# The Public Health Risk of Companion Animal to Human Transmission of Antimicrobial Resistance During Different Types of Animal Infection

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**Abstract.** Antimicrobial resistance represents a major threat to human health. As a result, we are faced with potential antimicrobial therapeutic failure, thus forcing physicians to use last resort antimicrobials, such as carbapenems, glycopeptides or polypeptides. During the last fifty years, the number of companion animals has substantially increased and there is a growing concern related to the use of antimicrobials in companion animals as a potential source for antimicrobial resistance to humans. Problems related with antimicrobial resistance and infection control in small animal hospitals are mimicking those in human hospitals. Transmission of pathogens or resistance genes such as methicillin-resistant staphylococci, extended spectrum beta-lactamase- or carbapenemase-producing and colistin-resistant Enterobacteriaceae between people and their pets have been documented or suggested. The public health risks associated with the transfer of antimicrobial-resistant bacteria from companion animals were recently reviewed by the European Medicine Agency which warned to the existence of antimicrobial resistance microbiological hazards coming from companion animals to humans. The magnitude to which these occur, and the risks posed by the different animal species is still inadequately studied. This is the main goal of the JPI-EC-AMR JTC 2016 Pet-Risk Consortium (Portugal, Germany, Switzerland, UK, Canada) JPIAMR/0002/2016 under the CIISA Antibiotic Lab Team Leader Coordination.

**Keywords:** Antimicrobial resistance · Animal infection · Public health risk

## 1 The Antimicrobial Use in Veterinary Medicine

The increase in antimicrobial resistance represents a major threat to human and animal health (WHO 2017a). As a result, we are now faced with the reduction of treatment options and with potential therapeutic failure leading veterinarians to use antimicrobials off-label and physicians to use last resort antimicrobials.

There is a growing concern related to the use of antimicrobials in food-producing and companion animals as a potential source for antimicrobial resistance to humans (Greko


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*et al*. 2009; Catry *et al*. 2010; van Duijkeren *et al*. 2014; Pomba *et al*. 2017). In fact, it is known that the use of antimicrobials increases the risk of antimicrobial resistance and the risk of colonization with antimicrobial-resistant bacteria (Barza and Travers 2002; Belas *et al*. 2014).

Since 2010, the European Medicine Agency started reporting data on antimicrobial sales for companion animals (EMA 2017b). Beta-lactams, including potentiated penicillins, were the most frequently sold for companion animals in most European countries, including Portugal (EMA 2017b). Furthermore, fluoroquinolones were the second most sold in Portugal.

It should be noted that the most sold antimicrobials in companion animals worldwide overlap those routinely used in human medicine and are considered as critically important antimicrobials to humans by the World Health Organization (WHO 2016b). Interestingly, the problems of antimicrobial resistance development and infection control in small animal hospitals are mimicking those in human hospitals (ECDC 2017). Furthermore, in contrast to food-producing animals, the prescription of antimicrobials only approved for human use may occur under the cascade principles in companion animals (Pomba *et al*. 2017). This represents an additional antimicrobial resistance selective pressure towards last resorts antimicrobials and warrants the need for a One Health approach to fighting the dissemination of antimicrobial resistance.

## 2 Risk of Transfer of Antimicrobial-Resistant Bacteria

The number of companion animals has significantly increased over the last 50 years (Guardabassi *et al*. 2004; Pomba *et al*. 2017). The closer contact between owners and companion animals creates opportunities for pathogen interchange through direct and indirect contact (Guardabassi *et al*. 2004; Damborg *et al*. 2016).

The public health risks associated with the transfer of antimicrobial-resistant bacteria from companion animals have been reviewed in the European Medicine Agency and its Antimicrobial Working Party reflection paper (Pomba *et al*. 2017). Pomba *et al*. (2017) alerted for existence of several antimicrobial resistance microbiological hazards coming from companion animals to humans (Table 1).

