The emergence of pan-resistant Gram-negative pathogens merits a rapid global political response

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Recent media coverage of New Delhi metallo-β-lactamase (NDM-1) put antibiotic resistance back on the political map if only for the wrong reasons, mainly the reaction to the naming of NDM-1 and the incorrect assumption that medical tourism was being deliberately targeted. However, work on NDM-1 has most certainly highlighted the rapid dissemination of new antibiotic resistance mechanisms via economic globalization. The example of NDM-1 has also magnified the desperate need for a publicly funded global antibiotic surveillance system rather than just national or regional systems. Furthermore, there is a pressing need to establish a global task force to enforce international transparency and accountability on antibiotic stewardship and the implementation of measures to curb antibiotic resistance. An international antibiotic stewardship index should be established that is related to each country’s gross domestic product (GDP) and assesses how much of their GDP is committed to publically funded health initiatives aimed at controlling antibiotic resistance.

Keywords: global antibiotic resistance, NDM-1, New Delhi metallo-β-lactamase, India, southern Asia

There are few antibiotic resistance mechanisms that have captured the attention of scientists, as well as politicians and the general public, more than New Delhi metallo-β-lactamase-1 (NDM-1). While methicillin-resistant Staphylococcus aureus (MRSA) and Clostridium difficile have monopolized the media headlines for some years, the advent of the ‘NDM-1 superbug’ (as it has been referred to in the media) heralds in a new era in antibiotic resistance both in the UK and abroad. The fact that this new resistance was not primarily clonally spread but could disseminate rapidly via plasmid transmission among the normal human Gram-negative intestinal flora was an important finding.1,2 Humans carry 10–100 trillion bacteria as normal flora, and the potential for NDM-1-positive bacteria as normal gut flora; therefore the potential for endogenous infections such as untreatable cystitis is frightening.3–6 We suspect that this carriage rate is similar elsewhere in southern Asia. As judged by the ‘WHO Global Strategy for Containing Antibiotic Resistance’, the WHO has historically failed to understand the indubitable link between antibiotic resistance and lack of adequate sanitation.7 For India, this is a particularly pressing issue, as approximately 700 million people lack basic sanitation and more people own mobile phones than toilets.8–10

In short, India’s sanitation is woefully inadequate and is one of the key reasons why so many Indians could be carrying Enterobacteriaceae expressing NDM-1. For this situation to arise in a country that claims to be a key economic global power and boasts more billionaires, millionaires and international offshore accounts than most other countries is bitterly regrettable and, as evidenced by NDM-1, also has profound international ramifications. Pound for pound, or dollar for dollar, the greatest impact global stakeholders could have on antibiotic resistance is to provide adequate sanitation and access to potable water—a basic human right that has been seemingly forgotten.11

The key chronological events surrounding the NDM-1 story and the political reaction are summarized in Table 1. The response of the Indian government and officials to reports on NDM-1 involved a damage limitation exercise driven by national pride and a perceived need to protect their pharmaceutical industry and their lucrative ‘medical tourism’ practice. Despite this response, the naming of the enzyme as NDM-1 no doubt forced the Indian government to finally initiate measures to curtail the continuing spread of resistance, culminating in a document on the ‘Indian strategy to tackle antibiotic resistance’.12 Likewise, an article published in April 201113 forced the government to admit the lack of uncontaminated potable water and to subsequently distribute chlorine tablets 1 week after the paper was published.13

India currently produces at least 30% of the world’s oral and injectable antibiotics, and could rightly argue they are supporting the WHO agenda of supplying the world with affordable medicines. However, overuse of antibiotics that are excreted by patients and find their way into hospital and community wastewater systems provides an environmental selection pressure for...
the emergence and persistence of multidrug-resistant (MDR) and pan-drug-resistant (PDR) bacteria.\textsuperscript{14–17} Perhaps, ironically, this industry that we are so globally reliant on also spawns superbugs; other industries such as tourism or ‘medical tourism’ then export them around the world.\textsuperscript{1}

The pipeline for new and promising antimicrobials against NDM-1 producers looks equally lamentable. ACHN-490 [a novel aminoglycoside ([neoglycoside])] is likely to have little or no activity due to the plethora of 16S rRNA methylases (ArmA, RmtC, RmtD) carried by NDM-1 producers.\textsuperscript{18} Leucyl tRNA synthetase inhibitors look promising, but data on emerging resistance are still not clear, and while β-lactam/β-lactamase inhibitors look encouraging,\textsuperscript{19,20} NDM-1 producers can produce up to nine different β-lactamases, thereby complicating the picture. However, unless international patent issues are adhered to and enforced, in the medium to long term it is irrelevant what the antibiotic pipeline produces. For example, before tigecycline was marketed in Europe, formulations were available in southern Asia, i.e. international patent applications were blatantly ignored. This is a major disincentive for pharmaceutical companies to spend $1 billion to develop novel antibiotics—an increasingly serious issue currently being addressed by national working parties\textsuperscript{21,22} and desperately requiring prominent political intervention. Equally, it is regrettable that at a crucial time when there is a desperate need for novel antibiotics, pharmaceutical companies are constantly merging and re-merging, resulting in a loss of focus and the shedding of vital expertise that is lost to other disciplines such as cancer research. The UK is also guilty of short-sightedness—in the last 10–15 years, university microbiology departments throughout the UK and elsewhere have either been merged into oblivion or abolished altogether, such that researchers with vital expertise (bacterial physiologists and geneticists) are far too few in number to adequately support industry in this epic battle. Thus, at a time when PDR Enterobacteriaceae are fast becoming a global reality, both academia and industry are ill equipped to respond.

