

Extended-spectrum β -lactamase/AmpC- and carbapenemase-producing *Enterobacteriaceae* in animals: a threat for humans?

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There has been a great and long-term concern that extended-spectrum β -lactamase (ESBL)/AmpC- and carbapenemase-producing *Enterobacteriaceae* occurring in animals may constitute a public-health issue. A large number of factors with complex interrelations contribute to the spread of those bacteria among animals and humans. ESBL/AmpC- or carbapenemase-encoding genes are most often located on mobile genetic elements favouring their dissemination. Some shared reservoirs of ESBL/AmpC or carbapenemase genes, plasmids or clones have been identified and suggest cross-transmissions. Even though exposure to animals is regarded as a risk factor, evidence for a direct transfer of ESBL/AmpC-producing bacteria from animals to humans through close contacts is limited. Nonetheless, the size of the commensal ESBL/AmpC reservoir in non-human sources is dramatically rising. This may constitute an indirect risk to public health by increasing the gene pool from which pathogenic bacteria can pick up ESBL/AmpC/carbapenemase genes. The extent to which food contributes to potential transmission of ESBL/AmpC producers to humans is also not well established. Overall, events leading to the occurrence of ESBL/AmpC- and carbapenemase-encoding genes in animals seem very much multifactorial. The impact of animal reservoirs on human health still remains debatable and unclear; nonetheless, there are some examples of direct links that have been identified.

Keywords:
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CTX-M
CMY
NDM
OXA-48
VIM
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Animal
Food

Introduction

Extended-spectrum β -lactamases (ESBL) and AmpC-producing *Enterobacteriaceae* (EPE) have emerged globally in humans and animals during the last decades, with the burning concern of animals being a possible source of ESBLs/AmpCs for humans. ESBL/AmpC genes are mostly located on mobile genetic elements such as plasmids, some of which are regarded as epidemic [1]. ESBL/AmpC enzymes may significantly differ in nature and prevalence between animals and humans, which leads to uncertainties on the real magnitude of their transfer from animals to humans [2]. Overall, certain combinations of ESBL/AmpC genes and plasmids seem to have more epidemiological success than others, and these

predominant combinations differ between animals and humans [1]. Furthermore, some given *Escherichia coli* lineages play a major role in the dissemination of ESBL/AmpC genes. In humans, a single *E. coli* clone, namely the ST131, accounts for a large fraction of *E. coli* infections and is frequently associated with the production of the CTX-M-15 ESBL type. In contrast, ST131 has been poorly reported in animals [3]. In fact, numerous data highlight the existence not only of shared reservoirs of ESBL/AmpC genes between animals and humans, but also of plasmids and clones, suggesting cross-transmissions. However, studies showing direct transmission are scarce [4,5], and finding identical resistance traits in different places does not necessarily prove a causal relationship.

Carbapenemases are also important causes of resistance in *Enterobacteriaceae* in humans, and carbapenemase genes are associated with a high potential of dissemination [6]. The public health risk related to carbapenemase-producing *Enterobacteriaceae* (CPE) occurring in animals has been questioned on several occasions [7,8]. Contrary to extended-spectrum cephalosporins (ESC),

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the use of carbapenems is highly limited in animals, which gives a quite different epidemiological picture. Nonetheless, CPE in non-human sources may constitute an underestimated reservoir subsequently at risk to humans.

This review will discuss the threat to humans represented by EPE/CPE found in animals or animal-derived food products. We will consider the risk from both zoonotic and commensal perspectives and analyse to what extent the global data set on ESBL/AmpC genes, plasmids and clones provides insight into the role of the food chain as a relevant source of such resistant bacteria for humans.

