

NDM-1 Superbug

New Delhi Metallo-beta-lactamase (NDM-1) is an enzyme that makes bacteria resistant to a broad range of beta-lactam antibiotics. These include the antibiotics of the **Carbapenem** family, which are the mainstay for the treatment of antibiotic-resistant bacterial infections. The gene for NDM-1 is one member of a large gene family that encodes beta-lactamase enzymes called carbapenemases. Bacteria that produce carbapenemases are often referred to in the news media as "superbugs" because infections caused by them are resistant to more than two wide spectrum antibiotics and are difficult to treat. Such bacteria are usually susceptible only to a few antibiotics possibly to polymyxin and tigecycline.

NDM-1 was first detected in a *Klebsiella pneumoniae* isolate from a Swedish patient of Indian origin in 2008. It was later detected in bacteria in India, Pakistan, the United Kingdom, the United States, Canada, Japan and Brazil. The most common bacteria that make this enzyme are Gram-negative such as *Escherichia coli* and *Klebsiella pneumoniae*, but the gene for NDM-1 can spread from one strain of bacteria to any another by horizontal gene transfer.

Enzyme function

Carbapenems are a class of beta-lactam antibiotics that are capable of killing most bacteria by inhibiting the synthesis of one of their cell wall layers. The carbapenems were developed to overcome antibiotic resistance mediated by bacterial beta-lactamase enzymes. However, the *bla*_{NDM-1} gene produces NDM-1, which is a carbapenemase beta-lactamase - an enzyme that hydrolyzes and inactivates these carbapenem antibiotics.

Carbapenemases confer the bacteria with particularly dangerous resistance mechanisms, since they can inactivate a wide range of different antibiotics. The NDM-1 enzyme is one of the class B metallo-beta-lactamase; other types of carbapenemase are class A or class D beta-lactamases. The class A *Klebsiella pneumoniae* carbapenemase (KPC) is currently the most common carbapenemase, which was first detected in North Carolina, USA, in 1996 and has since spread worldwide. A later publication indicated that Enterobacteriaceae that produce KPC were becoming common in the United States.

The resistance conferred by this gene (*bla*_{NDM-1}), therefore, aids the expansion of bacteria that carry it throughout a human host, since they will face less opposition/competition from populations of antibiotic-sensitive bacteria, which will be diminished by the original antibacterial treatment.

Origin and spread

The NDM-1 enzyme was named after New Delhi (wrongly so), the capital city of India, as it was first described by Yong et al. in December 2009 in a Swedish national who fell ill with an antibiotic-resistant bacterial infection that he acquired in India. The infection was unsuccessfully treated in a New Delhi hospital, and, after the patient's repatriation to Sweden, a carbapenem-resistant *Klebsiella pneumoniae* strain bearing the novel gene was identified. The authors concluded that the new resistance mechanism "clearly arose in India, but there are few data support that these are arising from India and suggest how widespread it is in India. Its exact geographical origin, however, has not been conclusively verified. In March 2010, a study in a hospital in Mumbai found that most carbapenem-resistant bacteria isolated from patients carried the *bla*_{NDM-1} gene.

In May 2010, a case of infection with *E. coli* expressing NDM-1 was reported in Coventry in the United Kingdom. The patient was a man of Indian origin who had visited India 18 months previously, where he had undergone dialysis. In initial assays the bacteria was fully resistant to all antibiotics

tested, while later tests found that it was susceptible to Tigecycline and Colistin. The authors warned that international travel and patients' use of multiple countries' healthcare systems could lead to the "rapid spread of NDM-1 with potentially serious consequences".

As of June 2010, there were three reported cases of Enterobacteriaceae isolates bearing this newly described resistance mechanism in the US, the Centers for Disease Control and Prevention (CDC) stated that "all three U.S. isolates were from patients having received recent medical care in India." However, US experts stated that it is unclear as to whether this strain is any more dangerous than existing antibiotic-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), which are already common in the USA.

In July 2010, a team in New Delhi reported a cluster of three cases of *Acinetobacter baumannii* bearing bla_{NDM-1} that were found in the intensive care unit of a hospital in Chennai, India in April 2010. As previously, the bacteria were fully resistant to all the aminoglycoside β -lactam and quinolone antibiotics, but were susceptible to Tigecycline and Colistin. This particularly broad spectrum of antibiotic resistance was heightened by the strain's expressing several different resistance genes in addition to bla_{NDM-1} .

