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Update on the epidemiology of carbapenemases in Latin America and the Caribbean

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Abstract

Introduction: Carbapenemases are β-lactamases able to hydrolyze a wide range of β-lactam antibiotics, including carbapenems. Carbapenemase production in *Enterobacterales*, *Pseudomonas aeruginosa* and *Acinetobacter* spp., with and without the co-expression of other β-lactamases is a serious public health threat. Carbapenemases belong to three main classes according to the Ambler classification: class A, class B and class D.

Areas covered: Carbapenemase-bearing pathogens are endemic in Latin America. In this review we update the status of carbapenemases in Latin America and the Caribbean.

Expert opinion: Understanding the current epidemiology of carbapenemases in Latin America and the Caribbean is of critical importance to improve infection control policies limiting the dissemination of multi-drug-resistant pathogens and in implementing appropriate antimicrobial therapy.

Keywords: *Acinetobacter baumannii*, carbapenemases, carbapenems, carbapenem resistance, carbapenem-resistant *Enterobacterales* (CRE), *Klebsiella pneumoniae*, Latin America, *Pseudomonas aeruginosa*.

Article highlights

- Carbapenemases are a significant health threat as carbapenems are considered “last resort antibiotics” for the treatment of severe Gram-negative infections.
- Currently in Latin America, there is broad dissemination of MDR Gram-negative pathogens harboring a diverse range of carbapenemases, particularly among *Enterobacterales* and the non-fermentative rods *Pseudomonas* spp. and *Acinetobacter* spp.
- Confirmatory testing for carbapenemases is one of the cornerstones for antimicrobial stewardship and infection control. When available, high performance methods like PCR and immunochromatographic assays should be implemented to get rapid and accurate results as the use of new drugs relies on the specific type of enzyme expressed.
- In recent years, several unusual Class A carbapenemases-bearing species and expression of rare combinations of beta-lactamases have been observed in Latin America. These include KPC in *Kluyvera spp., Raoultella spp., Serratia spp. and Morganella spp*. Coexpressing MCR-1.
- New reports of Class B carbapenemases include NDM-1, NDM-2 and IMP-1 in *Klebsiella spp., Citrobacter spp., Providencia spp., Acinetobacter, Enterobacter spp. and E. coli*.
- New reports of Class D carbapenemases in *Acinetobacter spp.* include OXA-58, OXA-64, OXA-65, OXA-68, OXA-69, OXA132, OXA-143 and OXA-180.
- Coexpression of two or more carbapenemases is becoming frequent in LATAM and poses a major diagnostic and therapeutic challenge because it limits the use of all currently available β-lactams.

1. Introduction

Dissemination of multidrug resistant (MDR) Gram-negative rods (GNR), particularly *Enterobacterales* and the non-fermentative rods like *Pseudomonas* spp. and *Acinetobacter* spp., is a major public health concern worldwide. Unfortunately, the pipeline for new antibiotics is limited and cannot solve today's antimicrobial resistant infections [1, 2]. Gram-negatives have developed several mechanisms of resistance to currently used antimicrobials, including the production of β-lactamases, efflux pumps, porin mutations, modifying enzymes and target modification. Additionally, horizontal transfer of resistance determinants to multiple drugs is also responsible for the rapid emergence of resistance worldwide [3]. Although GNR may develop resistance to carbapenems due to several mechanisms, the most clinically relevant and epidemiologically important is the production of β-lactamases with around 3000 variants reported today according to Bush and Bradford [4]. Within these β-lactam–hydrolyzing enzymes, the carbapenemases play a fundamental role, as carbapenems have been considered the "last resort antibiotics" for the treatment of severe Gram-negative infections. Indeed, in 2017 the WHO published the Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. It catalogues 12 bacterial families that pose the greatest threat to human health. In this list the critical priorities include carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, as well as Extended-Spectrum-β-lactamases (ESBL)-producing and carbapenem-resistant *Enterobacterales* [5].

This review is intended to update the epidemiological publication of carbapenemases in Latin America (LATAM) and the Caribbean published by our group in 2016 [6]. This new epidemiological review includes published data from the second semester of 2016 to 2019 in the following LATAM and the Caribbean countries: Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, French Guiana, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay, Venezuela, the Greater Antilles (Cuba, Dominican Republic, Haiti, Jamaica, and Puerto Rico), and the Lesser Antilles (Guadeloupe, Trinidad and Tobago) The search included available official reports as well as peer-reviewed reports using specific databases (PubMed, SciELO, Google Scholar and published Abstracts from the ICAAC via WorldCat® website). This update on the new reports of carbapenemases in this geographical area will provide an important tool for all health-care providers and for the scientific community to improve their understanding of the epidemiology of carbapenemases.

2. Challenges in carbapenemases detection in Latin America

The selection of the right detection test for a particular bacterial species highly depends on the regional and local epidemiology, costs, performance, and turnaround times [7]. Detecting carbapenemases by the clinical microbiology laboratory is challenging. Any isolate with reduced susceptibility to carbapenems (except *Proteus spp., Morganella spp. and Providencia spp.*, because of their intrinsic resistance to imipenem) should be suspicious as having a carbapenemase. However, initial testing of isolates usually relies on the minimum inhibitory concentrations (MICs) or disk zone diameters, and both tests have inherent variability; for example some carbapenemase producers (mostly OXA-48 and KPC) may test as susceptible with the current Clinical and Laboratory Standards

Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC breakpoints and many laboratories will not further confirm their MIC or disk zone diameter test results with molecular tests. The falsely susceptible result will then contribute to undetected carbapenemases and their "silent" dissemination as well as the underestimation of the real carbapenemase problem [8, 9].

When an isolate is not susceptible to any carbapenem, laboratories are required to perform confirmatory testing. The most common tests used in Latin America are the modified Hodge test (MHT), modified carbapenem inactivation test (mCIM), colorimetric methods (Carba NP/Blue Carba) and tests that differentiate the type of enzyme, like synergy with boronic acid for class A or EDTA for class B beta-lactamases, and which are described in Table 1. However, all these methods have limitations. MHT may not detect metallo-β-lactamases (MBL) causing false negatives. In contrast, ESBLs and AmpC plus porin mutations may give false positive results in the MHT test. Synergy testing is not always easy to read because small amounts of the enzyme can lead to false negatives. EDTA can interact with the outer membrane porin causing false positives synergy, and co-production of enzymes (class A + class B) can cause false negative synergy. Also, there are no specific inhibitors for OXA-48 *vs* other carbapenemases [10].

Some of these pitfalls can be overcome by commercial immunochromatographic tests (NG Carba 5 or Coris Resist-5 [11]) or PCR based methods that detect the specific type of enzyme and the presence of several enzymes (Table 1). However, these methods detect a limited number of targets or enzyme variants and new enzymes or variants can be missed. In contrast, next generation sequencing (NGS), can provide a comprehensive and broad detection of enzymes, but is not commonly available in clinical laboratories in LATAM and the Caribbean because of its elevated cost.

Pseudomonas aeruginosa is a leading nosocomial pathogen and infections can be difficult to treat because its rapid development of resistance. The emergence of MDR isolates is a serious public health threat that affects patients within specialized units (intensive care units [ICUs], hematology-oncology wards or burn units). Resistance to carbapenems is mediated either by a combination of efflux pumps, AmpC overexpression and porin loss or acquisition of carbapenemases, especially MBL [6, 12]. Although new compounds have been added to the armamentarium against MDR *P. aeruginosa*, resistance even to these new drugs including the β-lactam/β-lactamase inhibitor combinations challenge the ability to successfully treat serious infections.

