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Original Article

Dynamics and characterization of carbapenemase-producing Enterobacterales isolated from clinical specimens in a private healthcare center in Lima, Peru, from 2018 to 2019

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Abstract

Introduction: Antimicrobial resistance is a major and growing concern worldwide. The study aimed to describe the occurrence and characterize the antimicrobial resistance profile of carbapenemase-producing Enterobacterales (CPE) isolated from clinical specimens at a private healthcare center in Lima, Peru, between January 2018 and December 2019.

Methodology: A total of 59 bacterial isolates were identified as CPE using the modified carbapenem inactivation method. Bacterial identification and antimicrobial susceptibility testing were performed using the Vitek 2 system, and colistin susceptibility was determined using the compact antimicrobial susceptibility panel. Five carbapenemase encoding genes, including *bla*$_{NDM}$, *bla*$_{IMP}$, *bla*$_{VIM}$, *bla*$_{OXA-48}$, and *bla*$_{KPC}$, were screened using PCR and lateral flow assay. Also, carbapenemases were screened using the boronic acid- and EDTA-based disk synergy methods. The dynamics of CPE were described every month.

Results: Carbapenemase-producing *Klebsiella pneumoniae* was the most prevalent agent (83.1%), followed by *Providencia* spp. (6.8%), *Escherichia coli* (5.1%), *Enterobacter cloacae* (3.4%), and *Citrobacter freundii* (1.6%). The isolation of *bla*$_{NDM}$-carrying CPE was frequent and increased during the second half of 2019, while *bla*$_{KPC}$ carriers were detected in the second half of 2018. One CPE carrying *bla*$_{OXA-48}$ was detected in June 2019. No other carbapenemase-encoding genes were detected.

Conclusions: This report is among the first to document CPE in private health care institutions in Lima, Peru. Results suggest that the emergence and spread of carbapenemases are becoming a latent and growing threat in private healthcare settings.

Key words: drug resistance; carbapenem-resistant Enterobacterales; health facilities; Peru.

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Introduction

Antimicrobial resistance (AMR) is a major and growing concern worldwide and a threat to global health security. Globally, and particularly in Latin America, AMR has increased alarmingly over the last few years [1,2]. Currently, resistance to first- and second-line antibiotics is widespread in both hospital and community settings [3]. Therefore, given the increased resistance to drugs commonly used in clinical practice, carbapenems are reserved for the treatment of infections caused by multidrug-resistant or extensively drug-resistant bacteria [2,4].

Carbapenems are β-lactam antibiotics with broad-spectrum activity [5]. These antibiotics represent the last line of therapeutic options against complicated bacterial infections caused by Gram-negative bacteria resistant to carbapenems, so the emergence and spread of mechanisms of carbapenem resistance constitute a threat to global health [6]. The most alarming and globally distributed mechanism is the production of enzymes that can hydrolyze several β-lactams, including carbapenems [7].

Carbapenem-resistant bacteria of clinical relevance include *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and members of the *Enterobacterales* group. Within the *Enterobacterales* group, *Klebsiella pneumoniae* and *Escherichia coli* are of particular concern as they frequently harbor carbapenemases [8]. The epidemiology, spread, and burden of carbapenemases have been poorly described in low- and middle-income countries, whereas most reports focus on outbreaks, molecular mechanisms, virulence determinants, and genetic characteristics [2]. However, despite the limited and varied documentation, the most frequently reported carbapenemases are *K. pneumoniae* carbapenemases (KPC), New Delhi metallo-β-lactamases (NDM), and OXA-type β-lactamases [2].

Carbapenem-resistant Enterobacterales, *A. baumannii*, and *P. aeruginosa* were recognized as highly priority antibiotic-resistant pathogens by the World Health Organization because infections with any of these bacteria have a significant impact on health care expenditures, morbidity, and mortality [9]. However, despite some reports of carbapenem-resistant

bacteria in Peru [10–16], the epidemiology of these agents remains poorly understood, especially in private healthcare institutions. This lack of information constrains efforts to identify appropriate therapeutic options that account for the dynamics and antimicrobial resistance profile of carbapenem-resistant bacteria [2]. The study aimed to describe the dynamics and characterization of carbapenemase-producing *Enterobacterales* (CPE) in one of the largest networks of private healthcare centers in Lima, Peru, over 2 years, and to characterize carbapenemase-encoding genes and antimicrobial resistance profiles of bacterial isolates.

