Carbapenamase-Producing *Acinetobacter baumannii* in China, Latin America and the Caribbean: A Systematic Review and Meta-Analysis

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ABSTRACT

INTRODUCTION Carbapenem-resistant *Acinetobacter baumannii* is a complex health problem, causing difficulties in clinical–therapeutic management worldwide. It is of particular concern in Latin America, the Caribbean and China, where it is an emerging health problem. Carbapenemases produced by these organisms inactivate carbapenem antibiotics. Monitoring circulating genotypes' geographic dispersion contributes to more effective control measures. However, exhaustive studies on carbapenem-resistant *A. baumannii* are scarce.

OBJECTIVES Study the production of carbapenemases in clinical isolates of *A. baumannii* resistant to carbapenem antibiotics and the geographic distribution of the sequences circulating in China, Latin America and the Caribbean.

DATA ACQUISITION We followed PRISMA indications. We carried out a systematic search in Pubmed, BVS and CKNI on papers on *A. baumannii* and carbapenemases published during 2015–2020 in English, Spanish and Chinese, and selected 29 cross-sectional studies that met the search criteria. Studies were evaluated using JBI Critical Appraisal tools, and quantitative data were collated for meta-analysis using the Metaprop library in Stata15.

DEVELOPMENT OXA-type carbapenemases were detected in all studies; among *A. baumannii* resistant to carbapenem antibiotics, predominant types were OXA-23, OXA-24, OXA-54 and OXA-72; metallobetalactamases were identified less frequently than OXA carbapenemases. Only one clinical isolate producer of Class A carbapenemases (KPC) was identified in Colombia. In total, 41 sequence types were identified; in Latin America and the Caribbean the most common types were: ST79, ST25, ST1 and ST15; in China, the sequences ST195, ST208, ST191, ST368 and ST369 were the most prevalent. ST2 was found in both regions.

CONCLUSIONS The most prevalent carbapenemases and sequence types vary by region, indicating different ancestral strains. Microbiological surveillance, antibiotic use optimization, adequate infection treatment and timely control strategies are essential for carbapenem-resistant *A. baumannii* prevention and control in geographies such as Latin America, the Caribbean and China where such resistance is an emerging health problem.

KEYWORDS Acinetobacter baumannii, carbapenemase, genotype, epidemiology, Latin America, Caribbean region, China

INTRODUCTION

The genus *Acinetobacter (Acinobacter spp.)* is made up of several species. These gram-negative bacilli are among the most common nosocomial pathogens worldwide. *Acinetobacter baumannii* is the most clinically relevant species, due to its ability to develop various mechanisms that lend themselves to antibiotic resistance. [1] A member of the beta-lactam class (the same class of antibiotics as penicillins and cephalosporins), carbapenemic antibiotics are the last resort in treating *A. baumannii* infections.

There has been a worldwide increase in carbapenem resistance observed in clinical isolates of *A. baumannii*.[2] The Latin American Antimicrobial Resistance Surveillance Network found *A. baumannii* to have high resistance to carbapenems in 15 countries in the region during 2014–2016. The percentage of resistant isolates varied from 8% to 89%.[3] In China in 2016, 71.4% of *A. baumannii* isolates were resistant to carbapenems.[4] WHO published a list of priority pathogens in 2017, including *A. baumannii, Pseudomonas aeruginosa,* and carbapenem-resistant *Enterobacteriacae spp*. as critical priorities.[5]

The main mechanism of carbapenem resistance in *A. baumannii* (CRAB) strains is carbapenemases production. The most common of these are Ambler's class D oxacillinases (OXAs). [2] Six subgroups of OXAs have been identified in *A. baumannii*: the species' intrinsic carbapenemase OXA-51–like, and the acquired carbapenemases OXA-23–like, OXA-24–like, OXA-58–like, OXA-143–like, and OXA-235–like.[6] Class B metallobetalactamases (MBLs) are also a major threat because they are often located in mobile genetic elements, easily transferable between bacteria. Four types of MBLs are frequently detected in *A. baumannii*: imipenemase (IMP), Verona imipenemase (VIM), Seoul imipenemase (SIM), and New Delhi beta-lactamase (NDM).[7]

Molecular characterization of *A. baumannii* isolates is very useful in identifying the source of an outbreak and in helping to control its spread. Multilocus sequence typing (MLST) is highly discriminative and has been applied successfully to several bacterial patho-

IMPORTANCE

This meta-analysis shows the different types of carbapenemases in *A. baumannii* in China, Latin America and the Caribbean, and the geographic distribution of the circulating sequence types. The data provide useful information for antibiotic resistance surveillance in the regions chosen for analysis, where this is an emerging health problem.

gens, including *A. baumannii*. Additionally, this typing allows for comparisons between laboratories and provides a powerful tool for conducting epidemiological studies worldwide.[8]

The emergence of carbapenem-resistant forms of *A. baumannii* is a complex global problem, difficult to manage both clinically and therapeutically. Monitoring carbapenemase genotypes and molecular epidemiology studies contribute to more effective control measures. However, comparative analyses of circulating forms in different geographies are scarce. This work is a systematic review of published information on carbapenemase production and sequence types characterized in *A. baumannii* isolates in China, Latin America and the Caribbean (LAC).