Detection of carbapenemase producers among carbapenem-resistant *P. aeruginosa* is important since many carbapenemase-encoding genes are plasmid-encoded and easily transferable. However, for clinical microbiology laboratories this is a challenge due to several factors. Phenotypic methods like MHT or boronic acid are not accurate. Differentiation of MBL from KPC producers may be based on the inhibitory properties of molecules like ethylenediaminetetraacetic acid (EDTA) and phenylboronic acid (PBA). But these tests require a significant degree of expertise for correct interpretation. As inhibition of carbapenemase activity by various inhibitors is more difficult in *P. aeruginosa* than in *Enterobacterales* due to its low outer membrane permeability, molecular detection of carbapenemase genes is an important alternative but remains costly. As an option, lateral

flow immunochromatographic assays detect carbapenemases in 15 minutes with high accuracy. These detection methods need to be implemented because a number of new antimicrobial therapies target specific beta-lactamases [13]. For detection of carbapenemase in *P. aeruginosa*, the CLSI Carba NP method has been extensively investigated and has offered a good sensitivity and specificity of 98% for the detection of Ambler class A, B and D carbapenemases. Similarly, in the same study, the modified carbapenem inactivation method (mCIM) was tested for *P. aeruginosa*, showing a sensitivity of 98% and specificity of 95% [14]. These results show that both the mCIM and the Carba NP tests are accurate for the detection of carbapenemase production among *P. aeruginosa* isolates.

On the other hand*, Acinetobacter baumannii complex* can be carbapenem resistant by several mechanisms involving porin mutations (like CarO), hyperproduction of AmpC and its intrinsic carbapenemase OXA-51 through insertion of IS*Aba*-1 [15]. Phenotypic methods to detect carbapenemase production in *A. baumannii* are not accurate enough to be applied in daily practice in hospitals; commercial PCR methods and lateral flow immunochromatography assays, if available, should be selected based on the most frequent carbapenemases in this specie like $bla_{\text{OXA-23}}$ and $bla_{\text{OXA-58}}$. Detecting and differentiating the type of carbapenemase in *A. baumannii complex* is costly and requires a high degree of expertise that is not available in non- specialized laboratories. But in contrast to *P. aeruginosa,* almost no new antibiotics are available for MDR *A. baumannii.* That means that the characterization of carbapenemases in *A. baumannii* is more of epidemiological interest than clinical relevance at this point. The Carba NP method has been also evaluated in *A. baumannii* showing a mean sensitivity of only 19% but a mean specificity of 100%. On the other hand, the mCIM test was evaluated in *A. baumannii* showing a mean sensitivity of 80%, performing better than Carba NP, but a mean specificity of only 53% with a significant site-to-site variability in the reported results [14]. Recently a modification to the mCIM method was proposed, where 0.5 M Tris-HCl buffer is used for extraction increasing the detection rates in *Acinetobacter* and *Pseudomonas,* to a sensitivity of 98% and specificity of 93% [16]. Interestingly, it was recognized that a larger inoculum of a 10 µL loopful instead of a 1 µL is required for reliable carbapenemase detection in *A. baumannii* and *P. aeruginosa*, being more apparent for VIM detection in *P. aeruginosa* and OXA detection in *A. baumannii* [7]. In spite of these recent results, the CLSI does not recommend Carba NP or mCIM for carbapenemase detection in *A. baumannii* complex [8].

The poor sensitivity of the Carba NP test in detecting several mechanisms of resistance of *A.baumanni* [17] was overcome by the CarbAcineto NP test where the lysis conditions are modified and the bacterial inoculum is increased. It has an overall sensitivity of 95% and a specificity of 100% for the acquired carbapenemases common to *A. baumannii* such as OXA-23-like, OXA-40-like, OXA-58-like, and OXA-143-like subgroups. For OXA-51-like enzymes though there were inconsistencies in the data [18].

MALDI-TOF MS had an overall sensitivity of 77% and a specificity of 100% for carbapenemase detection in diverse bacterial species and, later with the simple addition of bicarbonate to the reaction buffer, it was possible to enhance the detection of OXA-48-like producer bacteria, increasing the overall sensitivity to 98%, without compromising the detection of other enzymes in other species [19]. Using this modification, MALDI-TOF MS

may identify carbapenemase activity in *A. baumannii*, with a sensitivity and specificity up to 100% [20].

3. Class A carbapenemases

All class A carbapenemases share a serine-residue at their active-site which confers the hydrolytic property to the enzyme. These are chromosomal and plasmid-located β-lactamases with a broad spectrum of hydrolytic activity against β-lactam antibiotics, including carbapenems. Class A carbapenemases are inhibited by new β-lactamase inhibitors such as avibactam and relebactam, while vaborbactam inhibits class A β-lactamases including the KPC-enzymes. Their location in mobile elements, allows them to be transferred and disseminated among a wide range of GNB [21]. These enzymes have predominantly been reported in several members of *Enterobacterales*, causing severe infections and outbreaks.

In the class A, the plasmid-borne KPC (*K. pneumoniae* carbapenemase) is the most clinically relevant [22]. Mainly associated with the transposable element Tn*4401*, KPC displays a wide geographical variation, with several clones disseminating within the same area but differing by their MLST-type, plasmid size and β-lactamase enzyme content [23]. The archetypical KPC is a Class A β-lactamase that hydrolyzes penicillins, cephalosporins, monobactams and carbapenems; it is inhibited by avibactam, vaborbactam and relebactam and is poorly inhibited by clavulanic acid and tazobactam. A review of KPC genes by Perez and Van Duin stated that there are currently 12 additional variants of the bla_{KPC} gene globally [24] while Naas et al. report 14 KPC variants in their BLDB database [25]. According to the US National Library of medicine, there are 47 KPC variants (https://www.ncbi.nlm.nih.gov/pathogens/isolates#/refgene/KPC).

Additionally, class A carbapenemases also include the chromosomal non-metallo-carbapenemases type A (NMC-A), the *Serratia marcescens* enzyme (SME), the plasmidic IMI (imipenem-hydrolyzing β-lactamase) and GES (Guiana extended-spectrum β-lactamase) enzymes [6, 22], as well as the less common SFC (*Serratia fonticola* carbapenemase), the BKC (Brazilian *Klebsiella* carbapenemase) [26], the BIC (Bicêtre carbapenemase) and the FRI (French imipenemase).

The class A carbapenemase NMC-A was the first class A carbapenemase found in Latin America, described in 2000 in *E. cloacae* from Argentina [27] and later in 2009 in the same species in Colombia [28].

In our former review, KPC variants in *Enterobacterales* were reported in most Latin American countries, including Mexico, Panamá, Puerto Rico and Cuba [6] while the GES-type carbapenemase was reported in Argentina, Brazil and Mexico [27, 29–33]. New information has contributed to our understanding of the dissemination of KPC in Latin America and highlights important differences between countries (Table 2).

For example, in Argentina an *E. coli* ST131 harboring an unknown variant of KPC in a Tn3-derived NTEKPC genetic platform was recently described for the first time in Latin America [34]. Interestingly, also in Argentina, a changing epidemiology of KPC in the clinical setting has been observed. This may be related to the dissemination of more

virulent lineages such as the *K. pneumoniae* hypermucoviscous ST25 and ST11, together with the emergence of the high-risk clone ST307 harboring *bla*$_{KPC-3}$ in the region [35].

Argentina also reported isolates of *S. marcescens* harboring the SME-4 carbapenemase [36], which was previously reported only in Brazil [37]. The discovery of new enzymes emphasizes the importance of introducing detection systems capable of detecting enzymes in addition to the "big five" carbapenemase classes (KPC, VIM, NDM, IMP, OXA-48) that are usually screened.

