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Review Article

Risk of Antimicrobial Resistance Development from Pet Animals to Humans: Case of *Enterobacteriaceae* Family

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Abstract

Antimicrobials are vital instruments for the treatment of contagious bacteriological infections in pet animals, as well as in humans. The demise of the effectiveness of antimicrobial substances can honestly deal with pet animal health and human health. A necessity for the enhancement of innovative antimicrobials for the treatment of multiresistant infections, specifically those caused by Gram-negative bacteria, has been recognized in human medicine, and an imminent subsequent demand in veterinary medicine is required. A distinctive feature associated with antimicrobial resistance and the risk of resistance development in pet animals is their close interaction in conjunction with humans. This generates chances for interspecies transmission of resistant bacteria. This review aims to recapitulate the current information on the use and indications for the Enterobacteriaceae family in pet animals and the spread of antimicrobial resistance among pet animals and their owners. The critical antimicrobial resistance microbiological threats from pet animals that directly or indirectly may cause adverse health effects in humans are carbapenemase-producing Enterobacteriaceae bacteria such as *Escherichia coli, Klebsiella spp., Enterobacter spp*. and *Salmonella spp*.

Keywords: Antimicrobial resistance; Antibiotics; Public health; Microbiology

Introduction

Throughout the last half of the century, the quantity of pet animals in contemporary civilization has considerably augmented, and a modification in their public part has arisen [1]. Awareness of their welfare has grown because of the close interaction between pets and their owners [2]. Humans could develop antimicrobial-resistant bacteria or the consequent resistance genes from food animals [3,4] and interaction with their pet animals [5,6]. Enterobacteriaceae and multidrug-resistant Gram-negative bacteria have become apparent in healthy and sick pets, suggesting a possible threat of the spread of these bacteria to humans from contaminated or inhabited pet animals [7]. Additionally, there is also the possibility to transfer resistance genes vice versa. To evaluate the hazards contained by the framework of treatments for new antimicrobials for pet animals, could arise a necessity for further data requirements concerning antimicrobial resistance [8]. Antimicrobials are used commonly in the routine procedure for medicinal and preventative reasons in pet animals [9]. Nevertheless, antimicrobial intake data for dogs and cats are repeatedly deficient and typically addressed to drug company trades [10]. Even if trade data provide a challenging assessment of antimicrobial consumption's enormity, data on the utilization of antimicrobials in various species are deficient [11]. Pet animal sales of antimicrobials are a small percentage of the global sales example of animals' antimicrobial agents.

Various antimicrobial products approved for human use are also used in pet animals in the treatment of the "cascade" [12]. Prevalent use of broad-spectrum antimicrobials has been described in pet animal practice in Europe (Figure 1). The most

used antimicrobials for dogs and cats are β-lactams, for example, amoxicillin and amoxicillin combined with clavulanic acid [13]. Shortage of verified diagnosis might take the lead to the abuse of antimicrobials [14]. Antimicrobial management has occurred to treat disorders in which effectiveness has not been demonstrated, for instance diarrhea in dogs for which antimicrobial treatment is generally not proposed [15,16]. Multidrug resistance bacteria have been described in pet animals, every so often cruelly conceding the therapy result. Since restricted reconnaissance and understanding of the zoonotic transmission of antimicrobial resistance between humans and pet animals, the level of spread and significance for public health is inadequately appreciated [17]. Within the next, the critical drug-resistant bacteria are assessed and the indication for their transmission among humans and their pet animals.

