Carbapenemase-producing bacteria in food-producing animals, wildlife and environment: A challenge for human health

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Abstract

Antimicrobial resistance is an increasing global health problem and one of the major concerns for economic impacts worldwide. Recently, resistance against carbapenems (doripenem, ertapenem, imipenem, meropenem), which are critically important antimicrobials for human cares, poses a great risk all over the world. Carbapenemases are β-lactamases belonging to different Ambler classes (A, B, D) and encoded by both chromosomal and plasmidic genes. They hydrolyze a broad variety of β-lactams, including carbapenems, cephalosporins, penicillins and aztreonam. Despite several studies in human patients and hospital settings have been performed in European countries, the role of livestock animals, wild animals and the terrestrial and aquatic environment in the maintenance and transmission of carbapenemase-producing bacteria has been poorly investigated. The present review focuses on the carbapenemase-producing bacteria detected in pigs, cattle, poultry, fish, mollusks, wild birds and wild mammals in Europe as well as in non-European countries, investigating the genetic mechanisms for their transmission among food-producing animals and wildlife. To shed light on the important role of the environment in the maintenance and genetic exchange of resistance determinants between environmental and pathogenic bacteria, studies on aquatic sources (rivers, lakes, as well as wastewater treatment plants) are described.

Introduction

The resistance against carbapenems is of great public concern, because they are among the most critically important antimicrobials for human treatments (WHO, 2017). In fact, these antimicrobials have the broadest spectrum of activity *in vitro* against Gram-positive and Gram-negative bacteria, including anaerobes (Zhanel *et al*., 2007). Hence, they are often used as "last-line agents" or "antibiotics of last resort" to treat infections caused by multidrug-resistant Gram-negative bacteria (GNB) (Zhanel *et al*., 2007; Nordmann *et al*., 2011; Patel and Bonomo, 2013). In order to preserve their efficacy, the use in animal species should be banned (WHO, 2015). Carbapenems (biapenem, doripenem, ertapenem, faropenem, imipenem, meropenem, panipenem) are potent members of the β-lactam family and occupy a unique position among β-lactams because they are resistant to most β-lactamases from Gram-positive and Gram-negative bacteria. In fact, even if carbapenems share a penicillin-like ring with penicillins and cephalosporins, they possess a carbon instead of a sulfone in the fourth position of the thyazolidinic mojety of the β-lactam ring (Kattan et al., 2008). Carbapenems are very efficient to treat a wide variety of infections such as complicated intra-abdominal infections, skin and skin structure infections, community-acquired and nosocomial pneumonia, complicated urinary tract infections, meningitis (meropenem only) and febrile pneumonia (Janssen *et al.,* 2015). Furthermore, the use of carbapenems is rising in humans in response to the increase of Extended-Spectrum Beta-Lactamase (ESBL)-producers and other multiresistant bacteria (Ashiru-Oredope *et al.,* 2012). All clinically available carbapenems have low oral bioavailability because they do not cross the gastrointestinal barrier readily and must be administered intravenously; however, the combination imipenem-cilastatin and ertapenem can also be delivered intramuscularly (Papp-Wallace *et al*., 2011). Since the use of carbapenems has never been licensed for food-producing animals in any country worldwide (WHO, 2015), their residues in foods of animal origin are not actually allowed. Among microorganisms involved in the antimicrobial resistance (AMR) phenomenon, GNB are becoming increasingly resistant to most antibiotics (Blair *et al*., 2014). Specifically, this trend is highlighted in Enterobacteriaceae, whose members are often involved into a wide variety of community and health-care infections (Grundmann *et al*., 2010; Nordmann *et al*., 2011; Albiger *et al*., 2015; Grundmann *et al*., 2017; Magiorakos *et al.,* 2017). However, during the last years, several studies have shown the worldwide increase, in terms of prevalence, of carbapenem resistance in non-fermenting microorganisms, such as *Pseudomonas* spp. and *Acinetobacter* spp. (Miriagou *et al*., 2010; Pfeifer *et al*., 2010; Papp-Wallace *et al*., 2011; EFSA, 2013).

The main mechanism of resistance to β-lactams among GNB is due to the presence of β-lactamases. Among over 1,000 of naturally occurring β-lactamases, carbapenemases with either serine-based or zinc-facilitated hydrolysis mechanisms are posing some of the most critical problems (Bush and Fisher, 2011). Among GNB, Carbapenem-Producing Enterobacteriaceae (CPE) are arising as an important challenge in health-care settings all over the world (Bush and Fisher, 2011; Nordmann *et al*., 2011) especially because they can acquire resistance by horizontal transfer of genes carried by mobile genetic elements (Woodford *et al*., 2014).

As well-known, the use of antimicrobials leads to a selective pressure for resistant strains both in humans and animals (Woodford *et al*., 2014). For instance, the detection of carbapenem-resistant bacteria in food-producing animals may be due to the use of extended-spectrum cephalosporins on farm. The exact relationship between extended-spectrum cephalosporin use and carbapenem-resistance has not fully been established (Mollenkopf *et al*., 2017), even if plasmids carrying genes conferring both resistance to carbapenems (bla_{VIM-1}) and third-generation cephalosporins (bla_{ACC-1}) have been recently found in bacteria isolated from livestock (Falgenhauer *et al.,* 2017). This finding needs further studies, since administration of these drugs is commonly reported when carbapenem-resistance microorganisms are found in

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food-producing animals. This short review is focused on the occurrence of carbapenemase-producing (CP) bacteria in food-producing animals, natural environment and wildlife and its major goal is to trace their spreading and evolution out of the human compartment. Only studies which demonstrated the occurrence of CP bacteria out of the human compartment are described. Even if data from food-producing animals and environmental sources are fragmentary and often their epidemiological links seem to be not clear, our efforts aimed to select the studies which clearly described *i)* the analytical methods used; *ii)* the genetic determinants for carbapenem-resistance; *iii)* the possible links between use of antimicrobials in livestock and selection of CP bacteria. When available, data on co-resistance to other antimicrobials and their genetic mechanisms of transmission are reported.

Materials and Methods

A systematic review of 308 studies published in the PubMed database between 1980 and 2018 was performed, with special interest for those reporting the detection of CP bacteria in food-producing animals, wildlife and the environment. We included three types of articles: *i*) the articles describing carbapenem-resistant bacteria isolated from livestock (pigs, cattle, poultry) and products thereof, included fish and molluscs, the natural environment and wild animals; *ii*) the articles describing the different classes and variants of carbapenemases shared by bacteria of human and animal origin; *iii*) the articles describing the genomic traits of CP microorganisms isolated from livestock, wild animals and the environment. Studies primarily focused on laboratory methods for detection of CP bacteria were excluded, as well as those regarding carbapenem-resistant bacteria from companion animals (dogs and horses) or insects (flies).

Among the articles found by the entry criteria, only those showing data on CP bacteria and bacterial carriage of carbapenemase genes were included in the review, thus excluding all studies focused on bacterial resistance to carbapenems not based on carbapenemases production.

Development of carbapenem-resistance

Bacteria show resistance to carbapenems through several mechanisms: production of β-lactamases (carbapenemases), efflux pumps and mutations that alter the expression and/or function of porins and penicillin-binding proteins (PBPs). CP microorganisms are usually only susceptible to polymyxins (e.g. colistin), fosfomycin and variably susceptible to tigecycline, although colistin resistance in CP *Klebsiella pneumoniae* isolates has been recently reported (Nordmann *et al*., 2009; Pena *et al*., 2014; Otter *et al*., 2017).

Still other mechanisms can be active, the production of specific β-lactamases, called carbapenemases, is the most important to confer resistance against carbapenems. In fact, carbapenemases are able to hydrolyze carbapenems efficiently, while most other β-lactamases hydrolyze them very slowly (Temkin *et al*., 2014). Furthermore, carbapenemases hydrolyze a broad variety of β-lactams, including cephalosporins, penicillins and aztreonam and are inhibited by the β-lactamase inhibitors, such as clavulanic acid, tazobactam and sulbactam (Drawz and Bonomo, 2010).

Carbapenemases have been classified in three classes: the Ambler class A, B and D β-lactamases (Ambler, 1980). Ambler class C β-lactamases, on the contrary, possess a slightly extended activity towards carbapenems, but primarily hydrolyze cephalosporines (AmpC) (Jaurin and Grundstrom, 1981). Based on their hydrolytic activity, carbapenemases are divided into two groups: *i)* serine carbapenemases, which utilize the amino acid serine for β-lactam hydrolysis by forming an acyl enzyme (Class A and D); *ii)* metallo carbapenemases, which require at least one active-site zinc ions to facilitate β-lactam hydrolysis (Class B) (Hall and Barlow, 2005).