Food-borne zoonotic pathogens as a source of ESBL/AmpC or carbapenemases

The use of antibiotics in agriculture is considered a cause of antimicrobial resistance selection in bacteria that may subsequently contaminate food products. In this respect, the use of ESC in broilers has certainly contributed to the spread of ESBL/AmpC-producing *Salmonella enterica* in the poultry sector [9]. *Salmonella enterica* is one of the two most common causes of food-borne gastroenteritis and can also induce invasive disease which may require antimicrobial treatment with ESC. Since the first reported ESBL-producing *S. enterica* isolate in Tunisia in 1988 [10], ESBL prevalence in this bacterial species has increased worldwide, mostly in low-income countries. ESBL-producing *S. enterica* ingested by consumers present an immediate risk for public health. A series of serovars, including *S. Enteritidis*, *S. Newport* or *S. Paratyphi B*, have been frequently recognized as ESBL or AmpC producers and associated with poultry production. Human cases associated with TEM-52-producing *S. Infantis* of poultry origin have been reported in France and Belgium, and a CTX-M-1-producing *S. Infantis* has recently been proved to cause human infections in Italy, most likely through broiler meat [11]. Also, the *bla*_{CTX-M-1}, *bla*_{CTX-M-15} and *bla*_{CMY-2} genes were reported in human isolates of the *S. Kentucky ST198-X1-SGI1* clone, which has widely disseminated across southern Asia, India, Africa and Europe in humans, food and various animal species [12]. The role of imported foodstuffs as a source for human exposure with ESBL-producing *S. enterica* has been hypothesized. Indeed, the emergence of human and meat isolates of *S. Newport*, *S. Agona* and *S. Anatum* producing CTX-M-8 in Germany might be related to food imported from Brazil where this enzyme has been widely recognized, in contrast to Europe [13]. Prevalence rates of ESBL-producing *S. enterica* in animals vary depending on the countries and continents. A study conducted among 699 *S. enterica* isolates from 1152 retail chickens reported a 24.6% rate of

ESBL producers in Shanghai, China. Conversely, the overall prevalence of human infections with ESBL/AmpC-producing *S. enterica* in Europe remains low—around 0.5% in two recent surveys conducted on >20 000 isolates in Germany and the UK [14,15].

Carbapenemase production in *S. enterica* has been reported in a limited number of human cases (Table 1). The first carbapenemase-producing *S. enterica* isolate was reported in 1998 in the USA. That strain being of serotype Cubana actually produced the KPC-2 carbapenemase [16]. Later, NDM-1, OXA-48-like or KPC-like carbapenemases have been identified in different *S. enterica* serovars, including *S. Senftenberg*, *S. Westhampton*, *S. Stanley*, *S. Saintpaul*, *S. Typhimurium* and *S. Kentucky ST198* (Table 1). At a global scale, carbapenemase resistance in *S. enterica* is still rare, including in countries where those enzymes are endemic. Most carbapenemase-producing *S. enterica* reported in humans were not reported to be associated with food sources; however, epidemiological data were scarce for most cases. To date, only three studies reported carbapenemase-producing *S. enterica* isolates directly recovered from animals (Table 2). VIM-1 was reported in *S. Infantis* in pig and poultry farms, flies and rodents, and manure in Germany [17]. An NDM-1-producing *S. Corvallis* isolate was recovered from a black kite (*Milvus migrans*) in Germany [18], suggesting that occasional vectors may be involved in the epidemiology of carbapenemase-producing *S. enterica*. Very recently, IMP-4-producing *S. Typhimurium* was reported from cats in Australia [19].

Shiga toxin-producing *E. coli* (STEC) are also among common causes of food-borne gastroenteritis, but ESBLs have been associated with STEC in very few cases [20–24]. In 2011, a food-borne outbreak likely associated with the consumption of fenugreek sprouts in Germany was caused by a Shiga toxin-producing Enteric Aggregative *E. coli* O104:H4 leading to 3817 human cases of bloody diarrhoea and/or haemolytic–uraemic syndrome, of which 53 were fatal [25]. Incidentally, some *E. coli* O104:H4 isolates had also acquired the *bla*_{CTX-M-15} gene, albeit without any consequence on the clinical outcome. So far, no carbapenemase gene was identified in STEC.

Overall, ESBL/AmpC-producing zoonotic pathogens contaminating food products constitute a direct risk for public health. In those bacteria, ESBL/AmpC-encoding genes were most probably acquired from the animal reservoir even though their exact origin is difficult to trace. The example of the O104:H4 *E. coli* epidemic is interesting as the *bla*_{CTX-M-15} gene present in some strains was located on an Inc11/ST31 plasmid also reported in other unrelated animal/human contexts. It highlights our limited understanding of the epidemiological distribution of specific ESBL genes/plasmids

