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REVIEW ARTICLE

Public Health Risk of Carbapenem-Resistant Enterobacteriaceae from Animals: A Scoping Review

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Abstract

Multidrug-resistant (MDR) Gram-negative bacteria cause a serious health risk worldwide. The increasing frequency of carbapenemase-producing organisms (CPOs) is especially concerning, due to the rapid dissemination of their transmissible genetic components containing carbapenemase genes, the lack of treatment alternatives for CPO-related infections, and the significant mortality incidences associated with these infections. Determining what an organism produces carbapenemase and, whether so, the particular carbapenemase order(s) associated with the degree of action that various substances show with particular carbapenemases varies. Additionally, CPOs are highly likely to spread amongst patients than non-CPOs carbapenem-resistant organisms, therefore more controlling prevention strategies are needed than they would be with non-CPOs. Humans and pets interact often, which facilitates the spread of Enterobacteriaceae that produce carbapenemases including Klebsiella pneumoniae, Klebsiella oxytoca, Escherichia coli, Enterobacter cloacae, Enterobacter xiangfangensis, and Salmonella enterica serovar Typhimurium. Also, carbapenems producing Pseudomonas aeruginosa and Acinetobacter baumannii were reported in companion animals. Current clinical practice relies on three main phenotypic assays to detect CPOs: (i) growth-based assays that measure carbapenem resistance based on organism growth in the presence of a carbapenem antibiotic (e.g., modified Hodge test and modified carbapenem inactivation method), (ii) hydrolysis methods that detect carbapenem degradation products [e.g., Carba NP test and matrix-assisted laser desorption–ionization time-of-flight mass spectrometry (MALDI-TOF MS)], and (iii) lateral flow immunoassays (LFIAs) that detect carbapenemase enzymes using specific antibodies. Even though no single test fits all the requirements for the most appropriate measure, as outlined in this review, there are numerous alternatives that are practical, accurate, affordable, and easy to use in clinical microbiology labs.

Keywords: Enterobacteriaceae, Carbapenem resistance, detection methods, companion animals, carbapenemase-producing organisms.

Introduction

Enterobacterales order comprises seven families, including *Enterobacteriaceae*, *Erwiniaceae*, *Pectobacteriaceae*, *Yersiniaceae*, *Hafniaceae*, *Morganellaceae*, and *Budviciaceae*, and 60 genera encompassing more than 250 species. *Enterobacteriaceae* are generally regarded as the majority taxonomically different among these seven families. Members of this family are part of the intestinal flora and are among the most frequent pathogens leading to infections, such as cystitis, pyelonephritis, pneumonia, meningitis, septicemia,

peritonitis, and device-related infections. These bacteria are responsible for both community-and hospital-acquired infections and have a high capacity to spread through hand-to-hand contact, contaminated food and water, and horizontal gene transfer mainly through plasmids and transposons [1].

Carbapenems are a class of antibiotics with a wide spectrum of activity against bacteria. They belong to the-lactam family. The first carbapenems, thienamycin, was discovered in 1976 as a natural product of *Streptomyces cattleya* [2]. Carbapenem has a penicillin ring similar to penicillin, but carbapenems have a sulfone (carbon) instead of penicillin (sulfone) at the fourth position of the thiazolidine moiety of the lactam ring [3]. While carbapenems have a limited role in veterinary medicine, there have been reports of carbapenem-resistant *Enterobacteriaceae* (CRE) and carbapenemase-producing *Enterobacteriaceae* (CPE) infections or invasion in pet animals around the world [4]. Carbapenems are used as "antibiotics of the last resort "to treat infections caused by MDR Gram-negative bacteria (GNB) [5]. Carbapenemases are the primary source of β-lactam resistance in GNB synergy between other β-lactamases and porin modifications, efflux pumps, and modifications to penicillin-binding proteins (PBPs). This forms the basis for the difference between CRE, which can be resistant to carbapenems by any of these mechanisms, and the more specific group of CPE. CPE has special importance and epidemiological relationships because carbapenemase genes are located on mobile genetic elements, such as plasmids, transposons, and integrons, and can be transferred horizontally between bacteria [6]. Like other β-lactamases, carbapenemases hydrolyze the β-lactam ring of penicillin, but they also hydrolyze carbapenems, cephalosporins, and monobactams [7]. Carbapenemases are divided into three Ambler classes: class A serine carbapenemases, class B metallo-β-lactamases (MBL), and class D OXA-lactamases (oxicillinases) [5,8]. According to their hydrokinetic activity, carbapenemases are divided into two categories: 1- serine carbapenemases that use the amino acid serine for hydrolyzing β-lactam forming an acyle enzyme (class A and D). 2- metallo carbapenemases that need at least one active -site zinc ions for hydrolyzing β-lactam (class B) [9].

Class A carbapenemases encompass a range of enzymes, such as *Klebsiella pneumoniae* (*K. pneumoniae*) carbapenemases (KPCs), impenem hydrolyzing B-lactamases (IMIs), Guyana extended-spectrum carbapenemases (GESs), *Serratia fonticola* carbapenemases, *Serratia marcescens* enzymes, and non-metallic carbapenemase A [5]. Of these, KPCs are particularly noteworthy because they can hydrolyze all β-lactams and strains carrying the bla_{kpc} gene exhibit resistance to other antibiotics. The most reported KPC variants are KPC-2 and KPC-3 [10, 11]. The bla_{KPC} gene is carried on a plasmid and can be horizontally transmitted [12]. IMI-1 carbapenemases, which are chromosomally encoded, are not clinically significant [13]. GES carbapenemases, on the other hand, feature a point mutation that leads to the incorporation of serine in place of glycine, resulting in carbapenemase activity.

New Delhi metallo-lactamases (NDM) and Verona integron-encoded metallo-lactamases (VIM) are the predominant class B carbapenemases. MBL, which is primarily encoded by

plasmids, enhances transmission between pathogens [14].

Class D carbapenemases, such as oxacillinase (OXA) enzymes, can efficiently hydrolyze oxacillin. OXA-48, for instance, has high hydrolytic activity toward penicillins but low hydrolytic activity toward carbapenems [15] and remains unaffected by β-lactamase inhibitors [16]. The genes responsible for carbapenem resistance are often associated with genes encoding resistance to non-lactam antibiotics, which causes MDR [1].

Carbapenemase-producing Gram-negative bacteria (CP-GNB) can now be identified using a variety of methods, including colorimetric biochemical methods such as the Carba NP test and growth-based carbapenem inhibition disc tests such as the modified Hodge test (MHT) and modified carbapenem inhibition procedures [17]. Although PCR remains the preferred method for submitting carbapenemase production, it is not feasible for regular carbapenemase-producing (CP)-Carbapenem-resistant *Enterobacteriaceae* (CRE) screening in less-developed nations due to its expensiveness and a shortage of required tools and professional knowledge in numerous clinical institutes [18,19]. Regardless of these drawbacks, PCR is limited to identifying carbapenemase genes, implying that it can neglect species with unknown carbapenemase genes [19]. The European Medicine Agency has categorized carbapenems as category A ("Avoid") antibiotics for veterinary usage, proving that they are not permitted for veterinary use in the European Union, excluding cases that treat pets [20]. The connection between pets and humans provides ideal circumstances for transmitting CPE [21]. The discovery of CPE in pets has prompted public health worries, as they may act as a reservoir for carbapenem resistance elements and help disseminate CRE [22].

The development of carbapenem resistance

Globally, the prevalence of bacteria harboring extended spectrum beta-lactamase (ESBL) genes has been growing during the last 20 years, especially in *E. coli* isolates obtained from the environment. These isolates can produce ESBLs that can break down almost all β-lactam agents except carbapenems [1,23]. The increased usage of carbapenems in clinical settings has led to a rise in the number of bacterial isolates that produce carbapenemases as well as β-lactamases that can degrade carbapenems [24]. Carbapenem resistance, which is the ability of bacteria to endure and thrive when surrounded by clinically relevant carbapenem levels, results from the overuse of carbapenems [25]. Resistance to carbapenems can occur via three primary mechanisms, as illustrated in Figure 1. The first mechanism is porin-mediated resistance, which involves reducing the uptake of carbapenems or altering the porin-encoding gene, leading to defects in or loss of porins [15,26]. For instance, resistance in *P. aeruginosa* is often caused by downregulation of the *OrpD* porin gene [27]. Elevated resistance levels in *Klebsiella pneumoniae* can result from the modified functions of *ompk35* and *ompk36* [28]. The second mechanism is the overabundance of efflux pumps, which can detect and eliminate a broad spectrum of antibiotics [29]. β-lactam resistance caused by efflux is a characteristic feature in GNB, such as *Acinetobacter* species and *Pseudomonas aeruginosa* [30]. Resistance to carbapenems may result from excessive expression of efflux pumps that are effective against them [31,32]. The third

mechanism is enzyme-mediated resistance, which is mainly caused by β-lactamases and carbapenemases that hydrolyze carbapenems and other β-lactam antibiotics [32]. Transposons, plasmids, and various mobile genetic elements contain genes that produce carbapenemases, which allow them to be transferred to different types of bacteria .Carbapenemases are categorized into three β-lactamase classes: A, B, or D. Classes A and D β-lactamases contain a serine residue in their active site [33]. Class B includes metallo-β-lactamases (MBLs) that use zinc ions to hydrolyze bonds [30]. β-lactamase inhibitors can inhibit SBLs, whereas metal-ion chelators can hinder the activity of MBLs [34]. In general, these pathways play a role in the emergence and dissemination of carbapenem resistance, which provides a serious risk to efficacious therapeutic approaches [35].

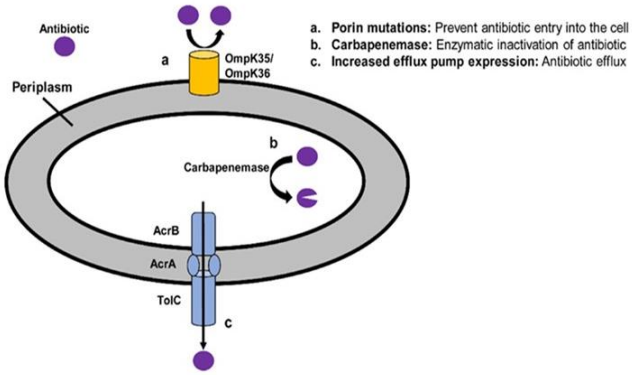

Figure 1: Mechanisms of carbapenem resistance [35]. The last access permission date: 30 June 2024.

Epidomological Study of Carbapenem-resistant *Enterobacteriaceae*

Carbapenem-resistant *Enterobacteriaceae* (CRE) extensive prevalence is mainly due to carbapenemase synthesis and the cross-dissemination of encoding genes through plasmids. The frequencies of CRE and carbapenemase organisms differed according to the location-specific area. The United States recorded the first occurrence of a *K. pneumoniae* (KPN) organism harboring a plasmid-mediated carbapenemase gene encoding *K. pneumoniae* carbapenemase (KPC) in 2001 [36]. Since then, bla_{KPC} has spread widely in the United States and South America, and outbreaks of KPC-producing *Enterobacteriaceae* have been reported in most European countries [5,37]. In China, the first KPC-producing CRE strain was identified in 2007 [38] and bla_{KPC-2} have since become the most widespread carbapenemase genes [39]. KPN was the most clinically identified CRE-producing KPC. The majority of KPC-producing KPN isolates were part of clonal complex 258 (CC258), proving that CC258 acquired the KPC-encoding gene at the beginning of the global CRE outbreak and propagated significantly [40]. ST11 is the most common sequence type in China, ST258 in the United States, and ST340, ST437, and ST512 in different areas [41]. Thus, the primary method of spreading KPC-producing KPN is clonal dissemination. It was first documented in India in 2009 as bla_{NDM}-

associated carbapenem-resistant KPN [42]. Later, other *Enterobacteriaceae* species were shown to carry *bla*$_{NDM}$ [43,44]. Asiatic nations such as China, India, Pakistan, and Bangladesh are the main sources of NDM-type β-lactamases [45]. The second most frequent carbapenemase detected in CRE in China in recent years was NDM [46], and *bla*$_{NDM}$ has become more prevalent in *Escherichia coli* [39]. A wide variety of *bla*$_{NDM}$-associated *E. coli* strains have been identified, with ST131, ST167, and ST410 being the predominant kinds [39]. This is due to the horizontal transmission of pandemic broad-host-range plasmids [47]. Since IMP-1 was discovered in Okazaki Prefecture, *bla*$_{IMP}$ has proliferated throughout Japan [48]. Currently, IMP-producing *Enterobacteriaceae* are found at the highest frequency in Japan, Taiwan, and China [1]. Sporadic *bla*$_{IMP}$ outbreaks have been reported in other countries [1,5,49]. *Enterobacteriaceae* producing VIM have been reported to be prevalent in Greece [14]. On the other hand, there have been notable outbreaks in some Asian countries, including Taiwan, China, and South Korea, in addition to various areas of Europe like the United Kingdom, Belgium, Spain, Italy, and Hungary. *Enterobacteriaceae* that produce VIM have been found to spread sporadically all over the world [1,50,51]. The term "oxacillinases" (OXA) implies the class D OXA-encoding genes causing oxacillin breaking. *Acinetobacter baumannii* isolated from the UK were reported to carry *bla*$_{OXA-23}$, the first OXA-encoding gene, in 1985 [52]. Later, it was shown that *Enterobacteriaceae* have multiple *OXA* family members such as OXA-23-like, OXA-48-like, OXA-40-like, OXA-51-like, and OXA-58-like [53]. In 2001, a KPN isolate from Turkey was found to contain OXA-48, the most frequent class D β-lactamase [54]. OXA-48 includes both traditional OXA-48 and its derivatives, OXA-181 and OXA-23 [47]. OXA-48, which produces CRE, is primarily present in North Africa as well as other Mediterranean, Middle Eastern, and European nations [55]. Recently, it was discovered that *Enterobacteriaceae* isolates contained several carbapenemases. For example, KPN isolates harbor *bla*$_{NDM-1}$ and *bla*$_{IMP-4}$ [56], whereas both *bla*$_{KPC}$ and *bla*$_{NDM}$ are carried by *Enterobacter cloacae* and *Citrobacter freundii* [57–59]. Furthermore, in 2017, *a Klebsiella oxytoca* isolate shared three carbapenemases: KPC-2, NDM-1, and IMP-4. Since then, plasmids carrying these three resistance genes have been detected in the majority of other *Enterobacteriaceae* family members, such as *E. coli, E. cloacae,* and *Klebsiella species* [60] (Figure 2) [1, 5, 8, 15, 16, 47, 61, 62]).

