Molecular epidemiology of carbapenemase encoding genes in *A. baumannii-calcoaceticus complex* infections in children: a systematic review

Mariana Chávez Rodríguez (b)¹, Abiel Homero Mascareñas De Los Santos (b)¹, Denisse Natalie Vaquera Aparicio (b)¹, Rebeca Aguayo Samaniego (b)¹, Rodrigo García Pérez (b)¹, Daniel Siller-Rodríguez (b)², Sara Paulina Rosales-González (b)¹, Patricia Lizeth Castillo-Morales (b)³ and José Iván Castillo Bejarano (b)^{1,2*}

¹Department of Pediatrics/Infectious Diseases Service, Hospital Universitario "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León, Francisco I. Madero Avenue, Mitras Centro, ZC 64460 Monterrey, México; ²Hospital Epidemiology and Surveillance Unit, Christus Muguerza Hospital Alta Especialidad, Hidalgo Avenue, Obispado, ZC 64060 Monterrey, México; ³Department of Endocrinology, Hospital Universitario "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León, Francisco I. Madero Avenue, Mitras Centro, ZC 64460 Monterrey, México

*Corresponding author. E-mail: jicastillobejarano@gmail.com

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Background: Acinetobacter baumannii-calcoaeticus complex is the leader pathogen for the World Health Organization's list due to the escalating prevalence of multidrug-resistant strains. Insights into the molecular characterization of carbapenemase genes in *A. baumannii-calcoaceticus* complex infections among children are scarce. To address this gap, we conducted a systematic review to describe the molecular epidemiology of the carbapenemase genes in *A. baumannii-calcoaceticus* complex infections in the pediatric population.

Methods: Adhering to the PRISMA 2020 guidelines for reporting systematic reviews, we conducted a review of in chore bibliographic databases published in English and Spanish, between January 2020 and December 2022. All studies conducted in patients ≤ 6 years with molecular characterization of carbapenemase-encoding genes in *A. baumannii-calcoaceticus* infections were included.

Results: In total, 1129 cases were reviewed, with an overall carbapenem-resistance rate of 60.3%. *A. baumannii-calcoaceticus* was isolated from blood cultures in 66.6% of cases. Regionally, the Eastern Mediterranean exhibited the highest prevalence of carbapenem resistance (88.3%). Regarding the carbapenemase genes, bla_{KPC} displayed an overall prevalence of 1.2%, while class B bla_{NDM} had a prevalence of 10.9%. Class D $bla_{OXA-23-like}$ reported a prevalence of 64%, bla_{OXA-48} and bla_{OXA-40} had a prevalence of 33% and 18.1%, respectively. Notably, the Americas region showed a prevalence of $bla_{OXA-23-like}$ at 91.6%.

Conclusion: Our work highlights the high prevalence of carbapenem-resistant *A. baumannii-calcoaceticus* and class D carbapenemase genes in children. Of note the distribution of different carbapenemase genes reveals considerable variations across WHO regions. To enhance epidemiological understanding, further extensive studies in children are imperative.

Introduction

The Acinetobacter genus comprises 82 valid species, typically causing healthcare-associated infections such as ventilator-associated pneumonia, urinary tract infections and sepsis.¹ Healthcareassociated infections caused by Acinetobacter baumannii*calcoaceticus* complex (*A. baumannii, A. calcaoaceticus, A. pitti, A. nosocomialis, A. seifertti, A. dijkshoorniaem*) are a public health treat due to its potential to become resistant to multiple antibiotics. Although, they possess similar phenotypic properties, accurate identification of clinically important members of this group is possible by molecular methods.^{2,3}