In Brazil, a new GES-type enzyme (GES-16) in *S. marcescens* was reported in hospitalized patients at a tertiary hospital in Rio de Janeiro [38]. Also recently, from a remote community of the Amazon in Brazil, the genomic analysis of a *Morganella morganii* revealed a *bla*$_{GES-5}$ that harbored a novel class 1 integron designated as In*1390* [39]. This was the first report of a *M. morganii* strain harboring a *bla*$_{GES-like}$ gene in this class of integron and showed how resistance can disseminate among different bacterial genera in remote areas. Another striking report from Brazil is the horizontal transfer of a plasmid harboring the *bla*$_{KPC-2}$ gene from *K. pneumoniae* to *E. cloacae* during meropenem therapy in a patient with a respiratory tract infection [40]. Brazil also described the first *mcr-1* gene in *K. pneumoniae* co-harboring *bla*$_{KPC-2}$ in Latin America [41]. Finally, Brazil, published for the first time a *Raoultella ornithinolytica* isolated from flies harboring *bla*$_{KPC-2}$ [42].

Peru reported for the first time in 2017 a *K. pneumoniae* isolate member of CG258 with the presence of the *bla*$_{KPC-2}$ gene [43]. One year later, the first isolate of KPC-2-producing *K. pneumoniae* was detected in Uruguay associated with the high-risk clone ST258 [44].

In Colombia, according to Rojas et al. [45], the start of the epidemic was driven by horizontal dissemination of mobile genetic elements carrying *bla*$_{KPC-2}$, from different genetic backgrounds and capsule types, which allowed the dissemination between *Enterobacterales* and *P. aeruginosa* isolates, followed by the introduction and subsequent spreading of clonal group 258 (CG258) isolates containing *bla*$_{KPC-3}$.

In another publication from Colombia, Ovalle et al. [46] reported an isolate of *Kluyvera cryocrescens* harboring an unknown variant of *bla*$_{KPC}$. To our knowledge, this might be the first report of a KPC-carrying *K. cryocrescens* isolate causing infection in humans.

Figure 1. New* class A carbapenemases reported from 2016 to 2019 in Latin America and the Caribbean.

* New reports based on: *i)* a new enzyme variant, *ii)* the first description of the enzyme in a new bacterial species or *iii)* the first description of the enzyme in the respective country.

4. Class B carbapenemases

Class B or MBLs are a heterogeneous group of enzymes, which depend on Zn^{2+} ions in their catalytic site [47]. Class B enzymes are not inhibited by clinically available β-lactamase inhibitors. They are inhibited *in vitro* by zinc binding agents EDTA and dipicolinic acid, as well as novel inhibitors such as durlobactam, nacubactam and zidebactam [48]. In addition, MBL are unable to hydrolyze aztreonam, hence, in the

absence of other resistance mechanisms, aztreonam is active against class B carbapenemase-producing organisms (CPO) [23, 49].

According to the US National Library Of medicine, there are 29 NDM variants (https://www.ncbi.nlm.nih.gov/pathogens/isolates#/refgene/NDM), 68 variants of VIM (https://www.ncbi.nlm.nih.gov/pathogens/isolates#/refgene/VIM) and 80 variants of IMP enzymes (https://www.ncbi.nlm.nih.gov/pathogens/isolates#/refgene/IMP).

Based on their known amino acid sequence, these enzymes are classified in three groups [47, 50]. B1 is the group, which includes the most prevalent MBLs, as NDM (New Delhi metallo-β-lactamase), VIM (Verona integron-encoded metallo-β-lactamase) and IMP (imipenemase), as well as the less common SPM (São Paulo metallo-β-lactamase), GIM (German imipenemase) and SIM (Seoul imipenemase) [6, 51-52]. B1 enzymes have the broadest hydrolytic activity including penicillins, cephalosporins and carbapenemases, as well as serine β-lactamase inhibitors. Although B3 enzymes have a similar configuration of the active site, their ability to hydrolyze carbapenems is lower compared to the first group. In contrast, the hydrolytic spectrum of B2 MBLs is limited to carbapenems, with poor activity against penicillins and cephalosporins [47].

Originally found in the chromosome of environmental and opportunistic pathogens such as *Bacillus cereus*, *Chryseobacterium* spp., *Aeromonas* spp. and *Stenotrophomonas maltophilia* [23, 51], MBL have shown a dramatic increase in *Enterobacterales* and *P. aeruginosa*, demonstrating their high potential to be transferred from the environmental resistome. In addition, NDM-1-producing strains may carry additional resistance determinants such as the genes coding for VIM, OXA-48, AmpC cephalosporinases and 16S-rRNA-methyl transferase providing resistance to aminoglycosides, rifampin and macrolides, among others [23].

New class B carbapenemases have been reported along the region in the recent years, as seen in Table 2. In 2017, Aires et al. reported the first NDM-1-producing *K. quasipneumoniae*, in Brazil [53]. In a following study, dissemination of NDM-1 among different *Enterobacterales* including the emerging pathogen *K. quasipneumoniae* subsp. *quasipneumoniae* was observed in the same patient [54].

In Mexico, a nosocomial outbreak with an NDM-1 carbapenemase was detected in different plasmids in four different *Enterobacterales*: *K. pneumoniae*, *E. cloacae*, *E. coli* and *P. rettgeri* associated with horizontal transfer [55].

Recently, the first description of an opportunistic pathogen *Citrobacter amalonaticus* co-expressing NDM-1 with a colistin-resistance gene named *mcr-1.5* was reported in Argentina [56]. In addition to the worrisome co-expression mentioned above, this strain of *C. amalonaticus* also harbored 14 additional genes conferring resistance to aminoglycosides, phenicols, trimethoprim and sulphonamides.

Interestingly, a recent publication from Marquez-Ortiz et al. described a relationship between plasmids from *P. rettgeri*, *A. baumannii and K. pneumoniae*, found in Colombia and Mexico. The author proposes what they defined as a “Russian doll model” for the dissemination of bla_{NDM-1} in Latin America with *P. rettgeri* playing a central role in the storage and dissemination of resistance genes [57].

MBL-producing *Acinetobacter ursingii* was recently reported from Argentina. Specifically, these isolates harbored *bla*$_{IMP-1}$, *bla*$_{NDM-2}$ and *bla*$_{OXA-58}$. This publication is the first report of *A. ursingii* harboring a MBL outside Japan and the Netherlands, suggesting that this species may be acting as a uncommon and unsuspected reservoir for carbapenemases [58]. Argentina also reported, for the first time in Latin America and for the second time in the world, the presence of the carbapenemase LMB-1 (Linz metallo-β-lactamase) [59], which is a novel B3-MBL from a clinical isolate of *C. freundii*, discovered in 2018 in *E. cloacae* in Austria [60]. The *bla*$_{LMB-1}$ from the Argentinian *C. freundii* gene was located on a 176-kb IncA/C2 plasmid and shared 99% of amino acid sequence identity with a MBL encoded by the marine bacterium *Rheinheimera pacifica*, which could be its progenitor species [59].

Whole-genome analysis of an extensively drug-resistant isolate of *Empedobacter falsenii* in Argentina revealed the presence of a novel MBL, called *bla*$_{EBR-2}$, suggesting a potential role of *E. falsenii* as a reservoir of β-lactamases [61].

In the case of Brazil, researchers recovered a VIM-2-producing *P. aeruginosa* isolate from a dog, its owner, and the domestic environment, suggesting a possible zooanthroponotic transmission of VIM-2-producing *P. aeruginosa* [62]. Also in Brazil, the migratory birds *Dendrocygna viduata* (the white-faced whistling duck) harbored *P. aeruginosa* carrying carbapenem-resistance genes in their gut microbiota, mainly *bla*$_{SPM-1}$ but also *bla*$_{OXA-56}$ (an ESBL). Interestingly, the SPM-1-producing isolates showed high MICs for all β-lactams, fluoroquinolones, and aminoglycosides, being susceptible only to polymyxin B and belonging to ST27. This publication suggests that these migratory birds may have played a role in the dissemination of SPM-1-producing *P. aeruginosa* within the Brazilian territory [63].