DATA ACQUISITION

We followed the SPIDER scheme in preparing this study.[9] We carried out a systematic review of all relevant publications in 2015–2020, adjusted according to recommendations contained in PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses.)[10]

Search strategy and article selection The search was carried out in the following databases: PubMed (Medline), BVS (Regional Portal, Virtual Health Library), and CNKI (Chinese database). We used the following keyword combinations: "carbapenem resistance" OR "carbapenemase producing" combined with "Acinetobacter baumannii" combined with the names of the following countries: "Argentina", "Bahamas", "Belize", "Bolivia", "Brazil", "Chile", "China", "Columbia", "Costa Rica", "Cuba", "Ecuador", "Guatemala", "Guyana", "Haiti", "Honduras", "Jamaica", "Mexico", "Nicaragua", "Panama", "Paraguay", "Peru", "Salvador", "Surinam", "Trinidad", "Uruguay", and "Venezuela". We selected articles in three stages: by title, by abstract content, and finally, according to information contained in the full text.

Inclusion criteria We included studies with the following characteristics: 1) observational studies with a cross-sectional design; 2) analysis of *A. baumannii* clinical isolates in adult populations; 3) reports on CRAB; 4) detection of class A, B and D carbapenemases by molecular methods such as reverse-transcriptase polymerase chain reaction testing (RT-PCR) or MLST; 5) carbapenemase genotype analysis in LAC or China published in 2015–2020 in English, Spanish or Chinese.

Exclusion criteria Studies with one or more of the following characteristics were excluded: 1) contained no information on CRAB; 2) studied isolation in pediatric populations; 3) did not report on class A, B and D carbapenemase classes; 4) duplicated other research; and 5) studies that reported experiments in nonhuman subjects or were review articles, conference abstracts, meta-analyses or systemic reviews.

Review articles and meta-analyses were only considered in this review's discussion section. Screening for inclusion was carried out individually by two team members. When there were differences of opinion, these were discussed with the principal investigator. Endnote X9 and Excel were used to manage references.

Study quality evaluation Study quality was evaluated by two researchers using the JBI Critical Appraisal Tools for Prevalence Studies.[11] This tool includes nine items, each of which was scored as either 'Yes' (when the requirement was met), as 'No' (when the requirement was not met) or as 'Not Clear' (if it was unknown whether the requirement was met) or as 'Not Applicable'.[11] Studies were considered high quality when their score was ≥80% of the maximum possible score (8 or more items scored "Yes"), average quality when their score was 70%–79% (6–7 items scored 'Yes'), and low quality when their score was <70% (6 or fewer items scored 'Yes').

Data extraction Two team members carried out data selection and extraction individually, as well as bias risk analysis. We organized data on carbapenemase genotypes in China, Latin America and the Caribbean into a matrix (Table 1).

Table 1: Data extraction characteristics

Term	Definition
Registration	Title, author, publication year
Study	Study type and investigation period
Region	Latin American and Caribbean countries and Chinese provinces
Sample	Sample size (CRAB number)
Intervention	Detection method: RT-PCR or MLST
Genotype	Number of carbapenem genotypes
Sequence type	Detected clones or genetic lines

CRAB: Carbapenem-resistant *A. baumannii*; MLST: Multilocus sequence typing; RT-PCR: Reverse-transcriptase polymerase chain reaction

Data analysis and statistics We carried out a quantitative study (meta-analysis) on *A. baumannii* carbapenemase genotypes and a qualitative study (qualitative descriptive synthesis) for sequence types, due to the great diversity of sequence types and differences between geographical areas. Two investigators undertook data analysis for the quantitative study. Statistical analysis was performed using the Metaprop module of Stata version 15 (StataCorp LLC U.S.A),[12] and obtained estimates of the combined prevalence of predominant *A. baumannii* carbapenemases in different regions, as well as their 95% confidence intervals (95% CI), which are represented in corresponding forest graphs (Figure 2).

We used either fixed-effect or random-effect models according to statistical heterogeneity between studies, which was assessed using the Cochran I2 statistic (a value of 0% indicates no heterogeneity; 25%, 50% and 75% are considered to have low, medium and high heterogeneity, respectively). Egger's weighted linear regression test, combined with a funnel plot, was used to assess publication bias. An assessment of 'no publication bias' was made when the regression line started from the origin of the ordinate axis (Y) (publication bias increases as the line moves away from the Y coordinate's origin). Statistical significance was assessed at 0.1 and not 0.05.[13]

DEVELOPMENT

Literature search, selection and validation We initially selected 334 articles, which were reduced to 318 after eliminating duplicates. Of these, 261 were excluded for failure to meet inclusion criteria or because they were outside the scope of this review. Finally, we fully reviewed a total of 57 articles, and 29 were selected that met all established criteria, which were then included in the meta-analysis (Figure 1).