Class A carbapenemases can be chromosomally encoded, such as NmcA (Non-metallo carbapenemase A), SME (*Serratia marcescens* enzyme), IMI-1 (Imipenem-hydrolyzing β-lactamase), SFC-1 (*Serratia fonticola* carbapenemase), BIC-1 (Bicêtre carbapenemase), PenA (penicillinase from *P. cepacia*), FPH-1 (from *Francisella philomiragia*) and several members of SHV family, or plasmid encoded, such as KPCs (*Klebsiella pneumoniae* carbapenemases), GES (Guiana extended spectrum β-lactamase), IMI-2, and FRI-1 (Aubron *et al*., 2005; Naas *et al*., 2016). Chromosomally mediated AMR is vertically transmitted to daughter cells, and these microorganisms can be clinically relevant if they produce severe infections requiring antimicrobial therapy. However, bacterial β-lactamase genes located on mobile plasmids pose a far greater health threat because they may be transmitted horizontally among commensal bacterial and pathogens, thus potentially disseminating β-lactam resistance to a great variety of bacterial species. For example, in 2001, evidence of horizontal gene transfer (CMY-2 AmpC β-lactamase) was demonstrated in food-producing animal and human isolates of *E. coli* and *Salmonella* resistant to cephamycins and third-generation cephalosporins (Winokur *et al*., 2001). Since then, other studies have observed the transfer of plasmid-mediated carbapenem resistance between different bacterial species (Goren *et al*., 2010; Rumbo *et al*., 2011; Hardiman *et al*., 2016). In addition, evidence for the transfer of CP gene-containing transposons between plasmids has been demonstrated, as the bla_{KPC-2} gene in *K. pneumoniae.* The bla_{KPC-2} gene is located on the Tn-3 related transposon Tn*4401* capable of high frequency of transposition (Nordmann *et al*., 2009; Cuzon *et al*., 2011). The transposon Tn*4401* has been also described in the plasmid pCOL-1 of *P. aeruginosa*, thus suggesting that it could be transferred among different microorganisms (Diene and Rolain, 2014).

KPCs are class A serine β-lactamases that spread primarily *via* the clonal dissemination of *K. pneumoniae* and some KPC-producing clones are dominant, such as the sequence type (ST) 258 (Cuzon *et al*., 2010), ST512 (Warburg *et al*., 2012) and ST11 (Cuzon *et al*., 2010; Baraniak *et al*., 2011). Beside the gene bla_{KPC-2} (Nordmann *et al*., 2009; Cuzon *et al*., 2011), other bla_{KPC} genes are present on a wide variety of plasmids, different for size, structure and nature (Gootz *et al*., 2009; Cuzon *et al*., 2010; Leavitt *et al*., 2010). KPCs comprise 22 variants that differ by one to five amino acid substitutions (Woodford *et al*., 2014). As KPC-1 sequence was found to be identical to KPC-2, KPC-1 is no longer a valid designation (Yigit *et al*., 2008).

Among class B metallo-β-lactamases (MBLs), the New Delhi metallo-β-lactamases (NDMs) and the Verona integron-encoded metallo-β-lactamases (VIMs) are the most common. NDM-producing species comprise *E. coli* (Mushtaq *et al*., 2011; Cuzon *et al*., 2013) and *K. pneumoniae* (Pitout *et al*., 2015) but also *Acinetobacter* spp. (Zhang *et al*., 2014) and *Pseudomonas* spp. (Walsh *et al*., 2011). Dissemination of bla_{NDM-1} occurs both by horizontal and vertical transfer, since the coding sequence may be found on different plasmids or located on the chromosome (Poirel *et al.,* 2011). To date, different variants of the NDM β-lactamases (NDM-1 to 7) have been identified in the Indian subcontinent (Rahman *et al*., 2014). VIM is an important MBL spread both in Enterobacteriaceae and non-fermenting bacteria. After the initial discovery of bla_{VIM-1} in a clinical isolate of *P. aerugi-*

nosa in Italy during 1997 (Lauretti *et al*., 1999), several variants have been reported in different species worldwide (Nordmann *et al*., 2011). The bla_{VIM-1} group is detected mainly in Enterobacteriaceae, while the bla_{VIM-2} group is found mainly in *Acinetobacter* and *Pseudomonas* species (Lee *et al*., 2003; Carattoli, 2009; Pena *et al*., 2014; Govender *et al*., 2015). Since the bla_{VIM} genes are often located within class 1 integrons that reside on broad-host range plasmids, they can be easily transferred between bacteria and contribute to the inter-species distribution of VIM-producing genes (Temkin *et al*., 2014; Mathers *et al*., 2015). Another important metallo-β-lactamase is IMP, which it is hardly blocked by β-lactamase inhibitors such as clavulanate, sulbactam and tazobactam (Ohsuka *et al*., 1995). As a consequence, strains producing IMP carbapenemase are difficult to control with β-lactams in combination with β-lactamase inhibitors (Senda *et al*., 1996), as amoxicillin-clavulanic acid combination. A total of 55 variants of the bla_{IMP} gene have been described (Shakibaie *et al*., 2017) carried by both Enterobacteriaceae and non-fermenting *Acinetobacter* and *Pseudomonas* species (Osano *et al*., 1994; Chu *et al*., 2001; Sidjabat *et al.,* 2015). The bla_{IMP} genes are located in class 1 integrons carried by plasmids and can spread horizontally among different species (Sidjabat *et al*., 2015).

To class D carbapenemases belongs the OXA type family which is composed by more than 400 enzymes classified in 12 subgroups, namely the OXA-23, OXA-24/40, OXA-48, OXA-51, OXA-58, OXA-134a, OXA-143, OXA-211, OXA-213, OXA-214, OXA-229, and OXA-235 (Evans and Amyes, 2014). The OXA-48 enzyme is a serine class D type- β-lactamase with high activity against penicillins but weak activity against expanded-spectrum cephalosporins and carbapenems (Walther-Rasmussen and Hoiby, 2006). It represents the most commonly detected carbapenemase around the world (Nordmann *et al*., 2011) and OXA-48 producing strains commonly carry ESBL genes which confer also resistance to expanded-spectrum cephalosporins (Temkin *et al*., 2014). The bla_{OXA-48} gene can be transferred by plasmids, transposon (Tn*1999*) or clonally (Carrër *et al*., 2010; Temkin *et al*., 2014), whereas its variant $bla_{OXA-181}$ is located on transposon Tn*2013* (Potron *et al*., 2011). Other OXA-type enzymes may be found in *Acinetobacter baumannii* (Higgins *et al*., 2013) and other non-fermentative rods, as *Pseudomonas aeruginosa* (Pfeifer *et al*., 2010).

Epidemiology of carbapenem-resistance among bacteria

Across the globe, first reports of carbapenemases occurred in the 1980s. For over 20 years there were no significant reports with an exception represented by a limited spread of IMP metallo-β-lactamase in *Aeromonas hydrophila* in Japan (Senda *et al*., 1996; Temkin *et al.,* 2014;). Afterwards, other cases were reported in London (1982) by Seoul imipenemase (SME-1) from *Serratia marcescens* (Yang *et al.,* 1990), in California (1984) by imipenemase (IMI-1) from *Enterobacter cloacae* (Rasmussen *et al.,* 1996) and in France (1990) by NMC-A from *Enterobacter cloacae* (Nordmann *et al.,* 1993).

The most frequently carbapenemases associated with Enterobacteriaceae worldwide are those belonging to the KPC family (Woodford *et al.,* 2011; Rimoldi et *al.,* 2017; van Duin and Doi, 2017; Kim *et al.,* 2018; Muggeo *et al.,* 2018). In 2017, among the European Union (EU) and European Economic Area (EEA) countries, the highest detection rates for KPC-producing *Klebsiella pneumoniae* human invasive isolates were reported from Greece (64.7%), Italy (29.7%) and Romania (22.5%), where the resistance situation for carbapenems remains problematic. On the contrary, very low to low prevalence (0.1-1.7%) were generally notified from northern and western European countries. Overall, the EU/EEA population weighted mean percentage for *K. pneumoniae* was 7.2% in 2017 (ECDC, 2018). Since resistance to carbapenems in *K. pneumoniae* is mediated by a wide range of carbapenemases, such as KPC, NDM, OXA-48-like and VIM, although with wide variation in prevalence (Grundmann *et al.,* 2017), CP *K. pneumoniae* strains may show resistance to all available β-lactams. Additionally, high percentage of isolates have co-resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides (ECDC, 2018).

