

# Genomic Characterization of a Multidrug-Resistant *Escherichia coli* Isolate Co-Carrying *bla*<sub>NDM-5</sub> and *bla*<sub>CTX-M-14</sub> Genes Recovered from a Pediatric Patient in China

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**Background:** Public health is seriously threatened by the rise of carbapenem-resistant Enterobacterales (CRE). However, the genomic characteristics of CRE detected in pediatric patients are largely unknown. Here, we reported the genomic characteristics of a multidrug-resistant *Escherichia coli* strain containing the plasmid-borne *bla*<sub>NDM-5</sub> and *bla*<sub>CTX-M-14</sub> genes recovered from a Chinese pediatric patient.

**Methods:** The genome sequence of *E. coli* strain B379 was determined using Illumina NovaSeq 6000 and Oxford Nanopore MinION. Multiple bioinformatics tools were used to annotate the genome sequence, identify antimicrobial resistance genes and plasmid replicons and perform the in silico multilocus sequence typing (MLST) analysis. Using BacWGSTdb 2.0 server, a core genome MLST (cgMLST) comparison was made between *E. coli* B379 and all ST746 *E. coli* strains downloaded from the public database.

**Results:** The *E. coli* B379 genome sequence is comprised of six contigs totaling 5,152,502 bp, including one chromosome and five plasmids. Nineteen antimicrobial resistance genes were predicted. The *bla*<sub>NDM-5</sub>, which is located on a 46,161 bp IncX3 plasmid and the *bla*<sub>CTX-M-14</sub> gene which is located on a 147,204 bp IncFII/IncFIA/IncFIB plasmid are two examples of these 19 genes. *E. coli* B379 was resistant to ampicillin, ampicillin/sulbactam, ceftriaxone, ceftazidime, imipenem, cefepime, ciprofloxacin, ertapenem, trimethoprim-sulfamethoxazole. This isolate belonged to ST746 and the closest relative was another one originating from a human material specimen in Denmark, which differed by 273 cgMLST alleles.

**Conclusion:** Our study reports the emergence of a multidrug-resistant *E. coli* strain co-carrying *bla*<sub>NDM-5</sub> and *bla*<sub>CTX-M-14</sub> recovered from a pediatric patient in China. These data would help us better understand the prevalence, genetic characteristics, and mechanisms of antimicrobial resistance of this recently identified multidrug-resistant bacteria in children.

**Keywords:** whole-genome sequencing, *Escherichia coli*, multidrug-resistant, *bla*<sub>NDM-5</sub>, *bla*<sub>CTX-M-14</sub>, pediatrics

## Introduction

*Escherichia coli* is not only a regular component of the gut flora of people but also one of the main sources of bacterial illnesses in people. For children, the number of available antimicrobial agents is restricted; in general, cephalosporins are recommended as the first-line therapeutic option, and carbapenems are often used for the treatment of serious Gram-negative extended spectrum  $\beta$ -lactamase-producing bacterial infections. Nonetheless, the emergence of third-generation cephalosporin and carbapenem-resistant *E. coli*, has exacerbated the situation significantly. A high-priority species of *E. coli* was identified as carbapenem-resistant and third-generation cephalosporin-resistant in a 2007 WHO publication of antibiotic-resistant bacteria that need medical attention.<sup>1,2</sup> Carbapenem-resistant *E. coli* has been

identified rarely in children; nevertheless, growing occurrences globally and a more medically complicated pediatric population imply that it may emerge as a serious threat to children.<sup>3</sup> Similarly to what has been found in adult populations, the incidence of infections caused by multidrug-resistant bacteria in children has increased over time. Carbapenem resistance has grown from 0% in 1999 and 2000 to 0.47% in 2010 and 2011 among Enterobacterales in children in the United States over the past decade.<sup>4</sup> The nosocomial infection rate of carbapenem-resistant Enterobacterales in the Chinese pediatric population was 0.08–0.15%, with a higher rate in neonatal intensive care unit (0.63–1.93%).<sup>5</sup>

