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Review

Global spread of antibiotic resistance: the example of New Delhi metallo-β-lactamase (NDM)-mediated carbapenem resistance

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The rapidity with which new types of antibiotic resistance can disseminate globally following their initial emergence or recognition is exemplified by the novel carbapenemase New Delhi metallo-β-lactamase (NDM). The first documented case of infection caused by bacteria producing NDM occurred in 2008, although retrospective analyses of stored cultures have identified the gene encoding this enzyme (bla_{NDM}) in *Enterobacteriaceae* isolated in 2006. Since its first description, NDM carbapenemase has been reported from 40 countries worldwide, encompassing all continents except South America and Antarctica. The spread of NDM has a complex epidemiology involving the spread of a variety of species of NDM-positive bacteria and the inter-strain, inter-species and inter-genus transmission of diverse plasmids containing bla_{NDM}, with the latter mechanism having played a more prominent role to date. The spread of NDM illustrates that antibiotic resistance is a public health problem that transcends national borders and will require international cooperation between health authorities if it is to be controlled.

Introduction

The ability of influenza virus to spread globally has long been recognized, with several pandemics having been recorded over the last 100 years. The pandemic spread of this infectious agent is due not only to person-to-person spread in local environments but also to the mobility of human populations facilitated by the ready availability of air and ground transportation systems. Individuals incubating an infection may travel between countries or even continents in a matter of hours or days, after which they become infectious, thus transmitting the infection over vast distances. However, there is increasing appreciation that influenza virus is not unique and that many other pathogens are also transmitted internationally, including bacteria that are resistant to antibiotics.

The global dissemination of antibiotic-resistant bacteria has received much attention, particularly over the last 100 years, following reports of the international spread of multi-resistant *Streptococcus pneumoniae* (Muñoz *et al.*, 1991), meticillin-resistant *Staphylococcus aureus* (Johnson, 2011; Stefani *et al.*, 2012) and resistant *Enterobacteriaceae*, particularly strains resistant to cephalosporins due to the production of CTX-M type extended-spectrum β-lactamases and strains producing carbapenemases such as KPC (van der Bij & Pitout, 2012). As a more current and pressing example of the rapidity with which a newly emergent type of antibiotic resistance can disseminate globally following its initial description, this article will focus on the problem of carbapenem resistance mediated by New Delhi metallo β-lactamase (NDM), a carbapenemase first reported in 2008 (Yong *et al.*, 2009).

Discovery of NDM

In the winter of 2007, a 59-year-old male patient of Indian descent who had lived in Sweden for many years travelled to India where he was hospitalized, initially in the Punjab, but then in New Delhi, for the management of a gluteal abscess. In January 2008 he was repatriated to a hospital in Orebro, Sweden, where, on the day after admission, a urine culture yielded an isolate of *Klebsiella pneumoniae* that was resistant to multiple antibiotics including carbapenems (ertapenem, imipenem and meropenem). This strain was not isolated from any subsequent cultures, but stool samples tested following transfer of the patient to a nursing home in March 2008 yielded a carbapenem-resistant strain of *Escherichia coli*. Phenotypic testing of both isolates suggested that the carbapenem resistance was due to the production of a metallo-β-lactamase (MBL), but PCR analysis failed to detect known MBL genes. Cloning and sequencing studies subsequently indicated that the resistance was due to a novel type of enzyme, which shared very little identity with other known MBLs, the most

closely related being VIM-1/2, with which it shared only 32 % identity. The novel MBL was designated NDM-1, as the authors of the report believed the resistance originated from India (Yong *et al.*, 2009). Occurrence of the same novel resistance gene in two different genera suggested that it was transferable, and conjugation experiments coupled with molecular studies confirmed that the $bla_{\text{NDM-1}}$ gene was located on transferable plasmids of 180 and 140 kb in the *K. pneumoniae* and *Escherichia coli* isolates, respectively.

A variant of NDM-1 (designated NDM-2) which differed by a single amino acid was reported in 2011 (Kaase *et al.*, 2011), and subsequently, a series of further variants (designated NDM-3–NDM-7) have been reported on the Lahey Clinic β-lactamase website (http://www.lahey.org/Studies/).

Epidemiological link of NDM with the Indian subcontinent

The putative epidemiological link between NDM-1 and the Indian subcontinent was further strengthened by a subsequent study which documented the isolation of NDM-1-positive *Enterobacteriaceae* from patients in India, Pakistan, Bangladesh and the UK in 2008–2009 (Kumarasamy *et al.*, 2010). NDM-positive *Enterobacteriaceae* were found to be geographically widespread in the Indian subcontinent, being recovered from ten areas in India, eight areas in Pakistan and one area of Bangladesh. Meanwhile, in the UK, the national reference laboratory of the Health Protection Agency had been independently investigating a growing number of unusual carbapenem-resistant isolates from UK patients. These isolates of *Enterobacteriaceae* displayed MBL phenotypes but, like the two 'Swedish' isolates, were negative for known carbapenemase genes. These had been sampled from patients in many UK hospitals, with the first received in August 2008. Cloning and DNA sequencing identified a novel MBL gene, which was subsequently found to be identical to $bla_{\text{NDM-1}}$. Of particular interest was the finding that at least 17 of the first 29 UK patients with NDM-positive bacteria (including isolates of *Escherichia coli*, *K. pneumoniae*, *Enterobacter* spp., *Citrobacter freundii*, *Morganella morganii* and *Providencia* spp.) had a history of travel to India or Pakistan within the previous year, with 14 having been hospitalized for a range of indications. Isolates positive for NDM-1 continued to be identified in the UK, and by May 2011, more than 100 such isolates had been received by the reference laboratory, with many patients from whom isolates had been obtained still having epidemiological links to India or Pakistan (Nordmann *et al.*, 2011).

The discovery of the likely importation of NDM-producing *Enterobacteriaceae* into the UK resulted in the release of a National Resistance Alert by the Department of Health in England, which highlighted the potential threat to public health and the need to isolate and screen patients with a history of travel to, and particularly hospitalization in, the Indian subcontinent. By way of contrast, the official response in India was to play down the extent of the problem, with some claiming that the study and the name of the enzyme were malicious propaganda aimed at undermining the subcontinent's medical tourism industry (Palmer, 2010; Walsh & Toleman, 2011, 2012). Despite this reaction, data have continued to accumulate, a fact which clearly indicates a substantial problem with NDM-positive bacteria in the Indian subcontinent. An investigation into the occurrence and characterization of carbapenem-resistant *Enterobacteriaceae* isolated in Indian hospitals in 2006–2007 recovered NDM-1-positive isolates from hospitals in New Delhi, Mumbai and Pune (Castanheira *et al.*, 2011), with these isolates pre-dating the hitherto first reported case of NDM-1 infection (Yong *et al.*, 2009). Subsequently, there were reports of NDM-1-positive *Acinetobacter* spp. and *Pseudomonas* spp. in a hospital in Pune in 2010 (Bharadwaj *et al.*, 2012), with NDM-1-positive *Acinetobacter* spp. also being found the same year in a hospital in Chennai (Karthikeyan *et al.*, 2010). Another study, also undertaken in 2010 at a tertiary referral hospital in Varanasi in north India, found that 54 (6.9 %) of 780 consecutive, non-duplicate clinical isolates of *Enterobacteriaceae* (comprising 30 *Escherichia coli*, 12 *K. pneumoniae* and 12 *Citrobacter* species) were positive for the $bla_{\text{NDM-1}}$ gene (Seema *et al.*, 2011). NDM-positive *Enterobacteriaceae* have also been seen in the neonatal setting in Indian hospitals, with two cases of neonatal sepsis due to *K. pneumoniae* (Roy *et al.*, 2011b) and a cluster of bloodstream infections due to *Escherichia coli* in a neonatal unit being reported (Roy *et al.*, 2011a). International surveillance of intra-abdominal infections in 2009 (comprising centres in Europe, North America, Latin America, the South Pacific, the Middle East and Asia) undertaken as part of the Study for Monitoring Antimicrobial Resistance Trends programme found NDM-1-positive isolates only in India. As in the other studies, the $bla_{\text{NDM-1}}$ gene was found in a range of species including *Escherichia coli*, *K. pneumoniae*, *Enterobacter cloacae*, *Providencia rettgeri* and *M. morganii* (Lascols *et al.*, 2011).

While the above reports provide evidence of the occurrence of NDM-1-positive bacteria in Indian hospitals, a finding of arguably greater public health importance was provided from an environmental study carried out in New Delhi in late 2010. This study showed the presence (by direct PCR) of the $bla_{\text{NDM-1}}$ gene in 51 of 171 seepage samples (water pools in streets or rivulets) and in two of 50 samples of drinking water. The two positive drinking-water samples and 12 of the 171 seepage samples yielded growth of a range of $bla_{\text{NDM-1}}$-positive bacteria including *Escherichia coli*, *K. pneumoniae*, *C. freundii*, *Shigella boydii*, *Vibrio cholerae* and *Aeromonas caviae* (Walsh *et al.*, 2011). This clearly showed for the first time that the problem of NDM-1 was not confined to hospital strains of bacteria, but was widespread in the community environment in India, highlighting the need for improvements in sanitary conditions as a key public health intervention. Interestingly, a recent report from Vietnam (described by the authors as a country with strong cultural and economic links with India) also documented environmental contamination with NDM, with two water samples from the Kim Nguu river, which flows through the centre of Hanoi, giving positive PCR results for $bla_{\text{NDM-1}}$ (Isozumi *et al.*, 2012). Both PCR-positive samples, which were obtained from river sites

3 km apart, yielded growth of NDM-positive *K. pneumoniae* of ST283, indicating a likely high level of contamination of the river with this carbapenem-resistant opportunist pathogen. It is noteworthy that a history of travel to Vietnam (but not involving hospitalization) was noted in one of five patients affected during an outbreak of carbapenem-resistant NDM-1-producing *Enterobacteriaceae* reported from Canada, suggesting yet again inter-continental transmission of this resistance determinant (Borgia *et al.*, 2012).

