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Review Article

Antibiotic Resistance in Cattle Livestocks in the Mediterranean Area With A One Health View

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Abstract

Antibiotics are used in livestock not only in case of infections but also in prophylactic treatments to favour growth of animals. They are often added to feed, with a high percentage of unmodified antibiotics reaching intact the environment and constituting new emerging contaminants. Especially in the past, the same antibiotics supplied to animals could also be used in humans. Antibiotic resistance onset can originate inside the animals, in the resistome of the intestine, with a similar mechanism as the antibiotic resistance triggering in humans. Once activated within cattle, antibiotic resistant bacteria and related antibiotic resistance genes can be spread via food, milk and meat, or via manure which can be spread into the environment during fertilization procedures. Antibiotic resistant bacteria and genes of antibiotic resistance can thus reach human beings and the resistance genetic determinants can be included in pathogenic bacteria, vitiating action of antibiotics against those pathogens. The Mediterranean area presents a high density of dairy cattle livestock and the problem of antibiotic resistance spread is of great concern. It is important to monitor the extent of antibiotic resistance diffusion and the possible consequent ineffectiveness of the known antibiotics against pathogenic bacteria. If from one hand it is of paramount importance to discover new antibiotics active against pathogenic bacteria, although this approach needs time, from the other hand it is mandatory to find new approaches facing with the problems of antibiotic resistance. A One Health approach, focusing on the co-operation of medical and veterinarian staffs, including people operating for environmental safeguard, could represent a valid method to actuate a decrease of the use of antibiotics in cattle livestock and to operate with a continuous control and a monitoring of the critical points, in order to counteract the challenge of antibiotic resistance. This minireview was focused on antibiotic resistance onset in cattle livestock in the Mediterranean area, calling attention on the high potential of spread of antibiotic resistance in humans, animals and in the environment, thus evidencing the need of a One Health approach to face with this concern.

Introduction

Antibiotics were discovered in the past century, with penicillin described in 1928 by Sir Alexander Fleming, resulting in a significant improvement in human health conditions. During the final phases of the Second World War, antibiotics began to be used in food animals, following accessibility to abundant productions of lyophilised preparations of penicillin, also made available for veterinarians [1]. The use of antibiotics in animals can be finalized to treatment of infectious disease, adopting metaphylaxis procedures, in which high doses of antibiotics are given for a short period with treatments extended to the whole flock to prevent the dissemination of illness in the flock, despite the exhibition of clinical symptoms in a few animals [2,3]. Concerning the antibiotics used to treat the most common diseases in cattle livestock, which include bovine pneumonia, diarrhoea, and shipping fever, they can comprehend amoxicillin, penicillin, erythromycin, quinolones, gentamicin, novobiocin, tylosin, tilmicosin, and tetracycline [4]. In case of pneumonia, the first choice antibiotics are represented by oxytetracyclines and spectinomycin, the second choice are constituted by florfenicol and macrolides, and the last choice of antibiotics represented by second-, third-, and fourth-generation cephalosporins [5]. In presence of clinical mastitis it is recommended the application of narrow-spectrum antibiotics, with β -lactams as first-choice antibiotics when mastitis originated from streptococci, and penicillin when the aetiological agents are staphylococci [5,6]. Antibiotics can be administered to the whole herd with the aim of preventing infectious mastitis, intramammary and during periods of non-breastfeeding [7].

In the mean time, antibiotics can be added to feed not only to treat infections, but to prevent the development of diseases and to promote growth of animals, through the procedure called prophylaxis. In this case the administration of antimicrobials in the feed or the drinking water occurs in low, sub therapeutic, doses for a longer period of time, usually for several weeks. Overall, the use of antibiotics in animals can overcome that in human beings [8]. Throughout the years, the use of antibiotics for nontherapeutic purposes in food animals has been more frequent than for therapeutic applications. It is estimated that in most developed nations, livestock alone use 50-80% of antibiotics produced [9]. The administered sub therapeutic doses of antibiotic are not sufficient to destroy the target bacteria, but can allow the more resistant of them to survive. Antibiotic resistance can be triggered when an administered dose of antibiotic provides an opportunity for bacteria to develop resistance [10]. In this minireview, a description of the use of antibiotics in cattle livestock is presented, focusing on onset of antibiotic resistances and on their spread via different mechanisms. A description of antibiotic resistance in cattle livestock of the Mediterranean area, and possible views with a One Health approach, are reported.