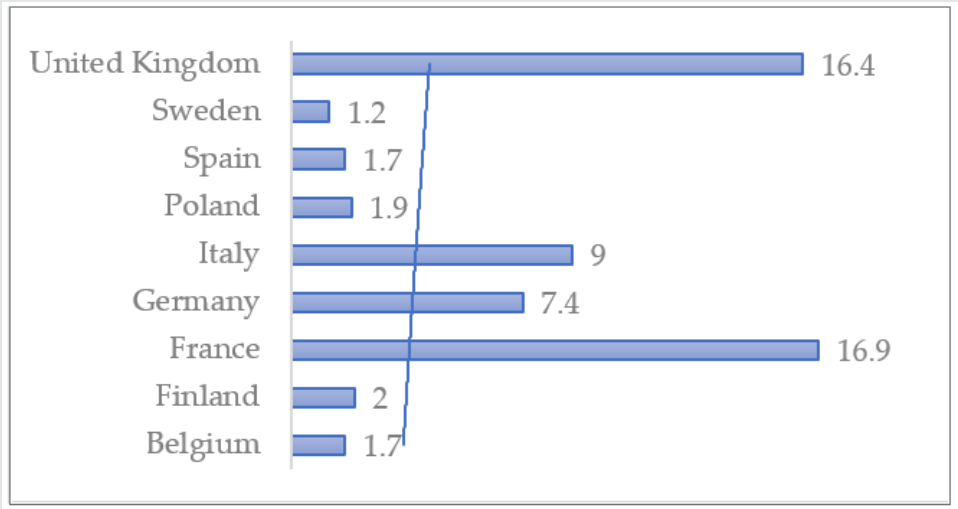

Figure 1: Distribution of sales, in tonnes of active ingredient in tablets used in pet animals, by country [13].

Enterobacteriaceae as a Significant Public Health Concern in Human Medicine

Representatives of the *Enterobacteriaceae* family comprise numerous species, for instance, *Escherichia coli, Enterobacter spp., Salmonella spp.*, and *Klebsiella spp.* [18]. Countless bacteria belonging to these species are symbiotic organisms of the digestive tract [19]. Increasing antimicrobial resistance among Enterobacteriaceae is evolving as an essential public health apprehension in human medicine. Enterobacteriaceae, which produce ESBLs, extended-spectrum cephalosporinases, and plasmid-mediated AmpC β-lactamases (ESBLs) are particularly important. Around are quite a few articles on ESBL-producing bacteria in pet animals [6]. *Escherichia coli, Salmonella spp., Enterobacter spp.*, and *Klebsiella spp*. as Potential Hazards Over the years, *E. coli* was reported continuously from the first recorded case in Japan in pet animals, followed by the emergence in humans in following years, to the incidence in ESBL-producing uropathogenic *E. coli* from pet animals in Spain [20]. Since that time, the number of statements relating to *E. coli* ESBLs in pet animals has grown precipitously [21]. CTX-M enzymes have developed a swiftly expanding family of ESBLs in bacteria from human infections. In pet animals, equally clinical and commensal isolates of *E. coli* frequently generate CTX-M type β-lactamases [22]. E. coli has lately become known as a global pandemic replicate in humans [23]. Descriptions of clinical infections in animals caused by *E. coli* are merger, which may be since its detection requires genotypic techniques. Various clinical *E. coli* isolates from pet animals are like human clinical *E. coli* isolates founded on their virulence genotype, and resistance characteristics, etc. Many E. coli strains such as ST156, ST405, ST410, and ST648 could be found both in humans and their pets [24]. The detection of duplicates in humans and dogs and cats may suggest their transmission through direct contact. Such transmission could likewise be a related component to the prompt and effective spreading of E. coli, even though, between humans, the incredibly critical transmission path is almost certainly "hand to hand" [25]. Salmonella spp. have been correlated with epidemics of nosocomial intestinal infections in pet animals in veterinary clinics and an animal sanctuary-some of the outburst as well engaged veterinary organization and other people in connection with pets [26].

In cases like this, pet animal sanctuaries could work as foci of transmission for *Salmonella spp*. among humans and animals if acceptable control measures are not provided [27]. Information on antibiotic resistance phenotypes and genotypes of *Salmonella spp*. in animals and humans in different countries and geographic regions is necessary to combat the spread of resistance [28]. This will improve the understanding of antibiotic resistance epidemiology, tracing new emerging pathogens, assisting in disease treatment, and enhancing the prudent use of antibiotics. However, the extent of antibiotic resistance in foodborne pathogens and humans in many developing countries remains unknown [29].

Among 25526 recorded isolates of salmonellae, 5086 isolated from humans, and 20440 from animals in 1994 and 1997 in France, the antibiotic resistance phenotype was determined for all human and 5336 animal isolates. In *Salmonella enterica serovar typhimurium*, one of the two most frequently isolated serovars from humans as well as animals, resistance to ampicillin was observed in 61% of both human and animal isolates in 1994 and in 73% of human and 53% of animal isolates in 1997.

