Dissemination of NDM Metallo- β -Lactamase Genes among Clinical Isolates of *Enterobacteriaceae* Collected during the SMART Global Surveillance Study from 2008 to 2012

D. Biedenbach,^a S. Bouchillon,^a M. Hackel,^a D. Hoban,^a K. Kazmierczak,^a S. Hawser,^b R. Badal^a

International Health Management Associates, Inc., Schaumburg, Illinois, USA^a; IHMA Europe Sàrl, Epalinges, Switzerland^b

The prevalence of carbapenemase enzymes continues to increase. Among the Ambler class B enzymes is the New Delhi metallo- β -lactamase (NDM). This particular enzyme is capable of hydrolyzing nearly all β -lactam antimicrobial agents and has spread rapidly, becoming a global problem. Therapeutic treatment options for patients infected with isolates which produce this enzyme are difficult to manage, as cross-resistance to other antimicrobial classes is common. The Study for Monitoring Antimicrobial Resistance Trends (SMART) is a global surveillance study evaluating the antimicrobial susceptibilities of numerous Gram-negative bacterial species recovered from people with intra-abdominal and urinary tract infections. The Clinical and Laboratory Standards Institute methods and a molecular analysis identified 134 isolates of *Enterobacteriaceae* (nine species) and one *Acinetobacter* sp. with *bla*_{NDM} genes. These isolates were collected in nine countries, and >95% of the isolates possessed the NDM-1 variant. The MIC₉₀ values were >4 mg/liter and >8 mg/liter for ertapenem and imipenem, respectively. No tested β -lactam or β -lactamase inhibitor combination had activity against these isolates. Resistance to amikacin (79.9%) and levofloxacin (82.8%) was common. Nearly all the isolates encoded additional enzymes, including AmpC cephalosporinases and extended-spectrum β -lactamases. There is an urgent need for infection control and continued global monitoring of isolates which harbor the NDM enzyme, as evidenced by recent outbreaks.

New Delhi metallo- β -lactamase (NDM)-positive *Enterobacteriaceae* were initially identified among patients hospitalized in India. These isolates have now spread to numerous countries worldwide and have been isolated from both the community and inpatient populations as well as from the environment (1–6). Twelve NDM enzyme variants have been identified in numerous species of *Enterobacteriaceae* and common nonfermentative Gram-negative bacilli (7, 8). Carbapenemase-producing *Enterobacteriaceae* are resistant to β -lactams and are commonly coresistant to aminoglycosides, tetracycline derivatives, fluoroquinolones, and other commonly prescribed antimicrobial agents. Infections caused by carbapenemase-producing *Enterobacteriaceae*, including isolates encoding NDM enzymes, have limited treatment options. A recently reported outbreak of carbapenemase-producing *Enterobacteriaceae* in Illinois by the U.S. Centers for Disease Control and Prevention (CDC) underpins the need for continued tracking and surveillance of these multidrug-resistant (MDR) pathogens (9). This outbreak of carbapenemase-producing *Enterobacteriaceae* contributed the majority of the NDM-positive isolates documented in the United States in 2013. Contamination of the endoscopic equipment used in most of these hospitalized patients emphasizes the importance of infection control in minimizing the transmission of MDR bacteria (9, 10). This outbreak also demonstrated that an infectious process may not be diagnosed among all patients, as many were colonized without an infectious progression.

NDM enzymes are commonly found on mobile genetic elements, are easily transmissible among Gram-negative pathogens, and are endemic in some countries (1, 2, 5). Institutional endemics associated with NDM enzymes present a similar problem, as documented by the recent CDC report (9). Physicians who treat infections caused by species that carry these resistance genes must be aware of the limited therapeutic options that are currently

available as the pharmaceutical industry continues to search for commercially viable metallo- β -lactamase (MBL) inhibitors or other stand-alone agents (11).

The Study for Monitoring Antimicrobial Resistance Trends (SMART) has monitored the *in vitro* susceptibility patterns of clinical Gram-negative bacilli collected worldwide from people with intra-abdominal infections (IAI) since 2002 and from those with urinary tract infections (UTI) since late 2009. This study reports the susceptibilities and epidemiologies of 135 molecularly characterized NDM-positive isolates from this global collection from 2008 to 2012.