Although a study in Mumbai failed to detect intestinal carriage of NDM-1-positive *Enterobacteriaceae* (Deshpande *et al.*, 2012), gut colonization was reported from Bangladesh and Pakistan (Islam *et al.*, 2012; Perry *et al.*, 2011). In the Bangladesh study, screening of consecutive clinical samples over a 1-month period in late 2010 yielded 403 Gram-negative isolates, of which 14 (3.5 %) were positive for NDM-1. The study in Pakistan comprised an investigation of the prevalence of faecal carriage of *Enterobacteriaceae* with NDM-1 at two military hospitals in Rawalpindi. In total, 64 NDM-1-positive isolates of *Enterobacteriaceae*, belonging to seven species, were recovered from 37 (18.5 %) of the stool samples taken from 200 patients. In terms of different patient populations, the rates of intestinal carriage in inpatients and outpatients were 27 % and 14 %, respectively (Perry *et al.*, 2011).

In addition to the widespread occurrence of NDM-1 in the Indian subcontinent, reports have continued to be published from many parts of the world, documenting isolation of NDM-1-positive bacteria from patients with epidemiological links to that part of the world. Such reports have emanated from geographically diverse regions of the globe including Australasia, the Far East, the USA, Canada, the Middle East and many countries in Europe (Fig. 1). While many of the patients had a history of hospitalization in India, Pakistan or Bangladesh, others had simply travelled in this region (Table 1), which may indicate community acquisition of NDM-positive bacteria through ingestion of contaminated water, with resulting gut carriage.

International transmission of NDM-positive bacteria from regions other than the Indian subcontinent

Although much work on NDM has been focussed on the Indian subcontinent, there are now many documented cases of international transmission involving movement of infected or colonized individuals from countries in other regions of the world. In particular, the Balkans has been highlighted as a possible secondary reservoir for the spread of NDM, based on the considerable numbers of reports of patients from whom NDM-positive bacteria have been isolated following medical repatriation from this geographical area (Table 2). Transmission of NDM between Balkan states has also been documented (Mazzariol *et al.*, 2012). Routine analysis of carbapenemase-producing Gram-negative bacteria isolated in the Belgrade Military Medical Academy in 2010 identified seven isolates of *Pseudomonas aeruginosa* that were positive for $bla_{\text{NDM-1}}$ (Jovcic *et al.*, 2011). Interestingly, none of the patients had a history of travel to the Indian subcontinent or to Europe, raising the possibility that such NDM-positive strains may be endemic in Serbia. However, other investigators commenting on the possible epidemiological picture of NDM in the Balkans (Livermore *et al.*, 2011) noted a published report that

Fig. 1. Countries from which NDM-positive bacteria have been reported. Triangles indicate an epidemiological link to the Indian subcontinent.

Table 1. Reports of NDM-positive bacteria from patients with epidemiological links to the Indian subcontinent

IV, intravenous; NR, not reported.

Country	Year	Species	Clinical source	Travel and healthcare history	Reference
Australia	Not stated	*Escherichia coli*	Urine	Medical transfer from a hospital in Bangladesh	Poirel *et al.* (2010b)
	2010	*K. pneumoniae*	Urine	No history of hospitalization but patient received unknown IV antibiotic in the community in India (Punjab) within 3 month prior to returning to Australia.	Sidjabat *et al.* (2011)
Austria	2009	*K. pneumoniae*	Sacral decubitus ulcer and stool	Prior history of hospitalization in Pakistan and India	Zarfel *et al.* (2011a); Zarfel *et al.* (2011b)
	2010	*Escherichia coli*	Wound	History of travel to India	Zarfel *et al.* (2011b)
Belgium	2010	*Escherichia coli*	Pus	Patient transferred from a hospital in Pakistan	Bogaerts *et al.* (2010)
Canada	2010	*K. pneumoniae*	Urine	Hospitalized in India (Mumbai) 1 month previously	Tijet *et al.* (2011); Peirano *et al.* (2011b)
	2010	*Escherichia coli*	Urine	Transferred from a hospital in India (Mysore)	Peirano *et al.* (2011a)
	2010	*K. pneumoniae* and *Escherichia coli*	Urine (*K. pneumoniae*) and perirectal swab (*K. pneumoniae* and *Escherichia coli*)	Transferred from a hospital in northern India	Mulvey *et al.* (2011)
	2010	*Providencia rettgeri*	Urine	Prior hospitalization in India (New Delhi)	Kus *et al.* (2011)
	2011	*K. pneumoniae*	Urine	Hospitalized in India (New Delhi) 2 months previously	Peirano *et al.* (2011b)
Denmark	NR	*Escherichia coli*	Stool	Prior hospitalization in Pakistan	Nielsen *et al.* (2012)
Finland	2010	*K. pneumoniae*	Faecal screen	Prior hospitalization in India	Österblad *et al.* (2012); Struelens *et al.* (2010)
	2011	*Escherichia coli*	Urine	History of travel in India	Österblad *et al.* (2012)
France	2009	*Escherichia coli*	Surface of breast tumour	Patient came from India (Darjeeling) but no history of hospitalization	Poirel *et al.* (2010a)
	2010	*C. freundii*	Urine	Transferred from a hospital in India (Pondicherry)	Poirel *et al.* (2011g)
	2011	*Escherichia coli*	Stool	Returned from India 10 days previously, but no history of health problems or hospitalization	Birgy *et al.* (2011)
Germany	2009	*Escherichia coli*	Tracheal secretions	Hospitalized in India 3 months previously	Pfeifer *et al.* (2011b)
Ireland	2011	*K. pneumoniae*	Urine	The patient (a 6-month-old child) was born in India and moved to Ireland at the age of 4 months	McDermott *et al.* (2012)
Italy	2011	*Escherichia coli*	Urine	Prior hospitalization in India (New Delhi)	Gaibani *et al.* (2011)
Hong Kong	2009	*Escherichia coli*	Urine	History of travel to India (without hospitalization) earlier in the year	Chu *et al.* (2011)
	2010	*Escherichia coli*	Rectal swab	Prior hospitalization in India (Punjab)	Tsang *et al.* (2012)
Japan	2009	*Escherichia coli*	Blood	Hospitalized in India 1 month previously	Chihara *et al.* (2011)
Kuwait	2010	*K. pneumoniae*	Sacral area wound swab	Just returned from India	Jamal *et al.* (2012)

Table 1. cont.

Country	Year	Species	Clinical source	Travel and healthcare history	Reference
Netherlands	2009	*K. pneumoniae*	Rectal swabs	History of travel to India but with no healthcare contact	Leverstein-Van Hall *et al.* (2010)
New Zealand	2009	*Escherichia coli*	Urine	Hospitalized in India 2 months previously	Williamson *et al.* (2012)
	2010	*Escherichia coli* *Proteus mirabilis*	Rectal swab Rectal swab	Hospitalized in India (New Delhi) 1 month previously	Williamson *et al.* (2012)
	2010	*Escherichia coli*	Rectal swab	Attended primary healthcare facility in India (Punjab) 1 month previously	Williamson *et al.* (2012)
	2010	*K. pneumoniae*	Rectal swab	Hospitalized in India (Mumbai) 2 months previously	Williamson *et al.* (2012)
Norway	2010	*Escherichia coli*	Urine and blood	History of hospitalization in India 8 months previously	Samuelsen *et al.* (2011)
	2010	*K. pneumoniae*	Catheter urine	History of hospitalization in India, during which urinary catheter was inserted	Samuelsen *et al.* (2011)
Oman	2009	*K. pneumoniae*	Urine	Prior hospitalization in India	Poirel *et al.* (2011a)
	2010	*K. pneumoniae*	Blood and urine	History of travel to India	Dortet *et al.* (2012b)
	2011	*K. pneumoniae*	Wound	History of travel to India	Dortet *et al.* (2012b)
	2011	*K. pneumoniae*	Abdomen	History of travel to India	Dortet *et al.* (2012b)
Reunion Island	2012	*S. enterica*	Urine	Patient transferred from a hospital in India (Chennai)	Cabanes *et al.* (2012)
Singapore	2010	*Escherichia coli*	Blood	Medical transfer from a hospital in Bangladesh (Dhaka)	Chan *et al.* (2011)
	2010	*K. pneumoniae*	Urine	Recent history of healthcare contact (indwelling catheter) in India	Koh *et al.* (2010)
	2010	*K. pneumoniae*	Urine	History of hospitalization (for 4 months) in Bangladesh	Koh *et al.* (2010)
Spain	NR	*Escherichia coli*	Stool	Bloody diarrhoea in India 6 days previously	Solé *et al.* (2011)
	2010	*K. pneumoniae*	Peritoneal abscess	Hospitalized in India for the previous 9 days	Oteo *et al.* (2012)
Switzerland	Not stated	*K. pneumoniae*	Urine	Prior hospitalization in India	Poirel *et al.* (2011h)
	Not stated	*Proteus mirabilis*	Rectal swab	Patient was of Pakistani origin	Poirel *et al.* (2011h)
Taiwan	Not stated	*K. pneumoniae*	Stools and anal swabs	Medical transfer from a hospital in Bangladesh (New Delhi)	Wu *et al.* (2010)
UK	Not stated	*Escherichia coli*	Routine screening swabs (perineum and throat)	Transferred from a medical centre in India (Goa)	Hornsey *et al.* (2011)
	Not stated	*Escherichia coli*	Blood	Hospitalized in India 18 months previously	Muir & Weinbren (2010)
USA	2010	*Escherichia coli*, *K. pneumoniae*, *Enterobacter cloacae*	Not stated	Patients had recent history of medical care in India	CDC (2010)
	2011	*K. pneumoniae* *Salmonella* sp.	Sputum Perirectal swab	Hospitalized in India 1 month previously	Savard *et al.* (2011)
	Not stated	*K. pneumoniae*	Nasal wash; sputum	History of hospitalization in Pakistan 4 months prior to presentation	Mochon *et al.* (2011)

stated patients from the Balkans travelled to Pakistan for commercial kidney transplants and that infections in this patient group were not uncommon (Ivanovski *et al.*, 2011), leading these authors to speculate that such medical tourism could have introduced NDM to the Balkans. This issue remains the subject of contention, but what can undoubtedly be said for the present is that, irrespective of their origin, NDM-positive bacteria pose a significant public health threat in both the Indian subcontinent and the Balkans, with such strains being onwardly disseminated to diverse geographical regions around the globe.

