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Characterization of Carbapenemases, Extended spectrum beta-lactamases, AmpC, Quinolone resistance and Aminoglycoside resistance determinants in Carbapenem -resistant Enterobacteriaceae clinical isolates in Mainland, China

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Abstract:

Carbapenem-reistant enterobacteriaceae (CRE) have been significant increasing recently and are highly endemic in China. Several studies demonstrated the prevalence of antibiotic resistance determinants (ARD) in CRE clinical isolates, but there was no comprehensive overview based on ARDs among CRE clinical isolates in Mainland, China. The objectives of this study was assess the prevalence and distribution pattern of carbapenemase genes, ESBL genes, AmpC-encoding genes, aminoglycoside resistant genes and PMQR among CRE clinical isolates in Mainland, China. A systematic literature review was performed by

searching different electronic databases including: Pubmed, Embase, CNKI, Wanfang and CQVIP. A random effect model was used to perform the meta-analysis based on comprehensive meta-analysis software.43 studies were included in this meta-analysis. The pooled prevalence of Carbapenemase genes, ESBL genes, AmpC-encoding genes, aminoglycoside resistance genes and PMQR genes in CRE clinical isolates of Mainland, China were 73.3% (95% CI=63.4-81.3), 81.8% (95%CI =74.3-87.4), 32.7% (95% CI=18.6-50.9), 60.6% (95% CI=47.4-72.4) and 70.8% (95%CI= 60.9-79), respectively. KPC (26.1%, 95%CI=18.1-36.1) was the most common type in Carbapenemase genes, followed by NDM (18.4%, 95% CI=12.2-26.7). KPC-2 (26.6%, 95% CI=18.3-36.9), NDM-1 (14%, 95% CI=9.4-20.1), IMP-4 (10.6%, 95% CI=6.6-16.6), VIM-1 (6.1%, 95% CI=3.3-11.3) and OXA-1 (9.8%, 95%CI=3.1-27.3) were the predominant type of a wide range of KPC, NDM, IMP, VIM and OXA variant genes. CTX-M-15 (32.2%, 95%CI= 20.1-47.1), SHV-12 (23.2%, 95% CI=16.5-31.5) and TEM-1 (54.5%, 95%CI=40-68.2) were the main type of CTX-M, SHV and TEM-1 variant genes. CMY-42 (17.1%, 95% CI=5.0-44.7), aac(6')-Ib (49.0%, 95% CI=36.4-61.6) and aac(6')-Ib-cr (37.5%, 95% CI=25.5-51.4) was the most frequently type of AmpC-encoding, aminoglycoside resistance and PMQR genes, respectively. KPC-2, TEM-1, CMY-42, aac(6')-Ib and aac(6')-Ib-cr were the most common type of Carbapenemase genes, ESBL genes, AmpC-encoding genes, aminoglycoside resistance genes and PMQR genes.

Keywords: Carbapenemases, ESBL, AmpC, Aminoglycosides, Fluoroquinolones, Carbapenem-resistant enterobacteriaceae

1. Introduction:

Carbapenem-reistant enterobacteriaceae (CRE) are within the top tier of the World Health Organization (WHO) list of antibiotic-resistant "priority pathogens" that have emerged as the greatest threat to public health worldwide [1]. CRE are defined as enterobacteria non-susceptible to any carbapenem antimicrobial or documented to produce a carbapenemas [2].These bacteria are common pathogens causing a variety of severe infections such as

ventilator-associated pneumonia(VAP), hospital-acquired pneumonia(HAP), community-acquired pneumonia (CAP), complicated urinary tract infections (cUTIs), complicated intra-abdominal infections (cIAIs) and bloodstream infections(BSIs). In China, CRE have been identified in almost every province [3,4] and the prevalence of CRE has been significant increasing recently [5, 6].

Severe infections caused by CRE lead to prolonged hospital stays and mortality rates as high as 50% in some reports [7-10]. Treatment of CRE infections is considered as a major problem for physician due to the complex antibiotic resistance mechanisms documented in these bacteria. In CRE, there are often concomitant carriage of a myriad resistant determinants including carbapenemases, extended-spectrum β-lactamases(ESBL), AmpC cephalosporinases (AmpC) associated with broad spectrum cephalosporin resistance, 16S rRNA methylases associated with resistance to aminoglycosides and plasmid-mediated quinolone resistance genes(PMQR), associated with quinolone resistance [11]. The precise molecular characterization of CRE can impact therapeutic decisions, i.e. Avibactam inhibits both Class A KPC and Class D OXA-48 [12], while relebactam and Vaborbactam inhibits only class A KPC [14,15]; plazomicin, a marketed aminoglycoside, is active against most CREs except strains producing New Delhi metallo-β-lactamases and co-expressing specific 16S rRNA methylases (ArmA and RmtC) [13]. Beside the usefulness in clinical practice, determination of the prevalence of the antibiotic resistance determinants in CRE can aid in developing rational antimicrobial therapy and infection control. In China, the prevalence of Capapenemases genes, ESBL genes, AmpC-encoding genes, aminoglycoside resistance genes and PMQR genes have been reported in several reports [3-4, 16]. However, most of these studies only reported the data based on one hospital or local or one type resistance genes, and no systematic study has yet been published. The aim of this study was to assess the prevalence and distribution pattern of Carbapenemase, ESBL, AmpC, aminoglycoside resistant and PMQR genes among CRE clinical isolates in Mainland, China using a systematic review and meta-analysis. This information might help in designing of national strategies to control the spread of these resistance determinants in Mainland China.

2. Materials and Methods

2.1 Search strategy:

We searched published studies in the following electronic, scientific literature databases: PubMed, Embase, CNKI, cqVIP and Wanfang database. The search strategy was designed to identify articles that focused on antibiotic resistance determinants in clinical isolates of CRE in Mainland China. Various combinations of the following keywords were used, including Carbapenem-reistant enterobacteriaceae, CRE, carbapenem resistant,antibiotic resistance determinants, antibiotic resistance gene, carbapenemase gene, EBSLs, quinolone resistant, aminoglycoside resistance genes, AmpC, Extended spectrumβ-lactamases and enterobacteriaceae. The last search was done on November10, 2019.