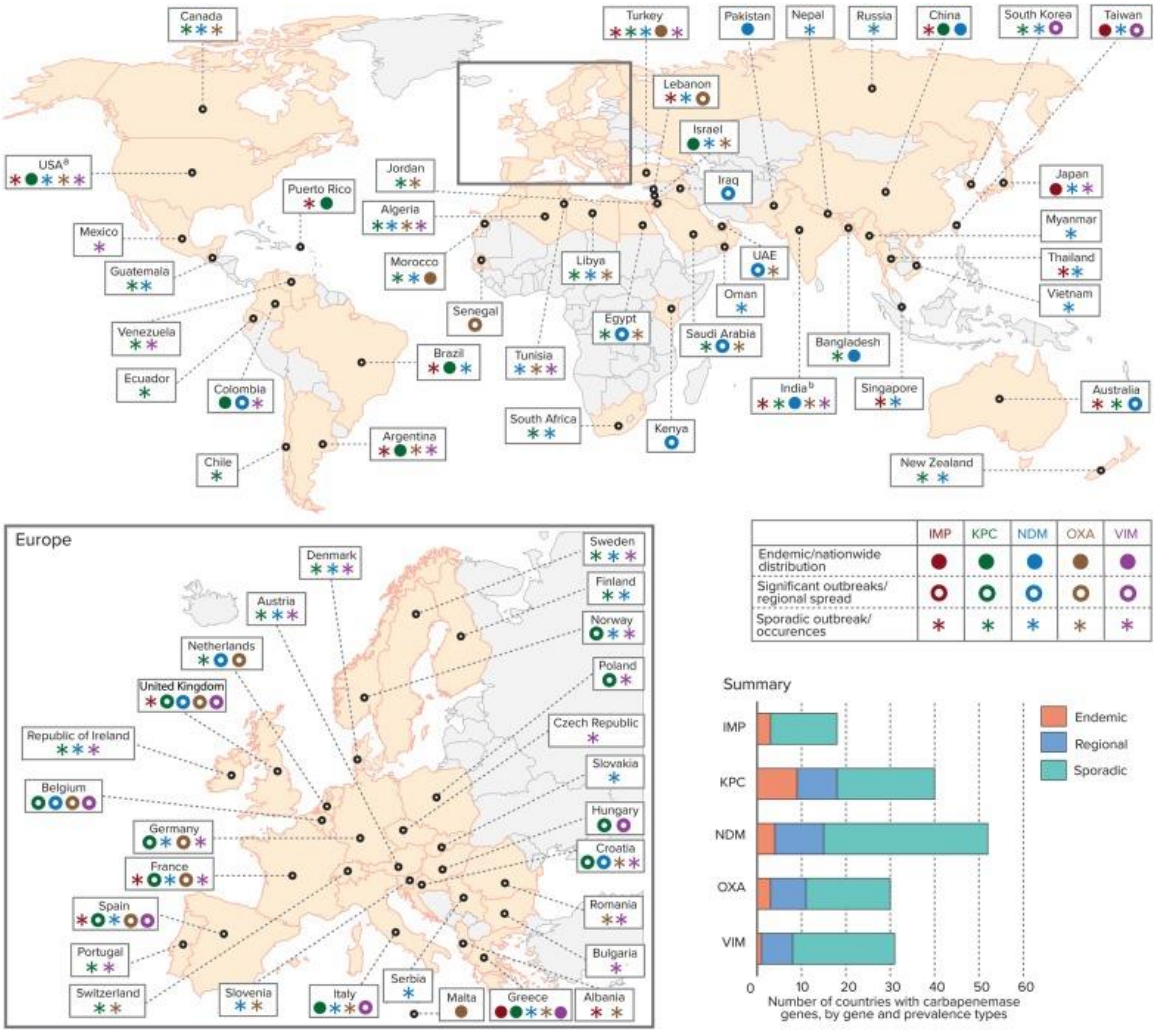

Figure 2: Global distribution of carbapenemases in *Enterobacteriaceae* by country and region. [a]KPCs are endemic to some US states. [b]OXA mainly refers to OXA-48, except in India where it refers to OXA-181. IMP, imipenem metallo-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase-type carbapenem-hydrolyzing β-lactamase; VIM, Verona integron-encoded metallo-β-lactamase. Data from [1, 5, 8, 15, 16, 47, 61, 62]. The last access permission date: 30 June 2024.

Prevalence of Carbapenem-resistant *Enterobacteriaceae* in companion animals globally

The World Organization for Animal Health (OIE) fails to find carbapenems, which are antibiotics required for animal consumption, and guidelines for restricting their administration vary globally [63]. Carbapenems are classified as "Avoid" in the European Union (EU) and are not allowed for use in animal healthcare unless specific requirements are met, which only applies to rare cases involving pets [20]. It is crucial to acknowledge the growing global presence of CP and CRE in pets. These pets can act as carriers of carbapenem-resistance genes, leading to the introduction of such genes. However, due to the absence of a global monitoring strategy, the incidence of carbapenem resistance in the veterinary field remains largely unknown. Additionally, antimicrobial susceptibility testing (AST) is the only method used to identify CP bacteria in veterinary medicine. To ensure successful therapy and prevent the dissemination of resistance to carbapenems in both humans and their surroundings, it is crucial for veterinarians to regularly evaluate and determine the prevalence of carbapenem-resistant bacteria. Unfortunately, there are limited comprehensive concepts available in the veterinary field, as reflected in the published literature [64]. To the best of our knowledge, CP isolates exhibiting KPC, NDM, VIM, IMP, or OXA-lactamases have been identified in at least 27 documented cases of bacterial infections and dissemination (Table 1). In summary, three studies have reported the presence of KPC-producing *E. coli* and *K. pneumoniae* in Brazilian and American dogs, as well as an IMP-4 enzyme in an isolate from a *Salmonella*-infected Australian cat. Additionally, VIM-2 was isolated from *P. aeruginosa* in South Korean dogs suffering from otitis and pyoderma, while VIM-1 *was* identified in *K. pneumoniae* in Spanish dogs [65-70]. Numerous NDM-5-producing *E. coli* strains have been identified in dogs and cats as shown in Table 1 [71-75] with one NDM-1-producing *Acinetobacter radioresistens* detected in a dog, six NDM-1-producing *E. coli* strains from dogs and cats in the United States, two NDM-1-producing *E. coli* strains from a dog in China, and one NDM-9 strain from a farm dog in China. Additionally, several OXA-48-like carbapenemase-producing *E. coli, K. pneumoniae, K. oxytoca*, and *E. cloacae* isolates were recovered from dogs, cats, and horses, representing one of the most frequent carbapenemases detected in companion animals alongside NDM-5 (Table 1) [81-86]. *Acinetobacter baumannii* bacteria that produce OXA-23 and OXA-66 have been isolated from clinical samples of dogs and cats through multiple investigations, as reported in previous studies [78, 87, 88]. Since 2009, CP bacteria have been found in pet animals, although the methods used in different studies vary considerably. Antimicrobial Susceptibility Testing (AST) is the primary method used to detect CP isolates in cases of infection, and selective culture media are the most used procedure for identifying commensal CP isolates (Table 1). It is worth noting that the majority of CP organisms obtained from pets fall under the "critical" classification of priority 1 on the World Health Organization (WHO) list of priority pathogens [89], emphasizing the importance of accurate surveillance and successful detection of carbapenem resistance mechanisms in these animals

Table 1. Carbapenems producing Gram-negative bacteria in companion animals globally

Enzyme	Country	Source	Year	Host	Detection method	Bacterial species	Reference
VIM-1	Spain	Commensal	2016	Dog	Selective culture media, meropenem synergy test	*K. pneumoniae*	[70]
	South Korea	Infection (SSTI)	2018	Dog	AST	*P. aeruginosa*	[69]
	Egypt	Commensal Diarrhea	2024	Dog Cat	Selective culture media AST	*K. Pneumoniae* *E. coli*	[93]
KPC-2	Brazil	Infection (UTI)	2018	Dog	Imipenem synergy test, modified Hodge testing, PCR	*E. coli*	[65]
	Brazil	Infection (UTI)	2021	Dog	Imipenem synergy test, AST	*K. pneumoniae*	[66]
	Egypt	Commensal Diarrhea	2024	Dog Cat	Selective culture media AST	*K. pneumoniae* *E. coli*	[93]
KPC-4	USA	Infection (UTI, SSTI)	2018	Dog	Biochemical Tests	*Enterobacter xiangfangensis*	[67]
IMP-4	Australia	Commensal	2016	Cats	AST	*Salmonella enterica serovar Typhimurium*	[68]
OXA-66	Germany	Infection (UTI, SSTI, URTI, CRBSI, suppurate inflammation)	2017	Dogs, Cats	Selective culture media	*A. baumannii*	[88]
OXA-23	Portugal	Infection (UTI)	2014		AST	*A. baumannii*	[87]
	Italy	Commensal	2018	Dogs, Cats	Selective culture media	*A. baumannii*	[78]
	Germany	Infection (UTI, Suppurate inflammation)	2017	Dogs, Cats	Selective culture media	*A. baumannii*	[88]
OXA-48	Germany	Infection	2009-2010	Dogs, Cats, Horses	Selective culture media for cephalosporin resistance and PCR	*E. coli, K. pneumoniae, Enterobacter Cloacae*	[90]
	Germany	Commensal,	2013	Dog	AST	*K. pneumoniae,*	[84]

		Infection (UTI, SSTI, URTI, CRBSI)				*E. coli*	
	Algeria	Commensal	2016	Dogs	PCR	*E. coli*	[72]
	USA	Infection (UTI, SSTI, Genital tract)	2016	Dogs, Cats	AST	*E. coli*	[95]
	France	Commensal	2017	Dog	Selective culture media	*E. coli*	[85]
	Algeria	Commensal	2017	Dogs, Cat, Horses	Selective culture media	*E. cloacae*, *E. coli*, *K. pneumoniae*	[86]
	Germany	Infection (UTI, SSTI, genital tract, otitis, URTI)	2018	Dogs, Cats, Horses	Selective culture media	*K. pneumoniae*, *E. cloacae*, *E. coli*, *K. oxytoca*	[83]
	Egypt	Commensal Diarrhea	2024	Dog Cat	Selective culture media AST	*K. pneumoniae*, *E. coli*	[93]
IMP-1	Egypt	Commensal Diarrhea	2024	Dog Cat	Selective culture media AST	*K. pneumoniae*, *E. coli*	[93]
NDM-9	China	Commensal	2017	Dog	Selective culture media	*E. coli*	[71]
OXA-181	Portugal	Infection (SSTI)	2021	Cat	Selective culture media and AST	*K. pneumoniae*	[91]
	Switzerland	Commensal	2018	Dogs, Cats	Selective culture media	*E. coli*	[81]
	Portugal	Commensal	2020	Dog	Selective culture media	*E. coli*	[82]
	Egypt	Commensal	2020	Dog	AST	*E. coli*	[21]
	Egypt	Commensal Diarrhea	2024	Dog Cat	Selective culture media AST	*K. pneumoniae*, *E. coli*	[93]
NDM-1	Italy	Commensal	2018	Dog	Selective culture media	*Acinetobacter radioresistens*	[78]
	USA	Infection (SSTI, UTI)	2013	Dogs, Cats	AST	*E. coli*	[79]
	China	Commensal	2017	Dogs	Selective culture media	*E. coli*	[71,80]

	Egypt	Commensal Diarrhea	2024	Dogs, Cats	Selective culture media AST	*K. pneumoniae,* *E. coli*	[93]
NDM-5	Egypt	Commensal	2020	Dog	AST	*E. coli*	[21]
	Italy	Infection (UTI)	2021	Dog	Meropenem synergy test	*E. coli*	[92]
	United Kingdom	Infection (SSTI)	2019	Dog	AST	*E. coli*	[74]
	USA	Infection (UTI, URTI)	2018	Dogs, Cats	AST	*E. coli*	[77]
	Finland	Infection (Otitis externa)	2018	Dogs	AST followed by modified Hodge testing, UV spectrometric detection of imipenem hydrolysis.	*E. coli*	[73]
	Egypt	Commensal Diarrhea	2024	Dog, Cat	Selective culture media AST	*K. pneumoniae,* *E. coli*	[93]
	South Korea	Commensal	2018	Dog, Cat	AST, PCR	*E. coli*	[76]
	USA	Infection (URTI)	2018	Dog	AST	*E. coli*	[75]
	China	Commensal	2017	Dogs	Selective culture media	*E. coli*	[71]
	Algeria	Commensal	2016	Dogs	PCR	*E. coli*	[72]

AST: antimicrobial susceptibility testing; CRBSI: catheter-related bloodstream infection; SSTI: skin soft tissue infection; URTI: upper respiratory tract infection; UTI: urinary tract infection**;** PCR: Polymerase chain reaction; KPC: *K. pneumoniae* carbapenemase; NDM: New Delhi metallo-β-lactamase; OXA-48: oxacillinase-type carbapenem-hydrolyzing β-lactamase; IMP: imipenem metallo-β-lactamase; VIM: Verona integron-encoded metallo-β-lactamase.

Prevalence of Carbapenem-resistant *Enterobacteriaceae* in Egypt

Several studies have indicated the presence of carbapenemase-resistant organisms (CROs) in farm animals, aquatic life, pets, wild animals, and their surroundings [94–98]. Animals can serve as carriers for carbapenem-resistant organisms, transmitted through food pathways and the surroundings released through waste products, leading to these carbapenem-resistant genes and vice versa. Animals have been found to be an extensive reservoir of multi-drug resistant (MDR) bacteria. Furthermore, the shortage of monitoring may have led to an inaccurate estimation of the prevalence of these species, minimizing any possible hazards to humans. In addition, the global spread of these strains is a pressing issue that highlights the need for continuous screening. Several studies have been conducted on carbapenemase genes [99-102]. However, the extent of carbapenem resistance among GNB and the underlying molecular mechanisms remain unclear. Several Egyptian reports, such as dairy cattle, tilapia species from Egyptian aquaculture farms, and broiler poultry processes, have been associated with CRE. Dairy cattle were harbor five *E. Coli* strains with *bla*$_{\text{OXA–48}}$ and one strain with *bla*$_{\text{OXA–181}}$ in 2014 [97]. Fish farms in Egypt producing tilapia in 2020, which carried *bla*$_{\text{KPC}}$, *bla*$_{\text{OXA-48}}$, and *bla*$_{\text{NDM}}$ *Enterobacter cloacae* complex, *K. pneumoniae*, and *E. coli* [103]. Furthermore, in 2016, 42% of the isolates from chicken samples in Egyptian broiler poultry farming possessed *bla*$_{\text{NDM}}$, indicating the presence of carbapenem-producing *K. pneumoniae* (CR-Kp). The authors found that 56% of the 49 fecal samples collected from workers and veterinarians working in poultry farms were positive for CR-Kp, with all strains carrying the three carbapenemase genes *bla*$_{\text{KPC}}$, *bla*$_{\text{OXA–48}}$, and *bla*$_{\text{NDM}}$. Moreover, compared to veterinarians (33%), farm workers (67%) had a greater incidence, revealing that direct contact between people and broilers could aid in spreading the disease. This is because farm workers remain on the farm through the growing phase and are constantly in contact with broilers. It was noted that there were non-genetic links between people and chickens, although clones and plasmids were not compared in this study [104]. *Pseudomonas mirabilis* bacteria encoding the *bla*$_{\text{NDM–1}}$, *bla*$_{\text{OXA–1}}$, and *bla*$_{\text{KPC}}$ genes were noticed to be prevalent among ducks on an Egyptian farm in 2021 [105]. Carbapenem-producing bacteria may find their way into the food supply chain, as shown by the 155 meropenem-resistant samples discovered in Egyptian retail chicken meat in the same year. A previous study reported a single *K. pneumoniae* ST147 strain and a single *E. coli* ST648 strain that produced NDM-1 and NDM-5, the *E. coli* strain also carried *bla*$_{\text{OXA–1}}$, *bla*$_{\text{TEM–1}}$, *bla*$_{\text{CTX–M–3}}$, and *aac (6')-Ib-cr*, whereas the *K. pneumoniae* strain harbored *bla*$_{\text{SHV–1}}$, *bla*$_{\text{CTX–M–15}}$, and *aac (6')-Ib-cr* genes [106]. NDM-producing *E. coli* ST648 has been reported in clinical isolates from India, United Kingdom, and Australia. The NDM-1-producing *K. pneumoniae* ST147 clone has been previously reported in hospitalized patients in Iraq, Oman, Tunisia, and Egypt [107]. In 2019, carbapenem-resistant *P. aeruginosa* (CRPA) was reported in buffaloes and cattle in Egypt, with a prevalence of 60 and 59% (Total samples = 50) of isolates harboring *bla*$_{\text{KPC}}$, *bla*$_{\text{OXA–48}}$, and *bla*$_{\text{NDM}}$, respectively. The authors also found carbapenem-resistance genes in drinking water within 67%