Table 2. Reports of NDM-positive bacteria from patients with epidemiological links to parts of the world other than the Indian subcontinent

ICU, intensive care unit.

Geographical region where patient was previously located	Country where isolate was obtained	Year of isolation	Species (source)	Healthcare history	Reference
The Balkans					
Kosovo	Austria	2010	*K. pneumoniae* (wound)	Patient transferred from hospital in Kosovo	Zarfel *et al.* (2011a); Zarfel *et al.* (2011b)
Montenegro	Belgium	Not stated	*K. pneumoniae* (sputum)	Patient transferred from hospital in Podgorcia	Bogaerts *et al.* (2010)
Serbia/Kosovo	Belgium	Not stated	*K. pneumoniae* (sputum) *Escherichia coli* (faecal swab)	Patient transferred from hospital in Kosovo, although previously hospitalized in Serbia	Bogaerts *et al.* (2010)
Bosnia and Herzegovina	Croatia	2009	*K. pneumoniae* (blood)	Patient transferred from hospital in Bosnia and Herzegovina	Mazzariol *et al.* (2012)
	Denmark	2010	*K. pneumoniae* (urine)	Patient transferred from a hospital in Bosnia and Herzegovina	Hammerum *et al.* (2010)
Serbia	France	2012	*P. aeruginosa* (urine)	Hospitalized in Serbia in the previous 3 months	Flateau *et al.* (2012)
	Germany	2007	*Acinetobacter baumannii* (multiple sites)	Patient transferred from a hospital in Serbia	Göttig *et al.* (2010); Pfeifer *et al.* (2011a)
	Netherlands	2008	*K. pneumoniae* (multiple sites)	Patient transferred from a hospital in Serbia (Belgrade)	Halaby *et al.* (2012)
	Switzerland	Not stated	*Escherichia coli* (rectal swab), *K. pneumoniae* (urine), *Acinetobacter baumannii* (rectal swab)	Patient transferred	Poirel *et al.* (2011h); Poirel *et al.* (2012a)
Iraq	France	2010	*K. pneumoniae* (rectal swab)	Patient transferred from a hospital in Iraq (Baghdad)	Poirel *et al.* (2011d)
	Lebanon	2010	*K. pneumoniae* (blood)	Patient transferred from Iraq	El-Herte *et al.* (2012)
	Lebanon	2010	*K. pneumoniae* (urine)	Patient transferred from Iraq	El-Herte *et al.* (2012)
	Turkey	2011	*K. pneumoniae* (blood)	Patient transferred from a hospital in Iraq (Baghdad)	Poirel *et al.*,(2012c)
Egypt	Czech Republic	2011	*Acinetobacter baumannii* (bronchoalveolar lavage; oral cavity swab)	Patient transferred from a hospital in Egypt	Hrabák *et al.* (2012)
	Germany	Not stated	*Acinetobacter baumannii* (central-venous-line catheter)	Patient transferred from the ICU of a hospital in Egypt	Kaase *et al.* (2011)
	United Arab Emirates	2009	*Acinetobacter baumannii* (urine)	Surgery in Egypt a year earlier but subsequent recurrent urinary tract infections treated with ceftriaxone or meropenem	Ghazawi *et al.* (2012)
Algeria	Belgium	2011	*Acinetobacter baumannii* (rectal swab)	Patient transferred from the ICU of a hospital in Algeria	Bogaerts *et al.* (2012)
Oran	France	2011	*Acinetobacter baumannii* (rectal swabs, blood catheter)	Patient transferred from the ICU of a hospital in Algeria	Boulanger *et al.* (2012)

Table 2. cont.

Geographical region where patient was previously located	Country where isolate was obtained	Year of isolation	Species (source)	Healthcare history	Reference
Cameroon	France	Not stated	*Escherichia coli* (rectal swab)	Patient transferred from a hospital in Douala	Dortet *et al.* (2012c)
Libya	Denmark	2011	*Acinetobacter baumannii* (colonizer)	Patients transferred from Libya, via Tunisia	Hammerum *et al.* (2012)
Reunion Island	France	2011	*K. pneumoniae* (rectal swab)	Patient transferred from a hospital in Reunion Island but prior hospitalization in Mauritius	Cabanes *et al.* (2012)
China	Taiwan	2010	*Klebsiella oxytoca* (pelvic abscess)	Patient transferred from a hospital in Nanchang Province of Jangxi in China	Lai *et al.* (2011)

The same consideration applies to the Middle East and North or Central Africa where NDM-positive bacteria have been reported from a range of countries including Afghanistan, Algeria, Cameroon, Egypt, Iraq, Israel, Kuwait, Lebanon, Morocco, the Sultanate of Oman and the United Arab Emirates (Fig. 1). In most cases, the literature comprises reports of patients being transferred from the Middle East or North or Central Africa to other parts of the world (Table 2). However, the converse is also known to have occurred, with importation of NDM-1-positive strains of *K. pneumoniae* from the Indian subcontinent into Kuwait and Oman (Dortet *et al.*, 2012b; Jamal *et al.*, 2012; Poirel *et al.*, 2011a). The complex epidemiological picture that can be seen with the inter-country transfer of resistant organisms is exemplified by a recent report that documented two patients with NDM-1-positive organisms associated with Reunion Island. In the first case, in late 2011, a patient who was transferred to a hospital in France was found upon rectal screening to be colonized with NDM-1-positive *K. pneumoniae*. Three months later, a patient transferred from a hospital in India to the same unit in Reunion Island yielded growth of NDM-1-producing *Salmonella enterica* subsp. *enterica* serotype Westhampton from a urine culture (Cabanes *et al.*, 2012).

Local spread of NDM following importation

Although there have been many reports of inter-country transmission of NDM-positive bacteria related to medical repatriation of hospitalized patients or patients returning home after a period of foreign travel, it is striking and fortunate that, with just a few exceptions (Hrabák *et al.*, 2012; Kumarasamy *et al.*, 2010; Poirel *et al.*, 2011b), most do not mention subsequent cross-infection. However, despite the paucity of documented instances of spread following importation of NDM-positive bacteria, it seems likely that local dissemination of these organisms in different countries has occurred, at least as gut colonization. Several lines of evidence support this. Firstly, reports from disparate parts of the world, including Canada (Kus *et al.*, 2011), China (Fu *et al.*, 2012; Ho *et al.*, 2012; Yang *et al.*, 2012), France (Arpin *et al.*, 2012), Guatemala (Pasteran *et al.*, 2012), Israel (Espinal *et al.*, 2011), Oman (Poirel *et al.*, 2011a), Kenya (Poirel *et al.*, 2011f), Kuwait (Jamal *et al.*, 2012), South Africa (Brink *et al.*, 2012), South Korea (Kim *et al.*, 2012) and Thailand (Rimrang *et al.*, 2012) have described the isolation of NDM-positive bacteria from patients with no history of foreign travel, implying that the organisms must have been acquired locally. In one study, isolation of NDM-1-producing *Acinetobacter pittii* was reported in 27 patients in an intensive care unit in China over a period of 13 months (June 2008–June 2009), none of whom had epidemiological links to South-West Asia (although links to the Balkans or other regions were not mentioned) (Yang *et al.*, 2012). In another report, this time from France, two patients who denied any foreign travel in the previous 5 years, and who shared the same hospital room, were both colonized in the gut with the same strain of NDM-1-positive *Escherichia coli*, which was also isolated from the urine of one of the patients (Denis *et al.*, 2012). Interestingly, both faecal and urine specimens from this patient remained positive when the patient was followed up 7 months later, indicating the potential for NDM-positive bacteria to persist at sites of colonization for prolonged periods of time. This has been confirmed in other studies which described gut carriage of NDM-positive *Escherichia coli* for periods of 13 (Poirel *et al.*, 2011e) and 10 months (D'Andrea *et al.*, 2011), while another report documented carriage of NDM-1-positive *K. pneumoniae* for more than 7 months (Kim *et al.*, 2012). Secondly, most NDM-positive bacteria reported to date have been isolated from patients who were clinically ill and consequently subjected to microbiological investigation following admission to hospital. Clearly, travellers to high-risk areas who become asymptomatically colonized with NDM-positive bacteria would not be subjected to such investigations and may act as undetected reservoirs of carbapenem-resistant bacteria on returning home. The lack of surveillance data on rates of asymptomatic gut carriage of NDM-positive bacteria, particularly in community settings in different countries, means that our current

Table 3. Reported cases of plasmid-encoded NDM

NR, Not reported.