2.2 Study selection

All original articles reported on the antimicrobial resistance determinants of CRE clinical isolates in Mainland China were considered. Inclusion and exclusion criteria are as follow:

Inclusion criteria:

Studies with the following characteristics were included:

1) published in Chinese or English 2) publication date between 1 January 2009 and 10 November 2019 3) reported genetic antibiotic resistance determinants 4) CRE isolated from human patients clinical samples

Exclusion criteria:

Articles were excluded if:

1) Samples were not human clinical isolates 2) samples did not come from Mainland China 3) samples were not CRE 4) Publication date were not from 2009-2019 5) studies based on CRE but not related to ARD 6) Samples from different studies were repeated 7) not experimental or observational studies, such as, case reports, letter, guidelines, or case series, reviews, etc. 8) validation of molecular techniques 9) not published in English or Chinese

2.3 Data Extraction

Endnote X9 (Thomson Reuters, NEWYORK, NY), a citation manager, was used to manage the retrieved articles and remove duplicated articles. The data extraction was done using a pretested and standardized format prepared in Microsoft Excel. The following data were extracted for each study: first author, publication year, study location, populations, antimicrobial susceptibility testing(AST) methods, ARD detection methods, species of CRE, sample sizes, number of strains with antibiotic resistance determinants (Carbapenemase genes, ESBL genes, AmpC-encoding genes, aminoglycoside resistance genes, PMQR) and numbers of strains with subtype of ARD.

2.4 Data analysis

Comprehensive Meta-analysis statistical software (Version 2.2) was used in statistical analysis. Heterogeneity between studies was assessed by Cochran's Q test and I-squared [17-19]. Considered the heterogeneities among studies, pooled prevalence of all type antibiotic resistant determinants in CRE were estimated using a random effect model. All estimated pooled prevalence were reported using 95% confidence intervals (CIs). Relative and cumulative frequencies were used to report the overall preponderance of Carbapenemase, ESBL, AmpC-encoding, aminoglycoside resistance, PMQR in CRE. The proportion of a subtype of Carbapenemase, ESBL, AmpC-encoding, aminoglycoside resistance and PMQR genes was calculated by dividing the number of clinical isolates in which the subtype was found by the number of CRE stains in the research.

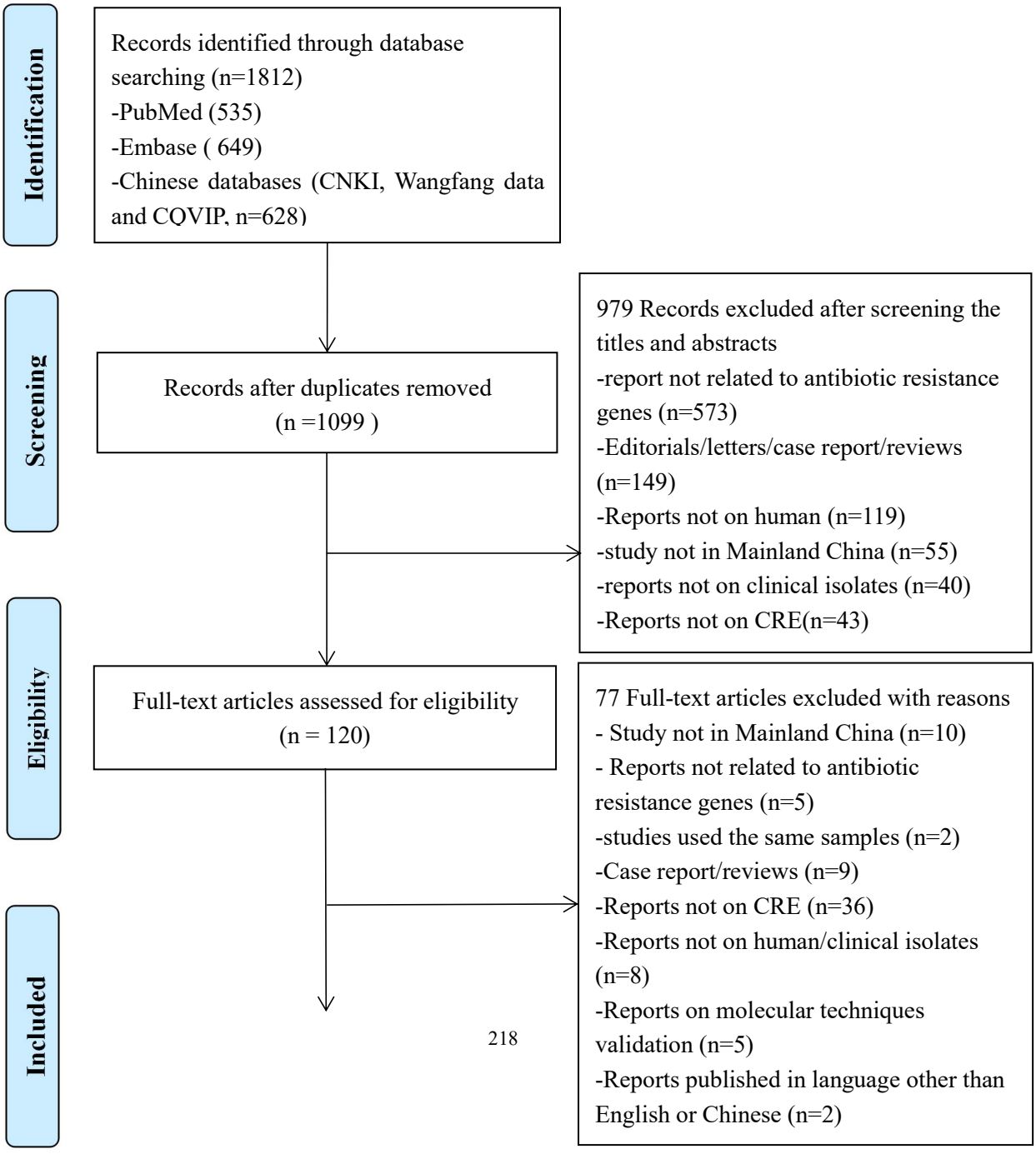
3. Results:

3.1 Search and selection of studies

1,812 articles published from 2009 to 2019 were identified from 5 electronic databases. Based on title and abstract screening, 713 articles were excluded for duplication, and 979 were excluded after title and abstract screening. Among the remaining 120 articles, 77 articles were excluded again for specific reasons (Figure1). Finally, 43 studies were included in this meta-analysis. Of the studies search and selection process was detailed in Figure 1.

