Review Article

Antibiotic Resistant Bacteria and Antibiotic Resistance Genes in Wildlife and their Spread, Focus on the Mediterranean Basin

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Abstract

Overuse of antibiotics in hospitals, animal husbandry and agriculture significantly contributed to the onset of antibiotic resistance. The subsequent spread of antibiotic-resistant bacteria and antibiotic-resistant genes contributed to aggravating the problem. An important contributor to the spread of antibiotic resistance is wildlife, which is ubiquitous and can move easily, thus contributing to the global spread of antibiotic resistant bacteria and antibiotic resistance genes. The first antibiotic-resistant bacteria isolated from wildlife were strains of *Escherichia coli* obtained from pigeons and crows, with resistance to chloramphenicol and multi-resistance, carrying conjugative R plasmids. The same strains of *Salmonella* spp. resistant to tetracyclines and strains of Methicillin-Resistant *Staphylococcus aureus* (MRSA) have been isolated from both wildlife, livestock and humans, suggesting the presence of a common mechanism of spread. The Mediterranean basin is important for the richness and uniqueness of its wildlife. The latter represents a mechanism for spread of antibiotic-resistant bacteria and antibiotic resistant genes. This mini-review focuses on antibiotic resistance in wildlife in the Mediterranean basin, including the spread of antibiotic-resistant bacteria belonging to the priority list of pathogenicity.

Introduction

Antibiotics are of paramount importance in clinical, veterinary and agricultural fields. Due to the dramatic increase in antibiotic use in recent years, the benefits of antibiotics have lost strength due to the widespread development of antibiotic resistance. This problem takes on serious aspects when the phenomenon of antibiotic resistance involves clinical pathogenic bacteria [1]. Bacterial resistance to antibiotics, especially multi-drug resistance, has become a global challenge, threatening human health, animal health and the safety of the environment. The number of human deaths attributable to multidrug resistance is projected to increase to 10 million by 2050, surpassing deaths from cancer [2]. Several mechanisms can preside over the onset of antibiotic resistance, depending on the modes of action, structures, and biochemical properties of different antibiotics. Resistance mechanisms can occur through the mutation of a target protein, through the acquisition of a gene capable of conferring resistance, through the efflux or inactivation of an antibiotic, or through the synthesis of a new target protein resistant to an antibiotic [3]. The ability of bacterial pathogens to acquire antibiotic resistance genes depends on the effectiveness in transferring genetic information. Furthermore, it should be considered that antibiotic resistance genes can also be transferred between phylogenetically distinct bacteria [1].

Although antibiotic resistance can be established in a bacterium through spontaneous mutation, horizontal gene transfer allows the dispersal of antibiotic resistance genes and allows bacteria to exchange their genetic materials, including antibiotic resistance genes, among diverse species, considerably favoring the development of multi-drug resistance [4]. Transfer of antibiotic resistance genes is at the base in the development of multidrug resistant bacteria. Horizontal gene transfer comprehends three mechanisms for DNA transfer in nature: i) conjugation among bacterial cells, with antibiotic resistance genes often carried on plasmids that can be transferred between different types of bacteria; ii) the natural transformation presides over the transfer of the DNA present in the environment inside the bacterial cells, iii) transduction, whit the participation of bacteriophages able to transfer bacterial DNA. Horizontal gene transfer allows exogenous DNA transfer from one bacterial cell to another, even if they are only distantly related. Bacteria with a plasmid that hosts an antibiotic resistance gene, acquired from another bacterium, can survive once exposed to the antibiotic [5]. By accumulating genes involved in different resistance mechanisms from the exogenous DNA, bacteria can acquire multidrug resistance, as in the case of *Acinetobacter* and *Enterobacter* strains, carrying plasmids conferring resistance to last-resort antibiotics [6]. Wildlife can spread antibiotic-resistant bacteria and antibiotic-resistant genes over large distances. The Mediterranean Basin is a highly communicated and commercial region, with wildlife that may play a role in the spread of antibiotic resistance. The spread of antibiotic resistance by wildlife and the spread of antibiotic resistance in the Mediterranean Basin will be described.