Carbapenem-resistance among human invasive *Escherichia coli* strains was still reported to be rare in all EU/EEA countries, with a population weighted mean percentage of 0.1% in 2017 (ECDC, 2018). Carbapenem-resistance combined with resistance to other important antimicrobial groups was commonly reported in *P. aeruginosa* in many EU/EEA countries in 2017, with a weighted mean of 17.4% (ECDC, 2018). Unlike other bacteria, carbapenem-resistance in *P. aeruginosa* is multifactorial, due to plasmid or integron-coded carbapenemases, increased expression of efflux systems, reduced porin expression and increased chromosomal cephalosporinase activity (Meletis *et al.,* 2012). Regarding *Acinetobacter baumanni*, the epidemiological situation for carbapenem-resistance strains has been worsening in several European countries. Like *K. pneumoniae* and *E. coli*, carbapenem-resistance in *A. baumannii* is often mediated by carbapenemases production. In 2017, several European countries reported high percentages of resistance against carbapenems in *Acinetobacter* spp., which ranged from 0.0% in some northern countries (Denmark, Norway and Sweden) to 96.2% (Croatia). southern and eastern countries, like Italy, Latvia, Bulgaria, Romania, Lithuania and Greece reported prevalence values of 78.7%, 79.4%, 80.4%, 87.4%, 88.5% and 94.8%, respectively (ECDC, 2018).

The so called 'big five' carbapenemase families collectively cause the greatest clinical concern. They include the KPC and OXA-48-like non-metallo-enzymes and the IMP, NDM and VIM metallo-enzymes (Nordmann *et al.,* 2011; Patel and Bonomo 2013). There are significant country and regional differences in the importance of these families. In Europe, the KPC, OXA-48-like, NDM and VIM enzymes commonly dominate (Cantón *et al.,* 2012), whereas IMP enzymes are more prevalent in the Far East and Australia (Chen *et al.,* 2014). Furthermore, the genes responsible for resistance to carbapenems are frequently associated with genes coding for resistance to non-β-lactam antimicrobials, giving rise to the so called multidrug resistant (MDR) microorganisms (Nordmann *et al.,* 2011).

Food-producing animals and carbapenemase-producing bacteria

The occurrence of CP bacteria in food-producing animals has been reported from several countries. Pigs and chickens represent the most investigated species, in which carbapenem-resistance in Enterobacteriaceae and non-fermenting microorganisms (*Acinetobacter* spp. and *Pseudomonas* spp.) has been most frequently observed. Different classes of carbapenemases have been found both in Enterobacteriaceae and non-fermenting bacteria carried by livestock animals (Patel and Bonomo 2013).

Pigs

The most important studies on the detection of CP bacteria in pigs are shown in Tables 1 and 2.

The first detection of CP microorganisms in this animal species dates back to

2011, when a VIM-1- producing *E. coli* strain was isolated from a pig farm holding 4,100 pigs in Germany (Fischer *et al.,* 2012). It was resistant to penicillin, cephalosporins, cephamycin, and amoxicillin/clavulanic acid, but was susceptible to aztreonam and intermediate/susceptible to carbapenems (imipenem, ertapenem and meropenem). By PCR, the isolate was found to harbor both the Amp-encoding gene bla_{ACC-1} and the carbapenemase-encoding gene bla_{VIM-1} located in a class 1 integron labelled In110. This integron had been previously identified in other enterobacteria, such as *Klebsiella oxytoca* and *Enterobacter cloacae*, as well as in *Pseudomonas aeruginosa* and *Pseudomonas putida* in Italy and Spain (Riccio *et al.,* 2005; Tato *et al.,* 2010). The German VIM-1-producing *E. coli* strain represented the first CP microorganism isolated from pigs in Europe, but its sequence type (ST88) had been previously identified also among chickens, cattle and humans in Germany (Fischer *et al.,* 2012). Retrospectively, it was observed that the VIM-1-positive *E. coli* ST88 strain was

Table 1. Carbapenemase-producing Enterobacteriaceae from livestock.

Bacterial species	Carbapenemase genes	Additional resistant genes *	Animal species	Source	Year	Country	Reference
E. coli	bla_{IMP-27}	bla_{ACC-1}, *aacA4 aadA1, strA-strB, sul1, tet(A)*	Pigs	Faeces	2011	Germany	Fischer *et al*., 2012
S. Infantis	bla_{VIM-1}	bla_{ACC-1}, *aacA4, aadA1, strA-strB sul1, catA1*	Pigs	Faeces Boot socks	2011	Germany	Fischer *et al*., 2013
E. coli	bla_{VIM-1}		Pigs	Faeces	2015	Germany	EFSA and ECDC, 2015
E. coli	$bla_{OXA-181}$	*mcr-1, blaCMY-2, armA*bla_{TEM-1B}, *aph(4)-Ia, aph(3)-Ia, aadA1, aadA2, aadA5, aac(3)-IVa, armA, qnrS1, floR, cmlA1, sul1, sul3, tet(A), tet(M), dfrA12, dfrA17*	Pigs	Faeces	2016	Italy	Pulss *et al*., 2017
E. coli	$bla_{OXA-181}$	bla_{TEM-1B}, *aph(3)-Ia, aadA1, aadA2, aac(3)-IId, Inu*(F), *qnrS1, floR, cmlA1, sul2, sul3, tet(A), tet(M), dfrA12*					
E. coli *P. mirabilis* *P. vulgaris* *E. colacae* *Citrobacter spp.* *M. morganii* *P. rettgeri*	bla_{IMP-27} bla_{IMP-27} bla_{IMP-27} bla_{IMP-27} bla_{IMP-27} bla_{IMP-27} bla_{IMP-27}	*aph(3)-Ia, sul2, sat1* *aph(3)-Ia, sul2, sat1* *aph(3)-Ia, sul2, sat1* *aph(3)-Ia, sul2, sat1* *aph(3)-Ia, sul2, sat1* *aph(3)-Ia, sul2, sat1* *aph(3)-Ia, sul2, sat1*	Pigs	Environmental samples on farm Faecal samples (sows and piglets)	2015-2016	Ohio, USA	Mollenkopf *et al*., 2017
K. pneumoniae	bla_{NDM-5}	bla_{TEM-1}, *blaSHV-1,* bla_{OXA-1}, *rmtB, oqxAB, qnrS1, qnrB2, aac(6)-Ib-cr*	Dairy cows	Faeces Milk	2015	China	He *et al*., 2017
E. coli	bla_{NDM-5}	$bla_{CTX-M-15}$, bla_{CMY-42}	Dairy cows	Milk Teats	2015	Algeria	Yaici *et al*., 2016
E. coli	bla_{OXA-48}		Chicken	Broiler Broiler meat	2016	Romania	EFSA and ECDC, 2018
S. Infantis	bla_{VIM-1}	bla_{ACC-1}, *aacA4, aadA1, strA-strB sul1, catA1*	Chicken	Dust from a holding unit	2011	Germany	Fischer *et al*., 2013
S. Indiana	bla_{NDM-1}, bla_{OXA-1}	$bla_{CTX-M-65}$, bla_{TEM-1}, catB3, floR sul1/2/3, dfrA12/17, aac(3)-IV, aac (6')-Ib-cr, aadA2, aadA5, aph(4)-Ia	Chicken	Carcass	2014	China	Wang *et al*., 2017
E. coli	bla_{NDM-1}		Chicken	Faeces of diseased chicken (diarrhoea)	2015	China	Liu *et al*., 2017
E. coli	bla_{NDM-1}	$bla_{CTX-M-9G}$, *mcr-1, flor3, fosA3*					
E. coli	bla_{NDM-1}	$bla_{CTX-M-1G}$, *mcr-1, flor3, fosA3*					
E. coli	bla_{NDM-1}	*fosA3*					
E. coli	bla_{NDM-4}						
E. coli	bla_{NDM-4}	$bla_{CTX-M-9G}$, *fosA3*					
E. coli	bla_{NDM-4}	$bla_{CTX-M-9G}$, *mcr-1, flor3, fosA3,rmtB*					
E. coli	bla_{NDM-4}	$bla_{CTX-M-1G}$, *mcr-1, flor3, fosA3,rmtB*					
E. coli	bla_{NDM-4}	$bla_{CTX-M-1G}$, $bla_{CTX-M-9G}$, *mcr-1, flor3, fosA3,rmtB*					
E. coli	bla_{NDM-5}						
E. coli	bla_{NDM-5}	$bla_{CTX-M9G}$, $bla_{CTX-M1G}$ *mcr-1,*					
E. coli	bla_{NDM-9}						
E. coli	bla_{NDM-9}	$bla_{CTX-M-9G}$, *mcr-1, flor3, fosA3*					
K. pneumoniae	bla_{NDM}	bla_{KPC}	Chicken	Internal organs of diseased chicken (respiratory disease)	2014	Egypt	Hamza *et al*., 2016
K. pneumoniae	bla_{NDM}	bla_{OXA-48}					
K. pneumoniae	bla_{NDM}	bla_{KPC}, bla_{OXA-48}					

