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# Widespread Dissemination of Carbapenem-Resistant *Escherichia coli* Sequence Type 167 Strains Harboring $bla_{NDM-5}$ in Clinical Settings in China

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**This study reports the increasing prevalence of clinical *Escherichia coli* of sequence type 167 (ST167) carrying both $bla_{NDM-1}$ and $bla_{NDM-5}$ on the conjugative IncX3 plasmid in various parts of China. Close surveillance is needed to monitor the future dissemination of ST167 strains that harbor $bla_{NDM-5}$ or other $bla_{NDM}$-like genes.**

The continuous emergence of carbapenem-resistant *Enterobacteriaceae* (CRE) strains in recent years has posed an increasing public health threat worldwide. The dissemination of mobile resistance elements, especially those carrying the New Delhi metallo-β-lactamase gene ($bla_{NDM-1}$), has been regarded as a major mechanism responsible for causing a dramatic increase in the prevalence of CRE in clinical settings. NDM-producing organisms were first reported on the Indian subcontinent and then in several Middle Eastern and Balkan countries in 2009 (1, 2). This gene has since spread to different species of *Enterobacteriaceae* and other Gram-negative bacteria throughout the world (3). The rapid increase in the prevalence of CRE may be due to both transmission of $bla_{NDM-1}$-carrying elements among the *Enterobacteriaceae* species and clonal spread of strains containing such elements (4, 5). Current evidence, however, suggests that the transmission of specific mobile resistance elements in CRE has a strong association with specific types of bacterial strains. For example, the $bla_{NDM-1}$-like genes are predominantly detected in multilocus sequence typing (MLST) sequence type 131 (ST131) and ST101 strains of *Escherichia coli* and ST11 strains of *Klebsiella pneumoniae* (5–8). The underlying mechanisms leading to the clustering of the $bla_{NDM-1}$-like genes in specific STs remain to be investigated.

In China, $bla_{NDM-1}$ was reported in 2011 (9). Since then, the gene has become detectable in most species of *Enterobacteriaceae* in various cities in China, and yet, there is a lack of information on the linkage of specific STs of *E. coli* to $bla_{NDM-1}$ carriage due to the sporadic and noncomprehensive nature of CRE-related data in China. Recently, four studies have reported several sporadic cases of clinical infections linked to *E. coli* ST167 carrying $bla_{NDM-5}$ in various parts of China (10–12). The gene was shown to be located on the IncX3 plasmid in two studies (11, 12).

In this work, we have conducted a more comprehensive investigation in order to better understand whether the *E. coli* ST167 strains are predominantly involved in the transmission of the $bla_{NDM-1}$ and $bla_{NDM-5}$ genes in hospitals in various parts of China. Clinical carbapenem-resistant *E. coli* strains, as determined by the Kirby-Bauer disk diffusion method according to CLSI guidelines, were obtained from 7 hospitals in various locations in China, as shown in Table 1, from 2013 to 2014. A total of 48 carbapenem-resistant *E. coli* isolates were obtained during the study period and screened for the presence of $bla_{NDM-1}$ as previously described (13). Twenty-five (52%) were found to carry $bla_{NDM}$ carbapenemase genes, among which 11 were isolated from patients in hematology departments, 4 from patients in intensive care units (ICUs), 4 from patients in pediatric surgery, 4 from patients in recovery departments, and the others from patients in burn departments and intensive medicine. Of these 25 isolates, 13 were recovered from blood samples and the others were recovered from urine or secretion samples.

These 25 *E. coli* isolates were subjected to further characterization by PCR and sequencing as previously described to determine the exact type of β-lactamase genes harbored by these isolates (13). The $bla_{NDM}$-like genes in 13 isolates were confirmed to be $bla_{NDM-1}$, and $bla_{NDM-5}$ was found to be present in 11 isolates, whereas $bla_{NDM-3}$ was detected in one strain. Other β-lactamase genes, such as those encoding CTX-M-14, CTX-M-15, SHV-12, and TEM-1, were also frequently detected in various strains (Table 1). The MICs of 10 antibiotics, including imipenem, meropenem, ceftazidime, ceftazidime, cefotaxime, amikacin, tobramycin, polymyxin B, cefoperazone-sulbactam, fosfomycin, aztreonam, levofloxacin, and ciprofloxacin, were determined for these isolates using the agar dilution method, and the results were analyzed according to the CLSI criteria of 2014 (14). All 25 $bla_{NDM-1}$-positive isolates were found to be resistant to most β-lactam antibiot-