Antibiotic Resistance in Wildlife

Antibiotic resistant bacteria in wild animals and genes of antibiotic resistance in the microbiota of multiple wildlife species, were detected. Wildlife has an ubiquitous distribution and some members move long distances, as in the case of birds and fish. It is thus possible that they play an important role in the global spread of antibiotic-resistant bacteria and resistance genes, affecting human health and public health [7]. The first bacteria isolated from wildlife were detected about fifty years ago, with antibiotic resistant *Escherichia coli* strains from pigeons and jungle crows evidencing resistance to chloramphenicol and multidrug resistance and carrying conjugative R plasmids [8]. Afterwards, *Salmonella* spp. strains resistant to antibiotics of the tetracycline class were isolated from wild animals, including canids, mustelids, birds, ungulates, with *S.* Typhimurium as the most common serotype [9]. Methicillin-Resistant *Staphylococcus aureus* (MRSA) detection in free-

living wild animals has revealed a very low prevalence, highlighting related resistances to livestock and humans [10]. Because ubiquity and mobility of wildlife, once diffused, antibiotic resistant bacteria can be transmitted to humans and livestock through fecal contamination of water, public areas and agricultural operations. Investigations have shown that antibiotic resistance is widespread in wild populations even though they have, reasonably, never been exposed to antibiotics.

The natural habitats most affected by human activities are those where the highest diversity of antibiotic resistance is observed in bacteria carried by wildlife. The ecological characteristics of wild species as well as the traits of their life history can serve to infer their potential role in the epidemiology of antibiotic resistance. Those wildlife species in contacts with humans, omnivores and carnivorous, appear to be at high risk of being potential carriers of antibiotic resistance. Furthermore, direct contacts, soil and water appear to be of primary importance in the flows involved in the transmission of antibiotic resistance via wildlife. Water is of great importance in the exchange of resistant genetic determinants and resistance to antibiotics. Aquatic environments possibly contaminated by wildlife with antibiotic-resistant bacteria can be critical points for the spread of antibiotic resistance [11].

It is noteworty to consider that different bacteria may share and exchange resistance genes through horizontal genes transfer. As consequence, bacteria that are not pathogenic for humans, may still carry and spread relevant resistance mechanisms that could be then acquired by bacterial strains pathogenic for human or even domestic animal. As an example, insects may aquire antibiotic resistance from other sources and could represent an important problem for human health. The resistance genes in the gut of the gypsy moth *Lymantria dispar* highlighted that insect guts could be a reservoir of antibiotic resistance genes, with the potential for significant dissemination [12]. Wildlife can promote the exchange of antibiotic resistant bacteria and resistance genes between the artificial and natural environments. Antibiotic resistant bacteria of *E. coli* and *Salmonella* spp. have been described in poultry, cattle and pig farms, as well as in humans, with these antibiotic-resistant bacterial strains spreading in the wild, infecting new wild animals, forming new host reservoirs of antibiotic resistance in the environment. Wild bird populations can be vectors of *E. coli*, *Salmonella* spp. and *Campylobacter* spp. furthermore, feces from bird flocks contribute to an increasing level of coliform bacterial contamination of drinking water reservoirs. Additionally, wild birds can transmit these pathogens directly to humans by contaminating agricultural fields or surface water used for recreation or crop irrigation [13]. Rodents can be a reservoir of antibiotic-resistant bacteria, transmissible to livestock and humans. Furthermore, these findings have implications for human and veterinary medicine regarding the use of antibiotics and the subsequent selection of antibiotic resistant bacteria [14]. Gulls may be a particularly important carrier of antibiotic resistance because of their close association with humans. During the past several decades, gull populations have increased worldwide due in large part to burgeoning human populations along coasts and the associated increase in availability of human-derived foods. Gulls can carry different potentially pathogenic bacteria as *Salmonella* spp., *Campylobacter* spp., *Listeria* spp. and vero cytotoxin-producing *E. coli* O157, which they likely acquire by feeding and loafing at sewage lagoons, garbage dumps and farms. The high concern of these mechanisms is evidenced by the presence of clinically relevant antibiotic resistant bacteria and antibiotic resistant genes detected in gull feces [15]. Strains of *E. coli* carrying Extended-Spectrum *beta*-Lactamases (ESBL) were evidenced outside clinical settings. The spread of *E. coli* (ESBL) in the environment outside of clinical and veterinary settings can be a consequence of the colonization of populations of wild animals, which can turn into an infectious source or even a reservoir of *E. coli* (ESBL) even in fragile environmental niches [16]. *E. coli* (ESBL)-producing strains were isolated from feces of Franklin's gull (*Leucophaeus pipixcan*) migrating from United States and in Canada, to the coast of Antofagasta, north of Chile. In fact, high rates of antibiotic resistance were evidenced, with about half of isolates exhibiting ESBL phenotype due to the presence of CTX-M-15, CTX-M-2, CTX-M-22, and CTX-M-3 related coding genes. Similar pathways were previously reported in the same gull species located in the Central Region of Chile, suggesting that gulls can behave as carriers, maintaining and spreading resistant bacteria acquired in the United States and/or Canada [17].