Medium-high scores were obtained upon evaluation of the cross-sectional observational studies (Table 2). In this study, 95% is

used as expected prevalence in calculating sample size, as carbapenemase production is the CRAB's dominant cause. Considering three studies on molecular isolate typing in hospitals,[14–16] the confidence level equal to 95% and precision equal to 5%, the estimated minimum CRAB sample size was 73. Consequently, we excluded 14 articles due to small sample size. Another 14 studies on carbapenemase genoptyping were excluded for only reporting detection of Class D carbapenemases.

Carbapenemase characteristics Of the 29 studies included in this systematic review, 12 were from LAC, involving 11 countries and 17 were from 11 Chinese provinces. OXA-type carbapenemases were detected in all studies. In LAC, OXA-23, OXA-24, OXA-58 and OXA-72 genotypes were predominant, with respective prevalences of 0.73 (0.54–0.89), 0.06 (0.00–0.17), 0.03 (0.01–0.06) and 0.02 (0.00–0.06). In China, OXA-23, OXA-24 and OXA-72 were the most common, with respective prevalences of 0.91 (0.84–0.96), 0.03 (0.01– 0.08), 0.02 (0.00–0.05).

Metallobetalactamases were less frequent than OXAs and were detected in only two countries in the Latin American and Caribbean region, with NDM 0.01 (0.00–0.01) as the predominant genotype, and in six Chinese provinces, with four predominant genotypes: NDM 0.02 (0.00–0.04), VIM 0.07 (0.00–0.21), IPM 0.02 (0.00–0.06) and SIM 0.01 (0.00–0.03) (Table 3). Only one clinical isolate Class A carbapenemase producer (KPC) was found, and it was isolated in Colombia.

Figure 1: Literature selection results (PRISMA)

CRAB: Carbapenemase resistant *Acinetobacter baumannii*; MDR: Multi-drug resistant; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; XDR: Extensively drug-resistant

According to the I2 values, high heterogeneity was observed among studies and we consequently used a random-effects model for the meta-analysis. Egger tests (p >0.1) and funnel plots show the characteristic shape of the asymmetric dispersion (Table 3 and Figure 2).

Molecular typing characteristics In 17 of the 29 studies, MLST was performed on CRAB isolates. In total, 41 sequence types (STs) were identified: 16 in LAC and 26 in China. Clear geographical differences were observed in predominant ST frequencies: ST79, ST25, ST1 and ST15 were more common in LAC; while ST195, ST208, ST191, ST368 and ST369 were found more frequently in China. ST2 was found in both (Table 2 and Figure 3).
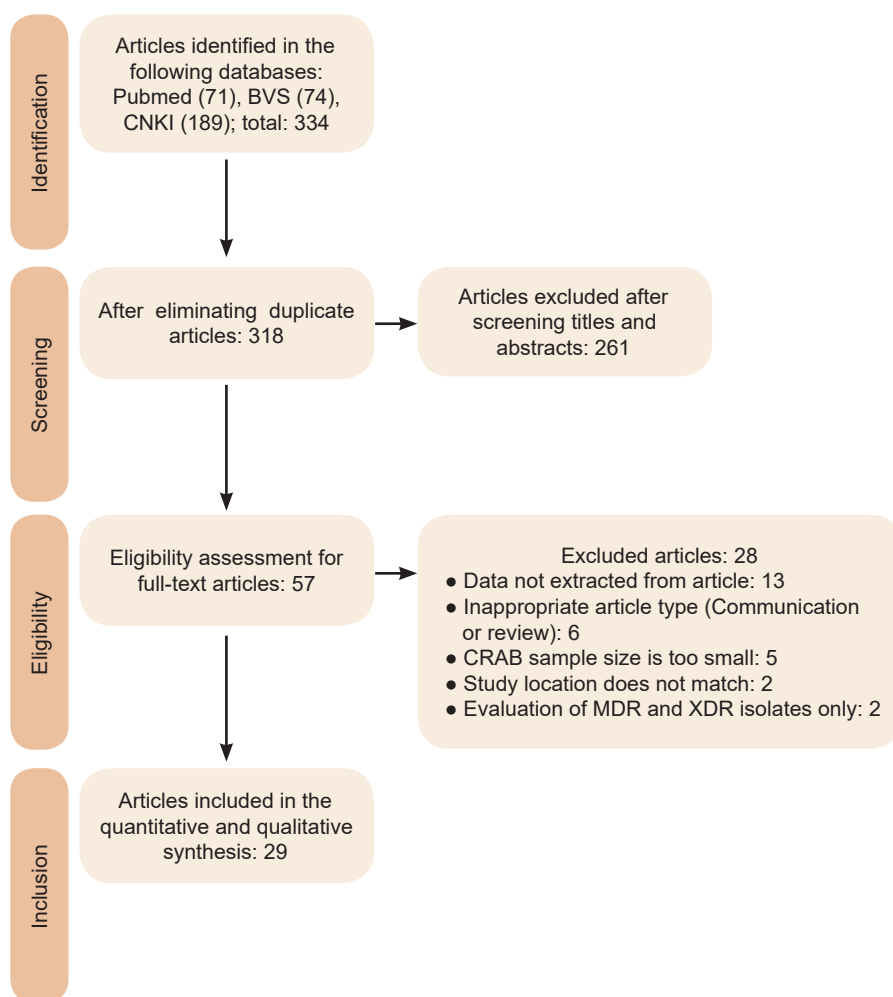
DISCUSSION