Mobile genetic elements containing genes encoding for carbapenemases, such as *Klebsiella pneumoniae* carbapenemase (KPC), metallo- $\beta$ -lactamases and oxacillinase 48 (OXA-48), have aided the fast worldwide spread of carbapenem-resistant *E. coli* in recent years.<sup>6</sup> Nearly all  $\beta$ -lactam antibiotics, including carbapenems, could be hydrolyzed by New Delhi metallo- $\beta$ -lactamase (NDM), an Ambler class B  $\beta$ -lactamase.<sup>7</sup> Numerous infections brought on by *E. coli* strains that produce NDM are reported to have a poor prognosis and a high death rate, particularly in individuals who are immunocompromised.<sup>8</sup> The horizontal transfer and dissemination of antibiotic resistance genes in carbapenem-resistant *E. coli* strains are usually carried by conjugative plasmids.<sup>9</sup> Despite the growing focus on carbapenem-resistant Enterobacterales in China, data on the epidemiology of these infections in children are still scarce. Here, we report the genomic features of a carbapenem-resistant *E. coli* from a Chinese pediatric patient that carried multiple antimicrobial resistance genes. This study provides deep insights into the characteristics and diversity of *bla*<sub>NDM-5</sub> harboring *E. coli* and further emphasizes their role in dissemination of carbapenem resistance.

## Materials and Methods

In August 2021, a pus sample from a 14-year-old hospitalized with severe appendicitis yielded the *E. coli* isolate B379. The identification was carried out using the GN panels (BioMérieux, France) and the VITEK 2 system (BioMérieux, France). The identified result was double-checked by a MALDI Biotyper (Bruker Daltonics, USA) and 16S rRNA gene sequencing. The VITEK 2 system (BioMérieux, France) was also used to test the antimicrobial susceptibility of *E. coli* B379 using the AST GN13 panels (BioMérieux, France) for the following antimicrobial agents: ampicillin, ampicillin-sulbactam, piperacillin-tazobactam, ceftriaxone, ceftazidime, cefepime, imipenem, ertapenem, aztreonam, levofloxacin, ciprofloxacin, trimethoprim-sulfamethoxazole, amikacin, gentamicin, and tobramycin. The Clinical and Laboratory Standards Institute (CLSI) 2021 standards were used to evaluate minimum inhibitory concentrations (MICs). Ethical approval of this study was obtained from the ethics committee of Children Hospital of Hangzhou (2021–71), China. Written informed consent from the patient's parents was obtained and utilized to publish the case details. Isolation of the clinical sample was part of the routine procedure of clinical laboratory.

Using a Genomic DNA Purification Kit, the genomic DNA was extracted (QIAGEN, USA). DNA concentration and purity were assessed using a NanoDrop™ spectrophotometer (Thermo Scientific, USA). The whole-genome sequencing was carried out on two platforms: Illumina NovaSeq 6000 for the short-reads and Oxford Nanopore MinION for the long-reads. The de novo assembly of Illumina and Nanopore reads was carried out using Unicycler 0.4.8.<sup>10</sup>

The NCBI Prokaryotic Genomes Annotation Pipeline (PGAP) automatically annotated the genome sequence. IslandViewer 4,<sup>11</sup> ISfinder,<sup>12</sup> PHASTER 2016,<sup>13,14</sup> CRISPRCasFinder,<sup>15</sup> and antiSMASH 5.0<sup>16</sup> were applied to identify the genomic islands, insertion sequence (IS) elements, clustered regularly interspaced short palindromic repeat (CRISPR) sequences, prophage sequences, and secondary metabolite gene clusters, respectively, using default parameters.

ABRicate 1.0.1 was used in conjunction with ResFinder 4.1, CARD 2020, SerotypeFinder 2.0 and PlasmidFinder 2.1 to predict acquired antimicrobial resistance genes, serotype and plasmid incompatibility (Inc) groups.<sup>17–19</sup> Virulence factors and open reading frames (ORFs) were identified by VirulenceFinder 2.0<sup>20</sup> and ORFfinder. BacWGSTdb 2.0 server was used to carry out in silico multilocus sequence typing (MLST) analysis and bacterial source tracing using a core genome MLST (cgMLST) analysis.<sup>21–23</sup> Circular and schematic maps of the *bla*<sub>NDM</sub> carrying plasmid were performed by BRIG v0.95<sup>24</sup> and SnapGene 6.1, respectively. The genetic surroundings of antibiotic resistance genes and the homologous areas shared between two plasmids were illustrated using Easyfig 2.2.5.<sup>25</sup>