prevalence and in stool human samples within 80% prevalence. Furthermore, phylogenetic analysis showed that cattle and water sequences were in one cluster and were more closely related to each other than to human isolates [108]. A single *E. coli* ST648 strain and a single *K. pneumoniae* ST147 strain that could express both NDM-1 and NDM-5 were found in an earlier investigation. *Aac (6')-Ib-cr, bla*$_{TEM-1}$, *bla*$_{CTX-M-3}$, and *bla*$_{OXA-1}$ were also found in the *E. coli* strain, whereas the *K. pneumoniae* strain had *bla*$_{SHV-1}$, *bla*$_{CTX-M-15}$, and *bla*$_{Aac}$ (6′)*-Ib-cr* genes [106]. Isolates from clinical samples in India, the United Kingdom, and Australia have all shown the presence of NDM-producing *E. coli* ST648 [107]. Earlier reports of hospitalized cases in Iraq, Oman, Tunisia, and Egypt identified the *K. pneumoniae* ST147 clone as the source of NDM-1 [107]. In Egypt in 2019, 59% of 50 cattle isolates and 60% of 50 buffalo isolates included carbapenem-resistant *P. aeruginosa* (CRPA), both of which carried *bla*$_{KPC}$, *bla*$_{OXA-48}$, and *bla*$_{NDM}$ [108]. According to the research, 80% of human fecal specimens and 67% of freshwater specimens tested positive for carbapenem-resistant genes. Furthermore, phylogenetic studies showed that sequences from livestock and freshwater formed a similar group and had a stronger link than isolates from individuals, as reported previously [108].

Detection of Carbapenem-resistant *Enterobacteriaceae*

Standardized and straightforward methods for susceptibility testing, such as broth microdilution, antibiotic sensitivity and automated screening techniques are commonly used. However, these methods may fail to detect inefficient carbapenemases, such as KPC variants and OXA-48, as indicated by the Clinical and Laboratory Standards Institute (CLSI) or European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [109,110]. Furthermore, Woodford *et al.* [111] found that programmed techniques may cause differences in finding of all carbapenemase manufacturers. Currently, carbapenemases can be determined mainly through observable screenings and molecular-based methods. Observable procedures and molecular-based methods are now both the most common strategies for determining carbapenemases. Currently used in clinical practice, phenotypic assays include growth-based ones those measure the resistance by observing growth in the presence of an antibiotic (such as the modified Hodge test [MHT] and modified carbapenem inactivation method [mCIM]), hydrolysis methods that detect the product of hydrolysis catalyzed by carbapenemase enzymes (such as Carba NP and matrix-assisted laser desorption ionization time-of-flight mass spectrometry [MALDI-TOF MS] methods), and lateral flow immunoassays that detect carbapenemase enzymes using specific antibodies. Nucleic acid-based carbapenemase detection directly identifies molecular determinants of carbapenemase production. The choice of carbapenemase detection test relies on various factors, such as the prevalence and molecular epidemiology of carbapenemase in the local area, the diagnostic performance characteristics, the required labor, cost, and turnaround time (TAT) of the test [112]. Fast TAT is essential for both therapeutic decision making and infection control, with ideal same-day results. Other factors to consider include the type of organisms to be tested (such as *Enterobacteriaceae* and/or glucose-nonfermenting Gram-negative bacteria),

ease of use, workflow, regulatory status, necessary equipment, and reagent preparation requirements. Despite the lack of a single assay with a favorable profile for all criteria, multiple options are available, enabling laboratories to select the method that best meets their requirements.

Screening methods for carbapenem-resistant *Enterobacteriaceae*

Culture-based methods are commonly used for CRE screening because they are relatively simple and easy to implement in routine microbiology laboratories as the necessary equipment and knowledge are already present. Different culture approaches have been described, including inoculation onto McConkey`s agar plates after broth enrichment Center for Disease Control and Prevention method (CDC method) [113], direct inoculation onto McConkey`s agar plates containing a meropenem disk [114], and direct inoculation onto specific selective chromogenic media [115-117]. Table 2 shows comparison of chromogenic media for detection of CRE. Although the CDC screening method is designed to maximize sensitivity, according to recent assessments, the performance of other culture-based methods is on par with or even superior. But because it takes a lot of time, the CDC approach has serious drawbacks for laboratory workflow. Numerous benefits, including affordability, simplicity in assessing possible colonies, and the ability to verify specimen accuracy, come with inoculating directly into McConkey`s agar plates with meropenem disks. For rapidly determining the existence of isolated strains that produce KPC, several researchers have proposed using another disk, which has meropenem and boronic acid. However, adding a meropenem disk after inoculation raised the individual's effort and raised the danger of other undesirable elements. The insensitivity of this approach is a significant issue, particularly for CPEs that usually show minimum inhibitory concentration (MICs) around or close to breakpoint [115]. Various chromogenic media have been created to simplify culture-based procedures [115-117]. These media typically incorporate carbapenem as a selective agent and a substrate that results in color changes when hydrolyzed by *Enterobacterales*. The advantages of this method include a simple workflow for inoculation and growth evaluation, presumptive species identification, and high sensitivity and specificity. OXA-48 has demonstrated minimal susceptibility to different enzymes in specific media prepared particularly for KPC [118]. To assure the accuracy of rectal samples, another non-specific plate would be administered simultaneous with chromatic media, which are significantly cost than McConkey`s agar. It is notable that all culture-based techniques can only detect all CRE forms; therefore, additional investigation is necessary to validate carbapenemase synthesis in the case of a positive finding [119, 120]. Even with these drawbacks, culture-based techniques nevertheless have certain special benefits, like the capacity to identify every form of CRE, including those that produce hitherto unidentified carbapenemase enzymes; the capacity to obtain viable organisms for phenotypic AST and the capacity to gather and preserve CRE strains.

Table 2: Comparison of chromogenic media for the detection of CRE

Chromogenic media	Sensitivity (%)	Specificity (%)	References
SUPERCARBA	95.6-96.5	60.7	[4]
CRE Agar	78	60-66	[4]
ChromID CARBA Smart	90	76-89	[4]
CHROMagar™ KPC	100	NDA	[4]
CHROMagar™ OXA-48	75.8	99.3	[4]

NDA, no data available

Phenotypic assays for carbapenemase-producing *Enterobacteriaceae* detection

The Modified Hodge Test (MHT) is widely used for CPE detection. It evaluates the development of an indicator strain at the junction of the area of inhibition and the growth zone formed by both the indicator and sample strains. This aids in identifying if the sample strain deactivates antibiotics [121]. MHT has low sensitivity (<50%) for identifying class B β-lactamases, but great specificity and sensitivity for identifying KPC producer. The Triton Hodge Assay was created to overcome this restriction, which can be done by using the Triton X-100. This technique improves the ability of clinical cases that produce NDM to in parallel identify additional carbapenemases and raises the accuracy of detection of these isolates to more than 90 percent [122]. However, clinical assessment may be impacted by false negatives and false positives outcomes [123]. The Carba NP Assay, a highly rapid and accurate colorimetric test with a reduced incorrect positives frequency compared to MHT, was established by Nordmann *et al.* [124]. The shift in color is visually assessed by the laboratory technician, and it measures the alteration in pH levels of the reagent solution caused by carbapenemase breakdown of imipenem. Additionally, employing tazobactam and EDTA, this method can determine carbapenemase forms initially [125]. The Blue-Carba assay was established by Pires *et al.* [126] after they found that using bromothymol blue instead of phenol red as the pH monitor increased the assay's accuracy. This procedure boosts the detection rate to 100% [127]. An electrochemical technique was presented by Bogaerts *et al.* [128] and was adapted from the classical Bogaerts–Yunus–Glupczynski (BYG) Carba assay [128]. Through this method, you can determine carbapenemase-producing strains in only thirty minutes instead of over two hours, and you can get actual, immediate findings [128]. Rapidec Carba NP (bioMérieux), Rosco Rapid Carb Screen, and Rapid Carb Blue Kits are some of the commercial items that are used. But most readily available fast colorimetric tests and manual assays are not adequate to identify OXA-48-type [112]. Unidentified mistakes cannot be prevented, even though the bicarbonate-based MBT

STAR-Carba kit (Bruker Daltonics) has increased specificity to determine OXA [129]. A significant visual assay is the carbapenem inactivation method (CIM). It gauges the size of *E. coli* ATCC 25922's inhibition zone following the test bacterium's deactivation of the carbapenem disk. The findings are extremely close to the polymerase chain reaction (PCR) identifying carbapenemase genes, such as KPC, NDM, VIM, IMP, OXA-48, and OXA-23 [130]. The Clinical and Laboratory Standards Institute (CLSI) suggested the modified CIM (mCIM) in 2017 [131], and a research investigation showed that it had 100% accuracy and validity [132]. Microbiological laboratories find mCIM to be a useful tool because of its affordability, ease of use, unambiguous standards, and accessibility in any lab. Many tests that rely on monitoring β-lactamase hydrolysis to detect carbapenemase-producing *Enterobacteriaceae* have been reported, including spectrophotometry [133]. To overcome the drawbacks of earlier techniques for determining the destructive action of carbapenemases in bacteria, Takeuchi *et al.* [134] devised a double wavelength evaluation procedure. With only 40 minutes needed for preparation and incubation—though the OXA testing period may need to be suitably extended—this procedure reduces the time as well as provides the rapid assessment of carbapenemase expression in bacteria. This approach also yielded results compatible with mCIM and showed higher sensitivity and specificity than carbaNP at a similar duration of incubation. It is restricting the quantity of samples. and need for a spectrophotometer, still restrict this technique's practicality [134]. The applying of matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) to identify breakdown carbapenem products as a method of detection for CPE was recommended by Hrabák *et al.* [135] in 2011. In order to improve the procedure's sensitivity, speed up the procedure, and make finding reading easier, a number of MALDI-TOF-based techniques have been suggested subsequently [136–140]. To overcome the main cause of incorrect findings, Papagiannitsis *et al.* [140] improved the detection limit for OXA-48-type from 76% to 98% by combining NH4HCO3 to the reaction mix. A MALDI-TOF-based technique was established by Lasserre *et al.* [139] that provides great accuracy and precision and can identify resistant *Enterobacteriaceae* from initial cultures in just thirty minutes. In 2018, a survey demonstrated that a MALDI-TOF-MS-based ertapenem hydrolysis assay could rapidly and accurately detect carbapenemase activity in *Enterobacteriaceae* strains isolated from positive blood cultures [141]. The high cost of the instruments prevents MALDI-TOF MS tests from being used widely in practical settings, despite the technique's inexpensiveness [139]. Apart from the techniques outlined above, carbapenemase inhibitor-based disc assays have demonstrated accuracy in identifying carbapenemases, including MBLs and KPCs [142,143]. For instance, ethylenediaminetetraacetic acid combined to a carbapenem disk can be beneficial for determining MBLs [143], while the use of boronic acid combined with an ertapenem or meropenem disk has been applied for monitoring KPC [144]. In order to rapidly identify OXA-48-like carbapenemases, Glupczynski *et al*. [145] established an immunochromatographic method that employed a single-clonal antibody. Furthermore, a bioluminescence-based

carbapenem susceptibility detection assay that could distinguish between carbapenemase-producing and non-carbapenemase-producing CRE with a sensitivity of 99% and specificity of 98% was reported in 2018 [146].

Molecular methods for identification of carbapenemase-producing *Enterobacteriaceae*

The approved high standard for determining the genes encoding carbapenemase is genetic methods [1]. Table 3 provides an overview of their benefits and drawbacks. Although it can take some time to determine one gene, PCR is a highly popular classical genetic typing technique. To solve this, scientists established and suggested a number of highly specific, time-saving, and sensitive PCR techniques [147]. For the quick identification of carbapenemases, including KPC, OXA-48, VIM, IMP, and NDM, multiplexed real-time PCR techniques were developed between 2006 and 2012 [148–150]. To correct for the error brought about by the variety of carbapenemases that resemble OXA-48 [151], several improved approaches have been developed, including a real-time PCR method using superior resolution melting analyses [151] as well as the use of a multiplex PCR method applying peptide-nucleic acid investigates for effectively detecting genes causing resistance in different types of *Enterobacteriaceae* strains [152]. To identify CPE, many different genetic methods have been used. To detect predominant carbapenemase genes, Walker *et al.* [153] implemented real-time PCR, PCR that was nested, and nanotechnology. In a brief amount of time, PCR-based cassette approach running on the GeneXpert platform that was designed for identifying CPE in rectal specimens demonstrated superior sensitivity and validity [154]. A perfectly accuracy and precision isothermal amplification by loop-mediated approach using hydroxynaphthol blue pigment (LAMPHNB) was devised by Srisrattakarn *et al.* [155]. In 2018, microfluidic chip technology, which allowed for the rapid detection of pathogens and their resistance genes [156]. The criteria for a practical assessment were fulfilled in 2018 when carbapenem-resistance genes were identified with significant accuracy and precision using lab-on-a-biochips method [46]. Commercial microarray-based Verigene Gram-negative culture of blood test has been applied for detecting carbapenemases [157], however the extremely expensive [158] limits its normal practical use. While the optimum method for identifying carbapenemase genes, the sequencing of the whole genome is restricted in its regular clinical application due to the expensive nature of the procedure, prolonged processing times, and challenging organization of information [159]. A new multiplex PCR was created by Yu *et al.* [160] to quickly and accurately identify the outbreak stain of CRKP ST258/ST11.

Lateral Flow Assay

The best diagnostic tests should be inexpensive and offer quick findings so that used in any microbiology lab. As a result, lateral flow assays (LFA) have emerged as a crucial weapon in the fight against antimicrobial resistance (AMR). When an infection occurs with a resistant isolate, the scenario calls for quick, on-site identification using affordable, efficient, and friendly to use techniques. In this manner, the rapid diagnostic test (RDT), commonly referred to as LFA technique, has shown to be useful in the identification and detection of isolates

resistant to antibiotics. As for any point of need test, LFA satisfies all the requirements set forth by the WHO, which are known as practical, accurate, defined, easy to use, quick and reliable, equipment-free and available [161,162]. Additionally, The P5 medicine concept can be integrated into the LFA, which has gained attention in the medical field. Optimal therapy for each patient is the goal of this concept, which employs a distinctive, indicative, protective, and collaborative approach [163]. LFIA tests are typically composed of a strip that contains several porous materials and allows liquids to flow through capillary action. The sample, which is dripped onto the conjugate pad (CP) from the sample pad (SP), is received by the CP, which is usually made of cellulose. The CP stores the conjugate, a labeled molecule that creates the signal on the strip. This signal is found on a nitrocellulose membrane that has been printed with various substances to create a test line and a control line. The control line functions as an internal control to verify that the flow is accurate and that the conditions are suitable, while the test line captures the object of interest. In conclusion, the absorbent pad serves as both a pump and a container for the liquid supplied on the SP, and the amount of sample that can be examined depends on its size. Every part is usually encased in a plastic cartridge and connects to the others. This cartridge has a reading frame, a specific sample loading place, safety, simple handling, pressure points to ensure direct contact, and an effective distribution of reagents across the strip. After the sample has been placed onto the SP, which may or may not undergo pre-treatment to lessen matrix effects, movement is ready to start. If the conjugate is present, it resuspends in the sample solution and forms a mixture with the analyte. Mixture migrates along the nitrocellulose membrane by capillary pressure, thereafter they accumulate on the test line and extra conjugate on the control line.