Carbapenemase types Antibiotic overuse has led to an increase in multi-drug–resistant *Acinetobacter.* More than 50% of *Acinetobacter spp.* isolates in the United States, South America, India and China are resistant to carbapenem antiobiotics.[46] This study verifies the high prevalence of OXAs in CRAB isolates in China, Latin America and the Caribbean. OXA-51–like carbapenemases (including OXA-51, 64, 65, 66, 68, 69, 70, 71, 78, 79, 80 and 82) occur naturally in *A. baumannii.*[47] OXA-24–like carbapenemases (including OXA-24, 25, 26, 40 and 72) have been found in both plasmid and chromosomal structures; OXA-58–like and OXA-23–like carbapenemases are encoded by plasmids,[48] which increases the probability of horizontal transmission. The plasmid-encoded carbapenemases OXA-23, OXA-24 and OXA-58 were the most frequently isolated carbapenemases in the two regions analyzed in this study. These results justify the non-inclusion of OXA-51 type carbapenemases, as their resistance to CRAB is intrinsic, and thus has little impact on amplifying carbapenem resistance in this species.

Carbapenemase OXA-72 was first identified in 2004 in an *A. baumannii* isolate from Thailand,[49] and subsequently detected in Brazil, Mexico, Ecuador, Peru, China and Europe. [27,43,45,50,51] PXA-231 and OXA-253 were identified in Brazil and Peru, respectively. Both belong to the OXA-143–like group. OXA-231 and OXA-253 were reported the first time in *A. baumannii* isolates from Brazil (in 2007 and 2014, respectively) and still appear mainly in that country.[52,53] The dissemination of this subgroup requires monitoring, as it has been described more recently in Iran (2017), Colombia (2017) and Peru (2018). [45,54,55]

Table 2: Studies included in the systematic review

| Author, year, reference | Year isolated | Detection method | Place | Number of CRAB isolates | Carbapenem type (number detected) | | | Sequence type (n/N) | The study met all selection and quality criteria[&] | The study did not meet these quality criteria: | | Study quality |
					Class A	Class B	Class D			Adequate sample size	Data analysis with sufficient coverage of identified sample	
Chen F. (2018)[17]	2011	PCR	Hu Nan	34	NA	IMP-5(22)	OXA-23(33) OXA-24(29)	NA	No	x	x	Medium
Chen Y. (2018)[18]	2013–2017	PCR	Guang Dong	66	ND	NDM-1(3)	OXA-23(60) OXA-24(19) OXA-58(3)	NA	No	x	−	High
Chen Y. (2017)[19]	2011–2013	PCR/MLST	Shang Hai	56	NA	ND	OXA-23(56)	ST208(28/56) ST191(12/56) ST540(7/56)	No	x	x	Media
Han L. (2017)[20]	2013	PCR	Shan Xi	45	ND	ND	OXA-23(44)	NA	No	x	−	High
Huang ZY. (2019)[21]	2016	PCR/MLST	Hu Nan	67	NA	VIM(54)	OXA-23(63) OXA-58(1)	ST195(28/67) ST368(9/67) ST829(8/67) ST210(2/67) ST90(2/67) ST136(2/67)	No	x	x	Medium
Jiang L. (2018)[22]	2017	PCR/MLST	Guang Dong	122	NA	VIM(7) SIM(2)	OXA-23(115)	ST195(10/28) ST208(9/28) ST1633(3/28) ST345(1/28) ST381(1/28) ST457(1/28)	No	−	x	High
Zhao L. (2018)[23]	2015–2016	PCR	An Hui	145	ND	IMP-4(4)	OXA-23(134) OXA-24(1)	NA	Yes	−	−	High
Song X. (2017)[24]	2013–2014	PCR	Shan Dong	32	ND	VIM(3)	OXA-23(28)	NA	No	x	−	High
Chen J. (2017)[25]	2015–2016	PCR	Jiang Xi	64	ND	VIM(56) NDM-1(17) SIM(12)	OXA-23(56) OXA-24(2)	NA	No	x	−	
Huang G. (2016)[26]	2012–2014	PCR/MLST	Chong Qing	248	NA	NA	OXA-23(163)	ST368(102/248) ST195 (31/248) ST191 (29/248) ST369 (29/248) ST208 (21/248) ST381 (7/248) ST136 (2/248) ST229 (1/248) ST457 (1/248)	Yes	−	−	High
Chen Y. (2018)[27]	2014–2016	PCR/MLST	Liao Ning	78	NA	ND	OXA-23(33) OXA-72(45)	ST2(9/78)	No	−	x	High

