National Collaborating Centre for Infectious Diseases
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Purple Paper

The W-5 of NDM-1: The Pinnacle of Antimicrobial Resistance

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Key Points

- NDM-1 is an enzyme that confers resistance to one of the most potent classes of antibiotics, known as carbapenems plus all other currently available β-lactam antimicrobials.
- The NDM-1 resistance pattern is on a set of genes that can easily move from one bacterium to another.
- The NDM-1 resistance gene has demonstrated its capacity to move into bacteria which carry many other resistance patterns.
- This new resistance pattern has been reported in many different types of commonly encountered bacteria such as *Escherichia coli* and *Klebsiella pneumoniae* in addition to pathogenic bacteria such as *Salmonella* and *Vibrio* species.
- The presence of NDM-1 along with other resistance traits has rendered some bacteria pan-resistant.
- There is no significant new antimicrobial drug development.
- Environmental contamination, potentially high reservoirs of carriage of NDM-1, and population mobility may be additive factors in the globalization of the public health threat of this antimicrobial resistance pattern.

What is NDM-1?

NDM- 1 refers to New Delhi metallo-β-lactamase-1 and although it is often referred to as the newest "superbug" in the lay press (1-3), it is actually an enzyme which confers resistance to one of the most potent classes of antibiotics, known as carbapenems. NDM-1 belongs to the broad family of β-lactamase enzymes which are carried by many microorganisms as a defense against β-lactam antibiotics and may be classified on a functional or molecular basis. (4-6). There are four major classes of β-lactamases based on their molecular structure, which have specific functional correlations with respect to their activity. Three of the classes of β-lactamases act by a serine-based (serine-β-lactamase) mechanism and one by a zinc-based (metallo-β-lactamase) mechanism (5, 6). The activities of these enzymes exhibit differing behaviour in the presence of metal chelators, with inhibition of activity of metallo-β-lactamases but no inhibition of activity of serine-β-lactamases (5, 6). The metallo-β-lactamases share several common features, including significant carbapenemase activity, absence of activity against monobactams such as aztreonam and resistance to specific β-lactamase inhibitors such as clavulanic acid (5, 6). The presence of carbapenemase activity may occur in either serine- or metallo-β-lactamases but have been typically most often been associated with the metallo-β-lactamases. The most frequently encountered metallo-β-lactamase type carbapenemases are the IMP-type, VIM-type and now NDM-1 type and the major serine-β-lactamase carbapenemase is the KPC (*Klebsiella pneumoniae* carbapenemase). The presence of metallo-β-lactamase carbapenemases is not new and knowledge of their existence in certain bacteria dates back to the 1960s (5). These enzymes have been found in genes that are considered "resident" within the chromosome of certain bacteria such as certain *Bacillus* spp., *Stenotrophomonas maltophilia*, *Aeromonas* spp., certain environmental Pseudomonads and flavobacteria (5). None of these bacteria were considered of major clinical significance and were infrequently encountered. However, what was new and of concern regarding the metallo-β-lactamase carbapenemases was heralded perhaps by the first description of a non-resident mobile metallo-β-lactamase carbapenemase of the IMP-type, within a strain of

Pseudomonas aeruginosa in Japan in 1987 (7). The carbapenemase resistance trait was found on a mobile plasmid and not surprisingly multiple reports of additional strains of *P. aeruginosa* and occasionally other bacteria such as *Serratia marcescens, Achromobacter and Klebsiella pneumoniae* appeared in Japan over the next few years (8, 9). Reports of the presence of the same type of mobile metallo-β-lactamase carbapenemases appeared over the next few years, with reports from Europe and Canada (involving an outbreak at two Calgary, Alberta hospitals in the 1990s), the vast majority involving *P. aeruginosa* (10, 11).

There have been several reports of NDM-1 from Canada, including the provinces of Alberta, British Columbia and Ontario. While there are links to the Indian subcontinent in many of the cases, there are increasing reports of patients with isolates containing NDM-1 without any primary links.

A second type of a mobile carbapenemase resistance trait was first described in Verona, Italy in 1999 and was hence named the VIM-type (12). This type of mobile metallo-β-lactamase carbapenemase resistance has been described widely throughout Europe, South America, parts of Asia and has been recently found in the United States (5, 13). The VIM-type carbapenemase resistance has been found again most commonly in strains of less commonly encountered bacteria such as *P. aeruginosa, Acinetobacter baunannii, Aeromonas hydrophila* and only rarely from members of the Enterobacteriaceae family (5, 6).