Table 1
Carbapenemase-producing *Salmonella enterica* isolates from humans

| Serovar | Date of isolation | Country | Travel/hospitalization History | Carbapenemase gene | References |
|----------------|-------------------|-----------|--------------------------------|-------------------------------|------------|
| Senftenberg | 2008 | UK | | <i>bla</i> _{NDM-1} | [78] |
| Senftenberg | 2011 | USA | India | <i>bla</i> _{NDM-1} | [79] |
| Senftenberg | 2011 | USA | India | <i>bla</i> _{NDM-1} | [80] |
| Agona | ND | Pakistan | | <i>bla</i> _{NDM-1} | [81] |
| Agona | 2012 | Japan | | <i>bla</i> _{IMP-1} | [82] |
| Westhampton | 2012 | France | India | <i>bla</i> _{NDM-1} | [83] |
| Stanley | 2012 | China | | <i>bla</i> _{NDM-1} | [84] |
| Senftenberg | 2012 | India | | <i>bla</i> _{NDM-1} | [85] |
| Kentucky ST198 | 2010 | Morocco | | <i>bla</i> _{VIM-2} | [12] |
| Kentucky ST198 | 2009 | Tunisia | | <i>bla</i> _{OXA-204} | [86] |
| Kentucky ST198 | 2012 | Lybia | Transferred to Switzerland | <i>bla</i> _{OXA-48} | [87] |
| Kentucky ST198 | 2013 | France | Algeria | <i>bla</i> _{OXA-48} | [86] |
| Paratyphi B | 2013 | UK | | <i>bla</i> _{OXA-48} | [78] |
| Typhimurium | 2013 | UK | Africa | <i>bla</i> _{OXA-48} | [78] |
| Typhimurium | 2013 | Colombia | | <i>bla</i> _{KPC-2} | [88] |
| Cubana | 1998 | USA | | <i>bla</i> _{KPC-2} | [16] |
| Schwarzengrund | 2013 | Argentina | | <i>bla</i> _{KPC-2} | [89] |

Table 2
Carbapenemase-producing *Enterobacteriaceae* from animals

| Bacterial species | Animal species | Date of isolation | Country | Carbapenemase gene | References |
|--|----------------|-------------------|-----------|--------------------------------|-------------------------------------|
| <i>Salmonella enterica</i> | Pig/poultry | 2011 | Germany | <i>bla</i> _{VIM-1} | [17] |
| <i>Escherichia coli</i> | Pig/poultry | 2011–2013 | Germany | <i>bla</i> _{VIM-1} | [58–60] |
| <i>Salmonella enterica</i> | Cat | unknown | Australia | <i>bla</i> _{IMP-4} | [19] |
| Diverse ^a | Silver gull | 2012 | Australia | <i>bla</i> _{IMP-4} | [64] |
| <i>Salmonella enterica</i> | Black kite | >2006 | Germany | <i>bla</i> _{NDM-1} | [18,90] |
| <i>E. coli</i> | Dog/cat | 2008–2009 | USA | <i>bla</i> _{NDM-1} | [61] |
| <i>E. coli</i> | Pig | 2014–2015 | China | <i>bla</i> _{NDM-1} | [91] |
| <i>E. coli</i> | Dog | 2014–2015 | Algeria | <i>bla</i> _{NDM-5} | [70,71] |
| <i>E. coli</i> | Cow | 2015 | Algeria | <i>bla</i> _{NDM-5} | [72] |
| <i>Klebsiella pneumoniae</i> | Cow | 2015 | China | <i>bla</i> _{NDM-5} | [76] |
| <i>E. coli</i> | Poultry | 2015 | China | <i>bla</i> _{NDM-5} | lv et al., poster ASM Microbe 2016 |
| <i>E. coli</i> | Poultry | 2015 | China | <i>bla</i> _{NDM-5} | [75] |
| <i>E. coli</i> | Dog/cat | 2015 | China | <i>bla</i> _{NDM-5} | Sun et al., poster ASM Microbe 2016 |
| <i>E. coli</i> | Cow | 2015 | India | <i>bla</i> _{NDM-5} | [77] |
| <i>K. pneumoniae</i> / <i>Klebsiella oxytoca</i> | Chicken meat | 2013 | Egypt | <i>bla</i> _{NDM-type} | [63] |
| Diverse ^b | Dog/cat/horse | 2009–2011 | Germany | <i>bla</i> _{OXA-48} | [65] |
| <i>E. coli</i> / <i>K. pneumoniae</i> | Dog | 2012 | Germany | <i>bla</i> _{OXA-48} | [66] |
| <i>E. coli</i> | Dog/cat | 2009–2013 | USA | <i>bla</i> _{OXA-48} | [67] |
| <i>E. coli</i> | Dog | 2015 | France | <i>bla</i> _{OXA-48} | [68] |
| <i>E. coli</i> | Chicken | 2013 | Lebanon | <i>bla</i> _{OXA-48} | [69] |
| <i>E. coli</i> | Dog | 2014–2015 | Algeria | <i>bla</i> _{OXA-48} | [71] |