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Currently, carbapenem-resistant Acinetobacter baumannii (CRAB) stands as the leading pathogen on the World Health Organization's (WHO) list of public health threats due to the high prevalence of multidrug-resistant strains.⁴ A. baumannii strains employ different mechanisms to develop antimicrobial resistance, including a chromosomally encoded carbapenemase gene bla_{0XA-51} , which could lead to overexpression; besides, it can acquire additional carbapenemases. Previous studies characterizing the molecular aspects of carbapenem-resistance strains in the adult population reported an endemic prevalence of bla_{OXA-23-like} and bla_{OXA-72} in Europe.⁵ In the Americas region, bla_{OXA-23-like} has been reported at a range of 51.2%-97.9%.^{6,7} bla_{NDM} is an MBL carbapenemase type is usually seen in Asia.⁸ Currently, insights into the molecular epidemiology of A. baumannii-calcoaceticus complex infections among children are scarce. To address this gap, we conducted a systematic review to describe the molecular epidemiology of the carbapenemase-encoding genes in A. baumannii-calcoaceticus *complex* infections in the pediatric population.

Methods

We realized a comprehensive literature review in major bibliographic databases, including Scopus (Elsevier, Amsterdam, the Netherlands), the Excerpta Medica Database (Embase [Elsevier, Amsterdam, the Netherlands]), Medline (US National Library of Medicine, Bethesda, Maryland), and Web of Science (Clarivate Analytics, Philadelphia, Pennsylvania). Our search covered articles published until May 2023, using the keywords: "A. baumannii", "carbapenem-resistance A. baumannii", "children", "pediatrics", "Class A carbapenemase", "metallo-β-lactamases" or "class B carbapenemase", "oxacillinases" or "Class D carbapenemase", and carbapenemase-encoding genes including "bla_{KPC"}, "bla_{NDM"}, "bla_{VIM"}, "bla_{IMP"}, "bla_{OXA-51}", "bla_{OXA-23-like"}, "bla_{OXA-24-like"}, "bla_{OXA-24-like"}, "bla_{OXA-40}", "bla_{OXA-48}", "bla_{OXA-58}" and "bla_{OXA-72}", as well as relevant MeSH (medical subject heading) terms. References were reviewed to identify additional relevant cases. Conference abstracts, letters to the editor, cases lacking descriptive information, or case series with missing data of interest were excluded. Eligible articles were defined as cohort or cross-sectional studies that reported the molecular characterization through polymerase chain reaction of carbapenemase genes in CRAB infections among patients under 18 years. For an article to be

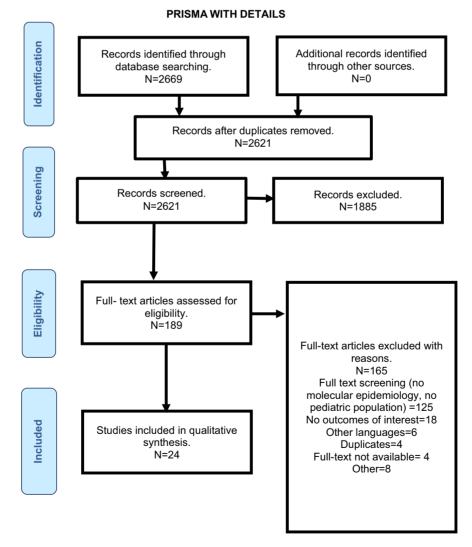


Figure 1. PRISMA Flow Chart.