| Author, year, reference | Year isolated | Detection method | Place | Number of CRAB isolates | Carbapenem type (number detected) | | | Sequence type (n/N) | The study met all selection and quality criteria& | The study did not meet these quality criteria: | | Study quality |
					Class A	Class B	Class D			Adequate sample size	Data analysis with sufficient coverage of identified sample	
Ning N. (2017)[29]	2009–2014	PCR/MLST	Bei Jing	101	NA	NA	OXA-23(95) OXA-40(1)	ST191(32/101) ST195(31/101) ST208(15/101) ST368(6/101) ST469(6/101) ST218(2/101) ST373(2/101) ST383(2/101) ST429(2/101) ST369(1/101)	No	–	x	High
Lu Q. (2019)[30]	2013–2015	PCR	Guang Xi	61	NA	NDM-1(1)	OXA-23(44)	NA	No	x	–	High
Zhang Y. (2019)[31]	2017	PCR/MLST	An Hui	28	ND	ND	OXA-23(25)	ST1779(8/28) ST1789(6/28) ST195(5/28) ST191(2/28) ST368(2/28) ST369(2/28)	No	x	–	High
Wu H. (2017)[32]	2015–2016	PCR/MLST	Shan Dong	55	NA	ND	OXA-23(55)	ST208(21/55) ST369(14/55) ST195(11/55) ST451(6/55) ST381(1/55)	No	x	x	Medium
Li P. (2015)[33]	Not mentioned	PCR	Beijing	145	NA	NA	OXA-23(134) OXA-58(1)	NA	No	–	x	High
Bado I. (2018)[34]	2010–2011	PCR/MLST	Uruguay	73	ND	ND	OXA-23(58) OXA-58(2)	ST79(20/73) ST958(1/73)	Yes	–	–	High
Camargo CH. (2016)[35]	2009–2013	PCR/MLST	Brazil	71	ND	ND	OXA-23(68) OXA-72(2)	ST79(16/71) ST1(16/71) ST15(20/71)	No	x	–	High
Castilho SRA. (2017)[36]	2010	PCR	Brazil	51	NA	NA	OXA-23(31) OXA-58(2)	NA	No	x	x	Medium
Castillo Y. (2019)[37]	2008–2013	PCR	Perú	46	ND	ND	OXA-23(44) OXA-24(1)	NA	No	x	–	High
Gonzalez-Villoria AM. (2016)[38]	2006–2013	PCR/MLST	México	192	NA	ND	OXA-24(70) OXA-23(57) OXA-58(23)	ST758(9/22) ST417(2/22)	No	–	x	High
Rodríguez CH (2017)[39]	2016	PCR/MLST	Argentina	100	NA	ND	OXA-23(100)	ST1(45/100) ST25(34/100) ST79(15/100)	No	–	x	High
Opazo-Capurro A. (2019)[40]	1990–2015	PCR/MLST	Chile	56	NA	ND	OXA-23(17) OXA-58(17)	ST162(4/56) ST15(3/56) ST109(2/56) ST318(1/56)	No	x	x	Medium
Ovalle MV. (2017)[41]	2012–2014	PCR	Colombia	97	KPC(1)	NDM(3) VIM(1)	OXA-23(87) OXA-24(1)	NA	Yes	–	–	High
Quiñones D. (2015)[42]	2010–2012	PCR	Cuba	220	NA	NDM (1)	OXA-23(130) OXA-24(35) OXA-58(5)	NA	Yes	–	–	High

| Author, year, reference | Year isolated | Detection method | Place | Number of CRAB isolates | Carbapenem type (number detected) | | | Sequence type (n/N) | The study met all selection and quality criteria[&] | The study did not meet these quality criteria: | | Study quality |
					Class A	Class B	Class D			Adequate sample size	Data analysis with sufficient coverage of identified sample	
Brisolla LC (2019) [44]	2008–2014	PCR/MLST	Brazil	107	NA	NA	OXA-23(104) OXA−231(2) OXA−72(1)	ST730(43/107) ST317(28/107) ST1(10/107) ST79(8/107) ST107(2/107) ST986(1/107) ST175(1/107) ST22(1/107)	No	–	x	High
Levy-Blitchtein S. (2018)[45]	2014–2016	PCR/MLST	Perú	78	ND	ND	OXA-23(11) OXA-24(55) OXA-72(10) OXA-253(2)	ST2(7/16) ST79(6/16) ST1(2/16) ST3(2/16) ST108(1/16)	Yes	–	–	High

All were cross-sectional studies.