In a recent report from two different Brazilian hospitals collected from 2000 to 2016 showed that certain species of *Acinetobacter* spp. (*A. pittii*, *A. bereziniae* and *A. junii*) harbored *bla*$_{IMP-1}$. This resistance gene was inserted into In86, a class 1 integron and the study demonstrated that this mobile element persisted for long periods, allowing their mobilization from *A. baumannii* to other *Acinetobacter* spp. [64].

Another publication from the north and northeast of Brazil reported a *K. pneumoniae* and *C. freundii* from two patients harboring *bla*$_{NDM-1}$ [65]. For the first time, clinical isolates of *P. mirabilis* and *S. marcescens* co-harboring *bla*$_{KPC-2}$ and *bla*$_{NDM-1}$ were reported [66].

Furthermore the co-expression of two or more carbapenemases, has also been reported in Brazil with the association of *bla*$_{NDM-1}$with *bla*$_{KPC-2}$ in several Gram-negatives pathogens, such as *K. pneumoniae P. mirabilis* and *S. marcescens* [66].

Brazil published a complete resistome of *P. aeruginosa* ST277, which included *bla*$_{SPM-1}$, *bla*$_{OXA-56}$ and *bla*$_{OXA-396}$, genes among others. This particular chromosomal pack is strongly associated with dissemination and persistence of this particular clone in Brazilian nosocomial infections [67]. Other reports also involve *P. aeruginosa* ST308 isolate carrying in addition to the *bla*$_{SPM}$ gene, the VIM-36 carbapenemase [68].

In Ecuador a NDM-1-producing *A. baumannii* was published [69] as well as in Peru [70], raising the possibility that given the fact that *A. baumannii* is an ubiquitous and promiscuous nosocomial pathogen, the acquisition of NDM-1 may contribute to an

increase in the prevalence of this important mechanisms in other nosocomial pathogens [70].

At the same time, Uruguay reported for the first time NDM-1 in a clinical isolate of *C. freundii* [71].

Peru, in 2018, published for the first time the co-harboring of the carbapenemases VIM-2 and the extended spectrum β-lactamases GES-1 and OXA-1 from an extensively drug resistant (XDR) isolate of *P. aeruginosa*, representing the first report of a VIM carbapenemase in this country [72].

Venezuela has also reported the co-expression of more than one carbapenemase class in clinical isolates of *Enterobacterales*. In 2016, the co-expression of VIM-2 and KPC-2 in several clinical isolates of *K. pneumoniae* ST833 was published [73] as well as in clinical isolates of *A. baumannii* harboring both, NDM-1 and OXA-23 carbapenemases [74].

In Chile, co-expression of carbapenemases was in *K. pneumoniae*, with the presence of both, NDM-1 and OXA-370 (a OXA-48-like carbapenemase) in clinical isolates was reported [75].

In Central America, Nicaragua has also recently reported the co-expression of carbapenemases in *P. aeruginosa*. Seventy percent of the carbapenem-resistant isolates analyzed carried VIM alone or in combination with a SPM or GIM carbapenemase [76].

In Costa Rica, a national surveillance program conducted between 2013 and 2017 allowed the molecular characterization of 267 isolates of *P. aeruginosa* harboring the carbapenemases IMP, VIM as well as the co-expression of both MBLs in 79.4%. Only 4.1% were harboring VIM and 16.5% had only the IMP carbapenemase [77].

Figure 2. New class B carbapenemases reported from 2016 to 2019 in Latin America and the Caribbean.

5. Class D carbapenemases

Class D β-lactamases or oxacillinases (OXA), originally from environmental bacteria like *Shewanella* spp. and deep-see microbiota, are plasmid- or chromosome-encoded β-lactamases. The class D enzymes were initially characterized by their ability to efficiently hydrolyze isoxazolyl-type β-lactams like oxacillin. Due to this substrate preference, these enzymes are traditionally referred to as oxacillinases or OXAs. However, this class is comprised of subfamilies characterized by diverse activities that include oxacillinase, carbapenemase, or cephalosporinase substrate specificity some of them able to hydrolyze carbapenems. For example, OXA-51 is intrinsic in *A. baumannii* [78] while other OXA-enzymes are acquired and/or can be found in *P. aeruginosa* as well as *Enterobacterales;* they are characterized by their wide variety of amino acid sequences and hydrolyzing profiles [6]. The hydrolytic activity of oxacillinases is mainly against penicillins and first-generation cephalosporins; in contrast to those which hydrolyze carbapenems, known as CHDLs (carbapenem-hydrolyzing class D β-lactamases), which possess a weak activity against expanded-spectrum cephalosporins and do not hydrolyze monobactams [22, 23].

Notably, the carbapenemase activity of CHDLs is weak and is inhibited by NaCl, but not by EDTA, sulbactam, clavulanic acid, tazobactam, relebactam or vaborbactam [23, 79-80]. Ceftazidime/avibactam retains activity against OXA-48 producers, as this enzyme does not hydrolyze ceftazidime. *In Enterobacterales* the most prevalent CHDLs is OXA-48, while other OXA variants such as, OXA-23, OXA-40, OXA-48-like, OXA- 51, OXA-58 and OXA-143 have been only reported *in Acinetobacter* spp. [6, 17].

There are several new reports in Latin America since 2016 (Table 2). In Mexico, isolates of *A. baumannii* resistant to carbapenems with a high prevalence of MBL as well as class D carbapenemases such as OXA-51 and OXA-72 were reported from clinical isolates of a tertiary care hospital with virulence profiles and innate immune responses [81].

A recent study from Argentina showed that OXA-23-producing *A. baumannii* had recently displaced the predominant OXA-58, which was the predominant OXA in this country for many years [82].

On the other hand, Brazil, Ecuador and Colombia reported OXA-72 for the first time in 2017. Specifically in Brazil, OXA-72 was described in *A. baumannii*, recovered from a hospitalized patient [83] and in Ecuador OXA-72 was noticed for the first time after an outbreak of carbapenem-resistant *A. baumannii* [84]. Few epidemiological reports from the French Guiana revealed OXA-23-producing *A. baumannii* carbapenem-resistant responsible for outbreaks in this territory as well as in the Amazon basin [85]. Little is known about the prevalence of class D carbapenemases in Central America. Nevertheless, a recent study conducted in Honduras showed that in a collection of *A. baumannii* isolates, OXA-23 and various OXA-51-like alleles such as OXA-64, OXA-65, OXA-68, OXA-69, OXA132 and OXA-180 were present. This study also showed the presence of the MBL NDM-1 in a couple of isolates tested [86]. The oxacillinase OXA-143 was detected for the first time in 2004 [87] and was recently isolated in Brazil [88]. Similarly, Peru reported carbapenem resistance in *A. baumannii* due to OXA-143 during its first epidemiological study [89].

Of interest, the first report in South America of a clinical isolate harboring $bla_{\text{OXA-48}}$ gene in *Raoultella ornithinolytica* was recently described in Ecuador in a 64-year-old male patient admitted to a hospital in Quito [90].

Figure 3. New class D carbapenemases reported from 2016 to 2019 in Latin America and the Caribbean.

6. Co-expression of different carbapenemases

The co-expression of different enzymes belonged to different classes of carbapenemases in GNB is a major diagnostic and therapeutic challenge. Phenotypic diagnostic methods are unreliable so molecular or immunochromatographic assays are required. From the therapeutic perspective, co-expression, especially of class B in combination with class A or D carbapenemases, limit the use of all currently available β-lactam/ β-lactamase inhibitors as monotherapy.

Reports of co-expression of different classes of carbapenemases in GNB are still limited. However, case reports are increasing and are especially worrisome in species of *Pseudomonas* and *Acinetobacter*, due to the ability to confer high intrinsic resistance, as seen in Table 3.