First Author	Year	Country	WHO Region	Characteristics of the study	Z	carbapenem resistance	Carbapenemase Genes tested.	Carbapenemase Genes detected
A. Karaasslan, et al. ¹⁴	2015	Turkey	Europe	Colonization study in rectal 5 swabs	55	30.9%	blavım, bla _{IMP} , bla _{NDM} , bla _{SPM} , bla _{KPC} , bla _{GES} , bla _{OXA-48} , bla _{OXA-51} , bla _{OXA-23-like} , bla _{OXA-24-like} , bla _{OXA-23}	bla _{NDM} _22% bla _{OXA-58} _11% bla _{OXA-23-like} _31% bla _{OXA-24} ike_37%
Abazar Pournajaf, et al. ²⁵	2018	Iran	Eastern Mediterranean	Study of skin samples in burn 7. patients	73	94.5%	blavın, bla _{ine} , bla _{sın} , bla _{sın} , bla _{nom} , bla _{sen} , bla _{ne} , bla _{sın} , bla _{kec} , bla _{GES} , bla _{OXA-51} , bla _{OXA-23-like} , bla _{OXA-24-like} , bla _{OXA-58}	bla _{VIM}
Amarela Lukic Grlic, et <i>a</i> l. ¹⁵	2019	Croatia	Europe	Clinical samples of different 1 origins, 10 infections, 2 colonization.	12	33.3%	blaoxa-23-like, blaoxa-24-like	bla _{oxa-23-like} 25% bla _{oxa-24-like} 75%
Btissam Arhoune, et al. ¹⁶	2019	Morocco	African	Intestinal carrier study 6	68	13.2%	bla _{0XA-51} , bla _{0XA-23-like} , bla _{0XA-24-like} , bla _{0XA-58} , bla _{VIM} , bla _{IMP} , bla _{NDM} , bla _{kPC}	bla _{0XA-23-like} 88%
Dongsub Kim et al. ¹²	2022	Corea	South-East Asia	Study in bloodstream 2 infection in patients in the ICU.	27	62.9%	blavın, bla _{iMP} , bla _{GIM} , bla _{NDM-1} , bla _{kPC} , bla _{OXA-51} , bla _{OXA-23-like} , blaoxa-24-like, bla _{OXA-58} , bla _{OXA-48}	bla _{oxa-23-like} 100%
Elena Bello-López et al. ³⁰	2020	Mexico	Americas	Study in pediatric population 2. of various clinical samples.	24	20.8%	blaoxa-51, blaoxa-23-like, blaoxa-24-like, blaoxa-58, blaoxa-214, blav1M, bla _{IMP} , blacTx-M, bla _{GIM} , bla _{NDM} , bla _{FPM} , bla _{FEN} , bla _{KPC} , bla _{GES} , bla _{PEL} .	bla _{oxa-23-like} 100%
G.A. Rocha, et al. ²⁸	2017	Brazil	Americas	Study of patients with cystic 3 fibrosis, samples from pediatric patients were selected, only respiratory samples.	32	31.%	blaoxa-51, blaoxa-23-iike, blaoxa-24-iike, blaoxa-58, blaoxa-143	bla _{oxa-23-like} 100%
Hao-Yuan Lee, et al. ¹	2017	Taiwan	South-East Asia	Study in neonatal patients 44 with bacteremia.	40	75%	blaoxa-51, blaoxa-23-like, blaoxa-40, blaoxa-58, blaoxa-54, bla _{ADC-1} , bla _{ADC-2} 9, bla _{IMP-1} , blav _{IM-1} , blav _{IM-2} , blaoxa-80	bla _{0xA-80} _100%
I.Gajic, et <i>al.</i> ²²	2021	Serbia	Europe	Case-control study in an outbreak in ICU.	13	100%	bla _{0XA-51} , bla _{0XA-23-like} , bla _{0XA-24-like} , bla _{0XA-58} , bla _{0XA-143} , bla _{0XA-66} , bla _{0XA-72}	bla _{oxa-66} —100% bla _{oxa-72} —100%
Jetsi Mancilla- Rojano, et <i>al.</i> ²⁹	2020	Mexico	Americas	Study performed on 8. previously identified strains from hospitalized patients.	88	38.6%	blaoxa-51, blaoxa-23-like, blaoxa-24-like, blaoxa-58	bla _{0XA-23-like} _51.1% bla _{0XA-24-like} _4.5% bla _{0XA-58} _2.3%