Methodology

Study site and Clinical isolates

Bacterial isolates were sourced from a private laboratory located in Lima, Peru, which actively cooperates with one of the significant networks of private healthcare centers. Specifically, the Microbiology department of the laboratory processes samples from three-level health facilities; all of which provide critical emergency, outpatient, and inpatient care. Additionally, the laboratory serves as a central hub, receiving samples from seven strategically located sites in Lima.

The laboratory routinely analyzes specimens for bacterial culture, including urine, blood, respiratory or wound secretions, stool, and others. These specimens were collected by trained medical personnel or self-collected by patients following instructions provided by trained personnel and then sent to the laboratory. Bacterial isolation and identification, as well as antimicrobial susceptibility testing (AST), are procedures routinely performed in the laboratory. Here, methods and results produced by the work performed in the laboratory are presented.

From January 1, 2018, to December 31, 2019, a total of 72 clinical isolates with resistance to at least one carbapenem, including imipenem (IPM), meropenem (MEM), or ertapenem (ETP), were identified. The modified carbapenem inactivation method (mCIM) [17] was used to identify carbapenem-producing Enterobacterales (CPE) among the 72 clinical isolates, resulting in a total of 59 isolates confirmed as CPE. All experiments described hereafter were performed using these 59 CPE isolates. The AST was performed on all CPE at a private laboratory by the broth microdilution method using the Vitek 2 system. Colistin susceptibility was determined by broth microdilution using the compact antimicrobial susceptibility panel (ComASP). Minimum inhibitory concentration (MIC) values were interpreted according to the Clinical Laboratory Standard Institute (CLSI) recommendations [17].

Antimicrobial Susceptibility Testing

The AST included 11 antimicrobial categories; penicillins (ampicillin), penicillins + β-lactamase inhibitors (amoxicillin-clavulanic acid [AMC], ampicillin-sulbactam, and piperacillin-tazobactam [TZP]), non-extended spectrum cephalosporins (cefazolin [CZ], and cefuroxime [CXM), extended-spectrum cephalosporins (cefixime [CFM], cefotaxime [CTM], ceftriaxone [CTR], ceftazidime [CAZ], and cefepime [CPM]), β-lactam + β-lactamase inhibitor (cefoperazone-sulbactam [CFS]), carbapenems (ETP, MEM, and IPM), monobactams (aztreonam [ATM]), aminoglycosides (gentamicin [GE], and amikacin [AK]), fluoroquinolones (ciprofloxacin[CIP], and levofloxacin [LEV]), folate pathway inhibitors (trimethoprim-sulfamethoxazole [SXT]), and polymyxins (colistin [CT]). Two additional antimicrobial categories were included in the AST for urinary isolates: nitrofuran (nitrofurantoin [NIT]) and phosphonic acids (200 μg fosfomycin [FO] + 50 μg of glucose-6-phosphate; Oxoid).

Serine carbapenemase (KPC) and metallo-β-lactamase (MBL) enzymes were screened as previously described using boronic acid- and ethylenediaminetetraacetic acid (EDTA)-based methods, respectively [18]. The screening was performed using the Kirby-Bauer disk diffusion method with ETP (10 μg), MEM (10 μg), IPM (10 μg), cloxacillin (500 μg), ATM (10 μg), TZP (110 μg), AMC (30 μg), EDTA (750 μg), and 3-aminophenylboronic acid (APB, 300 μg) in BD Mueller-Hinton agar as described by the CLSI [17]. *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were used as controls in the AST, and *K. pneumoniae* ATCC BAA-1705 was used as a positive control in the screening of carbapenemases.

Lateral flow immunoassays

The "RESIST-4 O.K.V.N." immunochromatographic lateral flow assay (Coris BioConcept, Gembloux, Belgium) was used to screen class D OXA-48 β-lactamases, KPC, NDM, and Verona integron-encoded MBL (VIM) following the manufacturer's instructions.

