

Pitch for Scientific American
Gram-negative resistance: Worse than we know
Maryn McKenna
<mmckenna@mindspring.com>

When the journal *Lancet Infectious Diseases* published a paper Aug. 11 on the identification and rapid spread of a novel resistance mechanism in gram-negative bacteria, New Delhi metallo-beta-lactamase (or NDM-1), the reaction was electric. The enzyme, transported on a plasmid, renders *E. coli*, *Klebsiella pneumoniae* and other *Enterobacteriaceae* — some of the most common causes of severe hospital-acquired infections — almost untreatable, by conferring resistance to the drug class called carbapenems, generally considered the “drugs of last resort” for gram-negative bacteria.

By the time the Lancet ID paper saw print, NDM-1 had been spreading for several years. It was first identified in 2008 in Sweden, in a man of South Asian origin who had been hospitalized in India. By 2009, the Health Protection Agency of the United Kingdom was publishing a national alert, and two months before the Lancet paper, the US Centers for Disease Control and Prevention put out its own bulletin, identifying NDM-1 in three patients in three states, each infected with a different gram-negative bacterium. In every country, the spread of NDM-1 was linked to people moving back and forth to South Asian, and especially to medical treatment there. The government of India reacted furiously to that interpretation and to the naming of the enzyme, denouncing a Western “pharma conspiracy” intended to undermine the subcontinent’s burgeoning medical-tourism industry.

In the ensuing month, some of the heat has died down. At the same time, NDM-1 is unquestionably spreading — currently, to Japan, Canada, Hong Kong, Australia and Belgium so far. But what’s been missed in the furor is that NDM-1 is only one of multiple carbapenem-resistance factors, otherwise known as carbapenemases, that have been moving across the globe with much less fanfare than this one.

Collectively, they pose the question: *Once antibiotic resistance factors begin to move from their point of emergence, can anything be done to stop them?*

The stage was set for these new resistance factors by the emergence in the 1980s of the extended-spectrum beta-lactamases (ESBLs), which confer resistance not only to antibiotics possessing the four-atom beta-lactam ring that originated with natural penicillin, but also to the most recent generations of cephalosporins. That left medicine reliant on the carbapenems — but in this decade, carbapenem resistance has spread via multiple mechanisms. In Europe and the Mediterranean, the silent culprit is oxacillinases. In the United States — and now in South America, Israel and China — the problem is *K. pneumoniae carbapenemases* or KPCs, first identified in a single isolate in North Carolina in 1996 and now endemic in New York City.

Why is this wave of carbapenem resistance, of which NDM-1 is just the most recent, so “worrying” and “insidious,” to use papers’ own language? Because carbapenemases are fostered by a unique array of conditions:

- They were originally found in bacteria that are common human gut flora, and therefore evade surveillance and can be carried undetected across borders.
- They spread easily via mobile genetic elements, between bacterial genera but also across classes (as vancomycin resistance did in the 1990s from *Enterococcus* to *S. aureus*, creating VRSA).
- They are spreading with particular speed in countries where antibiotics are easily accessed over the counter; before NDM-1 emerged, other carbapenemase resistance was flagged by researchers in India.
- They confer very high-level resistance, a particular problem for gram-negative bacteria, for which almost no new drugs are in the pipeline because they are more complex to develop than drugs for gram-positives.

The story of carbapenemases touches problems of population movement, disease surveillance, antibiotic misuse, healthcare economics and market conditions for drug development. It describes a more profound challenge than the battle to control MRSA, considered the leading organism in the international epidemic of drug resistance. And without exaggeration, it raises the possibility that the 70 years of the antibiotic miracle may be coming to an end; for most carbapenem-resistant strains, only a few older and highly toxic drugs still work, and for one strain of NDM-1, no drugs work at all.

--

Maryn McKenna is the author of *SUPERBUG: The Fatal Menace of MRSA*, a narrative account of the 50-year history of drug-resistant staph, published in March 2010 by Free Press/Simon & Schuster. She is a journalist for national magazines and a former staff member at the Center for Infectious Disease Research and Policy at the University of Minnesota. Previously, she was the senior medical writer at the Atlanta Journal-Constitution, where she was the only US journalist assigned to full-time coverage of the CDC. She is also the author of *BEATING BACK THE DEVIL: On the Front Lines with the Disease Detectives of the Epidemic Intelligence Service* (Free Press 2004).

--

Papers likely to be referenced in this article:

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study
Karthikeyan K Kumarasamy MPhil, Mark A Toleman PhD, Prof Timothy R Walsh et al.
The Lancet Infectious Diseases - 1 September 2010 (Vol. 10, Issue 9, Pages 597 - 602)
DOI: 10.1016/S1473-3099(10)70143-2

Goren MG, Carmeli Y, Schwaber MJ, Chmelnitsky I, Schechner V, Navon-Venezia S. Transfer of carbapenem-resistant plasmid from *Klebsiella pneumoniae* ST258 to *Escherichia coli* in patient. Emerg Infect Dis 2010 Jun. Available from <http://www.cdc.gov/EID/content/16/6/1014.htm>

Krishna B. New Delhi metallo-beta-lactamases: A wake-up call for microbiologists. Indian J Med Microbiol 2010;28:265-6

Nordmann P, Cozon G, Naas T. The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria. Lancet Infect Dis 2009; 9: 228–36

Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: An emerging public-health concern. Lancet Infect Dis 2008;8 :159-66.

Bratu, S., Landman, D., Haag, R., Recco, R., Eramo, A., Alam, M., Quale, J. Rapid spread of carbapenem-resistant *Klebsiella pneumoniae* in New York City: A new threat to our antibiotic armamentarium (2005) Archives of Internal Medicine, 165 (12), pp. 1430-1435.