The extent of carbapenemase encoding genes in public genome sequences

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Abstract

Genome sequences provide information on the genetic elements present in an organism, and currently there are databases containing hundreds of thousands of bacterial genome sequences. These repositories allow for mining patterns concerning antibiotic resistance gene occurrence in (pathogenic) bacteria in e.g. natural environments or animal reservoirs, and link these to relevant metadata such as bacterial host species, year and country of isolation, and co-occurrence with other resistance genes.

In this study we use public repositories to investigate the dissemination of carbapenemase-encoding genes, the emergence and spread of which is considered a grave public health concern.

Based on publicly available genome sequences from PATRIC and public resistance gene identification tools, we found 7,884 bacterial genomes, belonging to 95 species, that carry in total 9,892 carbapenemase-encoding genes (CEGs), amongst which *bla*$_{\text{NDM}}$, *bla*$_{\text{OXA}}$, *bla*$_{\text{VIM}}$, *bla*$_{\text{IMP}}$ and *bla*$_{\text{KPC}}$. We were able to distinguish between chromosomally located resistance genes (4,137; 42%) and plasmid-located resistance genes (5,753; 58%). We detected a large proportion of identified CEGs in multiple bacterial species (8,361 out of 9,892; 85%). For example, the New Delhi metallo-beta-lactamase NDM-1 was found in 42 distinct bacterial species, and present in seven different reservoirs.

These data complement previous systematic reviews, in which carbapenem-resistant Enterobacteriaceae were found in wildlife, livestock and companion animals. Our data show the extent of carbapenem-resistance far beyond the canonical species *Acetinobacter baumannii, Klebsiella pneumoniae* or *Pseudomonas aeruginosa*. Considering the apparent ease with which resistance genes are exchanged between species, we see a need for comprehensive surveillance and transmission analyses, akin to previous extensive surveys that focused on extended spectrum beta-lactamases. This may help to fully appreciate the spread of CEGs and determine ways in which transmission to humans can be minimized.

Introduction

Twenty-five years since the sequencing revolution started we see the availability of hundreds of thousands of bacterial genomes [1], enabling a vast number of comparative analyses leading to e.g. virulence factor prediction [2] or metabolic pathway modelling [3]. The extensive genome resource PATRIC [1] includes detailed information on resistance genes [4], and amongst the many different uses for these cumulated data, they also aim at predicting AMR phenotypes in individual genomes. However, the accumulation of all genetic data with their associated metadata on bacterial host species, isolation source, year of isolation, and co-occurrence with other clinical resistance genes, also allows for a global view into the dissemination of resistance genes, for example of carbapenemase-encoding genes in high priority pathogens [5].

Recently, Köck et al. [6] performed a systematic literature review on the occurrence of carbapenem-resistant Enterobacteriaceae (CRE). The authors concluded that the prevalence of CRE in wildlife, livestock and companion animals and directly exposed humans poses public health risks. This review was limited to Enterobacteriaceae and environmental prevalence of CRE had not been included, even though genes encoding most acquired carbapenemases are believed to have transferred from environmental bacteria into species with clinical relevance [7]. We propose that evaluating carbapenemase-encoding genes (CEGs) and their associated metadata from genomic databases may add to the broader picture of the distribution of these genes throughout relevant (non-human) reservoirs, and may highlight transmission between bacterial species via mobile genetic elements. These databases can show whether other bacterial species can represent CEG reservoirs, even when the original researchers of these genomes may not have annotated the carbapenem-resistance potential of these species. We aim to tabulate carbapenemase-encoding genes from an extensive genome database, in order to appraise their distribution.

Materials and Methods

Dataset and curation

All available 175,882 bacterial genomes (August 2018) and their corresponding metadata (e.g. bacterial species, reservoir (e.g. forest, chicken) were downloaded from PATRIC [1]. Annotated genes were subjected to the Resistance Gene Identifier (RGI [8], perfect and strict matches only), and the genes were filtered for 'protein homolog model' only. The Beta-lactamase database [9] was searched for carbapenemase-encoding genes only, and a total of 566 CEGs were found (Supplementary Table S1). These were used in a BLAST query of all resistance genes in the database (100% identity over 100% of the alignment length), and MOB-suite was used to predict their genomic location (chromosome, plasmid) [10]. Metadata from the genomes were queried against the NCBI taxonomy database (www.ncbi.nlm.nih.gov/taxonomy), and the corresponding taxonomic lineage of the host was retrieved.

Results and Discussion

Carbapenemase-encoding genes in publicly available genomes

From the collection of nearly 2 million resistance genes in ~176,000 sequenced bacterial genomes, we identify 9,892 CEGs in 7,884 bacterial genomes. These 7,884 genomes belong to 95 species (18 of which without a specific species designation, Supplementary Table S1), from 32 genera and 15 families, showing that the distribution of these high-priority resistance genes extends far beyond the well-known carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacteriaceae*.

Considering that the number of unique genomes is lower than the number of CEGs, we deduce that the majority (6,191 CEGs) are present in single copy in their genome, whereas 3,701 genes were present either in multicopy in some genomes or that two or more different CEGs were present in some genomes (Table 1). Co-expression of carbapenemase genes, for example, $bla_{\text{OXA-48}}$ and $bla_{\text{NDM-1}}$, together with other resistance genes that might be present on the plasmids, reduces treatment options [11].

We found that identical CEGs are frequently shared between bacterial species. Of the 9,892 CEGs, we find that 1,531 are only encountered in a single bacterial species, whereas 8,361 genes (85%) are found in more than one species. We detect the well-known CEGs $bla_{\textit{NDM-1}}$, $bla_{\textit{KPC-2}}$, $bla_{\textit{IMP-1}}$ and $bla_{\textit{OXA-48}}$ in 42, 37, 15 and 14 species, which shows that a vast number of bacterial species act as CEG reservoirs, with some species harboring a truly large diversity of resistance genes. For example, the 4,502 *A. baumannii* genomes here collectively harbor 98 distinct CEGs, and the 3,285 *K. pneumoniae* genomes contain 41 distinct CEGs. $bla_{\text{IMP-1}}$ was most often detected in *Enterobacter hormaechei* and *Klebsiella pneumoniae,* but also in *Acintobacter baumannii*, *Acintobacter junii*, *Acinetobacter pittii*, *Acinetobacter nosocomialis*, *Enterobacter cloacae*, *Enterobacter kobei, Enterobacter asburiae*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Serratia marcescens*. bla_{OXA48} was predominantly found in *K. pneumoniae*, but also in *E. coli, Enterobacter aerogens, E. cloacae*, *E. hormaechei*, *E. kobei, Citrobacter freundii, Citrobacter koseri*, *Shewanella* sp. (on chromosome), *Kluyvera ascorbata, Proteus mirabilis* and *Raoultella ornithinolytica*. $bla_{\text{NDM-1,}}$ bla_{KPC2} and $bla_{\text{KPC-3}}$ were most often identified in *K. pneumoniae*, followed by *E. coli* and *Enterobacter cloacae*. Figure 1 shows the distribution of CEGs over the different environments and species.