*When reported by the authors.

widely distributed in the fattening-pig farm tested in 2011, demonstrating that persistence and dissemination of CP microorganisms on farm was possible (Fischer *et al.,* 2017). In 2011-2012, another German study revealed the occurrence of VIM-1-producing *Salmonella* Infantis from two pig farms and one broiler farm (Fischer *et al*., 2013a). The isolates carried both the gene bla_{ACC-1} and the gene bla_{VIM-1}; the bla_{VIM-1} gene was located on a class 1 integron harbored by a ~300kb IncH12 plasmid, which also carried the bla_{ACC-1} gene. The sequence type (ST32) and PFGE pattern of the isolates were shared with other *S.* Infantis strains of human, poultry and pig origin previously detected in Germany (Fischer *et al.,* 2017). Noteworthy, *S.* Infantis is among the top five *Salmonella* serovars responsible for human salmonellosis in Europe, ranking in fourth place in 2017, after Enteritidis, Typhimurium and monophasic Typhimurium (EFSA and ECDC, 2018a) and responsible for severe cases of human salmonellosis, characterized by septicemia and even death (Naas *et al.,* 2011). As a consequence, the detection of carbapenemase-producing *S.* Infantis in pigs and poultry, which are considered its main reservoir, is of great concern (Hauser *et al.,* 2012; EFSA, 2013; Hindermann *et al.,* 2017).

Further studies revealed that in VIM-1-producing *S.* Infantis and VIM-1-producing *E. coli*, isolated on the same farms, the bla_{VIM-1} gene was located on the IncH12 plasmid, also found in human strains. The IncH12 plasmid in *S.* Infantis (pRH-R27) was a mosaic plasmid with high homology to the plasmids isolated from the human strains, while the IncH12 plasmid in *E. coli* (pRH-R178) was a deletion derivative of the pRH-R27 found in *S.* Infantis, suggesting that selective evolution of plasmids in the livestock environment is possible (Falgenhauer *et al.,* 2017). Since carbapenems are not used in animal husbandry in Germany, the source of the bla_{VIM-1} gene could be identified in the selective pressure caused by third-generation cephalosporins. In fact, pRH-R27 and pRH-R178 plasmids harbored a plasmid-encoded AmpC β-lactamase (bla_{ACC-1}) which confers resistance to third-generation cephalosporins (Falgenhauer *et al.,* 2017).

As recently observed, the presence of genes encoding resistance to antimicrobials frequently used in swine production (*e.g* sulfonamides, cephalosporins) might be favored by minimal selective concentrations of the agents (below almost up to 140-fold the MIC value). Therefore, even a very low drug concentration found in livestock environments and in treated humans and animals might be sufficiently high to select and maintain plasmids carrying resistance in the bacterial populations (Gullberg *et al.,* 2014).

In 2015, mandatory monitoring for ESBL-/AmpC-/carbapenemase-producing *E. coli* was performed on caecal contents from 6,167 fattening pigs, 2,347 calves under one year of age and 10,679 meat samples thereof in 23 member states and two non-member states in Europe. As recommended by EUCAST (2015) a screening breakpoint for cefotaxime and/or ceftazidime (> 1 mg/L) was applied to screen for ESBL and AmpC-producers. Lower ECOFF breakpoints were applied for meropenem (> 0.125mg/L), imipenem (> 0.5 mg/L) and ertapenem (> 0.06 mg/L) to screen for CP *E. coli.* Regarding ESBL and AmpC producers, prevalence was high for the former (31.9% and 36.8% in pigs and calves, respectively) and low for the latter (9.75 and 4.8% in pigs and calves, respectively) (EFSA and ECDC, 2017b). One VIM-1 *E. coli* strain was reported from pigs by Germany, thus confirming persistence of VIM-1-producing *E. coli* in the German pig population for at least four years (Irrgang *et al.,* 2016). In addition, a CP *E. coli* strain was isolated from pig meat in Belgium (EFSA and ECDC, 2017b).

Recently, the occurrence of $bla_{OXA-181}$ *E. coli* from two pigs reared in an Italian farm was reported. The two strains were not genetically related, belonging to sequence types ST359 and ST641. One of the isolates carried also the colistin-resistance gene *mcr-1* and the aminoglycoside-resistance gene *armA*. The gene $bla_{OXA-181}$ was located on a 51.5-kb non-conjugative IncX3 plasmid and the *mcr-1* gene on a 33.3-kb transferable IncX4 plasmid; both plasmids showed high similarity to human and animal ones, demonstrating that antimicrobial resistance plasmids are largely distributed in *E. coli* strains (Pulss *et al.,* 2017).

The occurrence of plasmid-borne carbapenemase genes among Enterobacteriaceae in pigs was also reported in the USA. From environmental and faecal samples collected from swine farrowing and nursery barns, 18 (5.6%) bla_{IMP-27}-harboring isolates belonging to the Enterobacteriaceae family (*E. coli, Proteus* spp., *Morganella* spp., *Providencia* spp., *Citrobacter* spp., *Klebsiella* spp.) were identified (Mollenkopf *et al.,* 2017). The bla_{IMP-27} is considered rare among the β-lactamase genes in the Unites States (Widmann *et al.,* 2012). Positive selection pressure due to cephalosporins use at farm was related to the higher prevalence of bla_{IMP-27} carrying isolates in the farrowing barn, compared to the nursery and finishing barns. In fact, ceftiofur was given to all piglets after birth (days 0 to 1) and to males at castration (day 5 to 7). In all the isolates, the bla_{IMP-27} gene was located on IncQ1 plasmids of ~10 kb, whose presence in multiple bacterial species strongly suggested that they were mobilizable (Mollenkopf *et al.,* 2017). IncQ are small (5.1 to 14.0 kb) plasmids able to replicate independently of their host, allowing to reach high copy numbers (Meyer, 2009). Even if IncQ plasmids are not self-transmissible, they can be mobilized by a type IV transporters provided by larger, self-transmissible, co-resident helper plasmids from incompatibility groups, including IncP, IncF, IncI, IncM, IncX, IncN, and IncW (Loftie-Eaton and

Table 2. Carbapenemase-producing non-Enterobacteriaceae from livestock.

Bacterial species	Carbapenemase genes	Additional resistant genes *	Animal species	Source	Year	Country	Reference
A. baumannii	bla_{NDM-1}	*aphA6, ble, msr(E)-mph(E)*	Pigs	Lungs of a diseased pig (pneumonia)	2011-2012	China	Zhang *et al*., 2013
Acinetobacter (related to *A. lwoffii*)	bla_{OXA-23}		Dairy cattle	Faeces	2010	France	Poirel *et al*, 2012
A. baumannii	$bla_{OXA-497}$		Dairy cattle	Faeces	2014	New Mexico and Texas, USA	Webb *et al*., 2016
A. lwoffii	bla_{NDM-1}	aphA6	Chickens	Faeces	2010	China	Wang *et al*, 2012

*When reported by the authors.

Rawlings, 2012). An experimental study evaluated the use of amoxicillin and ertapenem in porcine models; each antimicrobial resulted in changes in the porcine gut microbiome causing elimination of key commensal bacteria and propagation of AMR genes, including β-lactamases. Specifically, amoxicillin promoted the selection of many AMR genes, efflux pumps and β-lactamases, while ertapenem triggered the emergence of genes encoding for β-lactamases and the bla_{IMP-27} carbapenemase (Connelly *et al.,* 2018). Besides this, other agents used in swine production, as heavy metals and disinfectants, could co-select for plasmids carrying resistance genes when there is no direct selective pressure (Johnson, 2017).