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**TABLE 1** Profiles of plasmids and β-lactamase genes recoverable in 25 $bla_{NDM}$-positive *E. coli* clinical isolates and the corresponding transconjugants

| Isolate[a] | MLST | β-Lactamase gene(s) in: | | Estimated size(s) (kb) of plasmid(s) in[b]: | | Plasmid type in transconjugant[c] |
|---|---|---|---|---|---|---|
| | | Parental strain | Transconjugant | Parental strain | Transconjugant | |
| SY91 | 167 | $bla_{NDM-5}$, $bla_{CTX-M-14}$ | $bla_{NDM-5}$ | 280, 160, 110, **60** | **60** | IncX3 |
| SY92 | 167 | $bla_{NDM-5}$, $bla_{CTX-M-14}$ | $bla_{NDM-5}$ | 280, 160, 110, **60** | **60** | IncX3 |
| SY93 | 167 | $bla_{NDM-5}$, $bla_{CTX-M-14}$ | $bla_{NDM-5}$ | 280, 135, **60** | **60** | IncX3 |
| JN102 | 167 | $bla_{NDM-5}$, $bla_{CTX-M-14}$, $bla_{CTX-M-15}$, $bla_{TEM-1}$ | $bla_{NDM-5}$, $bla_{TEM-1}$ | 110, 90, 60 | **60** | IncX3 |
| JN105 | 167 | $bla_{NDM-5}$, $bla_{CTX-M-15}$, $bla_{TEM-1}$ | $bla_{NDM-5}$, $bla_{TEM-1}$ | 160,135, 100, **60** | **65** | IncX3 |
| JN106 | 167 | $bla_{NDM-5}$, $bla_{CTX-M-15}$, $bla_{TEM-1}$ | $bla_{NDM-5}$, $bla_{TEM-1}$ | 160,135, 100, **60** | **60** | IncX3 |
| BJ114 | 167 | $bla_{NDM-5}$, $bla_{CTX-M-14}$ | $bla_{NDM-5}$, $bla_{CTX-M-14}$ | 160, 100,80, **60** | **200** | IncX3 |
| LZ135 | 167 | $bla_{NDM-5}$, $bla_{CTX-M-15}$ | $bla_{NDM-5}$ | 150, **100** | **105, 100, 90** | IncFrepB |
| JN103 | 167 | $bla_{NDM-1}$, $bla_{CTX-M-14}$, $bla_{CTX-M-15}$, $bla_{TEM-1}$ | $bla_{NDM-1}$, $bla_{TEM-1}$ | 200, **160,** 110 | **160** | UT |
| SRM94 | 167 | $bla_{NDM-1}$, $bla_{TEM-1}$ | $bla_{NDM-1}$, $bla_{TEM-1}$ | **160** | **160** | IncF |
| JX6 | 167 | $bla_{NDM-1}$, $bla_{CTX-M-14}$, $bla_{TEM-1}$, $bla_{SHV-12}$ | $bla_{NDM-1}$, $bla_{TEM-1}$, $bla_{SHV-12}$ | 110, 100, **60** | **65** | IncX3 |
| JX34 | 167 | $bla_{NDM-1}$, $bla_{CTX-M-15}$, $bla_{TEM-1}$, $bla_{SHV-12}$ | $bla_{NDM-1}$, $bla_{TEM-1}$, $bla_{SHV-12}$ | 210, 110, **60** | **60** | IncX3 |
| BJ119 | 405 | $bla_{NDM-5}$, $bla_{CTX-M-15}$ | $bla_{NDM-5}$ | 130,70,**60** | **60** | IncX3 |
| SRM282 | 533 | $bla_{NDM-5}$, $bla_{CTX-M-14}$ | $bla_{NDM-5}$ | 200, 120, **60** | **60** | IncX3 |
| WH97 | 410 | $bla_{NDM-1}$, $bla_{CTX-M-14}$, $bla_{CTX-M-15}$ | $bla_{NDM-1}$, $bla_{CTX-M-14}$ | 100, 75, 60 | **60** | IncN |
| JX45 | 359 | $bla_{NDM-1}$, $bla_{CTX-M-15}$, $bla_{TEM-1}$, $bla_{SHV-12}$ | $bla_{NDM-1}$, $bla_{TEM-1}$, $bla_{SHV-12}$ | 160, 100, **60** | **60** | IncX3 |
| WH32 | 1284 | $bla_{NDM-1}$ | $bla_{NDM-1}$ | 160, **68** | **230** | IncN |
| SY96 | 2749 | $bla_{NDM-1}$, $bla_{CTX-M-15}$ | $bla_{NDM-1}$ | 240, 170, **60** | **330, 60** | IncN |
| SRM251 | 3489 | $bla_{NDM-1}$, $bla_{SHV-12}$ | $bla_{NDM-1}$, $bla_{SHV-12}$ | 165, **60**, 48 | **60** | IncX3 |
| BJ128 | 5699 | $bla_{NDM-1}$, $bla_{CTX-M-14}$ | $bla_{NDM-1}$, $bla_{CTX-M-14}$ | **200,**100,80 | **200** | UT |
| LZ136 | 167 | $bla_{NDM-5}$, $bla_{CTX-M-15}$, $bla_{TEM-1}$ | | 150, **90** | NC | |
| JX33 | 167 | $bla_{NDM-1}$, $bla_{CTX-M-15}$ | | **160**, 125, 100 | NC | |
| BJ116 | 101 | $bla_{NDM-3}$, $bla_{CTX-M-15}$ | | **165**, 90, 85 | NC | |
| WH36 | 1284 | $bla_{NDM-1}$ | | **200** | NC | |
| SRM49 | 5138 | $bla_{NDM-1}$, $bla_{CTX-M-14}$, $bla_{TEM-1}$ | | 155, 125, **100**, 80 | NC | |