Horizontal gene transfer is an important evolutionary force for adaptation, and mobile genetic elements are well-known vectors for gene exchange, especially for antibiotic resistance genes [12]. We evaluated the genomic location of CEGs and found that 4,137 (42%) were predicted to be chromosomally located, 5,753 (58%) were predicted to be plasmid-located, which shows that a large proportion of CEGs have an enhanced capacity for horizontal gene transfer. $\mathit{bla}_{\text{IMP1}}$ was most often located on IncN or IncW plasmids, $\mathit{bla}_{\text{KPC2}}$ on IncFII or IncU plasmids, $\mathit{bla}_{\text{KPC-3}}$ on IncFIA or IncFII plasmids, $\mathit{bla}_{\text{NDM-1}}$ on IncA/C plasmids, $\mathit{bla}_{\text{NDM-5}}$ on IncX3 plasmids and $\mathit{bla}_{\text{OXA-48}}$ on Inc L/M plasmids. Previous genomic epidemiology studies may not have fully appreciated the widespread character of CEG dissemination [13].

We distinguished 11 different resistance reservoirs of which the human isolates represented the largest reservoir of CEGs in this study (8,099 genes, 82%). However, this does not mean this reservoir is the major reservoir for resistance genes, but rather reflects the more frequent sampling of humans. In addition, more CEG-reservoir combinations exist as this analysis is limited to the isolates present in the database. Many non-human reservoirs also contained more than one type of CEG (Table 2).

Conclusions

Large genome repositories represent treasure troves for comparative analyses in different fields of study, even though these databases do not represent surveillance data and therefore analysis is limited to those isolates that are present in the database, nor are they free of annotation errors. Still, regarding antibiotic resistance, genome sequence collections allow for an alternative view on the distribution of resistance genes and exchange potential between bacteria and reservoirs.

Carbapenemase-encoding genes are distributed over a large number of bacterial species, with some genes, such as *bla*$_{NDM-1}$, present in at least 42 different species, in at least seven distinct non-human reservoirs. These numbers show the breadth of reservoirs and the vast potential for resistance gene exchange and transmission.

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Table 1. The distribution of the 9,892 carbapenemase-encoding genes in 7,884 bacterial genomes. The majority of genes (6,191) is present in single copy in its genome, although 3,701 genes reside in a genome with one or more additional carbapenemase-encoding genes.

	Different CEGs		
Genes per genome	**1**	**2**	**3**
1	**6191**	**0**	**0**
2	**81**	**1567**	**0**
3	**21**	**52**	**32**
4	**4**	**8**	**0**
5	**1**	**4**	**1**
6	**0**	**2**	**0**

Table 2. Diversity of CEGs in the 11 reservoirs from the genome database

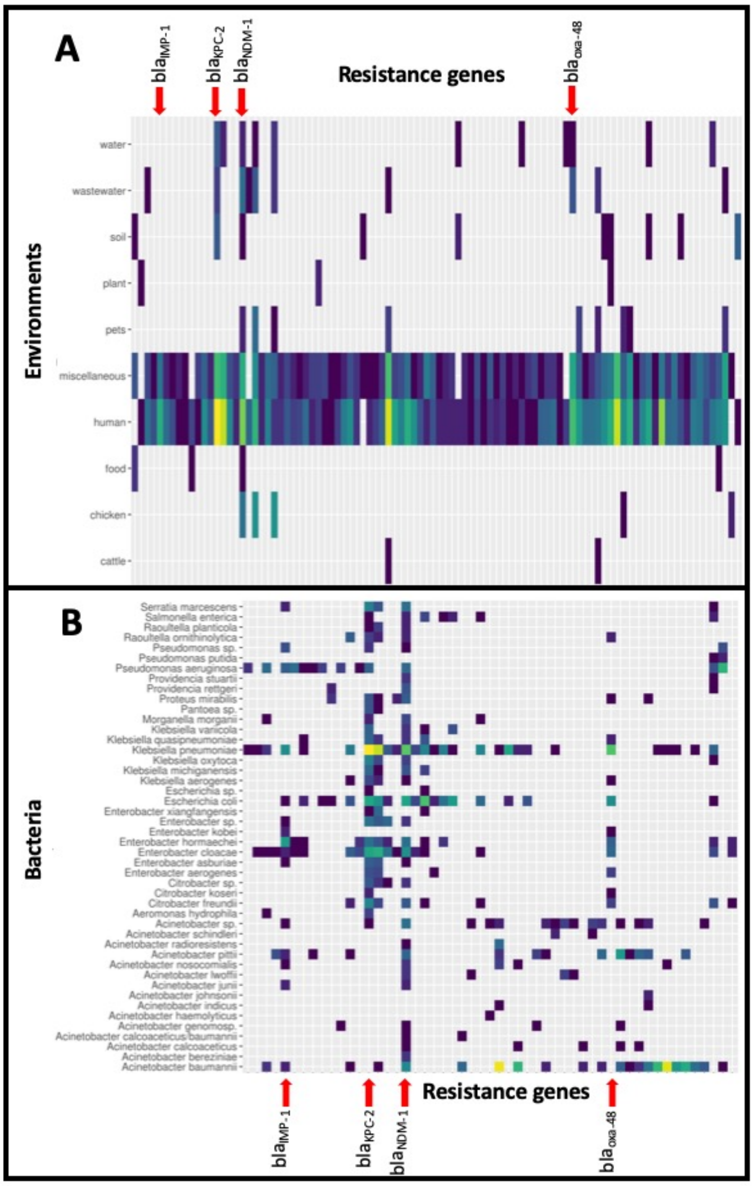
Reservoir	# Distinct CEGs	CEGs	# Species	Species*
Pig	1	NDM-1	1	*A. baumannii*
Cattle	3	OXA-146,OXA-23,OXA-58	1	*A. indicus*
Plant	3	CGB-1,OXA-120,OXA-65	2	*A. baumannii, C. indologenes,*
Chicken	5	NDM-1,NDM-5,NDM-9,OXA-68,VIM-48	5	*A. baumannii, E. coli, K. pneumoniae, S. enterica, P. putida*
Food	5	BcII-1,IMP-27,NDM-1,OXA-497,VIM-1	6	*A. baumanni, B. cereus, B. thuringensis, E. coli, V. parahaemolyticus, S. enterica*
Pets	9	NDM-1,NDM-5,NDM-9,OXA-23,OXA-500,OXA-58,OXA-68,OXA-69,VIM-2	6	*A. baumannii, A. gandensis, A. pittii, A. radioresistens, E. coli, P. aeruginosa*
Soil	10	BcII-1,KPC-2,NDM-1,OXA-213,OXA-273,OXA-64,OXA-65,OXA-72,OXA-91,VIM-5	10	*A. baumannii, A. calcoaceticus, Acinetobacter sp., B. cereus, B. subtilis, C. braakii, C. freundii, Erythrobacter sp., P. guariconensis, P. plecoglossicida*
Wastewater	11	GES-5,KPC-2,NDM-1,NDM-4,NDM-5,NDM-9,OXA-23,OXA-48,OXA-58,SHV-38,VIM-2	11	*A. johnsonii, A. junii, Acinetobacter sp., A. hydrophila, C. freundii, E. cloacae, E. kobei, E. coli, Escherichia sp., K. pneumoniae, Pseudomonas sp.*
Water	13	KPC-2,KPC-3,NDM-1,NDM-5,NDM-9,OXA-269,OXA-273,OXA-280,OXA-360,OXA-444,OXA-48,OXA-72,SPM-1	14	*A. calcoaceticus, A. johnsonii, A. pittii, A. schindleri, E. cloacae, E. coli, G. pentaromativorans, K. pneumoniae, K. quasipneumoniae, K. variicola, P. aeruginosa, Pseudomonas sp., Ralstonia sp., V. cholerae*
Miscellaneous	109		48	***
Human	175		73	***