The third major type of a mobile carbapenemase resistance trait, the so called KPC (*Klebsiella pneumoniae* carbapenemase) resistance is a serine-β-lactamase, was first described in 1996 in North Carolina in the United States (14) and has been subsequently described in multiple countries around the world (15). This KPC resistance is different than the others in that it has been most frequently encountered in strains of the commonly encountered *Klebsiella pneumoniae* but also other members of the Enterobacteriaceae family including *E. coli*, *Proteus* spp. *Enterobacter* spp., *Citrobacter* spp. and *Serratia* spp (15). It has also been seen in other non-Enterobacteriaceae Gram-negative organisms including *P. aeruginosa* and *Salmonella* spp. (15). The KPC type of carbapenemase resistance has been associated with multiple nosocomial outbreaks and has been difficult to contain (16). It has been described in Canada in an Ottawa hospital with intrahospital transmission (17) and a recent outbreak has just been reported from Montreal (18).

NDM-1 represents the most recent type of mobile metallo-β-lactamase carbapenemase to appear but it is behaving differently than most of the other previously described mobile serine- or metallo-β-lactamase carbapenemases, in terms of the rapidity of its spread and the scope of organisms in which it is found.

When did we first know about NDM-1?

The first published report and description of NDM-1 was in 2009 (19). The description of the case involved a Swedish patient receiving treatment for a *K. pneumoniae* urinary tract infection in a Swedish hospital, but who had previously been hospitalized in New Delhi, India. The gene was characterized and was found to be a novel metallo-β-lactamase gene and hence the term, NDM-1, was coined as a purely descriptive term. In addition to finding the gene on an easily transferable plasmid within the *K. pneumoniae* strain, it was also found on a plasmid in an *E. coli* strain isolated from the patient's feces (19). However what galvanized the public's attention was the release of a major paper in August 2010 by Kumarasamy and colleagues (20) identifying 37 isolates of members of the Enterobacteriaceae family carrying the NDM-1 gene in 29 patients, in the United Kingdom during 2008-9. The majority of the isolates (78.6%) were identified as *K. pneumoniae* and *E. coli* and were identified from urine, blood and wound or burn swabs. Seventeen of the 29 patients had travelled to the Indian subcontinent within a one year period and 14 of them had been admitted in India for hospital care. The reasons for admission included medical

tourism and illnesses occurring while travelling abroad. Isolates harbouring the NDM-1 gene were identified from multiple geographic regions in India and Pakistan, the majority of which were again found in strains of *E. coli* and *K. pneumoniae*. Isolates of *K. pneumoniae* from the area of Haryana were found to be clonal which suggested horizontal spread of a single strain. The isolates were characterized by their resistance to carbapenems, β-lactam antibiotics, aminoglycosides and fluoroquinolones which have been the mainstays for therapy for enteric Gram-negative bacillary infections (20). Although most isolates remained sensitive to colistin and tigecycline, at least one of them was considered to be pan-resistant. Analysis for the location of the bla_{NDM-1} gene in the isolates from this study revealed that the NDM-1 gene was most frequently associated with plasmids and was sometimes carried on more than one plasmid. Three of the isolates from the UK had the bla_{NDM-1} gene found on the chromosome. Collectively these findings suggested considerable mobility of the gene. The authors concluded that there was considerable potential for the international spread of the NDM-1 gene on these mobile plasmids (20).

Where has NDM-1 been identified to date?