So, how will it end? Since various countries have blatantly ignored previous suggestions for 10 years, will the WHO World Health Day\textsuperscript{23} that was held on 6 April 2011 have any impact?—probably not! First, it could be argued that capitalism has plunged the international community into this quagmire, so it may be that capitalism in the form of litigation is a plausible solution. Countries that have been sensible and prudent will spend $10–$100 thousand per patient dealing with serious long-term MDR and PDR infections that have been imported from other ‘not-so-prudent’ countries. These ‘prudent’ countries may legally pursue other countries through the international courts, forcing them to yield and finally accept a modicum of international responsibility and accountability.

Second, the name of NDM-1 alone managed to effect change because it inadvertently embarrassed a nation and held it firmly under the international spotlight, eventually resulting in a publication on antibiotic resistance in India.\textsuperscript{24} Thus, can it be that an international antibiotic stewardship index scoring system might cause the same dramatic effect? Such an index would focus attention on national activities of antimicrobial stewardship (both community and hospital), sales of non-prescription antibiotics, and international antibiotic surveillance programs. Accordingly, each country would be ranked, as has been done previously for other areas, such as the international transparency index.\textsuperscript{25} This cause could conceivably be highlighted at the annual European Antibiotic Awareness Day on 18 November,\textsuperscript{26} but with an increasing emphasis on global resistance. Such a ranking system should be established by an appointed international group of experts that is publically funded and complete-ly dissociated from any political influence. Perhaps like the carbon tax, ‘negligent’ countries, and in particular wealthy ‘negligent’ countries, who do not commit a reasonable proportion of their GDP\textsuperscript{24} levels to public health issues should have a substantial international antibiotic tax levied upon them. The revenue from such a tax could be pooled through reputable international organizations (WHO) and used to fund antimicrobial drug discovery and development programmes. Critics of such a proposal should reflect on the UK MRSA rates, which were publically reported, engaged both the local and national press, and forced wide-ranging measures to reduce MRSA rates throughout the UK.\textsuperscript{27}

Third, it is clear that in the case of NDM-1, medical and non-medical tourism have played a significant role in disseminating

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**Table 1. Key chronological events of the NDM-1 story**

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<thead>
<tr>
<th>Date</th>
<th>Event</th>
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<tbody>
<tr>
<td>10 August 2010</td>
<td>Lancet Infect Dis press release on NDM-1</td>
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<tr>
<td>12 August 2010</td>
<td>First Lancet Infect Dis article on NDM-1 published\textsuperscript{1}</td>
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<tr>
<td>12–20 August 2010</td>
<td>Indian co-authors placed under immense pressure by Indian media\textsuperscript{7}</td>
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<td>Late August 2010</td>
<td>Indian researchers told not to work on NDM-1</td>
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<tr>
<td>September 2010</td>
<td>Indian scientists told it is illegal to send isolates out of India</td>
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<tr>
<td>October 2010</td>
<td>Meeting in New Delhi to formalize status of work on NDM-1</td>
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<tr>
<td>October–November 2010</td>
<td>Indian government sets up ‘Task Force’ to tackle antibiotic resistance</td>
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<tr>
<td>March 2011</td>
<td>Indian strategy to tackle antibiotic resistance published\textsuperscript{12}</td>
</tr>
<tr>
<td>March 2011</td>
<td>GARP report of antibiotic resistance in India published\textsuperscript{26}</td>
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<tr>
<td>7 April 2011</td>
<td>Second Lancet Infect Dis paper on NDM-1 published on WHO antibiotic resistance press day\textsuperscript{3}</td>
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<tr>
<td>8–9 April 2011</td>
<td>Indian government criticism of second paper</td>
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<tr>
<td>13 April 2011</td>
<td>Indian government distributes chlorine tablets\textsuperscript{13}</td>
</tr>
<tr>
<td>April 2011</td>
<td>Indian government announces grants to work on NDM-1</td>
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GARP, Global Antibiotic Resistance Partnership.
NDM-1 around the planet via air travel. Therefore, not only should there be an air travel carbon dioxide emissions tax, but also a dissemination of infectious disease (DID) tax of 1%. Such revenues would be enormous, but must be designated for research into bird flu, H1N1 and, of course, PDR bacterial pathogens. Not only would this vastly increase research capacity into PDR pathogens, but it would put the issue foremost in the minds of the general public and politicians—exactly where it belongs!

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Transparency declarations
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References