The concerns surrounding the role of companion animals in the dissemination of resistant bacteria to humans are strengthened by numerous studies reporting the colonization and/or infection of companion animals with bacteria harboring clinically relevant antimicrobial resistance mechanisms or bacteria belonging to high-risk clonal lineages to humans (Guardabassi *et al*. 2004; Damborg *et al*. 2016; Pomba *et al*. 2017).

This has been one of the main focus of the research conducted in the Antibiotic Resistance Laboratory in Enterobacteriaceae, non-Enterobacteriaceae, Staphylococci and Enterococci (Féria *et al*. 2001a; Féria *et al*. 2001b; Caniça *et al*. 2004; Delgado *et al*. 2007; Braga *et al*. 2011; Couto *et al*. 2011; Pinho *et al*. 2013; Catry *et al*. 2015; Couto *et al*. 2015a; Razuaskas *et al*. 2015a; Razuaskas *et al*. 2015b; Couto *et al*. 2016a; Couto *et al*. 2016b; Razuaskas *et al*. 2016; Pomba *et al*. 2017; Costa *et al*. 2018; Marconi *et al*. 2018; Marques *et al*. 2018; Rodrigues *et al*. 2018; Belas *et al*. 2019; Marques *et al*. 2019a; Marques *et al*. 2019b).

**Table 1.** Microbiological hazards from companion animals to humans identified by EMA (adapted from Pomba *et al*., 2017).

| Antimicrobial-resistant bacteria | Type of hazard | Source |
|---|---|---|
| MRSA | Direct hazard[a] | Dogs, cats and horses |
| MRSP | Direct hazard | Dogs, cats and horses |
| VRE | Indirect hazard[b] | Dogs and horses |
| ESBL-producing Enterobacteriaceae | Indirect hazard | Dogs, cats and horses |
| Carbapenem-resistant Gram-negative bacteria | Indirect hazard[b] | Dogs and cats |
| Colistin-resistant *E. coli* | Indirect hazard | Dogs and cats |

Legend:
[a]Low number of cases of human infections originating from companion animals.
[b]No human infections originating from companion animals have been reported. However, regarding carbapenems, co-colonization has been recently reported (Grönthal *et al*. 2018).

## 3 Antimicrobial Resistance Mechanisms and Bacteria of Concern

### 3.1 Staphylococci

Portugal is among the European countries with higher frequency of methicillin-resistance in invasive *Staphylococcus aureus* from humans (ECDC 2009). Methicillin-resistant Staphylococcus aureus (MRSA) have been detected in a wide number of animal species (Catry *et al*. 2010; Pomba *et al.* 2017), including in Portugal (Coelho *et al*. 2011; Couto *et al*. 2014b; Beça *et al*. 2015; Couto *et al*. 2015b; Couto *et al*. 2016a; Rodrigues *et al*. 2018).

In companion animals, MRSA has been isolated from skin and soft-tissue infections, post-surgical wound infections, urinary tract infections and pneumonia (Catry *et al.* 2010; Pomba *et al*. 2017). In a study from Portugal, conducted in the Antibiotic Resistance Laboratory, several MRSA were detected in companion animals with skin and urinary tract infections (Couto *et al*. 2016c). Notably the MRSA strains isolated from companion animals belonged to CC5 which is a lineage associated with human infection in Portugal (Couto *et al*. 2015a; Couto *et al*. 2016c).

In fact, the similarity of MRSA clonal lineages isolated from companion animals and humans has been reported worldwide (Weese and Duijkeren 2010; Pomba *et al*. 2017). In another study about the clonal diversity, virulence patterns and antimicrobial and biocide susceptibility among human, animal and environmental MRSA in Portugal, *S. aureus* clonal lineages from companion animals (CC5 and CC22) were associated with specific sets of virulence genes and often with a lower number of resistance genes than isolates belonging to the livestock associated CC398 (Couto *et al*. 2015b). Colonization of companion animals with MRSA has been previously reported ranging from 0% to 7% (Leornardo and Markey 2008; Catry *et al*. 2010; Pomba *et al*. 2017). In one study from Portugal, 1.4% of cats and 0.7% of dogs were reported to be colonized by MRSA (Couto *et al*. 2014b).

