

REVIEW

Antimicrobial resistance in wildlife

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Summary

1. The spread of antimicrobial resistance is of major concern for human health and leads to growing economic costs. While it is increasingly hypothesized that wildlife could play an important role in antimicrobial-resistant bacteria dynamics, empirical data remain scarce.

2. The present work builds on a systematic review of the available data in order to highlight the main information we have and to suggest research pathways that should be followed if we aim to fill the gaps in our current knowledge.

3. To achieve this goal, we address four questions: (i) Which resistant bacteria are the most frequently observed in wildlife? (ii) How are resistant bacteria exchanged between wildlife and the other hosts involved? (iii) In which habitats are those resistant bacteria found? (iv) Are resistances associated with certain ecological traits of the host?

4. *Synthesis and applications.* We highlight the strong link existing between the impact of human activities on natural habitats and the carriage of antimicrobial-resistant bacteria by wildlife. Furthermore, we underline that omnivorous, anthropophilic and carnivorous species are at high risk of being carriers and potentially spreaders of antimicrobial-resistant bacteria. Identifying among those groups key sentinel species may be of particular interest to implement ecosystem contamination surveillance. Finally, we discuss possible exchange routes for antimicrobial-resistant bacteria between humans and wildlife. Considering that water is of major importance in those exchanges, a critical way to control antimicrobial resistance spread may be to limit aquatic environment contamination by antimicrobial-resistant bacteria and antibiotics.

Key-words: antibiotic resistance, antibiotic-resistant bacteria, emerging infectious disease, *Escherichia coli*, health ecology, *Klebsiella pneumoniae*, MRSA, pathogens, *Salmonella spp.*, transmission routes

Introduction

Antimicrobial resistance (AMR) is a major threat for human health world-wide, impairing our capacity to treat an increasing number of infections (WHO 2014). In addition, it entails a considerable increase in treatment costs,

as resistance makes necessary the use of expensive last-generation molecules and implies extra hospitalization costs. AMR is also a crucial issue in agriculture since it makes more complex the maintenance of domestic animal health, leading to additional economic costs. Furthermore, available data show that numerous wildlife species carry antimicrobial-resistant bacteria (AMRB) in a wide range of habitats, which raises the question of their role

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in AMRB dynamics at the interface between human populations, domestic animals and natural ecosystems.

There is thus an urgent need to understand the dynamics of AMR: how it spreads, how it passes from one compartment to another and how and why it is maintained within bacterial populations. These dynamics are greatly complicated both by the large diversity of antimicrobial resistance mechanisms (Fig. 1a) and by the horizontal transfer of resistance genes existing between bacteria (Fig. 1b; Tenover 2006). Indeed, the dissemination of AMR has been largely attributed to inter- and intraspecific DNA exchange, mainly through the horizontal transfer of plasmid-located resistance genes, which is the most important mechanism at the origin of acquisition of resistance in bacterial pathogens of human health concern (Carattoli 2013). Plasmids are extrachromosomal DNA molecules capable of autonomous replication and can confer resistance to the major classes of antimicrobials, including β -lactams, aminoglycosides, tetracyclines, chloramphenicol, sulphonamides, trimethoprim, macrolides and quinolones (Carattoli 2009).

The main measures currently applied in European countries are to cut down on the use of antibiotics in both human and domestic animals, since it has become clear that the two compartments are closely linked (Angulo, Nargund & Chiller 2004). These measures are based on

the assumption that AMR is associated with fitness costs that allow susceptible bacteria to overcome resistant ones, when there is no selective pressure linked to antimicrobial drugs. Yet it appears that these costs are extremely variable (Andersson & Hughes 2010) and can be reduced or even turned into fitness benefits by compensatory mutations (Luo *et al.* 2005). Additionally, the same mechanism or a mechanism found on the same genetic element can confer resistance to both antimicrobial drugs and pollutants (Baker-Austin *et al.* 2006). Thus, the pollution of environmental reservoirs can contribute to the development and maintenance of AMRB. Finally, AMRB are naturally found in soils in the absence of anthropogenic antimicrobial drugs due to the natural production of antibiotic molecules by some bacteria and fungi (Keen & Montforts 2012).