During these periods, resistance to co-amoxiclav was between 45% and 66% for both types of the isolate. Resistance to ampicillin was associated with resistance to streptomycin, spectinomycin, sulphonamide, tetracycline and chloramphenicol in over 70% of isolates [30]. Resistance to ampicillin as well as co-amoxiclav never exceeded 7% in *Salmonella enteritidis*. While *Salmonella hadar* was practically absent among the human isolates in 1994, this serovar was the third most frequent in 1997, and at that time, 92% were resistant to nalidixic acid. Among the animal *S. hadar* isolates, the prevalence of resistance to nalidixic acid increased from 3% in 1994 to 72% in 1997. None of these isolates manifested high-level resistance to ofloxacin. The levels of resistance to aminoglycosides (<3%) and trimethoprim-suphamethoxazole (<14%) remained practically unchanged in all three serovars. The resistance markers of 463 ampicillin-resistant *S. typhimurium* isolated in 1997 were determined. Among the 24 phenotypes observed, six multiresistant phenotypes, representing 82% of these isolates (as compared with 80% in 1994), were associated with the PSE-1 gene typically found in the lysotype DT104 of this serovar [30]. Being as by *E. coli*, extended-spectrum cephalosporinases and plasmid-mediated AmpC β-lactamases producing strains of Salmonella *spp*. are of disquiet [24]. Antibiotic of the cephalosporin type licensed for use in veterinary medicine resistance was detected in more than 10% of cats and 21% of dog *Salmonella spp*. isolates with detected β-lactamases, respectively [31]. The main issue and problem are that there is limited knowledge of ESBLs in other *Enterobacteriaceae* of pet animals. *Klebsiella spp*. from the human epidemic clone was isolated from dogs and cats in Spain [32]. It was found to be highly resistant to aminoglycosides due to the ArmA methyltransferase. The emergence and clonal spread of *Klebsiella spp*. in dogs were first reported in Germany [33]. While in Singapore, an analysis of 186 diagnostic reports collected from a veterinary clinic between 2014 to 2016 showed that sick companion animals could carry bacteria of significance to human health [34]. Among the 186 specimens submitted, 82 showed polymicrobial growth (45%, 82/186), and in total, 359 bacteria were isolated. Of the 359 bacteria reported, 45% (162/359) were multi-drug resistant, and 18% (66/359) were extended-spectrum-β-lactamase species. Resistance to broad-spectrum antibiotics was also observed among individual species. Namely, methicillin-resistance among *Staphylococcus pseudintermedius* (63%, 32/51) and Staphylococcus aureus (50%, 4/8); fluoroquinolone-resistance among *Escherichia coli* (40%,17/42) and carbapenem-resistance among *Klebsiella pneumoniae* (7%, 2/30) were noted [34].

This analysis suggests that sick pets may contribute to the pool of clinically relevant antibiotic-resistant bacteria and play a role in the spread of antibiotic resistance. Antibiotic-resistant bacteria such as *Klebsiella pneumoniae* are common in the digestive tract and upper respiratory tract of animals and humans [35]. Several studies have shown that this bacterium is found in humans and in animals, one of which is pigs that are known to be a reservoir for the spread of this bacteria [36]. Not only in pigs, but this antibiotic-resistant bacterium is also known to be found in other food-producing animals, as well as in pet animals. Many cases of *Klebsiella pneumoniae* in humans have been reported, but *Klebsiella pneumoniae* in humans related to animals or strains related to animals and humans were also reported [37]. Control and prevention are needed to prevent the spread of antibiotic-resistant bacteria from animal to animal, animal to human and vice versa, and the surrounding environment.

Conclusion

In humans, the control of resistance is based on hygienic measures: prevention of cross-contamination and decreased antibiotic usage. In animals kept together, sanitary measures, such as prevention of oral-fecal contact, are hardly achievable. Consequently, lessening the need for antibiotics is the only possible way of managing resistance in pet animals. This can be achieved by improving pet animal welfare systems and eradicating or vaccinating against infectious diseases. Furthermore, eliminating antibiotics as preventive measures in pet animals would decrease antibiotic use and minimize transmission from animal to human resistance. This would not only diminish the public health risk of dissemination of resistant bacteria or resistant genes from pets to humans but would also be of significant importance in maintaining the efficacy of antibiotics in human medicine and veterinary medicine as well. A more extensive study to better understand the extent of distribution and the factors affecting antibiotic-resistant bacteria's transmission to and from pets is more than necessary.

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