The risk of transmission of MRSA between companion animals and humans has been demonstrated highlighting the role of both species in this issue (Damborg *et al*. 2016; Pomba *et al*. 2017). Interestingly, veterinary staff seems to be at higher risk of being colonized by MRSA (Baptiste *et al*. 2005; Loeffler *et al*. 2005; Catry *et al*. 2010, Pomba *et al*. 2017). Besides MRSA, companion animal health care providers from Portugal also had a high frequency of colonization by methicillin resistant *Staphylococcus epidermidis* (MRSE) (Rodrigues *et al*. 2018). MRSAs colonizing humans from this study belonged to the major human healthcare clone in Portugal (ST22-t032-IV), the livestock-associated MRSA (ST398-t108-V) and to the New York-/Japan-related clone (ST105-t002-II) (Rodrigues *et al*. 2018). Furthermore, *S. epidermidi*s is an important nosocomial pathogen responsible for life-threatening infections associated with the use of medical devices and in immunocompromised individuals, whose management is hindered by frequent resistance to antimicrobials (Costa *et al*. 2018).

Most infections in companion animals are caused by *Staphylococcus pseudintermedius*, especially in dogs (Couto *et al*. 2016a; Couto *et al*. 2016b). The detection of multidrug-resistant methicillin-resistant *S. pseudintermedius* (MRSP) is increasingly being reported leading to significant therapeutic limitation in small animal veterinary medicine (Couto *et al*. 2014b; Couto *et al*. 2016a; Couto *et al*. 2016b; Pomba *et al*. 2017). A significant increase in the detection of multidrug-resistant MRSP has been recently noted in companion animals from Portugal (Lisbon) (Couto *et al*. 2016a). Although methicillin-susceptible *S. pseudintermedius* isolates are genetically diverse, a limited number of MRSP clones have spread worldwide resembling the worldwide dissemination of MRSA (Van Duijkeren *et al*. 2011; Pomba *et al*. 2017). Like MRSA, the emergence of MRSP represents a great problem for small animal veterinary medicine since *S. pseudintermedius* is the primary staphylococcal species colonizing healthy dogs and cats. MRSP colonization is more common in dogs than in cats. Furthermore, MRSP can cause many types of infections in companion animals as skin and ear infections, surgical site infections, gingivitis, hepatitis, urinary tract infections, respiratory infections, arthritis, peritonitis and septicaemia (Van Duijkeren *et al*. 2011; Pomba *et al*. 2017). It is important to keep in mind that veterinary hospitals and clinics play an important role in the dissemination control of MRSP (Pomba *et al*. 2017).

In Portugal, the Antibiotic Resistance Laboratory has conducted extensive studies about the *S. pseudintermedius* (MRSP and MSSP) colonization and infection in dogs and cats to characterize their clonality, antimicrobial susceptibility, biocide susceptibility and immunogenic properties (Couto *et al*. 2014a; Couto *et al*. 2015b; Couto *et al*. 2016c; Couto *et al*. 2016b). A worrying finding from these studies was the significant increase in staphylococci resistance, mainly *S. pseudintermedius,* to a large number of antimicrobials over the last 16 years (Couto *et al*. 2016a). Importantly, this included an increase in the detection of multidrug-resistant MRSP and the *mecA* gene (Couto *et al*. 2016b). The increase of MRSP in Portugal was linked to the dissemination of the S. pseudintermedius clonal lineage ST71-II-III, which is also the most disseminated clonal lineage in dogs and cats from Europe (Kadlec *et al*. 2010; Perreten *et al*. 2010).

Colonization of humans with *S. pseudintermedius* seems to be uncommon and transient, however owners and veterinarians in contact with infected companion animals may have a higher risk of being MRSP positive (Pomba *et al*. 2017). There are some

reports of colonization of veterinarians by MRSP that could suggest an occupational risk (Sasaki *et al*. 2007; Ishihara *et al*. 2010; Paul *et al.* 2011; Soedarmanto *et al*. 2011; Gómez-Sanz *et al*. 2013; Chanchaithong *et al*. 2014; Pomba *et al.* 2017). Furthermore, in 2014 a cluster of infections in a tertiary hospital due to MRSP clone ST71 was described in humans (Starlander *et al*. 2014).