In South China a large survey on lungs, liver and lymph nodes of pigs, chickens and ducks was performed in 2011-2012. One bla_{NDM-1} *A. baumannii* isolate was detected in the lungs of a swine with pneumonia and sepsis, reared on a farm where different β-lactams, third- and fourth-generation cephalosporins (ceftriaxone and ceftiofur), aminoglycosides and quinolones were commonly administered to the pigs. This evidence suggests for selective pressure favoring the emergence of carbapenem-resistance among microorganisms. The bla_{NDM-1} gene in *A. baumannii* was identified on a ~ 47 kb transferable plasmid (Zhang *et al.,* 2013). At last, a worrisome finding comes from India and concerns the detection of Shiga-toxin producing *E. coli* (STEC) carrying the bla_{NDM} gene in piglets. In the farms of origin, history of usage of several antimicrobials, including third-generation cefalosporis, was reported. The STEC isolates were positive for *stx1, stx2, eae* and *hlyA* genes and were also resistant to extended-spectrum beta-lactams and other antimicrobials (Pruthvishree *et al*., 2017), thus representing a very dangerous multidrug-resistant pathogen.

Cattle

The studies on CP bacteria in cattle are shown in Tables 1 and 2. The first report was about the genus *Acinetobacter*: Isolates closely related to *A. lwoffii* harboring the bla_{OXA-23} gene were detected from dairy cattle in France in 2010. The transposon Tn*2008* was identified as vehicle for the bla_{OXA-23} gene spread among *Acinetobacter* spp. (Poirel *et al.,* 2012). Interestingly, the bla_{OXA-23} gene is widespread in *A. baumannii*, an opportunistic nosocomial pathogen which has become one of the most relevant multidrug-resistant microorganisms in hospitals all over the world, with transposon Tn*2008* as its major vehicle (Antunes *et al.,* 2014). In Germany, strains of *A. indicus*-like carrying a chromosomal bla_{OXA-23} gene were isolated from nasal swabs of cattle. Although pathogenicity and zoonotic potential of the microorganism require further investigations, the emergence of CP bacteria from cattle harboring bla_{OXA-23} with genetic relatedness to human clinical isolates is of concern (Klotz *et al*., 2017). In the USA, dairy cattle were found to shed *A. baumannii* harboring the novel $bla_{OXA-497}$ gene, which is part of the OXA-51-like enzyme group, and *Pseudomonas* spp. with conserved domains of various carbapenemase-producing genes. In the farms of origin, third-generation cephalosporins (ceftiofur) were commonly used (Webb *et al.,* 2016).

Klebsiella pneumoniae harboring bla_{NDM-5} genes was isolated from milk and faecal samples of dairy cows with mastitis in China (Jiangsu Province) (He *et al.,* 2017). This was the first report of bla_{NDM-5} – carrying *K. pneumoniae* from cattle, but bla_{NDM-5} *E. coli* and bla_{NDM-5} *K. pneumoniae* had been previously isolated from human patients in several countries, including the UK (Hornsey *et al.,* 2011), Singapore (Balm *et al.,* 2013), Algeria (Sassi *et al.,* 2014), Japan (Nakano *et al.,* 2014), Denmark (Hammerum *et al.,* 2015), The Netherlands (Bathoorn *et al.,* 2015), Spain (Pitart *et al.,* 2015), the USA (de Man *et al.,* 2015), Australia (Wailan *et al.,* 2015), South Korea (Cho *et al.,* 2015), India (Krishnaraju *et al.,* 2015) and China (Liu *et al.,* 2016; Zhang *et al.,* 2016). In the Chinese dairy farms, selective pressure due to β-lactams (amoxicillin, ceftiofur) used to treat cattle with mastitis could have favored the emergence of bla_{NDM-5}-harboring *K. pneumoniae* isolates. In all the isolates, the bla_{NDM-5} gene was found on a ~46 kb self-transmissible IncX3 pNDM-MGR194-like plasmid. Nevertheless, since the strains belonged to five different sequence types, clonal dissemination within the farms could be only partly responsible of their widespread. Interestingly, the genetic context of the IncX3 plasmid was nearly the same of a human *K. pneumoniae* plasmid designated pNDM-MGR194, previously reported in India, and also closed to bla_{NDM-5}-carrying plasmids harbored by human *E. coli* strains in China (He *et al.,* 2017). Most of these isolates were recovered from human clinical specimens and one isolate of bla_{NDM-5} *E. coli* from a dog in Algeria (Yousfi *et al.,* 2015). These evidences seem to support for transmission of IncX3 plasmids from human sources to animal ones. Recently, the bla_{NDM} genes (bla_{NDM-1} and bla_{NDM-5}) have frequently been reported to be located on IncX3 plasmids among several species of Enterobacteriaceae (*E. coli, K. pneumoniae*, *Citrobacter freundii* and *E. cloacae*) in China (Ho *et al.,* 2012; Chen *et al.,* 2016) implying that IncX3 plasmids may provide an efficient vehicle for dissemination of human bla_{NDM} genes within bacterial strains of animal origin. Therefore, the role of the IncX3 plasmid in the spread of the bla_{NDM-5} gene (maybe of human origin) in the Chinese dairy farms was suggested and opened options to re-transmission of bla_{NDM-5}-carrying plasmid/bacteria from animals to humans through the dairy food chain (He *et al.,* 2017). This hypothesis seems to be confirmed by the occurrence of the IncX3 plasmid carrying the gene bla_{NDM-5} in *E. coli* strains isolated from teats and milk of dairy cows in Algeria (Yaici *et al.,* 2016).

Poultry

The most interesting studies on detection of CP bacteria in poultry are shown in Tables 1 and 2.

Regarding EU countries, presumptive CP commensal *E. coli* isolates from broilers and broiler meat were reported by 2 member states in 2016 (11 isolates from Cyprus and 3 isolates from Romania). In Romania, the *E. coli* isolates from broilers were identified to carry the bla_{OXA-48} gene (EFSA and ECDC, 2018b).

Most studies on poultry have been performed in China and African countries. In China, one isolate of NDM-1-producing *A. lwoffii* resistant to eight of nine β-lactams, including imipenem, meropenem and ertapenem, was detected from 396 anal swab samples collected from chickens. The gene bla_{NDM-1} was located on a ~270-kb self-transferable plasmid, designated pAL-01. Although the use of carbapenems in food-producing animals is banned in China, other β-lactams such as penicillin and cephalosporins (cefradine, ceftiofur and cefotaxime) are commonly used, as observed in the above-mentioned chicken farm (Wang *et al.,* 2012).

Also, from China, a bla_{NDM-1} and bla_{OXA-1}-harboring *Salmonella* Indiana isolate from a chicken carcass at slaughter was reported. The strain carried other β-lactamases, amynoglicosides, phenicol and trimethoprim/sulphamethoxazole resistance genes for a total of more than 20 antimicrobial resistances (Wang *et al.,* 2017). The occurrence of such extensively-drug resistance (XDR) phenotype in the genus *Salmonella* is of the greatest concern for human heath, due to its zoonotic attitude and widespread in the food chain.

High prevalence of *E. coli* carrying both resistance against colistin (gene *mcr-1*) and carbapenems (genes bla_{NDM-1}, bla_{NDM-4}, bla_{NDM-5} and bla_{NDM-9}) was reported in broil-

ers by another Chinese study. In the isolates, dissemination of *mcr-1* and bla_{NDM} genes was not clonal, but due to different plasmids (Liu *et al.,* 2017).

In Egypt, a study on carbapenem-resistant *K. pneumoniae* in broiler chickens reared in different farms, drinking water on farms and humans working in contact with chickens was performed. CP *K. pneumoniae* was isolated from 15% of broilers and 6% of water samples. Among the poultry isolates (n=15), all of them were bla_{NDM}-positive, including 11 isolates harboring bla_{KPC}, bla_{OXA48} and bla_{NDM} and four harboring either bla_{KPC} and bla_{NDM} or bla_{OXA-48} and bla_{NDM}. The isolates from drinking water (n=3) were positive for bla_{KPC} and bla_{NDM} (n = 1) or for all three genes (n = 2). In Egypt, a high proportion (56%) of *K. pneumoniae* isolates from humans were positive for the three carbapenemase genes. This finding suggests that a high incidence of CP *K. pneumoniae* in humans may contribute to its dissemination among food-producing animals and the livestock environment, thus increasing the risk of foodborne transmission to the consumers (Hamza *et al.,* 2016).