There are two primary formats of LFIA: the non-competitive or sandwich immunoassay, which is applied for high molecular weight compounds such as proteins with multiple antigenic sites; and competing or suppressing immunoassay form, which is used for tiny molecular weight antigens. In the sandwich immunoassay, a colored test line indicates a positive result, while in the competitive immunoassay, a weak or nonexistent test line signals a positive result. In most cases, the test line and conjugate contain antibodies specific to the target being identified.

The five primary carbapenemases—KPC-, NDM-, VIM-, and IMP-type as well as OXA-48-like—are the focus of the NG-Test CARBA 5, the immunochromatography assay. It is packaged in a separate cassette and includes two separate K-SeTs: A separate one for VIM and NDM monitoring, and second for OXA-163, OXA-48-like, and KPC monitoring. The same bacterial lysis mixture, which is packaged together, should be used with both cassettes at the same time. The K-SeT for IMP detection is included as a supplementary investigation for RESIST-5 O.O.K.N.V. and is part of the IMP K-SeT [164]. The procedures were performed according to the supplier's recommendations. To begin the lysis one separate cell of at night proliferation was removed from the plate and placed in an Eppendorf container or container with extraction reagent. The sample area of the cassette was then filled with approximately 100 ml of the mixture, and it was allowed to migrate for 15 minutes.

Subsequently the data was evaluated until the baseline line in the control region colored red. Fifteen minutes later, it was observed whether the lines in the cassette's screening region had become red [165]. Table 3 outlines the benefits and drawbacks of various detection methods.

Table 3 Advantages and disadvantages of CRE detection methods

Detection methods	Advantages	Disadvantages	Reference
Screening method	Sensitive Convenient Relatively low-cost way.	Nonspecific method for all carbapenemase.	[4]
MHT	Detecting KPC Simple Inexpensive	False-positive and false-negative Insufficient for MBLs Time consuming	[165]
Coloremetric assay	Detecting KPC and most MBLs type carbapenemases Simple and inexpensive	Insufficient for OXA-48 Specific reagents Various infecting factors	[165]
mCIM	Detecting all Carbapanemeses Clear criteria of judgment Simple Cost-effectiveness	Time consuming	[165]
Spectrophotometer method	High sensitivity and specificity Time saving Simple and inexpensive	Specific instrument (spectrophotometer) Various influencing factors No standard equation and cut-off value Small sample size	[165]
MALDI–TOF-based methods	Detecting KPC and NDM Time saving Easy to perform Low measurement cost	Insufficient for OXA-48 No clear protocol and standard analysis Expensive equipment	[165]
Molecular-based methods	Gold standards Detecting all carbapanemeses genes Type carbapenemase genes	High technical requirements Insufficient for expression of genes High measurement cost	[165]
Lateral Flow Assay	Speed	Variation in sample volume can diminish specificity and sensitivity	[166]

Ease of use	False negative result
Inexpensive	False positive result
Good application for primary screening	Sample need an additional pre-treatment

MHT: modified hodge test, MBL:metallobetalactamase, mCIM: modified carbapenem inactivation method, MALDI-TOF: matrix-assisted laser desorption ionization time-of-flight mass spectrometry, KPC: *K. pneumoniae* carbapenemase, NDM: New Delhi metallo-β-lactamase, OXA-48: oxacillinase-type carbapenem-hydrolyzing β-lactamase.

Treatment of carbapenem-resistant *Enterobacteriaceae* infections

When treating infections brought on by Gram-positive bacteria that are resistant to carbapenems, glycopeptides are thought to be an efficient substitute for carbapenems. Alternative therapies for carbapenem-resistant Gram-negative bacteria, particularly CRE, are restricted since these bacteria typically have resistance elements to aminoglycosides, β-lactams, and fluoroquinolones [167,168]. In these instances, it is essential to consult microbiologists because amikacin sensitivity exists in certain CREs. Fosfomycin, polymyxins (colistin), and tigecycline are examples of antibiotics that had been administered infrequently because of worries about their poisoning and effectiveness [169,170]. For pandrug-resistant bacterial infections, double-carbapenem association treatment may be taken into investigation; nevertheless, there is a paucity of information surrounding this treatment [171, 172]. *In vivo* investigations have yielded uncertain findings, despite particular in vitro investigations demonstrating the cooperative advantages of specific antibacterial compounds for carbapenem-resistant gram-negative microorganisms. Regarding resistance emergence or practical reaction for instance, colistin combined meropenem failed to achieve superior results than colistin alone [173,174]. However, a few compounds may work well together, such as colistin and rifampicin [175,176], carbapenem and sulbactam [176], colistin and carbapenem [177], and carbapenem with an aminoglycoside [178]. A novel aminoglycoside antibiotic categorized as the next generation agent is plazomicin [25]. Sub-inhibitory concentration of plazomicin were utilized together with colistin, meropenem, and fosfomycin in an investigation by Rodriguez-Avila *et al.* [179] demonstrated a potent bactericidal action on strains of *K. pneumoniae* that produced carbapenemase. The effects of ESBLs and KPC can be neutralized by new β-lactamase blockers such as relebactam, avibactam, and vaborbactam [180]. New combinations of β-lactam/β-lactamase blockers, such as imipenem/cilastatin/relebactam, ceftazidime/avibactam, and meropenem/vaborbactam, have been authorized by the US FDA (MD, USA) for the management of cases of CRE [170,181,182]. A siderophore cephalosporin called cefiderocol was created for managing diseases brought on by bacteria with resistance. By adhering to penicillin-binding protein 3, it can enter the periplasmic region of Gram-negative organisms by energy-requiring process and disrupt the formation of cell walls of bacteria [183–185]. Some ESBLs and carbapenemases have been observed

to be resistant with cefiderocol [183–185]. The novel antibiotic eravacycline has a wide range of actions, including the capacity to target CRE [186].

Prevention and Control of carbapenem-resistant *Enterobacteriaceae*

Antimicrobial resistant (AMR) has been investigated by the emergence of several procedures, such as the One Health approach, the National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB) by the United States (2020–2025), the EU Harmonized AMR Monitoring Program carried out in Italy in 2021, and the application of antimicrobial agent threat evaluation. The United Nations Political Declaration on AMR of 2016 observed the One Health approach, which finds that disease can spread from people to animals and inversely and that human health is strongly associated with animal health. In all cases, AMR should be controlled because surroundings can serve as a reservoir for novel resistant microbes [187–189]. Consequently, to avoid AMR from arising and transmitting, a comprehensive strategy is needed. US, UK, and European countries have all established One Health-based AMR control. Although the undervaluation of the effect of AMR on land and marine species as well as the surroundings is a consequence of its lack of application in most developing nations [189]. The mismanagement of antibiotics, including their excessive use in the control of infections, as growth promoters, and in the treatment of livestock and farmed fish, as well as the presence of various environmental contaminants, such as agricultural waste, sewage, and heavy metals, may help propagate resistance to antibiotics among humans and animals. may help propagate resistance to antibiotics among humans and animals [187,190]. This highlights the importance of adopting a One Health approach, which is a multidisciplinary strategy aimed at preventing, predicting, detecting, and responding to antibiotic resistance. Increasing global awareness of AMR and the adverse effects a result of overuse and improper administration of antibiotics, decreasing the consumption of antimicrobials in farming and their discharge into the surroundings, increasing worldwide drug resistance monitor to more accurate assumed and estimate resistance strategies, improving rapid practical assessments, and the progress of vaccines and replacements for antibiotics are some of the most significant approaches for controlling AMR from a One Health perspective [191], expanding the field's studies, developing a worldwide discovery program for preliminary studies of new therapies, encouraging the purchase of novel medications and pharmaceutical advancements, and forming an international alliance for the fight against AMR. The surroundings, aquaculture, farm animals, human healthcare, and other fields must all be coordinated in order to achieve this overall strategy. A One Health AMR monitoring system is essential, according to prior studies, to determine the importance of the issue particularly with regard to carbapenem resistance to spot changes, understand the linkages between various circumstances, and discover patterns. The propagation of genes and organisms resistant to carbapenem would be prevented by such a system [187,190,192]. Furthermore, as resistant species from aquatic settings and animal diseases resulting from AMR bacteria may have both inherent resistance and the capacity for cross transmission, these routes of transmission need to be taken into perspective. The risk

of silent dissemination of serious MDR bacteria by the human-pet relationship, known as zooanthroponosis, makes carbapenem-resistant infections in pets extremely worrisome [190]. Interestingly, genes producing resistance to antibiotics can be found in commensal bacterial flora and then passed onto organisms that can infect humans and animals. Moreover, a considerable portion of antibiotics (75–90%) that animals discharge without breaking down can be released into surroundings [71], where they may serve as AMR gene carriers [192].

Conclusion

Monitoring for carbapenemase-producing organisms is uncommon in veterinary field. However, imipenem and meropenem are often used as AST alternatives. On the other hand, recent studies prove that pets with carbapenemase-encoding genes can directly be transmissible to individuals. Proper identification of CP bacteria is essential in preventing infections, particularly to stop the transmission of its resistance factors, which can have significant consequences on human health through restricting the choice of antimicrobial therapies. Although they have been assessed and utilized in human medicine, not all screening means are suitable for application in the field of veterinary for example, most laboratories might not be able to afford automated mass spectrometers or PCR instruments due to factors like little assumed positive sample numbers, the requirement for specialized staff, or the costly nature of instruments and reagents. Whereas molecular determination of the genes producing carbapenemase is the method of choice, phenotypic analysis for resistant to carbapenem can be a valuable substitution for ordinary assessment in veterinary medicine. Applying commercially available CP-selective culture media into the veterinary microbiology workflow can accelerate and lower the cost of regular CP bacterial detection in practical veterinary facilities. In addition, note the challenges and greater rate of OXA-48-like CP bacteria found in pets. It is essential to apply a highly accurate and effective selective culture medium for OXA-48-like carbapenemases, alternatively or including temocillin in regular AST of pet samples. In veterinary microbiology labs where a significant number of community-based resistance (CR) infections are assumed, alternative methods, such as immunochromatographic lateral flow tests or biochemical tests, may also be beneficial. Although these methods may not be required now, it is still crucial to consider them in case the critical health consequences of confusion and the underestimated rate of CP bacteria are not investigated. To reduce false positive results, it is essential to choose high sensitivity and specificity when applying any procedure. If a positive result is obtained, it is crucial to advise specialists to implement infection prevention measures and report the case to a specialized laboratory for further examination. To better understand the relationship between the animal-human-environment triad and the general increase in carbapenem resistance, it is necessary to evaluate CP bacteria in pets as part of the One Health Strategy to eliminate AMR.

Conflict of Interest

Authors have no conflict of interest to declare.

References

[1] Nordmann, P.; Naas, T. and Poirel, L. (2011): Global spread of carbapenemase

producing *Enterobacteriaceae*. Emerg Infect Dis. 17, 1791-19798.

[2] Kahan, JS.; Kahan, FM.; Goegelman, R. Currie, SA.; Jackson, M.; Stapley, EO.; Miller, TW.; Miller, AK.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, HB.and Birnbaum, J. (1979): Thienamycin, a new b-lactam antibiotic. I. Discovery, taxonomy, isolation and physical properties. J Antibiot (Tokyo) 32,1–12.

[3] Kattan, JN.; Villegas, MV. and Quinn, JP. (2008): New developments in carbapenems. Clin Microbiol Infect. 14, 1102-11.

[4] Silva, J.M.D.; Menezes, J.; Marques, C. and Pomba, C.F. (2022): Companion animals-an overlooked and misdiagnosed reservoir of carbapenem resistance. Antibiotics (Basel) 11, 533.

[5] Patel, G. and Bonomo, RA. (2013): "Stormy waters ahead": global emergence of carbapenemases. Front Microbiol. 4:1–17.

[6] Ansari, M.; Munir, T. and Saad, N. (2018): Phenotypic identification, frequency distribution and antibiogram of carbapenemase producing Enterobacteriaceae in clinical isolates. J Coll Physicians Surg Pak. 28:274–278.

[7] Levy Hara. G.; Gould, I.; Endimiani, A.; Pardo, PR.; Daikos, G.; Hsueh, PR.; Mehtar, S.; Petrikkos, G.; Casellas, JM.; Daciuk, L.; Paciel, D.; Novelli, A.; Saginur, R.; Pryluka, D.; Medina, J. and Savio, E. (2013): Detection, treatment, and prevention of carbapenemase-producing Enterobacteriaceae: Recommendations from an International Working Group. J Chemother. 25:129–140.

[8] Queenan, AM. and Bush, K. (2007): Carbapenemases: The versatile b-lactamases. Clin Microbiol Rev. 20:440–458.

[9] Hall, BG. and Barlow, M. (2005): Revised Ambler classification of β-lactamases. J Antimicrob Chemother. 55:1050-1.

[10] Nordmann, P.; Cuzon, G. and Naas, T. (2009): The real threat of Klebsiella pneumoniae carbapenemase-producing bacteria. Lancet Infect. Dis. 9, 228–236

[11] Pfeifer, Y.; Cullik, A. and Witte, W. (2010): Resistance to cephalosporins and carbapenems in Gram-negative bacterial pathogens. Int. J. Med. Microbiol. 300, 371–379.

[12] Cuzon, G.; Naas, T.; Truong, H.; Villegas, MV.; Wisell, KT.; Carmeli, Y.; Gales, AC.; Venezia, SN.; Quinn, JP. and Nordmann, P. (2010): Worldwide diversity of Klebsiella pneumoniae that produce beta-lactamase blaKPC-2 gene. Emerg. Infect. Dis. 16, 1349–1356.

[13] Miltgen, G.; Bonnin, RA.; Avril, C.; Benoit-Cattin, T.; Martak, D.; Leclaire, A.; Traversier, N.; Roquebert, B.; Jaffar-Bandjee, MC.; Lugagne, N.; Filleul, L.; Subiros, M.; de Montera, AM.; Cholley, P.; Thouverez, M.; Dortet, L.; Bertrand, X.; Naas, T.; Hocquet, D. and Belmonte, O.(2018): Outbreak of IMI-1 carbapenemase-producing colistin-resistant Enterobacter cloacae on the French island of Mayotte (Indian Ocean). Int. J. Antimicrob. Agents, 52, 416–420.

[14] Walsh, TR.; Toleman, MA.; Poirel, L. and Nordmann, P. (2005): Metallo-β -lactamases: the quiet before the storm? Clin. Microbiol. Rev. 18, 306–325.