Species	Country where isolate obtained	Sequence type	Plasmid size (kb)	Plasmid Inc group	Co-resistances	Reference
Escherichia coli	Australia	101	50	Untypable	NR	Poirel *et al.* (2010b)
	Canada	101	75	Untypable	NR	Peirano *et al.* (2011a)
	Canada	405	129	A/C	bla_{CMY-6}	Mulvey *et al.* (2011)
	Canada	1193	130	A/C	bla_{CMY-6}; *rmtC*	Borgia *et al.* (2012)
	China	744	50	Untypable	None	Ho *et al.* (2012)
	Denmark	101	–	A/C	bla_{CMY-4}; *armA*	Nielsen *et al.* (2012)
	France	405	120	F	$bla_{CTX-M-15}$; $bla_{OXA-1;}$ *aacA4*	Dortet *et al.* (2012c)
	France	10	150	A/C	bla_{OXA-10}; bla_{CMY-16}	Denis *et al.* (2012); Poirel *et al.* (2011c)
	France	131	110	F	Aminoglycosides, trimethoprim, sulphonamides (genes not specified)	Poirel *et al.* (2010a); Poirel *et al.* (2011c)
	Hong Kong	–	88.8	L/M	bla_{TEM-1}; $bla_{DHA-1;}$ *aacC2*; *armA*; *sul1*;*mel*; *mph2*	Ho *et al.* (2011)
	India	648	120	F	*armA*	Nordmann *et al.* (2012a); Poirel *et al.* (2011c)
	India	131	87	FII	$bla_{OXA-1;}$ *aacC2*; *aacC4*; *aadA2*; *dfrA12*	Bonnin *et al.* (2012a)
	Japan	38	196	A/C	bla_{TEM-1}; $bla_{CMY-4;}$ *aadA2*; *armA*; *sul1*;*mel*; *mph2*; *dfrA12*	Sekizuka *et al.* (2011)
	New Zealand	101	>100	Untypable	*rmtC*	Williamson *et al.* (2012)
	New Zealand	361	>100	Untypable	NR	Williamson *et al.* (2012)
	New Zealand	2488	>100	Untypable	NR	Williamson *et al.* (2012)
	Spain	156	300	HII	bla_{TEM-1}; $bla_{CTX-M-15;}$ $bla_{DHA-1;}$ *armA*	Solé *et al.* (2011)
	Switzerland		130	F	bla_{TEM-1}; *armA*	Poirel *et al.* (2011h)
	UK	648	>100	F	*aadA5*; *dfrA17*; *rmtB*	Hornsey *et al.* (2011)
K. pneumoniae	Australia	147	70		$bla_{CMY-6;}$ *aac-6'-1b*; *rmtC*	Sidjabat *et al.* (2011)
	Canada	16	102	A/C	bla_{CMY-6}	Mulvey *et al.* (2011)
	Canada	340	120	FII	Not reported	Peirano *et al.* (2011b)
	Canada	147	150	A/C	$bla_{SHV-12;}$ *armA*	Peirano *et al.* (2011b); Tijet *et al.* (2011)
	Canada	231	130	A/C	bla_{CMY-6}; *rmtC*	Borgia *et al.* (2012)
	China	483	50	Untypable	None	Ho *et al.* (2012)
	China	–	50	Untypable	None	Ho *et al.* (2012)
	Croatia	25	–	A/C	$bla_{CTX-M-15;}$ $bla_{CMY-16;}$ *qnrA6*	Mazzariol *et al.* (2012)
	France	14	150	Untypable	*rmtC*	Poirel *et al.* (2011c)
	France	15	270/300*	Untypable	$bla_{CTX-M-15;}$ $bla_{OXA-1;}$ *aac(6')-Ib*-like; *armA*; *qnrB1*	Arpin *et al.* (2012)
	France	147	100	Untypable	NR	Poirel *et al.* (2011c); Poirel *et al.* (2011d)
	Guatemala	17	–	Untypable	$bla_{SHV-12;}$	Pasteran *et al.* (2012)

Table 3. cont.

Species	Country where isolate obtained	Sequence type	Plasmid size (kb)	Plasmid Inc group	Co-resistances	Reference
	India		160	A/C	NR	Kumarasamy & Kalyanasundaram (2012)
	India	14	180	Untypable	*arr-2*; *ere*C; *aad*A1; *cml*A7	Yong *et al.* (2009)
	Kenya	14	120	A/C_2	*rmtC*	Poirel *et al.* (2011f)
	Mauritius	231	120	A/C	$bla_{CMY-6;}$ *rmtC*	Poirel *et al.* (2012b)
	Morocco	15	250	Untypable	$bla_{CTX-M-15;}$ bla_{OXA-1}	Poirel *et al.* (2011b)
	The Netherlands	15	70	II	NR	Halaby *et al.* (2012)
	New Zealand	11	>100	Untypable	NR	Williamson *et al.* (2012)
	Oman	14	170	L/M	*armA*	Poirel *et al.* (2011a)
	Oman	340	170	Untypable	*armA*	Poirel *et al.* (2011a)
	South Korea	340	50, 60, 70, 100	N	NR	Kim *et al.* (2012)
	Spain	231	120	F1b	NR	Oteo *et al.* (2012)
	Switzerland	147	150	A/C	*rmtA*	Poirel *et al.* (2011h)
	Switzerland	25	150	A/C	$bla_{OXA-10;}$ bla_{CMY-16}; *qnrA6*	Poirel *et al.* (2011h)
	Turkey	38	80	FIb	*rmtB*	Poirel *et al.* (2012c)
K. oxytoca	Taiwan	–	–	Untypable	*armA*; *aacC2*	Lai *et al.* (2011)
C. freundii	France	–	65	Untypable	NR	Poirel *et al.* (2011g)
Acinetobacter lwoffii	China	–	270	–	*AphA6*	Wang *et al.* (2012)
Acinetobacter pittii	China	–	45		*AphA6*; ble_{MBL}	Yang *et al.* (2012)
Proteus mirabilis	Switzerland	–	150	A/C	$bla_{OXA-10;}$ bla_{CMY-16}; *armA*	Poirel *et al.* (2011h)
Providencia stuartii	Afghanistan	–	178	A/C	$bla_{OXA-10;}$ *armA*; *sul1*; *qnrA1*; *aac(6')*; *cmlA7*	McGann *et al.* (2012)

*Two isolates with different sized plasmids obtained from same patient.

views of the extent of the spread of NDM may well be an underestimate.

The contribution of clonal expansion and gene transfer to the spread of NDM

While the epidemiology of many infectious diseases can be described solely in terms of the spread of the causative pathogens, the epidemiology of antibiotic resistance is significantly more complex in many bacteria, not least in the *Enterobacteriaceae*. Dissemination of many types of resistance involves not just the spread of the resistant organisms, but also the inter-strain, inter-species or even inter-genus spread of the resistance genes. Gene spread among bacteria can be mediated by a range of genetic mechanisms including transformation, transduction and conjugative plasmid transfer (Sykes, 2010), although observations to date only implicate plasmid transfer in the spread of bla_{NDM} genes.

Some insight into the relative roles of strain spread versus plasmid spread in India was provided by Kumarasamy *et al.* (2010) in their paper on NDM from India, Pakistan and the UK. These workers found that isolates of NDM-positive *K. pneumoniae* from Haryana in northern India were clonal and contained plasmids that were non-conjugative, while isolates from Chennai in South India and those from the UK were clonally diverse and contained plasmids that were readily transferable. It was noteworthy, however, that among 21 isolates of *K. pneumoniae* from the UK, there were two pairs of related isolates (designated on the basis of their PFGE profiles) that were from epidemiology-linked patients, and hence, thought likely to represent cases of cross-infection (Kumarasamy *et al.*, 2010).

Molecular investigations involving both the characterization of isolates of NDM-positive bacteria and the characterization of the plasmids containing bla_{NDM} genes show a highly complex picture. Firstly, bla_{NDM} has been found both in a wide range of species and genera of Gram-negative bacteria, and in a diverse range of clones and strains within individual species, as indicated by the variation in multi-locus sequence types (STs) and PFGE profiles, respectively (Table 3). For example, bla_{NDM} has been reported in at least 11 different STs of both *Escherichia coli* and *K. pneumoniae* to date, indicating a high level of inter-lineage and inter-species gene transfer. The plasmids encoding NDM also appear highly heterogeneous on the basis of molecular size, incompatibility type and linked antibiotic resistance genes (Table 3). While bla_{NDM} has commonly been found on plasmids in *Enterobacteriaceae*, it is notable that there has only been one report of plasmid-mediated NDM in *Acinetobacter baumannii* (Chen *et al.*, 2011), although diverse plasmids encoding NDM have been found in other species of *Acinetobacter* (Fu *et al.*, 2012; Yang *et al.*, 2012). The former study reported four different strains of *Acinetobacter baumannii* containing plasmids of different sizes (30–50 kb) encoding NDM, and although transferable to *Escherichia coli in vitro*, the plasmids appeared unstable and were readily lost after subculture in antibiotic-free medium. In all other reported isolates of *Acinetobacter baumannii*, the bla_{NDM} gene was located on the chromosome (Bogaerts *et al.*, 2012; Bonnin *et al.*, 2012b; Boulanger *et al.*, 2012; Espinal *et al.*, 2011; Hrabák *et al.*, 2012; Kaase *et al.*, 2011; Karthikeyan *et al.*, 2010; Pfeifer *et al.*, 2011a; Poirel *et al.*, 2012a). Nonetheless, there is still evidence of gene spread in *Acinetobacter baumannii*, as several studies have found the bla_{NDM} gene located between two direct repeats of the IS*Aba125* element, thus forming a composite transposon (Tn*125*) (Bogaerts *et al.*, 2012; Boulanger *et al.*, 2012; Espinal *et al.*, 2011; Hrabák *et al.*, 2012; Pfeifer *et al.*, 2011a; Poirel *et al.*, 2012a). Further investigation of the immediate genetic environment of the bla_{NDM} gene in isolates of *Acinetobacter baumannii* and *Enterobacteriaceae* revealed the presence of a novel bleomycin resistance gene designated ble_{MBL} (*ble* gene associated with the metallo-B-lactamase gene NDM) (Dortet *et al.*, 2012a). The ble_{MBL} and bla_{NDM} genes were co-expressed, being under the control of the same promoter located upstream of bla_{NDM} at the extremity of IS*Aba125*. Bleomycin refers to a family of structurally related glycopeptides produced by *Streptomyces verticillus* that have antibacterial properties but which are also used in cancer chemotherapy. Bleomycin(s) may also be found in the environment. It was therefore postulated that selective pressure promoting the spread of NDM-positive isolates might be due not only to use of β-lactam or other antibiotics to which NDM-positive isolates might be resistant but also to the use of anti-cancer drugs and to naturally occurring bleomycin molecules in the environment (e.g. water seepage samples) (Dortet *et al.*, 2012a). In terms of the initial emergence of NDM in human pathogens, it has been hypothesized that the bla_{NDM}–ble_{MBL} pairing may have been integrated first into the chromosome of *Acinetobacter baumannii* from an unknown environmental species, where it became associated with IS*Aba125*, and then was transposed onto plasmids capable of replication and conjugative transfer in *Enterobacteriaceae*, with the downstream copy and most of the upstream copy of IS*Aba125* subsequently being lost from some isolates (Nordmann *et al.*, 2012b). In this regard, it is noteworthy that plasmid-encoded $bla_{NDM\text{-}1}$ and ble_{MBL} have also recently been reported in isolates of *Acinetobacter pittii* in China, with the $bla_{NDM\text{-}1}$ gene in this instance being flanked by two insertion sequences, namely IS*Aba125* and IS*Aba11*, the latter having 99 % identity with an insertion sequence found in *Acinetobacter baumannii* ATCC 17978 (Yang *et al.*, 2012).