Since the first report of the production of KPC in *P. aeruginosa* in Colombia in 2007 [91] and five years later, the co-production of KPC and VIM [92], several other isolates were identified in Colombia [46, 93] (Table 3). In addition, species of *Pseudomonas* harboring bla_{KPC} and bla_{NDM}, as well as bla_{NDM} and bla_{VIM} were reported by the Colombian National Institute of Health (INS). Other countries have reported the *P. aeruginosa* bearing bla_{KPC} and bla_{SPM} from a hospital outbreak in Brazil, bla_{VIM} and bla_{GIM} in Nicaragua, as well as bla_{VIM} and bla_{SPM}, and bla_{VIM} and bla_{IMP} in 212 isolates between 2013 and 2017 in Costa Rica [94-96].

Several species of *Acinetobacter* co-harboring different carbapenemase-encoding genes with unknown variants of carbapenemases such as bla_{VIM} and bla_{NDM}, bla_{OXA-23} in combination with bla_{KPC}, bla_{NDM} and bla_{VIM}. bla_{OXA-58} in combination with bla_{NDM}, bla_{OXA-23} together with bla_{OXA-51}, bla_{OXA-71} ($bla_{OXA-51-like}$), $bla_{OXA-255}$ ($bla_{OXA-23-like}$) and bla_{OXA-24} in combination with $bla_{OXA-143}$ were reported in Colombia. [46]. In Uruguay, isolates of *A. baumannii* co-harboring bla_{OXA-23} and bla_{OXA-58} were reported, while in Venezuela one isolate harbored bla_{NDM-1} and bla_{OXA-23}. Two other isolates from Honduras were reported to carry $bla_{OXA-180}$ together with bla_{NDM-1} and bla_{OXA-23} in combination with bla_{OXA-64}. In a report by Faccone et al. [58], nine isolates of *A. ursingii* expressed IMP-1 and OXA-58.

A study from 2019 of 100 sequential, epidemiologically unrelated carbapenem-resistant *A. baumannii* isolates from 11 hospitals in 10 Argentinian provinces revealed that all these isolates were coexpressing bla_{OXA-23} and bla_{OXA-51} genes [97]. Interestingly, carbapenem-resistant *A. baumannii* isolates from this study were principally associated with ST1 (45%), ST25 (34%) and ST79 (15%).

Regarding *Enterobacterales*, the presence of undetermined variants of bla_{VIM} in combination with bla_{KPC} or bla_{NDM} were reported in Colombia [46]. Similarly, there are reports from Brazil and Mexico of *K. pneumoniae* co-harboring bla_{KPC-2} and bla_{NDM-1} [98-99] and the co-expression of KPC-2 and VIM-2 in 19 isolates of *K. pneumoniae* belonging to the ST388 from a pediatric ward in Venezuela [73]. In Mexico one isolate of *P. rettgeri* carrying bla_{NDM-1} and an unknown variant of bla_{IMP} was reported [55].

7. Conclusions

The emergence of carbapenemases among diverse GNB throughout the world is a public health concern and LATAM and the Caribbean are not the exception. Since our last publication, new carbapenemases of class A, B and D have been published. Countries such as Argentina, Brazil, Chile, Colombia and Mexico account for most of these reports. In contrast Bolivia, Paraguay, most Central American and the Caribbean countries have fewer reports. Detection needs a high index of suspicion and usually a reference lab with high performance diagnostic assays plus surveillance programs run by research centers; this may explain why in many countries in Latin America underreporting or apparent absence of these enzymes is still common. *Enterobacterales, Pseudomonas* spp. and

Acinetobacter spp. are still the main carriers of carbapenemases in LATAM and the Caribbean.

Despite all the limitations in the region, reports of emerging pathogens and uncommon bacterial species harboring carbapenemases including novel enzymes like LMB-1 have become more frequent since 2016.

The reports of increasing numbers and novel variants of carbapenemases suggests that better surveillance programs together with better diagnostic techniques are being implemented in this geographical region. A major concern is the co-expression of carbapenemases of different classes, as they represent a diagnostic and therapeutic challenge and deserve more attention as silent dissemination may occur. As more publications appear, countries should be aware that these enzymes have successfully spread beyond countries and are not endemic in a specific country anymore. Better surveillance programs, diagnostic resources and educational programs for prescribers will need to be implemented in each LATAM and the Caribbean country to decrease the impact of dissemination of these MDR infections with limited treatment options.

8. Expert opinion

Carbapenemases are versatile enzymes with different hydrolyzing profiles and expression levels even in the same molecular class. New carbapenemases are continuously being reported around the world while existing ones are gradually spreading within and between countries. In particular, LATAM countries have been considered an endemic geographic area for several carbapenemases and the fact that some of these countries have not reported carbapenemases yet maybe due to the scarcity of samples submitted to the microbiology laboratories before beginning the antibiotic therapy, limitations of microbiology laboratories or the lack of surveillance programs rather than the absence of these enzymes. Carbapenemase-producing microorganisms have become a public health threat worldwide and LATAM and the Caribbean are not the exception. The threat lies on their ability to easily spread among different bacteria; their capability to cause outbreaks within and between hospitals, cities, and countries; their broad hydrolysis profile which substantially limits antibiotic treatment options; and their co-resistance to other antibiotics, which leaves very few or no therapeutic options.

Despite new therapeutic options and promising alternatives currently in different phases of development, in the coming years there may still be a significant increase in multidrug resistant and pan-resistant infections associated with high morbidity and mortality. Surveillance and control programs should be reinforced in those countries that are reporting such infections now and implemented in those that are not. However, getting these programs to work is a monumental effort. Hospital acquired infections secondary to MDR bacteria will probably continue to rise if no efforts are made, resulting in unprecedented hospital costs. There is an urgent need for strong national surveillance networks, antimicrobial stewardship programs, and point of care diagnostics to identify MDR infections to define the best treatment approach and implement infection control protocols.

Antimicrobial stewardship programs should be in place in every hospital to support clinical decisions with prompt and accurate identification/reporting using “expert rules”. Microbiology laboratories are also encouraged to test report susceptibilities to new antimicrobials and confirm the presence of class A, B or class D carbapenemases.

Since phenotypic identification is difficult due to the lack of specificity and sensitivity, other confirmatory tests should be implemented. Rapid identification is fundamental for antimicrobial stewardship and infection control programs to decrease mortality and widespread dissemination of these MDR bacteria. Designing and implementing national surveillance systems is a top priority within LATAM. Such systems should be able to adequately identify CPO, clones associated with their dissemination, quantify the clinical impact of these MDR bacteria in terms of morbidity and mortality and implement appropriate therapeutic guidelines tailored to every country and every facility within those, and accurate infection control strategies. Joint efforts are required from hospitals, governments and international organizations to achieve these goals.

To detect the GNR coproducing carbapenemases that have been reported more frequently in our region, we will require more specific tests such as lateral flow immunochromatographic assays and multiplex PCR, as rapid tests for carbapenemases detection. The increased costs of these tests can be justified by making therapy more specific and efficacious, thereby lowering antibiotic use and reducing the morbidity and mortality of resistant infections.

In addition, the continuous implementation of standard and contact precautions accompanied by an infection control program based on the local epidemiology for each country and eventually each institution plays a fundamental role in the control of dissemination of MDR microorganisms. The use of both precautions can guarantee the containment in the horizontal transmission of antibiotic-resistant bacteria. In addition to the contact precautions for patients with an identified MDR isolate, standard precautions, which are infection prevention practices that apply to the care of all patients, independent of their infection or colonization status, have an essential role in the prevention of transmission given the fact that colonization with MDR bacteria is frequently undetected due, in some case, to lack of sensitivity of the traditional laboratory tests. Implementation and adherence to standard and contact precautions measurements such as hand hygiene, use of gloves, safe infection practices, frequent cleaning of surfaces and equipment, correct isolation practices (particularly during outbreaks) and MDR testing for all new admissions to an specific unit, among others, have demonstrated to have a great impact in the containment of dissemination of these resistant microorganisms.