*) for the full names, please refer to Supplementary Table S2

**) the list of genes is in the Supplementary Table S3

***) the list of species is in the Supplementary Table S4

Figure 1. Distribution of the 9,892 carbapenemase-encoding genes in the bacterial species (a) and the non-human reservoirs (b). Horizontal lines represent reservoirs (A) or bacterial species (B) that collectively harbor different CEGs. Vertical lines represent CEGs that occur in many different bacterial species or reservoirs: four genes have been highlighted. The figure was simplified by removing the rare CEGs, and the full data is available in Supplementary Table S5.



Supplementary Table S1

566 carbapenemases retrieved from the beta-lactamase database (March 2018).

Separately provided due to size

Supplementary Table S2

Species in which carbapenemase-encoding genes are identified.

	Bacterial species
1	*Achromobacter denitrificans*
2	*Achromobacter sp.*
3	*Acinetobacter baumannii*
4	*Acinetobacter bereziniae*
5	*Acinetobacter calcoaceticus*
6	*Acinetobacter calcoaceticus/baumannii*
7	*Acinetobacter dijkshoorniae*
8	*Acinetobacter gandensis*
9	*Acinetobacter genomosp.*
10	*Acinetobacter guillouiae*
11	*Acinetobacter haemolyticus*
12	*Acinetobacter indicus*
13	*Acinetobacter johnsonii*
14	*Acinetobacter junii*
15	*Acinetobacter lwoffii*
16	*Acinetobacter nosocomialis*
17	*Acinetobacter pittii*
18	*Acinetobacter radioresistens*
19	*Acinetobacter schindleri*
20	*Acinetobacter soli*
21	*Acinetobacter sp.*
22	*Aeromonas caviae*
23	*Aeromonas hydrophila*
24	*Aeromonas sp.*
25	*Alcaligenes faecalis*
26	*Bacillus cereus*
27	*Bacillus subtilis*
28	*Bacillus thuringiensis*
29	*Chryseobacterium gleum*
30	*Chryseobacterium indologenes*
31	*Citrobacter braakii*
32	*Citrobacter farmeri*
33	*Citrobacter freundii*
34	*Citrobacter koseri*
35	*Citrobacter sp.*
36	*Citrobacter werkmanii*
37	*Elizabethkingia miricola*
38	*Elizabethkingia sp.*
39	*Enterobacter aerogenes*

40	*Enterobacter asburiae*
41	*Enterobacter cloacae*
42	*Enterobacter hormaechei*
43	*Enterobacter kobei*
44	*Enterobacter ludwigii*
45	*Enterobacter mori*
46	*Enterobacter sp.*
47	*Enterobacter xiangfangensis*
48	*Erythrobacter sp.*
49	*Escherichia coli*
50	*Escherichia sp.*
51	*Gallaecimonas pentaromativorans*
52	*Klebsiella aerogenes*
53	*Klebsiella grimontii*
54	*Klebsiella michiganensis*
55	*Klebsiella oxytoca*
56	*Klebsiella pneumoniae*
57	*Klebsiella quasipneumoniae*
58	*Klebsiella sp.*
59	*Klebsiella variicola*
60	*Kluyvera ascorbata*
61	*Kluyvera intermedia*
62	*Leclercia adecarboxylata*
63	*Leclercia sp.*
64	*Morganella morganii*
65	*Mycobacterium tuberculosis*
66	*Pandoraea pnomenusa*
67	*Pantoea sp.*
68	*Pluralibacter gergoviae*
69	*Proteus mirabilis*
70	*Providencia rettgeri*
71	*Providencia sp.*
72	*Providencia stuartii*
73	*Pseudomonas aeruginosa*
74	*Pseudomonas guariconensis*
75	*Pseudomonas plecoglossicida*
76	*Pseudomonas putida*
77	*Pseudomonas sp.*
78	*Pseudomonas stutzeri*
79	*Ralstonia mannitolilytica*
80	*Ralstonia pickettii*
81	*Ralstonia sp.*
82	*Raoultella ornithinolytica*
83	*Raoultella planticola*

84	*Salmonella enterica*
85	*Serratia marcescens*
86	*Serratia sp.*
87	*Shewanella bicestrii*
88	*Shewanella putrefaciens*
89	*Shewanella sp.*
90	*Shigella sonnei*
91	*Staphylococcus aureus*
92	*Staphylococcus epidermidis*
93	*Streptomyces sp.*
94	*Vibrio cholerae*
95	*Vibrio parahaemolyticus*