^a *E. coli*, *Escherichia fergusonii*, *K. pneumoniae*, *Enterobacter aerogenes*, *Proteus mirabilis*, *Kluyvera georgiana*, *Citrobacter freundii*, *Enterobacter cloacae*, *Proteus penneri*, *Citrobacter braakii*.

^b *K. pneumoniae*, *Enterobacter cloacae*.

combinations in distinct settings. Noticeably, ESBL/AmpC encoding genes in food-borne bacteria probably only represent the tip of the iceberg with regard to the overall colonization rate of EPE in non-human sources. To date, carbapenemase-producing *S. enterica* poses a limited public health concern at a world scale.

Do contacts with animals enhance the risk of ESBL/AmpC transfer to humans?

On-farm studies investigating the transfer of ESBL/AmpC producers from food animals to workers are limited [4]. Such a transfer is complex to elucidate because livestock and humans may harbour identical ESBL/AmpC genes but located on different plasmids and/or within different *E. coli* clones. Also, the finding of the same ESBL/AmpC-producing clone in food animals and humans does not necessarily prove a transfer as EPE are present in the farm environment, which is a common source for animals and humans. In the Netherlands, a cross-sectional study was conducted on 50 broiler farms including 20 broilers per farm and 228 people in contact [5]. Multivariable modelling has considered numerous risk factors, such as hours spent in the broiler house, performance of activities in the farm or type of person, that were further investigated in molecular studies on ESBL genes, plasmids and clones. In this study, farmers and employees were at a higher risk of ESBL carriage than partners and family members who had less contact. In addition, the distribution of ESBL genes, plasmids and *E. coli* clones strongly suggested a transfer of ESBL producers from broilers to humans. Hence, occupational exposure should be regarded as a risk of ESBL transfer from livestock to humans. However, more data are required to quantitatively estimate the risk for humans related to such situations.

Direct contact with pets may also be a source of ESBL/AmpC genes for humans but evidence of transfers is even rarer than for livestock. Some studies compared the resistance profiles and/or clonal relationship of faecal isolates from dogs and owners, and very few of them have focused on ESBL/AmpCs. Molecular similarities among isolates from dogs and humans were found occasionally [26], such as from dogs and humans living in the same household. However the significance of these data is difficult to infer at a larger scale, and the direction of the ESBL/AmpC transfer is

difficult to prove [27]. To summarize, there is no convincing evidence that pet ownership poses a higher risk to humans of becoming colonized or infected with EPE.

Common ESBL/AmpC genes, plasmids and/or clones between animals and humans

Numerous studies have compared the molecular features of ESBL/AmpC genes, plasmids or clones between animal and human sources [28–30]. Similarly to what is observed in humans, the most frequent ESBL enzymes circulating in animals belong to the CTX-M group [31]. In Asian countries, CTX-M-14 predominates in humans, pets and poultry, which may possibly indicate cross-contamination, but also a common third source. It is actually the only example where such an ESBL enzyme is so uniformly distributed [2]. Indeed, CTX-M-1 predominates in animals in Europe, but not in humans. In contrast, CTX-M-15 is widely distributed in humans but poorly in animals, with the notable exception of cattle [32]. A recent study in Lebanese cattle proved an overrepresentation of CTX-M-15-producing *E. coli* that were of different genetic backgrounds (ST10, ST617, ST58, ST69) [33]. Noticeably, none of them belonged to ST131, which is the most widespread in humans [3]. However, non-ST131 CTX-M-15-producing *E. coli* were recently identified in certain human subgroups, suggesting possible changes in the CTX-M-15 epidemiology [34]. More globally, except for the ST131 *E. coli* lineage, which seems to be associated with the human host, other sequence types of CTX-M-producing *E. coli*, such as ST410, ST38 or ST10, were found in human and animal sources [35,36]. Among AmpC enzymes, CMY-2 is the predominant one in the animal sector, mostly from poultry [2,37,38].