## Results and Discussion

The entire genome sequence of *E. coli* B379 is made up of six contigs with a combined length of 5,152,502 bp that have been closed and circularized. Contig 1 (4,801,759 bp) belonged to the chromosome, while other contigs belonged to different plasmids (contig 2, 152061 bp; contig 3, 147204 bp; contig 4, 46161 bp; contig 5, 2809 bp; contig 6, 2508 bp). The strain's overall G+C content was 50.87%. Total 4643 coding sequences (CDSs), 119 RNAs (22 rRNA, 86 tRNA, and 11 ncRNA) genes were identified. At least 56 genomic islands are present in the *E. coli* B379 genome, as well as a number of IS elements, the majority of which belong to the IS1, IS3 and IS5 families. The genome contains a total of 11 CRISPR sequences and 15 prophage sequences. It is also possible to anticipate the existence of four putative secondary metabolite gene clusters, including the yersiniabactin, O-antigen, turnerbactin and colicin V. In addition, *E. coli* B379 also contained several virulence factors, including *astA*, *gad*, *terC*, *fyuA*, and *irp2* carried by the chromosome; and *iucABCD*, *iucC*, *iutA*, *sitA*, and *traT* carried by the plasmids. According to in silico serotype prediction, *E. coli* B379 belongs to the nontypeable O:H44 subgroup.

Antimicrobial susceptibility tests revealed that the isolate was resistant to ampicillin/sulbactam, ceftriaxone, ampicillin, ceftazidime, cefepime, imipenem, ertapenem, ciprofloxacin, and trimethoprim–sulfamethoxazole (Table 1). The genes for resistance to  $\beta$ -lactams (*bla*<sub>TEM-1B</sub>, *bla*<sub>CTX-M-14</sub> and *bla*<sub>NDM-5</sub>), quinolones [*aac*(6')-*Ib-cr*], sulphonamide (*sul1*, *sul2*, *sul3*) and trimethoprim (*dhfrA1*) are found in *E. coli* B379. The isolate has target changes in the proteins GyrA (S83L) and ParC (S80I) that confer fluoroquinolone resistance. The multidrug resistance to aminopenicillins, cephalosporins, carbapenems, quinolones, sulphonamide, and trimethoprim was well explained by these results. There are several other resistance genes, such as, aminoglycoside [two copies of *aadA1*, *aac*(6')-*Ib-cr*, *aac*(6')-*Ib3*, *aadA3*], macrolide [*mdf*(A), *erm*(42), *erm*(B)], tetracycline [*tet*(B)], amphenicol (*floR*, two copies of *cmlA1*), which may result resistance to tobramycin, azithromycin, chloramphenicol, and tetracycline.