Supplementary Table S3

The list of carbapenemases encoded by *bla*-genes in the miscellaneous and human reservoirs

Miscellaneous (109 genes)

BcII-1,GES-5,GIM-1,IMI-12,IMP-1,IMP-13,IMP-14,IMP-18,IMP-19,IMP-34,IMP-4,IMP-8,IMP-9,KPC-2,KPC-3,KPC-4,KPC-6,NDM-1,NDM-19,NDM-5,NDM-6,NDM-7,NDM-9,NmcA,OXA-100,OXA-103,OXA-104,OXA-106,OXA-109,OXA-113,OXA-120,OXA-121,OXA-126,OXA-144,OXA-172,OXA-181,OXA-202,OXA-208,OXA-211,OXA-212,OXA-213,OXA-214,OXA-217,OXA-223,OXA-23,OXA-232,OXA-235,OXA-24,OXA-242,OXA-244,OXA-245,OXA-254,OXA-259,OXA-263,OXA-264,OXA-267,OXA-272,OXA-276,OXA-277,OXA-281,OXA-282,OXA-283,OXA-301,OXA-314,OXA-334,OXA-338,OXA-340,OXA-343,OXA-344,OXA-360,OXA-374,OXA-378,OXA-381,OXA-402,OXA-407,OXA-421,OXA-431,OXA-48,OXA-500,OXA-506,OXA-51,OXA-510,OXA-545,OXA-58,OXA-60,OXA-64,OXA-65,OXA-66,OXA-67,OXA-68,OXA-69,OXA-70,OXA-71,OXA-72,OXA-78,OXA-82,OXA-83,OXA-90,OXA-91,OXA-92,OXA-94,OXA-98,SME-4,SPM-1,VIM-1,VIM-2,VIM-33,VIM-48,VIM-7

Human (175 genes)

BlaB-9,CGB-1,DIM-1,GES-2,GES-20,GES-24,GES-5,GES-6,GIM-1,IMI-1,IMI-2,IMI-4,IMI-7,IMI-9,IMP-1,IMP-10,IMP-13,IMP-14,IMP-18,IMP-19,IMP-26,IMP-27,IMP-34,IMP-4,IMP-45,IMP-6,IMP-7,IMP-8,KPC-12,KPC-18,KPC-2,KPC-3,KPC-31,KPC-32,KPC-33,KPC-4,KPC-5,KPC-6,KPC-7,KPC-8,NDM-1,NDM-21,NDM-4,NDM-5,NDM-6,NDM-7,NDM-9,NmcA,OXA-100,OXA-104,OXA-106,OXA-107,OXA-109,OXA-111,OXA-113,OXA-117,OXA-120,OXA-121,OXA-123,OXA-126,OXA-128,OXA-132,OXA-134,OXA-143,OXA-144,OXA-151,OXA-162,OXA-164,OXA-172,OXA-180,OXA-181,OXA-204,OXA-207,OXA-208,OXA-214,OXA-217,OXA-219,OXA-223,OXA-225,OXA-23,OXA-231,OXA-232,OXA-234,OXA-235,OXA-237,OXA-239,OXA-24,OXA-241,OXA-242,OXA-244,OXA-245,OXA-259,OXA-260,OXA-261,OXA-262,OXA-263,OXA-264,OXA-265,OXA-268,OXA-270,OXA-271,OXA-272,OXA-273,OXA-276,OXA-277,OXA-281,OXA-282,OXA-283,OXA-284,OXA-285,OXA-300,OXA-301,OXA-304,OXA-305,OXA-312,OXA-314,OXA-317,OXA-337,OXA-338,OXA-340,OXA-360,OXA-374,OXA-378,OXA-383,OXA-402,OXA-407,OXA-417,OXA-421,OXA-424,OXA-425,OXA-426,OXA-431,OXA-441,OXA-444,OXA-48,OXA-499,OXA-500,OXA-501,OXA-502,OXA-

503,OXA-506,OXA-51,OXA-533,OXA-535,OXA-58,OXA-64,OXA-65,OXA-66,OXA-68,OXA-69,OXA-70,OXA-71,OXA-72,OXA-75,OXA-78,OXA-80,OXA-82,OXA-83,OXA-88,OXA-90,OXA-91,OXA-92,OXA-94,OXA-95,OXA-96,OXA-98,OXA-99,SME-2,SME-4,SPM-1,VIM-1,VIM-2,VIM-24,VIM-36,VIM-4,VIM-5

Supplementary Table S4

The list of bacterial species in the human and miscellaneous reservoirs

Bacterial species in the human reservoirs carrying CEGs in their genome

Human

1 *Pantoea sp.*
2 *Serratia sp.*
3 *Aeromonas sp.*
4 *Leclercia sp.*
5 *Klebsiella sp.*
6 *Shewanella sp.*
7 *Pseudomonas sp.*
8 *Providencia sp.*
9 *Citrobacter sp.*
10 *Escherichia sp.*
11 *Shigella sonnei*
12 *Enterobacter sp.*
13 *Escherichia coli*
14 *Aeromonas caviae*
15 *Enterobacter mori*
16 *Proteus mirabilis*
17 *Achromobacter sp.*
18 *Acinetobacter sp.*
19 *Enterobacter kobei*
20 *Citrobacter koseri*
21 *Klebsiella oxytoca*
22 *Acinetobacter soli*
23 *Kluyvera ascorbata*
24 *Pseudomonas putida*
25 *Elizabethkingia sp.*
26 *Morganella morganii*
27 *Citrobacter farmeri*
28 *Kluyvera intermedia*
29 *Salmonella enterica*
30 *Serratia marcescens*
31 *Pandoraea pnomenusa*
32 *Enterobacter cloacae*
33 *Acinetobacter pittii*
34 *Providencia rettgeri*
35 *Citrobacter freundii*
36 *Aeromonas hydrophila*
37 *Klebsiella aerogenes*
38 *Klebsiella grimontii*
39 *Klebsiella variicola*
40 *Providencia stuartii*

