

## CONCLUSIONS

The prevalence of NDM enzyme continues to increase. The most important identified reservoirs are colonized or infected individuals from endemic areas or centers with outbreaks, but the contaminated goods from these endemic areas also play a part. An international effort is needed to control the spread of these multiresistant pathogens. With limited treatment options, scientists need to develop new antibiotics and novel molecules to treat NDM-positive bacterial infections.<sup>[10,84]</sup> There is an urgent need for infection control and continued global monitoring of isolates that harbor the NDM enzyme, as evidenced by recent outbreaks.

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**Received:** 16-12-2014 **Edited by:** Xin Chen

**How to cite this article:** Wei WJ, Yang HF, Ye Y, Li JB. New Delhi Metallo- $\beta$ -Lactamase-Mediated Carbapenem Resistance: Origin, Diagnosis, Treatment and Public Health Concern. *Chin Med J* 2015;128:1969-76.

**Source of Support:** This study was supported by grants from National Natural Science Foundation of China (No. 81101288 and 81172737).

**Conflict of Interest:** None declared.