Antibiotic Resistance in Cattle Livestocks

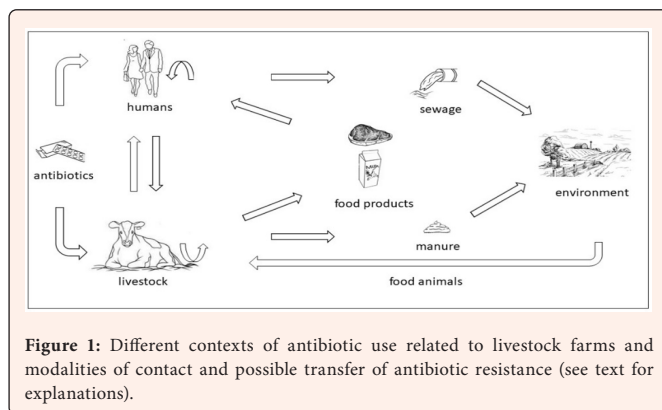
The overuse or misuse of antibiotics caused selection of resistant bacteria, according to the World Health Organization, the antibiotic resistance was defined as follows: "Antimicrobial resistance... is resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it." [11]. The onset of antibiotic-resistant bacteria can occur soon after their first contact. It was known that *Staphylococcus aureus* strains isolated in 1948,

evidenced resistance to penicillin, and in the same year, soon after the antibiotic use, resistance to streptomycin was observed in *Mycobacterium tuberculosis* isolates. Few years later, in the 1950s, antibiotic resistance was detected in other pathogenic bacteria, such as *Escherichia coli*, *Shigella* spp. and *Salmonella enterica*, and in the 1960s, in Enterobacteriaceae, antibiotic-resistant bacteria such as Extended Spectrum β -Lactamases (ESBLs), Vancomycin-Resistant *Enterococcus* spp. (VRE), Methicillin-Resistant *Staphylococcus aureus* (MRSA), and multidrug-resistant *Acinetobacter baumannii* were highlighted. Concerning outbreaks resulting from resistant bacteria originated from animals, this is of very high concern [7].

Bacteria can be resistant to one or to several different antibiotics, as multidrug resistant bacteria. Resistance to antibiotics can be developed through the multiplication of bacteria developing a natural mutation conferring resistance to the antibiotic, or can be developed by the horizontal resistance genes transfer between bacteria. Horizontal transmission of resistance genes represents a major cause of increasing antibiotic resistance. It can occur in different ways: i) through natural processes of gene transfer inside cells, via a mechanism called transformation; ii) via mobile segments of DNA known as transposons and plasmids, in the conjugation mechanism; iii) by transferment of DNA via bacteriophages in the process of transduction [12,13]. Genes for antibiotic resistance in bacteria isolated from patients suffering of *Escherichia coli* urinary tract infections and *Salmonella* infections were recovered also in bacteria isolated from animals, probably due to gene transfer. Food-producing animals represents a major reservoir for mobile genetic elements, as integrons, carrying antimicrobial drug-resistant genes. They may also serve as a source for the transfer of these genes not only to *Escherichia coli* and *Salmonella* but also to other members of Enterobacteriaceae family and other bacterial species [3,14].