3.2 Characteristics of included studies

Of the 43 studies, 41studies reported on Carbapenemase genes (TableS.1), 29 on ESBL genes (TableS.2), 12 on AmpC-encoding genes (TableS.3), 11 on aminoglycoside resistance genes (TableS.4) and 14 on PMQR (TableS.5). 12 studies reported on Carbapenem resistant *Klebsiella pneumonia* (CRKP) [20, 31-34, 38, 41, 43, 46-47, 51, 59], 6 studies reported on Carbapenem- resistant *Enterobacter cloacae* (CRECL) [22, 27, 44-45, 58], 5 studies reported on Carbapenem-resistant *Escherichia coli* (CRECO) [26, 36-37, 50, 55] and 1 study reported on *Proteus mirabilis* [57], the other studies reported on a group of Enterobacteriaceae. For resistance gene detection methods, all studies were based on PCR/Sequencing, except 3 studies based on whole genome sequencing [24, 34, 36].



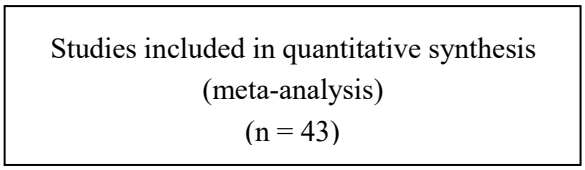
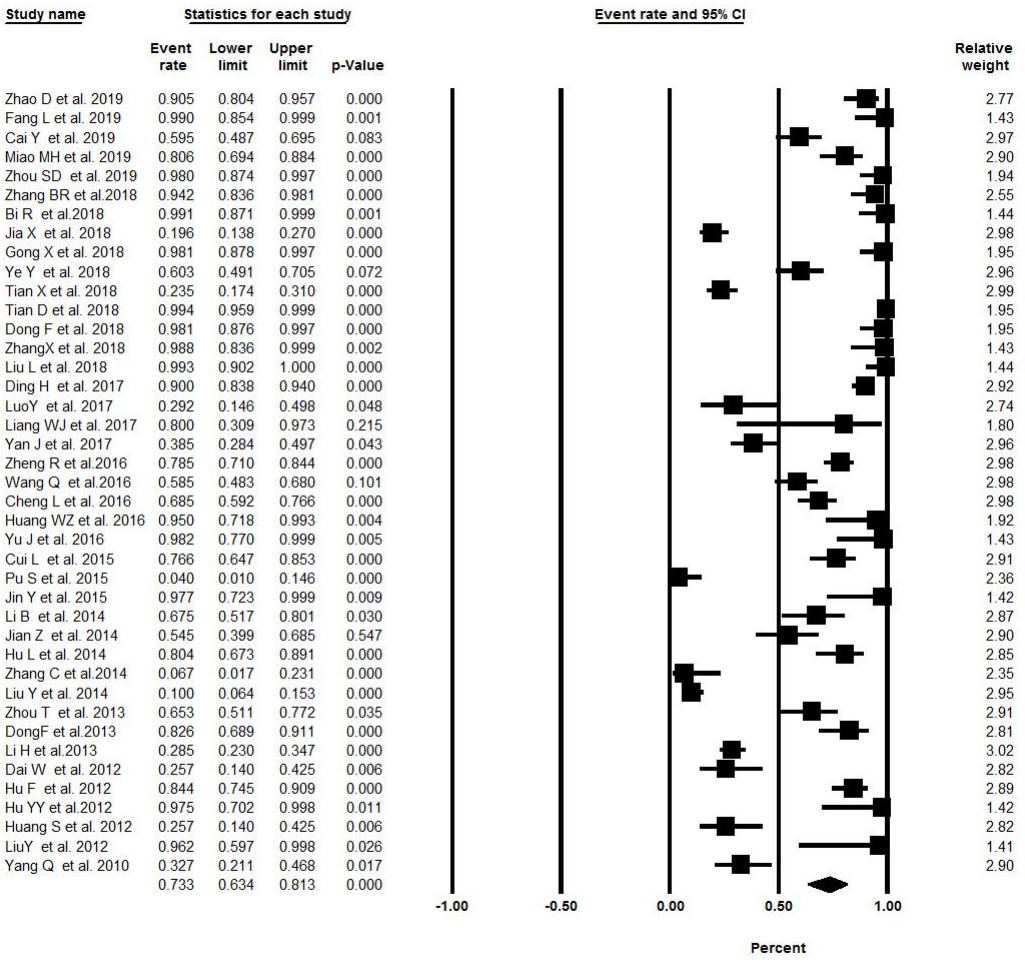


Figure 1. Flow chart of search and selection studies. CNKI: China National Knowledge Infrastructure; CQVIP: Chongqing VIP