Molecular testing

The Isolate II Genomic DNA kit (Bioline, Luckenwalde, Germany) was used to extract bacterial DNA according to the manufacturer's instructions. Five

genes were screened as follows; *bla*$_{NDM}$ (Forward: 5'-AGC ACA CTT CCT ATC TCG AC-3'; Reverse: 5'-GGC GTA GTG CTC AGT GTC-3'), *bla*$_{IMP}$ (Forward: 5'-GGY GTT TWT GTT CAT ACW TCK TTY GA-3'; Reverse: 5'-GGY ARC CAA ACC ACT ASG TTA TCT-3′) and *bla*$_{VIM}$ (Forward: 5'-AGT GGT GAG TAT CCG ACA G-3'; Reverse: 5'-ATG AAA GTG CGT GGA GAC-3') in a multiplex polymerase chain reaction (PCR); and *bla*$_{OXA-48}$ (Forward: 5'-ATG CGT GTA TTA GCC TTA TCG G-3'; Reverse: 5'-TGA GCA CTT CTT TTG TGA TG-3') and *bla*$_{KPC}$ (Forward: 5'-AAC AAG GAA TAT CGT TGA TG -3'; Reverse: 5'-AGA TGA TTT TCA GAG CCT TA-3') in another multiplex PCR reaction. PCRs were performed in a 25.0 µL reaction mixture containing 2.0 µL of bacterial DNA, 0.2 µL of DNA Polymerase (5.0 U/µL), 5.0 µL of 5X Bioline MyTaq Red Reaction Buffer, 0.5 µL of each primer (10.0 µM), and 16.8 µL of water. PCR amplification was performed as described elsewhere [19]. PCR products were separated by 1.5% agarose gel electrophoresis and stained with SafeView. *K. pneumoniae* ATTCC BAA-1705, ATCC BAA-2146, and ATCC BAA-2524 were used as positive controls.

Statistical analysis

Multidrug resistance (MDR) was defined as resistance to ≥ 1 agent in ≥ 3 different antimicrobial categories. CPEs were classified as multidrug-resistant (MDR according to their resistance profile as described elsewhere [20]. The resistance profile of the non-urinary isolates included MIC results for 11 antimicrobial categories obtained with the Vitek 2 system. The profile of urinary isolates also included the nitrofuran and phosphonic acids categories, resulting in 13 antimicrobial categories. The number of isolations was reported monthly throughout the two-year study period. The univariate analysis and the agreement between methods used here were assessed using the Kappa coefficient in Stata v17 (StataCorp, 2021, Stata Statistical Software: Release 17, College Station, TX: StataCorp LLC).

Ethical statement

The research project and its procedures were approved by the research committee (Code: 20220036), which approved the characterization of clinical isolates collected in a network of private healthcare centers. In addition, the research was nested within two surveillance protocols, which supported the use of de-identified clinical isolates. These protocols were approved by Universidad Peruana Cayetano Heredia's ethics committee (Codes: 208187, 100535) as part of the collaborative efforts between the investigators.

Results

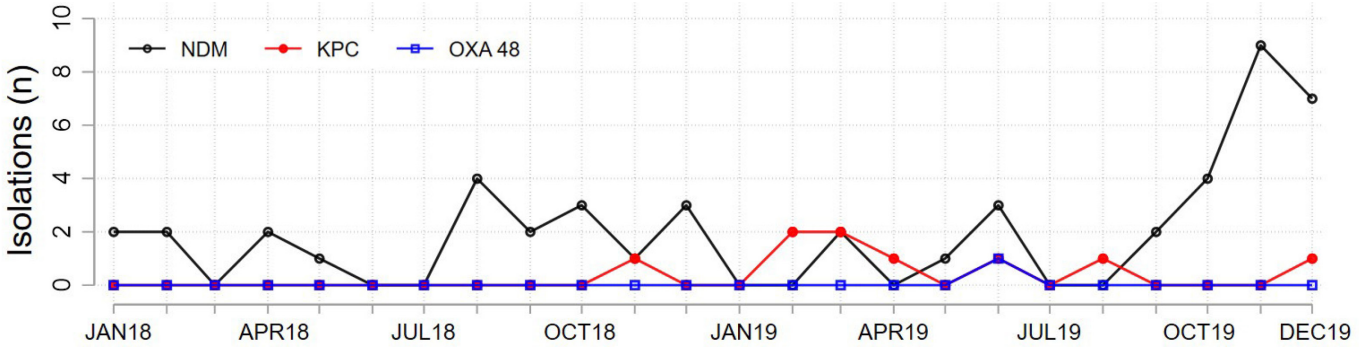
Among the 72 clinical isolates, 59 unique and non-duplicated isolates were confirmed as CPE. Specifically, the 59 CPE characterized were isolated from samples collected from the same number of patients between January 1, 2018, and December 31, 2019. The most frequent source of isolation was urine (26/59, 44.1%), and *K. pneumoniae* was the most prevalent CPE (49/59, 83.1%) (Table 1). The number of

Table 1. Antimicrobial resistance rates of carbapenem-producing Enterobacterales.