While MRSA strains isolated from companion animals are mainly related to different human-associated MRSA clones, the scenario for MRSP is different. Diverse SCC*mec* elements occur among the different MRSP genetic lineages, suggesting that the *mec*A gene has been acquired by different *S. pseudintermedius* strains on multiple occasions. (Pomba *et al.* 2017). Transfer of SCC*mec* elements between different staphylococcal species is possible, which is a concern.

### 3.2 Enterococci

Enterococci are opportunistic pathogens, that have become an important cause of nosocomial and community-acquired infections, such as septicemia, endocarditis, UTI and diarrhea. Moreover, these bacteria are an important key indicator for several human and veterinary resistance surveillance systems (Torres *et al*. 2018). *Enterococcus faecalis* and *Enterococcus faecium* are the most common species isolated from human and companion animal infections. Enterococci are intrinsically resistant to several antimicrobials which have important therapeutic implications (Torres *et al.* 2018). Therefore, acquired resistance to ampicillin/penicillin and to high-level gentamicin, a classic therapeutic synergetic combination, strongly limits the treatment options against enterococcal infections (Chow, 2000). Such resistance mechanisms have been described in enterococci isolated from companion animals from Portugal (Delgado *et al*. 2007; Marques *et al*. 2018b).

Some studies provide that healthy livestock, wildlife, food-producing animals and companion animals can harbour pathogenic Enterococci that can be transferred via food chain or through close contact with humans. Furthermore, some Enterococci species are able to evolve from being simple commensal bacteria to being pathogenic to humans and animals through the acquisition of virulence factors encoded in mobile genetic elements (Bortolaia and Guardabassi 2015; Pillay *et al*. 2018).

For instance, the *E. faecalis* ST16 clonal lineage is considered a zoonotic pathogen and food and industries seem to have contributed to its dissemination (Torres *et al*. 2018). Furthermore, this clonal lineage is frequent among high-level gentamicin resistant strains harboring the bifunctional enzyme (Ruiz-Garbajosa *et al*. 2006). Other important Enterococci high-risk clonal complexes (CC) associated with nosocomial infections in humans include the *E. faecalis* CC6 (formerly CC2) and the ampicillin-resistant *E. faecium* CC17 (Leavis *et al*. 2006; Kuch *et al*. 2012).

Due to its clinical relevance, the Antibiotic Resistance Laboratory has contributed with epidemiological studies about the antimicrobial resistance and population structure of enterococci isolated in Portugal (Delgado *et al*. 2007; Pomba *et al*. 2010; Braga *et al*. 2011; Braga *et al.* 2013; Marques *et al*. 2018a). In one of these studies, the first report of a biocide resistance mechanism in *E. faecalis* and its dissemination amongst the genus Enterococcus was reported (Braga *et al*. 2011).

Ampicillin-resistance and/or high-level gentamicin resistance in enterococci from companion animals with UTI in Portugal (Lisbon) over 16 years was low when compared

with the resistance frequencies detected in Enterobacteriaceae (Marques *et al*. 2019a). However, many of these isolates belonged to *E. faecalis* ST16, *E. faecalis* CC6 and to the ampicillin-resistant *E. faecium* CC17. Interestingly, a previous study has shown that healthy dogs seem to be reservoirs of ampicillin-resistant *E. faecium* CC17 (Damborg *et al*. 2009).

The acquired resistance to vancomycin due to *van* gene carriage is another resistance mechanism of great importance in human medicine (Pomba *et al*. 2017). Ampicillin-resistance in *E. faecium* from Europe seams to often predict the increase in the rates of vancomycin-resistant enterococci (VRE) within some years (Werner *et al*. 1904). Although, the level of ampicillin-resistant *E. faecium* in companion animals with UTI was low, higher frequencies have been reported in other parts of Europe (Damborg *et al*. 2009). Therefore, active surveillance is imperative.