MATERIALS AND METHODS

Country and patient demographics. From 2008 to 2012, the SMART prospectively collected up to 100 consecutive nonduplicate isolates of aerobic and facultative Gram-negative bacilli from patients with IAI and, starting in 2010, 50 isolates from patients with UTI each year at participating sites worldwide. A total of 8,604 isolates collected globally were molecularly characterized for β -lactamase genes (extended-spectrum β -lactamases [ESBLs], AmpC cephalosporinases, and carbapenemases).

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Address correspondence to D. Biedenbach, dbiedenbach@ihmainc.com.

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TABLE 1 Geographic distribution of isolates producing NDM variants during the SMART (2008 to 2012)

Country of origin	No. of isolates with NDM enzyme variant:				Total
	NDM-1	NDM-4	NDM-5	NDM-6	
India	68 ^a	2		1	71
Vietnam	29	1			30
Serbia	22				22
Philippines	6				6
Saudi Arabia	1		1		2
Egypt	1				1
Georgia	1				1
Guatemala	1				1
United States	1				1
Total	130	3	1	1	135

^a Includes one *A. baumannii* isolate.

Isolates found to carry the *bla*_{NDM} gene were from IAI (89 isolates) and UTI (46 isolates) sources from nine countries. Among the countries that participated in the SMART, NDM-positive isolates were found in India (seven medical centers), in Vietnam (four centers), in Serbia (two centers), and in one center each in Egypt, Guatemala, Georgia, Saudi Arabia, the Philippines, and the United States during this surveillance period. It must be noted that isolates from India were available from only 2008 to 2010.

Identification, susceptibility, and characterization of carbapenemases. Isolates were identified to the species level at each participating site and submitted to the central reference laboratory (International Health Management Associates, Inc., Schaumburg, IL, USA) for identification confirmation and susceptibility testing. Antimicrobial susceptibility testing was performed by the central laboratory following Clinical and Laboratory Standards Institute (CLSI) guidelines (12). Susceptibilities to carbapenems (ertapenem and imipenem) and comparator agents (amikacin, ampicillin-sulbactam, cefepime, cefotaxime, ceftazidime, ceftiofur, ciprofloxacin, levofloxacin, and piperacillin-tazobactam) were determined using CLSI breakpoint criteria (13). Aztreonam, which is active against MBLs, was not tested. Quality control (QC) testing was performed on each day of testing using the CLSI-recommended QC isolates from strains *Escherichia coli* ATCC 25922, *E. coli* ATCC 27853, and *Pseudomonas aeruginosa* ATCC 27853 (13).

Isolates with ertapenem MIC values of ≥ 0.5 $\mu\text{g/ml}$ were screened for genes encoding ESBLs (SHV, TEM, CTX-M), AmpC cephalosporinases (CMY, DHA, FOX, MOX, ACC, MIR, ACT), and carbapenemases (KPC, NDM, IMP, VIM, OXA-48) using a combination of microarray and multiplex PCR assays as described by Hoban et al. (24). Genes encoding ESBLs and carbapenemases were sequenced to determine enzyme variants.

RESULTS

A total of 135 isolates from IAI (89 isolates) and UTI (46 isolates) sources carried genes encoding NDM. Of these isolates, 106 (78.5%) also carried genes that encoded additional ESBL enzymes. Patients with NDM-positive isolates ranged from <1 to 86 years of age, with a median age of 51 years. The majority of these patients were male (68.1%). *bla*_{NDM} was detected in nine species of *Enterobacteriaceae* and in one *Acinetobacter baumannii* isolate. Species of *Enterobacteriaceae* included *Klebsiella pneumoniae* (62 isolates), *E. coli* (44 isolates), *Citrobacter freundii* (4 isolates), *Morganella morganii* (3 isolates), *Enterobacter asburiae* (1 isolate), *Enterobacter cloacae* (15 isolates), *Klebsiella oxytoca* (1 isolate), *Proteus mirabilis* (2 isolates), and *Providencia rettgeri* (2 isolates).