	GEN	AMK	TMP/SMX	CST [a]	NIT [b]	FOF [b]
Urine						
K. pneumoniae (n = 22)	77.3 (17/22)	36.4 (8/22)	90.9 (20/22)	25.0 (2/8)	77.3 (17/22)	59.1 (13/22)
E. coli (n = 2)	100.0 (2/2)	50.0 (1/2)	50.0 (1/2)	0.0 (0/1)	0.0 (0/2)	0.0 (0/2)
Providencia spp. (n = 2)	100.0 (2/2)	0.0 (0/2)	100.0 (2/2)	N.T.	100.0 (2/2)	0.0 (0/2)
Blood						
K. pneumoniae (n = 4)	100.0 (4/4)	50.0 (2/4)	50.0 (2/4)	33.3 (1/3)	N.T.	N.T.
Wound swabs						
K. pneumoniae (n = 13)	92.3 (12/13)	23.1 (3/13)	53.8 (7/13)	0.0 (0/12)	N.T.	N.T.
E. coli (n = 1)	0.0 (0/1)	100.0 (1/1)	100.0 (1/1)	0.0 (0/1)	N.T.	N.T.
Tissue						
K. pneumoniae (n = 3)	100.0 (3/3)	33.3 (1/3)	33.3 (1/3)	0.0 (0/2)	N.T.	N.T.
Enterobacter cloacae (n = 2)	100.0 (2/2)	0.0 (0/2)	100.0 (2/2)	0.0 (0/2)	N.T.	N.T.
Providencia spp. (n = 1)	0.0 (0/1)	0.0 (0/1)	100.0 (1/1)	N.T.	N.T.	N.T.
Citrobacter freundii (n = 1)	0.0 (0/1)	100.0 (1/1)	100.0 (1/1)	N.T.	N.T.	N.T.
Respiratory secretions						
K. pneumoniae (n = 3)	66.7 (2/3)	66.7 (2/3)	33.3 (1/3)	0.0 (0/2)	N.T.	N.T.
Providencia spp. (n = 1)	0.0 (0/1)	0.0 (0/1)	100.0 (1/1)	N.T.	N.T.	N.T.
Central venous catheter tip						
K. pneumoniae (n = 4)	100.0 (4/4)	0.0 (0/4)	50.0 (2/4)	25.0 (1/4)	N.T.	N.T.
Total						
All Enterobacterales	81.4 (48/59)	32.2 (19/59)	71.2 (42/59)	7.4 (4/54)	77.3 (17/26)	59.1 (13/26)

Data are presented as % (n/N); GEN: gentamicin; AMK: amikacin; TMP/SMX: trimethoprim-sulfamethoxazole; CST: colistin; NIT: nitrofurantoin; FOF: fosfomycin. N.T.: Not tested. [a] Colistin susceptibility was performed only when it was requested by the treating physician. [b] Nitrofurantoin and fosfomycin susceptibility were performed only in urinary isolates.

Figure 1. Carbapenemase-producing Enterobacterales isolated from clinical specimens collected at a private healthcare center between January 2018 and December 2019.



CPE isolates was lower during 2018 (22/59, 37.3%), and NDM-producing strains were consistently frequent during both 2018 (21/22, 95.5%) and 2019 (29/37, 78.4%). Interestingly, a significant increase in NDM-producing strains was observed in the last quarter of 2019 (Figure 1). The first KPC-producing strain was isolated in November 2018, and the only OXA-48-producing strain was identified in June 2019 (Figure 1).

All CPE isolates exhibited resistance to all drugs of eight antimicrobial categories: penicillins, penicillins + β-lactamase inhibitors, non-extended and extended-spectrum cephalosporins, β-lactam + β-lactamase inhibitor, carbapenems, monobactams, and fluoroquinolones. The overall resistance was 81.4% (48/59) to gentamicin, 32.2% (19/59) to amikacin, 71.2% (42/59) to trimethoprim-sulfamethoxazole, and 11.4% (4/35) to colistin. The four colistin-resistant bacteria were classified as "non-wild-type" strains based on the CLSI recommendations [17]. Detailed antimicrobial resistance rates by bacteria and isolation sources are summarized in Table 1.

Taking into account the 11 antimicrobial categories used in all CPE, all clinical isolates (59/59) were classified as MDR. Interestingly, one carbapenemase-producing *K. pneumoniae* isolated from a central venous catheter tip was resistant to all 11 categories, and two other carbapenemase-producing *K. pneumoniae* isolated from urine were resistant to all 13 categories.