41	*Shewanella bicestrii*
42	*Alcaligenes faecalis*
43	*Pseudomonas stutzeri*
44	*Klebsiella pneumoniae*
45	*Enterobacter asburiae*
46	*Raoultella planticola*
47	*Acinetobacter lwoffii*
48	*Citrobacter werkmanii*
49	*Enterobacter ludwigii*
50	*Chryseobacterium gleum*
51	*Pseudomonas aeruginosa*
52	*Enterobacter aerogenes*
53	*Acinetobacter baumannii*
54	*Enterobacter hormaechei*
55	*Acinetobacter genomosp.*
56	*Pluralibacter gergoviae*
57	*Acinetobacter johnsonii*
58	*Elizabethkingia miricola*
59	*Klebsiella michiganensis*
60	*Acinetobacter bereziniae*
61	*Leclercia adecarboxylata*
62	*Acinetobacter schindleri*
63	*Ralstonia mannitolilytica*
64	*Klebsiella quasipneumoniae*
65	*Raoultella ornithinolytica*
66	*Acinetobacter nosocomialis*
67	*Staphylococcus epidermidis*
68	*Acinetobacter haemolyticus*
69	*Enterobacter xiangfangensis*
70	*Acinetobacter calcoaceticus*
71	*Acinetobacter dijkshoorniae*
72	*Acinetobacter radioresistens*
73	*Acinetobacter calcoaceticus/baumannii*

Bacterial species in the miscellaneous reservoirs carrying CEGs in their genome

	Miscellaneous
1	*Pantoea sp.*
2	*Ralstonia sp.*
3	*Bacillus cereus*
4	*Citrobacter sp.*
5	*Vibrio cholerae*
6	*Enterobacter sp.*
7	*Escherichia coli*
8	*Streptomyces sp.*

9	*Acinetobacter sp.*
10	*Proteus mirabilis*
11	*Klebsiella oxytoca*
12	*Pseudomonas putida*
13	*Acinetobacter junii*
14	*Serratia marcescens*
15	*Morganella morganii*
16	*Salmonella enterica*
17	*Ralstonia pickettii*
18	*Enterobacter cloacae*
19	*Acinetobacter pittii*
20	*Klebsiella aerogenes*
21	*Citrobacter freundii*
22	*Providencia rettgeri*
23	*Providencia stuartii*
24	*Klebsiella variicola*
25	*Klebsiella pneumoniae*
26	*Enterobacter asburiae*
27	*Acinetobacter lwoffii*
28	*Raoultella planticola*
29	*Staphylococcus aureus*
30	*Bacillus thuringiensis*
31	*Pseudomonas aeruginosa*
32	*Enterobacter aerogenes*
33	*Acinetobacter baumannii*
34	*Enterobacter hormaechei*
35	*Shewanella putrefaciens*
36	*Acinetobacter johnsonii*
37	*Acinetobacter genomosp.*
38	*Klebsiella michiganensis*
39	*Acinetobacter bereziniae*
40	*Acinetobacter schindleri*
41	*Acinetobacter guillouiae*
42	*Acinetobacter nosocomialis*
43	*Raoultella ornithinolytica*
44	*Acinetobacter haemolyticus*
45	*Mycobacterium tuberculosis*
46	*Acinetobacter calcoaceticus*
47	*Achromobacter denitrificans*
48	*Acinetobacter radioresistens*

Supplementary Table S5

Presence of carbapenem-encoding genes in environmental reservoirs

resistancegene	reservoirs
SHV-38	wastewater
BcII-1	miscellaneous,soil,food
BlaB-9	human
CGB-1	human,plant
DIM-1	human
GES-2	human
GES-20	human
GES-24	human
GES-5	human,miscellaneous,wastewater
GES-6	human
GIM-1	human,miscellaneous
IMI-1	human
IMI-12	miscellaneous
IMI-2	human
IMI-4	human
IMI-7	human
IMI-9	human
IMP-1	miscellaneous,human
IMP-10	human
IMP-13	miscellaneous,human
IMP-14	miscellaneous,human
IMP-18	miscellaneous,human
IMP-19	miscellaneous,human
IMP-26	human
IMP-27	human,food
IMP-34	miscellaneous,human
IMP-4	human,miscellaneous
IMP-45	human
IMP-6	human
IMP-7	human
IMP-8	human,miscellaneous
IMP-9	miscellaneous
KPC-12	human
KPC-18	human
KPC-2	human,wastewater,miscellaneous,soil,water
KPC-3	human,miscellaneous,water
KPC-31	human
KPC-32	human
KPC-33	human
KPC-4	human,miscellaneous
KPC-5	human

KPC-6	miscellaneous,human
KPC-7	human
KPC-8	human
NDM-1	human,wastewater,miscellaneous,water,chicken,pets,soil,pig,food
NDM-19	miscellaneous
NDM-21	human
NDM-4	wastewater,human
NDM-5	human,miscellaneous,chicken,pets,wastewater,water
NDM-6	miscellaneous,human
NDM-7	human,miscellaneous
NDM-9	miscellaneous,pets,chicken,human,water,wastewater
NmcA	human,miscellaneous
OXA-100	human,miscellaneous
OXA-103	miscellaneous
OXA-104	miscellaneous,human
OXA-106	miscellaneous,human
OXA-107	human
OXA-109	human,miscellaneous
OXA-111	human
OXA-113	miscellaneous,human
OXA-117	human
OXA-120	human,plant,miscellaneous
OXA-121	human,miscellaneous
OXA-123	human
OXA-126	human,miscellaneous
OXA-128	human
OXA-132	human
OXA-134	human
OXA-143	human
OXA-144	human,miscellaneous
OXA-146	cattle
OXA-151	human
OXA-162	human
OXA-164	human
OXA-172	human,miscellaneous
OXA-180	human
OXA-181	human,miscellaneous
OXA-202	miscellaneous
OXA-204	human
OXA-207	human
OXA-208	human,miscellaneous
OXA-211	miscellaneous
OXA-212	miscellaneous
OXA-213	soil,miscellaneous
OXA-214	human,miscellaneous
OXA-217	human,miscellaneous

OXA-219	human
OXA-223	miscellaneous,human
OXA-225	human
OXA-23	human,miscellaneous,wastewater,pets,cattle
OXA-231	human
OXA-232	miscellaneous,human
OXA-234	human
OXA-235	miscellaneous,human
OXA-237	human
OXA-239	human
OXA-24	human,miscellaneous
OXA-241	human
OXA-242	human,miscellaneous
OXA-244	miscellaneous,human
OXA-245	human,miscellaneous
OXA-254	miscellaneous
OXA-259	miscellaneous,human
OXA-260	human
OXA-261	human
OXA-262	human
OXA-263	human,miscellaneous
OXA-264	miscellaneous,human
OXA-265	human
OXA-267	miscellaneous
OXA-268	human
OXA-269	water
OXA-270	human
OXA-271	human
OXA-272	miscellaneous,human
OXA-273	water,human,soil
OXA-276	human,miscellaneous
OXA-277	miscellaneous,human
OXA-280	water
OXA-281	miscellaneous,human
OXA-282	human,miscellaneous
OXA-283	miscellaneous,human
OXA-284	human
OXA-285	human
OXA-300	human
OXA-301	human,miscellaneous
OXA-304	human
OXA-305	human
OXA-312	human
OXA-314	miscellaneous,human
OXA-317	human
OXA-334	miscellaneous