3.3 Pooled antibiotic resistance genes proportions

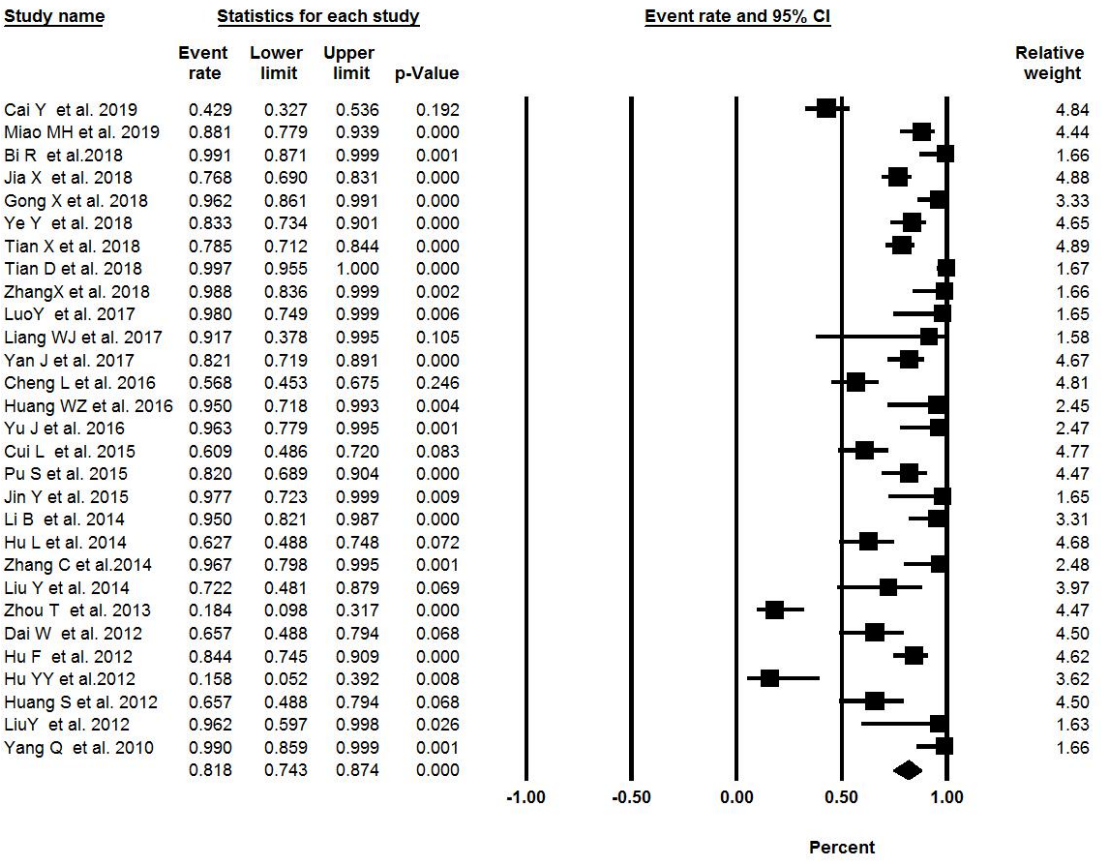
The pooled proportions of Carbapenemase genes in CRE was 73.3% (95% CI=63.4-81.3; I^2=94.16; Q=684.61 (*P*=0); Figuare 2A); The pooled proportions of ESBL genes in CRE was 81.8% (95%CI=74.3-87.4; I^2=86.80; Q=212.1 (*P*=0); Figuare 2B); The pooled proportions of AmpC-encoding genes in CRE was 32.7% (95% CI=18.6-50.9; I^2=94.49; Q=199.80 (*P*=0); Figuare 2C); The pooled proportions of aminoglycoside resistance genes in CRE was 60.6% (95% CI=47.4-72.4; I^2=81.71; Q=54.689 (*P* =0); Figuare 2D); The pooled proportion of PMQR genes in CRE was 70.8%(95% CI=60.9-79; I^2=76.34; Q=54.94 (*P*=0); Figuare 2E).

A Carbapenemase Genes



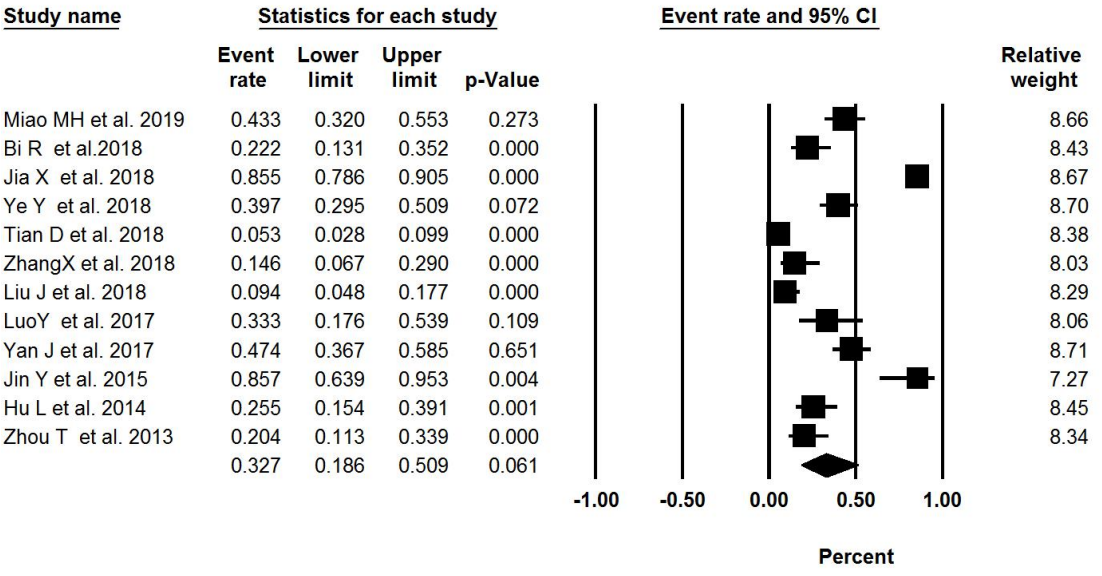
Random effects model,p=0; Cochran's Q=684.61,I square=94.16