Fish and molluscs

To prevent bacterial infections in farmed fish, antimicrobials are often used in intensive aquaculture practises (Rogers and Basurco, 2009). This situation supports the occurrence of AMR bacteria in seafood products (Roschanski *et al.,* 2017). Furthermore, fish and molluscs may acquire AMR bacteria from water sea polluted by sewage and agriculture drains. Although investigations on CP bacteria in fishery products are very rare, some important data can be achieved from literature. The studies focused on the detection of CP bacteria in seafood are shown in Table 3.

In 2013, *A. baumannii* isolates harboring the chromosomally encoded bla_{OXA-51} gene and the acquired bla_{OXA-23} gene were detected from two *Pagellus acarne* fished in the Mediterranean See. The microorganisms were resistant to aminoglycosides, third-generation cephalosporins and carbapenems (imipenem, meropenem, ertapenem). They belonged to the widespread clone *A. baumannii* ST2, which had reached fish living in the Mediterranean Sea (Brahmi *et al.,* 2016). Another study focused on CP bacteria contamination of frozen seafood (included octopus, squid, clams, mussels and shrimps) imported from China and Korea identified bla_{OXA-48}-harboring *Stenotrophomonas maltophilia, Pseudomonas putida* and *Myroides odoratimimus* isolates (Morrison and Rubin, 2015).

Recently, a strain of VIM-1 producing *E. coli* ST10 has been isolated from Venus clams (*Ruditapes philippinarum*) harvested in the Italian Mediterranean Sea, suggesting that CP *E. coli* have reached the seafood chain of this country. Moreover, since Venus clams are often eaten raw, ideal conditions for transmission and spread to the consumers of CP bacteria and/or transfer of the respective plasmids could occur (Roschanski *et al.,* 2017).

Environment and carbapenemase-producing bacteria

The studies focused on the detection of CP bacteria from different environmental sources are shown in Table 4. Environmental contamination with antimicrobials, AMR bacteria and their transfer-

Table 3. Carbapenemase-producing Enterobacteriaceae and non-Enterobacteriaceae from fishery and wild animals.

Bacterial species	Carbapenemase genes	Additional resistant genes *	Animal species	Source	Year	Country	Reference
E. coli	bla_{VIM-1}	bla_{ACC}, bla_{SHV12}, *aacA4-like, aadA1, aph(3')-XV, catB2, dfrA14-like, mph(A), qnrS1, strA-like, strB like, sul1, sul2*	Venus clams *(Ruditapes philippinarum)*	N.S.	2016	Mediterranean Sea (Italy)	Roschanski *et al.*, 2017
A. baumannii	$bla_{aOXA-23}$, bla_{OXA-51}	*aac(6')-Ib, aac(3')-I*	Fish *(Pagellus acarne)*	Gills Gut	2013	Mediterranean Sea (Algeria)	Brahmi *et al.*, 2016
S. maltophilia	bla_{OXA-48}		Seafood medley **	Edible product	N.S.	China	Morrison and Rubin, 2015
M. odoratimimus	bla_{OXA-48}		Clams				
P. putida	bla_{OXA-48}		Squid			Korea	
Stenotrophomonas spp.	bla_{OXA-48}		Sea squirt				
S. Corvallis	bla_{NDM-1}	*fosA3*	Black kites *(Milvus migrans)*	N.S.	N.S.	Germany	Fischer *et al.*, 2013
E. coli	bla_{VIM-1}		Yellow-legged gulls *(Larus michaellis)*	Faeces	2012	France	Vittecoq *et al.,* 2017
E. coli	bla_{IMP-4}	*qacG, aacA4, catB3*	Silver gulls *(Chroicocephalus novaehollandiae)*	Faeces	2012	Australia	Dolejska *et al.*, 2016
E. coli	bla_{IMP-4}, bla_{IMP-38}						
K. pneumoniae	bla_{IMP-4}	*qacG, aacA4, catB3*					
K. pneumoniae	bla_{IMP-26}	*qacG, aacA4, catB3*					
E. cloacae	bla_{IMP-4}	*qacG, aacA4, catB3*					
C. freundii	bla_{IMP-38}	*qacG, aacA4, catB3*					
P. mirabilis	bla_{IMP-4}	*qacG, aacA4, catB3*					
E. coli	bla_{OXA-48}		Wild boars	Faeces	2016	Algeria	Bachiri *et al.*, 2017
K. pneumoniae	bla_{OXA-48}		*(Sus scrofa)*				

N.S., not specified.*when reported by the authors. **Seafood medley contains squid, octopus, mussels and shrimp.

able resistance genes can pose a serious threat not only to human health, but to the natural environment microbial evolution as well (Martinez, 2009). Due to their use in livestock farming, antimicrobials may residue in manure applied to soil in agriculture practices. Besides this, AMR bacteria shed by animals may contaminate agricultural areas. In this way, both antimicrobials and AMR bacteria may be run-off from soil and reach surface water, then contributing to contamination of soil, crops and wild animals (Laxminarayan *et al.,* 2013). To their turn, wild animals can enter in close contact with sewage and garbage, thus leading to a wide spread of AMR bacteria and resistance genes, with detrimental consequences for the entire ecosystem (Pesapane *et al.,* 2013).

Bacteria carrying highly transferable resistant genes are of concern, because mobile elements could reach a wide variety of settings in which other bacterial species are present. For example, the use of water from polluted rivers in agriculture and aquaculture increases such risk of AMR bacteria spreading to more than one food chain (EFSA, 2013). One example is given by *Salmonella* in poultry, *E. coli* in livestock or *K. pneumoniae* in dairy cattle. Therefore, when AMR bacteria and their transferable resistant genes are lead to food-producing animals through polluted environment, the risk for potential contamination of their derived products should not be ignored (EFSA, 2013). The studies focused on the detection of CP bacteria from different environmental sources are shown in Table 4.

The detection of carbapenemase-encoding genes in bacteria from livestock environmental samples was reported in pig-fattening farms in Germany, where VIM-1-positive *Salmonella* Infantis was isolated from boot socks taken outside of the farms and VIM-1-producing *E. coli* from manure and flies. Indeed, manure and insects can act as vectors of AMR bacteria at farm

Table 4. Carbapenemase-producing Enterobacteriaceae and non-Enterobacteriaceae from the environment.

Bacterial species	Carbapenemase genes	Additional resistant genes *	Source	Year	Country	Reference
S. Infantis *E. coli*	bla_{VIM-1} bla_{VIM-1}	bla_{ACC-1} bla_{ACC-1}	Boot socks outside pig farms Manure and flies (Pig farms)	2011-2012	Germany	Fischer *et al*., 2017
Klebsiella spp., *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., *Raoultella* spp., *Aeromonas* spp., *Kluyvera* spp.	bla_{KPC-2}		Hospital sewage WWTP **	2011	Brazil	Picao *et al*., 2013
E. coli *C. freundii* *K. pneumoniae* *K. pneumoniae*	bla_{OXA-48} bla_{OXA-48} bla_{KPC-2} bla_{OXA-48}		WWTP **	2015-2016	Switzerland	Zurfluh *et al*., 2017
K. pneumoniae *K. pneumoniae* *E. coli*	bla_{KPC-2} bla_{OXA-48} bla_{OXA-48}	bla_{TEM-1}, bla_{SHV-26}, bla_{FOX} bla_{TEM-1}, bla_{SHV-1}, $bla_{CTX-M-15}$ bla_{TEM-1}, $bla_{CTX-M-24}$	WWTP **	2011-2012	Austria	Galler *et al*., 2014
P. aeruginosa *Brevundimonas diminuta* *Rhizobium radiobacter* *Pseudomonas monteilii* *Ochrobactrum anthropic* *Acinetobacter johnsonii*	bla_{VIM-13} bla_{VIM-13} bla_{VIM-13} bla_{VIM-13}, bla_{VIM-2} bla_{VIM-13} bla_{OXA-58}	*aacA4, sul1* *aacA4, sul1* *aacA4, sul1* *aacA4, sul1*	Hospital sewage water	N.S.	Spain	Scotta *et al*., 2011
P. aeruginosa	bla_{VIM-2}	*aacA4, aacA7 aacC1*	Hospital sewage water; river	2001-2005	Portugal	Quinteira and Peixe, 2006
K. pneumoniae	bla_{IMP-8}, bla_{IMP-10}, bla_{IMP-13}	$bla_{CTX-M-15}$, $bla_{SHV-12a}$	Rivers	2010	Tunisia	Chouchani *et al*., 2013
E. coli *K. pneumoniae* *C. freundii* *V. cholerae* *Shigella boydii* *Pseudomonas spp.* *Stenotrophomonas maltophilia* *P. aeruginosa*	bla_{NDM-1} bla_{NDM-1} bla_{NDM-1} bla_{NDM-1} bla_{NDM-1} bla_{NDM-1}		Seepage water Tap water	2010	India	Walsh *et al*., 2011
A.baumannii	bla_{OXA-23}		Seine River	N.S.	France	Girlich *et al*. 2010a
P. fluorescens	bla_{BIC-1}		Seine River	N.S.	France	Girlich *et al*., 2010b

N.S., not specified. *when reported by the authors. **WWTP: waste water treatment plant.

level, maintaining and distributing AMR microorganisms over long periods of time. Furthermore, the detection of both VIM-1 producing *S.* Infantis and *E. coli* on the same farm was suggestive of the inter-species gene transfer at farm level (Fischer *et al.,* 2017).