Healthy dogs and cats may become colonized by VRE. Furthermore, VRE isolated from companion animals may also belong to clonal lineages associated with hospital-acquired infections (Pomba *et al*. 2017).

## 4 Enterobacteriaceae and Non-Enterobacteriaceae

There are a large number of studies reporting the detection of extended spectrum beta-lactamases (ESBLs) - producing bacteria in companion animal infections and in colonized animals (Ewers *et al*. 2012; Belas *et al*. 2014; Pomba *et al*. 2014a; Damborg *et al*. 2015; Pomba *et al*. 2017).

Detection
of carbapenemase-producing Enterobacteriaceae and non-Enterobacteriaceae are still a rare event; however, reports in healthy and sick animals are increasing by the day, and will likely become a serious problem in the future (Pomba *et al*. 2014b; Chanchaithong *et al*. 2014; Gentilini *et al*. 2018; Grönthal *et al*. 2015; Köck *et al*. 2018).

The Antibiotic Resistance Laboratory has made the first description of an OXA-23-producing ST2 MDR *Acinetobacter baumannii* in a cat with urinary tract infection (UTI) (Pomba *et al*. 2014a). Just recently, the transmission of a canine clinical NDM-5 *Escherichia coli* between an infected dogs and humans was confirmed for the first time (Grönthal *et al*. 2015) giving additional scientific support to the concerns surrounding the close contact of companion animals with humans (Pomba *et al*. 2017).

Although less studied than other Gram-Negative bacteria, *Pseudomonas aeruginosa* is an important pathogen causing otitis and pyoderma in companion animals (Pomba *et al*. 2017). Notably, carbapenem-producing strains have already been detected in dogs (Hyun *et al*. 2018). Also, some infections caused by these bacteria are in association with other pathogens, such as MRSP (Lupo *et al*. 2017).

In an ongoing study conducted in the Antibiotic Resistance laboratory, *P. aeruginosa* causing external otitis in companion animals from Portugal (Lisbon) showed high resistance levels towards fluoroquinolones and aminoglycosides, which are frequently used topically. Furthermore, resistance to imipenem and doripenem was also noted (Marconi *et al*. 2018).

Companion animals have been found to be colonized by *E. coli* and *Klebsiella. pneumoniae* belonging to important clonal lineages to humans (Pomba *et al*. 2014b;

Johnson *et al*. 2016; Pomba *et al*. 2017; Marques *et al*. 2018; Belas *et al*. 2019; Marques *et al*. 2019a). Since many pathogenic bacteria, are thought to make part of the normal gut flora (Podschun and Ullmann 1998; Drzewiecka 2016; Johnson *et al*. 2016; Martin *et al*. 2016), gut colonization of companion animals may also represent an important hazard. Interestingly, pet ownership (dogs, cats and other companion animals) was suggested to be a risk factor for human gut colonization by ESBL-producing *E. coli* (Meyer *et al*. 2012).

Regarding Enterobacteriaceae, companion animals from the same household may be colonized and share the uropathogenic *E. coli* O25B: H4: B2-ST131 clonal lineage (Johnson *et al*. 2009; Johnson *et al*. 2016). More importantly, humans and dogs with UTI have been shown to share the index uropathogenic *E. coli* with household members including the family dogs and cats (Murray *et al*. 2004; Johnson and Clabots 2016). Just recently, in a study conducted by the Antibiotic Resistance Laboratory, companion animals and humans living in close contact were screened for colonization by *K. pneumoniae* and *Proteus mirabilis* (Marques *et al*. 2018a; Marques *et al*. 2019a). Interestingly, some dogs and humans were shown to be colonized in the gut by undistinguishable (by PFGE and MLST) *K. pneumoniae* strains, suggesting the possibility of transmission between dogs and humans (Marques *et al*. 2018a).