Since the original description and designation of NDM-1 (19) in Sweden and the major paper in the Lancet Infectious Diseases describing cases in India, Pakistan and the United Kingdom (20), isolates containing the NDM-1 gene have been described in multiple countries from virtually all continents including Europe, North America, Australia, Africa, and Asia (21). There have been several reports of NDM-1 from Canada, including the provinces of Alberta, British Columbia and Ontario (22-24). While there are links to the Indian subcontinent in many of the cases, there are increasing reports of patients with isolates containing NDM-1 without any primary links. There has been speculation for a secondary link via several Balkan countries, including Bosnia, Kosovo, Montenegro, and Serbia to European countries (25). A recent report describes the clonal dissemination of an NDM-1 containing *A. baumannii* in an Israeli rehabilitation ward among 5 elderly patients without any epidemiologic evidence for travel or hospitalization in India (26). Similarly, a recent report from Canada also highlights the presence of the NDM-1 gene in a strain of *Morganella morganii* isolated from the urine of an elderly patient who had no travel history (27). In addition to the presence of NDM-1 in multiple members of the Enterobacteriaceae family, it has now been reported in multiple other Gram-negative bacteria including *Acinetobacter baumannii*, *Vibrio cholerae*, *Shigella boydii*, *Aeromonas caviae* and *Pseudomonas aeruginosa* (26, 28-30). The presence of the NDM-1 gene in 2 of 50 samples of drinking water and 51 of 171 seepage samples from New Delhi and the growth of bacteria from 12 of 171 seepage samples and 2 of 50 water samples, including several new bacterial species in which NDM-1 has not previously been reported was disconcerting from a public health perspective, especially given its presence in species of *Vibrio* and *Shigella*, providing an enormous potential for widespread dissemination (30). Collectively, these latter findings suggest a widespread presence of the plasmids containing the NDM-1 gene in an environmental setting from an endemic area, a worldwide spread of the plasmid(s) containing the NDM-1 gene, the beginnings of dissemination within non-endemic countries and a spectrum of presence in multiple species of Gram-negative bacteria, some of which are major pathogens from a public health perspective.

The presence of NDM-1 on a very mobile plasmid, its presence on different plasmids, the ability to integrate into the chromosome and the co-carriage of so many resistance traits set it apart from other resistance traits we have encountered previously.

Who will be affected by NDM-1?

Initial studies have suggested that the presence of bacterial isolates harbouring the NDM-1 gene had a history of travel, hospitalization or medical tourism in the Indian subcontinent (19-21). Recent retrospective data suggest that bacteria harbouring the NDM-1 gene were more widespread in health care facilities in India (31). In data collected from 14

hospitals throughout India in the SENTRY Program during 2006-07, 2.7% of 1443 Enterobacteriaceae were resistant to at least one carbapenem and almost 40% of these isolates were found to harbour NDM-1. Typing revealed multiple molecular patterns and dissemination both within and between sites and the authors concluded that NDM-1 had already disseminated widely throughout India as early as 2006 (31). Another study, which has been recently published, revealed relatively high fecal carriage rates of NDM-1 harbouring bacteria, mostly *E. coli* and *Enterobacter* spp., with 27.1 % of inpatients and 13.8% of outpatients positive in a prevalence survey from a military population in Pakistan (32). If these carriage rates are reflective of the general population within the Indian subcontinent, with a population of approximately 1.6 billion, the potential exists for hundreds of millions of carriers of isolates harbouring the NDM-1 resistance trait. With the recent finding of NDM-1 in almost 30% of seepage samples and 4% of drinking water samples in a major metropolitan area in India (31), increasing medical tourism (33), and the increasing mobility of populations – annually, approximately 2 billion persons are migratory over some distance, with half crossing international borders (34), it is not difficult to understand the enormous potential for the worldwide dissemination of NDM-1 to both susceptible and non-susceptible populations.

Why is NDM-1 different from other resistant traits?

The concerns over this new type of resistance have been outlined previously (21, 35, 36). What is different about NDM-1 resistance compared to all types of carbapenem resistance described to date, firstly, is the unique niche it has found for itself in genetic terms, finding itself to be associated with a plasmid with remarkable promiscuity and the co-carriage of up to 14 other resistance traits (21, 35). The genetic features of the bla_{NDM-1} gene from different species of the Enterobacteriaceae family collected from around the world have been recently examined and suggest an even greater diversity (37) than initially described. The gene was shown to be carried by several different plasmid types, which co-harboured other resistance traits including other ß-lactamase genes, quinolone resistance genes, and 16S RNA methylase genes and was shown to be integrated into the chromosome in some strains (37). The presence of NDM-1 on a very mobile plasmid, its presence on different plasmids, the ability to integrate into the chromosome and the co-carriage of so many resistance traits set it apart from other resistance traits we have encountered previously.

There has been no significant new drug development for antimicrobials and it does not appear that any new drug therapy is on the horizon, which raises significant concerns for the future.