[a] Isolate identification codes indicate the source of the isolate as follows: WH, Wuhan, capital city of Hubei Province; SY, Shenyang, capital city of Liaoning Province; JX, Jiaxing, city of Zhejiang Province; LZ, Lanzhou, capital city of Gansu Province; JN, Jinan, capital city of Shandong Province; SMR, People's Hospital of Zhejiang Province in Hangzhou, capital of Zhejiang Province; BJ, Beijing.

[b] Plasmids harboring $bla_{NDM}$ genes are denoted in boldface. NC, nonconjugative.

[c] UT, untypeable.

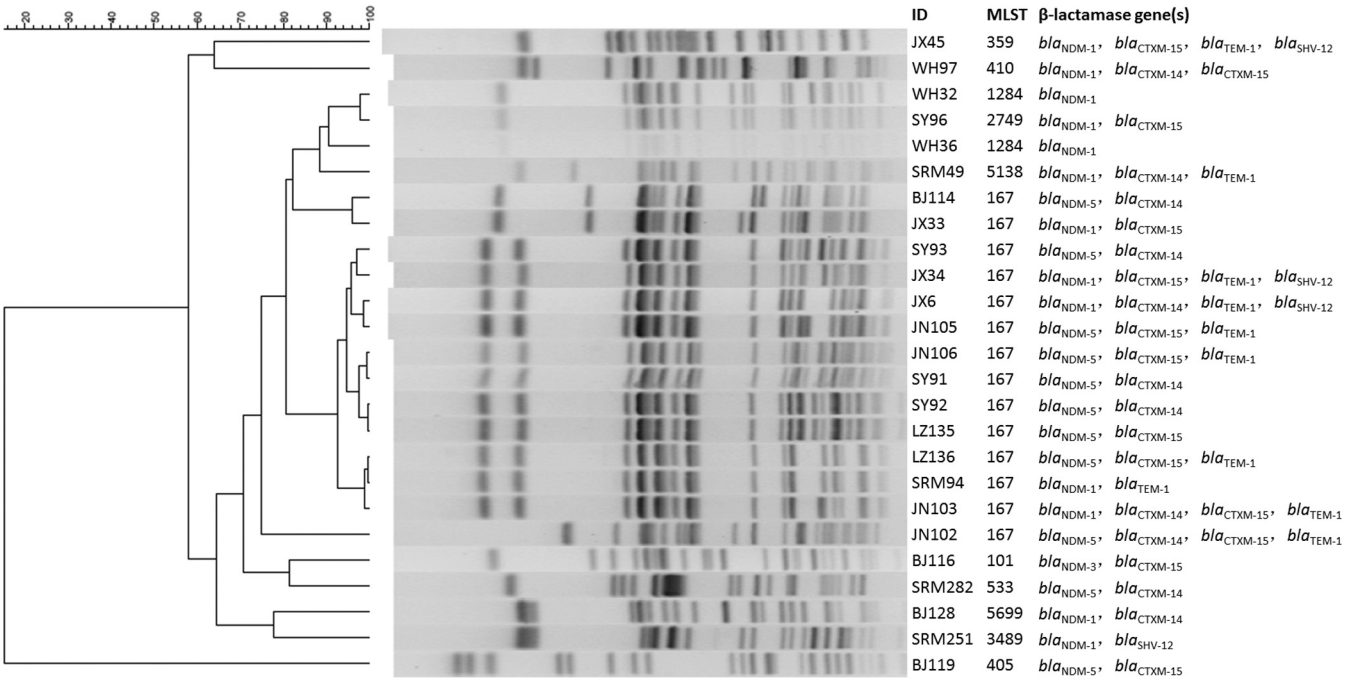


**FIG 1** PFGE patterns of 25 $bla_{NDM}$-positive clinical *E. coli* isolates.

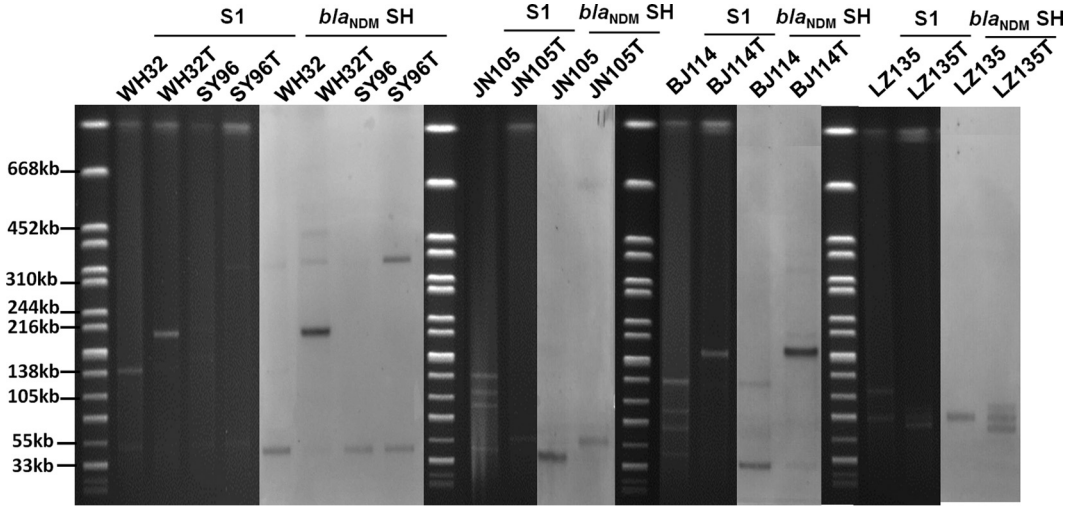


**FIG 2** S1-PFGE (S1) and Southern hybridization ($bla_{NDM}$ SH) of representative $bla_{NDM}$-positive *E. coli* clinical isolates and the corresponding transconjugants. Uppercase Ts denote transconjugants; the strain identification codes are described in Table 1.

ics, including extended-spectrum cephalosporins and the carbapenems. The MICs for imipenem and meropenem were between 4 and 64 μg/ml. These isolates were also resistant to fluoroquinolones (100%), aztreonam (88%), tobramycin (64%), amikacin (32%), and fosfomycin (16%). All isolates were susceptible to polymyxin B.

To assess the genetic relatedness of these 25 isolates, pulsed-field gel electrophoresis (PFGE) and sequence typing were performed as previously described (13). Fourteen of the 25 isolates belonged to ST167, among which 11 exhibited very similar, although not identical PFGE patterns, while 3 showed different PFGE patterns (Fig. 1). Other strains belonged to 9 other STs and displayed very diverse PFGE patterns, suggesting that these *E. coli* strains were not genetically related to each other even though a number of strains were recovered from the same hospital (Fig. 1). Among the 11 $bla_{NDM-5}$-positive isolates, 9 were associated with ST167, while 2 were associated with ST405 and ST533, respectively, suggesting the tight association of ST167 and $bla_{NDM-5}$. On the other hand, 5 ST167 *E. coli* strains were found to carry $bla_{NDM-1}$, and the isolate which harbored the $bla_{NDM-3}$ gene was found to belong to ST101.