The most common NDM variant identified was NDM-1 (96.3%), as shown in Table 1. Three isolates from two sites in India

and one in Vietnam contained genes encoding NDM-4. One NDM-5 and one NDM-6 variant were detected in Saudi Arabia and India, respectively. Isolates with genes encoding NDM had ertapenem MIC values ranging from 1 mg/liter to >4 mg/liter ($\text{MIC}_{50/90}$, $>4/>4$ mg/liter) and imipenem MIC values ranging from 2 to >8 mg/liter ($\text{MIC}_{50/90}$, $>8/>8$ mg/liter). All of the tested cephalosporins, piperacillin-tazobactam, and ampicillin-sulbactam had highly resistant MIC values against all the isolates (data not shown). Aztreonam, which is stable to MBLs, was not included on the panel. The only tested antimicrobial agents that had any nonresistant MIC values were levofloxacin (12.7% susceptible) and amikacin (16.4% susceptible). Isolates were not screened for genes conferring resistance to levofloxacin or amikacin, and there was no correlation observed between levofloxacin or amikacin susceptibility profiles and geographic distribution. The single NDM-positive *A. baumannii* isolate was collected in India and was highly resistant to all the tested antimicrobial agents with the exception of levofloxacin, which had an intermediate MIC value of 4 $\mu\text{g/ml}$.

Of the 106 NDM-positive *Enterobacteriaceae* isolates that also carried genes encoding ESBLs, 99 (93.4%) carried *bla*_{CTX-M}, 93 (93.9%) of which encoded CTX-M-15. These isolates were from India, Serbia, the Philippines, Saudi Arabia, Guatemala, Vietnam, and Georgia (Table 2). The identifications of CTX-M-15 in India and CTX-M-14 in Vietnam follow the general prevalence of these enzymes in these countries. Vietnam was the only country in this study in which other CTX-M variants were detected (five CTX-M-14 isolates and two CTX-M-27 isolates). Four variants of SHV (SHV-2, SHV-2A, SHV-12, and SHV-28) with ESBL activity were detected in India (seven isolates), Vietnam (three isolates), Serbia (three isolates), and Guatemala (one isolate). One isolate from Serbia encoded TEM-15. Most of the isolates encoding ESBLs did not encode carbapenemases other than NDM, with the exception of one isolate from Serbia which carried VIM-1 and two isolates from the same center in India that carried OXA-181 (a variant of OXA-48). Among the 106 NDM-positive *Enterobacteriaceae* producing ESBLs, 13.2% were susceptible to amikacin and levofloxacin.

Isolates encoding either NDM alone or NDM with various AmpC enzymes were observed in six countries (Table 2). A gene encoding a CMY-type cephalosporinase was detected in half of these isolates. The susceptibilities of this collection of isolates to amikacin and levofloxacin were 28.6% and 10.7%, respectively.

DISCUSSION

The increasing prevalence of carbapenemase-producing *Enterobacteriaceae* is a significant public health concern. NDM enzymes, like other carbapenemases, will be difficult to control, and further importation and dissemination are inevitable (1, 14). NDM enzymes are already found among multiple species and in numerous countries worldwide (15–20). Speculation that *Acinetobacter pittii* may be an NDM reservoir for dissemination to enteric species has been the focus of several investigations, but it still requires definitive confirmation (21). It has also been documented that rivers, lakes, and drainage water might provide potential spread from the environment into the community (3). These studies emphasize that NDM spread is a multifactorial problem that continues to evolve (6).

A specific example of such dissemination has been documented between India and Vietnam, which have strong economic

TABLE 2 Distribution of 106 NDM-positive *Enterobacteriaceae* isolates that also encode ESBL enzymes and additional β -lactamases from nine countries^a