Important sources of AMR pathogenic bacteria worldwide are represented by hospitals, which release their sewage drains and wastewater in the environment (Baquero *et al.,* 2008). The spread of CP bacteria from hospitals is a serious menace for the entire ecosystem. Several studies have been performed on aquatic environments, such as hospital sewage, wastewater treatment plants (WWTPs), lakes and rivers and most reports assess that a common way for carbapenemase genes to enter the environment is represented by wastewater. Hospital effluents are normally mixed with urban effluents and treated in WWTPs, to be discharged in the aquatic environment (Verlicchi *et al.,* 2012). In WWTPs, AMR bacteria and their resistant genes can survive (Yang *et al.,* 2016), thus persisting in the environment and spreading back to animals and humans.

WWTPs have been investigated in different countries. In Brazil, the bla_{KPC-2} gene was identified in isolates of *Aeromonas* spp. and Enterobacteriaceae belonging to the genera *Klebsiella, Enterobacter, Citrobacter, Serratia, Kluyvera* and *Roultella* present in hospital effluents and WWTPs. The bla_{KPC-2} gene of such isolates was successfully transferred *in vitro* to the recipient strain *E. coli* J53, showing that it was located either on conjugative or transferable plasmids; this finding supported the hypothesis that the bla_{KPC-2} gene could have been transferred to environmental bacteria, such as *Aeromonas, Kluyvera* and *Roultella,* from clinical isolates discharged in the hospital sewage (Picão *et al.,* 2013). The acquisition of mobile resistant genes could be promoted by selective pressure exerted by the antimicrobials which are commonly found in hospital sewage (Brown *et al.,* 2006). In Switzerland, in wastewater samples collected before and after the influx of hospital sewage, the increasing of OXA-48 *E. coli,* OXA-48 *C. freundii* and KPC-2- or OXA-48 *K. pneumoniae* downstream the hospital wastewater influx was demonstrated (Zurfluh *et al*., 2017). In Austria, KPC-2 *K. pneumoniae*, OXA-48 *E. coli* and OXA-48 *K. pneumoniae* strains were detected from a WWTP collecting from both domestic and hospital effluents, showing that CP Enterobacteriaceae could escape from clinical settings to be released into the aquatic environment (Galler *et al.,* 2014). In China, KPC-2 producing bacteria belonging to the genera *Klebsiella, Enterococcus, Escherichia, Shigella, Wautersiella, Acinetobacter* and *Stenotrophomonas* were recovered from WWTP effluent samples. Chlorination treatment was not effective, being different genes (bla_{KPC-2}, bla_{GES-1} and bla_{IMP-1}) detected in large amounts in all sections of the plant. In this study, horizontal transfer of bla_{KPC-2} gene was demonstrated in *Paenibacillus* spp., an environmental microorganism which was never found before to harbor carbapenemase genes (Yang *et al.,* 2016). In Tunisia, bla_{KPC}, bla_{NDM} and $bla_{OXA-48\ like}$ genes were detected in high concentrations from hospital wastewater samples, demonstrating the widespread of CP bacteria in hospitals as well as their potential source of environment pollution (Nasri *et al.,* 2017). In Spain, VIM-13-producing *P. aeruginosa* was found in the sewage water of a hospital, together with isolates of VIM-13-producing *Brevundimonas diminuta, Rhizobium radiobacter, Pseudomonas monteilii, Ochrobactrum anthropic* and *Acinetobacter johnsonii.* These findings suggested that the environmental microbiota could represent a reservoir of resistance genes, probably acquired by genetic transfer from pathogens like *P. aeruginosa* (Scotta *et al.,* 2011).

Other studies support the hypothesis that "sewage habitats" may represent a niche for AMR microorganisms, enhancing the potential transfer of genetic determinants among different bacterial species (Scotta *et al.,* 2011) and bacterial dissemination to rivers (Novais *et al.,* 2005) and coastal waters (Quinteira and Peixe, 2006). In Portugal, bla_{VIM-2}-harboring *P. aeruginosa* strains were isolated from a river and a hospital sewage downstream. The bla_{VIM-2} gene was located on a class 1 integron (Quinteira and Peixe, 2006). In Tunisia, bla_{IMP-8}, bla_{IMP-10} and bla_{IMP-13} *K. pneumoniae* isolates were identified from polluted rivers and class 1 integrons were considered the vectors for transmission of bla_{IMP} genes among the bacteria (Chouchani *et al.,* 2013). Even seepage water (for example, water pools in streets) might be a source of CP bacteria, as bla_{NDM}-harboring *K. pneumoniae, E. coli, C. freundii, Shigella boydii, Vibrio cholerae, Aeromonas caviae, P. aeruginosa, P. putida, S. maltophilia* and other species in India (Walsh *et al.,* 2011). From the Seine River, in Paris (France), bla_{OXA-23}-harboring *A. baumannii* was recovered (Girlich *et al.,* 2010a), together with bla_{BIC-1}-harboring *P. fluorescens* (Girlich *et al.,*2010b). The enzyme BIC-1, a novel class A chromosome-encoded β-lactamase, hydrolyzes penicillins, carbapenems and cephalosporins, except ceftazidime and monobactams (Girlich *et al.,* 2010b); it shares high identity with SFC-1 from *Serratia fonticola* (Henriques *et al.,* 2004) and the plasmid-encoded KPC-2 from *Klebsiella* spp. (Yigit *et al.,* 2003).

At last, the role of natural environment in maintaining and spreading CP microorganisms can be suggested by a study conducted in Switzerland in ready-to-eat vegetables, where OXA-181-producing *Klebsiella variicola* was identified from a coriander mix sample imported from Thailand/Vietnam (Zurfluh *et al.,* 2015). This finding not only sheds light on the potential role of vegetables in transmitting CP bacteria to the consumers, but suggests that such a role is very likely attributable to environmental contamination. Nevertheless, contamination of vegetables does not necessary derive from the original harvesting environment, and might originate from the different processing and commercial steps they are subjected as well.

In conclusion, the environment can host CP bacteria both from human and animal sources, maintaining and distributing AMR microorganisms and their genetic determinants to different settings. As recently suggested (Scotta *et al.,* 2011), the environment microbiota can support the genetic transfer among bacteria, especially mediated by class 1 integrons, from pathogenic to environmental microorganisms. The role of the natural environment as reservoir of CP bacteria is probably more important than what we actually hypothesized. In Europe as well as in other parts of the world, more efforts should be warranted especially in countries where human pathogenic CP microorganisms are endemic.