Conjugation experiments were performed for these 25 isolates as previously described (13). Twenty of the 25 isolates tested could successfully transfer their carbapenem-resistant phenotype to *E. coli* strain J53. In addition to the resistance to carbapenems, 1, 2, 2, 3, and 6 of the 20 transconjugants also exhibited resistance to fosfomycin, fluoroquinolone, amikacin, tobramycin, and aztreonam, respectively. S1 nuclease digestion combined with PFGE (S1-PFGE) and Southern hybridization were performed on the parental strains and their corresponding transconjugants to identify the $bla_{NDM-1}$- and $bla_{NDM-5}$-bearing plasmids concerned. Multiple plasmids with sizes ranging from ~48 kb to ~280 kb were detected in the parental strains, with $bla_{NDM-1}$ and $bla_{NDM-5}$ being predominantly located on an ~60-kb plasmid. However, several plasmids of various sizes were also found to carry $bla_{NDM-1}$ and $bla_{NDM-5}$ (Table 1). Among the 20 transconjugants, most were found to harbor one plasmid, with the ~60-kb conjugative plasmid being the most prevalent (Table 1). Transconjugants from strains LZ135 and SY96 were found to carry more than one $bla_{NDM}$-encoding plasmid, with one being transferred from the parental strain and one or two new plasmids not being detectable in the parental strain (Table 1; Fig. 2). Some transconjugants were found to harbor $bla_{NDM}$-encoding plasmids with different sizes than those from the parental strains, such as parental strains BJ114, WH32, and LZ135 (Table 1; Fig. 2). To doubly confirm that these transconjugants were correct, PFGE was performed on them, together with the recipient strain *E. coli* EC600. The results indicated that these transconjugants were indeed *E. coli* EC600; the large $bla_{NDM}$-encoding plasmids were obvious on some of them, such as BJ114-T, WH32-T, and WH96-T, while the transconjugants carrying small $bla_{NDM}$-encoding plasmids, such as LZ135-T and JN105-T, showed PFGE profiles identical to that of *E. coli* EC600, suggesting that the PFGE data for these transconjugants was consistent with the S1-PFGE and Southern hybridization data (Fig. 3). This phenomenon could be due to the recombination events between the $bla_{NDM-1}$-positive and -negative plasmids present in the parental strains or the repetition of multiple copies of one mobile element (unpublished observation on plasmids from other bacteria in our laboratory). The incompatibility groups of the detectable plasmids were determined by PCR replicon typing as previously described (14). Most of the conjugative plasmids

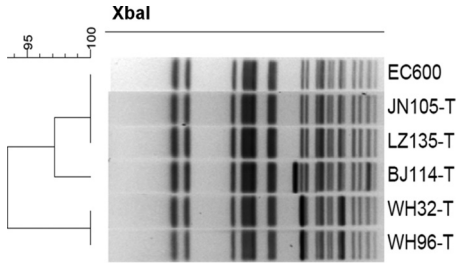


**FIG 3** Comparison of PFGE profiles of transconjugants carrying different sizes of plasmids from their parental strains to the PFGE profile of the recipient strain, *E. coli* EC600.