The low reversibility of AMR is all the more worrying in that in some cases resistance is associated with enhanced virulence. As an illustration, the different steps leading to methicillin resistance acquisition in *Staphylococcus aureus* are associated with virulence modifications (Cameron, Howden & Peleg 2011). The methicillin-resistant strain of *S. aureus* (MRSA), USA300, appears to have caused a strong increase in severe cutaneous infections observed in the USA in the 2000s (Chadwick *et al.* 2013). It is an example of bacteria in which AMR and

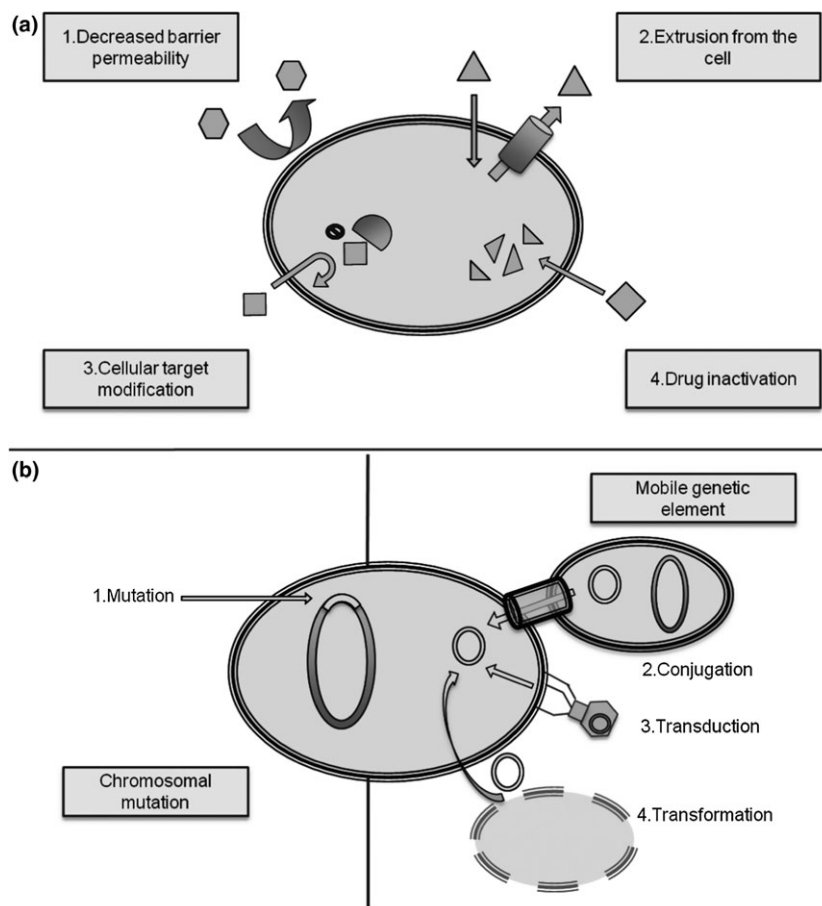


Fig. 1. The complexity of antimicrobial resistance mechanisms (a) and their transmission routes between bacteria (b). (a) Main antimicrobial resistance mechanisms: (1) Decrease in the membrane permeability to a drug. (2) Active extrusion of the drug out of the cell. (3) Modification of the cellular target of a drug. (4) Inactivation of the drug. (b) Mechanisms of antimicrobial resistance acquisition: the resistance to a drug can result from a mutation (1). The mutated bacteria that become resistant will be selected in the presence of the drug. This type of resistance will only be passed to the next generation within a particular strain. In contrast, some resistances can be carried by plasmids that can be transmitted from one bacterial species to another through either cell-to-cell conjugation (2), phage-mediated transduction (3) or transformation by extracellular DNA (4).

virulence are associated. Similarly, the *Escherichia coli* group called ST131 is characterized by both multidrug resistance and high virulence (Da Silva & Mendonça 2012). However, the link between resistance and virulence is highly diverse. Even within a single bacterial species such as *E. coli*, the association between virulence factor and resistance determinant carriage greatly varies according to the resistance mechanisms involved and the vertebrate host species studied (Da Silva & Mendonça 2012).

Considering the significant impact AMR has worldwide on both the economy and human health, it is a matter of urgency to improve our understanding of the role each compartment (i.e. domestic animals, human populations, wildlife and environmental reservoirs) plays in the maintenance and the dispersal of AMR within bacterial populations. However, while considerable efforts have been made to increase our knowledge of AMR dynamics in human populations and domestic animals, much less attention has been paid to wildlife. Yet over the last decade, accumulated evidence has revealed the presence of antibiotics and AMRB in wildlife and natural environments (Allen *et al.* 2010). Studies highlighted the presence of AMR in all ecosystems including the most isolated ones such as Antarctica (Miller, Gammon & Day 2009) and in a wide range of species (Allen *et al.* 2010).

Here, our purpose was to review currently available data concerning AMR in wildlife with the aim of drawing the major lessons that can be inferred from it. To achieve this goal, we carried out searches on the Web of Science (<https://access.webofknowledge.com/>) and PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) databases using the following terms ('Antimicrobial' OR 'antibiotic') AND 'resistance' AND ('wildlife' OR (('mammal' OR 'bird' OR 'reptile' OR 'amphibian' OR 'fish' OR 'invertebrate') AND ('wild' OR 'free-ranging')))). We ended our research on 20 May 2015. From the resulting list of references, we selected those presenting novel data about any resistant bacteria carried by any wild animal but excluding those living in captivity. We completed the reference selection with additional articles cited in four recent review papers (Guenther, Ewers & Wieler 2011; Wellington *et al.* 2013; Radhouani *et al.* 2014; Sousa *et al.* 2014). This left us with 210 peer-reviewed articles mainly pertaining to birds and mammals in Europe and North America

(Table 1). Only the most relevant are cited in the text body of the present paper. The full list of articles is presented in Appendix S1 (Supporting information).