The *mcr-1* gene that conferred resistance to colistin, an antibiotic of last resort used in the treatment of multidrug-resistant bacterial infections in humans, was discovered in *E. coli* isolated from domestic pigs in China in 2015 [6]. Since then, the *mcr-1* gene has been found in other contexts, including gulls. Gulls can facilitate the transmission of *E. coli* strains carrying *mcr-1* to humans and livestock through fecal contamination of water, public areas and areas prone to agricultural activities. Additionally, *E. coli* species have the potential to replicate in the environment, and gulls can contaminate an environment such as beach sand with a high load of viable *E. coli* carrying *mcr-1*, which can be passed on to other bacteria [18]. The presence of antibiotic resistance in wildlife was highlighted in different ecosystems, including isolated environment such as Antarctica [19]. The migratory capacity of several gull species such as the Franklin's gull, migrating across America from Canada to Chile, could result in the dissemination of antibiotic resistant bacteria and related genes over extensive geographic areas, dispersing antibiotic resistance from regions with high levels of antibiotic resistance to less affected areas [17]. Gulls are also present in most urban and rural environments, and their feces are extensively dispersed in the environment [20]. Different feeding habits, habitat use and life strategies of wild bird species affect their bacterial community composition and structure, and also their exposition and acquisition of antibiotic resistance. There is great potential for wild birds to spread antibiotic resistance genes into habitats that can thus represent a risk for humans, even over long distances due to their migratory behaviour [21].

Reptiles living in closer proximity to humans potentially have the possibility to be exposed to bacteria of human origin and can represent a potential source for spread of antibiotic resistance. Strains of the species *E. coli* and *Salmonella enterica* were isolated from the feces of land iguanas (*Conolophus* sp.), marine iguanas (*Amblyrhynchus cristatus*), giant tortoises (*Geochelone nigra*), and seawater samples collected from different sites from Galápagos Islands. Antibiotic-resistant bacteria were found in reptile feces from tourism sites and from seawater close to a public use beach. *E. coli* strains isolated from locations proximate to a port town, showed resistance to ampicillin, doxycycline, tetracycline, and trimethoprin/sulfamethoxazole [22]. The Antillean iguana (*Iguana delicatissima*) exposed to different anthropogenic pressures showed the presence of acquired resistances in their cloacal microbiota. A high frequency of *E. coli* was found in samples obtained from anthropized sites, highlighting the presence of multidrug-resistant strains. Human-associated bacteria and their determinants of antibiotic resistance can then be transferred to wildlife, which, in turn, can act as a reservoir of antibiotic resistance [23]. Figure 1 represents a general view of antibiotic resistant bacteria and of antibiotic resistant genes spread in wildlife.
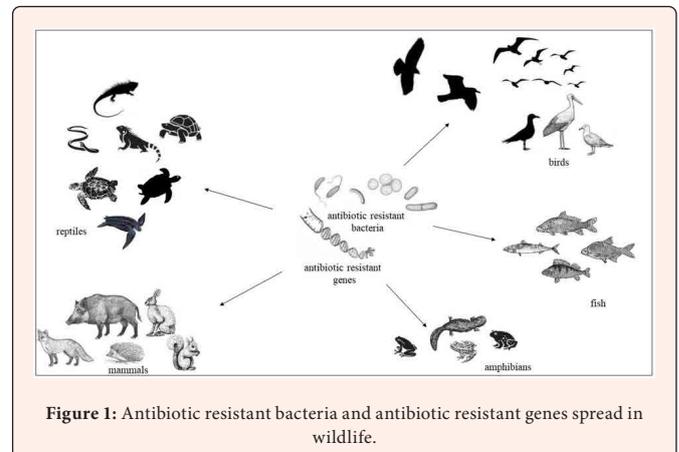

Figure 1: Antibiotic resistant bacteria and antibiotic resistant genes spread in wildlife.