**TABLE 2** Characteristics of conjugative plasmids carried by the 20 transconjugants

| Transconjugant[a] | Result of screening for[b]: *repB* | ISL*3*-$bla_{SHV-12}$ | *bleo*-$bla_{NDM-1}$ | $bla_{NDM-1}$-*insH* | *topB-ftsH* | Estimated plasmid size(s) (bp) | Plasmid type[c] | β-Lactamase gene(s) |
|---|---|---|---|---|---|---|---|---|
| SY91-T | + | | + | | + | 60 | IncX3 | $bla_{NDM-5}$ |
| SY92-T | + | | + | | + | 60 | IncX3 | $bla_{NDM-5}$ |
| SY93-T | + | | + | | + | 60 | IncX3 | $bla_{NDM-5}$ |
| JN102-T | + | | + | | + | 60 | IncX3 | $bla_{NDM-5}$, $bla_{TEM-1}$ |
| JN105-T | + | | + | | + | 65 | IncX3 | $bla_{NDM-5}$, $bla_{TEM-1}$ |
| JN106-T | + | | + | | + | 60 | IncX3 | $bla_{NDM-5}$, $bla_{TEM-1}$ |
| BJ114-T | + | | + | | + | 200 | IncX3 | $bla_{NDM-5}$, $bla_{CTX-M-14}$ |
| LZ135-T | | | + | | | 105, 100, 90 | IncFrepB | $bla_{NDM-5}$ |
| JN103-T | | | + | | + | 160 | UT | $bla_{NDM-1}$, $bla_{TEM-1}$ |
| SRM94-T | | | + | | | 160 | IncF | $bla_{NDM-1}$, $bla_{TEM-1}$ |
| JX6-T | + | + | + | + | + | 65 | IncX3 | $bla_{NDM-1}$, $bla_{TEM-1}$, $bla_{SHV-12}$ |
| JX34 | + | + | + | + | + | 60 | IncX3 | $bla_{NDM-1}$, $bla_{TEM-1}$, $bla_{SHV-12}$ |
| BJ119-T | + | | + | | + | 60 | IncX3 | $bla_{NDM-5}$ |
| SRM282-T | + | | + | | + | 60 | IncX3 | $bla_{NDM-5}$ |
| WH97-T | | | + | | | 60 | IncN | $bla_{NDM-1}$, $bla_{CTX-M-14}$ |
| LX45-T | + | + | + | + | + | 60 | IncX3 | $bla_{NDM-1}$, $bla_{TEM-1}$, $bla_{SHV-12}$ |
| WH32-T | | | + | | + | 230 | IncN | $bla_{NDM-1}$ |
| SY96-T | | | + | | | 330, 60 | IncN | $bla_{NDM-1}$ |
| SRM251-T | + | + | + | + | + | 60 | IncX3 | $bla_{NDM-1}$, $bla_{SHV-12}$ |
| BJ128-T | | | + | | | 200 | UT | $bla_{NDM-1}$, $bla_{CTX-M-14}$ |

[a] Identification codes are described in Table 1; the uppercase Ts denote transconjugants.
[b] Primers were designed based on the IncX3 plasmid, namely, pNDM-HN380 (NC_019162). Primers targeting *repB* (positions 54029 to 1127) and *topB-ftsH* (positions 28908 to 33069) were used to screen for X3-specific conjugative plasmids, the primer targeting ISL*3 tnpA*-$bla_{SHV-2}$ (positions 4395 to 8093) was used to screen for the $bla_{SHV-2}$ gene, the primer targeting *bleo*-$bla_{NDM-1}$ (positions 17,418 to 18,100) was used to screen for the conservative $bla_{NDM-1}$ mobile element, and the primer targeting $bla_{NDM-1}$-*insH* (positions 17768 to 20103) was used to screen for the upstream transposase gene.
[c] UT, untypeable.

were of the IncX3 type, with a size of ~60 kb. Other types included IncN (3 plasmids), FrepB (1 plasmid), IncF (1 plasmid), and untypeable (2 plasmids) (Table 1). Most of the $bla_{NDM-5}$-bearing plasmids belonged to the IncX3 types, of which seven were harbored by the ST167 strains and one each was harbored by an ST405 and an ST533 strain. One $bla_{NDM-5}$ gene was found to be located on a FrepB plasmid in an ST167 strain, and one was in a nonconjugative plasmid in an ST167 strain. The $bla_{NDM-1}$-bearing plasmids in five ST167 strains included IncX3 (2 plasmids), IncF (1 plasmid), and untypeable (1 plasmid) conjugative plasmids and one nonconjugative plasmid (Table 1).

All conjugative plasmids were screened for their similarity to previously reported IncX3 plasmids, as shown in Table 2. Our screening data showed that all IncX3 $bla_{NDM}$-positive plasmids were positive for *repB*, *topB-ftsH*, and *bleo*-$bla_{NDM-1}$, some of which harbored the $bla_{SHV-2}$ gene (positive for ISL*3 tnpA*-$bla_{SHV-2}$). Plasmids of the other types were only positive for *bleo*-$bla_{NDM-1}$. The data suggested that all plasmids, including IncX3 types and other types, carried the conserved fragment $bla_{NDM-1}$-*bleMBL-trpF*.

In summary, this study provides strong evidence that ST167 strains in clinical settings in China exhibited close linkages with $bla_{NDM}$ genes, and particularly, a $bla_{NDM-5}$ variant with higher hydrolytic activity than $bla_{NDM-1}$. Close surveillance is needed to monitor future dissemination of ST167 strains that harbor the $bla_{NDM}$-like genes in China and other parts of the world.

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