Table 1. Characteristics of all studies included

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First Author	Year	Country	WHO Region	Characteristics of the study	z	carbapenem resistance	Carbapenemase Genes tested.	caroapenemase Genes detected
Mohanned Mohammed Hamza. et al. ¹⁷	2020	Iraq	Eastern Mediterranean	Multicentric study including various clinical samples.	27	59.2%	Bla _{NDM}	Bla _{NDM} 40%
Mónica Cerezales, et al. ¹⁸	2018	Bolivia	Americas	Study on various clinical samples in one center.	36	88.8%	Bla _{OXA-23-like}	Bla _{0XA-23-like} —100%
Neda Yousef Nojookambari et al. ¹⁰	2021	Iran	Eastern Mediterranean	Study on various clinical samples in one center.	60	%06	Blatem, blashu, blactx-m, blaveb, blaper, blaces, blatmp, blavim, blanom, blaoxa-51, blaoxa-24-like, blacka-32-like, blacka-ce	bla _{oxa-24-like} _36.6% bla _{oxa-23-like} _93.3% bla _{oxa-58} _3.3%
Olga Tsiatsiou, et al. ²³	2014	Greece	Europe	ICU outbreak study, miscellaneous clinical samples.	Ø	100%	Bla _{IMP} , bla _{VIM} , bla _{OXA-23-like} , bla _{OXA-24-like} , bla _{OXA-58}	bla _{0XA-58} _100%
R. Zarrilli, et al. ²⁴	2012	Italy	Europe	Study in neonates to define carrier status and colonization in nasopharyngeal and rectal swabs.	22	100%	bla _{oxA-23-like}	bla _{oxa-23-like} _100%
Reza Ranjbar, et al. ²⁷	2019	Iran	Eastern Mediterranean	Study in skin sample in burned patients.	55	92.7%	bla _{NDM} , bla _{VIM} , bla _{KPC} , bla _{IMP} , bla <u>ovazor</u> , bla <u>ovazos</u> , bla <u>ovazos</u> , ite	bla _{oxa-40} _54.5% bla _{oxa-23-like} _85.1%
Sandip Patil et al. ²⁶	2019	China	Western Pacific	Study in a pediatric center, diverse clinical samples.	10	60%	Mcr-I, blactx-M, blaNDM-1, blakec, blateM, blaSsHv, blaGES, blacARB, blaveB, blaoxa-48, blasME, blavIM	bla _{NDM-1} _20% bla _{KPC} _10% bla _{OXA-48} _10 bla _{OXA-48} _10%
Somdatta Chatterjee, et al. ²¹	2016	India	South-East Asia	Study in blood samples from neonates with sepsis.	68	50%	bla _{NDM} , bla _{VIM} , bla _{IMP} , bla _{OXA-58} , bla _{OXA-24-like} , bla _{OXA-23} -like	bla _{NDM} _22% bla _{OXA-23} like_49%
Theodoros Karampatakis, et al. ¹⁹	2019	Greece	Europe	Study in diverse clinical samples in an intensive care unit.	17	100%	Bla _{TEM} , bla _{SHV} , bla _{CTX-M} , bla _{VIM} , bla _{NDM} , bla _{KPC} , bla _{OXA-48} , bla _{OXA-58} , bla _{OXA-23} _{like}	bla _{0xa-58} _5.9% bla _{0xa-23 like} _29.4%
Xiao Xu, et al. ¹³	2021	China	Western Pacific	Study in clinical samples in a pediatric intensive care unit.	131	67.9%	bla _{OXA-24-like} , bla _{OXA-58} , bla _{OXA-23-like}	bla _{OXA-23-like} —91% bla _{OXA-23-like} —81%
Xing Wang, et <i>a</i> l. ²⁰	2020	China	Western Pacific	Study of clinical and environmental samples from a pediatric hospital.	88	69.3%	bla _{oxa-23-like} , bla _{oxa-5} 8, bla _{oxa-24-like} , bla _{v I} M, bla _{IMP}	pl
Yanling Feng, et <i>al.</i> ⁸	2021	China	Western Pacific	Study of stool samples from hospitalized patients to screen for carriers of resistant bacteria.	112	1.7%	Blanpm, blavım, blakec, blaımp, blaoxa-66, blaoxa-72, blaoxa-80, blaoxa-40, blaoxa-48, blaoxa-58, blaoxa-24-ilke, blaoxa-23-ilke	Bla _{NDM} _20%