The use of antibiotics in cattle livestock has the potential to stimulate the development and dissemination of antibiotic resistant genes among different types of enteric bacteria characteristic for ruminants, as well as potentially pathogenic species related to the focal microbiome. Some of these bacteria may be pathogenic to humans, and hence could pose a threat to human health if they additionally acquire resistances. Moreover, non-pathogenic bacteria from manure might transfer antibiotic resistant genes to pathogens existing in manure, soil, or food consumed by animals or humans [15,16]. Furthermore, manure from dairy cows, commonly used as a soil fertilizer, may harbour diverse new variants of antibiotic resistant genes from the gut microbiota of cattle [17].

Genes of Antibiotic Resistance



The most widely-used antibiotics in cattle production systems are tetracyclines, being used to treat skin, respiratory and gastrointestinal tract diseases. Furthermore, tetracycline resistance may develop rapidly because tetracycline antibiotic resistant genes are often located on mobile genetic elements [18]. The presence of five classes of tetracycline resistance genes in bovine focal samples was showed along with two classes of sulfonamide resistance genes and five classes of erythromycin resistance genes. These features may suggest that treatment with this antibiotic may enhance antibiotic resistance genes transfer. An increase in the number of *Escherichia coli* isolates carrying *bla*CMY-2 was observed, probably originated from a higher frequency of plasmid-mediated antibiotic resistant genes transfer by horizontal genes transfer to other enteric bacteria, including potential zoonotic pathogens [19]. A strain carbapenemase-producing *Acinetobacter* spp. harbouring the *bla*OXA-23 carbapenemase gene have been isolated from dairy cattle faces, along with *Acinetobacter baumannii* with

the *bla*OXA-497 gene [8]. *Klebsiella pneumoniae* harbouring the *bla*NDM-5 gene was also isolated from samples of faces from dairy cows with mastitis from Jiangsu Province, China, and in all isolates, the *bla*NDM-5 gene was found [20]. From dairy cows, including one co-producing the transferrable colistin resistance gene *mcr-1* and another co-harboring the carbapenemase gene *bla*VIM-2 were isolated [8]. In enterococci isolated from French cattle, intrinsic *vanC*-mediated and acquired *vanA*-mediated vancomycin resistance was reported [21]. These examples indicate that the genetic information of antibiotic resistance diffused from cattle livestock can reach different compartments and can extend to human pathogens, thus representing a real threat for human health. A possible scheme of interactions among different contexts related to cattle livestock and how these compartments interact among themselves, functioning as ways of communications and possible exchanges for antibiotic resistant bacteria and related genes of resistance, is reported in Figure 1.

Spread of Antibiotic Resistance from Cattle Livestocks

The antibiotic resistome evidences the pool of genes codifying for an antibiotic resistance phenotype with bacterial populations able to transfer antibiotic resistance genes by horizontal transfer to other microbial ecosystems. Both human and animal resistome comprehend strains spreading genes of antibiotic resistance, as result of intensive antibiotics use and bacterial genetic transfer [22]. In the case of the Livestock-Associated Methicillin Resistant *Staphylococcus aureus* (LA-MRSA) in dairy cattle, the first probable case of MRSA transmission between humans and cows were reported. Five isolates of MRSA were cultured from the samples collected from cows with asymptomatic mastitis. In the same time, nasal swabs were collected from different people, having contacts: the dairyman, veterinarian and some of their family members. The dairyman, the veterinarian and several members of the veterinarian's family tested positive for MRSA. DNA sequencing was performed on all of the MRSA isolates revealing to have identical antibiotic sensitivity profile and were of the same clonal lineage type. This study confirmed the transmission of MRSA between cattle's and the farm workers and between people in a family environment, confirming the risk of intra- and interspecies transmission of LA-MRSA [23]. A way of transmission of resistant bacteria and resistance genes from food animals to people is represented by food products of animal origin. In fact, they can be often contaminated with bacteria, and thus likely constituting the main route of transmission. Direct contact with animals or the animal environment, however, may also be of significance, depending on the type of bacteria. Such foods as fruits and vegetables contaminated by animal waste or contaminated water may also constitute a transmission route. Thus, antibiotic resistance is a food safety challenge. Mastitis is an inflammation of the mammary gland causing decreased milk production and quality, decreased cheese yield, increased cost of treatment, labour and culling and is mainly caused by bacteria of the species *Staphylococcus aureus*. Mastitis is also caused by many other bacteria such as *Streptococcus* spp., *Escherichia coli*, *Pseudomonas* spp., and *Mycoplasma* spp. Currently, the use of antibiotics is the most common treatment and β -lactams are the most frequently classes used for the treatment of mastitis. Resistance to antibiotics may be acquired and resistant bacteria may contaminate food products and they could be transmitted to humans through the food chain [24].