Other EPE were subjected to an animal/human comparison but evidence of transfer was not obvious either. Exchanges of ESBL-producing *Klebsiella pneumoniae* isolates between humans and pets have been suggested, such as for the CTX-M-15-producing ST15 *K. pneumoniae* clone widely disseminated in humans and also recognized in pets and horses [39,40] or the human ST101 *K. pneumoniae* clone dominant in Italy also found as a CTX-M-15 producer in dogs [41]. However, a study conducted in Switzerland showed that numerous ESBL-producing *K. pneumoniae* lineages were associated with human infections, that were different from

the DHA-producing ST11 *K. pneumoniae* clone in a veterinary setting [42]. On the contrary, the CTX-M-15-producing ST114 *Enterobacter cloacae* clone recently reported as a high-risk clone in humans was predominant in cats, dogs and horses [43]. Finally, a common cluster of VEB-6-positive SGI1-V-carrying *Proteus mirabilis* isolates from humans, dog and turkey meat was identified in Europe [44–46].

Many research groups compared ESBL/AmpC-producing *E. coli* isolates and ESBL/AmpC genes from human and poultry sources [4,5,29,30,47]. In a study, 19% of human isolates harbouring ESBL-producing *E. coli* clones were identical to those found in chicken meat, and 39% of the ESBL-positive chicken meat isolates belonged to *E. coli* genotypes also found in human isolates [30], thereby suggesting a clonal spread. Other clues sustaining exchanges of ESBL/AmpC producers between poultry and humans result from the comparison of ESBL-encoding plasmids, instead of focusing on ESBL/AmpC genes or *E. coli* backgrounds [48]. Whole-genome sequencing also reported similar Inc11/ST3 plasmids spreading *bla*_{CTX-M-1} in unrelated humans and food animals [49]. The Inc11/ST3 plasmid was also found in 83.3% of CTX-M-1-producing *E. coli* in humans with closely related restriction profiles compared with those found in animals [50]. Indistinguishable or closely related IncN plasmids bearing *bla*_{CTX-M-1} were recovered from diverse *E. coli* lineages of Danish pigs, pig farm employees and manure samples [51].

All these studies investigated animal and human populations that were not all necessarily in direct contact. In conclusion, most epidemiological data were based on the comparison of molecular

features of ESBL/AmpC genes, plasmids or clonal backgrounds, and so far limited information actually sustain clear transmission pathways.

What is the ESBL/AmpC colonization rate of the non-human reservoir?

The size of the ESBL/AmpC animal reservoir is a crucial question with respect to risk assessment issues. Similarly to the situation in humans, ESCs are widely used in animals and contribute to the selection of ESBL/AmpC producers in that sector. Although restrictions on the use of ESCs in animals have mostly been set up in Europe (Denmark, The Netherlands, France), numerous countries outside Europe still have not implemented specific regulations. International food trades are major driving forces for the transfer of EPE within the food chain—and subsequently to human populations—so that ESC usage in a single country may result in high rates of EPE in another country [52]. This has been clearly shown by the spread of CMY-2-producing *E. coli* in the Swedish broiler production pyramid next to the importation of top breeders carrying the *bla*_{CMY-2} gene. Co-selection with other antibiotics than ESCs is also an important driver as most ESBL/AmpC-producing bacteria are multi-drug resistant. Altogether, the ESBL/AmpC prevalence is inevitably rising worldwide in both animals and humans and, consequently, so is the risk of cross-transmission.