Enzyme(s) by organism	No. of isolates with the indicated enzyme(s) and collected from:									Total no.
	Egypt	Georgia	Guatemala	India	Philippines	Saudi Arabia	Serbia	United States	Vietnam	
<i>Acinetobacter baumannii</i>				1						1
NDM-1, OXA-23				1						1
<i>Citrobacter freundii</i>				1			2		1	4
CMY-2, NDM-1							1		1	2
CTX-M-15, CMY-2, NDM-1							1			1
SHV-12, NDM-1				1						1
<i>Enterobacter asburiae</i>				1						1
CTX-M-15, ACT, NDM-1				1						1
<i>Enterobacter cloacae</i>			1	5			2		7	15
CTX-M-14, NDM-1									1	1
CTX-M-15, ACT, NDM-1				1						1
CTX-M-15, ACT, NDM-1, OXA-181				2						2
CTX-M-15, CMY-2, NDM-1				1						1
CTX-M-15, CTX-M-14, ACT, NDM-1									1	1
CTX-M-15, NDM-1				1			1		1	3
NDM-1							1		2	3
SHV-12, CTX-M-14, NDM-1									1	1
SHV-12, CTX-M-15, NDM-1			1							1
SHV-12, NDM-1									1	1
<i>Escherichia coli</i>				30	1	1	1		11	44
CMY II, DHA, NDM-1									1	1
CMY II, NDM-1				1					4	5
CTX-M-15, CMY-2, NDM-1				20					1	21
CTX-M-15, CMY-2, NDM-4				2						2
CTX-M-15, CMY-2, NDM-5						1				1
CTX-M-15, DHA, NDM-1				1	1					2
CTX-M-15, NDM-1				3					2	5
CTX-M-15, NDM-6				1						1
CTX-M-27, CMY-2, NDM-1									1	1
NDM-1				1			1		2	4
SHV-12, CMY-2, NDM-1				1						1
<i>Klebsiella oxytoca</i>				1						1
CTX-M-15, CMY-2, NDM-1				1						1
<i>Klebsiella pneumoniae</i>	1			28	5	1	15	1	11	62
CMY-2, NDM-1				1			2			3
CTX-M-14, ACT, NDM-1									1	1
CTX-M-14, NDM-1									1	1
CTX-M-15, CMY-2, DHA, NDM-1				1					2	3
CTX-M-15, CMY-2, NDM-1				3			3		2	8
CTX-M-15, DHA, NDM-1				3						3
CTX-M-15, NDM-1				13	4	1	6		1	25
CTX-M-15, NDM-4									1	1
CTX-M-27, CMY-2, NDM-1									1	1
DHA, NDM-1				1						1
NDM-1	1			1	1			1	1	5
SHV-12, CMY-2, NDM-1							1			1
SHV-12, CTX-M-15, NDM-1				3			1			4
SHV-2, CMY-2, NDM-1, VIM-1							1			1
SHV-28, NDM-1									1	1
SHV-2A, CTX-M-15, NDM-1				1						1
SHV-2A, DHA, NDM-1				1						1
TEM-15, CTX-M-15, NDM-1							1			1

(Continued on following page)

TABLE 2 (Continued)

Enzyme(s) by organism	No. of isolates with the indicated enzyme(s) and collected from:									Total no.
	Egypt	Georgia	Guatemala	India	Philippines	Saudi Arabia	Serbia	United States	Vietnam	
<i>Morganella morganii</i>				3						3
CTX-M-15, DHA, NDM-1				1						1
CTX-M-15, FOX, NDM-1				1						1
DHA, NDM-1				1						1
<i>Proteus mirabilis</i>							2			2
CMY II, NDM-1							2			2
<i>Providencia rettgeri</i>		1		1						2
CMY II, DHA, NDM-1				1						1
CTX-M-15, CMY II, NDM-1		1								1
Total	1	1	1	71	6	2	22	1	30	135

and cultural links, providing a readily available transmission route (3). Although India and Vietnam provided the largest number of NDM-positive isolates in the current study, and analysis of clonality via typing of isolates was not performed, there were multiple differences in enzyme combinations observed, suggesting that clonal dissemination may have played a minor role. This suggests that a more complex situation is involved when trying to analyze country-to-country and global dissemination information. The outbreak of NDM-positive isolates from patients in Illinois emphasizes that hospitalized patients are at risk of infections caused by MDR pathogens (9). The epidemic NDM scenario in this hospital may be a harbinger of a much larger problem, as this difficult-to-treat enzyme disseminates into the community (1, 3, 4), as has been the case for carbapenemase-producing *Enterobacteriaceae* isolates producing other class B as well as class A and D enzymes (5).

Although the majority of NDM-positive isolates from this surveillance study were from patients hospitalized in India and limited to observations from 2008 to 2010, this resistance mechanism continues to disseminate to other countries, as documented by recent scientific literature and data shown here. The large number of NDM-positive isolates that were collected from Vietnam and Serbia is unusual based on lack of literature from these specific countries and should be explored further. Large global surveillance studies, such as the SMART, are crucial evidence-based models for documenting resistance and prevalence trends among such pathogens in the community and hospital settings (22, 23). Limiting patient infections and surveillance of patients colonized with carbapenemase-producing *Enterobacteriaceae* are of paramount importance to hospital epidemiology and patient safety. While diagnostic susceptibility data should provide advanced information when an MDR carbapenemase-producing *Enterobacteriaceae* isolate is observed, further molecular characterization of such strains may be needed in order to help provide appropriate epidemiological control. Hospitals should have established protocols that protect patients and the surrounding community from this global health threat.

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All of the authors are employees of International Health Management Associates, Inc., or IHMA Europe Sarl, a wholly owned subsidiary of IHMA, Inc.

We declare no conflicts of interest in this investigation.

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