Together with the correct implementation and adherence to these precautions, the rational use of antibiotic is of prime importance to avoid the increase of MDR microorganisms. In hospital settings, antibiotics are probably the most common therapy administrated. This fact undoubtedly contributes to the emergence of resistance among pathogenic bacteria. Therefore, the correct knowledge and understanding of the local epidemiology, together with the avoiding of unnecessary antibiotic use and the optimization of the administration of antimicrobial agents will minimize the appearance of resistance, the horizontal transmission of MDR bacteria and at the same time, will contribute to better outcome for those infected patients. Consequently and based on the current epidemiology for carbapenemase-resistant and MDR bacteria, it is necessary to design strategies aimed to

achieve the optimal use of all antibiotics. Each medical institution in the LATAM region should have a local program that constantly monitors the prevalence of MDR microorganisms, the utilization of antibiotics and its effectiveness. These strategies should include a multidisciplinary team involving the pharmacy, the infection control team, the physicians and nursing staff and should promote infection control practices, the implementation of standard and contact precaution and naturally, the rational use of antibiotics.

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Annotation for references

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

**** Reference [6]:** K. Escandón-Vargas, S. Reyes, S. Gutiérrez, and M. V. Villegas, “The epidemiology of carbapenemases in Latin America and the Caribbean,” *Expert Rev. Anti. Infect. Ther.*, vol. 15, no. 3, pp. 277–297, 2017.

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* **Reference [17]:** T. J. Gniadek, K. C. Carroll, and P. J. Simner, “Carbapenem-Resistant Non-Glucose-Fermenting Gram-Negative Bacilli: the Missing Piece to the Puzzle,” *J. Clin. Microbiol.*, vol. 54, no. 7, pp. 1700–1710, 2016.

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*** Reference [35]:** D. Cejas *et al.*, “Changing epidemiology of KPC-producing Klebsiella pneumoniae in Argentina: Emergence of hypermucoviscous ST25 and high-risk clone ST307,” *J. Glob. Antimicrob. Resist.*, vol. 18, pp. 238–242, 2019.

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Firts report in the American continent of *E. coli* harboring the carbapenemase OXA-244.

Table 1.

TEST	DIAGNOSTIC PERFORMANCE	TURNAROUND TIME	COSTS	SCOPE	LIMITATIONS	RECOMMENDATION
MultiPlex PCR methods	Sensitivity 100% Specificity 98%	1 h	$$$$	Detection of carbapenemases belonging to class A (KPC), class D (OXA-48) and class B (VIM, NDM, IMP)	Limited to specific carbapenemase variants disclosed in the package insert.	To implement this assay, when same day results are required or in outbreak situations.
Lateral flow immunocromatography	Sensitivity 100% Specificity 95%	15 min	$$$	Detection of single or multiple carbapenemase production of class A (KPC), class D (OXA-48) and class B (VIM, NDM,-IMP)	Limited to specific carbapenemase variants disclosed in the package insert.	To implement this assay, when same day results are required or in outbreak situations
Carba NP / Blue Carba	Sensitivity 84%, Specificity 100%	2h	$$	Detection of Carbapenemase mediated resistance classes A, B or D.	Unable to differentiate the carbapenemase class. False negative results in mucoid isolates of *Klebsiella and Pseudomonas*. False negative results in some OXA-48 enzymes.	To implement this test when same day results are required to confirm or rule out carbapenemase production. Adding an ancillary test to differentiate carbapenemase types is highly recommended.
Modified carbapenem inactivation test mCIM and eCIM	Sensitivity 98-100% Specificity 99-100 %	18-24h	$	Detection of Carbapenemase mediated resistance classes A, B or D. The eCIM will be able to detect MBLs when no other enzyme is present.	False positives with some *E. cloacae* isolates. False negatives with some OXA-48 enzymes. Unable to detect isolates coproducing enzymes.	To implement this test when there is no availability of molecular or immunochromatographic tests and/or same day results are not required.
Sinergy test with boronic acid	Sensitivity 92% Specificity 94 %	18-24 h	$	Detection and differentiation of class A carbapenemases (KPC) when no other carbapenemase is produced	False positive results in chromosomal AmpC producers. Unable to detect and differentiate multiple carbapenemase production.	To implement this test when there is no availability of molecular or immunochromatographic tests and to differentiate Class A carbapenemases. It should be used with a capture test like mCIM or Carba NP.

Sinergy test with EDTA or Dipicolinic Acid	Sensitivity 92% Specificity 94 %	18-24 h	$	Detection and differentiation of class B carbapenemases (VIM-NDM) when no other carbapenemase is produced.	False positive results in *Enterobacterales and P. aeruginosa* due to membrane permeability. Unable to detect and differentiate multiple carbapenemase production.	To implement this test when there is no availability of molecular or immunochromatographic tests and to differentiate Class B carbapenemases. It should be used only with a capture test like mCIM or Carba NP.
Modified Hodge Test (MHT)	Sensitivity: 95%, Specificity 91%	18-24 h	$	Acceptable performance to detect KPC in *E. coli and K. pneumoniae* when no other carbapenemase is produced	False negative results in MBL producers. False positives in isolates that overproduce AmpC. Unable to detect carbapenemases in *P. aeruginosa*.	Consider MHT replacement for a better test like mCIM, Carba NP or Lateral flow immunocromatography. If there is no availability of other tests, implement MHT plus Sinergy tests and always run internal and external quality controls.

Table 1. Methods commonly used in Latin America to detect carbapenemases in *Enterobacterales and P. aeruginosa*.

Table 2.

Class/Family	Enzyme variant	Bacteria	Country	References
Class A				
KPC	KPC-2	*K. pneumoniae, K. oxytoca, K. aerogenes, E. coli, S. marcescens, C. freundii, R. planticola, R. ornithinolytica, P. mirabilis, K. quasipneumoniae, E. cloacae, E. kobei S. enterica* serotype Javiana	Argentina, Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Mexico, Paraguay, Peru, Uruguay, Venezuela	[34-35], [40-41], [44-45], [66], [74], [98-99], [100-109] [110-119], [120-129], [130]
		P. aeruginosa	Brazil, Colombia	[131-133]
		A. baumannii	Brazil, Puerto Rico	[101-134]
	KPC-3	*K. pneumoniae*	Argentina, Brazil, Colombia, Mexico Trinidad	[35], [45], [125], [135-137]
		A. baumannii	Brazil	[101]
	KPC-4	*K. pneumoniae*	Ecuador	[138]
	KPC-5	*K. pneumoniae*	Ecuador	[138]
	KPC-9	*K. pneumoniae*	Ecuador	[138]
	KPC-24	*K. pneumoniae*	Chile	[103]
	KPC (unknown variant)	*K. pneumoniae, K. oxytoca, K. aerogenes, Klebsiella* spp., *E. coli, E. cloacae, Enterobacter* spp., *C. freundii, Citrobacter* spp., *P. mirabilis, P. rettgerii, Pantoea* spp., *S. marcescens, Serratia* spp., *Kluyvera cryocrescens*	Brazil, Colombia, Ecuador, Mexico, Paraguay, Peru, Venezuela	[55], [101], [139–158]
		Pseudomonas spp.	Colombia	[145]
		Acinetobacter spp.	Colombia	[145]
GES	GES-5	*Morganella morganii*	Brazil	[39]
	GES-16	*S. marcescens*	Brazil	[38]
SME	SME-4	*S. marcescens*	Argentina, Brazil	[36-37]
Class B				