Prospects for the future spread of NDM

The rapidity with which a new type of resistance can emerge in bacteria able to cause infections in humans and disseminate to become a global public health threat is clearly exemplified by NDM carbapenemase. The earliest known NDM-positive organism (an *Escherichia coli* strain isolated in New Delhi) was collected in 2006 (Castanheira *et al.*, 2011), since then, NDM-positive isolates have been reported from 40 countries covering all continents except South America and Antarctica. What is notable about the global transmission of NDM is that although this has involved both strain spread and gene spread, so far, the latter appears to have been the dominant

mechanism of dissemination. However, it is possible that the epidemiology of NDM may change, as the bla_{NDM-1} gene has been found in bacterial strains belonging to lineages with known epidemic or pandemic potential. These include, for example, *Escherichia coli* of ST101 (Mushtaq *et al.*, 2011; Nielsen *et al.*, 2012; Peirano *et al.*, 2011a; Poirel *et al.*, 2010b; Williamson *et al.*, 2012), which has spread widely in Spain, and ST131(Rogers *et al.*, 2011) which has spread globally, with both lineages being associated with the spread of cephalosporin resistance mediated by CTX-M-type extended-spectrum β-lactamases. Moreover, it is noteworthy that another type of carbapenemase, designated KPC (for *Klebsiella pneumoniae* carbapenemase), has spread widely due predominantly to dissemination of a particular clone of *K. pneumoniae* of ST258 (Woodford *et al.*, 2011). Hence, it is not unreasonable to be concerned that NDM may increasingly adopt a similar mode of transmission. The epidemiology of strain spread and the patient populations affected may vary, however, depending on the species and strains in which the bla_{NDM} gene is found. For example, NDM-positive *Acinetobacter baumannii* may be more likely to infect hospitalized patients, particularly those in high-dependency units, as these are typically the patient groups at greatest risk of infection or colonization with acinetobacters. In contrast, NDM-positive *Escherichia coli* strains, particularly those causing gut colonization, may be a cause of lower urinary tract infections, in either the community or hospital setting. Clearly, ongoing surveillance will be critical in monitoring future trends in the spread of NDM. It may be the case however, that surveillance will need to be expanded from monitoring infection and colonization in humans to encompass animals, as a recent report has documented isolation of NDM-positive *Escherichia coli* from companion animals in the USA (Shaheen *et al.*, 2012).

Concluding remarks

It is now evident that globalization plays a major role in the rapid dissemination of antibiotic resistance (van der Bij & Pitout, 2012), with the spread of NDM providing just one example of how antibiotic resistance can rapidly disseminate internationally. The increasing recognition of the global extent of the problem posed by resistant pathogens has been reflected in a number of reports from bodies such as the World Health Organization (WHO, 2012) and the European Centre for Disease Prevention and Control (ECDC, 2009) and also by international initiatives such as the formation of a Transatlantic Taskforce on Antimicrobial Resistance between the USA and the European Union (TATFAR, 2012). The problem is all the more pressing, particularly for resistance in Gram-negative bacteria, due to the paucity of new antibiotics in the development pipeline (Livermore, 2011; Wise *et al.*, 2011). As the clinical and public health threat posed by antibiotic resistance clearly now has an international dimension, activities to monitor and control the problem need to be international in scope. Although surveillance activities such as the pan-European surveillance of antimicrobial resistance undertaken by the European Antimicrobial Resistance Surveillance Network are already yielding valuable insight into the epidemiology of resistance in a range of pathogens (ECDC, 2010), routine surveillance and an ability to undertake reliable susceptibility testing are still lacking in many parts of the world, particularly those resource-poor regions which have inadequate infrastructure due to poverty and other factors such as political unrest. Overcoming these difficulties poses a major challenge, and there can be no escaping the fact that international cooperation will be critical in attempts to control the global threat to public health posed by antibiotic resistance.

References

Arpin, C., Noury, P., Boraud, D., Coulange, L., Manetti, A., André, C., M'Zali, F. & Quentin, C. (2012). NDM-1-producing *Klebsiella pneumoniae* resistant to colistin in a French community patient without history of foreign travel. *Antimicrob Agents Chemother* **56**, 3432–3434.

Bharadwaj, R., Joshi, S., Dohe, V., Gaikwad, V., Kulkarni, G. & Shouche, Y. (2012). Prevalence of New Delhi metallo-β-lactamase (NDM-1)-positive bacteria in a tertiary care centre in Pune, India. *Int J Antimicrob Agents* **39**, 265–266.

Birgy, A., Doit, C., Mariani-Kurkdjian, P., Genel, N., Faye, A., Arlet, G. & Bingen, E. (2011). Early detection of colonization by VIM-1-producing *Klebsiella pneumoniae* and NDM-1-producing *Escherichia coli* in two children returning to France. *J Clin Microbiol* **49**, 3085–3087.

Bogaerts, P., Verroken, A., Jans, B., Denis, O. & Glupczynski, Y. (2010). Global spread of New Delhi metallo-β-lactamase 1. *Lancet Infect Dis* **10**, 831–832.

Bogaerts, P., Rezende de Castro, R., Roisin, S., Deplano, A., Huang, T. D., Hallin, M., Denis, O. & Glupczynski, Y. (2012). Emergence of NDM-1-producing *Acinetobacter baumannii* in Belgium. *J Antimicrob Chemother* **67**, 1552–1553.

Bonnin, R. A., Poirel, L., Carattoli, A. & Nordmann, P. (2012a). Characterization of an IncFII plasmid encoding NDM-1 from *Escherichia coli* ST131. *PLoS ONE* **7**, e34752.

Bonnin, R. A., Poirel, L., Naas, T., Pirs, M., Seme, K., Schrenzel, J. & Nordmann, P. (2012b). Dissemination of New Delhi metallo-β-lactamase-1-producing *Acinetobacter baumannii* in Europe. *Clin Microbiol Infect* **18**, E362–E365.

Borgia, S., Lastovetska, O., Richardson, D., Eshaghi, A., Xiong, J., Chung, C., Baqi, M., McGeer, A., Ricci, G. & other authors (2012). Outbreak of carbapenem-resistant *Enterobacteriaceae* containing blaNDM-1, Ontario, Canada. *Clin Infect Dis* **55**, e109–e117.

Boulanger, A., Naas, T., Fortineau, N., Figueiredo, S. & Nordmann, P. (2012). NDM-1-producing *Acinetobacter baumannii* from Algeria. *Antimicrob Agents Chemother* **56**, 2214–2215.

Brink, A. J., Coetzee, J., Clay, C. G., Sithole, S., Richards, G. A., Poirel, L. & Nordmann, P. (2012). Emergence of New Delhi metallo-beta-lactamase (NDM-1) and *Klebsiella pneumoniae* carbapenemase (KPC-2) in South Africa. *J Clin Microbiol* **50**, 525–527.

Cabanes, F., Lemant, J., Picot, S., Simac, C., Cousty, J., Jalin, L., Naze, F., Boisson, V., Cresta, M. P. & other authors (2012). Emergence of *Klebsiella pneumoniae* and *Salmonella* metallo-beta-lactamase (NDM-1) producers on Reunion Island. *J Clin Microbiol* **50**, 3812.

Castanheira, M., Deshpande, L. M., Mathai, D., Bell, J. M., Jones, R. N. & Mendes, R. E. (2011). Early dissemination of NDM-1- and OXA-181-producing *Enterobacteriaceae* in Indian hospitals: report from the

SENTRY Antimicrobial Surveillance Program, 2006–2007. *Antimicrob Agents Chemother* **55**, 1274–1278.

CDC (2010). Detection of *Enterobacteriaceae* isolates carrying metallo-beta-lactamase - United States, 2010. *MMWR Morb Mortal Wkly Rep* **59**, 750.

Chan, H. L., Poon, L. M., Chan, S. G. & Teo, J. W. (2011). The perils of medical tourism: NDM-1-positive *Escherichia coli* causing febrile neutropenia in a medical tourist. *Singapore Med J* **52**, 299–302.

Chen, Y., Zhou, Z., Jiang, Y. & Yu, Y. (2011). Emergence of NDM-1-producing *Acinetobacter baumannii in* China. *J Antimicrob Chemother* **66**, 1255–1259.

Chihara, S., Okuzumi, K., Yamamoto, Y., Oikawa, S. & Hishinuma, A. (2011). First case of New Delhi metallo-β-lactamase 1-producing *Escherichia coli* infection in Japan. *Clin Infect Dis* **52**, 153–154.

Chu, Y. W., Tung, V. W., Cheung, T. K., Chu, M. Y., Cheng, N., Lai, C., Tsang, D. N. & Lo, J. Y. (2011). Carbapenemases in enterobacteria, Hong Kong, China, 2009. *Emerg Infect Dis* **17**, 130–132.

D'Andrea, M. M., Venturelli, C., Giani, T., Arena, F., Conte, V., Bresciani, P., Rumpianesi, F., Pantosti, A., Narni, F. & Rossolini, G. M. (2011). Persistent carriage and infection by multidrug-resistant *Escherichia coli* ST405 producing NDM-1 carbapenemase: report on the first Italian cases. *J Clin Microbiol* **49**, 2755–2758.