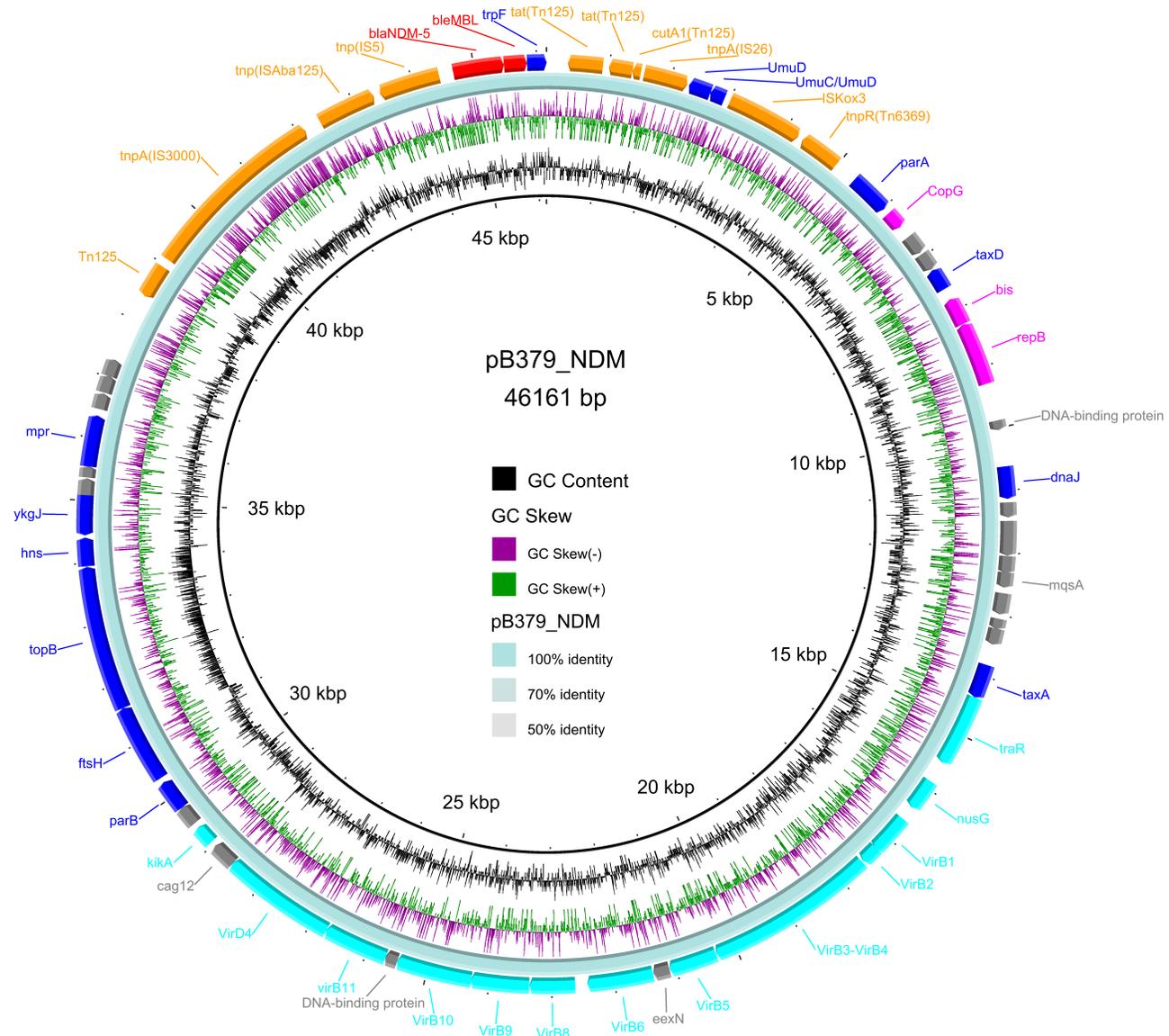
**Table 1** Multidrug Resistance Profile of *bla*<sub>NDM-5</sub>-Carrying *E. coli* B379 in This Study

Antimicrobial Agents	MICs
Ampicillin	≥64
Ampicillin-sulbactam	≥32
Piperacillin–tazobactam	64
Ceftriaxone	≥64
Ceftazidime	≥64
Cefepime	≥64
Aztreonam	≤1
Imipenem	8
Ertapenem	≥8
Levofloxacin	1
Ciprofloxacin	1
Trimethoprim–sulfamethoxazole	≥320
Amikacin	4
Gentamicin	2
Tobramycin	8

**Abbreviation:** MICs, minimal inhibitory concentrations.

The IncX3 plasmid (pB379\_NDM) carrying the carbapenem resistance gene *bla*<sub>NDM-5</sub> and a 46,161 bp size had a G + C content of 46.7%. Using the approach developed by Norman et al,<sup>26,27</sup> plasmid pB379\_NDM was found to include genes involved in replication (*repB*, *copG* and *bis*), stability (*ftsH*, *topB*, *taxA*, *parB*, *hns*, *ykgJ*, *mpr*, *parA*, *trpF*, *umuD*, *taxD* and *dnaJ*), propagation (*virB1*, *virB2*, *virB3/virB4*, *virB5*, *virB6*, *virB8*, *virB9*, *virB10*, *virB11*, *traR*, *nusG*, *virD4*, and *kikA*), and adaptation (*tnpA*-IS3000-IS*Aba125*-IS5-*bla*<sub>NDM-5</sub>-*bla*<sub>MBL</sub>-Tn125-IS26-ISKox3-*tnpR*) (Figure 1). Only one resistance gene *bla*<sub>NDM-5</sub>, which is responsible for carbapenem resistance, was present on the IncX3 plasmid. An insertion sequence called IS*Aba125* that contains the genes IS5 and IS3000 exists upstream of *bla*<sub>NDM-5</sub>, according to analysis of the genetic environment surrounding the gene. The *bla*<sub>NDM-5</sub> is located following the *ble*<sub>MBL</sub>, *trpF*, *tat*, *catA1*, and IS26 elements.

Interaction with the host or the adaptative response during horizontal transfer may cause the potential insertions or deletions of IS sequences and transposons on *bla*<sub>NDM-5</sub> genetic surroundings, which could also be regarded as the variable region of the plasmid (Figure 1). pB379\_NDM both had 100% query coverage and identity with multiple *bla*<sub>NDM-5</sub>-carrying IncX3 plasmids, according to a BLAST search. These plasmids were isolated from a variety of

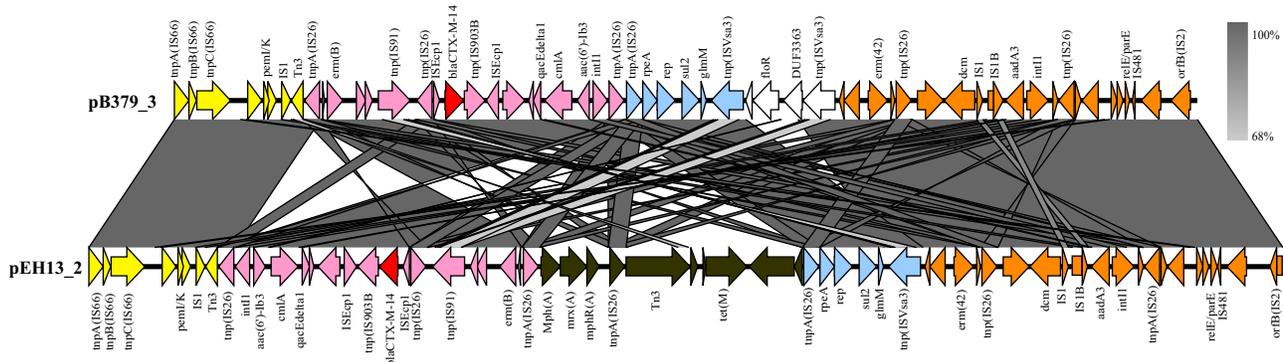


**Figure 1** Circular map of plasmid pB379\_NDM. Genes at the outermost ring shown in blue, aqua, fuchsia, and orange were respectively involved in stability, propagation, replication, and application. The resistance genes were indicated in red. Hypothetical protein or other coding sequences (CDSs) are indicated in gray.

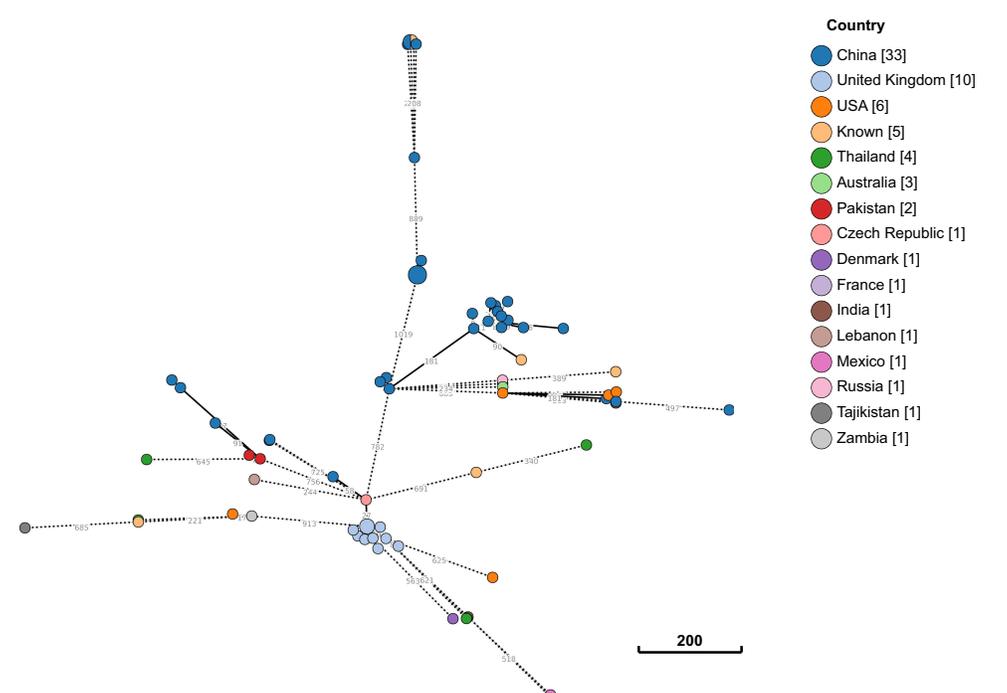


*ISEcp1* exists upstream of *bla*<sub>CTX-M-14</sub> and downstream of the *IS903B* and truncated *ISEcp1*, and the transposition element located on the structure with two *IS26* with the opposite direction. Therefore, the *bla*<sub>CTX-M-14</sub> and the associated *ISEcp1*-derived promoter might be able to move by the actions of *IS26* elements. Another difference was that the plasmid pB379\_3 carried fluoroquinolone resistance genes but the plasmid pEH13\_2 carried *tet(M)* and *mph(A)* genes (Figure 3). There were several insertion sequences in the MDR region, which may result from insertions, deletions and homologous recombination event of these insertion sequences. Other antimicrobial resistance genes, ie, *bla*<sub>TEM-1B</sub>, two copies of *aadA1*, *aac(6')-Ib-cr*, *sul1*, *sul3*, *dfrA1*, *mdf(A)*, *tet(B)*, *cmlA1* was located on the chromosome.

In silico MLST analysis indicated that, *E. coli* strain B379 belongs to sequence type (ST)746. To explore the worldwide genomic epidemiological characteristics of *E. coli* strains, the phylogenetic relationships between *E. coli* B379 and a total of 72 ST746 *E. coli* strains currently deposited in the NCBI GenBank database were investigated. According to cgMLST analyses, the closest relative of *E. coli* B379, another ST746 strain (*E. coli* KTE154) isolated from human feces in Denmark in 2010, differs by 273 cgMLST loci (Figure 4). This Denmark strain only carried one



**Figure 3** Linear comparison of MDR region of plasmid pB379\_3 with pEH13\_2. Genes are denoted by arrows. The same color denotes the same gene cluster of them. White and black represent different regions between the two plasmids. Shading indicates regions of homology (>95% nucleotide identity).



**Figure 4** Phylogeny between *E. coli* B379 and all ST746 strains currently available in public database. The clonal relationship between two isolates is depicted by lines connecting the circles. The scale bar indicates the allelic difference between two isolates. In square brackets, the number of isolates from each nation is shown.

antimicrobial resistance genes [*mdf(A)*], suggesting that horizontal transmission was responsible for the acquisition of the *bla*<sub>CTX-M-14</sub> and *bla*<sub>NDM-5</sub> genes in *E. coli* B379.

Currently, the majority of research focuses on the spread of carbapenemases among carbapenem-resistant Enterobacterales strains isolated from adult patients, while just a few of studies examine the spread of carbapenemases-producing strains isolated from children.<sup>29</sup> The World Health Organization has determined that children who have carbapenem-resistant Enterobacterales strains in fecal samples are at a high risk because they are more likely to be exposed via close contact.<sup>30</sup> A recent study investigated the carriage and molecular epidemiology of carbapenem-resistant Enterobacterales from fecal samples of outpatient children in Shanghai. They demonstrated the rate of carbapenem-resistant Enterobacterales colonization in feces collected from children was 3.6%, which was less than what had been observed in patients from community settings in other countries.<sup>31</sup> Another study collected a total of 935 non-duplicate carbapenem-resistant Enterobacterales strains from 36 hospitals in 24 provinces across China from 2016 to 2018. They found the prevalence of *bla*<sub>NDM-5</sub>-carrying *E. coli* isolates from children was 32.9%.<sup>32</sup> Globally, clonally different carbapenem-resistant *E. coli* strains (ie, ST405, ST131, ST156, and ST101) have been described; however in this work, a sporadic clone ST746 *E. coli* strain was discovered. This clonal lineage has been previously discovered from a wastewater treatment plant in South Korea, which also confer a high level of resistance to multiple antimicrobial agents, including carbapenems.<sup>33</sup> To our knowledge, this is the first report of a multidrug-resistant ST746 *E. coli* isolate co-carrying *bla*<sub>NDM-5</sub> and *bla*<sub>CTX-M-14</sub> genes recovered from a pediatric patient in China.

## Conclusion

Carbapenem-resistant *E. coli* infection remains an uncommon but serious threat in children. Our study reported the genomic characteristics of a multidrug-resistant *E. coli* strain carrying *bla*<sub>NDM-5</sub> and *bla*<sub>CTX-M-14</sub> genes recovered from a Chinese teenage patient. These data would contribute to the comprehensive understanding of the carbapenem resistance mechanisms and transmission dynamics of this bacteria among children.

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## Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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