A total of 50 bla_{NDM}-positive, eight bla_{KPC}-positive, and one bla_{OXA-48}-positive isolate were identified among the 59 CPE. We did not detect bla_{IMP}- nor bla_{VIM}-producers, and no discrepancies between PCR and lateral flow results (Kappa = 1.000, Table 2) were observed. Using phenotypic methods, 48 CPE were classified as producers of class B metallo-β-lactamases (ETP + EDTA + MEM) and the other eight as producers of class A serine carbapenemases (MEM + APB + IMP). Three CPE tested negative by phenotypic methods (Table 2): two bla_{NDM}-positive and one bla_{OXA-48}-positive *K. pneumoniae*. Overall, the agreement between the phenotypic methods and the PCR or lateral flow method was 0.826 (95% confidence interval: 0.599 – 1.000).

Discussion

CPEs represent a major threat to public health. In the last decade, the incidence of CPE has been steadily increasing. In Peru, the first CPE identified was *K. pneumoniae* in 2013 [13]. After the first report and over the following years, various CPE were detected and characterized from clinical specimens collected mainly from public healthcare institutions [10–12,14–16]. Despite multiple reports, the epidemiology of CPE in private healthcare institutions remained poorly studied and understood. In Lima, Peru, there exists a notable socio-economic stratification that significantly influences the landscape of health and disease. The diverse socio-economic classes present in the city play a crucial role in shaping the prevalence, spread, and

Table 2. Antimicrobial resistance characterization by PCR, lateral flow, and phenotypic methods.

	PCR and lateral flow			Phenotype detection		
	NDM	**KPC**	**OXA-48**	**ETP + EDTA + MEM**	**MEM + APB + IPM**	**Negative**
K. pneumoniae (n = 49)	41	7	1	39	7	3
E. coli (n = 3)	2	1	0	2	1	0
Providencia spp. (n = 4)	4	0	0	4	0	0
E. cloacae (n = 2)	2	0	0	2	0	0
Citrobacter spp. (n = 1)	1	0	0	1	0	0

No discrepancy was observed between PCR and lateral flow results; therefore, the results are presented together. NDM: New Delhi metallo-β-lactamases. KPC: *K. pneumoniae* carbapenemases. OXA-48: OXA-48 β-lactamase. ETP: Ertapenem. EDTA: Ethylenediaminetetraacetic acid. MEM: Meropenem. APB: 3-aminophenyl boronic acid. IPM: Imipenem.

impact of diseases. To our knowledge, this report is among the first to retrospectively describe the epidemiology and antimicrobial resistance profiles of all CPE isolated in a laboratory of one of the most critical and largest private healthcare networks in Lima over two years. This contribution aims to enhance bacterial resistance surveillance in the region, which is crucial for public health management.

Carbapenemase-producing *K. pneumoniae* are the most common CPE isolates and have rapidly spread globally [15]. Our results are consistent with reports elsewhere [2,12]; among CPE, *K. pneumoniae* is frequently isolated from various clinical specimens and persists over time. Although the isolation frequency of *E. coli*, *E. cloacae*, *Providencia* spp., and *C. freundii* has been low, it is pertinent to note that these carbapenem-resistant pathogens also pose a threat to public health. Furthermore, it is essential to note that carbapenemase-encoding genes detected in this study have also been reported locally in public settings [2,12,16]. Overall, CPEs represent a significant threat to local public health given their high resistance to commonly used antimicrobials, thus requiring evidence-based strategies to limit their spread in both private and public settings.