Denis, C., Poirel, L., Carricajo, A., Grattard, F., Fascia, P., Verhoeven, P., Gay, P., Nuti, C., Nordmann, P. & other authors (2012). Nosocomial transmission of NDM-1-producing *Escherichia coli* within a non-endemic area in France. *Clin Microbiol Infect* **18**, E128–E130.

Deshpande, P., Vadwai, V., Shetty, A., Dalal, R., Soman, R. & Rodrigues, C. (2012). No NDM-1 carriage in healthy persons from Mumbai: reassuring for now. *J Antimicrob Chemother* **67**, 1046–1047.

Dortet, L., Nordmann, P. & Poirel, L. (2012a). Association of the emerging carbapenemase NDM-1 with a bleomycin resistance protein in *Enterobacteriaceae* and *Acinetobacter baumannii. Antimicrob Agents Chemother* **56**, 1693–1697.

Dortet, L., Poirel, L., Al Yaqoubi, F. & Nordmann, P. (2012b). NDM-1, OXA-48 and OXA-181 carbapenemase-producing *Enterobacteriaceae* in Sultanate of Oman. *Clin Microbiol Infect* **18**, E144–E148.

Dortet, L., Poirel, L., Anguel, N. & Nordmann, P. (2012c). New Delhi metallo-β-lactamase 4-producing *Escherichia coli* in Cameroon. *Emerg Infect Dis* **18**, 1540–1542.

ECDC (2009). *The bacterial challenge: time to react.* Stockholm: European Centre for Disease Prevention and Control.

ECDC (2010). EARSS Annual Reports.

El-Herte, R. I., Araj, G. F., Matar, G. M., Baroud, M., Kanafani, Z. A. & Kanj, S. S. (2012). Detection of carbapenem-resistant *Escherichia coli* and *Klebsiella pneumoniae* producing NDM-1 in Lebanon. *J Infect Dev Ctries* **6**, 457–461.

Espinal, P., Fugazza, G., López, Y., Kasma, M., Lerman, Y., Malhotra-Kumar, S., Goossens, H., Carmeli, Y. & Vila, J. (2011). Dissemination of an NDM-2-producing *Acinetobacter baumannii* clone in an Israeli rehabilitation center. *Antimicrob Agents Chemother* **55**, 5396–5398.

Flateau, C., Janvier, F., Delacour, H., Males, S., Ficko, C., Andriamanantena, D., Jeannot, K., Merens, A. & Rapp, C. (2012). Recurrent pyelonephritis due to NDM-1 metallo-beta-lactamase producing *Pseudomonas aeruginosa* in a patient returning from Serbia, France, 2012. *Euro Surveill* **17**, 17.

Fu, Y., Du, X., Ji, J., Chen, Y., Jiang, Y. & Yu, Y. (2012). Epidemiological characteristics and genetic structure of blaNDM-1 in non-*baumannii Acinetobacter* spp. in China. *J Antimicrob Chemother* **67**, 2114–2122.

Gaibani, P., Ambretti, S., Berlingeri, A., Cordovana, M., Farruggia, P., Panico, M., Landini, M. P. & Sambri, V. (2011). Outbreak of NDM-1-producing *Enterobacteriaceae* in northern Italy, July to August 2011. *Euro Surveill* **16**, 20027.

Ghazawi, A., Sonnevend, A., Bonnin, R. A., Poirel, L., Nordmann, P., Hashmey, R., Rizvi, T. A., B Hamadeh, M. & Pál, T. (2012). NDM-2 carbapenemase-producing *Acinetobacter baumannii* in the United Arab Emirates. *Clin Microbiol Infect* **18**, E34–E36.

Göttig, S., Pfeifer, Y., Wichelhaus, T. A., Zacharowski, K., Bingold, T., Averhoff, B., Brandt, C. & Kempf, V. A. (2010). Global spread of New Delhi metallo-β-lactamase 1. *Lancet Infect Dis* **10**, 828–829.

Halaby, T., Reuland, A. E., Al Naiemi, N., Potron, A., Savelkoul, P. H., Vandenbroucke-Grauls, C. M. & Nordmann, P. (2012). A case of New Delhi metallo-β-lactamase 1 (NDM-1)-producing *Klebsiella pneumoniae* with putative secondary transmission from the Balkan region in the Netherlands. *Antimicrob Agents Chemother* **56**, 2790–2791.

Hammerum, A. M., Toleman, M. A., Hansen, F., Kristensen, B., Lester, C. H., Walsh, T. R. & Fuursted, K. (2010). Global spread of New Delhi metallo-β-lactamase 1. *Lancet Infect Dis* **10**, 829–830.

Hammerum, A. M., Larsen, A. R., Hansen, F., Justesen, U. S., Friis-Møller, A., Lemming, L. E., Fuursted, K., Littauer, P., Schønning, K. & other authors (2012). Patients transferred from Libya to Denmark carried OXA-48-producing *Klebsiella pneumoniae*, NDM-1-producing *Acinetobacter baumannii* and meticillin-resistant *Staphylococcus aureus. Int J Antimicrob Agents* **40**, 191–192.

Ho, P. L., Lo, W. U., Yeung, M. K., Lin, C. H., Chow, K. H., Ang, I., Tong, A. H., Bao, J. Y., Lok, S. & Lo, J. Y. (2011). Complete sequencing of pNDM-HK encoding NDM-1 carbapenemase from a multidrug-resistant *Escherichia coli* strain isolated in Hong Kong. *PLoS ONE* **6**, e17989.

Ho, P. L., Li, Z., Lai, E. L., Chiu, S. S. & Cheng, V. C. (2012). Emergence of NDM-1-producing *Enterobacteriaceae* in China. *J Antimicrob Chemother* **67**, 1553–1555.

Hornsey, M., Phee, L. & Wareham, D. W. (2011). A novel variant, NDM-5, of the New Delhi metallo-β-lactamase in a multidrug-resistant *Escherichia coli* ST648 isolate recovered from a patient in the United Kingdom. *Antimicrob Agents Chemother* **55**, 5952–5954.

Hrabák, J., Stolbová, M., Studentová, V., Fridrichová, M., Chudáčková, E. & Zemlickova, H. (2012). NDM-1 producing *Acinetobacter baumannii* isolated from a patient repatriated to the Czech Republic from Egypt, July 2011. *Euro Surveill* **17**, 17.

Islam, M. A., Talukdar, P. K., Hoque, A., Huq, M., Nabi, A., Ahmed, D., Talukder, K. A., Pietroni, M. A., Hays, J. P. & other authors (2012). Emergence of multidrug-resistant NDM-1-producing Gram-negative bacteria in Bangladesh. *Eur J Clin Microbiol Infect Dis* **31**, 2593–2600.

Isozumi, R., Yoshimatsu, K., Yamashiro, T., Hasebe, F., Nguyen, B. M., Ngo, T. C., Yasuda, S. P., Koma, T., Shimizu, K. & Arikawa, J. (2012). $bla_{\text{NDM-1}}$-positive *Klebsiella pneumoniae* from environment, Vietnam. *Emerg Infect Dis* **18**, 1383–1385.

Ivanovski, N., Masin, J., Rambabova-Busljetic, I., Pusevski, V., Dohcev, S., Ivanovski, O. & Popov, Z. (2011). The outcome of commercial kidney transplant tourism in Pakistan. *Clin Transplant* **25**, 171–173.

Jamal, W., Rotimi, V. O., Albert, M. J., Khodakhast, F., Udo, E. E. & Poirel, L. (2012). Emergence of nosocomial New Delhi metallo-β-lactamase-1 (NDM-1)-producing *Klebsiella pneumoniae* in patients admitted to a tertiary care hospital in Kuwait. *Int J Antimicrob Agents* **39**, 183–184.

Johnson, A. P. (2011). Methicillin-resistant *Staphylococcus aureus*: the European landscape. *J Antimicrob Chemother* **66** (Suppl. 4), iv43–iv48.

Jovcic, B., Lepsanovic, Z., Suljagic, V., Rackov, G., Begovic, J., Topisirovic, L. & Kojic, M. (2011). Emergence of NDM-1 metallo-β-lactamase in *Pseudomonas aeruginosa* clinical isolates from Serbia. *Antimicrob Agents Chemother* **55**, 3929–3931.

Kaase, M., Nordmann, P., Wichelhaus, T. A., Gatermann, S. G., Bonnin, R. A. & Poirel, L. (2011). NDM-2 carbapenemase in *Acinetobacter baumannii* from Egypt. *J Antimicrob Chemother* **66**, 1260–1262.

Karthikeyan, K., Thirunarayan, M. A. & Krishnan, P. (2010). Coexistence of $bla_{\text{OXA-23}}$ with $bla_{\text{NDM-1}}$ and *armA* in clinical isolates of *Acinetobacter baumannii* from India. *J Antimicrob Chemother* **65**, 2253–2254.

Kim, M. N., Yong, D., An, D., Chung, H. S., Woo, J. H., Lee, K. & Chong, Y. (2012). Nosocomial clustering of NDM-1-producing *Klebsiella pneumoniae* sequence type 340 strains in four patients at a South Korean tertiary care hospital. *J Clin Microbiol* **50**, 1433–1436.

Koh, T. H., Khoo, C. T., Wijaya, L., Leong, H. N., Lo, Y. L., Lim, L. C. & Koh, T. Y. (2010). Global spread of New Delhi metallo-β-lactamase 1. *Lancet Infect Dis* **10**, 828.

Kumarasamy, K. & Kalyanasundaram, A. (2012). Emergence of *Klebsiella pneumoniae* isolate co-producing NDM-1 with KPC-2 from India. *J Antimicrob Chemother* **67**, 243–244.

Kumarasamy, K. K., Toleman, M. A., Walsh, T. R., Bagaria, J., Butt, F., Balakrishnan, R., Chaudhary, U., Doumith, M., Giske, C. G. & other authors (2010). Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis* **10**, 597–602.