[&]: Quality criteria: 1. The sample was appropriate to address the target population, 2. The sample was obtained using an adequate method, 3. The sample size was adequate 4. Participants and the context are described in detail 5. Data analysis was carried out with sufficient coverage of the identified sample 6. Effective methods were used to identify diseases or health problems 7. The sample was measured using standard and reliable methods for all participants 8. The statistical analysis was appropriate 9. Response rate was adequate or low response rate was adequately managed.

n: number of times the sequence was found; N: total isolates studied; NA: Not applicable (detection not performed); ND: Not detected;

X: did not meet the requirement; –: met the requirement.

**Table 3: Meta-analysis of carbapenemase genotypes in China, Latin America and the Caribbean**

Place	Subgroups		Number of studies	n/N	Prevalence (95% CI)	Heterogeneity, I2 (%)	Heterogeneity p value	Egger's test
Latin America and the Caribbean	Class D	OXA-23	11	804/1217	0.73 (0.54–0.89)	98.06	>0.001	0.42
		OXA-24	11	162/1217	0.06 (0.00–0.17)	96.96	>0.001	0.36
		OXA-58	11	49/1217	0.03 (0.01–0.06)	85.97	>0.001	0.87
		OXA-72	11	42/1217	0.02 (0.00–0.06)	88.20	>0.001	0.94
	MBLs	NDM	9	4/933	0.01 (0.00–0.01)	0.00	>0.05	0.40
		VIM	9	1/933	–	–	–	–
		IMP	9	0/933	–	–	–	–
		SIM	9	0/933	–	–	–	–
China	Class D	OXA-23	17	1290/1499	0.91 (0.84–0.96)	94.42	>0.001	0.36
		OXA-24	17	51/1499	0.03 (0.01–0.08)	92.34	>0.001	0.11
		OXA-58	17	5/1499	–	–	–	–
		OXA-72	17	45/1499	0.02 (0.00–0.05)	91.07	>0.001	0.66
	MBLs	NDM	14	21/1005	0.02 (0.00–0.04)	74.58	>0.001	0.57
		VIM	14	120/1005	0.07 (0.00–0.21)	97.36	>0.001	0.60
		IMP	14	26/1005	0.02 (0.00–0.06)	85.77	>0.001	0.21
		SIM	14	14/1005	0.01 (0.00–0.03)	57.92	>0.001	0.54

MBLs: Metallobetalactamases; n: Number of isolates with the genotype; N: Total number of carbapenem-resistant *A. baumannii* isolates
Number of studies: number of studies in which carbapenemases were identified

Figure 2: Forest plot and funnel plot for OXA-23 carbapenemase prevalence in China, Latin America and the Caribbean
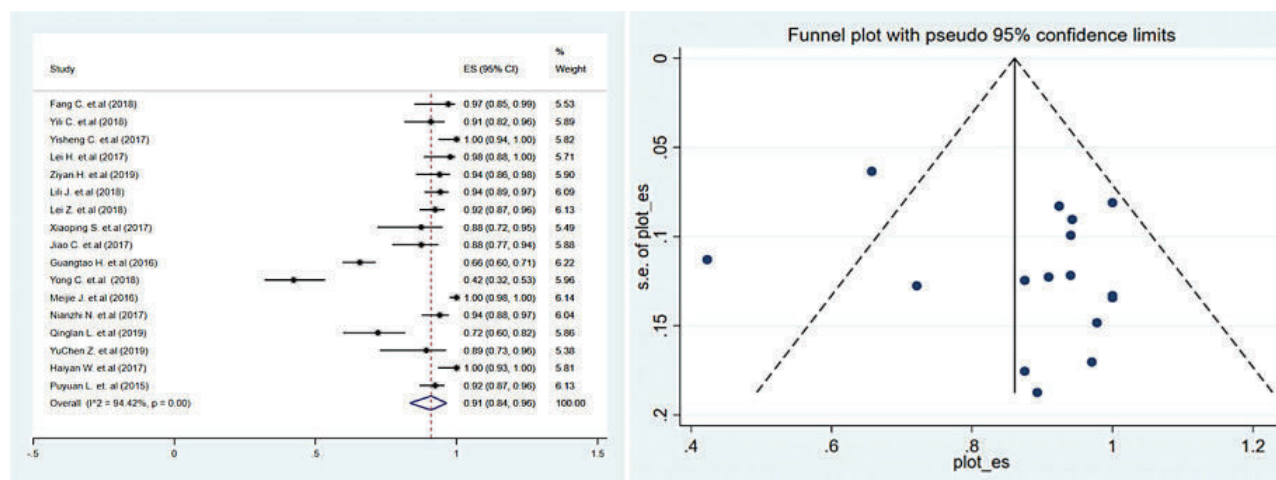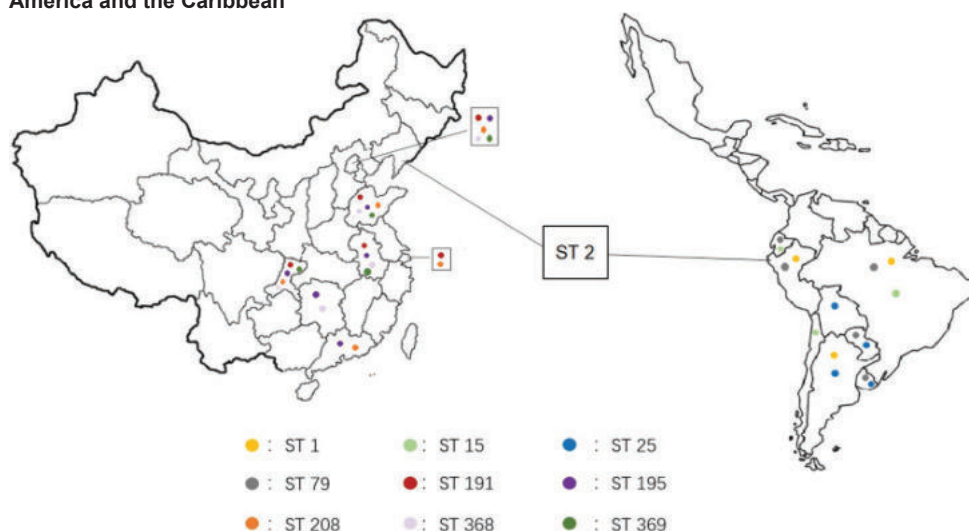