B ESBL Genes



Random effects model,p=0; Cochran's Q=212.1,I square=86.8

C AmpC-encoding Genes



Random effects model,p=0; Cochran's Q=199.8,I square=94.49

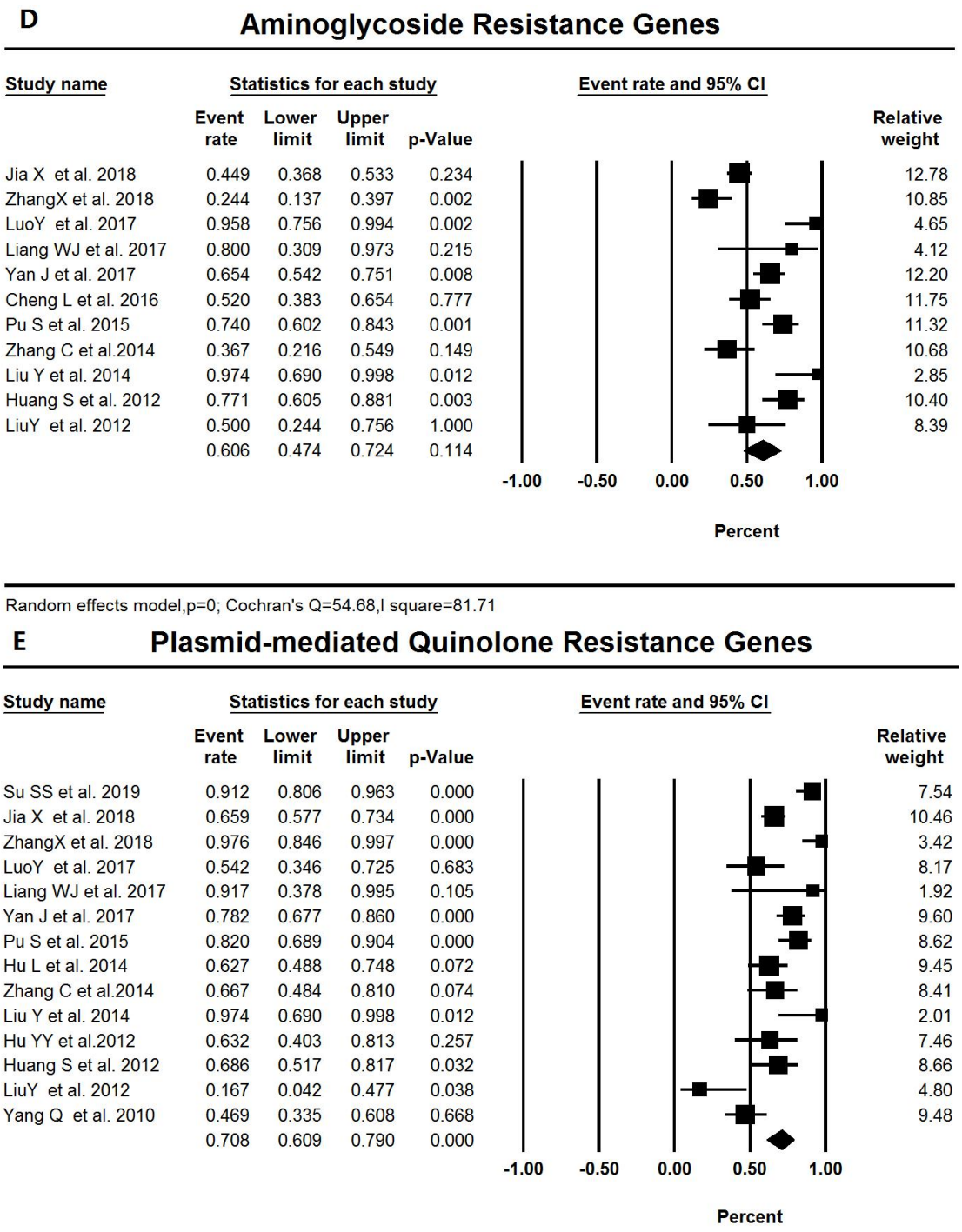


Figure 2. Forest plots of antibiotic resistance determinants proportions in CRE clinical isolates in Mainland China. Carbapenemase genes (A), ESBL genes (B), AmpC-encoding genes (C), aminoglycoside resistance genes (D), plasmid-mediated quinolone resistance genes (E).

3.4 Preponderance of Carbapenemase genes

Of the Carbapenemase genes, *KPC, NDM, IMP, VIM, OXA* and *GIM* but *GES* (0/929) [24-26, 32-34, 36, 39, 41-43, 46-47, 52-53, 56, 60], SME(0/1060) [24-27, 32, 34, 36, 38, 41-42, 45-47, 50, 52-53, 56, 58-60] have been identified (Table1). The pooled prevalence of *KPC, NDM, IMP, VIM, OXA* and *GIM* among CRE, respectively, were 26.1% (95% CI=18.1-36.1), 18.4% (95% CI=12.2-26.7), 11.2% (95% CI=7.8-15.8), 1.8% (95% CI=1.2-2.7), 2.2% (95% CI=1.0-4.5), 3.9% (95% CI=0.7-18.3). *KPC-2* (26.6%,95% CI=18.3-36.9) was the most frequently type in KPC, *NDM-1* (14%,95% CI=9.4-20.1) in *NDM*, *IMP-4* (10.6%, 95% CI= 6.6-16.6) in *IMP*, *VIM-1* (6.1%, 95%CI=3.3-11.3) in *VIM*, *OXA-1* (9.8%, 95% CI=3.1-27.3) in *OXA* if all single study omitted. No *OXA-48* (0/1708) has been identified in CRE.