OXA-337	human
OXA-338	miscellaneous,human
OXA-340	human,miscellaneous
OXA-343	miscellaneous
OXA-344	miscellaneous
OXA-360	human,miscellaneous,water
OXA-374	miscellaneous,human
OXA-378	miscellaneous,human
OXA-381	miscellaneous
OXA-383	human
OXA-402	human,miscellaneous
OXA-407	human,miscellaneous
OXA-417	human
OXA-421	human,miscellaneous
OXA-424	human
OXA-425	human
OXA-426	human
OXA-431	human,miscellaneous
OXA-441	human
OXA-444	human,water
OXA-48	human,miscellaneous,wastewater,water
OXA-497	food
OXA-499	human
OXA-500	miscellaneous,human,pets
OXA-501	human
OXA-502	human
OXA-503	human
OXA-506	human,miscellaneous
OXA-51	human,miscellaneous
OXA-510	miscellaneous
OXA-533	human
OXA-535	human
OXA-545	miscellaneous
OXA-58	wastewater,miscellaneous,human,pets,cattle
OXA-60	miscellaneous
OXA-64	human,miscellaneous,soil
OXA-65	human,miscellaneous,soil,plant
OXA-66	human,miscellaneous
OXA-67	miscellaneous
OXA-68	human,miscellaneous,pets,chicken
OXA-69	human,miscellaneous,pets
OXA-70	human,miscellaneous
OXA-71	human,miscellaneous
OXA-72	human,miscellaneous,water,soil
OXA-75	human
OXA-78	miscellaneous,human

OXA-80	human
OXA-82	human,miscellaneous
OXA-83	human,miscellaneous
OXA-88	human
OXA-90	human,miscellaneous
OXA-91	human,miscellaneous,soil
OXA-92	human,miscellaneous
OXA-94	human,miscellaneous
OXA-95	human
OXA-96	human
OXA-98	human,miscellaneous
OXA-99	human
SME-2	human
SME-4	human,miscellaneous
SPM-1	miscellaneous,human,water
VIM-1	human,miscellaneous,food
VIM-2	miscellaneous,pets,human,wastewater
VIM-24	human
VIM-33	miscellaneous
VIM-36	human
VIM-4	human
VIM-48	chicken,miscellaneous
VIM-5	human,soil
VIM-7	miscellaneous

Presence of carbapenem-encoding genes in bacterial species

resistancegene	**species**
SHV-38	Klebsiella pneumoniae
BcII-1	Bacillus cereus,Bacillus thuringiensis
BlaB-9	Elizabethkingia sp.,Elizabethkingia miricola
CGB-1	Chryseobacterium gleum,Chryseobacterium indologenes
DIM-1	Pseudomonas aeruginosa
GES-2	Enterobacter cloacae
GES-20	Pseudomonas aeruginosa,Klebsiella pneumoniae
GES-24	Enterobacter cloacae,Klebsiella pneumoniae
GES-5	Klebsiella pneumoniae,Pseudomonas aeruginosa,Enterobacter cloacae,Morganella morganii,Aeromonas hydrophila,Acinetobacter baumannii
GES-6	Pseudomonas aeruginosa
GIM-1	Acinetobacter pittii,Enterobacter cloacae
IMI-1	Enterobacter cloacae
IMI-12	Enterobacter asburiae
IMI-2	Enterobacter mori
IMI-4	Enterobacter cloacae
IMI-7	Enterobacter cloacae