We investigated the available studies with reference to four questions: (i) Which bacteria species are the most frequently found to be resistant to antimicrobial drugs in wild vertebrates? (ii) How do wildlife species get colonized by AMRB and which exchanges of such bacteria occur between humans, domestic animals and wildlife? (iii) What characterizes the habitats that are the most contaminated by AMR? (iv) What ecological or life-history traits, if any, favour the colonization and potential infection by AMRB in wildlife?

Given the huge heterogeneity of the data reported in the studies we gathered that notably differ by the vertebrate host species they focus on, the bacterial species they search for and the methods they use to isolate bacterial strains and determine their antimicrobial resistance pattern, we decided not to present any meta-analysis. Indeed, considering recent discussions on this issue in the literature (e.g. Kriston 2013; Melsen *et al.* 2014), we felt that in our case discussing the results of primary studies would be more useful than relying on a meta-analysis, which would summarize data that we consider highly inhomogeneous.

To conclude, we underline the gaps that remain in our knowledge of the wildlife compartment and its epidemiological links with human and domestic animal populations, and we suggest important paths to explore to anticipate future resistance transfer between compartments and to avoid human health crises.

AMR diversity in human pathogens carried by wildlife

In the vast majority of studies focusing on AMR in wildlife, the goal is not to investigate the whole bacterial community present in a host population but rather to assess whether a bacterial species (or strain) can be found in a particular host population. Similarly, not every resistant determinant known in the focus pathogen is systematically searched for, but only a selection of them. It is essential to consider, while trying to obtain information from the currently available data, that they only represent results

Table 1. Host groups and regions studied in the 210 articles analysed in our review

Region	Amphibians and reptiles	Birds	Fish	Invertebrates	Mammals	Total
Africa	1	1	1	0	9	12
Asia	1	10	2	1	6	20
Europe	4	72	7	6	53	142
North America	4	33	2	0	24	63
Oceania	0	0	0	0	3	3
Polar regions	0	5	0	0	2	7
South America	4	1	0	0	4	9
Total	14	122	12	7	101	256

The overall total exceeds 210 since some studies concern several groups or regions.

concerning what has been searched for. Generally, the search is driven by human health concerns associated with the focus bacteria or the focus resistance mechanisms. Indeed, only three bacterial groups were studied in more than 10% of the 210 studies we analysed: *E. coli* (115 studies), *Salmonella spp.* (54 studies) and *Enterococcus spp.* (43 studies).

Escherichia coli is part of the normal intestinal flora in humans. Nevertheless, it is the most frequent cause of urinary tract and bloodstream infections world-wide. In *E. coli*, the resistance of major concern is resistance to third-generation cephalosporins and carbapenem mainly conferred by enzymes known as extended-spectrum β -lactamases (ESBLs) and carbapenemases (WHO 2014). In wildlife, *E. coli* is the most commonly targeted bacteria in AMR studies. ESBL-producing *E. coli* are now frequently found in wildlife (reviewed in Guenther, Ewers & Wieler 2011), notably in birds and mammals (see for example Costa *et al.* 2006; Literak *et al.* 2010; Silva *et al.* 2011; Gonçalves *et al.* 2013). By contrast, resistance to carbapenems that are now present in *E. coli* in livestock and companion animals (Guerra, Fischer & Helmuth 2014) has not been reported in *E. coli* in wildlife despite searches focused on mammals, birds and reptiles (e.g. Navarro-Gonzalez *et al.* 2013).

Bacteria of the genus *Salmonella* are a major cause of foodborne illness throughout the world. *Salmonella* can be found in the intestines of many animals, including poultry and pigs. Most *Salmonella* strains cause gastroenteritis, while some strains, particularly *Salmonella enterica* serotypes Typhi and Paratyphi, cause enteric fever. During the late 1990s and early 2000s, several clones of multiresistant *Salmonella* emerged, and since then they have expanded world-wide. For example, in *S. enterica* serotype Typhimurium, a genomic element that carries resistance to five antimicrobials may spread horizontally among serotypes. In wildlife, *S. enterica* serotype Typhimurium presenting this pentaresistance has been detected in mammals (Caleja *et al.* 2011) and birds (Čížek *et al.* 2007).