Table1. Relative and cumulative frequencies of Carbapenemase genes

Genotype	N	P(95%CI)*			References
		P	L	U	
KPC	**2834**	**26.1**	**18.1**	**36.1**	[20-60]
KPC-2	2786	26.6	18.3	36.9	[20-24, 26-36, 38-60]
KPC-3	46	2.2	0.3	13.9	[23]
NDM	**2182**	**18.4**	**12.2**	**26.7**	[20-28, 30-35, 38-41, 43, 44, 47, 49, 51, 52, 55, 56]
NDM-1	2182	14	9.4	20.1	[20-28, 30-35, 38-41, 43, 44, 47, 49, 51, 52, 55, 56]
NDM-4	54	3.7	0.9	13.6	[26]
NDM-5	736	9.2	3.6	21.6	[23, 24, 26, 28, 30, 31, 34, 36, 40]
NDM-7	201	3.3	0.7	13.5	[26, 28, 40]
NDM-9	105	3	1.0	9.0	[24, 26]
IMP	**2824**	**11.2**	**7.8**	**15.8**	[20-56, 58-60]
IMP-1	886	2.8	1.5	5.2	[22, 29, 35, 36, 39, 44, 54, 56]
IMP-2	155	6.5	3.5	11.6	[29, 56]

IMP−4	2114	10.6	6.6	16.6	[22-24, 27, 28, 30-36, 38-40, 42, 43, 46-49, 51-54, 60]
IMP-8	987	6.1	3.7	9.8	[27, 28, 30, 44, 45, 47, 49, 52-55, 58, 60]
IMP-26	205	6.2	3.1	12.2	[22, 49, 55, 58]
IMP-38	107	9.1	1.3	42.9	[20, 48]
VIM	**2279**	**1.8**	**1.2**	**2.7**	[20-29, 31-33, 35-39, 41-53, 55, 56, 58-60]
VIM-1	302	6.1	3.3	11.3	[23, 28, 29, 43, 56]
VIM-2	408	0.8	0.2	2.9	[51, 54]
OXA	**2097**	**2.2**	**1.0**	**4.5**	[20-39, 28-31, 43, 46-48, 51-53, 56, 60]
OXA-1	241	9.8	3.1	27.3	[24, 30, 33]
OXA-23	144	3.5	1.4	8.5	[21, 24, 53]
OXA-48	1708	0	0	0	[20, 22-29, 31-39, 43, 47, 48, 51, 52]
OXA-66	51	3.9	1.0	14.4	[24]
OXA-69	78	12.8	7.0	22.2	[29]
OXA-232	170	42.4	35.1	49.9	[31]
GIM	**891**	**2.1**	**1.2**	**3.7**	[24-25, 29, 31-32, 34, 36, 41, 46-47, 52-53, 56, 60]

N, number; P, proportion; L, lower limit; U, upper limit; *Score confidence interval

3.5 Preponderance of ESBL genes

The pooled prevalence of *CTX-M, SHV* and *TEM* among CRE, respectively, were 60.4% (95% CI=49.6-70.2), 41.0% (95% CI=29.6-53.5) and 50.1% (95% CI=39.9-60.2) (Table2). *CTX-M-15* (32.2%, 95% CI=20.1-47.1) was the most frequently gene in *CTX-M*, followed by *CTX-M-14* (28.5%, 95%CI=19.5-39.7) and *CTX-M-24* (19.3%, 95% CI=2.3-71); *SHV-12* (23.2%, 95% CI=16.5-31.5) was the most frequently gene in *SHV*, followed by *SHV-11* (20.7%, 95%CI=8.8-41.4); *TEM-1* (54.5%, 95%CI=40-68.2) was the most frequently gene in *TEM*.

Table2. Relative and cumulative frequencies of ESBL genes

Genotype	N	P(95% CI)*			References
		P	L	U	
CTXM	**1474**	**60.4**	**49.6**	**70.2**	[22-23, 26, 28, 29-31, 33, 36-38, 41-47, 49-52, 55-60]
CTX-M-1	282	3.2	0.6	15.5	[30, 42, 44, 52]
CTX-M-2	219	1.2	0.3	3.9	[29, 44, 56]
CTX-M-3	584	11.8	6.9	19.6	[23, 30, 38, 45, 47, 49, 50, 52, 55, 58]
CTX-M-9	331	11.3	8.3	15.2	[23, 30, 44, 49]
CTX-M-14	1102	28.5	19.5	39.7	[23, 26, 29-31, 33, 36, 41, 43, 45-47, 49-52, 55-56, 58, 59]
CTX-M-15	890	32.2	20.1	47.1	[23, 26, 28-29, 31, 33, 36-38, 41, 43, 46, 47, 49, 51, 56, 59]
CTX-M-24	227	19.3	2.3	71	[30, 38]
CTX-M-38	74	2.7	0.7	10.2	[41]
CTX-M-52	227	2.9	0.8	10.2	[30, 38]
CTX-M-55	233	11.3	2.1	42.6	[26, 30, 50]
CTX-M-64	54	1.9	0.3	12	[26]
CTX-M-65	212	13.4	6.1	27	[23, 26, 47, 49]
CTX-M-84	51	2.0	0.3	12.6	[49]
CTX-M-90	54	1.9	0.3	12	[26]
CTX-M-123	54	1.9	0.3	12	[26]
SHV	**1391**	**41.0**	**29.6**	**53.5**	[22-23, 26, 28, 30-31, 33, 36, 38, 41-47, 49-52, 55-60]
SHV-1	484	8.5	1.4	37.5	[30-31, 41, 47, 49]
SHV-2	149	19.5	13.9	26.6	[30]
SHV-5	221	1.1	0.3	4.2	[31, 49]
SHV-11	555	20.7	8.8	41.4	[30, 31, 33, 41, 47, 49, 51, 59]

SHV-12	799	23.2	16.5	31.5	[22-23, 30, 31, 41, 44, 47, 49, 51, 55, 58-59]
SHV-26	189	6.4	0.7	40.2	[30, 47]
SHV-27	41	4.9	1.2	17.5	[33]
SHV-28	165	3.2	1.4	7.5	[41, 47, 49]
SHV-31	114	7.2	3.6	13.7	[41, 47]
SHV-33	40	5	1.3	17.9	[47]
SHV-36	125	1.6	0.4	6.3	[41, 49]
SHV-145	40	2.5	0.4	15.7	[47]
SHV-160	74	2.7	0.7	10.2	[41]
TEM	1534	**50.1**	**39.9**	**60.2**	[22-23, 26-28, 30-31, 33, 36-38, 41-47, 49-52, 55-60]
TEM-1	902	54.5	40	68.2	[22, 26, 30-31, 33, 36-37, 41, 43, 44, 46-47, 49, 51, 57, 59-60]
TEM-6	70	37.1	26.7	49.0	[55, 58]
TEM-30	84	19	12	28.9	[22]