A study by a multi-national team was published in the August 2010 issue of the journal *The Lancet Infectious Diseases*. This examined the emergence and spread of bacteria carrying the bla_{NDM-1} gene. This reported on 37 cases in the United Kingdom, 44 isolates with NDM-1 in Chennai, 26 in Haryana, and 73 in various other sites in Pakistan and India. The authors' analysis of the strains showed that many carried bla_{NDM-1} on plasmids, which will allow the gene to be readily transferred between different strains of bacteria by horizontal gene transfer. All the isolates were resistant to multiple different classes of antibiotics, including beta-lactam antibiotics, fluoroquinolones, and aminoglycosides, but most were still susceptible to the polymyxin antibiotic colistin.

On August 21, 2010, Ontario, Canada had its first confirmed case of the "superbug" in Brampton. There were other confirmed cases in British Columbia and Alberta.

In August 2010, a chemical compound GSK 299423 (still experimental), was found to significantly fight against antibiotic-resistant bacteria by making such bacteria unable to reproduce, citing a likely treatment to the NDM-1 strain.

On September 6, 2010, Japan detected its first ever case of the NDM-1 enzyme. In May 2009, a Japanese man in his 50s who had recently returned from vacation in India was struck with a fever and hospitalized, later making a full recovery. Hospital officials confirmed that test carried out after the patient's recovery was positive for the NDM-1 enzyme.

Indian response

The Indian health ministry has disputed the conclusion of the August 2010 *Lancet* study that the gene originated in India, describing this conclusion as "unfair" and stating that Indian hospitals are perfectly safe for treatment. Indian politicians have described linking this new drug resistance gene to India as "malicious propaganda" and blamed multinational corporations for what they describe as selective malignancy. A senior politician (BJP) has instead argued that the journal article is bogus and represented an attempt to scare medical tourists away from India. The Indian Ministry of Health released a statement "strongly refuting" naming the enzyme "New Delhi". The primary author of the 2010 *Lancet* study, who is based in the University of Madras, has stated that he does not agree with the part of the article that advises people to avoid elective surgeries in India.

All the same an editorial in the March 2010 issue of the *Journal of Association of Physicians of India* blamed the emergence of this gene on the widespread misuse of antibiotics in the Indian healthcare system, stating that Indian doctors have "not yet taken the issue of antibiotic resistance seriously" and

noting little control over the prescription of antibiotics by doctors and even pharmacists. The *Times of India* states that there is general agreement among experts that India needs both an improved policy to control the use of antibiotics and a central registry of antibiotic-resistant infections..

Lancet Apology

On January 12th 2011, the editor of The Lancet, Richard Horton apologized and acknowledged that naming a superbug after New Delhi was an “error”.

First death

In August 2010, the first reported death due to bacteria expressing the NDM-1 enzyme was recorded as a Belgian man who had become infected while being treated in a hospital in Pakistan. He died despite being administered colistin, a powerful antibiotic. A doctor involved in his treatment said, "He was involved in a car accident during a trip to Pakistan. He was hospitalized with a major leg injury and then repatriated to Belgium, but he was already infected"

Summary of the *Lancet* article

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: A molecular, biological, and epidemiological study

Karthikeyan K Kumarasamy, Mark a Toleman, Timothy W et al. Lancet Infect Dis 2010; 10: 597–602

Background: Gram-negative Enterobacteriaceae with resistance to carbapenem conferred by New Delhi metallo- β -lactamase 1 (NDM-1) are potentially a major global health problem. We investigated the prevalence of NDM-1, in multidrug-resistant Enterobacteriaceae in India, Pakistan, and the UK.

Methods: Enterobacteriaceae isolates were studied from two major centers in India—Chennai (south India), Haryana (north India)—and those referred to the UK’s national reference laboratory. Antibiotic susceptibilities were assessed, and the presence of the carbapenem resistance gene bla_{NDM-1} was established by PCR. Isolates were typed by pulsed-field gel electrophoresis of XbaI-restricted genomic DNA. Plasmids were analyzed by S1 nuclease digestion and PCR typing. Case data for UK patients were reviewed for evidence of travel and recent admission to hospitals in India or Pakistan.

Findings: We identified 44 isolates with NDM-1 in Chennai, 26 in Haryana, 37 in the UK, and 73 in other sites in India and Pakistan. NDM-1 was mostly found among *Escherichia coli* (36) and *Klebsiella pneumoniae* (111), which were highly resistant to all antibiotics except to tigecycline and colistin. *K pneumoniae* isolates from Haryana were clonal but NDM-1 producers from the UK and Chennai were clonally diverse. Most isolates carried the NDM-1 gene on plasmids; those from UK and Chennai were readily transferable whereas those from Haryana were not conjugative. Many of the UK NDM-1 positive patients had travelled to India or Pakistan within the past year, or had links with these countries.

Interpretation The potential of NDM-1 to be a worldwide public health problem is great, and co-ordinated international surveillance is needed.