The bla_{NDM} gene was the most prevalent, followed by bla_{KPC}. The detection frequencies described here are similar to those previously reported in 2019 for public healthcare institutions in Peru. Specifically, the Peruvian National Institute of Health identified 78 CPE from 30 public institutions across the country, of which 55 (70.5%) carried bla_{NDM} and 23 (29.5%) carried bla_{KPC} [10]. KPC was the first carbapenemase reported in Peru [13]. However, the unexpected spread of NDM has become a significant concern. NDM may be linked to a virulence clone, specifically the ST348 clone, which was responsible for a major hospital outbreak in 2020 [11]. This clone is the only molecular information we currently have on NDM strains. The similar distribution could suggest that the dispersion and dynamics of CPEs did not differ significantly between public and private healthcare institutions during 2019. However, further analyses are required to understand the dynamics better. For instance, an exploratory temporal analysis allowed us to identify the late emergence of bla_{KPC} carriers in 2018 and a notable increase of bla_{NDM} carriers towards the second half of 2019. Interestingly, $bla_{\text{OXA-48}}$ was detected in only one strain during the study period. The $bla_{\text{OXA-48}}$ gene is among the most common carbapenemase-encoding genes in the Middle East and Europe [21]. The first reports of $bla_{\text{OXA-48}}$ in the Americas were in the United States and Argentina, among *K. pneumoniae* strains [22]. However, to date, the spread of $bla_{\text{OXA-48}}$ in the Americas appears to have been low [2]. A recent study suggested that OXA-48 spreads in Peru during 2018 [23]. Notably, the report of $bla_{\text{OXA-48}}$ in this study constitutes one of the first in a Peruvian private healthcare setting.

The detection and characterization of carbapenemases are crucial for determining appropriate antibiotic therapy. The use of molecular methods for detecting carbapenemases may not be feasible; therefore, laboratories may rely on phenotypic methods (such as disk synergy tests) to detect and characterize carbapenemases. In this study, we observed three discrepancies while using the disk synergy method; two bla_{NDM} carriers and one $bla_{\text{OXA-48}}$ carrier were not correctly classified. High MIC values could explain the failure to detect NDM for IMI and/or high enzyme activity [24]. The inability to detect OXA-48 may be due to the limited sensitivity of the APB and EDTA synergy methods for detecting class D carbapenemases. It is important to note that, to date, methods using APB and EDTA are not reliable for detecting class D carbapenemases, and that other reliable methods, such as those based on temocillin, were not tested here. Therefore, in settings with a high frequency of Class D carbapenemases (such as OXA-48), the use of APB- and EDTA-based methods may lead to an underestimation of this resistance mechanism. Moreover, based on our findings, lateral flow tests could be rapid and reliable tools for detecting multiple carbapenemases. Our findings are consistent with other reports described elsewhere, which suggested that molecular and lateral flow assays exhibit a very high degree of agreement [25,26]. Specifically, compared to the PCR, the lateral flow assay used here displayed an overall accuracy of 99.5% and a specificity of 100.0% for the detection of $bla_{\text{OXA-48}}$, bla_{KPC}, bla_{VIM}, and bla_{NDM}, and a sensitivity of 100.0% for the detection of $bla_{\text{OXA-48}}$, $bla_{KPC,}$ and bla_{VIM}, and a sensitivity of 95.0% for bla_{NDM} [24].

Our study is subject to various limitations. The isolates were collected from a single private healthcare institution; therefore, the results presented here could not be extrapolated to other private settings, nor could they be used as a reference for different settings. Also, no molecular typing was performed to identify clonal complexes. Therefore, our results do not support the increase or dispersion of a particular clonal complex over time. Future studies may integrate clonal complexes and epidemiological data to better elucidate the factors that shape the emergence and spread of CPE

and to inform prevention and control programs and treatment guidelines.

The influence of varying socioeconomic contexts on the treatment, antibiotic prescriptions, and outcomes of infectious diseases has been extensively discussed [27–29]. It underscores the significance of understanding bacterial resistance surveillance across diverse territories. This study provides a retrospective overview of the epidemiology and dynamics of CPE in a private healthcare institution in Lima. This retrospective view of 2018–2019 revealed that the emergence and dispersion of CPE were not characteristic of public healthcare institutions and provides a baseline for the further characterization of CPE and for various ongoing studies.

Conclusions

In summary, our findings suggest that the emergence and spread of *bla*$_{NDM}$-carrying *K. pneumoniae* and other CPE are a worrying and latent concern in the studied healthcare institution. Despite intermittent detection of CPE, our results underscore that carbapenemase presence is an ongoing and evolving phenomenon. In this regard, the notorious increase in CPE over time could be viewed as a warning for laboratories to implement reliable tools that enable rapid and accurate identification of carbapenemases. In addition, the increase could be considered a call for the development of further research across healthcare institutions.

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Authors' contributions

TOG and HBP conceptualized, designed the methodology, and conducted the research. TOG and SL analyzed and interpreted the data and drafted the manuscript. HBP and JT assisted with data analysis and interpretation. TGO and HBP managed funding and provided research resources. All authors approved the final version of the manuscript and assume responsibility for the article.

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Conflict of interest

No conflict of interest is declared.

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