N, number; P, proportion; L, lower limit; U, upper limit; *Score confidence interval

3.6 Preponderance of AmpC-encoding genes

CMY-42 (17.1%, 95% CI=5.0-44.7) was the most frequently AmpC-encoding genes in CRE, followed by *DHA-1* (12.4%, 95% CI=5.2-26.8), *CMY-2* (8.2%, 95% CI=4.2-15.4), *ACT* (5.5%, 95% CI=1.3-20.1), *EBC* (4.1%, 95% CI=0.5-28.2), *MIR-3* (2.0%,1/51) and *CMY-6* (1.2%, 95% CI =0.4-3.6). No FOX (0/379), MOX (0/379) and CIT (0/379) have been identified in CRE [52, 46, 61, 31, 26].

Table3 Relative and cumulative frequencies of AmpC-encoding genes

Genotype	N	P(95% CI)*			References
		P	L	U	
EBC	541	4.1	0.5	28.2	[26,27,31,61,36,46,52]

DHA-1	562	12.4	5.2	26.8	[23,26,31,33,61,36,46,49,52]
ACT	118	5.5	1.3	20.1	[23,49]
CMY-42	78	17.1	5.0	44.7	[26,36]
CMY-2	172	8.2	4.2	15.4	[23,26,49]
CMY-6	255	1.2	0.4	3.6	[31,61]
MIR-3	51	2.0	0.3	12.6	[49]

N, number; P, proportion; L, lower limit; U, upper limit; *Score confidence interval

3.7 Preponderance of aminoglycoside resistance genes

Of the aminoglycoside resistance genes, *aac(6')-Ib, armA, rmtB, aac(3)-IIa-like, aadA1*, *aadA5* and *strA* but *rmtA* (0/103), *rmtC* (0/103), *rmtD* (0/103) [59, 41, 33] and *rmtE* (0/50) [41] have been identified (Table4). The prevalence of *aac(6')-Ib, armA, rmtB* in CRE, respectively, were 49.0% (95% CI=36.4-61.6), 8.9% (95% CI=3.6-20.4) and 15.9% (95% CI=7.0-32.2). The frequencies of *aac(3)-IIa-like*, *aadA1, aadA5* and *strA* in CRE from the single article reported , respectively, were 58.3% (14/24), 80% (4/5), 50.0% (12/24) and 33.3% (8/24).

Table4 Relative and cumulative frequencies of aminoglycoside resistance genes

Genotype	N	P(95% CI)*			References
		P	L	U	
aac(6')-Ib	399	49.0	36.4	61.6	[27, 38, 41, 45, 50, 51, 58]
aac(3)-IIa-like	24	58.3	38.3	81.3	[36]
aadA1	5	80.0	30.9	97.3	[37]
aadA5	24	50.0	31	69	[36]
strA	24	33.3	17.6	53.9	[36]
armA	476	8.9	3.6	20.4	[27, 33, 36, 38, 41, 45, 50-51, 58, 59]
rmtB	476	15.9	7.0	32.2	[27, 33, 36, 38, 41, 45, 50-51, 58, 59]

N, number; P, proportion; L, lower limit; U, upper limit; *Score confidence interval

3.8 Preponderance of PMQR genes

Of PMQR genes, *qnrA, qnrB, qnrD, qnrS, aac (6')-Ib-cr and oqxA/B* but *qnrC* (0/252) [27, 33, 36, 50, 57] and *qepA* (0/164) [62, 33, 36-37, 51, 57] have been observed (Table5). The prevalence of *qnrA, qnrB, qnrD, qnrS, aac (6')-Ib-cr* and *oqxA/B* in CRE, respectively, were 5.9% (95% CI=2.8-11.9), 27.4% (95% CI=17.0-41.0), 3.3% (95% CI=0.2-40.6), 22.3% (95% CI= 14.8-32.3), 37.5% (95% CI=25.5-51.4) and (85.4%, 35/41).

Table5 Relative and cumulative frequencies of PMQR genes

Genotype	N	P(95% CI)*			References
		P	L	U	
qnrA	607	5.9	2.8	11.9	[62, 27, 23, 36-38, 45, 49-51, 57-60]
qnrB	607	27.4	17.0	41.0	[62, 27, 23, 36-38, 45, 49-51, 57-60]
qnrD	252	3.3	0.2	40.6	[27, 33, 36, 50, 57]
qnrS	607	22.3	14.8	32.3	[62, 27, 23, 36-38, 45, 49-51, 57-60]
aac (6')-Ib-cr	607	37.5	25.5	51.4	[62, 27, 23, 36-38, 45, 49-51, 57-60]
oqxA/B	41	85.4%	71	93.3	[33]

N, number; P, proportion; L, lower limit; U, upper limit; *Score confidence interval

4. Discussion

To our knowledge, this was the first systematic review and meta-analyses to address the prevalence of Cabapenemases, ESBL, AmpC-encoding, aminoglycoside resistant and PMQR genes among CRE clinical isolates in Mainland China. Based on the results of this study, the pooled prevalence of Carbapenemase genes in CRE clinical isolates of Mainland China was 73.3% (95% CI=63.4-81.3), and *KPC* (26.1%, 95% CI=18.1-36.1) was the most widely spread Carbapenemase gene, followed by *NDM* (18.4%, 95% CI=12.2-26.7). Our finding are similar to the previous reports by China CRE Network [3-4]. *KPC-2* and *KPC-3* were the

most common type in CRE of United Stated [63]. In our study, Just *KPC-2* was the most frequently type among CRE of China. To date, *NDM-1* remains the most common *NDM* variant isolated in the seven NDM variants (*NDM1-NDM7*) [64], our study showed the similar result. At the present time, IMP-type Enterobateriaceae were mainly found in Japan and Taiwan, China [65], and *IMP-1* was the most widespread type in Japan [66] but Taiwan, China with *IMP-8* [67]. In our study, *IMP-4* (10.6%, 95% CI=6.6-16.6) was the most common type in Mainland, China. The epicenter of VIM-type Enterobateriaceae was Greece, *VIM-2* was predominate type worldwide but *VIM-1* in our study same as in Greece [68]. As for *OXA*, the commonest type was *OXA-48*. *OXA-48* producing CRE were mainly concentrated in Middle East (Turkey), North Africa and European countries, rare in China [69, 70]. *OXA-48*, as well *GES* and *SME*, was not found in our study.