Secondly, this new resistance pattern has been reported in many different types of commonly encountered bacteria (20, 21, 33, 36). Pitout (21) in an editorial accompanying the landmark publication by Kumarasamy and colleagues (20) which identified 37 isolates of members of the Enterobacteriaceae family carrying the NDM-1 gene, called emphasis to the presence of the NDM-1 gene in *E. coli* which is the most common cause of urinary tract infections in the community worldwide and suggested serious therapeutic shortfalls would ensue if physicians were to frequently encounter isolates with the resistance patterns described. Many additional publications have corroborated the finding of the NDM-1 gene in *E. coli* from multiple sites around the world (22,23,35). Unlike some of the other mobile metallo-β-lactamase carbapenemase resistance traits which had been found only in selected, less frequently encountered strains such as *P. aeruginosa, A. baunannii* and *Aeromonas hydrophila* (5,6,13), NDM-1 has a much wider spectrum of organisms in which it may be carried.

Thirdly, the NDM-1 resistance pattern is carried within very mobile broad-host range types of plasmids which allow the resistance trait to move with ease from one bacterium to another (20, 37), which is again different from what has been encountered previously. This latter point was illustrated by the recent finding of the NDM-1 gene in *V. cholerae* and *S. boydii* (31).

Finally, as to why NDM-1 resistance is different from what has been encountered previously is the paucity of the drugs potentially capable of treating infections due to one of these new multi-resistant strains and the increased toxicity of the remaining agents that are available (35, 36). Some authors have suggested that "broad-spectrum beta-lactam resistance due to NDM-1 heralds the end of the antibiotic era for treatment of infections caused by Gram-negative bacteria" (38). As mentioned previously, many of the strains which are already resistant to multiple antibacterial agents by virtue of the carriage of plasmids already carrying multiple resistance traits, acquired the NDM-1 trait, rendering the organism susceptible to only two agents, colistin and tigecycline (20). Colistin is an older drug from the polymyxin class that has rates of nephrotoxicity ranging from 14% to 58% (39-41). Furthermore, recent reports of colistin resistance have been reported in strains of KPC-containing *K. pneumoniae* (42, 43). The sensitivity of tigecycline, a bacteriostatic rather than bactericidal agent, has been variable and reports of both resistance and breakthrough bacteremia while on the therapy, due to an NDM-1 harbouring *E. coli*, have raised concerns about this drug (20, 44). Furthermore, in 2010, the U.S. Food and Drug Administration issued a warning of an increased risk of death with tigecycline compared to other antibiotics used to treat a variety of serious infections (45). Unfortunately, there has been no significant new drug development for antimicrobials and it does not appear that any new drug therapy is on the horizon, which raises significant concerns for the future.

Hence it is easy to see how the NDM-1 resistance trait is formidable, different from what we have encountered previously and has achieved a pinnacle of success from an evolutionary perspective of resistance.

How can NDM-1 resistance be prevented?

The prevention of the spread of NDM-1 as a resistance trait is no easy task. The fundamental processes for the control of antimicrobial resistance have been outlined many times and include surveillance, infection prevention and control and antimicrobial stewardship. At present there are no co-ordinated international surveillance programs to look at NDM-1 or carbapenem resistance patterns in Gram-negative bacteria. There have been calls for action, including a recent article which outlined an urgent need to regard the emergence and spread of antimicrobial-resistant bacteria, especially those involving new pan-resistant strains, as a public health emergency of international concern (PHEIC) and thus be notifiable to the World Health Organization under the International Health Regulations (46). The authors argued that the International Health Regulations framework would provide a global surveillance infrastructure and global public health response. Regarding infection prevention and control, the Public Health Agency of Canada have published guidelines on measures to be undertaken for healthcare workers in healthcare settings where carbapenem-resistant Gram-negative bacilli, including NDM-1, are encountered (47). The document recommends the use of routine practices and contact precautions for patients colonized or infected with these organisms in healthcare settings. The use of contact precautions does not apply in the prehospital and home care settings**.** It also recommends specific attention should be given to laboratory testing/surveillance, screening, hand hygiene, accommodation, personal protective equipment, patient care equipment, environmental cleaning, laundry/waste management, reporting, and antimicrobial stewardship (47).

The best approach to the resistance trait of NDM-1 and indeed all antimicrobial resistance is the most challenging which is curbing the overuse and misuse of antimicrobials in the veterinary, agri-food and human settings. The overuse of antibiotics has been likened to an ecological tragedy akin to the "tragedy of the commons" (36) and although there have been some successes, it is a difficult task. There are many countries where prescriptions of antimicrobials are unregulated in both humans and animals and this makes the task of preventing inappropriate usage even more difficult. There are many programs that have been established to reduce inappropriate use of antimicrobials, both in Canada and other countries but are beyond the scope of this article.

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Production of this document has been made possible through a financial contribution from the Public Health Agency of Canada.
The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada.