Enterobacterales with acquired carbapenemases, 2018

Background

The acquired or transferable (as opposed to chromosomally encoded) carbapenemases found in Enterobacterales[1] belong to three of the four major classes of β-lactamases: classes A, B and D.[2] Class A acquired carbapenemases include the *Klebsiella pneumoniae* carbapenemases, the so-called KPCs, and the imipenem-hydrolyzing β-lactamase or IMI carbapenemase. Class B metallo-β-lactamases (MBLs) include several types of acquired carbapenemases, the most common being the New Delhi metallo-β-lactamases (NDMs), and the IMP and VIM metallo-β-lactamases. Class D acquired carbapenemases in Enterobacterales belong to the OXA-48 group of β-lactamases. DNA mutations resulting in changes in the amino acid sequence of the carbapenemase have produced an ever increasing range of subtypes or variants of each type of carbapenemase. For example, since the first NDM (NDM-1) was described in 2009, a further 20 subtypes (designated NDM-2 to NDM-24) have been described, with each subtype differing by at least one amino acid from any other subtype.

Methods

In New Zealand, diagnostic microbiology laboratories are requested to refer all isolates of possible carbapenemase-producing Enterobacterales (CPE) to ESR for confirmation and further investigation. At ESR isolates are screened for carbapenemases using inhibitor-based tests and the carbapenem inactivation method. PCRs are performed for the genes encoding KPC and IMI (*bla*$_{KPC}$ and *bla*$_{IMI}$); NDM, IMP, VIM and SIM type MBLs (*bla*$_{NDM}$, *bla*$_{IMP}$, *bla*$_{VIM}$, and *bla*$_{SIM}$); and the OXA-48-like carbapenemases (*bla*$_{OXA\text{-}48\text{-}like}$). When any of these carbapenemase genes are detected, the gene is sequenced to determine the subtype. Basic epidemiological data, including overseas travel and hospitalisation history, is collected for patients with confirmed CPE.

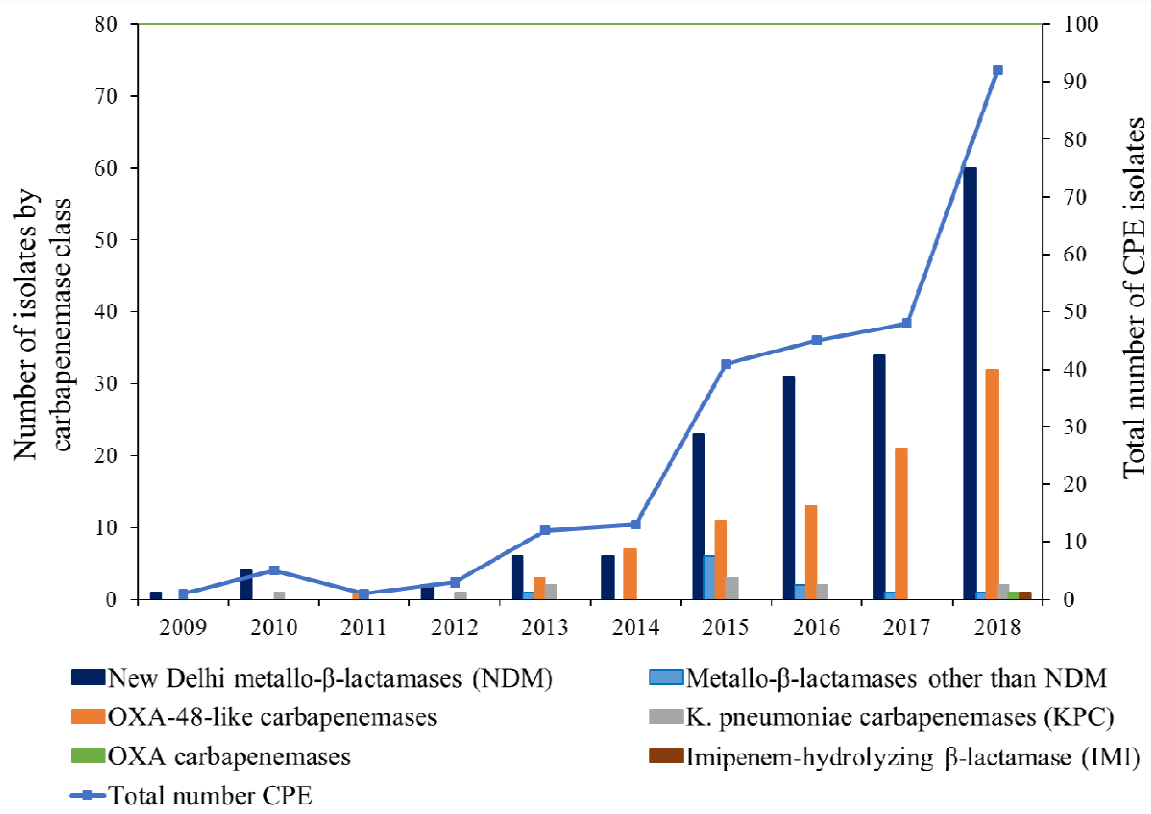
1. Recent taxonomic changes have narrowed the definition of the family Enterobacteriaceae. Some genera previously included in the family Enterobacteriaceae (eg, *Hafnia*, *Morganella*, *Proteus*, *Providencia*, *Serratia* and *Yersinia*) are now included in other families in the order Enterobacterales. We are therefore now using the order name Enterobacterales to cover the genera previously included in the family Enterobacteriaceae.
2. Queenan AM, Bush K. Carbapenemases: the versatile β-lactamases. Clin Microbiol Rev 2007; 20: 440-58.

This report summarises information on CPE confirmed by ESR in 2018. Reports on CPE confirmed between 2009, when the first isolate was identified in New Zealand, and 2017 are available at https://surv.esr.cri.nz/antimicrobial/AccqEnterobacteriaceae.php.

Results

93 distinct CPE were isolated from 76 patients in 2018. Nine patients had ≥2 distinct CPE isolates (see Table 1, footnote 3). There were almost twice as many CPE isolates confirmed in 2018 than were found in 2017, when 48 isolates were identified (Figure 1).

Figure 1. Number of carbapenemase-producing Enterobacterales (CPE) isolates identified in New Zealand, by carbapenemase class, each year from 2009 to 2018



Note: Multiple, distinct CPE isolates from the same patient are included, but duplicate isolates of the same species with the same type(s) of carbapenemase(s) from the same patient are excluded. In 2018, there were four CPE isolates that carried the genes encoding for both NDM and OXA-48-like carbapenemases. These four isolates are counted in the number of isolates for both these carbapenemase classes.

63.44% (59/93) of the CPE confirmed in 2018 were isolated from specimens taken to screen for multidrug-resistant organisms. Among the 34 CPE from clinical specimens, 22 (64.7%) were from urinary sources, 10 (29.4%) were from skin and soft tissue infections, and two (5.9%) were from blood.

Two thirds (62/93) of the CPE confirmed in 2018 were isolated in laboratories in the Auckland region, with the next biggest contribution from the Wellington region (14.0%, 13/93). 41.9% of the patients with CPE were ≥65 years of age, 32.3% were 45-64 years old, 15.1% were 15-44 years old, and 10.8% were under 15 years of age.

Types of carbapenemases identified

The data in this section takes into account all carbapenemase genes of different classes found in CPE isolates. More than one class of carbapenemase was identified in four CPE isolates in 2018 (see Table 1, footnote 4): two *K. pneumoniae* isolates had NDM-5 and OXA-232, one *K. pneumoniae* isolate had NDM-5 and OXA-181, and one *E. coli* isolate had NDM-5 and OXA-181.

Similar to what has been observed in earlier years, the most frequently identified carbapenemases among CPE identified in New Zealand in 2018 were the various subtypes of NDM (Table 1 and Figure 1). NDM carbapenemases accounted for 61.9% (60/97) of the carbapenemases identified in 2018, and have accounted for 62.1% (167/279) of carbapenemases identified in CPE in New Zealand to date. The only other MBL type identified in 2018 was IMP, which accounted for 1.0% (1/97) of the carbapenemases identified in 2018. IMP and VIM MBLs have accounted for 3.9% (11/279) of all carbapenemases identified in CPE in New Zealand.

In 2018, the second most common carbapenemases identified were OXA-48-like carbapenemases, which accounted for a 33.0% (32/97) of the carbapenemases identified in 2018 (Table 1), and have accounted for 31.5% (88/279) of all carbapenemases identified in CPE in New Zealand.

Two of the carbapenemases identified in 2018 were KPC types. KPCs have accounted for 3.9% (11/279) of all carbapenemases identified in CPE in New Zealand. In New Zealand, KPCs have been identified exclusively in *K. pneumoniae*.

Table 1. Types of carbapenemases identified among carbapenemase-producing Enterobacterales by species, 2018

Carbapenemase type and subtype	Number of isolates					
	Species					All species
	Escherichia coli	*Klebsiella pneumoniae*	*Citrobacter sp.*	*Enterobacter cloacae complex*	*Other species*	
NDM	**32**	**16**	**4**	**3**	**5**	**60**
NDM-1	3	10	1	3	5[1]	22
NDM-4	0	0	1	0	0	1
NDM-5	26	4	0	0	0	30
NDM-7	1	0	1	0	0	2
NDM-9	1	1	0	0	0	2
NDM-25	1	1	1	0	0	3
IMP	**0**	**0**	**0**	**1**	**0**	**1**
IMP-4	0	0	0	1	0	1
OXA-48-like	**25**	**5**	**0**	**1**	**1**	**32**
OXA-48	12	1	0	0	0	13
OXA-181	13	2	0	1	1[2]	17
OXA-232	0	2	0	0	0	2
KPC	**0**	**2**	**0**	**0**	**0**	**2**
KPC-3	0	2	0	0	0	2
IMI	**0**	**0**	**0**	**1**	**0**	**1**
IMI-2	0	0	0	1	0	1
OXA-23	**0**	**0**	**0**	**0**	**1[3]**	**1**
Total	**56[4]**	**20[4]**	**4**	**6**	**7**	**97[4, 5]**

1 Includes one *Klebsiella oxytoca*, one *Proteus penneri*, one *Proteus mirabilis*, and two *Providencia stuartii*.

2 *K. oxytoca*

3 *Klebsiella quasipneumoniae*

4 The 56 *E. coli* isolates include one isolate with NDM-5 + OXA-181. Therefore 57 carbapenemases of different classes were identified among the 56 *E. coli* isolates. The 20 *K. pneumoniae* isolates include two isolates with NDM-5 + OXA-232 and one isolate with NDM-1 + OXA-181. Therefore 23 carbapenemases of different classes were identified among the 20 *K. pneumoniae* isolates. Correspondingly, a total of 97 carbapenemases of different classes were identified among the total 93 CPE isolates.

5 The 93 isolates include multiple, distinct CPE from nine patients:

- *E. coli* with NDM-5 and *E. coli* with OXA-181;
- *E. coli* with NDM-5, *E. coli* with NDM-7 and *E. coli with* OXA-181
- *E. coli* and *K. pneumoniae* with NDM-9;
- *E. coli* and *E. cloacae* complex with OXA-181;
- *E. coli, K. pneumoniae* and *Citrobacter youngae* with NDM-25;
- *E. coli, K. pneumoniae, P. stuartii and P. penneri* with NDM-1.
- *E. coli, K. pneumonaie, K oxytoca, P stuartii, E. cloacae* complex and *Citrobacter freundii* with NDM-1
- *K. pneumoniae* and *P. mirabilis* with NDM-1;
- *K. pneumoniae* with NDM-1 and *C. freundii* and NDM-7.

In 2018 the first plasmid-associated IMI carbapenemase gene was identified in New Zealand. The IMI-2 gene was identified in an *Enterobacter cloacae* isolate, and its location was confirmed using Illumina and MinION sequencing. The IMI-1 gene was first identified on the chromosome of *E. cloacae* in the USA in 1984. Initially reports of the IMI carbapenemase from clinical isolates were rare, although recently a number of IMI subtypes have been reported on plasmids, both in *Enterobacter* sp. and in other species.

2018 was also the first year that an OXA-23 carbapenemase was identified in a CPE in New Zealand. The OXA-23 carbapenemases have been reported worldwide in *Acinetobacter baumannii*, however their presence in Enterobacterales is rare.

Probable place of acquisition of carbapenemase–producing Enterobacterales

Travel history was reported for the patients from whom all 93 CPE were isolated in 2018. 68.8% (64/93) of the CPE, from patients for whom travel history was reported, were from patients who had been overseas. The Indian subcontinent was by far the most common probable place of acquisition (Table 2).

62.5% (40/64) of the CPE apparently acquired overseas were from patients who were hospitalised overseas. Of the 24 CPE isolated from patients who had been overseas but not hospitalised there, 17 were probably acquired on the Indian subcontinent.

Seven of the nine patients who had ≥2 distinct CPE had recently been overseas: three patients had been hospitalised on the Indian subcontinent, one patient had been in India but was not reported to have been hospitalised there, two patients had been hospitalised in other parts of Asia, and one patient had been hospitalised in the Pacific. Of the four CPE isolates that had more than one class of carbapenemase, three were from patients who had been hospitalised in India and one who had been hospitalised in the Pacific.

Transmission of carbapenemase–producing Enterobacterales in New Zealand

There were 29 isolates, from 21 patients who had no history of recent overseas travel. The likely source of six CPE from six patients was not identified. The remaining 23 isolates were associated with the five probable CPE cross-transmission events in 2018.

The first event occurred in Middlemore Hospital, Auckland. The index case, who had been hospitalised in the Pacific, was on the same service as three other patients who probably acquired their CPE at Middlemore Hospital. Four distinct NDM-1 producing

Enterbacterales were isolated from the index case, six from the second case, four from the third case and one from the fourth case.

The second event also occurred at Middlemore Hospital and involved probable transmission of one isolate between two patients on the same ward. The likely index patient had recently been hospitalised in India.

The third event involved a cluster of eight *E. coli* isolates with OXA-48 that were isolated from eight patients in the Wellington region. The investigation into the source of this cluster his ongoing.

The other two transmission events involved probable transfer within two households. The first household transmission event involved three patients belonging one family. Two family members are thought to have acquired their CPE in New Zealand. The likely index patient had recently been in India. The second household transmission event involved two patients. One patient had recently travelled to South-East Asia and the other patient is thought to have acquired their CPE in New Zealand.

Table 2. Probable place of acquisition of carbapenemase-producing Enterobacterales, 2018

Carbapenemase type and subtype	Number of isolates[1]							
	Probable region of acquisition							
	Indian subcontinent	New Zealand[2]	Other parts of Asia[3]	Pacific	Europe	Middle East	Unknown[4]	Total
NDM	**25**	**18**	**9**	**3**	**1**	**0**	**0**	**56**
NDM-1	1	15	3	2	1	0	0	22
NDM-4	1	0	0	0	0	0	0	1
NDM-5	20	3	2	1	0	0	0	26
NDM-7	1	0	1	0	0	0	0	2
NDM-9	2	0	0	0	0	0	0	2
NDM-25	0	0	3	0	0	0	0	3
IMP	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**1**
IMP-4	0	1	0	0	0	0	0	1
OXA-48-like	**12**	**9**	**3**	**1**	**1**	**1**	**1**	**28**
OXA-48	0	9	2	0	1	1	0	13
OXA-181	12	0	1	1	0	0	1[4]	15
KPC	**0**	**0**	**0**	**0**	**2**	**0**	**0**	**2**
KPC-3	0	0	0	0	2	0	0	2
IMI	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**1**
IMI-2	0	0	0	1	0	0	0	1
OXA-23	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**1**
NDM and OXA-48-like	**3**	**0**	**0**	**1**	**0**	**0**	**0**	**4**
NDM-5 and OXA-181	2	0	0	0	0	0	0	2
NDM-5 and OXA-232	1	0	0	1	0	0	0	2
Total	**40**	**29**	**12**	**6**	**4**	**1**	**1**	**93**

Footnotes on next page

Footnotes for Table 2:

1 Includes multiple isolates from nine patients who had ≥2 distinct CPE (see Table 1, footnote 5). Seven of the nine patients who had ≥2 distinct CPE had recently been overseas: four to the Indian subcontinent, two to other parts of Asia, and one patient to the Pacific. All had been hospitalised overseas, except one patient who had travelled to India.

2 Includes 23 isolates from five probable CPE cross-transmission events in New Zealand: 13 isolates with NDM-1, eight with OXA-48, one with NDM-5 and one with IMP-4. The other six isolates were from patients with no recent travel history, and the likely source of the CPE was not determined.

3 All Asia other than the Indian subcontinent.

4 Unknown includes one patient that had recent travel history to both India and Singapore.