Kus, J. V., Tadros, M., Simor, A., Low, D. E., McGeer, A. J., Willey, B. M., Larocque, C., Pike, K., Edwards, I. A. & other authors (2011). New Delhi metallo-β-lactamase-1: local acquisition in Ontario, Canada, and challenges in detection. *CMAJ* **183**, 1257–1261.

Lai, C. C., Lin, T. L., Tseng, S. P., Huang, Y. T., Wang, J. T., Chang, S. C., Teng, L. J., Wang, J. T. & Hsueh, P. R. (2011). Pelvic abscess caused by New Delhi metallo-β-lactamase-1-producing *Klebsiella oxytoca* in Taiwan in a patient who underwent renal transplantation in China. *Diagn Microbiol Infect Dis* **71**, 474–475.

Lascols, C., Hackel, M., Marshall, S. H., Hujer, A. M., Bouchillon, S., Badal, R., Hoban, D. & Bonomo, R. A. (2011). Increasing prevalence and dissemination of NDM-1 metallo-β-lactamase in India: data from the SMART study (2009). *J Antimicrob Chemother* **66**, 1992–1997.

Leverstein-Van Hall, M. A., Stuart, J. C., Voets, G. M., Versteeg, D., Tersmette, T. & Fluit, A. C. (2010). Global spread of New Delhi metallo-β-lactamase 1. *Lancet Infect Dis* **10**, 830–831.

Livermore, D. M. (2011). Discovery research: the scientific challenge of finding new antibiotics. *J Antimicrob Chemother* **66**, 1941–1944.

Livermore, D. M., Walsh, T. R., Toleman, M. & Woodford, N. (2011). Balkan NDM-1: escape or transplant? *Lancet Infect Dis* **11**, 164.

Mazzariol, A., Bošnjak, Z., Ballarini, P., Budimir, A., Bedenić, B., Kalenić, S. & Cornaglia, G. (2012). NDM-1-producing *Klebsiella pneumoniae*, Croatia. *Emerg Infect Dis* **18**, 532–534.

McDermott, H., Morris, D., McArdle, E., O'Mahony, G., Kelly, S., Cormican, M. & Cunney, R. (2012). Isolation of NDM-1-producing *Klebsiella pnemoniae* in Ireland, July 2011. *Euro Surveill* **17**, 17.

McGann, P., Hang, J., Clifford, R. J., Yang, Y., Kwak, Y. I., Kuschner, R. A., Lesho, E. P. & Waterman, P. E. (2012). Complete sequence of a novel 178-kilobase plasmid carrying $bla_{\text{NDM-1}}$ in a *Providencia stuartii* strain isolated in Afghanistan. *Antimicrob Agents Chemother* **56**, 1673–1679.

Mochon, A. B., Garner, O. B., Hindler, J. A., Krogstad, P., Ward, K. W., Lewinski, M. A., Rasheed, J. K., Anderson, K. F., Limbago, B. M. & Humphries, R. M. (2011). New Delhi metallo-β-lactamase (NDM-1)-producing *Klebsiella pneumoniae*: case report and laboratory detection strategies. *J Clin Microbiol* **49**, 1667–1670.

Muir, A. & Weinbren, M. J. (2010). New Delhi metallo-β-lactamase: a cautionary tale. *J Hosp Infect* **75**, 239–240.

Mulvey, M. R., Grant, J. M., Plewes, K., Roscoe, D. & Boyd, D. A. (2011). New Delhi metallo-β-lactamase in *Klebsiella pneumoniae* and *Escherichia coli*, Canada. *Emerg Infect Dis* **17**, 103–106.

Muñoz, R., Coffey, T. J., Daniels, M., Dowson, C. G., Laible, G., Casal, J., Hakenbeck, R., Jacobs, M., Musser, J. M. & other authors (1991). Intercontinental spread of a multiresistant clone of serotype 23F *Streptococcus pneumoniae*. *J Infect Dis* **164**, 302–306.

Mushtaq, S., Irfan, S., Sarma, J. B., Doumith, M., Pike, R., Pitout, J., Livermore, D. M. & Woodford, N. (2011). Phylogenetic diversity of *Escherichia coli* strains producing NDM-type carbapenemases. *J Antimicrob Chemother* **66**, 2002–2005.

Nielsen, J. B., Hansen, F., Littauer, P., Schønning, K. & Hammerum, A. M. (2012). An NDM-1-producing *Escherichia coli* obtained in Denmark has a genetic profile similar to an NDM-1-producing *Escherichia coli* isolate from the UK. *J Antimicrob Chemother* **67**, 2049–2051.

Nordmann, P., Poirel, L., Walsh, T. R. & Livermore, D. M. (2011). The emerging NDM carbapenemases. *Trends Microbiol* **19**, 588–595.

Nordmann, P., Boulanger, A. E. & Poirel, L. (2012a). NDM-4 metallo-β-lactamase with increased carbapenemase activity from *Escherichia coli*. *Antimicrob Agents Chemother* **56**, 2184–2186.

Nordmann, P., Dortet, L. & Poirel, L. (2012b). Carbapenem resistance in *Enterobacteriaceae*: here is the storm! *Trends Mol Med* **18**, 263–272.

Österblad, M., Kirveskari, J., Hakanen, A. J., Tissari, P., Vaara, M. & Jalava, J. (2012). Carbapenemase-producing *Enterobacteriaceae* in Finland: the first years (2008–11). *J Antimicrob Chemother* **67**, 2860–2864.

Oteo, J., Domingo-García, D., Fernández-Romero, S., Saez, D., Guiu, A., Cuevas, O., Lopez-Brea, M. & Campos, J. (2012). Abdominal abscess due to NDM-1-producing *Klebsiella pneumoniae* in Spain. *J Med Microbiol* **61**, 864–867.

Palmer, R. (2010). A disease – or gene – by any other name would cause a stink. *Nat Med* **16**, 1059.

Pasteran, F., Albornoz, E., Faccone, D., Gomez, S., Valenzuela, C., Morales, M., Estrada, P., Valenzuela, L., Matheu, J. & other authors (2012). Emergence of NDM-1-producing *Klebsiella pneumoniae* in Guatemala. *J Antimicrob Chemother* **67**, 1795–1797.

Peirano, G., Ahmed-Bentley, J., Woodford, N. & Pitout, J. D. (2011a). New Delhi metallo-β-lactamase from traveler returning to Canada. *Emerg Infect Dis* **17**, 242–244.

Peirano, G., Pillai, D. R., Pitondo-Silva, A., Richardson, D. & Pitout, J. D. (2011b). The characteristics of NDM-producing *Klebsiella pneumoniae* from Canada. *Diagn Microbiol Infect Dis* **71**, 106–109.

Perry, J. D., Naqvi, S. H., Mirza, I. A., Alizai, S. A., Hussain, A., Ghirardi, S., Orenga, S., Wilkinson, K., Woodford, N. & other authors (2011). Prevalence of faecal carriage of *Enterobacteriaceae* with NDM-1 carbapenemase at military hospitals in Pakistan, and evaluation of two chromogenic media. *J Antimicrob Chemother* **66**, 2288–2294.

Pfeifer, Y., Wilharm, G., Zander, E., Wichelhaus, T. A., Göttig, S., Hunfeld, K. P., Seifert, H., Witte, W. & Higgins, P. G. (2011a). Molecular characterization of $bla_{\text{NDM-1}}$ in an *Acinetobacter baumannii* strain isolated in Germany in 2007. *J Antimicrob Chemother* **66**, 1998–2001.

Pfeifer, Y., Witte, W., Holfelder, M., Busch, J., Nordmann, P. & Poirel, L. (2011b). NDM-1-producing *Escherichia coli* in Germany. *Antimicrob Agents Chemother* **55**, 1318–1319.

Poirel, L., Hombrouck-Alet, C., Freneaux, C., Bernabeu, S. & Nordmann, P. (2010a). Global spread of New Delhi metallo-β-lactamase 1. *Lancet Infect Dis* **10**, 832.

Poirel, L., Lagrutta, E., Taylor, P., Pham, J. & Nordmann, P. (2010b). Emergence of metallo-β-lactamase NDM-1-producing multidrug-

resistant *Escherichia coli* in Australia. *Antimicrob Agents Chemother* **54**, 4914–4916.

Poirel, L., Al Maskari, Z., Al Rashdi, F., Bernabeu, S. & Nordmann, P. (2011a). NDM-1-producing *Klebsiella pneumoniae* isolated in the Sultanate of Oman. *J Antimicrob Chemother* **66**, 304–306.

Poirel, L., Benouda, A., Hays, C. & Nordmann, P. (2011b). Emergence of NDM-1-producing *Klebsiella pneumoniae* in Morocco. *J Antimicrob Chemother* **66**, 2781–2783.

Poirel, L., Dortet, L., Bernabeu, S. & Nordmann, P. (2011c). Genetic features of bla_{NDM-1}-positive *Enterobacteriaceae*. *Antimicrob Agents Chemother* **55**, 5403–5407.

Poirel, L., Fortineau, N. & Nordmann, P. (2011d). International transfer of NDM-1-producing *Klebsiella pneumoniae* from Iraq to France. *Antimicrob Agents Chemother* **55**, 1821–1822.

Poirel, L., Hervé, V., Hombrouck-Alet, C. & Nordmann, P. (2011e). Long-term carriage of NDM-1-producing *Escherichia coli*. *J Antimicrob Chemother* **66**, 2185–2186.

Poirel, L., Revathi, G., Bernabeu, S. & Nordmann, P. (2011f). Detection of NDM-1-producing *Klebsiella pneumoniae* in Kenya. *Antimicrob Agents Chemother* **55**, 934–936.

Poirel, L., Ros, A., Carricajo, A., Berthelot, P., Pozzetto, B., Bernabeu, S. & Nordmann, P. (2011g). Extremely drug-resistant *Citrobacter freundii* isolate producing NDM-1 and other carbapenemases identified in a patient returning from India. *Antimicrob Agents Chemother* **55**, 447–448.