Wildlife and carbapenemase-producing bacteria

Actually, the potential role of wildlife in the maintaining and dissemination of resistance genes and AMR bacteria in the natural environment and livestock animals is far to be fully understood. AMR bacteria can colonize wild animals following contact with sewage, human waste or animal manure, with serious issues for public and animal health and ecosystem functions (Pesapane *et al.,* 2013). The intake of water polluted with faeces or human waste seems to be the most important route for wild birds to acquire AMR bacteria of human origin (Guenther *et al.,* 2011). In addition, the intake of polluted water with feaces of livestock animals could have the same importance for wild birds and wild animals to acquire AMR bacteria of farm origin. At present, \only four studies have detected CP

bacteria in wild animals (Table 3). The first report originated from Germany, where a strain of bla_{NDM-1} *Salmonella* Corvallis belonging to ST1541 was isolated from black kites (*Milvus migrans*). The bla_{NDM-1} gene was located on the ~180 kb IncA/C conjugative plasmid pRH-1738 (Fischer *et al.,* 2013b). Since the IncA/C plasmids are among the most common plasmids associated with the bla_{NDM-1} gene in humans (Carattoli, 2013) and *S.* Corvallis was more common in South-East Asia, North Africa and Nigeria rather than in Europe, Fischer and colleagues (2013b) supposed that the isolate might have originated from non-European countries and transferred to Germany through the black kite migratory route. The sequence of the plasmid pRH-1738 confirmed this hypothesis (Villa *et al.,* 2015) and the additional presence of the resistant gene for fosfomicin (*fos*A3), which is common in Asia, strongly supported for the Asiatic origin of the bla_{NDM-1} *fos*A3-harboring *S.* Corvallis (Qin *et al.,* 2014).

In France, VIM-1-producing *E. coli* in yellow-legged gulls (*Larus michaellis*) has been recently reported (Vittecoq *et al.,* 2017). In the geographical area of the study, yellow-legged gulls live in close contact with humans and all the CP isolates from gulls were closely related to carbapenem-sensitive *E. coli* of human patients hospitalized in the area. Since the bla_{VIM-1} gene is uncommon in France, but can be frequently found in human isolates from Greece, Italy and Spain (Cantón *et al.,* 2012; Mathlouthi *et al.,* 2017) the authors warned over the potential role of wild birds as carriers of carbapenem-resistance bacteria and their encoding genes from endemic countries (Vittecoq *et al.,* 2017).

In south-east Australia, large-scale transmission of IMP-producing bacteria into wild birds was reported. *E. coli* strains harboring bla_{IMP-4}, bla_{IMP-38} or bla_{IMP-26} genes, *K. pneumoniae* harboring bla_{IMP-4} or bla_{IMP-26} genes, *Citrobacter freundii* harboring bla_{IMP-38} gene and *Enterobacter aerogenes* and *Proteus mirabilis* harboring bla_{IMP-4} gene were isolated from silver gulls (*Chroicocephalus novaehollandiae*). The bla_{IMP-4} gene was carried by various conjugative plasmids, mostly IncHI2-N plasmid type, and was associated with a class 1 integron (Dolejska *et al.,* 2016). Interestingly, bla_{IMP-4} is the most commonly detected gene among CPE affecting human patients in Australia (Sidjabat *et al.,* 2015; Espedido *et al.,* 2008). PCR mapping revealed the bla_{IMP-4}-qacG-aacA4-catB3 cassette array in 65% of *E. coli* isolates and 80% of non-*E. coli* isolates of gull origin (Dolejska *et al.,* 2016). The same cassette array was found in Enterobacteriaceae from humans in other Australian tows (*i.e.* Sydney and Melbourne) (Espedido *et al.,* 2008), strongly suggesting the human origin of the IMP-producing *E. coli* and the other Enterobacteriaceae detected in gulls. The hypothesis was also supported by the feeding habits of the gulls on waste depots, where garbage and sewage were almost exclusively related to human activities and the risk of transmission of bacteria from the human compartment to the wild one was high (Dolejska *et al*., 2016).

Thus, even if carbapenem-resistance in bacteria from wild animals is rarely reported, the emergence of NDM-1 and IMP carbapenemases in wild birds should not be ignored because of their migratory habits and the consequent ability of long-distance transportation of AMR resistant bacteria and their related genes.

Regarding wild mammals, the first report of OXA-48 producing Enterobacteriaceae originated from Africa. In Algeria, faecal samples from 168 wild boars (*Sus scrofa*) and 212 barbary macaques (*Macaca sylvanus*) were collected between 2014 and 2016 and tested for carbapenem-resistant genes. Two bla_{OXA-48} carrying *E. coli* ST635 and one bla_{OXA-48} carrying *K. pneumoniae* ST13 were isolated from wild boars, thus confirming dissemination of CP bacteria to wild animals (Bachiri *et al.,* 2018) in a country where occurrence of carbapenem-resistant bacteria in humans (Sassi *et al.,* 2014), pets (Yousfi *et al.,* 2015) and livestock animals (Yaici *et al.,* 2016) had been previously reported.

Future studies

This review has shed light on the main scientific gaps which require future studies, summarized as follows: *i)* CP bacteria occurrence in food-producing animals, especially pigs, cattle and poultry, has not been sufficiently investigated in the countries characterized by high prevalence of CP bacterial infections is humans; *ii)* the correlation between CP bacteria occurrence and antimicrobial use at farm should be better investigated, with special regard to third- and fourth-generation cephalosporins use; *iii)* the observed co-resistance against cephalosporins and carbapenems needs to be investigated by genomic sequencing of the isolates; *iv)* comparative genomic studies of CP isolates from humans, animals and the environment should be encouraged to investigate the likely transmission pathways between the different compartments.

Conclusions

Several factors may contribute to select AMR bacteria in a host, due to their opportunity to become more prevalent as the result of killing the sensitive bacterial population by antimicrobials to which they exhibit reduced susceptibility. As a consequence, the AMR bacteria can become dominant among the previously resident bacterial population (Baquero *et al.,* 2011). Besides this, for many classes of antibiotics, selection of plasmids carrying resistance determinants occurs especially at antimicrobial concentrations far below the MIC value of a susceptible strain. Low antimicrobial concentrations kill only a fraction of the cells, whereas the rest of the bacterial population may evolve to reduced susceptibility or resistance. Accordingly, even the low levels of antibiotics often present in treated animals and humans as well as in polluted natural environments could enhance selection and enrichment of bacteria with transferable resistance genes and thereby contribute to the emergence, maintenance and transmission of AMR bacteria (Guerra *et al.,* 2014; Gullberg *et al.,* 2014).

Among AMR bacteria, CP microorganisms are of particular concern for public health because carbapenems are considered the "last-line defence" drugs against human infections by multidrug resistant Gram-negative bacteria (Zhanel *et al.,* 2007; Nordmann *et al.,* 2011; Patel and Bonomo, 2013). Despite the use of carbapenems in food-producing animals is banned in Europe and other countries (WHO, 2015), detection of CP microorganisms in livestock has been reported in EU as well as non-EU countries. Selection pressure exerted by β-lactams antimicrobial treatments in farm animals, as well as CP bacteria transmission from human sources, are considered responsible for the occurrence of CP microorganisms in livestock. Likely, meat and milk might become a source of CP bacteria for the consumers, with the worst scenario to be displayed in countries with high prevalence of CP bacterial infections in humans.

In this context, the role of hospital sewage and WWTPs in the environmental distribution of human CP bacteria has been effectively assessed. Furthermore, human activities on natural habitats, as the use of manure to amend soil in agricultural practises, strongly contribute to the diffusion and maintenance of resistance bacteria and their transferable genetic elements in the terrestrial and aquatic environments. In this scenario, wild animals, and especially migratory birds, may amplify both mainte-

nance and long-distance distribution of CP microorganisms.

Recently, pollution of the aquatic environment by AMR bacteria, and especially CP bacteria, has attracted the greatest attention all over the world. Accordingly, even the fishery chain might be responsible for transmission of CP bacteria and their transferable genetic determinants to consumers.

According to the epidemiology of CP bacteria, monitoring studies in food-producing animals, environment and wildlife should be warranted especially in the geographical areas where prevalence of CP invasive bacteria in humans is high. For instance, in Europe, southern and eastern countries reported the highest prevalence of carbapenem-resistant bacteria in human settings. In decreasing order, CP bacterial infections are mostly reported by Greece, Italy, Romania, Cyprus and Bulgaria for *K. pneumoniae*; by Romania, Latvia, Slovakia, Greece and Hungary for *P. aeruginosa*; by Croatia, Greece, Lithuania, Romania and Bulgaria for *Acinetobacter* spp. (ECDC, 2018).

Several studies agree that antibiotic resistance plasmids and other transferable elements are circulating among livestock and wild animals worldwide and across vertebrate species barriers (Chang *et al*., 2015). Although the overall prevalence of CP microorganisms in food-producing animals and wildlife appears to be low, CP bacteria transmission from food-producing animals to their derived products could be a threat to consumers, thus promoting mobile carbapenemase gene pools in human enteric flora and supporting transmission of resistant determinants between commensal and pathogenic microorganisms with unknown, but potentially severe, consequences for human health.

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