Enterococci are ubiquitous bacteria in various environmental habitats and are commensal of mammals, birds, some reptiles and invertebrates (Aarestrup 2006). Some species have emerged as important causes of nosocomial and community-acquired infections (Van den Bogaard *et al.* 2002; Radhouani *et al.* 2012). They have innate resistance to many antimicrobial agents and they can carry a variety of acquired antibiotic resistance genes, which can be transmitted to other pathogenic bacteria (Murray 1991; Spera & Farber 1994). They are frequently studied in both wild and domestic animals since they are suitable as indicators of antimicrobial resistance in Gram-positive bacteria.

In addition to *E. coli*, *Salmonella spp.* and *Enterococcus spp.*, AMR has been occasionally studied in a few other bacterial groups, among which four were searched for in at least 5% of the articles we considered: *Campylobacter spp.*,

Enterobacter spp., *Klebsiella spp.* and *Staphylococcus spp.* In this article, our aim was to identify the main patterns that can be inferred from the available data. However, we emphasize the fact that those data concern essentially the three pathogens presented above and a few other bacteria, mostly enteric. Future research should aim to widen the range of bacteria groups studied, especially considering that, due to horizontal transfer, groups that are not major human pathogens may, nevertheless, contribute to spreading resistance mechanisms that are clinically relevant. For example, *Kluyvera ascorbata* is a rare bacteria that can occasionally cause severe infections in humans (Ruffini *et al.* 2008). It also has been isolated from wild animals (e.g. Lee *et al.* 2008). Despite the rarity of the severe human cases, *K. ascorbata* is of concern due to its ability to transfer genes encoding for ESBLs to other Enterobacteriaceae. Moreover, as further discussed in our conclusions, culture-independent methods may also help to broaden the range of AMR genes investigated in wildlife. As an illustration, an innovative study recently led on gulls in the USA revealed that the focus population carried a huge variety of AMR genes that were previously unrecognized (Martiny *et al.* 2011).

When considering current knowledge on AMRB found in wildlife, it is also important to keep in mind that the methods usually used to detect AMRB provide information on the presence of resistant strains, but do not assess the proportion of bacteria they represent in the studied population. This quantitative aspect may be an essential component of AMRB dynamics, and methods enabling the investigation of this issue should be used in future studies.

Exchanges

Mounting evidence attests the occurrence of AMRB exchanges between wildlife, humans and domestic animals. When investigating these exchanges, it is important to note that even bacteria of the same species harbouring the same resistance genes may not have the same origin since they may not belong to the same clonal complex. Yet, more and more studies show that identical or near identical strains, belonging to the same clonal complex, are circulating in wildlife, humans and domestic animals (e.g. Paterson *et al.* 2012; Monecke *et al.* 2013). Nevertheless, identifying similar pathogens in two compartments does not offer a basis for determining how and in which direction the exchanges took place. Thus, it is often very difficult to disentangle the transmission routes of AMRB between two compartments. As an illustration within the references we analysed, we could not draw any statistically based conclusion about the source of AMRB carriage in wildlife since this source could not be precisely determined with certainty in any study. Indeed, several possible transmission routes exist between the focus compartments including direct contact with infected individuals, their tissues or their faeces, water and soil. The

complex network of AMRB transmission routes existing between humans, livestock and the environment has been extensively discussed (Martinez 2009; Allen *et al.* 2010; Davies & Davies 2010); here, we focus on the role of wildlife in this network and rapidly describe the main transmission routes involved.

CONTACT

Humans and domestic animals can be in contact with wildlife species that live or feed near habitations and rearing estates. For example, rodent faeces can be touched by humans or their animals and be ingested if they contaminate food. Additionally, rodents living in the vicinity of human habitations and rearing estates can be in direct contact with animal faeces and manure. Moreover, humans can directly touch wild animals they trap, hunt or treat as veterinarians. This transmission route is known to be important for many zoonotic diseases such as tularaemia or brucellosis (e.g. Stewart 1996). There is no reason to think that it might not be important in AMRB exchanges.

Thus, it would be worthwhile to undertake studies aimed at assessing the risk of antimicrobial transmission linked to hunting and trapping practices. Such studies could build on the networks of game meat surveillance that exist in many countries. Wild animals can also ingest contaminated meat from domestic animals. It has been proven that animal products commonly contain AMRB (Overdevest 2011) and wildlife can occasionally feed on dead animals (e.g. stillborn calves or lambs) or on their giblets when they are not collected after home slaughter. Such contamination routes could be important to take into account with a view to controlling the spread of AMR to wildlife.