[15] Logan, LK. and Weinstein, RA. (2017): The epidemiology of carbapenem-resistant Enterobacteriaceae: the impact and evolution of a global menace. J. Infect. Dis. 215(Suppl. 1), S28–S36.

[16] Poirel, L.; Potron, A. and Nordmann, P. (2012): OXA-48-like carbapenemases: the phantom menace. J. Antimicrob. Chemother. 67, 1597–1606.

[17] Zhong, H.; Wu, ML.; Feng, WJ.; Huang, SF. and Yang, P. (2020): Accuracy and applicability of different phenotypic methods for carbapenemase detection in Enterobacteriaceae: A systematic review and meta-analysis. Journal of global antimicrobial resistance, 21:138–47.

[18] Azimi, L.; Talebi, M.; Owlia, P.; Pourshafie, MR.; Najafi, M. and Lari, ER. (2016): Tracing of false negative results in Phenotypic methods for identification of carbapenemase by Real-time PCR. Gene, 576:166–70

[19] Nordmann, P.; Gniadkowski, M.; Giske, C. G.; Poirel, L.; Woodford, N.; Miriagou, V. and European Network on Carbapenemases (2012): Identification and screening of carbapenemase-producing Enterobacteriaceae. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases, 18:432–8.

[20] EMA (2019): Categorisation of Antibiotics in the European Union; European Medicines Agency: London, UK.

[21] Ramadan, H.; Gupta, S.K.; Sharma, P.; Ahmed, M.; Hiott, L.M.; Barrett, J.B.; Woodley, T.A.; Frye, J.G. and Jackson, C.R. (2020): Circulation of emerging NDM-5-producing Escherichia coli among humans and dogs in Egypt. Zoonoses Public Health, 67:324–9

[22] Pomba, C.; Rantala, M.; Greko, C.; Baptiste, K.E.; Catry, B.; Van Duijkeren, E.; Mateus, A.; Moreno, M.A.; Pyörälä, S.; Ružauskas, M.; Sanders, P.; Teale, C.; Threlfall, E.J.; Kunsagi, Z.; Torren-Edo, J.; Jukes, H. and Törneke, K. (2017): Public health risk of antimicrobial resistance transfer from companion animals. J. Antimicrob. Chemother, 72, 957-968.

[23] Blair, J. M.; Webber, M. A.; Baylay, A. J.; Ogbolu, D. O. and Piddock, L. J. (2015). Molecular mechanisms of antibiotic resistance. Nature reviews. Microbiology, 13, 42–51.

[24] Tzouvelekis, LS.; Markogiannakis, A.; Psichogiou, M.; Tassios, PT. and Daikos, GL. (2012): Carbapenemases in Klebsiella pneumoniae and other Enterobacteriaceae: an evolving crisis of global dimensions. Clin. Microbiol. Rev. 25, 682–707.

[25] Durante-Mangoni, E.; Andini, R. and Zampino, R. (2019): Management of carbapenem-resistant Enterobacteriaceae infections. Clin. Microbiol. Infect.25, 943–950.

[26] Yang, D.; Guo, Y. and Zhang, Z. (2009): Combined porin loss and extended spectrum β-lactamase production is associated with an increasing imipenem minimal inhibitory concentration in clinical Klebsiella pneumoniae strains. Curr. Microbiol. 58, 366–370.

[27] Farra, A.; Islam, S.; Str°alfors, A.; S¨orberg, M. and Wretlind, B. (2008): Role of outer membrane protein OprD and penicillin-binding proteins in resistance of Pseudomonas aeruginosa to imipenem and meropenem. Int. J. Antimicrob. Agents, 31, 427–433.

[28] García-Fernández, A.; Miriagou, V.; Papagiannitsis, C. C.; Giordano, A.; Venditti, M.; Mancini, C. and Carattoli, A. (2010): An ertapenem-resistant extended-spectrum-β-lactamase-producing Klebsiella pneumoniae clone carries a novel OmpK36 porin variant. Antimicrob. Agents Chemother. 54, 4178–4184.

[29] Lomovskaya, O.; Zgurskaya, HI.; Totrov, M. and Watkins, WJ. (2007): Waltzing transporters and “the dance macabre” between humans and bacteria. Nat. Rev. Drug Discov. 6, 56–65.

[30] King, DT.; Sobhanifar, S. and Strynadka, NCJ. (2017): The mechanisms of resistance to β-lactam antibiotics. In:

Handbook of Antimicrobial Resistance. Berghuis A, Matlashewski G, Wainberg MA, Sheppard D (Eds). Springer New York, NY, USA, 177–201.

[31] Meletis, G.; Exindari, M.; Vavatsi, N.; Sofianou, D. and Diza, E. (2012): Mechanisms responsible for the emergence of carbapenem resistance in Pseudomonas aeruginosa. Hippokratia, 16, 303–307.

[32] Meletis, G. (2016): Carbapenem resistance: overview of the problem and future perspectives. Ther. Adv. Infect. Dis. 3, 15-21.

[33] Jacoby, GA. and Munoz-Price, LS. (2005): The new β-lactamases. N. Engl. J. Med. 352, 380–391.

[34] Dougherty, TJ. and Pucci, MJ. (2012): Antibiotic discovery and development. Springer Science and Business Media, NY, USA.

[35] Eichenberger, EM. and Thaden, JT. (2019): Epidemiology and Mechanisms of Resistance of Extensively Drug Resistant Gram-Negative Bacteria. Antibiotics (Basel). 6; 8:37.

[36] Yigit, H.; Queenan, A. M.; Anderson, G. J.; Domenech-Sanchez, A.; Biddle, J. W.; Steward, C. D.; Alberti, S.; Bush, K. and Tenover, F. C. (2001): Novel carbapenem-hydrolyzing betalactamase, KPC-1, from a carbapenem-resistant strain of Klebsiella pneumoniae. Antimicrob. Agents Chemother. 45, 1151–1161.

[37] Munoz-Price, L. S.; Poirel, L.; Bonomo, R.A.; Schwaber, M.J.; Daikos, G.L.; Cormican, M.; Cornaglia, G.; Garau, J.; Gniadkowski, M.; Hayden, M.K.; Kumarasamy, K.; Livermore, D.M.; Maya, J.J.; Nordmann, P.; Patel, J.B.; Paterson, D.L.; Pitout, J.; Villegas, M.V.; Wang, H.; Woodford, N. and Quinn, J.P. (2013): Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. Lancet Infect. Dis. 13, 785–796.

[38] Wei, Z.Q.; Du, X.X.; Yu, Y.S.; Shen, P.; Chen, Y.G. and Li, L.J. (2007): Plasmid mediated KPC-2 in a Klebsiella pneumoniae isolate from China. Antimicrob. Agents Chemother. 51, 763–765

[39] Zhang, R.; Liu, L.; Zhou, H.; Chan, E.W.; Li, J.; Fang, Y.; Li, Y.; Liao, K. and Chen, S. (2017): Nationwide surveillance of clinical Carbapenem-resistant Enterobacteriaceae (CRE) strains in China. EbioMedicine ,19, 98–106.

[40] Bowers, J.R.; Kitchel, B.; Driebe, E.M.; MacCannell, D.R.; Roe, C.; Lemmer, D.; de Man, T.; Rasheed, J.K.; Engelthaler, D.M.; Keim, P. and Limbago, B.M. (2015): Genomic analysis of the emergence and rapid global dissemination of the clonal group 258 Klebsiella pneumoniae pandemic. PloS One, 10: e0133727.

[41] Chen, L.,Mathema, B., Chavda, K. D., DeLeo, F. R., Bonomo, R. A. and Kreiswirth, B. N. (2014). Carbapenemase-producing Klebsiella pneumoniae: molecular and genetic decoding. Trends Microbiol. 22, 686–696.

[42] Yong, D.; Toleman, M.A.; Giske, C.G.; Cho, H.S.; Sundman, K.; Lee, K. and Walsh, T.R. (2009): Characterization of a new metallo-beta-lactamase gene, blaNDM-1, and a novel erythromycin esterase gene carried on a unique genetic structure in Klebsiella pneumoniae sequence type 14 from India. Antimicrob. Agents Chemother. 53, 5046–5054.

[43] Tsang, K.Y.; Luk, S.; Lo, J.Y.; Tsang, T.Y.; Lai, S.T. and Ng, T.K. (2012): HongKong experiences the 'Ultimate superbug': NDM-1 Enterobacteriaceae. Hong Kong Med. J. 18, 439–441.

[44] Berrazeg, M.; Diene, S.; Medjahed, L.; Parola, P.; Drissi, M.; Raoult, D. and Rolain, J. (2014): New Delhi Metallo-beta-lactamase around the world:an eReview using Google Maps. Euro Surveill. 19:20809.

[45] Dortet, L.; Poirel, L. and Nordmann, P. (2014): Worldwide dissemination of the NDM-type carbapenemases in Gram-negative bacteria. Biomed. Res. Int. 2014:249856.

[46] Zhang, Y.; Wang, Q.; Yin, Y.; Chen, H.; Jin, L.; Gu, B.; Xie, L.; Yang, C.; Ma, X.; Li, H.; Li, W.; Zhang, X.; Liao, K.; Man, S.; Wang, S.; Wen, H.; Li, B.; Guo, Z.; Tian, J.; Pei, F. and Wang, H. (2018): Epidemiology of Carbapenem-Resistant Enterobacteriaceae infections: report from the China CRE Network. Antimicrob. Agents Chemother. 62: e1882-17.

[47] Pitout, J.D.; Nordmann, P. and Poirel, L. (2015): Carbapenemase-Producing Klebsiella pneumoniae, a key pathogen set for global nosocomial dominance. Antimicrob. Agents Chemother. 59, 5873–5884.

[48] Ito, H.; Arakawa, Y.; Ohsuka, S.; Wacharotayankun, R.; Kato, N. and Ohta, M. (1995): Plasmid-mediated dissemination of the metallo-beta-lactamase gene blaIMP among clinically isolated strains of Serratia marcescens. Antimicrob. Agents Chemother. 39, 824–829.

[49] Poirel, L.; Lagrutta, E.; Taylor, P.; Pham, J. and Nordmann, P. (2010): Emergence of metallo-β-lactamase NDM-1-producing multidrug-resistant Escherichia coli in Australia. Antimicrobial agents and chemotherapy, 54, 4914-4916.

[50] Vatopoulos, A. (2008): High rates of metallo-beta-lactamase-producing Klebsiella pneumoniae in Greece–a review of the current evidence. Euro Surveill. 13:8023.

[51] Glasner, C.; Albiger, B.; Buist, G.; Tambić Andrasević, A.; Canton, R.; Carmeli, Y.; Friedrich, A.W.; Giske, C.G.; Glupczynski, Y.; Gniadkowski, M.; Livermore, D.M.; Nordmann, P.; Poirel, L.; Rossolini, G.M.; Seifert, H.; Vatopoulos, A.; Walsh, T.; Woodford, N.; Donker, T.; Monnet, D.L. and European Survey on Carbapenemase-Producing Enterobacteriaceae (EuSCAPE) Working Group (2013): Carbapenemase-producing Enterobacteriaceae in Europe: a survey among national experts from 39 countries. Euro Surveill. 18:20525

[52] Donald, H.M.; Scaife, W.; Amyes, S.G. and Young, H.K. (2000): Sequence analysis of ARI-1, a novel OXA beta-lactamase, responsible for imipenem resistance in Acinetobacter baumannii 6B92. Antimicrob. Agents Chemother. 44, 196–199.

[53] Evans, B.A. and Amyes, S.G. (2014): OXA β-lactamases. Clin. Microbiol. Rev. 27, 241–263.

[54] Poirel, L.; Héritier, C.; Tolün, V. and Nordmann, P. (2004): Emergence of oxacillinase-mediated resistance to imipenem in Klebsiella pneumoniae. Antimicrob Agents Chemother. 48:15-22.

[55] Stewart, A.; Harris, P.; Henderson, A. and Paterson, D. (2018): Treatment of infections by OXA-48-producing Enterobacteriaceae. Antimicrob. Agents Chemother. 62: e01195-18.

[56] Chen, Z.; Wang, Y.; Tian, L.; Zhu, X.; Li, L.; Zhang, B.; Yan, S. and Sun, Z. (2015): First report in China of Enterobacteriaceae clinical isolates coharboring blaNDM-1 and blaIMP-4 drug resistance genes.Microb. Drug Resist. 21, 167–170.

[57] Feng, J.; Qiu, Y.; Yin, Z.; Chen, W.; Yang, H.; Yang, W.; Wang, J.; Gao, Y. and

Zhou, D. (2015): Coexistence of a novel KPC-2-encoding MDR plasmid and an NDM-1-encoding pNDMHN380- like plasmid in a clinical isolate of Citrobacter freundii. J. Antimicrob. Chemother. 70, 2987–2991.

[58] Du, H.; Chen, L.; Chavda, K.D.; Pandey, R.; Zhang, H.; Xie, X.; Tang, Y.W. and Kreiswirth, B.N. (2016): Genomic characterization of Enterobacter cloacae isolates from China that coproduce KPC-3 and NDM-1 carbapenemases. Antimicrob. Agents Chemother. 60, 2519–2523.

[59] Yang, B.; Feng, Y.; McNally, A. and Zong, Z. (2018): Occurrence of Enterobacter hormaechei carrying blaNDM-1 and blaKPC-2 in China. Diagn. Microbiol. Infect. Dis. 90, 139–142.

[60] Wang, J.; Yuan, M.; Chen, H.; Chen, X.; Jia, Y.; Zhu, X.; Bai, L.; Bai, X.; Fanning, S.; Lu, J. and Li, J. (2017): First report of Klebsiella oxytoca strain simultaneously producing NDM-1, IMP-4, and KPC-2 carbapenemases. Antimicrob. Agents Chemother. 61: e0877-17.

[61] Carrër, A.; Poirel, L.; Yilmaz, M.; Akan, O.A.; Feriha, C.; Cuzon, G.; Matar, G.; Honderlick, P. and Nordmann, P. (2010): Spread of OXA-48-encoding plasmid in TurKey and beyond. Antimicrob Agents Chemother 54:1369–73.

[62] Badal, R.; Kazmierczak, K. and Hackel, M. (2014): Geographic distribution of carbapenemases found in Enterobacteriaceae—SMART 2012 [abstract C-799]. Presented At: 54th Interscience Conference on Antimicrobial Agents and Chemotherapy.

[63] World Organisation for Animal Health (OIE): OIE List of Antimicrobial Agents of Veterinary Importance. In Proceedings of the FAO2/OIE/WHO3 Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance, Geneva, Switzerland, 1–5 December 2003; Volume Xxviii, pp. 1–10.

[64] Mader, R.; Damborg, P.; Amat, J. P.; Bengtsson, B.; Bourély, C.; Broens, E.M.; Busani, L.; Crespo-Robledo, P.; Filippitzi, M.E.; Fitzgerald, W.; Kaspar, H.; Madero, C.M.; Norström, M.; Nykäsenoja, S.; Pedersen, K.; Pokludova, L.; Urdahl, A.M.; Vatopoulos, A.; Zafeiridis, C. and Madec, J.Y.; EU-JAMRAI (2021): Building the European Antimicrobial Resistance Surveillance Network in Veterinary Medicine (EARS-Vet). Eurosurveillance, 26, 2001359.