(A)
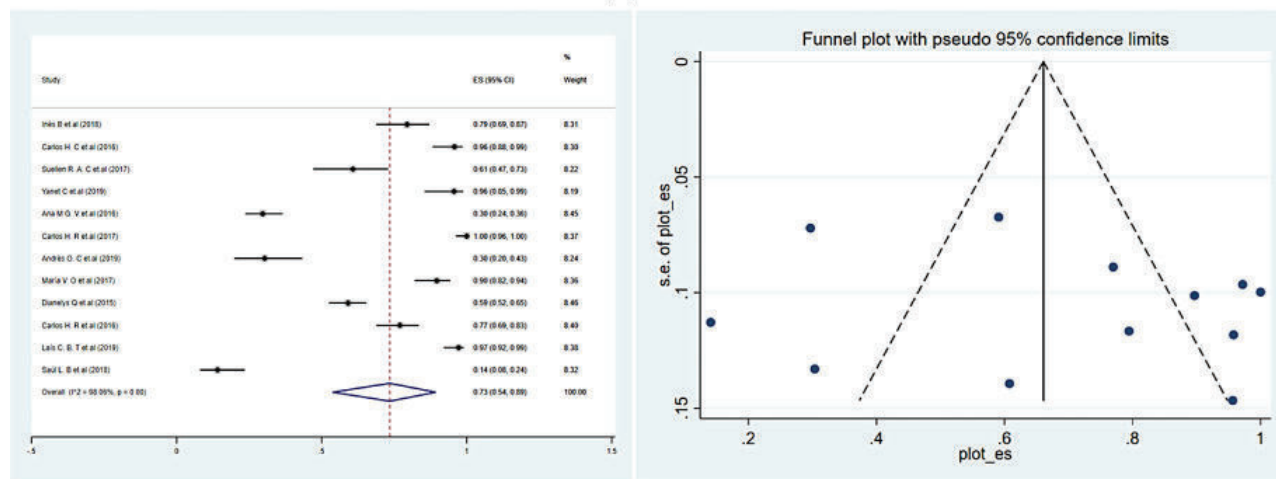
(B)

A: OXA-23 carbapenemase prevalence in China
B: OXA-23 carbapenemase prevalence in Latin America and the Caribbean

Figure 3: *Acinetobacter baumannii* sequence type (ST) geographic distribution in China, Latin America and the Caribbean

Eight provinces in China conducted multilocus sequence studies using MLST; ST195 and ST208 were the most common. These two sequence types have been found in other regions of the world and tend to become the dominant STs once introduced.[63–65] A study of the clinical and molecular characteristics of CRAB-produced bacteremia in China showed clones ST195 and ST208 to be predominant, and bacteremia resulting from *A. baumannii* clone ST195 was associated with higher lethality.[66] Clones ST191, ST368 and ST369 are moderately prevalent in China and are more commonly found in Asia than the rest of the world. Hospital infection by *A. baumannii* clones ST191 and ST369 has also been reported in China and South Korea.[67,68] The STs that are the most common in China are rarely reported in LAC; only ST369 has been reported in Mexico in 2020.[69] This may be the result of differing clonal ancestries in both regions and selection pressure from different antimicrobial use habits.