WATER

Water seems to be a major transmission media for AMRB (Taylor, Verner-Jeffreys & Baker-Austin 2011), as suggested by the evidence of the presence of those bacteria in treated water rejected in rivers (Galvin *et al.* 2010), in rivers themselves (Dhanji *et al.* 2011), in lakes (Hamelin *et al.* 2006) and even in sea water (Zhao & Dang 2012). Furthermore, there is clear evidence of the exchanges of resistance genes between environmental bacteria and human pathogens, which can occur in aquatic systems (Wellington *et al.* 2013). AMRB found in water can originate either from human or from domestic animal populations. It should be noted that the four pathogens of major concern cited above (*S. aureus*, *E. coli*, *K. pneumoniae* and *Salmonella spp.*) can persist in water for varying periods according to strains and environmental conditions and have all been recovered from aquatic habitats (Filali *et al.* 2000; Martinez-Urtaza *et al.* 2004; Dolejska *et al.* 2009; Goodwin *et al.* 2012).

First, sewage treatment plants, even the most modern, usually remove neither all antibiotic molecules nor AMRB from the treated sewage (Rizzo *et al.* 2013). The contaminated water is then spread into rivers allowing the dispersal of antibiotics and AMRB downstream. Similarly, livestock effluents containing AMRB and antibiotics can contaminate the aquatic environment. In this case, part of the effluent is not treated at all as contaminated pastures and fields can be directly connected to rivers and groundwater due to run-off and infiltration. Whatever the source of the water contamination, it generally increases downstream of human activity areas (e.g. Pruden, Arabi & Storteboom 2012) and mechanisms of AMR can then be transmitted to wildlife because either they inhabit and/or feed in an aquatic environment or because they drink the water.

In both marine and freshwater habitats, it is a matter of urgency to study the impact of aquaculture on the spread of AMRB. Aquaculture may be the key to success in feeding the growing global human population, but globally it relies on the utilization of large amounts of antibiotics (Cabello *et al.* 2013). The vast majority of aquaculture farms directly discharge both leftover antibiotics and organic matter (faeces and fish alimentation residues) into the surrounding water. Growing evidence shows that these practices are linked to antibiotic accumulation around the farms and favour the development and spread of AMRB below the pans and over distances that may be over one kilometre and probably more, depending on currents (Buschmann *et al.* 2012). Regrettably, few studies focusing on this impact of aquaculture have included research on bacteria infecting wildlife living in aquatic habitats near aquaculture farms. Within our list, only two articles addressed this issue (González *et al.* 1999; Burr *et al.* 2012). Both were led in freshwater. González *et al.* (1999) highlighted antimicrobial resistance in only four AMRB strains: three from water and just one from a wild pike, which did not permit any comparison with wild and farmed trout that were studied in parallel. By contrast, Burr *et al.* (2012) showed that within a single lake, farmed perch *Perca fluviatilis* carried a higher proportion of AMRB than wild individuals of the same species. The diversity of resistance highlighted was also higher in farmed animals and strains did not cluster according to the status (i.e. wild or captive) of the perch. Yet those results were not discussed in the light of the treatments used in farmed perch. Similarly, González *et al.* did not include any information about the treatments used in farmed trout. It is of major importance to include this component in future studies to gain a better understanding of the impact of aquaculture as wild fishes and aquatic mammals can travel long distances and spread AMR. In addition, bivalves inhabiting the surrounding environments could also be contaminated, especially filter feeders, and be at risk if they are eaten by humans (Soonthornchaikul & Garelick 2009).

SOIL

Antimicrobial resistance exists naturally in soil communities, notably due to the production of antibiotics by some soil bacteria and fungi (Keen & Montforts 2012). But the presence of AMRB in soil can also be the result of direct faeces or urine deposition (e.g. in pastures), of manure use (Heuer, Schmitt & Smalla 2011) or of effluent flows (Wellington *et al.* 2013). This could be an important transmission route with regard to the control of AMR spread (Heuer, Schmitt & Smalla 2011). Aerial transmission has also been suggested as possibly playing a role in AMRB dispersal (Allen *et al.* 2011). Wind could contribute to the spread of small particles of soil contaminated by antibiotics or AMRB. Thus, air should not be excluded from our AMR understanding framework, and studies should be undertaken to investigate its potential role in the spread of AMR. Finally, whatever the source of the soil contamination, wild species feeding in exposed fields could be infected by AMRB and spread them further.

More studies should focus on improving our understanding of the routes that allow AMR exchanges between epidemiological compartments, which is essential to meet the challenge of resistance spread control. AMR associated with drug use in cattle farms may spread both to soil through manure and to neighbouring watersheds through effluents. Targeting these two routes may help to reduce the risk of AMR spread associated with this activity (Pruden *et al.* 2013). Considering AMR genes as environmental contaminants and using methods that allow searching directly for these genes rather than for the bacteria carrying them may help in efficiently following the spread of AMR in all the components of the AMR transmission network. For example, methods involving polymerase chain reaction (PCR) use could permit searching for specific AMR genes whose spread is particularly worrying or that could be used as general AMR contamination markers (Pruden *et al.* 2006; Gillings *et al.* 2015). Overall, it is crucial to raise the awareness of the strong interconnectedness between habitats and compartments induced by multiple exchange routes, which implies that AMR issues must be tackled simultaneously in human populations, domestic animals, wildlife and environmental reservoirs.