There is evidence of increasing gut colonization with EPE in animals, albeit depending on the countries and food sectors. In the Netherlands, from the late 1990s to 2010, the proportion of ESBL-

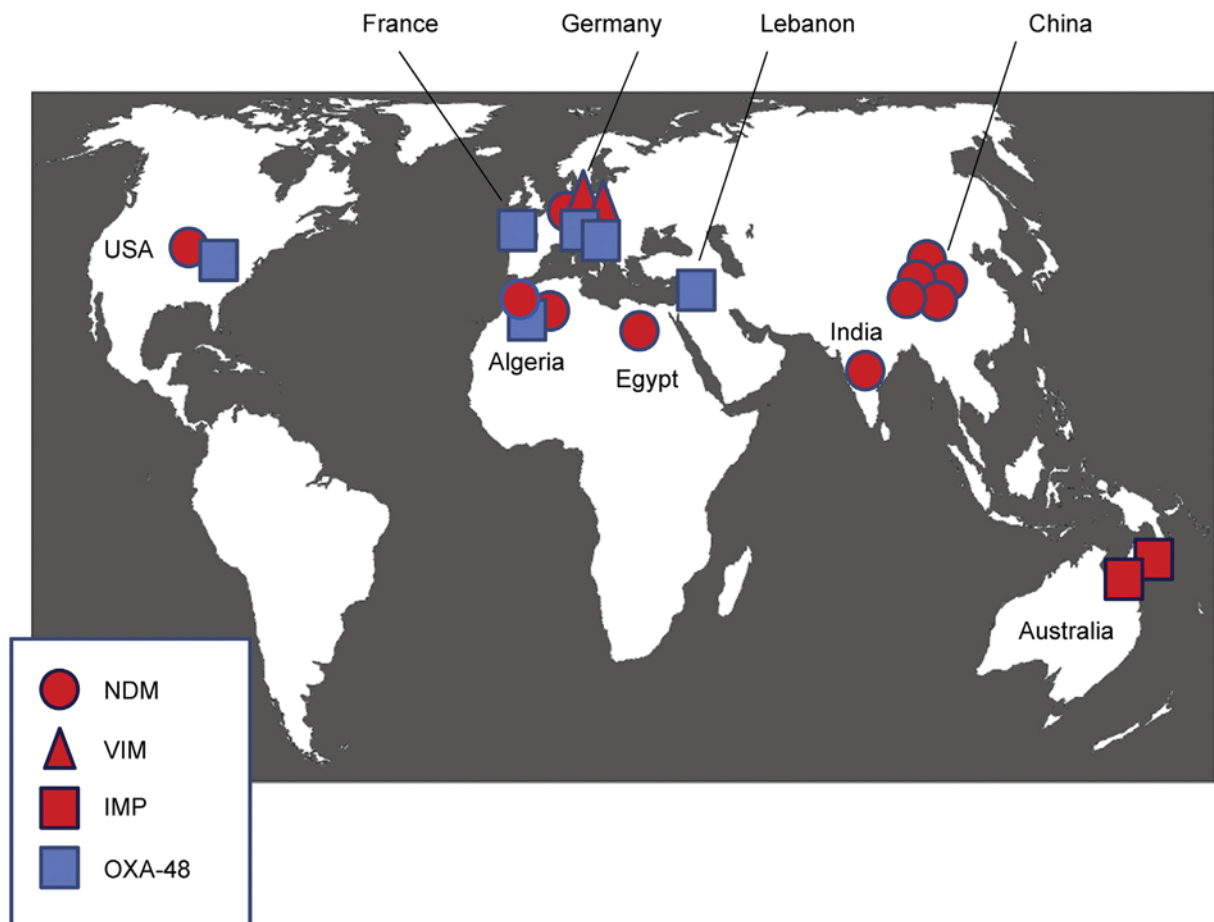


Fig. 1. Geographical distribution of carbapenemase-producing *Enterobacteriaceae* reported in animals or animal-derived products according to the major carbapenemases families.

producing *E. coli* has risen from 4% to 39% in calves [53]. The surface contamination of food products with EPE has also been abundantly reported, both from domestic and imported food, and mainly from broiler meat [54,55]. EPE present on food are not necessarily of animal origin as human handling is also a source of food contamination. The risk to humans through food intake is also highly dependent on whether those foodstuffs are consumed raw or not. Yet, robust quantitative data are still lacking to conclude that there is real enrichment of the human microbiota with ESBL/AmpC-producing *E. coli* isolates via the food chain.