Antibiotic Resistance in Wildlife in the Mediterranean Basin

The Mediterranean Basin includes five Asian countries (Cyprus, Israel, Lebanon, Syria, and Turkey), ten European countries (Albania, Bosnia-Herzegovina, Croatia, France, Greece, Bosnia-Herzegovina, Italy, Monaco, Montenegro, Slovenia, and Spain) and five African countries (Algeria, Egypt, Libya, Morocco, and Tunisia) (Figure 2). The Mediterranean Basin represents one of the Global Biodiversity Hotspots and is characterized by high communications and exchanges. This basin presents a variety of aspects, including lofty mountains, ancient rivers, deserts, forests, and many thousands of islands. It constitutes a mosaic of natural and cultural landscapes, where human civilization and wild nature have coexisted for centuries. This area contains a high richness in terms of animal and plant diversity, in virtue of a unique conjunction of geography, history, and climate [24]. This basin is important for the richness and uniqueness of its wild fauna and flora that reside there and for the millions of migratory birds that, from the extreme European and African continent, use the Mediterranean wetlands and other habitats as a resting or breeding place [25]. This basin is characterized by a wildlife that play a key role in communicating a wide variety of features, including antibiotic resistance [26].

Figure 2: Countries bordering the Mediterranean basin, one of the global biodiversity hotspots.

As an example of wildlife involved in antibiotic resistance dissemination between different environmental compartments, a study on wildlife in Andalusia, Spain, evidenced how the introduction of antibiotic resistance genes into the bacterial communities of wild bird can influence and increase their diffusion. It emerges that sources and sinks of antibiotic resistance genes and dissemination rates of antibiotic resistance bacteria and antibiotic resistance genes by birds, are important factors for antibiotic resistance diffusion [21]. The gut microbiome abundance of antibiotic resistance genes was investigated in faeces from migratory waterbirds wintering in South West Spain, including the white stork *Ciconia ciconia* and lesser black-backed gull *Larus fuscus*, omnivorous and opportunistic birds that use highly anthropogenic habitats such as landfills and urban areas, the greylag goose *Anser anser* and the common crane *Grus grus*, herbivores and diffused in more natural habitats. Samples of fresh faeces from these species were analysed to quantify the abundance of genes encoding resistance to sulfonamides (*sul1*), beta-lactams (*bla*TEM, *bla*KPC and *bla*NDM), tetracyclines (*tetW*), fluoroquinolones (*qnrS*), and colistin (*mcr-1*). The study evidenced that bacterial communities in gull faeces were the richest and most diverse of the group investigated. Faecal communities in storks and gulls, regularly feeding in landfills, were the most similar. Faeces from birds that feed in landfills as stork and gull, contained a significantly higher abundance of genes of antibiotic resistance (*sul1*, *bla*TEM, and *tetW*). Genes conferring resistance to last resort

antibiotics such as carbapenems (*bla*KPC) and colistin (*mcr-1*), were only observed in faeces from gulls. These wild bird species are reservoirs of antibiotic resistance genes that they may disseminate across environments, representing a risk for their further spread to humans [21].

Multidrug resistant strains of the species *E. coli* were detected in the fecal microbiota of yellow-legged gulls (*Larus michahellis*) in Morocco. Among isolates, one showed resistance to ertapenem and contained the *bla*OXA-48 gene. Moreover, the plasmid-mediated genetic determinats for quinolone resistance (*aac(6')-Ib-cr, qnrS1, qnrB1*), were detected in nine out of the isolated strains of *E. coli*. Thirteen isolates carried one of the Shiga toxin *E. coli*-associated genes: *stx1*, *stx2* and *eae* genes. According to these investigations, it emerge that gull feces may create potential public health risk in the Moroccan environment by spreading dangerous antibiotic resistance gene determinats [27]. Specimens of Mediterranean herring gulls (*Larus cachinnans*) were investigated as a possible reservoir of antibiotic resistant bacteria and of cassette-borne resistance genes located in class 1 integrons. Bacterial strains of the family *Enterobacteriaceae* were collected from cloacal swabs of 92 chicks captured in a natural reserve in the North East of Italy. High percentages of resistance to ampicillin and streptomycin were highlighted. Resistance to trimethoprim/sulfamethoxazole were found at high percentages in *Proteus* spp. and *Citrobacter* spp. strains. Strains *Proteus* spp. showed resistance to chloramphenicol. Among isolates, 10% carried the *intl1* gene. Integron variable regions showed the presence of several different cassette arrays, with *dfrA1–aadA1a* and *aadB–aadA2* cassette arrays as the most frequently detected. It was thus concluded that bacterial strains isolated from Mediterranean herring gulls could represent a reservoir of antibiotic resistant bacteria and of genes of antibiotic resistance. In virtue of their feeding habits and their ability to fly over long distances, these free-living birds may allow the circulation of antibiotic resistant bacteria between different environments [28]. *Caretta caretta* is the most abundant sea turtle species in the Mediterranean Sea. Cloacal swabs collected from stranded or recovered loggerhead sea turtles *C. caretta* of Mediterranean, from the Aeolian Archipelago, allowed isolation of Gram negative bacteria assigned to *Enterobacteriaceae*, *Shewanellaceae* and *Vibrionaceae* families. Antibiotic resistance was revealed mostly for ampicillin and sulfamethoxazole/trimethoprim. The presence of antibiotic resistant strains was recovered also in healthy sea turtle *C. caretta*, confirming that this wild species constitutes a carrier of antibiotic resistance spread for its migratory life cycle, representing a challenge for marine environments and, consequently, for human health [29]. Dissemination of wildlife representants in the Mediterranean Basin, related antibiotic resistant bacteria, eventual genetic determinants of resistance, origin and type of analyzed samples, were described in Table 1.