Habitats: where is the resistance?

To understand and control AMR flows, one of the first steps is to determine in which kind of habitat they usually take place and why. It is now established that AMRB are ubiquitous in natural ecosystems. As an illustration, multiresistant *E. coli* have been isolated from water in Antarctica (Miller, Gammon & Day 2009). Spatial analysis is essential to understand AMR dynamics as it allows the consideration of contamination gradients across habitats and the potential consequences of wild species dispersion as well

as human and domestic animal movements (Singer, Ward & Maldonado 2006). However, data allowing comparison of AMRB prevalence across different habitats are scarce, and studies focusing on collecting such spatial data should be encouraged.

Only 10% of the articles we considered allowed us to draw some conclusions concerning the differences of AMR across habitats in terms of prevalence. Indeed, most of the authors either focus on only one kind of habitat or work in different sites but omit to describe them in detail. In certain cases, the study areas are also very large (an administrative region or a state) and include various habitats. Among the 21 suitable articles, we used chi-square tests or Fisher's exact tests when the application conditions of chi-square test were not met to compare the proportions of AMRB carriers between the host groups inhabiting different habitats when such analysis was not initially led by the authors. We chose a *P*-value threshold of 0.05 and applied a Bonferroni correction when several pairwise tests were used to analyse the results of the same study. Eleven studies highlighted a significantly higher prevalence of AMRB within the habitat considered that was the most impacted by human activities compared to more preserved sites, while 10 did not detect any contrast. Resistance mechanism diversity could only be compared in 19 of those articles and was significantly higher in nine of them in the most anthropized places, while no difference was underlined in the remaining 10 papers. Interestingly, none of the articles highlighted a reverse trend neither concerning prevalence nor diversity of AMRB. Thus, available data suggest that the diversity of resistance mechanisms detected, as well as the proportion of individual hosts carrying AMRB, increases with the proximity to human activities. Regrettably in most cases, habitats are just classified according to their main 'function' (e.g. natural reserve, farm, city, sewage plant, etc.). Some authors also use human or livestock density to characterize the study sites (Guenther *et al.* 2010). Such indexes that could be compared across studies should be more widely used. Land-use classification according to satellite data could also be relevant.

As discussed in part II, water seems to play a major role in the dispersal of antibiotics and AMRB to natural ecosystems. As an illustration of this role, studies carried out on marine mammals to date have shown that they carry highly diverse AMRB (Schaefer *et al.* 2009) and that AMRB prevalence has been alarmingly increasing over the last decade (Wallace *et al.* 2013). Furthermore, with the global loss of natural wetlands, waterbirds have become increasingly dependent on alternative and artificial habitats including wastewater treatment wetlands (Murray & Hamilton 2010), which could favour the transmission to wild birds of AMRB of human origin. Thus, aquatic habitats may be more impacted by AMR contamination than terrestrial ones. Yet, comparing AMRB prevalence in aquatic vs. terrestrial host species is challenging since few studies focus on both groups. Among

our references, 68 focus on aquatic species only (we considered as aquatic all species that either live or feed in water), 109 on terrestrial ones, one did not give any detail on the bird species studied and only 32 searched for AMRB in both groups. Among them, only 13 gave enough information to draw some conclusions. In most cases, authors did not investigate this aspect and we used chi-square tests or Fisher's exact tests when the application conditions of chi-square test were not met to compare AMRB distribution between groups. Only three studies gave significant results ($P < 0.05$); they all highlighted a higher AMRB prevalence in aquatic species.

Host species ecology and contamination risks

To understand the role of wildlife in AMRB dynamics, it is essential to identify among potential host species those ecological traits that favour the carriage of such bacteria since: i) it can help to infer the origin of the habitat contamination by the AMRB and ii) it is crucial to take into account the concerned animal species' characteristics (e.g. diet, life span) in order to predict the role they could play in AMRB evolution, maintenance and dispersal.

A species can be characterized by its habitat, which influences the contamination risk by AMRB. As stated above, the habitats that are the more closely linked to human activities appear to be the most highly contaminated by AMRB (Allen *et al.* 2010). Thus, species inhabiting these habitats appear to be the most strongly impacted. Beyond the habitat occupied by species, two other major ecological traits can influence their role in AMR dynamics, as well as their risk of contamination by any pollutant: i) how they use the habitat resources, notably what they eat and drink, and ii) how they move within their habitat and from this habitat to other places.