Bacterial antibiotic resistance can originate from antibiotic residues present in wastewater from animal production farms. These antibiotics residues can persist in soil and in aquatic environments. Transfer of antibiotic resistance occurs via spread of bacterial resistant strains or, indirectly, by horizontal gene transfer to other commensal or pathogenic bacteria, and commensal bacteria of the gastrointestinal tract, as *Enterococcus* spp., important carriers of antibiotics resistance expansion [25]. An agricultural land in the Azores archipelago, where pasture for dairy and beef cattle breeding was the main land use, was characterized for the antibiotic resistance profile of enterococci isolated from soils, evidencing many Vancomycin-Resistant (VRE) strains, often associated with penicillin and aminoglycoside resistance, and which present serious difficulties in therapeutic treatment. Among them, a VRE strain of *Enterococcus faecalis* was characterized, harbouring the *vanA*, the *aph3'* and *aac6'-Ie-aph(2')-Ia* antibiotic resistance genes, [25]. The environment represents a potential reservoir of antibiotics as well as antibiotic-resistant pathogens, which can then enter the food chain, leading to the selection of an antibiotic-resistant microbiota [26]. A tetracycline-resistant *Escherichia coli* strain and its *tetA* gene were tested for the capacity to survive in manure compost and the incidence of oxytetracycline-resistant bacteria and the persistence of the *tetA* gene in cow farms was examined. Both oxytetracycline-resistant *Escherichia coli* and the resistance *tetA* gene persisted for many days in cow manure compost. High concentrations of antibiotic resistance genes and the presence of antibiotic-resistant bacteria may pose a risk to public health because these bacteria and genes could be transferred to natural soil microorganisms and then enter the human chain [27]. Livestock farms are important pollution sources



of antibiotic resistant genes and antibiotic resistant bacteria that can be spread in the air of the surrounding environments due to intensive use of antibiotics in the livestock context. Bioaerosol has been found to be an important spread route of antibiotic resistant genes. Many studies have confirmed the association of antibiotic resistance between farm animals and farmers. The genus *Staphylococcus* is well known for the potential zoonotic pathogenic species and frequently colonize the skin and upper respiratory tracts of human and animals, among which *Staphylococcus aureus* is considered to be an important zoonotic pathogen [28,29]. Spread of airborne antibiotic resistant *Staphylococcus* spp. could pose a significant risk to human health and dissemination of livestock farms *Staphylococcus* spp. via aerosol emission to the adjacent environment represents an important concern [30].

Antibiotic Resistance from Cattle Livestocks in the Mediterranean Basin

The Mediterranean region is a cultural melting pot built from very important and developed civilizations. Even though the Mediterranean region reveals strong differences in terms of consumer behaviour or socio-cultural profiles, natural conditions or economic situations, main common issues relative to animal production can be pointed out. Concerning the domestication and stabilization of the animals in the history, the transition from foraging and hunting to farming and herding represents an important step. Since the use of animal meat began long after domestication, the initial