Table 1: Antibiotic resistant bacteria and genes of antibiotic resistance in Mediterranean Basin wildlife.

Wildlife	Antibiotic Resistant Bacteria (ARB)	Antibiotics	Antibiotic Resistance Genes (ARGs)	Type of Sample	Site of Origin	Potential Suggested Origin for the ARB or ARGs	References
sea turtles (*Caretta caretta*)	*Shewanella* sp., *Enterobacter* spp., *Citrobacter freundii*, *Pseudomonas*, *Vibrio*, *Klebsiella*, *Morganella*, *Providencia*, *Hafnia*, *Achromobacter*, *Leclercia*	ampicillin, sulfamethoxazole/ trimethoprim, ciprofloxacin, tetracycline, chloramphenicol, kanamycin, streptomycin, nalidixic acid		cloacal swabs	Aeolian Archipelago, Southern Thyrrenian Sea, Sicily, Italy		[29]
lesser black-backed gull (*Larus fuscus*)	*Acinetobacter* spp., *Enterococcus* spp., *Enterobacteriaceae*, *Pseudomonas* spp., *Staphylococcus* spp., *Streptococcus* spp.		*sul1, bla*TEM, *tetW, bla*KPC, *mcr-1*	freshly-voided faeces	Andalusia, Spain; South-West Spain		[21]

yellow-legged *Larus michahellis*	*Escherichia coli*	amoxicillin, tetracycline, ertapenem, quinolones	*bla*OXA-48, *aac(6')-Ib-cr*, *qnrS1, qnrB1*	cloacal swabs	Mogador Island, Essaouira archipelago, Morocco		[27]
herring gulls (*Larus cachinnans*)	*Enterobacteriaceae, Proteus* spp., *Citrobacter* spp.	ampicillin, streptomycin, chloramphenicol	*dfrA1–aadA1a, aadB–aadA2, estX* cassette	cloacal swabs	natural reserve in the North East of Italy	waste-handling facilities, crops, waters, and urban areas	[28]
yellow-legged gulls (*Larus michahellis*)	*Escherichia coli*	tetracycline, ampicillin, streptomycin	*bla*CTX-M	cloacal swabs	Camargue, southern France	result of long-time direct or indirect exposure to human activities in an area with relatively high antibiotic pressure	[30]
Larus fuscus, Larus cachinnans	*Escherichia coli*	beta-lactams	*bla*CTX-M	faeces	Matosinhos and Leça da Palmeira beaches, Porto, Portugal	beaches may play a major role in dissemination of resistance determinants	[31]
Larus michahellis	Non-O1/Non-O139 *Vibrio cholerae*	third-generation cephalosporins	*bla*KPC, *bla*VIM, *bla*OXA-48, *bla*IMP-1	cloacal swabs	island of Carteau, Port-Saint-Louis, France	feeding habits mainly relying on anthropogenic resources	[32]
Larus michahellis	*Escherichia coli*	quinolones, gentamicin, amikacin	*bla*KPC-2, *bla*VIM	cloacal swabs	the city of Barcelona, Spain	carbapenem-resistant isolates recovered from gulls share the same sequence types as those recovered from human samples	[33]
Larus michahellis	*Escherichia coli*	β-lactam antibiotics, except aztreonam	*bla*VIM-1	cloacal swabs	Port-Saint-Louis, South France	gulls and humans share the same pool of *Escherichia coli* strains	[34]
Larus michahellis, pigeons	*Escherichia coli, Cronobacter sakazakii, Hafnia alvei, Proteus hauseri, Serratia marcescens*	beta-lactams, including broad spectrum cephalosporins	*bla*TEM-1, CTX-M-15, CTX-M-1	faeces	urban parks and beaches of Marseille, France	important role of urban birds in the proliferation of multidrug-resistant bacteria from wild birds to humans	[35]
Larus spp.	*Escherichia coli, Klebsiella pneumoniae*	colistin, beta-lactams	*mcr-1*, SHV-12, CTX-M-14, SHV-110, CTX-M-15	faecal samples collected in 2009	Spain and Portugal, including a landfill in Emporda, Spain	mcr genes can originate in aquatic bacteria (*Shewanella spp.*) and be subsequently selected through the use of antibiotics in aquaculture	[36]
wild birds	*Escherichia coli, Enterobacter cloacae*		*bla*CTX–M–9, *bla*SHV–12, *mcr*-9 g	cloacal samples	Hérault department, South of France	interface of wild animals and human communities	[37]