Table 1. Continued

Yili Chen, et al. ⁹	2018	China	Western Pacific	Study of clinical simples in	86	77.9%	Blavım, bla _{IMP} , bla _{KPC} , bla _{OXA-66} ,	bla _{0XA-24-like} _28.8%
				patients hospitalized in ICU.			bla _{oxA-72} , bla _{oxA-80} , bla _{oxA-40} ,	bla _{0XA-23-like} —90.9%
							bla _{0XA-48} , bla _{0XA-58} , bla _{0XA-24-like} ,	bla _{0XA-58} 4.5%
							bla _{oxA-23-like} , bla _{NDM}	bla _{NDM} —4.5%
Yunfen Zhu,	2022	China	Western Pacific	Study of diverse clinical	77	59.7%	blavım, bla _{IMP} , bla _{NDM} , bla _{AIM} , bla _{SPM} ,	bla _{VIM} _100%
et al. ¹¹				samples in pediatric			bla _{BIC} , bla _{GIM} , bla _{OXA-23-like} ,	bla _{IMP} —67.5%
				patients.			bla _{0XA-51} , bla _{0XA-10} , bla _{0XA-24-like}	bla _{NDM} _31.1%
								bla _{0XA-23-like} 100%

included, the following information was required: (i) Author, (ii) Country, (iii) WHO region, (iv) age group, (v) specimen, (vi) sample size, (vii) prevalence of carbapenem-resistant, and (viii) carbapenemase genes.

Two independent reviewers (Mariana Chávez-Rodrígez & Rebeca Aguayo-Samaniego) collected the required information from all eligible articles. Disagreements were resolved through consensus, and in cases where consensus could not be reached, a third reviewer (José Iván Castillo Bejarano) made the final decision. Data of interest were collected into a database using Microsoft Excel 2020 (Redmond, Washington), which was designed before the extraction phase. The collected information included continuous and categorical variables, organizing epidemiological characteristics descriptively.

Descriptive statistics, including frequencies with percentages for dichotomous variables were utilized to summarize the collected data. SPSS version 24 (IBM, Armonk, New York, USA) was used to calculate statistics. The review protocol was registered and continuously updated on the International Prospective Register of Systematic Reviews-PROSPERO website (https://www.crd.york.ac.uk/prospero/) with the assigned ID number 512592 and was submitted to our institutional INVEST KER Platform for Systematic Reviews.

Results

In this systematic review, 2669 possible studies were reviewed (Figure 1). After screening, 189 articles were retrieved for full reading, with 24 studies meeting the established inclusion criteria. Among these, 20 were published from 2018 to 2023, with China being the leading country in terms of publications. The studies were classified based on WHO regions, revealing six studies in the European Region and the Western Pacific Region, four in the Eastern Mediterranean Region and the Region of the Americas, three in the Southeast Asia Region, and only one study in the African Region. The studies were analysed and the percentage of carbapenems resistance, the carbapenemase genes tested and detected were identified for more details go to Table 1.^{1,8–30}

The sample size varied, totaling 1229 patients, with an overall prevalence of carbapenem resistance at 60.3%. According to the WHO regions, the only study included from the African Region presented the lowest prevalence at 13.2%, followed by the Region for the Americas at 45%, the Western Pacific Region at 53.7%, the South-East Asia Region at 60%, the European Region at 63.7%, and the highest prevalence in the Eastern Mediterranean Region at 88.3%.

Regarding age groups, 11 studies encompassed all pediatric age groups (neonates, infants, preschoolers, school-aged children and adolescents), 6 studies excluded neonates and infants, and 6 studies solely included neonates, while only one study excluded neonates and infants.

The origin of the isolates varied; most studies included diverse samples, with 9 of them focusing on a single origin (blood 3/9, skin and feces 2/9, respiratory and rectal swab 1/9).

Blood samples were included in 66.6% of the studies, respiratory samples in 54.1% respiratory samples, skin samples in 33.3%, urine samples in 24%, catheter and cerebrospinal fluid in 20.8%, fecal and rectal swab samples 16.6%, peritoneal fluid samples 12.5% and other isolates (stomach fluid, abscess, exudate, mediastinal tissue, cholesteatoma) 25%.