NDM	NDM-1	*K. pneumoniae, K. quasipneumoniae, E. cloacae, E. xiangfangensis, Enterobacter* spp., *P. rettgeri, C. freundii, C. amalonaticus, S. marcescens, E. coli, P. mirabilis,*	Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Uruguay, Venezuela	[53-54], [55-56], [66], [71], [74], [98], [99], [103], [125], [159–164]
		A. baumannii, A. ursingii, A. haemolyticus	Argentina, Colombia, Ecuador, Honduras, Mexico, Peru	[58], [69], [70], [86], [159], [165]
	NDM (unknown variant)	*K. pneumoniae, Klebsiella* spp., *E. coli, E. cloacae*, *Enterobacter* spp., *C. freundii, P. rettgeri, P. stuartii, P. mirabilis, M. morgannii*	Brazil, Colombia, Ecuador, Nicaragua, Peru	[65], [145], [146], [166–170]
		Pseudomonas spp.	Colombia	[145]
		Acinetobacter spp.	Colombia	[145]
VIM	VIM-1	*A. baumannii*	Mexico	[171]
	VIM-2	Enterobacterales	Colombia	[125]
		P. aeruginosa	Brazil	[172]
	VIM-7	*P. aeruginosa*	Brazil	[173]
	VIM-24	Enterobacterales	Colombia	[125]
	VIM-36	*P. aeruginosa*	Brazil	[174]
	VIM (unkown variant)	*Klebsiella* spp.,*C. freundii, Enterobacter* spp.,	Colombia, Mexico	[55], [145]
		P. aeruginosa, Pseudomonas spp.	Brazil, Colombia, Nicaragua	[95], [132], [145], [175]
		A. baumannii, Acinetobacter spp.	Colombia	[145], [176]
IMP	IMP-1	*A. pittii, A. bereziniae, A. junii*	Argentina, Brazil	[58], [64]
	IMP (unkown variant)	*P. rettgeri*	Colombia, Mexico	[55], [145]
		Pseudomonas spp., *P. aeruginosa*	Colombia, Nicaragua	[95], [145]
		A. baumannii	Colombia	
SIM	SIM (unkown variant)	*P. aeruginosa*	Nicaragua	[95]
SPM	SPM-1	*P. aeruginosa*	Brazil	[63], [94], [175], [177–180]

	SPM (unkown variant)	*P. aeruginosa*	Nicaragua	[95]
CfiA		*Bacteroides fragilis*	Argentina	[181]
EBR	EBR-2	*Empedobacter falsenii*	Argentina	[61]
GIM	GIM (unkown variant)	*P. aeruginosa*	Nicaragua	[95]
LMB	LMB-1	*C. freundii*	Argentina	[59]
Class D				
OXA-23-like	OXA-23	*Acinetobacter spp., A. baumannii*, *A. calcoaceticus-A. baumannii* complex	Argentina, Bolivia, Brazil, Colombia, Chile, French Guiana, Peru, Mexico, Uruguay, Venezuela	[74], [85], [88], [89], [97], [111], [139], [145], [182–194]
	OXA-133	*A. baumannii*	Argentina	[82]
	OXA-239	*A. baumannii*	Colombia	[195]
OXA-40-like	OXA-40/24	*A. baumannii*	Brazil, Mexico	[171], [184]
	OXA-72	*A. baumannii, A. pittii*	Brazil, Ecuador, Peru, Mexico	[81], [84], [89], [185], [189], [196]
OXA-48-like	OXA-23	*A. baumannii*	Colombia	[145]
	OXA-48	Enterobacterales, *C. freundii, E. cloacae, K. oxytoca, K. oxytoca, K. pneumoniae, R. ornithinolytica*	Argentina, Brazil, Colombia, Mexico, Ecuador	[90], [98], [168], [197]
	OXA-232	*E. coli, K. pneumoniae*	Mexico	[98], [198]
	OXA-244	*E. coli*	Colombia	[199]
OXA-51-like	OXA-51	*Acinetobacter spp., A.baumannii, A. calcoaceticus-A. baumannii* complex	Argentina, Brazil, Colombia, Chile, Mexico, Uruguay	[46], [81], [197], [200], [82], [97], [101], [139], [183], [186], [190], [195]
	OXA-64	*A. baumannii*	Honduras	[86]
	OXA-69	*A. baumannii*	Chile, Honduras	[86], [186]
	OXA-132	*A. baumannii*	Honduras	[86]
	OXA-180	*A. baumannii*	Honduras	[86]

	OXA-219	*A. baumannii*	Chile	[186]
OXA-58-like	OXA-58	*A. baumannii, A. seifertii, A. ursingii*	Argentina, Brazil, Colombia, Chile, Uruguay	[58], [186], [190], [200–202]
OXA-143-like	OXA-143	*A. baumannii*	Brazil, Peru	[88], [89]
	OXA-231	*A. baumannii*	Brazil	[185]
	OXA-253	*A. baumannii*	Brazil, Peru	[182], [89]

Table 2. New carbapenemases reported from 2016 to 2019 in Latin America and the Caribbean.

Table 3.

Microorganism	Enzyme family							Description	Country	References
	KPC	NDM	IMP	VIM	SPM	OXA	GIM			
Klebsiella spp.	■	■						KPC-UV/NDM-UV	Colombia	[145]
K. pneumoniae	■	■						KPC-2/NDM-1	Brazil, Mexico	[98], [99]
K. pneumoniae	■			■				KPC-2/VIM-2	Venezuela	[73]
E. coli	■			■				KPC-UV/VIM-UV	Colombia	[145]
E. coli	■	■				■		KPC-2/NDM-1/OXA-232	Mexico	[98]
Enterobacter spp.	■			■				KPC-UV/VIM-UV	Colombia	[145]
Citrobacter spp.	■			■				KPC-UV/VIM-UV	Colombia	[145]
P. rettgerii		■	■					NDM-1/IMP-UV	Mexico	[55]
S. marcescens	■		■					KPC-2/IMP-10	Brazil	[100]
Pseudomonas spp.	■			■				KPC-UV/VIM-UV	Colombia	[145]
Pseudomonas spp.		■		■				NDM-UV/VIM-UV	Colombia	[145]
P. aeruginosa	■			■				KPC-2/VIM-2	Colombia	[93]
P. aeruginosa	■				■			KPC-UV/SPM-UV	Brazil	[94]
P. aeruginosa				■	■			VIM-UV/SPM-UV	Nicaragua	[95]
P. aeruginosa				■			■	VIM-UV/GIM-UV	Nicaragua	[95]
P. aeruginosa			■	■				IMP-UV/VIM-UV	Costa Rica	[96]
Acinetobacter spp.		■		■		■		NDM-UV/VIM-UV	Colombia	[145]
Acinetobacter spp.	■					■		KPC-UV/OXA-23	Colombia	[145]
Acinetobacter spp.		■				■		NDM-UV/OXA-23	Colombia	[145]
Acinetobacter spp.				■		■		VIM-UV/OXA-23	Colombia	[145]
Acinetobacter spp.						■		OXA-24/OXA-143	Colombia	[145]
A. baumanii						■		OXA-71/OXA-255	Colombia	[195]
A. baumanii						■		OXA-23/OXA-51	Colombia, Argentina	[97], [203]
A. baumanii		■				■		OXA-180/NDM-1	Honduras	[86]
A. baumanii						■		OXA-23/OXA-64	Honduras	[86]
A. baumanii						■		OXA-23/OXA-58	Uruguay	[190]
A. baumanii		■				■		OXA-23/NDM-1	Venezuela	[74]
A. ursingii			■			■		IMP-1/OXA-58	Argentina	[58]

Table 3. New reported cases, from 2016 to 2019 of Gram-negative bacilli co-harboring different carbapenemase-encoding genes in Latin America and the Caribbean.