Besides beta-lactams, the dissemination of colistin resistance plasmids mcr-1 to 7 has been recently on the spotlight (Yang *et al*. 2018). The dissemination of MDR carbapenemase-producing bacteria in human medicine has led to the need to return to old antimicrobials such as colistin. The recent identification of the colistin resistance gene mcr-1 in food-production animals and companion animals in multiple countries is a concern (Liu *et al*. 2016; Perreten *et al*. 2010; Schwarz *et al*. 2016). In Portugal, mcr-producing Enterobacteriaceae have been identified in retail meat (Figueiredo *et al*. 2016); clinical strains (Campos *et al*. 2011; Mendes *et al*. 2018) and food producing animals (Kieffer *et al*. 2017; Freitas-Silva *et al*. 2018). Moreover, a recent report of a mcr-1-containing *E. coli* in a person and in multiple dogs and cats heightens these concerns (Zhang *et al*. 2016).

## 5 The Future

The current scientific knowledge seems to support the suspicion that companion animals may act in the dissemination of resistant and pathogenic bacterial clones to humans and vice versa.

However, several questions still remain answered. Skin (including ear) and urinary tract infections are the most frequent infection in companion animals. Previously published data, including from the Antibiotic Resistance Laboratory (Féria *et al*. 2001a; Féria *et al*. 2001b; Caniça *et al*. 2004; Delgado *et al*. 2007; Braga *et al*. 2011; Couto *et al*. 2011; Pinho *et al*. 1099; Catry *et al*. 2015; Couto *et al*. 2015a; Razuaskas *et al*. 2015a; Razuaskas *et al*. 2015b; Couto *et a*l. 2016a; Couto *et al*. 2016b; Razuaskas *et al*. 2016; Pomba *et al*. 2017; Costa *et al*. 2018; Marques *et al*. 2018a; Rodrigues *et al*. 2018; Belas *et al*. 2019; Marques *et al*. 2019a; Marques *et al*. 2019b), have shown that bacteria causing skin infections and UTIs in companion animals are sometimes associated with major resistance mechanisms and bacterial clonal lineages. Furthermore, several studies

support the sharing/transmission of important bacterial clonal lineages between companion animals and humans (Johnson and Clabots 2016; Murray *et al*. 2004; Johnson *et al*. 2009; Johnson *et al*. 2016; Marques *et al*. 2018a; Marques *et al*. 2019b). However, the extent to which such transfer occur is still poorly studied. The main goal of the JPI-EC-AMR JTC 2016 Pet-Risk Consortium (Portugal, Germany, Switzerland, UK, Canada) JPIAMR/0002/2016 under CIISA Antibiotic Lab Team Leader Coordination is to clarify the extent of transmission and whether different types of infections may convey additional risk to humans or vice-versa. This project will stand on edge using Next Generation Sequencing technologies to unequivocally evaluate the transmission of clinically relevant antimicrobial mechanisms and pathogenic bacteria.

As a laboratory devoted to the study of antimicrobial resistance in veterinary medicine, it is its mission to reach out to the society (clinicians and owners) in the pursuit of better antimicrobial use practices. The development of antimicrobial stewardship programs as long started in human medicine and are urgently needed in veterinary medicine (Loyd and Page 2017). Antimicrobial stewardship programs are complex and require the interaction of multidisciplinary teams. Such programs aim at creating strategies to promote the rational use of antimicrobials, improve infection control measures and consequently decrease the spread of pathogenic and resistant bacteria (Loyd and Page 2017).

Evidence based learning is the key to fight antimicrobial resistance in a One health approach and pursuing the 5Rs of antimicrobial stewardship: Responsibility, Reduction, Refinement, Replacement and Review (Weese *et al*. 2013; Loyd and Page 2017). Recently, the European Society of Clinical Microbiology and Infection Diseases Study Group on Veterinary Microbiology started regular post-graduate courses of antimicrobial stewardship in veterinary medicine representing a landmark towards a better future and in which the Antibiotic Resistance Laboratory team leader collaborates as a regular speaker.

The future of antibiotic resistance and pathogenic bacteria is still uncertain, but the Antibiotic Resistance laboratory will continue to focus its efforts in obtaining useful epidemiological data, guide antimicrobial use through the establishment of antimicrobial stewardship programs, and reaching the society to increase awareness and help to improve this worldwide problem.

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