[65] Sellera, F.P.; Fernandes,M.R.; Ruiz, R.; Falleiros, A.C.M.; Rodrigues, F.P.; Cerdeira, L. and Lincopan, N. (2018): Identification of KPC-2-Producing Escherichia Coli in a Companion Animal: A New Challenge for Veterinary Clinicians. J. Antimicrob. Chemother. 73, 2259–2261.

[66] Sellera, F.P.; Fuga, B.; Fontana, H.; Esposito, F.; Cardoso, B.; Konno, S.; Berl, C.; Cappellanes, M.H.; Cortez, M.; Ikeda, M.; de Souza, C.M.; Cerdeira, L. and Lincopan, N. (2021): Detection of IncN-PST15 One-Health Plasmid Harbouring blaKPC-2 in a Hypermucoviscous Klebsiella Pneumoniae CG258 Isolated from an Infected Dog, Brazil. Transbound. Emerg. Dis. 68, 3083–3088.

[67] Daniels, J.B.; Chen, L.; Grooters, S.V.; Mollenkopf, D.F.; Mathys, D.A.; Pancholi, P.; Kreiswirth, B.N. and Wittum, T.E. (2018): Enterobacter cloacae Complex Sequence Type 171 Isolates Expressing KPC-4 Carbapenemase Recovered from Canine Patients in Ohio. Antimicrob. Agents Chemother. 62, e01161-18.

[68] Abraham, S.; O'Dea, M.; Trott, D.J.; Abraham, R.J.; Hughes, D.; Pang, S.; McKew, G.; Cheong, E.Y.L.; Merlino, J.; Saputra, S.; Malik, R. and Gottlieb, T. (2016): Isolation and Plasmid Characterization of Carbapenemase (IMP-4) Producing Salmonella enterica Typhimurium from Cats. Sci. Rep. 6, 35527.

[69] Hyun, J.E.; Chung, T.H. and Hwang, C.Y. (2018): Identification of VIM-2 Metallo-β-Lactamase-Producing Pseudomonas aeruginosa Isolated from Dogs with Pyoderma and Otitis in Korea. Vet. Dermatol. 29, 186-e68.

[70] González-Torralba, A.; Oteo, J.; Asenjo, A.; Bautista, V.; Fuentes, E. and Alós, J.I. (2016): Survey of carbapenemase-producing Enterobacteriaceae in companion dogs in Madrid, Spain. Antimicrob. Agents Chemother. 60, 2499-2501.

[71] Wang, Y.; Zhang, R.; Li, J.; Wu, Z.; Yin, W.; Schwarz, S.; Tyrrell, J.M.; Zheng, Y.; Wang, S.; Shen, Z.; Liu, Z.; Liu, J.; Lei, L.; Li, M.; Zhang, Q.; Wu, C.; Zhang, Q.; Wu, Y.; Walsh, T.R. and Shen, J. (2017): Comprehensive resistome analysis reveals the prevalence of NDM and MCR-1 in Chinese poultry production. Nat. Microbiol. 2, 16260.

[72] Yousfi, M.; Touati, A.; Mairi, A.; Brasme, L.; Gharout-Sait, A.; Guillard, T. and De Champs, C. (2016): Emergence of Carbapenemase-Producing Escherichia Coli Isolated from Companion Animals in Algeria. Microb. Drug Resist. 22, 342–346.

[73] Grönthal, T.; Österblad, M.; Eklund, M.; Jalava, J.; Nykäsenoja, S.; Pekkanen, K. and Rantala, M. (2018): Sharing More than Friendship-Transmission of NDM-5 ST167 and CTX-M-9 ST69 Escherichia Coli between Dogs and Humans in a Family, Finland, 2015. Euro Surveill. 23, 1700497.

[74] Reynolds, M.E.; Phan, H.T.T.; George, S.; Hubbard, A.T.M.; Stoesser, N.; Maciuca, I.E., Crook, D.W. and Timofte, D. (2019): Occurrence and Characterization of Escherichia coli ST410 Co-Harbouring BlaNDM-5, BlaCMY-42 and BlaTEM-190 in a Dog from the UK. J. Antimicrob. Chemother. 74, 1207–1211.

[75] Tyson, G.H.; Li, C.; Ceric, O.; Reimschuessel, R.; Cole, S.; Peak, L. and Rankin, S.C. (2019): Complete Genome Sequence of a Carbapenem Resistant Escherichia coli Isolate with BlaNDM-5 from a Dog in the United States. Microbiol. Resour. Announc. 8, 22–23.

[76] Hong, J.S.; Song,W. and Jeong, S.H. (2020): Molecular Characteristics of NDM-5-Producing Escherichia coli from a Cat and a Dog in South Korea. Microb. Drug Resist. 26, 1005–1008.

[77] Cole, S.D.; Peak, L.; Tyson, G.H.; Reimschuessel, R.; Ceric, O. and Rankin, S.C. (2020); New Delhi Metallo-β-Lactamase-5–Producing Escherichia coli in Companion Animals, United States. Emerg. Infect. Dis. 26, 381–383.

[78] Gentilini, F.; Turba, M.E.; Pasquali, F.; Mion, D.; Romagnoli, N.; Zambon, E.; Terni, D.; Peirano, G.; Pitout, J.D.D.; Parisi, A.; Sambri, V. and Zanoni, R.G. (2018): Hospitalized Pets as a Source of Carbapenem-Resistance. Front. Microbiol. 9, 2872.

[79] Shaheen, B.W.; Nayak, R. and Boothe, D.M. (2013): Emergence of a New DelhiMetallo-β-Lactamase (NDM-1)-Encoding Gene in Clinical Escherichia coli Isolates Recovered from Companion Animals in the United States. Antimicrob. Agents Chemother. 57, 2902–2903.

[80] Cui, L.; Lei, L.; Lv, Y.; Zhang, R.; Liu, X.; Li, M.; Zhang, F. and Wang, Y. (2018). blaNDM-1-Producing

Multidrug-Resistant Escherichia coli Isolated from a Companion Dog in China. J. Glob. Antimicrob. Resist. 13, 24–27.

[81] Nigg, A.; Brilhante, M.; Dazio, V.; Clément, M.; Collaud, A.; Brawand, S.G.; Willi, B.; Endimiani, A.; Schuller, S. and Perreten, V. (2019): Shedding of OXA-181 carbapenemase-producing Escherichia coli from companion animals after hospitalisation in Switzerland: an outbreak in 2018. Euro. Surveill. 24,1900071

[82] Brilhante, M.; Menezes, J.; Belas, A.; Feudi, C.; Schwarz, S.; Pomba, C. and Perreten, V. (2020): OXA-181-producing extraintestinal pathogenic Escherichia coli sequence type 410 isolated from a dog in Portugal. Antimicrob. Agents Chemother. 64, e02298-19.

[83] Pulss, S.; Stolle, I.; Stamm, I.; Leidner, U.; Heydel, C.; Semmler, T.; Prenger-Berninghoff, E. and Ewers, C. (2018): Multispecies and clonal dissemination of OXA-48 carbapenemase in Enterobacteriaceae from companion animals in Germany, 2009-2016. Front. Microbiol. 9, 1265.

[84] Stolle, I.; Prenger-Berninghoff, E.; Stamm, I.; Scheufen, S.; Hassdenteufel, E.; Guenther, S.; Bethe, A.; Pfeifer, Y. and Ewers, C. (2013): Emergence of OXA-48 Carbapenemase-Producing Escherichia coli and Klebsiella pneumoniae in Dogs. J. Antimicrob. Chemother. 68, 2802–2808.

[85] Melo, L.C.; Boisson, M.N.G.; Saras, E.; Médaille, C.; Boulouis, H.J.; Madec, J.Y. and Haenni, M. (2017): OXA-48-Producing ST372 Escherichia coli in a French Dog. J. Antimicrob. Chemother. 72, 1256–1258.

[86] Yousfi, M.; Touati, A.; Muggeo, A.; Mira, B.; Asma, B.; Brasme, L.; Guillard, T. and de Champs, C. (2018): Clonal Dissemination of OXA-48-Producing Enterobacter cloacae Isolates from Companion Animals in Algeria. J. Glob. Antimicrob. Resist. 12, 187–191.

[87] Pomba, C.; Endimiani, A.; Rossano, A.; Saial, D.; Couto, N. and Perreten, V. (2014): First Report of OXA-23-Mediated Carbapenem Resistance in Sequence Type 2 Multidrug-Resistant Acinetobacter baumannii Associated with Urinary Tract Infection in a Cat. Antimicrob. Agents Chemother. 58, 1267–1268.

[88] Ewers, C.; Klotz, P.; Leidner, U.; Stamm, I.; Prenger-Berninghoff, E.; Göttig, S.; Semmler, T. and Scheufen, S. (2017): OXA-23 and ISAba1–OXA-66 Class D β-Lactamases in Acinetobacter baumannii Isolates from Companion Animals. Int. J. Antimicrob. Agents 49, 37–44.

[89] World Health Organization (WHO) (2002): Towards a Common Language for Functioning, Disability and Health: ICF. WHO, Geneva. http://www.who.int/classifications/icf/training/icfbeginnersguide.pdf.

[90] Schmiedel, J.; Falgenhauer, L.; Domann, E.; Bauerfeind, R.; Prenger-Berninghoff, E.; Imirzalioglu, C. and Chakraborty, T. (2014): Multiresistant Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae from Humans, Companion Animals and Horses in Central Hesse, Germany. BMC Microbiol. 14, 187.

[91] Moreira da Silva, J.; Menezes, J.; Salas, C.; Marques, C.; Teodoro, S.; Amaral, A.J. and Pomba, C. (2021): Clinical/Research Abstracts Accepted for Presentation at the ISFM 2021 World Feline Congress. J. Feline Med. Surg. 23, 851–858.

[92] Alba, P.; Taddei, R.; Cordaro, G.; Fontana, M.C.; Toschi, E.; Gaibani, P.; Marani, I.; Giacomi, A.; Diaconu, E.L.; Iurescia, M.; Carfora, V. and Franco, A.

(2021): Carbapenemase IncF-Borne BlaNDM-5 Gene in the E. Coli ST167 High-Risk Clone from Canine Clinical Infection, Italy. Vet. Microbiol. 256, 109045.

[93] Tartor, Y.H.; Ammar, A.M.; Abdelkhalek, A.; Hassan, K.A.; Shaker, A.; Elnahriry, S.S, Nekouei, O. and Elsohaby, I. (2024): Emergence of pandrug-resistant carbapenemase-producing Enterobacterales in dogs and cats: a crosssectional study in Egypt. Front. Cell. Infect. Microbiol. 14:1318585

[94] Anderson, REV. and Boerlin, P. (2020). Carbapenemase-producing Enterobacteriaceae in animals and methodologies for their detection. Can J Vet Res.84:3–17.

[95] Liu, X.; Thungrat, K. and Boothe, D.M. (2016): Occurrence of OXA-48 Carbapenemase and Other β-Lactamase Genes in ESBL-Producing Multidrug Resistant: Escherichia coli from Dogs and Cats in the United States, 2009–2013. Front. Microbiol. 7, 1057.

[96] Al Bayssari, C.; Olaitan, A.O.; Dabboussi, F.; Hamze, M. and Rolain, J.M. (2015): Emergence of OXA-48-producing Escherichia coli clone ST38 in fowl. Antimicrob Agents Chemother. 59:745–6.

[97] Braun, S.D.; Ahmed, M.F.; El-Adawy; H.; Hotzel, H.; Engelmann, I.; Weiß, D.; Monecke, S. and Ehricht, R. (2016): Surveillance of extended-spectrum beta-lactamase-producing Escherichia coli in dairy cattle farms in the Nile Delta, Egypt. Front Microbiol. 7:1020.

[98] Pulss, S.; Semmler, T.; Prenger-Berninghoff, E.; Bauerfeind, R. and Ewers, C. (2017): First report of an Escherichia coli strain from swine carrying an OXA-181 carbapenemase and the colistin resistance determinant MCR-1. Int J Antimicrob Agents. 50:232–6.

[99] Abdelaziz, M.O.; Bonura, C.; Aleo, A.; Fasciana, T. and Mammina, C. (2013): NDM-1- and OXA-163-producing Klebsiella pneumoniae isolates in Cairo, Egypt, 2012, JGAR. 1, 213–215.

[100] Diab, M.; Fan, N.; El-Said, M.; El-Dabaa, E. and El-Defrawy, I. (2013): Saber M. Occurrence of VIM-2 Metallo-β-lactamases in imipenem resistant and susceptible Pseudomonas aeruginosa clinical isolates from Egypt. Afri J Microbiol. 7:4465–72.

[101] Helal, S.F.; El-Rachidi, N.G.; AbdulRahman, E.M. and Hassan, D.M. (2014): The presence of blaKPC-mediated resistance in Enterobacteriaceae in Cairo University hospitals in Egypt and its correlation with in vitro carbapenem susceptibility. J Chemother. 26:125-8.

[102] Zafer, M.M.; Al-Agamy, M.H.; El-Mahallawy, H.A.; Amin, M.A. and Ashour, E.D.S. (2015): Dissemination of VIM-2 producing Pseudomonas aeruginosa ST233 at tertiary care hospitals in Egypt. BMC Infect Dis. 15:122.

[103] Hamza, D.; Dorgham, S.; Ismael, E.; El-Moez, S.I.A.; Elhariri, M.; Elhelw, R. and Hamza, E. (2020): Emergence of b-lactamase- and carbapenemase-producing Enterobacteriaceae at integrated fish farms. Antimicrob Resist Infect Control. 9, 67.

[104] Hamza, E.; Dorgham, S.M. and Hamza, D.A. (2016): Carbapenemase-producing Klebsiella pneumoniae in broiler poultry farming in Egypt. J Glob Antimicrob Resist. 7:8–10.

[105] Algammal, A.M.; Hashem, H.R.; Alfifi, K.J.; Hetta, H.F.; Sheraba, N.S.; Ramadan, H. and El-Tarabili, R.M. (2021): atpD gene sequencing, multidrug resistance traits, virulence-determinants, and antimicrobial resistance genes of

emerging XDR and MDR-Proteus mirabilis. Sci Rep. 11:9476.

[106] Shi, X.; Li, Y.; Yang, Y.; Shen, Z.; Cai, C.; Wang, Y.; Walsh, T.R.; Shen, J.; Wu, Y. and Wang, S. (2021): High prevalence and persistence of carbapenem and colistin resistance in livestock farm environments in China. J Hazard Mater. 406:124298.

[107] Sadek, M.; Poirel, L.; Nordmann, P.; Nariya, H.; Shimamoto, T. and Shimamoto, T. (2020): Genetic characterisation of NDM-1 and NDM-5-producing Enterobacterales from retail chicken meat in Egypt. J Glob Antimicrob Resist. 23:70–1.

[108] Elshafiee, E.A.; Nader, S.M.; Dorgham, S.M. and Hamza, D.A. (2019): Carbapenem-resistant Pseudomonas aeruginosa originating from farm animals and people in Egypt. J Vet Res. 63:333–7.

[109] Fattouh, R.; Tijet, N.; McGeer, A.; Poutanen, S.M.; Melano, R.G. and Patel, S.N. (2016): What is the appropriate meropenem MIC for screening of carbapenemase producing Enterobacteriaceae in low-prevalence settings? Antimicrob Agents Chemother. 60:1556 –1559.