ESBL and plasmid encoding AmpC genes were mostly detected in CRE. In China, 45.8% Taiwanese CRE harbored various ESBL genes (80% were the *CTX-M* types) and 62.0% harbored AmpC genes (70.6% were *DHA* and 22.3% were *CMY*) [67]. In Mainland, 61.6% CRKP harbored ESBL genes (mainly *CTX-M 65* and *CTX-M-14*) and 14.4% harbored AmpC genes (*DHA-1* and *ACT-20*) [70]. In our study, the pooled proportions of ESBL genes in CRE was 81.8% (95% CI=74.3-87.4) and AmpC genes was 32.7% (95% CI=18.6-50.9). *CTX-M, SHV-* and *TEM*-type enzymes were the most clinically significant ESBL variants. *CTX-M* (60.4%, 95% CI=49.6-70.2) was the most common type, followed by *TEM* (50.1%, 95% CI=39.9-60.2) and *SHV* (41.0%, 95% CI=29.6-53.5) among CRE in our study. *CTX-M-15* and *CTX-M-14*, *SHV-12* were the dominant CTX-M and SHV variants in enterobacteriaceae of the Asia-Pacific area [71, 72]. In China, *CTX-M-14* was the most common CTX-M type but *CTX-M-15* with a steady increase has been identified [73]. *CTX-M-15*, *SHV-12* and *TEM-1* were identified as the common ones along with a wide range of other *CTX-M, SHV* and *TEM* variant genes in this study. According our study, *CMY-42* was the most prevalent AmpC gene, followed by *DHA1* among CRE in Mainland, China. But *CMY-2* was the most frequently type in *Enterobacteriaceae* especially in *E.coli* worldwide [74], and the similar result was found in the study based on Asia-Pacific region [71,72].

In terms of frequency, acetyltransferases (AAC), nucleotidyltransferases (ANT), and

phosphotransferases (APH), aminoglycoside-modifying enzymes (AMEs) are the most important determinant of aminoglycoside resistance in Enterobacteriaceae and many other Gram-negative bacteria [75]. In addition, 16S rRNA methylases is another major mechanisms of resistance to aminoglycosides in Enterobaceriaceae and *rmtB* has revealed a worldwide distribution among Enterobacteriaceae. Omitted single report, *aac(6')-Ib* (49.0%, 95% CI=36.4-61.6) was the most common ARD, followed by *rmtB* in our study. The similar results were reported in Spain [76]. In UK, *armA* was the most common, followed by *rmtC* [77]. *RmtD* has only been reported from South America [75], *RmtA, rmtC, rmtD* and *rmtE* were not found in our study.

So far, Qnr peptides, the aminoglycoside acetyltransferase variant *aac(6')-Ib-cr* and plasmidic efflux pumps *QepA* and *OqxAB* are three known plasmid-mediated quinolone resistance mechanisms [78]. And PMQR have been mainly found in Enterobacteriaceae. *aac(6')-Ib-cr* was the most commonly reported PMQR followed by *qnr* gene in Enterobacteriaceae in Mediterranean countries [81]. *qnrB* was the most predominant family in Enterobacter cloacae non-susceptible to Ertapenem in North-Eastern France [79], the similar result was found in Spain [80]. Omitted the single report, *aac(6')-Ib-cr* was the most common PMQR in our study, followed by *qnrB*. Efflux pump *qepA* was identified in very few studies, no *qepA* was found in this study. The prevalence of *oqxAB* was relatively lower in Enterobacteriaceae of human origin than that of the animal or environmental sources [82], but *oqxAB* was reported in one article with a rate of 85.4% in our study.

This review was limited to the studies published in the English, Chinese languages and in peer-reviewed journals after 2009. Limiting our search was justified given the prevalence of antibiotic resistance determinants in CRE in recent years. In addition, publication bias had to be considered since results of negative finding may not have been published. Second, significant heterogeneity was found among included studies. Third, no standard test for antibiotic resistance determinants, the methods differed between studies. PCR/sequencing were most commonly adopted in these articles. Finally, many of studies identified the limited antibiotic resistant genes in CRE, which might have masked the real gene diversity in Mainland China. Therefore, the prevalence of antibiotic resistant genes in CRE in Mainland

China requires further study.

5. Conclusions

The pooled prevalence of Carbapenemase, ESBL, AmpC-encoding, aminoglycoside resistance and PMQR genes in CRE clinical isolates of Mainland China were 73.3%, 81.8%, 32.7%, 60.6% and 70.8%, respectively. *KPC-2, NDM-1, IMP-4, VIM-1* and *OXA-1* were the predominant type of a wide range of *KPC, NDM, IMP, VIM* and *OXA* variant genes. Among these, *KPC-2* was the most common type of carbapenemase genes. *CTX-M-15, CTX-M-14, SHV-12* and *TEM-1* were the main type of *CTX-M, SHV* and *TEM-1* variant genes. *TEM-1* was the most common type of ESBL genes, while *CMY-42* was the most prevalent AmpC-encoding gene. As for aminoglycoside resistance genes and PMQR genes, a*ac(6')-Ib* was the most common type in aminoglycoside resistance genes and *aac(6')-Ib-cr* in PMQR genes, followed by *qnrB*. The current review provided information the prevalence and distribution pattern of carbapenemase, ESBL, AmpC, aminoglycoside resistances and PMQR genes among CRE clinical isolates in Mainland China. This information might help in guiding rational drug use in clinic and in designing measures that efficiently control the spread of these resistance determinants in Mainland China.

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