motivation that would have prompted populations to domesticate ruminants may have been based on the use of the milk [31]. Following the domestication of livestock species, including cattle, and their subsequent dispersal throughout the Mediterranean Basin, it was evidenced that the location of colonist farming enclaves during the Neolithic expansion in the Mediterranean Basin dates 10,500-9,000 B.P. and document the arrival of early pioneers. It was hypothesized that the Neolithic expansion originated somewhere in the Northern Levant, near Cyprus, from which the pioneer colonists transported the economically important fauna, including livestock species as cattle [32]. Beef and veal production is concentrated in France, Italy and Spain. Turkey and Egypt also have a significant production. In the Mediterranean area, large spatial differences also characterize the livestock subsector, with meat production included in a range from 0,1 to 143.9 10⁴ tonnes in the period between 2014 and 2018 [33]. In the Mediterranean basin, during the period from 2014 to 2018, France, Turkey and Italy were detected as the main milk producers, with averages equal to 262.7 10⁵, 197.2 10⁵ and 119.3 10⁵ tonnes, respectively [33].

Features in cattle livestock of the Mediterranean countries concerning isolated antibiotic-resistant bacterial strains, genes of resistance and native sampling sites, were described in Table 1. Antibiotic resistant strains of the species *Staphylococcus aureus* were recovered in almost all tested cattle livestock of Mediterranean countries, mostly isolated from raw milk in presence of mastitis, often with resistance to methicillin (MRSA), and the corresponding resistant genes *mecA* and *mecC* (Table 1).

Table 1: Antibiotic resistant bacteria and genetic determinants of resistance in dairy cattle in the Mediterranean area. MRSA=Methicillin Resistant *Staphylococcus aureus*; VRSA=Vancomycin Resistant *Staphylococcus aureus*; CoNS=Coagulase Negative *Staphylococci*; CoPS=Coagulase Positive *Staphylococci*; NAS=Non-Aureus *Staphylococci*; ESBLs=Extended Spectrum *Beta*-Lactamases.

Countries	Isolated Resistant Bacteria	Antibiotics	Antibiotic Resistance Genes	Samples Origin	References
Albania	<i>Staphylococcus aureus</i>	tetracycline, oxacillin, erythromycin, ampicillin		raw milk	[34]
	<i>Staphylococcus aureus</i> , CoNS, (isolated 2 MRSA and 1 VRSA strains)	penicillin G, tetracycline, methicillin, vancomycin		raw milk in presence of mastitis	[35]
	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i>	penicillin, oxacillin, ampicillin, amoxicillin+clavulanic acid		raw milk	[36]
	<i>Escherichia coli</i>	amoxicillin, tetracycline, amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole	<i>tetA</i> , <i>blaTEM-1</i>	raw milk in presence of mastitis	[37]
	Algeria	<i>Staphylococcus aureus</i> , (isolated 4 MRSA strains)	penicillin G, fusidic acid, tobramycin, methicillin		raw milk
Bosnia-Herzegovina	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , <i>Enterobacteriaceae</i>	penicillin G, bacitracin, trimethoprim/sulfamethoxazole		raw milk in presence of mastitis	[39]
Croatia	<i>Staphylococcus aureus</i>	penicillin and ampicillin		dairy cattle mastitis	[40]
	<i>Escherichia coli</i> , <i>Staphylococcus aureus</i> , streptococci, NAS	ampicillin, amoxicillin-clavulanic acid, cefoxitin, levofloxacin, ciprofloxacin, doxycycline HCl, gentamicin, floropenicol, sulfamethoxazoletrimethoprim,	<i>mecA</i> , <i>blaZ</i> , <i>aph(3')-IIIa</i> , <i>cfb</i> , <i>tetA</i> , <i>sul1</i> , <i>fimH</i> , <i>tsh</i>	raw milk in presence of mastitis	[41]
	<i>Streptococcus aureus</i> , <i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , (isolated 5MRSA strains)	penicillin, oxacillin, streptomycin, ceftriaxone, enrofloxacin, levofloxacin, methicillin		raw milk in presence of mastitis	[42]
	Egypt	<i>Escherichia coli</i> (ESBL)	3 rd generation cephalosporins	<i>blaCTX-M15</i> , <i>blaCTX-M9</i> , <i>blaTEM</i> , <i>blaSHV</i> , <i>blaOXA-48</i> , <i>blaOXA-181</i>	rectal swabs, environmental samples from the stalls
	<i>Streptococcus uberis</i> , <i>Escherichia coli</i> , CoPS	tetracycline, third-generation cephalosporin, amoxicillin, tetracycline		dairy cattle mastitis	[44]
	<i>Streptococcus uberis</i> , <i>Escherichia coli</i> , CoPS, CoNS, <i>Streptococcus dysgalactiae</i>	penicillin G, macrolides, tetracycline		dairy cattle mastitis	[45]
	France	<i>Staphylococcus aureus</i> (MRSA)	methicillin	<i>mecA</i> , <i>mecC</i>	raw milk/nasal and rectalswabs