gulls	*Enterobacteriaceae*	multidrug-resistance		fecal samples	Lisbon coastline, Portugal	gut microbiota for transfer of resistance genes within bacterial species	[38]
pigeons (*Columba livia*)	*Acinetobacter* spp.	carbapenem	*bla*OXA-23, *bla*OXA-51-like, *bla*OXA-58.		Marseille, France, Annaba, Algeria	environmental reservoirs	[39]
	Acinetobacter baumannii	carbapenem	OXA-23		Mediterranean Sea near the Bejaia coast, Algeria		[40]
Pagellus acarne							
wild boars, Barbary macaques	*Escherichia coli, Klebsiella pneumoniae*		CTX-M-15		Béjaïa and Jijel, Algeria	different ecological niches and different hosts	[41]
horse	*Acinetobacter baumannii*	carbapenem	*bla*OXA-51		Lebanon		[42]
wild-growing Mediterranean mussel (*Mytilus galloprovincialis*)	*Aeromonas* spp.		*bla*CTX-M-15, *bla*SHV-12, *bla*PER-1, *bla*FOX-2		Adriatic Sea, Croatia	resistant Aeromonas strains harboured by mussels	[43]
wood mice (*Apodemus sylvaticus*), black rats (*Rattus rattus*), European rabbits (*Oryctolagus cuniculus*), and greater white-toothed shrews (*Crocidura russula*)	*Escherichia coli*	tetracycline, quinolones	*bla*CTX-M-1	faeces	a hunting estate in Los Alcornocales Natural Park, Cádiz, Southern Spain	different ecosystems	[44]
little wild animals	*Klebsiella pneumoniae*		CTX-M-15		the Paris area, France		[45]
wild bird					Greece		[46]
seagulls	*Escherichia coli*	ESBL-positive	*bla*TEM-52, *bla*CTX-M	fecal droppings	Berlengas Island, Portugal	different ecosystems	[47]
wild boar	*Escherichia coli, Enterococcus* spp.	tetracyclines,		faeces	Portugal	livestock, humans, and the environment	[48]
		aminoglycosides					
wild ungulates	*Escherichia coli*	colistin	*mcr-1*		Portugal	different time points and geographical regions	[49]
wild birds	*Campylobacter* spp.	streptomycin		cloacal swabs	Turkey		[50]
mammals, birds, reptiles, streptomycin, shellfish, amphibians, snails	*Salmonella* spp.	β-lactams, ciprofloxacin, quinolones, aminoglycosides, chloramphenicol, colistin sulfate, trimethoprim-sulfamethoxazole, tetracycline, streptomycin, ampicillin, nalidixic acid		intestine, spleen, liver and/ or lymph nodes	Campania and Calabria regions, southern Italy	domestic animals, wildlife and humans	[51]
Caretta caretta	*Aeromonas* spp.	*beta*-lactams, sulfonamides, quinolone, tetracycline	*bla*TEM, *qnrS, sulII, tetA*		coasts of Sicily, Mediterranean Sea, Italy		[52]

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Priority Antibiotic Resistant Bacteria in Wildlife in the Mediterranea Basin