IMI-9	Enterobacter sp.
IMP-1	Pseudomonas aeruginosa,Acinetobacter junii,Serratia marcescens,Acinetobacter baumannii,Pseudomonas sp.,Enterobacter cloacae,Enterobacter kobei,Acinetobacter nosocomialis,Acinetobacter pittii,Acinetobacter sp.,Escherichia coli,Klebsiella pneumoniae,Enterobacter hormaechei,Enterobacter sp.,Enterobacter asburiae
IMP-10	Pseudomonas sp.
IMP-13	Pseudomonas aeruginosa,Enterobacter cloacae,Enterobacter hormaechei
IMP-14	Pseudomonas aeruginosa,Enterobacter cloacae,Klebsiella pneumoniae,Escherichia coli,Klebsiella quasipneumoniae,Enterobacter hormaechei
IMP-18	Pseudomonas aeruginosa
IMP-19	Acinetobacter pittii,Pseudomonas aeruginosa
IMP-26	Escherichia coli,Pseudomonas aeruginosa
IMP-27	Proteus mirabilis,Providencia rettgeri,Escherichia coli
IMP-34	Pseudomonas aeruginosa,Acinetobacter genomosp.
IMP-4	Enterobacter cloacae,Klebsiella pneumoniae,Escherichia coli,Citrobacter freundii,Acinetobacter baumannii,Acinetobacter pittii,Raoultella ornithinolytica,Providencia sp.,Klebsiella aerogenes
IMP-45	Pseudomonas aeruginosa
IMP-6	Escherichia coli
IMP-7	Pseudomonas aeruginosa
IMP-8	Enterobacter cloacae,Enterobacter hormaechei,Pseudomonas aeruginosa
IMP-9	Pseudomonas aeruginosa
KPC-12	Klebsiella pneumoniae
KPC-18	Enterobacter cloacae
KPC-2	Citrobacter sp.,Pseudomonas aeruginosa,Citrobacter freundii,Enterobacter aerogenes,Enterobacter cloacae,Escherichia coli,Klebsiella oxytoca,Klebsiella pneumoniae,Enterobacter asburiae,Klebsiella michiganensis,Proteus mirabilis,Klebsiella variicola,Klebsiella grimontii,Serratia marcescens,Citrobacter koseri,Citrobacter braakii,Kluyvera intermedia,Aeromonas hydrophila,Enterobacter sp.,Klebsiella quasipneumoniae,Salmonella enterica,Pantoea sp.,Pseudomonas sp.,Citrobacter farmeri,Raoultella planticola,Raoultella ornithinolytica,Enterobacter hormaechei,Klebsiella aerogenes,Pluralibacter gergoviae,Enterobacter xiangfangensis,Morganella morganii,Escherichia sp.,Leclercia sp.,Serratia sp.,Aeromonas sp.,Achromobacter sp.,Acinetobacter sp.
KPC-3	Enterobacter cloacae,Escherichia coli,Klebsiella oxytoca,Klebsiella pneumoniae,Serratia marcescens,Enterobacter asburiae,Klebsiella quasipneumoniae,Raoultella planticola,Citrobacter sp.,Enterobacter sp.,Enterobacter aerogenes,Enterobacter xiangfangensis,Enterobacter hormaechei,Klebsiella aerogenes,Citrobacter freundii,Klebsiella michiganensis,Acinetobacter baumannii,Proteus mirabilis,Raoultella ornithinolytica,Pantoea sp.
KPC-31	Klebsiella pneumoniae
KPC-32	Klebsiella pneumoniae
KPC-33	Klebsiella pneumoniae
KPC-4	Enterobacter cloacae,Klebsiella pneumoniae,Escherichia coli,Enterobacter sp.,Citrobacter sp.,Enterobacter hormaechei
KPC-5	Enterobacter hormaechei
KPC-6	Proteus mirabilis,Klebsiella pneumoniae,Enterobacter cloacae
KPC-7	Klebsiella pneumoniae
KPC-8	Klebsiella pneumoniae
NDM-1	Enterobacter cloacae,Acinetobacter baumannii,Acinetobacter pittii,Citrobacter freundii,Escherichia coli,Klebsiella oxytoca,Klebsiella pneumoniae,Proteus mirabilis,Providencia stuartii,Serratia marcescens,Enterobacter asburiae,Acinetobacter junii,Raoultella planticola,Acinetobacter bereziniae,Providencia rettgeri,Acinetobacter sp.,Acinetobacter lwoffii,Klebsiella michiganensis,Klebsiella sp.,Vibrio cholerae,Shewanella putrefaciens,Citrobacter sp.,Morganella morganii,Enterobacter hormaechei,Acinetobacter nosocomialis,Klebsiella quasipneumoniae,Enterobacter sp.,Acinetobacter genomosp.,Bacillus subtilis,Acinetobacter soli,Acinetobacter radioresistens,Klebsiella variicola,Acinetobacter calcoaceticus,Acinetobacter dijkshoorniae,Klebsiella aerogenes,Citrobacter werkmanii,Pseudomonas aeruginosa,Leclercia adecarboxylata,Pseudomonas sp.,Raoultella ornithinolytica,Salmonella enterica,Acinetobacter calcoaceticus/baumannii,Vibrio parahaemolyticus
NDM-19	Klebsiella pneumoniae
NDM-21	Escherichia coli
NDM-4	Escherichia coli,Klebsiella pneumoniae,Enterobacter cloacae
NDM-5	Escherichia coli,Klebsiella michiganensis,Klebsiella pneumoniae,Klebsiella quasipneumoniae,Enterobacter xiangfangensis,Citrobacter freundii,Salmonella enterica,Klebsiella variicola,Streptomyces sp.,Enterobacter hormaechei,Escherichia sp.,Enterobacter cloacae
NDM-6	Escherichia coli,Enterobacter aerogenes,Klebsiella pneumoniae
NDM-7	Escherichia coli,Klebsiella pneumoniae,Salmonella enterica,Enterobacter hormaechei

NDM-9	Klebsiella variicola,Escherichia coli,Salmonella enterica,Klebsiella pneumoniae
NmcA	Enterobacter cloacae,Enterobacter ludwigii
OXA-100	Acinetobacter baumannii,Acinetobacter calcoaceticus/baumannii
OXA-103	Acinetobacter radioresistens
OXA-104	Acinetobacter baumannii
OXA-106	Acinetobacter baumannii
OXA-107	Acinetobacter baumannii
OXA-109	Acinetobacter baumannii
OXA-111	Acinetobacter baumannii
OXA-113	Acinetobacter baumannii
OXA-117	Acinetobacter baumannii
OXA-120	Acinetobacter baumannii
OXA-121	Acinetobacter baumannii
OXA-123	Acinetobacter baumannii
OXA-126	Acinetobacter baumannii
OXA-128	Acinetobacter baumannii
OXA-132	Acinetobacter baumannii
OXA-134	Acinetobacter sp.,Acinetobacter lwoffii
OXA-143	Acinetobacter baumannii
OXA-144	Acinetobacter baumannii
OXA-146	Acinetobacter indicus
OXA-151	Pandoraea pnomenusa
OXA-162	Klebsiella pneumoniae
OXA-164	Acinetobacter baumannii
OXA-172	Acinetobacter baumannii
OXA-180	Acinetobacter baumannii
OXA-181	Escherichia coli,Klebsiella pneumoniae,Citrobacter freundii,Morganella morganii,Salmonella enterica,Aeromonas caviae,Enterobacter cloacae
OXA-202	Acinetobacter baumannii
OXA-204	Klebsiella pneumoniae
OXA-207	Acinetobacter baumannii
OXA-208	Acinetobacter baumannii
OXA-211	Acinetobacter johnsonii
OXA-212	Acinetobacter johnsonii
OXA-213	Acinetobacter calcoaceticus
OXA-214	Acinetobacter sp.,Staphylococcus epidermidis,Acinetobacter haemolyticus
OXA-217	Acinetobacter baumannii
OXA-219	Acinetobacter baumannii
OXA-223	Acinetobacter baumannii
OXA-225	Acinetobacter baumannii
OXA-23	Acinetobacter baumannii,Acinetobacter pittii,Acinetobacter radioresistens,Acinetobacter sp.,Acinetobacter gandensis,Acinetobacter nosocomialis,Klebsiella pneumoniae,Acinetobacter indicus
OXA-231	Acinetobacter baumannii
OXA-232	Escherichia coli,Klebsiella pneumoniae,Shigella sonnei
OXA-234	Acinetobacter baumannii
OXA-235	Acinetobacter baumannii
OXA-237	Acinetobacter baumannii