Greece	<i>Staphylococcus aureus</i> (MRSA)	methicillin	<i>mecA</i>	bulk-tank milk, dairy products, nasal swabs, swabs from dairy plants	[47]
	<i>Escherichia coli</i> (ESBL)	cefquinome, amoxicillin-clavulanic acid, aztreonam, ampicillin, colistin, trimethoprim-sulfamethoxazole, streptomycin	<i>mcr-1</i> , <i>bla</i> TEM1, <i>bla</i> CTXM, <i>bla</i> SHV	raw milk in presence of mastitis	[48]
Israel	<i>Enterobacteriaceae</i>	ciprofloxacin, gentamicin		manure	[49]
	<i>Mycoplasma bovis</i>	penicillin, cephalosporins, fluoroquinolones		raw milk in presence of mastitis	[50]
Italy	<i>Streptococcus</i> spp., <i>Staphylococcus</i> spp.	amoxicillin, ampicillin, tetracycline, trimethoprim-sulfamethoxazole		dairy cattle mastitis	[24]
	phylum Firmicutes, phylum Bacteroidetes	flumequine	<i>ermA</i> , <i>ermB</i> , <i>bla</i> oxa-1, <i>oqxA</i> , <i>qnrS</i>	manure/soil	[51]
	<i>Clostridioides difficile</i>	clindamycin, moxifloxacin, linezolid, vancomycin		manure/boot swabs	[52]
Lebanon	<i>Streptococcus uberis</i> , <i>Streptococcus agalactiae</i> , <i>Escherichia coli</i> , <i>Staphylococcus aureus</i>	macrolides, tetracycline, ampicillin, tetracycline	<i>bla</i> TEM, <i>bla</i> OXA, <i>bla</i> CMY-II, <i>mecA</i>	raw milk in presence of mastitis	[53]
	<i>Staphylococcus aureus</i> , <i>Listeria monocytogenes</i> , <i>Escherichia coli</i>	gentamicin, streptomycin		raw milk	[54]
	<i>Staphylococcus</i> spp.	gentamicin, oxacillin, clindamycin		traditional dairy products	[55]
Lybia	<i>Enterococcus</i> spp., <i>Escherichia coli</i>	vancomycin, ampicillin, trimethoprim/sulfamethoxazole, gentamicin	<i>bla</i> TEM	rectal swabs	[56]
Morocco	<i>Enterococcus</i> spp.	ampicillin, streptomycin, tetracycline		raw milk	[57]
Portugal	<i>Enterococcus faecium</i>	vancomycin		rectal swabs	[58]
	<i>Enterobacteriaceae</i>	tetracycline, trimethoprim/sulfamethoxazole, ciprofloxacin, chloramphenicol	<i>tetA</i> , <i>tetM</i> , <i>dfr1a</i> group, <i>sul3</i> , <i>qnrS</i> , <i>qnrB</i> , <i>oqx</i> , <i>catI</i> , <i>catII</i>	manure	[59]
	<i>Enterococcus faecalis</i>	vancomycin	<i>vanA</i> , <i>aph3'</i> , <i>aac6'-Ie-aph2'-Ia</i>	soils exposed to livestock agricultural practices	[25]
Spain			<i>macB</i> , <i>masbA</i> , <i>parY</i> , <i>proB2</i> , <i>tetQ</i>	ruminal content	[60]
	<i>Mycoplasma bovis</i>	macrolides, lincosamides, tetracyclines		nasal, auricular, and conjunctival swabs, synovial fluid	[61]
Tunisia	<i>Escherichia coli</i>	tetracycline, trimethoprim/sulfamethoxazole, amoxicillin		manure	[62]
	<i>Escherichia coli</i> (ESBL)	colistin	<i>mcr-1</i>	manure/raw milk	[63]
	<i>Staphylococcus xylosum</i> , <i>Staphylococcus warneri</i>	methicillin, penicillin, erythromycin, tetracycline, trimethoprim-sulfamethoxazole, clindamycin	<i>mecA</i> , <i>ermB</i> , <i>ermT</i> , <i>ermC</i> , <i>mphC</i> , <i>tetK</i> , <i>dfrA</i> , <i>InuB</i>	raw milk in presence of mastitis	[64]
Turkey	<i>Staphylococcus aureus</i> (MRSA)	methicillin	<i>mecA</i>	bulk tank milk	[65]
	<i>Streptococcus</i> spp. Lancefield's serogroup B and serogroup F	neomycin, trimethoprim sulphamethoxazole, gentamicin		raw milk in presence of mastitis	[66]