Poirel, L., Schrenzel, J., Cherkaoui, A., Bernabeu, S., Renzi, G. & Nordmann, P. (2011h). Molecular analysis of NDM-1-producing enterobacterial isolates from Geneva, Switzerland. *J Antimicrob Chemother* **66**, 1730–1733.

Poirel, L., Bonnin, R. A., Boulanger, A., Schrenzel, J., Kaase, M. & Nordmann, P. (2012a). Tn125-related acquisition of blaNDM-like genes in *Acinetobacter baumannii*. *Antimicrob Agents Chemother* **56**, 1087–1089.

Poirel, L., Lascols, C., Bernabeu, S. & Nordmann, P. (2012b). NDM-1-producing *Klebsiella pneumoniae* in Mauritius. *Antimicrob Agents Chemother* **56**, 598–599.

Poirel, L., Ozdamar, M., Ocampo-Sosa, A. A., Türkoglu, S., Ozer, U. G. & Nordmann, P. (2012c). NDM-1-producing *Klebsiella pneumoniae* now in Turkey. *Antimicrob Agents Chemother* **56**, 2784–2785.

Rimrang, B., Chanawong, A., Lulitanond, A., Wilailuckana, C., Charoensri, N., Sribenjalux, P., Phumsrikaew, W., Wonglakorn, L., Kerdsin, A. & Chetchotisakd, P. (2012). Emergence of NDM-1- and IMP-14a-producing *Enterobacteriaceae* in Thailand. *J Antimicrob Chemother* **67**, 2626–2630.

Rogers, B. A., Sidjabat, H. E. & Paterson, D. L. (2011). *Escherichia coli* O25b-ST131: a pandemic, multiresistant, community-associated strain. *J Antimicrob Chemother* **66**, 1–14.

Roy, S., Singh, A. K., Viswanathan, R., Nandy, R. K. & Basu, S. (2011a). Transmission of imipenem resistance determinants during the course of an outbreak of NDM-1 *Escherichia coli* in a sick newborn care unit. *J Antimicrob Chemother* **66**, 2773–2780.

Roy, S., Viswanathan, R., Singh, A. K., Das, P. & Basu, S. (2011b). Sepsis in neonates due to imipenem-resistant *Klebsiella pneumoniae* producing NDM-1 in India. *J Antimicrob Chemother* **66**, 1411–1413.

Samuelsen, O., Thilesen, C. M., Heggelund, L., Vada, A. N., Kümmel, A. & Sundsfjord, A. (2011). Identification of NDM-1-producing *Enterobacteriaceae* in Norway. *J Antimicrob Chemother* **66**, 670–672.

Savard, P., Gopinath, R., Zhu, W., Kitchel, B., Rasheed, J. K., Tekle, T., Roberts, A., Ross, T., Razeq, J. & other authors (2011). First NDM-positive *Salmonella* sp. strain identified in the United States. *Antimicrob Agents Chemother* **55**, 5957–5958.

Seema, K., Ranjan Sen, M., Upadhyay, S. & Bhattacharjee, A. (2011). Dissemination of the New Delhi metallo-β-lactamase-1 (NDM-1) among *Enterobacteriaceae* in a tertiary referral hospital in north India. *J Antimicrob Chemother* **66**, 1646–1647.

Sekizuka, T., Matsui, M., Yamane, K., Takeuchi, F., Ohnishi, M., Hishinuma, A., Arakawa, Y. & Kuroda, M. (2011). Complete sequencing of the bla_{NDM-1}-positive IncA/C plasmid from *Escherichia coli* ST38 isolate suggests a possible origin from plant pathogens. *PLoS ONE* **6**, e25334.

Shaheen, B. W., Nayak, N. & Boothe, M. (2012). First reported case of New Delhi metallo (NDM) carbapenem-positive gene in *Escherichia coli* from companion animals in the United States. In *Abstracts of the 52nd ICAAC*, abstract C2–1219. San Francisco, CA: American Society for Microbiology.

Sidjabat, H., Nimmo, G. R., Walsh, T. R., Binotto, E., Htin, A., Hayashi, Y., Li, J., Nation, R. L., George, N. & Paterson, D. L. (2011). Carbapenem resistance in *Klebsiella pneumoniae* due to the New Delhi Metallo-β-lactamase. *Clin Infect Dis* **52**, 481–484.

Solé, M., Pitart, C., Roca, I., Fàbrega, A., Salvador, P., Muñoz, L., Oliveira, I., Gascón, J., Marco, F. & Vila, J. (2011). First description of an *Escherichia coli* strain producing NDM-1 carbapenemase in Spain. *Antimicrob Agents Chemother* **55**, 4402–4404.

Stefani, S., Chung, D. R., Lindsay, J. A., Friedrich, A. W., Kearns, A. M., Westh, H. & Mackenzie, F. M. (2012). Meticillin-resistant *Staphylococcus aureus* (MRSA): global epidemiology and harmonisation of typing methods. *Int J Antimicrob Agents* **39**, 273–282.

Struelens, M. J., Monnet, D. L., Magiorakos, A. P., Santos O'Connor, F., Giesecke, J. & European NDM-1 Survey Participants (2010). New Delhi metallo-beta-lactamase 1-producing *Enterobacteriaceae*: emergence and response in Europe. *Euro Surveill* **15**, 15.

Sykes, R. (2010). The 2009 Garrod lecture: the evolution of antimicrobial resistance: a Darwinian perspective. *J Antimicrob Chemother* **65**, 1842–1852.

TATFAR (2012). *Recommendations for future collaboration between the U.S. and EU. Transatlantic Taskforce on Antimicrobial Resistance, 2011.* Stockholm: ECDC.

Tijet, N., Alexander, D. C., Richardson, D., Lastovetska, O., Low, D. E., Patel, S. N. & Melano, R. G. (2011). New Delhi metallo-β-lactamase, Ontario, Canada. *Emerg Infect Dis* **17**, 306–307.

Tsang, K. Y., Luk, S., Lo, J. Y., Tsang, T. Y., Lai, S. T. & Ng, T. K. (2012). Hong Kong experiences the 'ultimate superbug': NDM-1 *Enterobacteriaceae*. *Hong Kong Med J* **18**, 439–441.

van der Bij, A. K. & Pitout, J. D. (2012). The role of international travel in the worldwide spread of multiresistant *Enterobacteriaceae*. *J Antimicrob Chemother* **67**, 2090–2100.

Walsh, T. R. & Toleman, M. A. (2011). The new medical challenge: why NDM-1? Why Indian? *Expert Rev Anti Infect Ther* **9**, 137–141.

Walsh, T. R. & Toleman, M. A. (2012). The emergence of pan-resistant Gram-negative pathogens merits a rapid global political response. *J Antimicrob Chemother* **67**, 1–3.

Walsh, T. R., Weeks, J., Livermore, D. M. & Toleman, M. A. (2011). Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. *Lancet Infect Dis* **11**, 355–362.

Wang, Y., Wu, C., Zhang, Q., Qi, J., Liu, H., Wang, Y., He, T., Ma, L., Lai, J. & other authors (2012). Identification of New Delhi metallo-β-lactamase 1 in *Acinetobacter lwoffii* of food animal origin. *PLoS ONE* **7**, e37152.

WHO (2012). *The Evolving Threat of Antimicrobial Resistance: Options for Action.* Geneva: World Health Organization.

Williamson, D. A., Sidjabat, H. E., Freeman, J. T., Roberts, S. A., Silvey, A., Woodhouse, R., Mowat, E., Dyet, K., Paterson, D. L. &

other authors (2012). Identification and molecular characterisation of New Delhi metallo-β-lactamase-1 (NDM-1)- and NDM-6-producing *Enterobacteriaceae* from New Zealand hospitals. *Int J Antimicrob Agents* **39**, 529–533.

Wise, R., Blaser, M., Carrs, O., Cassell, G., Fishman, N., Guidos, R., Levy, S., Powers, J., Norrby, R. & other authors (2011). The urgent need for new antibacterial agents. *J Antimicrob Chemother* **66**, 1939–1940.

Woodford, N., Turton, J. F. & Livermore, D. M. (2011). Multiresistant Gram-negative bacteria: the role of high-risk clones in the dissemination of antibiotic resistance. *FEMS Microbiol Rev* **35**, 736–755.

Wu, H. S., Chen, T. L., Chen, I. C., Huang, M. S., Wang, F. D., Fung, C. P. & Lee, S. D. (2010). First identification of a patient colonized with Klebsiella pneumoniae carrying $bla_{\text{NDM-1}}$ in Taiwan. *J Chin Med Assoc* **73**, 596–598.

Yang, J., Chen, Y., Jia, X., Luo, Y., Song, Q., Zhao, W., Wang, Y., Liu, H., Zheng, D. & other authors (2012). Dissemination and characterization of NDM-1-producing *Acinetobacter pittii* in an intensive care unit in China. *Clin Microbiol Infect* **18**, E506–E513.

Yong, D., Toleman, M. A., Giske, C. G., Cho, H. S., Sundman, K., Lee, K. & Walsh, T. R. (2009). Characterization of a new metallo-beta-lactamase gene, $bla_{\text{NDM-1}}$, and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence type 14 from India. *Antimicrob Agents Chemother* **53**, 5046–5054.

Zarfel, G., Hoenigl, M., Leitner, E., Salzer, H. J., Feierl, G., Masoud, L., Valentin, T., Krause, R. & Grisold, A. J. (2011a). Emergence of New Delhi metallo-β-lactamase, Austria. *Emerg Infect Dis* **17**, 129–130.

Zarfel, G., Hoenigl, M., Würstl, B., Leitner, E., Salzer, H. J., Valentin, T., Posch, J., Krause, R. & Grisold, A. J. (2011b). Emergence of carbapenem-resistant *Enterobacteriaceae* in Austria, 2001–2010. *Clin Microbiol Infect* **17**, E5–E8.