The burden of EPE in animals is also highlighted by the colonization of wild animals and remote environmental niches, which are not supposed to be exposed to significant amounts of antimicrobials. The number of studies reporting EPE in non-domestic animals has been increasing, most of them focused on birds [56,57]. Considering the migratory behaviour of some birds, together with the possibility of acquiring ESBL/AmpC-producing strains through feeding on human wastes, farms, sewage or other contaminated places, bird-related transmission is regarded as a potential threat for spreading ESBL/AmpC-producing *E. coli*. Nonetheless, the prevalence of those bacteria appears much lower in wildlife than in farmed animals even though large population studies are still limited. Further spatial and temporal investigations on the different ESBL/AmpC-producing *E. coli* genetic backgrounds in wildlife are also needed to clarify possible similarities with those of domestic animals and humans. Finally, EPE have also been reported in vegetables, fruits or wastewater, meaning that the ESBL/AmpC burden should be considered as a global and ecological pollution.

Carbapenemase producers in animals: a threat to humans?

Carbapenems are last-resort drugs to treat infections with multidrug-resistant Gram-negative bacteria [6]. In veterinary medicine, carbapenems have no legal indication and are not used in routine practice, at least for food-producing animals. Position papers from the European Medicine Agency clearly stated that carbapenems should not be used in animal therapy. Subsequently, in contrast to the human medicine, reports of carbapenemase producers in animals are scarce.

The global distribution of the carbapenemase families reported in animals is presented in Fig. 1. Carbapenemases in *S. enterica* in humans and animals are presented above (Tables 1 and 2). However, VIM-1 was not only reported in *S. Infantis* but also in *E. coli* in pig and poultry farms, along with their close environment [58,59] (Fig. 2, Table 2). Of note, a recent retrospective study on those positive pig farms in Germany showed that the VIM-1-producing *S. enterica* and *E. coli* could persist over time in one single farm [60]. CPE were also reported from companion animals (Fig. 2, Table 2). NDM-1-producing *E. coli* were reported from five dogs and a cat in the USA [61] and from pigs in China [62], while NDM-type-producing *Klebsiella* spp. were reported from retail chicken meat in Egypt [63]. IMP-4-producing *Enterobacteriaceae* were found to be highly prevalent in Australian gulls [64]. OXA-48-producing *E. coli* and/or *K. pneumoniae* were isolated from dogs, cats and a horse in Germany [65,66], the USA [67] and France [68] and from chicken in Lebanon [69]. In Algeria, five carbapenemase-producing *E. coli* were detected in dogs, including four OXA-48- and a NDM-5-producing