Studies offering a basis for comparison of AMRB prevalence in species with different diets within a habitat are scarce. Within our reference list, 101 articles focused on a single species, among which 43 were carnivorous (including piscivores, insectivores and scavengers), 25 were herbivorous and 33 were omnivorous. Among the 109 papers that searched for AMRB in several species, only 35 provided data that allowed comparing AMRB prevalence across species with different diets. The others either studied several species sharing the same diet (34 papers) or did not give enough details to permit any statistical comparison between groups (40 papers). In particular, some authors either do not list the species they sampled (sometimes just referred to as wild birds or wild mammals) or do not give the number of individuals sampled, only referring to those that yielded positive AMRB results. To analyse the results of the 35 studies providing exploitable data, we used chi-square tests or Fisher's exact tests when the application conditions of chi-square test were not met to compare AMRB distribution between the different host species involved grouped into three types of diets: carnivores, omnivores and herbivores. We chose a

P -value threshold of 0.05 and applied a Bonferroni correction when several pairwise tests were used to analyse the results of the same study. In 25 studies, no significant difference was highlighted between the proportions of individuals carrying AMRB across groups. The results of six articles were consistent in showing that carnivorous and omnivorous species were more likely to carry AMRB than herbivorous species (see details in Table 2). By contrast, two papers gave opposite results underlining higher AMRB prevalence in herbivorous than in carnivorous and omnivorous ones (see details in Table 2). Finally, two papers underlined a higher proportion of AMRB carriers in carnivorous than in omnivorous species, while one reported opposite results.

Thus, available data suggest that carnivorous and omnivorous species are generally the most at risk of AMRB carriage. Among bird species, raptors and gulls present high colonization rates with AMRB (Poeta *et al.* 2008; Guenther *et al.* 2010). Similarly, mammalian predators and omnivorous species appear to carry a wide diversity of AMRB (Navarro-Gonzalez *et al.* 2012; Gonçalves *et al.* 2013). Yet, few studies allowed the investigation of this issue and more than two-thirds of them gave non-significant results. Thus, more studies focusing simultaneously on several species living in the same habitat but differing by their diet are needed to be able to draw firm conclusions on this point. Moreover, a direct causal link between these contamination rates and diet remains to be highlighted. The gut microbiota is known to be influenced by diet along with phylogeny and physiology of the host (Muegge *et al.* 2011). At least in mammals, the maximum diversity of bacteria is observed in herbivorous species, an intermediate level of diversity characterizes the predators, while omnivorous species have the lowest bacteria diversity in contrast to what is known regarding AMRB (Ley *et al.* 2008). To understand this contrast, it is important to recall that the data we have concerning the AMRB found in wildlife are based on what has been searched for, meaning that we have information mostly on human pathogens. Available results argue in favour of undertaking research in order to understand the fate of AMRB throughout food chains (Teale 2002).

It is no doubt important to take into account the species that have the highest dispersal capacity due to the role they could play in the spread of AMRB. Thus, the studies reporting AMRB carriage in migratory birds (e.g. Palmgren *et al.* 1997; Middleton & Ambrose 2005; Foti *et al.* 2011) are of particular interest. Similarly, top predators generally forage across large distances (Schoener 1968; Gittleman & Harvey 1982). They could represent a natural reservoir of AMR that could disperse AMRB over large areas. Such species may be key elements of AMR dynamics in natural ecosystems. Omnivorous species often feed on anthropogenic decay and near human habitations and farms, meaning that they could represent a major epidemiological link between domestic animals, humans and wildlife. Furthermore, small anthropophilic

Table 2. Studies underlining significant differences in antimicrobial-resistant bacteria (AMRB) carriage across host groups with distinct diets

Host group	Focus bacteria	AMRB carriage across groups	Reference
Mammals	<i>E. coli</i> and <i>Salmonella spp.</i>	Omnivorous > herbivorous	Dias <i>et al.</i> (2015)
Birds	<i>E. coli</i>	Carnivorous > omnivorous	Guenther <i>et al.</i> (2010)
Mammals	<i>Enterococcus spp.</i>	Omnivorous > herbivorous	Mallon <i>et al.</i> (2002)
Mammals	<i>Bacillus spp.</i> , <i>Enterococcus spp.</i> and <i>Staphylococcus spp.</i>	Herbivorous > omnivorous	Meyer <i>et al.</i> (2014)
Mammals	<i>E. coli</i>	No difference in prevalence but more multiresistant strains in carnivorous than in omnivorous	Nhung <i>et al.</i> (2015)
Birds	<i>E. coli</i>	Omnivorous > herbivorous	Sato <i>et al.</i> (1978)
Birds and mammals	<i>E. coli</i>	Carnivorous > herbivorous	Smith <i>et al.</i> (2014)
Birds	<i>E. coli</i>	Omnivorous > carnivorous	Tausova <i>et al.</i> (2012)
Birds, mammals and reptiles	<i>Salmonella spp.</i>	Carnivorous > herbivorous	White & Forrester (1979)
Mammals	<i>E. coli</i>	Omnivorous > herbivorous	Williams <i>et al.</i> (2011)

To analyse the results of the 35 studies providing exploitable data, we used chi-square tests or Fisher's exact tests when the application conditions of chi-square test were not met to compare AMRB distribution between the different host groups. In addition to the 10 papers presented above, 25 studies did not highlight any significant difference between the proportions of individuals carrying AMRB across groups ($P > 0.05$, Bonferroni correction was applied when several pairwise tests were used to analyse the results of a single study).

prey species such as rodents could represent a bridge between human/domestic animals and their predators.