The data obtained in this review show that MBLs have a very low prevalence and are mainly of the NDM, VIM and IPM types. Five Chinese provinces reported MBLs; Hu Nan and Jian Xi provinces, in particular, have very high prevalence of this type of carbapenemases. In LAC, only Cuba and Colombia detected MBLs, both of which had very low prevalence rates. A meta-analysis of Iranian isolates reported a prevalence of 21.9% and 6.2% of OXA-24 and OXA-58 carbapenemase isolates, respectively, and higher prevalences of MBLs (IMP, 16.7%; VIM, 12.3% and NDM, 2.7%)[56] than those found in LAC and China. A study in Egypt reported a prevalence of 95.7% IMP, 7,1% VIM and 42.9% GIM in *A. baumannii* isolates.[57] The emergence and spread of MBL-producing *A. baumannii* strains has been reported in the United States, Canada, Europe, Japan, Australia, Africa and the Middle East.[58] The differences in OXA and MBL prevalence between countries is likely due to pressures of antimicrobial selection, horizontal transfer of carbapenemase genes by mobile genetic elements (plasmids) between species, propagation of clones carrying these genes or to a combination of all these factors.

Detected sequence types MLST is considered the gold standard for detecting bacterial sequence types and is highly useful in epidemiology. This review includes 17 studies based on MLST. Due to the great diversity in sequence types and the differences between countries and provinces, we only carried out a descriptive qualitative study on these articles (Figure 3). In the case of LAC, these studies mainly originated in South America (namely in Brazil, Peru, Argentina, Colombia, Chile, Bolivia, Ecuador, Paraguay and Uruguay). The most common sequence types in the region were ST79, ST25, ST1 and ST15. ST79 had the widest geographic spread, and was detected in Ecuador, Peru, Brazil, Paraguay, Uruguay and Argentina,[34,35,39,43,45] which implies greater current dissemination than had been reported earlier (in a review carried out in 2018).[59] ST25 was detected in Bolivia, Paraguay, Uruguay and Argentina,[39,43] and had been previously identified in Honduras (2012) and Brazil (2013).[60,61] ST1 was found in isolates from Peru, Brazil and Argentina,[39,44,45] and was the predominant Argentinian isolate. ST15 was detected in Ecuador, Chile and Brazil; it was associated with carbapenemase production (mainly OXA-23–like carbapenemases), and has had rapid dissemination, mainly in South America.[62]

ST2 was found in both regions (Peru in LAC and Liao Ning in China). ST2 is prevalent in some countries in Pacific Asia and Europe,[70–74] but has not been reported with any frequency in LAC in the last five years. Although this study found ST2 to be associated with OXA-72, other studies have described ST2 *A. baumannii* clones as mainly being producers of OXA-23.[74–76] ST2's dissemination in LAC merits consideration.

This study has provided estimates of the prevalence of different types of carbapenemases in *A. baumannii* in LAC and China, and the geographical distribution of different circulating CRAB STs and supports adjustments to resistance surveillance programming and antimicrobial management.

Study limitations There were some Latin American and Caribbean countries and Chinese provinces that produced no studies that met our selection criteria. Consequently, there is no information on carbapenemase-producing CRAB strain genotypes in these regions. Additionally, most studies do not detect Class A carbapenemases. This exclusion may have led to an overrepresentation of other carbapenemase classes and this preferential study of certain classes may have introduced bias. Finally, while the Egger test in not statistically significant and publication bias is unlikely, there is considerable heterogeneity between studies, as suggested by the asymmetric and sparse shape of the funnel plots. This could be due to insufficient sample size in the included studies, or to some variation (either geographical or temporal) in the strains or other methodological aspects such as differences in sample inclusion and exclusion criteria, among other factors.

CONCLUSION

A. baumannii resistance to carbapenem antibiotics is a global threat, and there is increasing diffusion of carbapenem-producing *A. baumannii* isolates and increasing geographic ST variation. Enzymes produced by regional isolates are generally very simi-

lar, while differences in STs are observed between China, Latin America and the Caribbean. Different regions have different epidemic CRAB strains, and it is important to consider local epidemiology in order to best tailor patient treatment. Studying circulating enzymes, clones and genetic lines facilitates understanding of region-specific resistance mechanisms.

Multidisciplinary collaboration is necessary (microbiologists, clinicians, epidemiologists and specialists in preventive medicine with experience in infection control), and will allow for early detection and study of resistance using molecular methods; adequate treatment, taking into consideration the patient's clinical status, common circulating strains, and infection characteristics; and adoption of epidemiological measures aimed at multi-drug–resistant infection prevention and control, reducing transmission at community- and hospital levels. A multidisciplinary approach can provide better results in managing a complex, multifactorial problem with major implications for public health. -//-

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