All the carbapenemase-encoding genes were detected by polymerase chain reaction. The global distribution of the

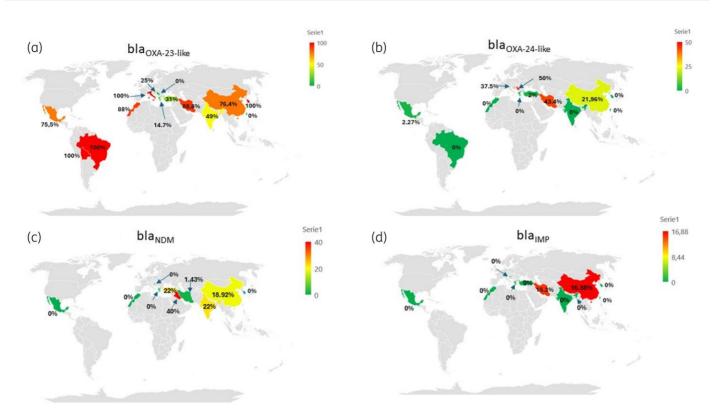


Figure 2. Global distribution of carbapenemase-encoding genes in *A. baumannii-calcoaceticus* complex infections in the pediatric population: a) Countries where bla_{OXA-23-like} has been reported, b) Countries where bla_{OXA-24-like} has been reported, c) Presence of Class B bla_{NDM}, d) Presence of Class B bla_{IMP}.

carbapenemase resistance genes in *A. baumannii-calcoaceticus* complex in pediatric patients is exhibited in Figure 2. For Class A carbapenemase, only bla_{KPC} was reported in 11 studies, with a prevalence of 1.4%. Class B carbapenemase bla_{ICU} was described in 15 studies with a prevalence of 10.9%; bla_{VIM} in 17 studies with a prevalence of 10.1%; and bla_{IMP} in 15 studies with a prevalence of 6.5%. Regarding Class D, bla_{OXA-51} was sought and detected in all studies due to its intrinsic profile in *A. baumannii*. Two studies additionally included the bla_{OXA-51} family members, bla_{OXA-66} and bla_{OXA-80} being detected in all strains. Bla_{OXA-23-like} was reported in 22 studies with a prevalence of 64%, bla_{OXA-58} in 19 studies with 6.7%, bla_{OXA-24-like} in 20 studies with 21%, bla_{OXA-48} 33%.

Concerning the distribution of carbapenemase genes in the different WHO regions, within the African region only one study met the characteristics of this review finding the presence of bla_{OXA-23-like} in 88% of the carbapenem-resistant strains. In the region of the Americas, a mean prevalence of 91.6% of $bla_{OXA-23-like}$ was reported, with the presence of bla_{OXA-58} and bla_{OXA-24-like} reported in less than 5% of the strains, with no detection of Class A and B carbapenemases. In Southeast Asia, the presence of bla_{OXA-23-like} was reported with a prevalence of 49.6%, with moderate detections of bla_{NDM} (22%). In Europe and the Western Pacific, $bla_{OXA-23-like}$ was found as the most prevalent gene with a range of 25%-100%, and class B carbapenemase bla_{NDM} had a mean detection of 7.3% and 18.9%, respectively. Lastly, in the Eastern Mediterranean region, bla_{OXA-23-like} had a prevalence of 63.45%, along with the identification of the bla_{OXA-40} member of the family $bla_{OXA-24-like}$, which

was not reported in any other region. Class A and B genes were found in lower proportions with a range of 4.3%–62.3%.

Discussion

Our work is the first systematic review of the molecular epidemiology of carbapenemase-encoding genes in *Acinetobacter baumannii-calcoaceticus* complex infections in the pediatric population. We identified a high prevalence of *Acinetobacter baumannii-calcoaceticus* complex in children with significant variation in the global distribution of carbapenemase genes among the WHO regions. *A. baumannii*, according to the WHO's list of urgent public threats, is the leading priority pathogen due to its variability in resistance mechanisms, with carbapenemase enzymes being the most important due to their transmissibility and association with treatment failures.³¹ The high prevalence of CRAB infections, at 60.3% in children, prompts us to investigate the global distribution of carbapenemases.³²