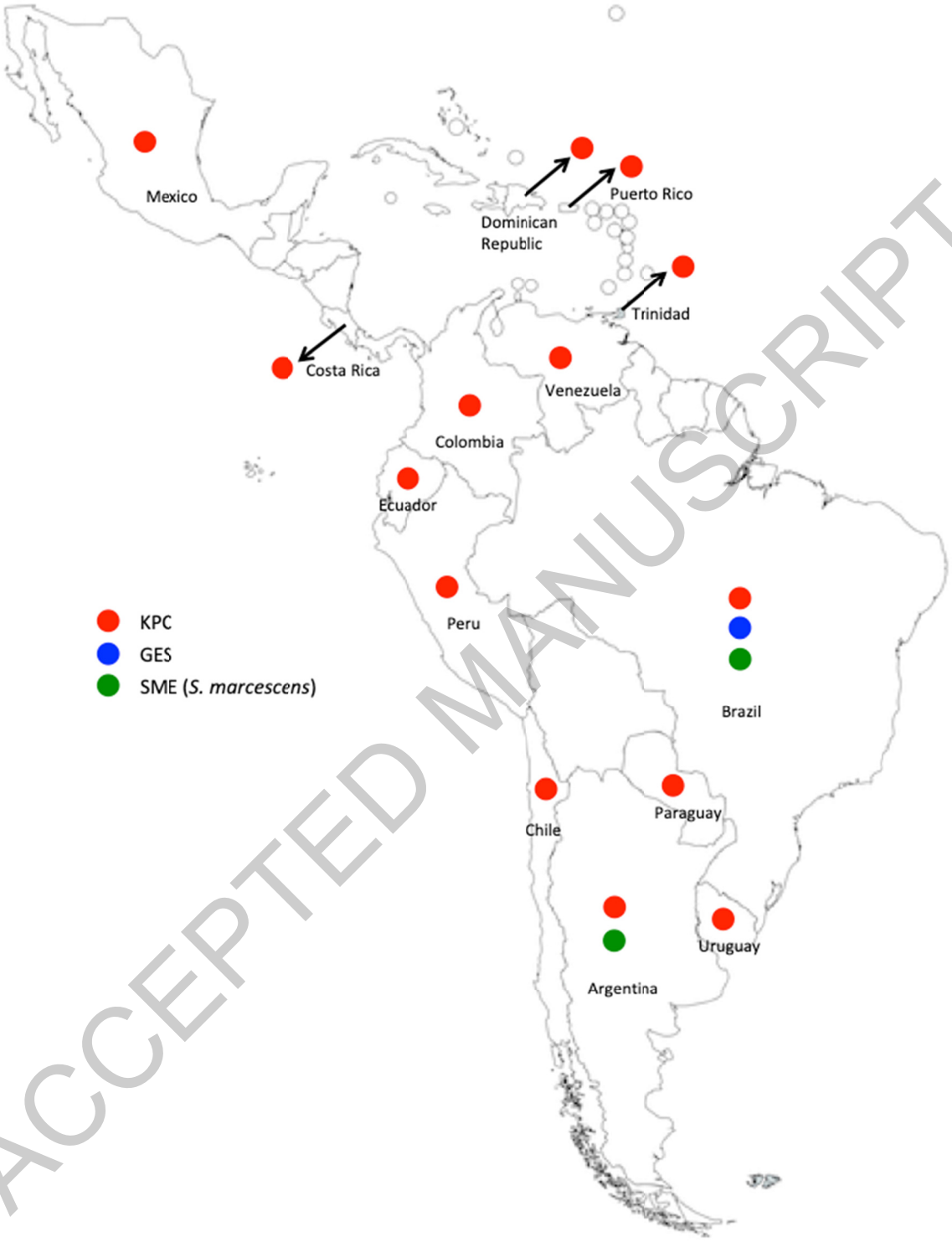

fig 1

fig 2

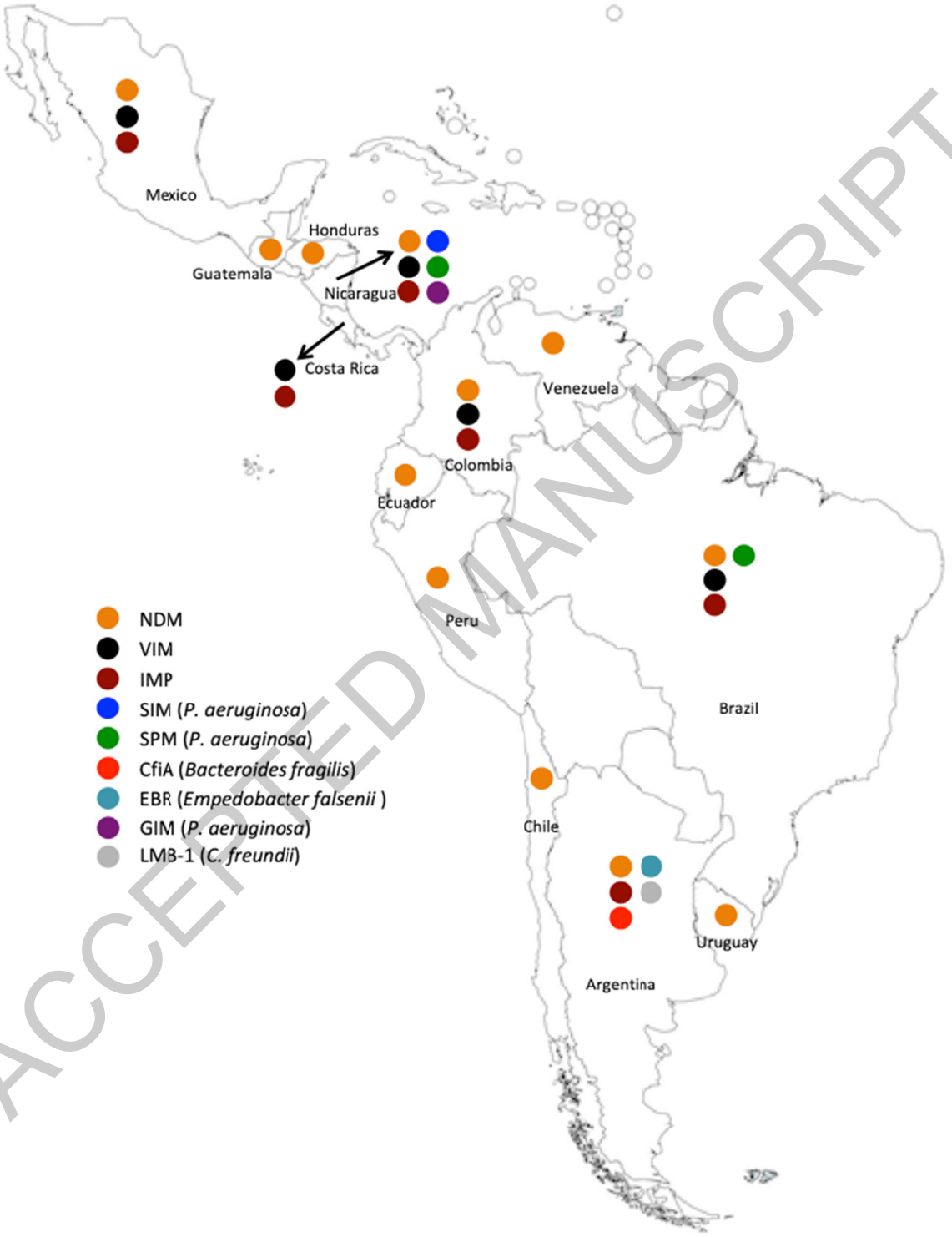

Fig 3