[110] Gagetti, P.; Pasteran, F.; Martinez, M.P.; Fatouraei, M.; Gu, J.; Fernandez, R.; Paz, L.; Rose, W.E.; Corso, A. and Rosato, A.E. (2016): Modeling meropenem treatment, alone and in combination with daptomycin, for KPC-Producing Klebsiella pneumoniae strains with unusually low carbapenem MICs. Antimicrob. Agents Chemother. 60, 5047–5050.

[111] Woodford, N.; Eastaway, A.T.; Ford, M.; Leanord, A.; Keane, C.; Quayle, R.M.; Steer, J.A.; Zhang, J. and Livermore, D.M. (2010): Comparison of BD Phoenix, Vitek2 and MicroScan automated systems for detection and inference of mechanisms responsible for carbapenem resistance in Enterobacteriaceae. J. Clin.Microbiol. 48, 2999–3002.

[112] Tamma, P.D.; Opene, B.N.; Gluck, A.; Chambers, K.K.; Carroll, K.C. and Simner, P. J. (2017): Comparison of 11 phenotypic assays for accurate detection of carbapenemase-producing Enterobacteriaceae. J. Clin. Microbiol. 55, 1046–1055.

[113] CDC. (2008): Laboratory protocol for detection of carbapenem-resistant or carbapenamase-producing, Klebsiella spp. and E. coli from rectal swabs. CDC, Atlanta, GA. http://www.cdc.gov/HAI/pdfs/labSettings/Klebsiella_or_ Ecoli.pdf. Accessed 30 Mar 2015.

[114] Giani, T.; Tascini, C.; Arena, F.; Ciullo, I.; Conte, V.; Leonildi, A.; Menichetti, F. and Rossolini, G.M. (2012): Rapid detection of intestinal carriage of Klebsiella pneumoniae producing KPC carbapenemase during an outbreak. J Hosp Infect. 81:119–22.

[115] Papadimitriou-Olivgeris, M.; Bartzavali, C.; Christofidou, M.; Bereksi, N.; Hey, J.; Zambardi, G. and Spiliopoulou, I. (2014): Performance of chromID CARBA medium for carbapenemases-producing Enterobacteriaceae detection during rectal screening. Eur J Clin Microbiol Infect Dis. 33:35–40.

[116] Vrioni, G.; Daniil, I.; Voulgari, E.; Ranellou, K.; Koumaki, V.; Ghirardi, S.; Kimouli, M.; Zambardi, G. and Tsakris, A. (2012): Comparative evaluation of a prototype chromogenic medium (ChromID CARBA) for detecting carbapenemase- producing Enterobacteriaceae in surveillance rectal swabs. J Clin Microbiol. 50(6):1841–6.

[117] Girlich, D.; Poirel, L. and Nordmann, P. (2013): Comparison of the SUPERCARBA, CHROMagar KPC,

and brilliance CRE screening media for detection of Enterobacteriaceae with reduced susceptibility to carbapenems. Diagn Microbiol Infect Dis. 75(2):214–7.

[118] Hoyos-Mallecot, Y.; Naas, T.; Bonnin, R.A.; Patino, R.; Glaser, P.; Fortineau, N. and Dortet. L. (2017): OXA-244-Producing Escherichia coli Isolates, a Challenge for Clinical Microbiology Laboratories. Antimicrob Agents Chemother. 24;61(9).

[119] Nordmann, P.; Gniadkowski, M.; Giske, C.G.; Poirel, L.; Woodford, N. and Miriagou, V. (2012): Identification and screening of carbapenemase-producing Enterobacteriaceae. Clin Microbiol Infect. 432–8.

[120] EUCAST. (2013): EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Resistance_mechanisms/EUCAST_detection_of_resistance_mechanisms_v1.0_20131211.pdf.

[121] Girlich, D.; Poirel, L. and Nordmann, P. (2012): Value of the modified Hodge test for detection of emerging carbapenemases in Enterobacteriaceae. J. Clin. Microbiol. 50, 477–479.

[122] Pasteran, F.; Gonzalez, L.J.; Albornoz, E.; Bahr, G.; Vila, A.J. and Corso, A. (2016): Triton hodge test: improved protocol for modified hodge test for enhanced detection of NDM and other carbapenemase producers. J. Clin. Microbiol. 54, 640–649. Doi: 10.1128/JCM.01298-15.

[123] Carvalhaes, C.G.; Picão, R.C.; Nicoletti, A.G.; Xavier, D.E. and Gales, A.C. (2010): Cloverleaf test (modified Hodge test) for detecting carbapenemase production in Klebsiella pneumoniae: be aware of false positive results. J. Antimicrob. Chemother. 65, 249–251.

[124] Nordmann, P.; Poirel, L. and Dortet, L. (2012): Rapid detection of carbapenemase producing Enterobacteriaceae. Emerg. Infect. Dis. 18, 1503–1507.

[125] Dortet, L.; Poirel, L. and Nordmann, P. (2012): Rapid identification of carbapenemase types in Enterobacteriaceae and Pseudomonas spp. By using a biochemical test. Antimicrob. Agents Chemother. 56, 6437–6440.

[126] Pires, J.; Novais, A. and Peixe, L. (2013): Blue-carba, an easy biochemical test for detection of diverse carbapenemase producers directly from bacterial cultures. J. Clin. Microbiol. 51, 4281–4283.

[127] Novais, Â.; Brilhante, M.; Pires, J. and Peixe, L. (2015): Evaluation of the recently launched rapid carb blue kit for detection of carbapenemase-producing Gram-negative bacteria. J. Clin. Microbiol. 53, 3105–3107.

[128] Bogaerts, P.; Yunus, S.; Massart, M.; Huang, T.D. and Glupczynski, Y. (2016): Evaluation of the BYG carba test, a new electrochemical assay for rapid laboratory detection of carbapenemase-producing Enterobacteriaceae. J. Clin. Microbiol. 54, 349–358.

[129] Rapp, E.; Samuelsen, Ø. and Sundqvist, M. (2018): Detection of carbapenemases with a newly developed commercial assay using matrix assisted laser desorption ionization-time of flight. J.Microbiol. Methods 146, 37–39.

[130] Van der Zwaluw, K.; de Haan, A.; Pluister, G.N.; Bootsma, H.J.; de Neeling, A.J. and Schouls, L.M. (2015): The carbapenem inactivation method (CIM), a simple and low-cost alternative for the Carba NP test to assess phenotypic carbapenemase activity in Gram-negative rods. PloS One 10: e0123690.

[131] Clinical and Laboratory Standards Institute (CLSI) (2017): Performance Standards for Antimicrobial Disk Susceptibility Tests. 12th Edition, Clinical and Laboratory Standards Institute, Wayne, PA.

[132] Kuchibiro, T.; Komatsu, M.; Yamasaki, K.; Nakamura, T.; Nishio, H.; Nishi, I.; Kimura, K.; Niki, M.; Ono, T.; Sueyoshi, N.; Kita, M.; Kida, K.; Ohama, M.; Satoh, K.; Toda, H.; Mizutani, T.; Fukuda, N.; Sawa, K.; Nakai, I.; Kofuku, T. and Wada, Y. (2018): Evaluation of the modified carbapenem inactivation method for the detection of carbapenemase-producing Enterobacteriaceae. J. Infect. Chemother. 24, 262–266.

[133] Bernabeu, S.; Poirel, L. and Nordmann, P. (2012): Spectrophotometry-based detection of carbapenemase producers among Enterobacteriaceae. Diagn.Microbiol. Infect. Dis. 74, 88–90.

[134] Takeuchi, D.; Akeda, Y.; Sugawara, Y.; Sakamoto, N.; Yamamoto, N.; Shanmugakani, R.K.; Ishihara, T.; Shintani, A.; Tomono, K. and Hamada, S. (2018): Establishment of a dual-wavelength spectrophotometric method for analysing and detecting carbapenemase producing Enterobacteriaceae. Sci. Rep. 8:15689.

[135] Hrabák, J.; Walková, R.; Studentová, V.; Chudácková, E. and Bergerová, T. (2011): Carbapenemase activity detection by matrix-assisted laser desorption ionization-time of flight mass spectrometry. J. Clin. Microbiol. 49, 3222–3227.

[136] Johansson, Å.; Nagy, E. and Sóki, J. (2014): Instant screening and verification of carbapenemase activity in Bacteroides fragilis in positive blood culture, using matrix-assisted laser desorption ionization–time of flight mass spectrometry. J. Med. Microbiol. 63, 1105–1110.

[137] Knox, J.; Jadhav, S.; Sevior, D.; Agyekum, A.; Whipp, M.; Waring, L.; Iredell, J. and Palombo, E. (2014): Phenotypic detection of carbapenemase-producing Enterobacteriaceae by use of matrix-assisted laser desorption ionization-time of flight mass spectrometry and the Carba NP test. J. Clin. Microbiol. 52, 4075–4077.

[138] Sauget, M.; Cabrolier, N.; Manzoni, M.; Bertrand, X. and Hocquet, D. (2014). Rapid, sensitive and specific detection of OXA-48-like-producing Enterobacteriaceae by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. J. Microbiol. Methods 105, 88–91.

[139] Lasserre, C.; De Saint Martin, L.; Cuzon, G.; Bogaerts, P.; Lamar, E.; Glupczynski, Y.; Naas, T. and Tandé, D. (2015): Efficient detection of carbapenemase activity in Enterobacteriaceae by matrix-assisted laser desorption ionization-time of flight mass spectrometry in Less Than 30 Minutes. J. Clin. Microbiol. 53, 2163–2171.

[140] Papagiannitsis, C.C.; Študentová, V.; Izdebski, R.; Oikonomou, O.; Pfeifer, Y.; Petinaki, E. and Hrabák, J. (2015): Matrix-assisted laser desorption ionization-time of flight mass spectrometry meropenem hydrolysis assay with NH4HCO3, a reliable tool for direct detection of carbapenemase activity. J. Clin. Microbiol. 53, 1731–1735.

[141] Yu, J.; Liu, J.; Li, Y.; Yu, J.; Zhu, W.; Liu, Y. and Shen, L. (2018a): Rapid detection of carbapenemase activity of Enterobacteriaceae isolated from positive blood cultures by MALDI-TOF MS. Ann. Clin. Microbiol. Antimicrob. 17:22.

[142] Tsakris, A.; Poulou, A.; Pournaras, S.; Voulgari, E.; Vrioni, G.; Themeli-Digalaki, K.; Petropoulou, D. and Sofianou, D. (2010): A simple phenotypic method for the differentiation of metallo-β-lactamases and class A KPC carbapenemases in Enterobacteriaceae clinical isolates. J. Antimicrob. Chemother. 65, 1664–1671.

[143] Franklin, C.; Liolios, L. and Peleg, A.Y. (2006): Phenotypic detection of carbapenem-susceptible metallo-β-lactamase-producing Gram-negative bacilli in the clinical laboratory. J. Clin. Microbiol. 44, 3139–3144.

[144] Doi, Y.; Potoski, B.A.; Adams-Haduch, J.M.; Sidjabat, H.E.; Pasculle, A.W. and Paterson, D.L. (2008): Simple diskbased method for detection of Klebsiella pneumoniae carbapenemase-type β-lactamase by use of a boronic acid compound. J. Clin. Microbiol. 46, 4083–4086.

[145] Glupczynski, Y.; Evrard, S.; Ote, I.; Mertens, P.; Huang, T.D.; Leclipteux, T. and Bogaerts, P. (2016): Evaluation of two new commercial immunochromatographic assays for the rapid detection of OXA-48 and KPC carbapenemases from cultured bacteria. J. Antimicrob. Chemother. 71, 1217–1222.

[146] Van Almsick, V.; Ghebremedhin, B.; Pfennigwerth, N. and Ahmad-Nejad, P. (2018): Rapid detection of carbapenemase-producing Acinetobacter baumannii and carbapenem-resistant Enterobacteriaceae using a bioluminescence-based phenotypic method. J. Microbiol. Methods. 147, 20–25.

[147] Ellington, M.J.; Findlay, J.; Hopkins, K.L.; Meunier, D.; Alvarez-Buylla, A.; Horner, C.; McEwan, A.; Guiver, M.; McCrae, L.X.; Woodford, N. and Hawkey, P. (2016): Multicentre evaluation of a real-time PCR assay to detect genes encoding clinically relevant carbapenemases in cultured bacteria. Int. J. Antimicrob. Agents, 47, 151–154.

[148] Swayne, R.L., Ludlam, H.A.; Shet, V.G.; Woodford, N. and Curran, M.D. (2011): Real-time TaqMan PCR for rapid detection of genes encoding five types of non-metallo- (class A and D) carbapenemases in Enterobacteriaceae. Int. J. Antimicrob. Agents, 38, 35–38.

[149] Mendes, R.E.; Kiyota, K.A.; Monteiro, J.; Castanheira, M.; Andrade, S.S.; Gales, A.C.; Pignatari, A.C. and Tufik, S. (2007): Rapid detection and identification of metallo betalactamase-encoding genes by multiplex real-time PCR assay and melt curve analysis. J. Clin. Microbiol. 45, 544–547.

[150] Monteiro, J.; Widen, R.H.; Pignatari, A.C.; Kubasek, C. and Silbert, S. (2012): Rapid detection of carbapenemase genes by multiplex real-time PCR. J. Antimicrob. Chemother. 67, 906–909.

[151] Hemarajata, P.; Yang, S.; Hindler, J.A. and Humphries, R.M. (2015): Development of a novel real-time PCR assay with high-resolution melt analysis to detect and differentiate OXA-48-Like b-lactamases in carbapenem-resistant Enterobacteriaceae. Antimicrob. Agents Chemother. 59, 5574–5580.

[152] Jeong, S.; Kim, J.O.; Jeong, S.H.; Bae, I.K. and Song, W. (2015): Evaluation of peptide nucleic acid-mediated multiplex real-time PCR kits for rapid detection of carbapenemase genes in Gram-negative clinical isolates. J.Microbiol. Methods, 113, 4–9.

[153] Walker, G.T.; Rockweiler, T.J.; Kersey, R.K.; Frye, K.L.; Mitchner, S.R.; Toal, D.R. and Quan, J. (2016): Analytical performance of multiplexed screening test for 10 antibiotic resistance genes from perianal swab samples. Clin. Chem. 62, 353–359.

[154] Tato, M.; Ruiz-Garbajosa, P.; Traczewski, M.; Dodgson, A.; McEwan, A.; Humphries, R.; Hindler, J.; Veltman, J.; Wang, H. and Cantón, R. (2016): Multisite evaluation of cepheid Xpert Carba-R Assay for detection of carbapenemase-producing organisms in rectal swabs. J. Clin. Microbiol. 54, 1814–1819.

[155] Srisrattakarn, A.; Lulitanond, A.; Wilailuckana, C.; Charoensri, N.; Wonglakorn, L.; Saenjamla, P.; Chaimanee, P.; Daduang, J. and Chanawong, A. (2017): Rapid and simple identification of carbapenemase genes, blaNDM, blaOXA-48, blaVIM, blaIMP-14 and blaKPC groups, in Gram-negative bacilli by in-house loop-mediated isothermal amplification with hydroxynaphthol blue dye. World J. Microbiol. Biotechnol. 33:130.

[156] Kim, S.; De Jonghe, J.; Kulesa, A.B.; Feldman, D.; Vatanen, T.; Bhattacharyya, R. P.; Berdy, B.; Gomez, J.; Nolan, J.; Epstein, S. and Blainey, P.C. (2017): High-throughput automated microfluidic sample preparation for accurate microbial genomics. Nat. Commun. 8:13919.