OXA-239	Acinetobacter baumannii
OXA-24	Acinetobacter baumannii,Acinetobacter calcoaceticus,Acinetobacter nosocomialis,Klebsiella pneumoniae
OXA-241	Acinetobacter baumannii
OXA-242	Acinetobacter baumannii
OXA-244	Klebsiella pneumoniae,Escherichia coli
OXA-245	Klebsiella pneumoniae
OXA-254	Acinetobacter baumannii
OXA-259	Acinetobacter baumannii
OXA-260	Acinetobacter baumannii
OXA-261	Acinetobacter baumannii
OXA-262	Acinetobacter baumannii
OXA-263	Acinetobacter baumannii
OXA-264	Acinetobacter haemolyticus
OXA-265	Acinetobacter haemolyticus
OXA-267	Acinetobacter calcoaceticus
OXA-268	Acinetobacter calcoaceticus
OXA-269	Acinetobacter calcoaceticus
OXA-270	Acinetobacter pittii
OXA-271	Acinetobacter pittii
OXA-272	Acinetobacter genomosp.,Acinetobacter pittii
OXA-273	Acinetobacter pittii,Acinetobacter baumannii,Acinetobacter sp.
OXA-276	Acinetobacter schindleri,Klebsiella pneumoniae,Acinetobacter sp.
OXA-277	Acinetobacter schindleri
OXA-280	Acinetobacter johnsonii
OXA-281	Acinetobacter johnsonii
OXA-282	Acinetobacter lwoffii
OXA-283	Mycobacterium tuberculosis,Acinetobacter lwoffii,Acinetobacter sp.,Acinetobacter guillouiae
OXA-284	Acinetobacter sp.
OXA-285	Acinetobacter sp.,Acinetobacter lwoffii
OXA-300	Acinetobacter bereziniae
OXA-301	Acinetobacter bereziniae
OXA-304	Acinetobacter sp.
OXA-305	Acinetobacter sp.
OXA-312	Acinetobacter baumannii
OXA-314	Acinetobacter baumannii
OXA-317	Acinetobacter baumannii
OXA-334	Acinetobacter johnsonii
OXA-337	Acinetobacter baumannii
OXA-338	Acinetobacter baumannii
OXA-340	Acinetobacter baumannii,Acinetobacter calcoaceticus
OXA-343	Acinetobacter baumannii
OXA-344	Acinetobacter baumannii
OXA-360	Acinetobacter sp.,Acinetobacter schindleri
OXA-374	Acinetobacter baumannii
OXA-378	Acinetobacter baumannii
OXA-381	Acinetobacter baumannii

OXA-383	Acinetobacter baumannii
OXA-402	Acinetobacter baumannii
OXA-407	Acinetobacter baumannii
OXA-417	Acinetobacter pittii
OXA-421	Acinetobacter pittii,Acinetobacter baumannii,Acinetobacter sp.
OXA-424	Acinetobacter baumannii
OXA-425	Acinetobacter baumannii
OXA-426	Acinetobacter baumannii
OXA-431	Acinetobacter baumannii
OXA-441	Acinetobacter baumannii
OXA-444	Ralstonia mannitolilytica,Ralstonia sp.
OXA-48	Enterobacter aerogenes,Enterobacter cloacae,Escherichia coli,Klebsiella pneumoniae,Shewanella sp.,Citrobacter freundii,Enterobacter kobei,Klebsiella aerogenes,Citrobacter koseri,Enterobacter hormaechei,Raoultella ornithinolytica,Proteus mirabilis,Klebsiella quasipneumoniae,Kluyvera ascorbata
OXA-497	Acinetobacter baumannii
OXA-499	Acinetobacter pittii
OXA-500	Acinetobacter baumannii,Acinetobacter pittii,Acinetobacter genomosp.,Acinetobacter sp.,Acinetobacter calcoaceticus
OXA-501	Acinetobacter pittii
OXA-502	Acinetobacter pittii,Acinetobacter baumannii
OXA-503	Acinetobacter pittii
OXA-506	Acinetobacter calcoaceticus,Acinetobacter pittii,Acinetobacter baumannii,Acinetobacter sp.
OXA-51	Acinetobacter baumannii
OXA-510	Acinetobacter baumannii
OXA-533	Acinetobacter pittii
OXA-535	Shewanella bicestrii
OXA-545	Acinetobacter baumannii
OXA-58	Acinetobacter sp.,Acinetobacter baumannii,Proteus mirabilis,Acinetobacter pittii,Acinetobacter johnsonii,Acinetobacter indicus
OXA-60	Ralstonia pickettii,Ralstonia sp.
OXA-64	Acinetobacter baumannii
OXA-65	Acinetobacter baumannii,Klebsiella pneumoniae
OXA-66	Acinetobacter baumannii,Klebsiella pneumoniae,Acinetobacter nosocomialis
OXA-67	Acinetobacter baumannii
OXA-68	Acinetobacter baumannii,Klebsiella pneumoniae
OXA-69	Acinetobacter baumannii
OXA-70	Acinetobacter baumannii
OXA-71	Acinetobacter baumannii
OXA-72	Acinetobacter baumannii,Acinetobacter pittii,Gallaecimonas pentaromativorans,Erythrobacter sp.,Staphylococcus aureus
OXA-75	Acinetobacter baumannii
OXA-78	Acinetobacter baumannii
OXA-80	Acinetobacter baumannii
OXA-82	Acinetobacter baumannii
OXA-83	Acinetobacter baumannii,Klebsiella pneumoniae
OXA-88	Acinetobacter baumannii
OXA-90	Acinetobacter baumannii
OXA-91	Acinetobacter baumannii,Acinetobacter sp.
OXA-92	Acinetobacter baumannii
OXA-94	Acinetobacter baumannii

OXA-95	Acinetobacter baumannii
OXA-96	Acinetobacter pittii
OXA-98	Acinetobacter baumannii
OXA-99	Acinetobacter baumannii
SME-2	Serratia marcescens
SME-4	Serratia marcescens
SPM-1	Pseudomonas aeruginosa
VIM-1	Salmonella enterica,Providencia stuartii,Klebsiella oxytoca,Klebsiella pneumoniae,Achromobacter denitrificans,Enterobacter cloacae,Providencia rettgeri,Serratia marcescens,Pseudomonas putida,Enterobacter hormaechei,Pseudomonas aeruginosa,Citrobacter freundii,Escherichia coli
VIM-2	Pseudomonas aeruginosa,Pseudomonas putida,Pseudomonas sp.,Pseudomonas stutzeri,Alcaligenes faecalis,Acinetobacter baumannii
VIM-24	Klebsiella pneumoniae
VIM-33	Klebsiella pneumoniae
VIM-36	Pseudomonas aeruginosa
VIM-4	Enterobacter cloacae,Citrobacter freundii,Enterobacter hormaechei
VIM-48	Pseudomonas putida
VIM-5	Enterobacter hormaechei,Pseudomonas guariconensis,Pseudomonas plecoglossicida
VIM-7	Pseudomonas aeruginosa