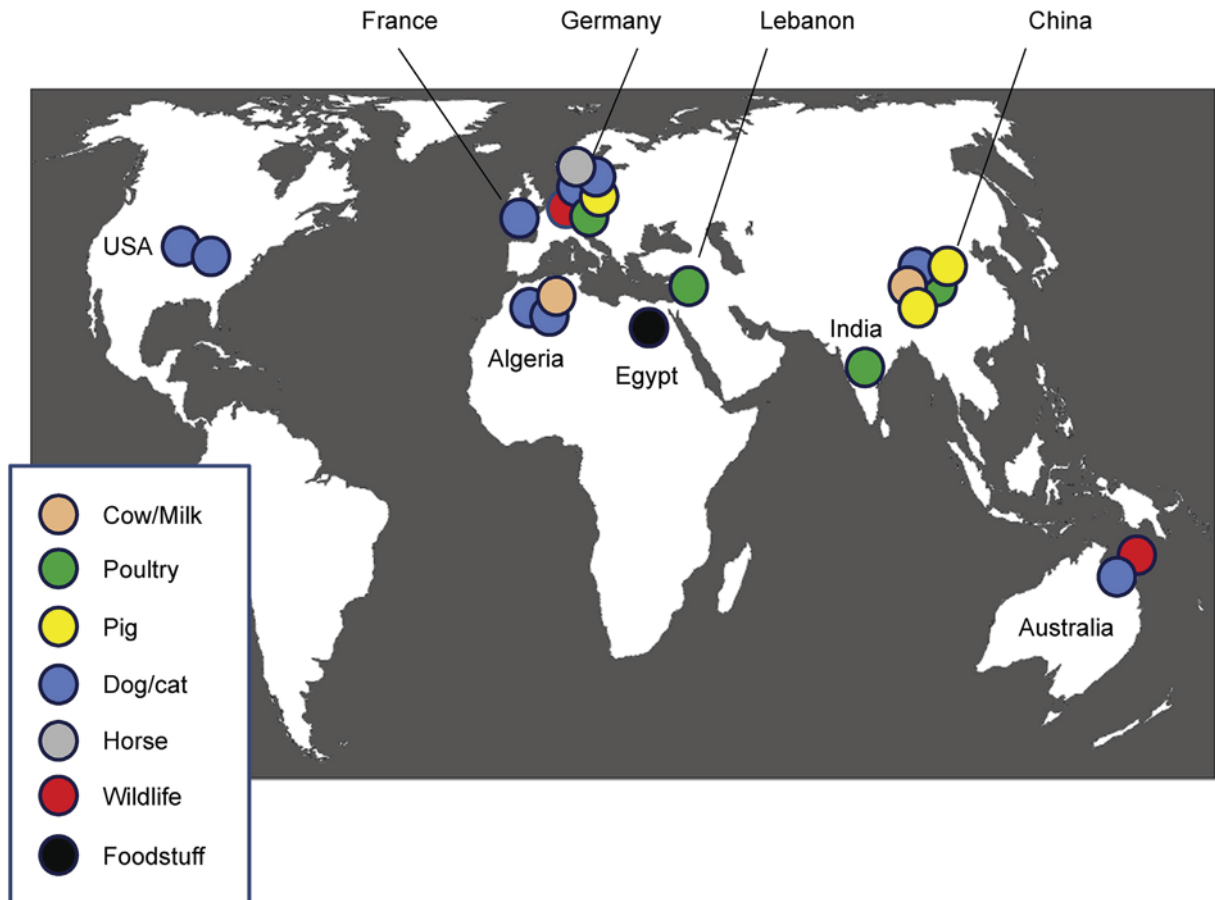


Fig. 2. Geographical distribution of carbapenemase-producing *Enterobacteriaceae* reported in animals or animal-derived products according to the animal species/food from which they have been isolated.

isolates that all co-expressed an ESBL enzyme. Of note, the same NDM-5-producing ST1284 *E. coli* clone was found in a diseased dog and in milk and milking cows [70–72]. The finding of NDM-5 in raw milk in a country where local consumption is common highlights the risk of direct transfer of NDM producers to humans in the community. NDM-5 was also reported recently in milk and dairy cows, poultry and dogs in China [73–76] and in cattle in India [77]. Both in Algeria and China, *bla*_{NDM-5} was located on the same IncX3-type plasmid. Again, a selective pressure with carbapenems seems unlikely in those animals, but domestic or food animals may act as secondary reservoirs possibly re-circulating NDM producers back to the human population.

Overall, the presence of CPE in animals is definitely worrying. At this stage of knowledge, acquired carbapenemases in animals are largely observational and most likely derived from human sources. For instance, IMP-4 was found in cats and gulls in Australia, a continent where IMP-4 is also the most common carbapenemase reported in humans. Nonetheless, most carbapenemase reports in animals resulted from side investigations within other studies and do not reflect a large and systematic screening with appropriate methods (using carbapenem-supplemented selective media, for instance). Another point is that those genes are mostly located on plasmids, which may carry other resistance genes such as tetracyclines, sulphonamides or phenicols widely used in veterinary medicine. Once introduced in the animal sector, those plasmids may be further co-selected and amplified by the use of other classes of antibiotics before spreading back to humans.

Conclusion

The wide spread of EPE in numerous (if not all) settings of the ecosphere highlights the current major scientific challenges to combat those resistant bacteria in a One-Health approach. The use of antibiotics in animals and humans is probably the main selective factor responsible for the increasing prevalence rate of ESBL/AmpCs, but many others should be considered, in particular the role of international trades of food animals and products thereof. Of note, other antimicrobials than ESC can select for EPE, such as tetracyclines, sulphonamides and trimethoprim widely used in animals, as many ESBL/AmpC genes are mostly located on plasmids carrying a series of multidrug resistance genes. However, such an alarming distribution of ESBL/AmpC genes does not necessarily indicate a similar alarming risk of transfer to humans. The situation with carbapenemases is quite different, most likely because of the very limited use of carbapenems in animals. At this stage of knowledge, CPE in animals should not be considered a major risk for humans. However, even though the menace is still ahead of us, the global recirculation of carbapenemase genes among animals and humans may well create new and worrying epidemiological pictures in the future.

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Transparency declaration

None to declare.

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