Life-history traits are also key to understanding the role of species in pathogen dynamics (Johnson *et al.* 2012) but they have rarely been taken into account in the study of AMR in wildlife. Among our reference list, data were too scarce to lead any analysis focusing on this issue. Yet they could have an important part to play in shaping the role of a species in antimicrobial dynamics. For example, a recent study on two rodent species (bank voles *Myodes glareolus* and wood mice *Apodemus sylvaticus*) in the UK showed that different seasonal population dynamics were associated with different AMRB carriage over time (Williams *et al.* 2011).

Concluding remarks

Despite growing evidence showing the presence of AMRB in numerous wildlife species living in diverse environments world-wide, studies focusing on this compartment remain scarce. In this article, we used a systematic review to underline key information concerning AMRB carriage in wildlife that can be inferred from the available literature:

- Firstly, the natural habitats that are the most strongly impacted by human activities are the ones in which the highest diversity of AMR is observed in bacteria carried by wildlife, including resistance mechanisms that are of major concern for human health.
- Secondly, ecological characteristics of species as well as their life-history traits can serve to infer their potential role in AMRB epidemiology. Omnivorous, anthropophilic and carnivorous species seem to be at high risk of being potential carriers and potentially spreaders of AMRB.

- Thirdly, AMRB exchanges occur between wildlife, humans and domestic animals but the transmission routes are difficult to disentangle. Direct contacts, soil and water seem to be of major importance in the flows involved.

- Finally, when studying AMRB exchanges, it is crucial to consider that different bacteria may share and exchange resistance genes through horizontal transfer. It may be important to consider bacteria that have never been found to infect humans since the resistance mechanisms they carry could be exchanged with human pathogens.

This work highlights both the important progress that has been made in our understanding of the role played by wildlife in AMRB dynamics and the wide gaps that remain in our understanding of the mechanisms involved.

We recommend that a wider diversity of bacteria should be studied since organisms that are not pathogenic for humans may still carry and spread relevant resistance mechanisms that could be acquired by human/domestic animal pathogenic strains. For instance, while insects may become an important protein source within the next decades, it will be necessary to study the AMRB they may carry when assessing the health risks potentially associated with the development of this new resource. The application of a culture-independent approach, functional metagenomics, allowed the identification of resistance genes in the gut of the gypsy moth *Lymantria dispar*, which proved that insect guts could be a reservoir of antibiotic resistance genes with the potential for dissemination (Allen *et al.* 2009). Culture-independent approaches include PCR-based methods and functional genomics (see Allen *et al.* 2010). Such methods should be developed and used in line with classical culture-based

approaches since they can bring complementary information. Indeed, the results from culture-based methods are highly variable depending on the culture media used (Garcia-Armisen *et al.* 2013) and give no access to the resistance genes carried by uncultivable bacteria.

Furthermore, it is important to stress that when trying to track the fate of AMRB in wildlife, it is essential to access negative results reporting the absence of particular resistance mechanisms in some wild species or some kind of habitats. As illustrated by the low number of articles that allowed statistical analysis of AMRB across habitats and species diets, it is essential to give detailed data concerning the species sampled, to describe focus habitats using comparable indexes such as human density or proportion of different land use and to present results for each species in each habitat. Such improvements seem essential to move forward from successive studies that give information about one particular species in one particular habitat to comparable data that would allow broad comparisons and give way to a better understanding of AMRB dynamics in wildlife.

Finally, data concerning AMRB prevalence in developing countries in wildlife are lacking, while AMR is of major concern in these regions, notably in South-East Asia (Jean & Hsueh 2011). More attention should be paid to this area where the close links existing between wildlife, domestic animals and humans have proved to promote the emergence of pathogens (Chen *et al.* 2013), including AMRB (Hasan *et al.* 2012).

Over the last decade, the One Health approach has been implemented in the study of most emerging diseases, and wildlife has been included in their modelling. It recognizes that the health of humans, animals and ecosystems are interconnected and involves applying a coordinated, collaborative, multidisciplinary and cross-sectoral approach to address potential or existing risks that originate at the animal–human–ecosystems interface. It is urgent to extend this fruitful approach to the study of the emergence and spread of AMR. Otherwise, this missing piece of the puzzle could impair our capacity to limit the emergence, maintenance and spread of resistance.

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Data accessibility

All data used and discussed in this article were previously published in the papers listed in Appendix S1.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Appendix S1. Complete list of the 210 articles gathered through systematic search.