The World Health Organization stated a global priority pathogens list of antibiotic-resistant bacteria to help in prioritizing the research and development of new and effective antibiotic treatments. *Mycobacterium tuberculosis*, the cause of human tuberculosis, was not subjected to review for inclusion in priority pathogens list of antibiotic-resistant bacteria as it is already a globally established priority for which innovative new treatments are urgently needed [53]. The list includes i) Priority 1, 'Critical': *Acinetobacter baumannii*, carbapenem-resistant; *Pseudomonas aeruginosa*, carbapenem-resistant; *Enterobacteriaceae* (*Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* spp., *Serratia* spp., *Proteus* spp., and *Providencia* spp, *Morganella* spp.), carbapenem-resistant, 3rd generation cephalosporin-resistant; ii) Priority 2: 'High': *Enterococcus faecium*, vancomycin-resistant; *Staphylococcus aureus*, methicillin-resistant, vancomycin intermediate and resistant; *Helicobacter pylori*, clarithromycin-resistant; *Campylobacter* spp., fluoroquinolone-resistant; *Salmonella* spp., fluoroquinolone-resistant; Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant; iii) Priority 3: 'Medium': *Streptococcus pneumoniae*, penicillin-non-susceptible; *Haemophilus influenzae*, ampicillin-resistant; *Shigella* spp., fluoroquinolone-resistant [53]. Extended-Spectrum *beta*-Lactamases (ESBLs) are mainly plasmid-encoded enzymes that confer resistance to *beta*-lactams, including broad spectrum cephalosporins. There are different mechanisms of transmission between bacteria, including horizontal gene transfer via mobile genetic elements such as recombinant plasmids, transposons or integrons. Enzymes ESBL mainly include class A β-lactamases, such as TEM, SHV and CTX-M type, conferring resistance to penicillin and cephalosporin classes [54].

Wildlife is one of the drivers of dissemination of genes conferring resistances to clinically important antibiotics. Wild birds were reported as vectors of Extended-Spectrum *beta*-Lactamase- (ESBL) and carbapenemase-encoding genes, thus acting as long-distance spreaders in case of migratory birds, and can represent a very serious concern [37]. Wild birds collected in France were characterized by a high proportion of ESBL-positive bacterial isolates. Isolates included strains of the species *E. coli and Enterobacter cloacae*, of which many carried the *bla*CTX−M−9 gene. *Enterobacteriaceae* strains isolated from wild birds within the rescue center in France, evidenced similar pathways of antibiotic resistance to nosocomial spreads observed at hospital. Since wild birds likely get back to nature after a few days or weeks, the presence of this critical bacteria represents a serious issue with regard to ESBL dissemination in natural environments [37]. Alarming levels of CTX-M genes in species of gulls in Europe indicated that the ability of these birds to reach several countries could contribute to the spread of ESBLs. Yellow-legged gulls (*Larus michahellis*) carried CTX-M type ESBL-producing *E. coli* in Marseille, South of France. Pigeons and gulls, migratory birds, have been pointed out as potential reservoirs and vectors for multidrug-resistant bacteria, especially gulls that are free-living aquatic birds [35]. Priority antibiotic resistant bacteria evidenced in the Mediterranean Basin related to wildlife have been focused in Table 2.

Table 2: Global Priority Pathogens in wildlife in the Mediterranean basin.

Priority Category	Pathogen	Antibiotic Resistance	Wildlife	Origin	References
critical	*Acinetobacter baumannii*	carbapenem	*Columba livia*	Marseille, France, Annaba, Algeria	[39]
critical	*Acinetobacter baumannii*	carbapenem	*Pagellus acarne*	Bejaia coast, Algeria	[40]
critical	*Escherichia coli*	carbapenem	*Larus michahellis*	Barcelona, Spain	[33]
critical	*Escherichia coli*	carbapenem	*Larus michahellis*	Port-Saint-Louis-du-Rhône, France	[11]
critical	*Escherichia coli*	carbapenem	*Larus michahellis*	Morocco	[27]
critical	*Klebsiella pneumoniae*, *Escherichia coli*	carbapenem	gulls	Lisbon coastline, Portugal	[38]
critical	*Escherichia coli*	third generation cephalosporin	*Larus michahellis*	Port Saint-Louis Carteau, Camargue, southern France	[30]
critical	*Escherichia coli*	third generation cephalosporin	wild birds	Zaragoza, Spain	[55]
critical	*Proteus mirabilis*	third generation cephalosporin	gulls	South of France	[56]
critical	*Escherichia coli*	third generation cephalosporin	*Larus michahellis*, *Columba livia*	Marseille, France	[35]
critical	*Escherichia coli*, *Enterobacter cloacae*	third generation cephalosporin	wild birds	Hérault department, South of France	[37]
critical	*Klebsiella pneumoniae*, *Escherichia coli*	third generation cephalosporin, carbapenem	wild European hedgehogs (*Erinaceus europeus*)	Catalonia, NE Spain	[57]
high	*Enterococcus faecium*	vancomycin	*Larus cachinnans*	Portugal	[58]
high	*Campylobacter jejuni*	fluoroquinolone	*Larus michahellis*	Spain	[59]
high	*Campylobacter* spp.	fluoroquinolone	*Larus michahellis*, *Ichthyaetus audouinii*	Ebro Delta, Spain	[60]
high	*Salmonella* spp.	fluoroquinolone	*Larus audouinii*	Spain	[61]