[157] Ledeboer, N.A.; Lopansri, B.K.; Dhiman, N.; Cavagnolo, R.; Carroll, K.C.; Granato, P.; Thomson, R.; Jr, Butler-Wu, S.M.; Berger, H.; Samuel, L.; Pancholi, P.; Swyers, L.; Hansen, G.T.; Tran, N.K.; Polage, C.R.; Thomson, K.S.; Hanson, N.D.; Winegar, R. and Buchan, B.W. (2015): Identification of Gram-negative bacteria and genetic resistance determinants from positive blood culture broths by use of the Verigene Gram-negative blood culture multiplex microarray-based molecular assay. J. Clin. Microbiol. 53, 2460–2472.

[158] Hill, J.T.; Tran, K.D.; Barton, K.L.; Labreche, M.J. and Sharp, S.E. (2014): Evaluation of the nanosphere Verigene BCGN assay for direct identification of Gram-negative bacilli and antibiotic resistance markers from positive blood cultures and potential impact for more-rapid antibiotic interventions. J. Clin. Microbiol. 52, 3805–3807.

[159] Patel, R. (2016): New developments in clinical bacteriology laboratories. Mayo. Clin. Proc. 91, 1448–1459.

[160] Yu, F.; Lv, J.; Niu, S.; Du, H.; Tang, Y.W.; Pitout, J.D.D.; Bonomo, R.A.; Kreiswirth, B.N. and Chen, L. (2018b): Multiplex PCR analysis for rapid detection of Klebsiella pneumoniae carbapenem-resistant (Sequence Type 258 [ST258] and ST11) and Hypervirulent (ST23, ST65, ST86, and ST375) Strains. J. Clin. Microbiol. 56: e0731-18.

[161] Naseri, M.; Ziora, Z.M.; Simon, G.P. and Batchelor, W. (2021): ASSURED-compliant Point-of-care Diagnostics for the Detection of Human Viral Infections. Rev. Med. Virol. 32, e2263.

[162] Land, K.J.; Boeras, D.I.; Chen, X.-S.; Ramsay, A.R. and Peeling, R.W. (2019): REASSURED Diagnostics to Inform Disease Control Strategies, Strengthen Health Systems and Improve Patient Outcomes. Nat. Microbiol. 4, 46–54.

[163] Tuena, C.; Semonella, M.; Fernández-Álvarez, J.; Colombo, D. and Cipresso, P. (2020): Predictive Precision Medicine: Towards the Computational Challenge. In P5 eHealth: An Agenda for the Health Technologies of the Future; Pravettoni, G., Triberti, S., Eds.; Springer International Publishing: Cham, Switzerland, pp. 71–86. ISBN 978-3-030-27993-6.

[164] Han, R.; Guo, Y.; Peng, M.; Shi, Q.; Wu, S.; Yang, Y.; Zheng, Y.; Yin, D. and Hu, F. (2021): Evaluation of the Immunochromatographic NG-Test Carba 5, RESIST-5 O.O.K.N.V., and IMP K-SeT for Rapid Detection of KPC-,

NDM-, IMP-, VIM-type, and OXA-48-like Carbapenemase Among Enterobacterales. Front. Microbiol. 11:609856.

[165] Cui, X.; Zhang, H. and Du, H. (2019): Carbapenemases in Enterobacteriaceae: Detection and Antimicrobial Therapy. Front. Microbiol. 10:1823

[166] Boutal, H.; Moguet, C.; Pommiès, L.; Simon, S.; Naas, T. and Volland, H. (2022): The Revolution of Lateral Flow Assay in the Field of AMR Detection. Diagnostics 12, 1744.

[167] Gupta, K. and Bhadelia, N. (2014): Management of urinary tract infections from multidrug-resistant organisms. Infect. Dis. Clin. North Am. 28, 49–59.

[168] Alizadeh, N.; Rezaee, M.A.; Kafil, H.S.; Barhaghi, M.H.S.; Memar, M.Y.; Milani, M.; Hasani, A. and Ghotaslou, R. (2018): Detection of carbapenem-resistant Enterobacteriaceae by chromogenic screening media. J. Microbiol. Methods, 153, 40–44.

[169] Morrill, H.J.; Pogue, J.M.; Kaye, K.S. and LaPlante, K.L. (2015): Treatment options for carbapenem-resistant Enterobacteriaceae infections. Open Forum Infect. Dis. 2, ofv050.

[170] Peri, A.M.; Doi, Y.; Potoski, B.A.; Harris, P.N.A.; Paterson, D.L. and Righi, E. (2019): Antimicrobial treatment challenges in the era of carbapenem resistance. Diagn. Microbiol. Infect. Dis. 94, 413–425.

[171] Giamarellou, H.; Galani, L.; Baziaka, F. and Karaiskos, I. (2013): Effectiveness of a double-carbapenem regimen for infections in humans due to carbapenemase-producing pandrug-resistant Klebsiella pneumoniae. Antimicrob. Agents Chemother. 57, 2388–2390.

[172] Ceccarelli, G.; Falcone, M.; Giordano, A.; Mezzatesta, M.L.; Caio, C.; Stefani, S. and Venditti, M. (2013): Successful ertapenem–doripenem combination treatment of bacteremic ventilator-associated pneumonia due to colistin-resistant KPC-producing Klebsiella pneumoniae. Antimicrob. Agents Chemother. 57, 2900–2901.

[173] Paul, M.; Daikos, G.L.; Durante-Mangoni, E.; Yahav, D.; Carmeli, Y.; Benattar, Y.D.; Skiada, A.; Andini, R.; Eliakim-Raz, N.; Nutman, A.; Zusman, O.; Antoniadou, A.; Pafundi, P.C.; Adler, A.; Dickstein, Y.; Pavleas, I.; Zampino, R.; Daitch, V.; Bitterman, R.; Zayyad, H. and Leibovici, L. (2018): Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. Lancet Infect. Dis. 18, 391–400.

[174] Falagas, M.E.; Rafailidis, P.I.; Kasiakou, S.K.; Hatzopoulou, P. and Michalopoulos, A. (2006): Effectiveness and nephrotoxicity of colistin monotherapy vs colistin–meropenem combination therapy for multidrug-resistant Gram-negative bacterial infections. Clin. Microbiol. Infect. 12, 1227–1230.

[175] Lagerb¨ack, P.; Khine, W.W.T.; Giske, C.G. and T¨angd´en, T. (2016): Evaluation of antibacterial activities of colistin, rifampicin and meropenem combinations against NDM-1-producing Klebsiella pneumoniae in 24 h in vitro time–kill experiments. J. Antimicrob. Chemother. 71, 2321–2325.

[176] Song, J.Y.; Kee, S.Y.; Hwang, I.S.; Seo, Y.B.; Jeong, H.W.; Kim, W.J. and Cheong, H.J. (2007): In vitro activities of carbapenem/sulbactam combination, colistin, colistin/rifampicin combination and tigecycline against carbapenem-resistant Acinetobacter baumannii. J. Antimicrob. Chemother. 60, 317–322.

[177] Deris, Z.Z.; Yu, H.H.; Davis, K.; Soon, R.L.; Jacob, J.; Ku, C.K.; Poudyal, A.; Bergen, P.J.; Tsuji, B.T.; Bulitta, J.B.; Forrest, A.; Paterson, D.L.; Velkov, T.; Li, J. and Nation, R.L. (2012): The combination of colistin and doripenem is synergistic against Klebsiella pneumoniae at multiple inocula and suppresses colistin resistance in an In Vitro Pharmacokinetic/Pharmacodynamic Model. Antimicrob. Agents Chemother. 56, 5103–5112.

[178] Yadav, R.; Landersdorfer, C.B.; Nation, R.L.; Boyce, J.D. and Bulitta, J.B. (2015); Novel approach to optimize synergistic carbapenem-aminoglycoside combinations against carbapenem-resistant Acinetobacter baumannii. Antimicrob. Agents Chemother. 59, 2286–2298.

[179] Rodr´ıguez-Avial, I.; Pena, I.; Picazo, J.J.; Rodr´ıguez-Avial, C. and Culebras, E. (2015): In vitro activity of the next-generation aminoglycoside plazomicin alone and in combination with colistin, meropenem, fosfomycin or tigecycline against carbapenemase-producing Enterobacteriaceae strains. Int. J. Antimicrob. Agents, 46, 616–621.

[180] Toussaint, K.A. and Gallagher, J.C. (2015). B-lactam/β-lactamase inhibitor combinations: from then to now. Ann. Pharmacother. 49, 86–98.

[181] Gibson, B. (2019): A brief review of a new antibiotic: meropenem-vaborbactam. Sr. Care Pharm. 34, 187–191.

[182] Smibert, O.; Satlin, M.J.; Nellore, A. and Peleg, A.Y. (2019): Carbapenem-resistant Enterobacteriaceae in solid organ transplantation: management principles. Curr. Infect. Dis. Rep. 21, 26–37.

[183] Falagas, M. E.; Skalidis, T.; Vardakas, K. Z.; Legakis, N. J. and Hellenic Cefiderocol Study Group (2017): Activity of cefiderocol (S-649266) against carbapenem-resistant Gram-negative bacteria collected from inpatients in Greek hospitals. J. Antimicrob. Chemother. 72, 1704–1708.

[184] Kohira, N.; West, J.; Ito, A.; Ito-Horiyama, T.; Nakamura, R.; Sato, T.; Rittenhouse, S.; Tsuji, M. and Yamano, Y. (2015): In vitro antimicrobial activity of a siderophore cephalosporin, S-649266, against Enterobacteriaceae clinical isolates, including carbapenem-resistant strains. Antimicrob. Agents Chemother. 60, 729–734.

[185] Ito-Horiyama, T.; Ishii, Y.; Ito, A.; Sato, T.; Nakamura, R.; Fukuhara, N.; Tsuji, M.; Yamano, Y.; Yamaguchi, K. and Tateda, K. (2016): Stability of Novel Siderophore Cephalosporin S-649266 against Clinically Relevant Carbapenemases. Antimicrob. Agents Chemother. 60, 4384–4386.

[186] Bassetti, M. and Righi, E. (2014): Eravacycline for the treatment of intra-abdominal infections. Expert Opin. Investig. Drugs, 23, 1575–1584.

[187] McEwen, S. A. and Collignon, P. J. (2018): Antimicrobial Resistance: a One Health Perspective. Microbiology spectrum, 6,10.1128.

[188] One Health High-Level Expert Panel (OHHLEP), Adisasmito, W. B.; Almuhairi, S.; Behravesh, C. B.; Bilivogui, P.; Bukachi, S. A.; Casas, N.; Cediel Becerra, N.; Charron, D. F.; Chaudhary, A.; Ciacci Zanella, J. R.; Cunningham, A. A.; Dar, O.; Debnath, N.; Dungu, B.; Farag, E.; Gao, G. F.; Hayman, D. T. S.; Khaitsa, M.; Koopmans, M. P. G. and Zhou, L. (2022): One Health: A new definition for a sustainable and healthy future. PLoS pathogens, 18, e1010537.

[189] Das, S. (2023): The crisis of carbapenemase-mediated carbapenem

resistance across the human-animal-environmental interface in India. Infect Dis Now. 53:104628.

[190] Velazquez-Meza, M.E.; Galarde-López, M.; Carrillo-Quiróz, B. and Alpuche-Aranda, CM. (2022): Antimicrobial resistance: One Health approach. Vet. World, 15:743– 9.

[191] Shein, A. M. S.; Wannigama, D. L.; Higgins, P. G.; Hurst, C.; Abe, S.; Hongsing, P.; Chantaravisoot, N.; Saethang, T.; Luk-In, S.; Liao, T.; Nilgate, S.; Rirerm, U.; Kueakulpattana, N.; Srisakul, S.; Aryukarn, A.; Laowansiri, M.; Hao, L. Y.; Yonpiam, M.; Ragupathi, N. K. D.; Techawiwattanaboon, T. and Chatsuwan, T. (2022): High prevalence of mgrB-mediated colistin resistance among carbapenemresistant Klebsiella pneumoniae is associated with biofilm formation, and can be overcome by colistin-EDTA combination therapy. Sci Rep. 12:12939.

[192] Ferri, M.; Ranucci, E.; Romagnoli, P. and Giaccone, V. (2017): Antimicrobial resistance: a global emerging threat to public health systems. Crit Rev Food Sci Nutr. 57:2857–76.

الملخص العربي

مخاطر الصحة العامة للبكتيريا المعوية المقاومة للكاربابينيم من الحيوانات: مراجعة تحديد النطاق

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تسبب مقاومة الأدوية المتعددة (MDR) للبكتيريا سالبة الجرام مخاطر صحية خطيرة في جميع أنحاء العالم. إن التواتر المتزايد للكائنات المنتجة للكاربابينيماز (CPOs) يثير القلق بشكل خاص ، نظرا لانتشارها السريع للمكونات الجينية القابلة للانتقال التي تحتوي على جينات الكاربابينماز ، ونقص بدائل العلاج للعدوى المرتبطة ب CPO ، وحالات الوفيات الكبيرة المرتبطة بهذه العدوى. إن تحديد ما ينتجه الكائن الحي من الكاربابينيماز ، وما إذا كان الأمر كذلك ، فإن ترتيب (رتبة) الكاربابينيماز المعينة المرتبطة به له تأثيرات علاجية أساسية لأن الأدوية المختلفة لها أنشطة مختلفة ضد الكاربابينيمازات المختلفة. بالإضافة إلى ذلك ، تنتشر CPOs بسرعة أكبر داخل المرضى من مسببات الأمراض غير المقاومة للكاربابينيم CP ، مما يتطلب استراتيجيات وقائية أكثر صرامة من تلك المستخدمة في دون وجود الكاربابينيمات. يتم تفاعل الانسان والحيوانات الأليفة كثيرًا ، مما يوفر عوامل مثالية لانتشار البكتيريا المعوية المنتجة للكاربابينيماز بما فى ذلك Klebsiella pneumoniae, Klebsiella oxytoca, Escherichia coli Enterobacter cloacae, Enterobacter xiangfangensis, and Salmonella enterica serovar Typhimurium. كما تم الإبلاغ عن وجود Pseudomonas aeruginosa و Acinetobacter baumannii المنتجة للكاربابينيماز في الحيوانات. تعتمد الممارسة السريرية الحالية على ثلاثة مقايسات نمطية مظهرية رئيسية للكشف عن CPOs: (i) المقايسات القائمة على النمو التي تقيس مقاومة الكاربابينيم بناء على نمو الكائن الحي في وجود مضاد حيوي للكاربابينيم (على سبيل المثال ، اختبار Hodge المعدل وطريقة تعطيل الكاربابينيم المعدلة) ، (ii) طرق التحلل المائي التي تكشف عن منتجات تحلل الكاربابينيم [على سبيل المثال ، اختبار Carba NP و MALDI-TOF MS]، و (ج) المقايسات المناعية للتدفق الجانبي التي تكشف عن إنزيمات الكاربابينماز باستخدام أجسام مضادة محددة. على الرغم من عدم وجود اختبار واحد يناسب جميع متطلبات الاختبار الأمثل ، كما هو موضح في هذه النظرة العامة ، إلا أن هناك العديد من الخيارات سهلة الاستخدام وفعالة من حيث التكلفة ودقيقة وعملية للاستخدام في مختبرات علم الأحياء الدقيقة السريرية ذات الأحجام المختلفة.