In the adult population, several studies have been conducted due to the growing importance of CRAB isolates in recent decades.¹³ One study published in 2018 by da Silva and colleagues,³³ conducted in two intensive care units in Brazil, reported the presence of bla_{OXA-23-like} in 15% of *A. baumannii* isolates identified as carbapenem-resistant. This study spanned a 2-year period, during which other genes encoding resistance to beta-lactams were sought but not identified. In another study conducted in Canada, a Nosocomial Surveillance Program was seeking Acinetobacter spp producers of beta-lactamases from 2010 to 2016, with $bla_{OXA-23-like}$ as the most common identified gene.³⁴

Regarding the neonatal population Hao-Yuan Lee and colleagues³⁵ studied neonates with A. baumannii bacteremia in Taiwan, where a low prevalence of carbapenem resistance was found in this age group. In India, Somdatta Chatterjee's study²¹ identified different Acinetobacter spp predominantly A. baumannii, with over 50% carbapenem resistance, particularly in the South-East Asia region. In contrast to general reports in the pediatric population, a prevalence of bla_{OXA-23-like} of 29.8% has been reported in this age group.^{21–23,34,28} Within the context of hospital outbreaks in neonatal intensive care units from Serbia²² and Greece,²³ Class D carbapenemases have been detected in diverse clinical samples; however, these outbreaks studies did not report the presence of bla_{OXA-23-like}, which was sought in both studies. In another study by Zarrilli and colleagues conducted in a neonatal intensive care unit from Naples, rectal and nasopharyngeal swabs were performed to define colonization states of A. baumannii, with bla_{OXA-23-like} being detected in all cases.²⁴

In the Eastern Mediterranean region, specifically in Iran, two studies were conducted on burn patients. Abrazar and colleagues²⁶ reported a prevalence of CRAB of 94.5% of cases from skin samples. They also identified the production of class B carbapenemase with a high prevalence of bla_{VIM} (62.3%), bla_{IMP} (30.4%) and bla_{NDM} (4.3%), co-detected with bla_{OXA-23-like}, which has a prevalence at 85.1%. Another study by Reza Ranjbar *et al.*²⁷ reported a prevalence of bla_{OXA-23-like} at 85.1%, without detections of carbapenemase genes of classes A and B.

In Latin America, several studies related to CRAB infections and their resistance mechanisms have been published primarily in Brazil. Although these studies were not specifically conducted in pediatric populations, understanding the epidemiology of CRAB in each hospital is crucial given its status as a primarily healthcare-associated infection. Lima and colleagues conducted a systematic review of burn patients, where they found that bla_{OXA} carbapenemase was the most prevalent in 85.1% of cases.³⁶ Another original study conducted in Brazil, focusing on patients with cystic fibrosis, detected colonization with *A. baumannii* in previously hospitalized pediatric patients, where a low prevalence of carbapenem resistance at 30% was reported, among these cases, $bla_{OXA-23-like}$ was the only identified gene.²⁸

Recent studies from our research team were conducted at our hospital in northeast Mexico; however, they were published after the closure of this project.^{37,38} We identified the class D carbapenemase gene bla_{OXA-24-like} in all children with CRAB infections. In another study with 21 non-duplicated isolates obtained from diverse clinical samples, we observed a high prevalence of the class B carbapenemase gene bla_{IMP} in 57% of isolates being co-detected with bla_{OXA-24-like} in all cases, and without detections of bla_{OXA-23-like}. These findings contrast with those reported by Bello-López and Mancilla-Rojano *et al.*, both included in this systematic review with a population from central Mexico, where bla_{OXA-24-like} was detected in less than 5%.^{27,28}

While we did not uncover a substantial number of studies due to the lack of molecular characterization, it remains imperative to persist in conducting research of this nature to broaden the global understanding of resistance genes. Understanding these genes is fundamental for developing strategies to mitigate transmission and for offering treatment options for these infections, which have emerged as significant public health concerns.

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Transparency declaration

All authors report no conflicts of interest with this article.

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