Wildlife as Sentinels of Antibiotic Resistance

Some wild species have been used as bioindicators or sentinels for the spread of resistant bacteria in the environment. Wildlife harbouring antibiotic resistant bacteria and carrying genes of antibiotic resistance are an indicator that antibiotic resistance of human or livestock origin are widespread in the environment. This could represent a challenge for human health, since wild animals could act as efficient antibiotic resistance reservoirs and epidemiological links between human, livestocks and natural environments [62]. Wildlife has been suggested to function as bioindicators or sentinels for antibiotic resistance [63,64]. Due to their well-understood ecologies and extended migrations, birds have been employed to track the spread of antibiotic resistance across environments [65,66]. Similarly, faecal samples from deer have been used to study patterns in antibiotic resistance distribution across Ireland [64]. However, with the large home-ranges of such animals it is challenging to pinpoint factors contributing to exposure risk. Moreover, small mammals hold potential for examining the carriage rates of antibiotic resistance in relation to agricultural exposure and as wider sentinels of antibiotic resistance, particularly in response to potential sources of anthropogenic pollution [67]. Sea turtles have been proposed as sentinel species in the western Mediterranean Sea and carriers of antibiotic-resistant bacteria due to their longevity and migratory lifestyle. The loggerhead sea turtle (*C. caretta*) is the most common species of sea turtle in the Mediterranean and can be used as a bioindicator [68].

Gulls can serve as useful sentinels for *mcr-1* and other clinically relevant forms of colistin resistance in the environment. In fact, seagulls show high mobility and through fecal shedding they can spread both pathogenic and antibiotic-resistant bacteria in different environments, also frequented by people [18]. The patterns observed in bacteria from several wild animals can represent indicators for specific resistance traits in the environment, including those to highest priority substances such as 3rd generation cephalosporins, fluoroquinolones and colistin. A continuous monitoring of the occurrence of such bacteria in wildlife is preferable, in reason of the possible role of wildlife as reservoir and disperser of resistant bacteria [62]. Wild ducks and geese could become spreaders of resistant bacteria and these wild species have been used as bioindicators or sentinels for the spread of resistant bacteria in the environment. Some

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wild bird populations, including wild ducks and geese belonging to different species within the *Anatidae* family can form large groups in crops producing food and feed, or on wetlands and lakes used as source of drinking water for humans and livestock, or for aquatics. Due to their capacity for long-range movements, they are potential spreaders of bacteria with antibiotic resistance genes beyond borders. The presence of antibiotic resistance genes has been revealed in bacteria from a wide variety of wild species across Europe, including resistance to high-priority substances such as 3rd-generation cephalosporins, fluoroquinolones, colistin or even carbapenems [62]. The presence of critically important antibiotic resistance strongly suggests that the use of selective isolation in the continuous monitoring of antibiotic resistance in wildlife is advisable. The possible role of wildlife as a sentinel for the spread of antibiotic resistance could represent an important tool in defending our health [62]. Interestingly, the persistence and spread in the environment of acquired antibiotic resistance and human-associated bacteria, while posing a threat to wildlife, can also be exploited as a tool to monitor the extent of antibiotic resistance and detect human impact and distribution in the environment [23].

Conclusion

Wildlife plays an important role in the spread of antibiotic resistant bacteria and antibiotic resistance genes due to its tendency to move from one place to another and to have contact with different districts, even over long distances. The same antibiotic-resistant bacteria and antibiotic-resistant genes have been detected in both wildlife and animal husbandry, the environment and humans. In particular, pathogenic bacteria can acquire antibiotic resistance genes from motile genetic elements, such as plasmids and transposons. In fact, the observation of the phenomenon of antibiotic resistant bacteria and antibiotic resistance genes in wildlife suggests a high variability and diffusion in different environments. The unpredictable behavior of wildlife can add variability to the antibiotic resistance problem and can increase the threats it poses. The Mediterranean basin records large movements of wild birds that can play a fundamental role in the dispersal of antibiotic resistance in the human and veterinary clinical setting, as well as in agriculture and the environment. Furthermore, wildlife can play a role in the dispersal of antibiotic-resistant bacteria included in the pathogenicity priority lists. The possible use of wildlife as sentinels for monitoring antibiotic resistance could provide an important tool to help understand and somehow address the problem.

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