One Health Approach to the Concern of Antibiotic Resistance

Health of people is connected to the health of animals and the environment and antibiotic resistance has clear links to each of these three domains. The contribution of livestock production to the global antibiotic resistance can create ideal conditions for bacteria to fix genes that confer resistance. These genes can subsequently be transmitted to human-adapted pathogens or to human gut microbiota via people, by mean of contaminated food or the environment. These compartments also provide ideal conditions for the amplification of genes that may have arisen in people or the environment. The fact that the antibiotics used in human and animal health largely comprise the same or very similar molecules, would be expected to drive the transmission of resistance between animals and people, either directly or via the environment. Multidrug-resistant strains as the common pathogens like *Escherichia coli*, *Klebsiella pneumoniae* and *Staphylococcus aureus* are of high concern and it thus emerge the need to consider the problem from a One Health point of view, including a strict collaboration among human health, animal health and environmental health. The One Health approach is well defined concerning the great problem of antibiotic resistance originated from cattle livestock, and diffusing in human contexts and in environmental compartments.

The relative roles of these three aspects in the development, transmission and persistence of antibiotic resistant bacteria and genes is poorly investigated. A One Health approach to dealing with antibiotic resistance, embracing all three domains, would represent a powerful tool and could open the way to a new approach to solve problems, where collaboration and pursuing common interests are at the base of the project [67]. Veterinarians and livestock producers must adapt to accept decreasing the consumption of antibiotics by livestock and in reducing the occurrence of antibiotic resistance in bacteria that inhabit livestock, humans, and the environment, affirming the "One Health" approach as an efficacy attitude against antibiotic resistance diffusion, for the future [68].

Conclusion

In this minireview, the great concern of antibiotic resistance is considered in relation to the use of antibiotics in cattle livestock. The strict relationships among animals, humans and environment allow the spread of antibiotic resistance triggered in cattle's to the humans and the environment by mean of food products, manure, direct contact, diffusion in air. The communications among these different sectors are very easy and continuous and characterized by different directions. Mediterranean basin is historically an important area for cattle livestock and this activity could have important consequences as spread from animal and environmental sites to human pathogens of antibiotic resistant bacteria and related genes of antibiotic resistance. Considering that antibiotic resistance spreads between different compartments and that this can lead to the onset of multi-resistant pathogenic bacteria not sensitive to the available antibiotics, there is a strong need to tackle the problem from different points of view. A One Health intervention aimed at reducing the consumption of antibiotics in cattle farms, at manage the dispersion of manure in the environment and at increasing the controls of food products, would constitute an important system of protection against the serious threat of antibiotic resistance.

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