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Editorial

Prudent use of antimicrobial agents: Not just for humans

Uso prudente de los agentes antimicrobianos: no solo para las personas

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The use of antimicrobial agents (AA) is required for the treatment of infectious diseases, but, at the same time, is the main cause for the selection of antimicrobial resistant bacteria. The wide use of AA in human medicine is a key cause of this problem, but not the only one, as other "non-human" uses of AA are also contributing to the alarming increase of resistant bacteria.

AA are used in animals for therapeutic and prophylactic purposes in order to cure and prevent bacterial diseases. In these cases, AA are administered under veterinary control. Another use of AA in animals, although banned since 2006 in the European Union (EU) but still allowed in other non-European countries (USA, Japan, Australia, among others), is as animal growth promoters (AGP). In this case, AA are added in sub-therapeutic doses and for long periods of time in the feed of healthy animals, conditions that could contribute to the selection of resistant bacteria. The use of AA as AGP has been the object of strong debate in the scientific community for its potential risk to human health. AA use as AGP is associated to the selection of resistant intestinal bacteria in animals (both zoonotics and commensals), that could be transferred to humans through the food chain; these selected bacteria could also transfer resistant genes to other human intestinal bacteria.[1,2] There are different regulations for AGP use in those countries where they are still allowed.[3] The use of avoparcin as AGP in the EU, a glycopeptide with a similar structure to vancomycin, is a clear example of the contribution of this use in the selection and dissemination of vancomycin-resistant enterococci in the animal ecosystem, with its potential risk to human health. After the EU banning of avoparcin as AGP in 1997, the prevalence of these resistant bacteria in intestinal samples of animals and healthy humans and in foods has significantly decreased.[2]

The use of AA to treat or to prevent infectious diseases in food producing animals (FPA) also contribute to the selection of resistant bacteria that can be transferred from animals to humans. The food chain is considered as a transmission vehicle of resistant bacteria to humans, although direct animal-human contact can be another transmission route. Some examples will be highlighted. The introduction of fluoroquinolones (FQ) in animal production was associated with an increase of FQ-resistant bacteria isolated from FPA (as *Campylobacter* or *E. coli*, among others) and, later, in zoonotic bacteria implicated in human infections.[2,4] However, in Australia, where FQ are not used in FPA, this association has not been observed. FQ use in poultry was banned in Denmark in 2003, and was followed by a decrease in the percentage of FQ-resistant *Campylobacter coli* isolates of chicken origin. Similarly, the US Food and Drug Administration (FDA) banned the use of enrofloxacin in poultry in 2005 due to its possible risk to human health.[2]

Another major cause of concern is the emergence and dissemination of extended-spectrum beta-lactamases (ESBL) among clinical *E. coli* isolates, especially those of the CTX-M group. Different studies have shown that the intestinal microbiota of FPA is a reservoir of ESBL-containing *E. coli* isolates.[5] These resistant bacteria have also been recovered in pets, wild animals and in food samples. Although the factors involved in this phenomenon are complex, the potential animal to human transference through the food chain cannot be ruled out. The low use of cephalosporins in animals (compared to humans) suggests that co-selection with other AA widely used in animals, such as sulphonamides or tetracycline, may be involved. As a matter of fact, most of the strains carrying ESBLs harbour tetracycline resistance genes or integron structures that contain sulphonamide resistance genes. The use of broad-spectrum cephalosporins in animals should continue to be restricted and carefully controlled due to the importance of ESBL-related resistance for human-health.[6]

It is also of great interest to mention the dissemination of a specific genetic variant of methicillin-resistant *Staphylococcus aureus* (MRSA), ST398, associated with the animal environment, particularly pigs, and that can be transferred to humans, mainly where there is close contact with colonized animals.[7] MRSA ST398 strains are often resistant to tetracycline. There is debate on the possible relationship between the high use of tetracycline in animals (especially in pigs) and the emergence of ST398 in animals.

The use of AA in companion animals or pets is also contributing to the resistance problem, both in pathogenic and in commensal bacteria, as these animals are considered as a reservoir for resistance bacteria.[8] Curiously, the use of AA in

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companion animals is not generally included in the debate on the antimicrobial resistance problem, even though their owners (especially children) do have a close contact with these, which could lead to the transfer of resistance bacteria from animals to humans, or vice versa. In this sense, identical FQ-resistant *C. jejuni* strains and MRSA have been recovered from companion animals and of their owners.[8] MRSA is emerging as an important pathogen in small animal clinics, and human contact with MRSA infected animals could represent a risk factor.[9] Similarly, at least 1% of annually-reported salmonellosis cases in the USA are probably associated with companion animals and cases of transmission of multiresistant *Salmonella* Typhimurium DT104 have been reported.[8]

Another sector of interest is aquaculture, which has seen a significant development in the nineties. Approximately 50% of world fish production comes from aquaculture and most of the intensive production systems are established in Asian countries.[10,11] AA are heavily used in aquaculture, although limited data are available on the type and amount of these. Regulations on the use of AA in this sector are limited or do not exist in some developing countries with high aquaculture activity, and different authors warn of the potential risk to human health of AA use in this sector.[10,11]

The use of AA in aquaculture contributes to the selection of antimicrobial resistant aquatic or fish pathogenic microorganisms. Frequently, resistance in fish pathogenic bacteria is plasmid mediated that can be horizontally transferred to other aquatic or terrestrial bacteria, including human pathogenic bacteria, such as *E. coli* or *Vibrio cholerae*. Another example could be the case of multiresistant *S.* Typhimurium DT104 that frequently harbour the *flo*R gene, which confer choramphenicol and florfenicol resistance. According to some authors, this resistance mechanism might have emerged in the aquatic bacteria associated with the high use of florfenicol in aquaculture, then being transferred to pathogenic bacteria, although there is some controversy about this.[10]

There is a general consensus that data on AA consumption in different fields, including animals, are needed to be able to correlate them with the antimicrobial resistance data, although it is known that these correlations are sometimes difficult to establish and interpret. There are limited data on antimicrobial consumption in animals in Europe and other continents. Nowadays, the EU has clearly decided to fill this information gap and, through the European Medicines Agency it is collating the sale AA data using a harmonized procedure.[12]

There are significant differences in AA consumption data, but by putting together the information from several recent sources,[12–14] we could say that more than half of AA in Europe are for non-human uses. According to some European data, more than 80% of AA used in veterinary are dedicated to FPA and the remaining ones for companion animals.[13–15] A report by the Union of Concerned Scientists in 2001 stated that 24.6 million pounds of AA were used in the USA for non-therapeutic purposes in FPA annually, representing 70% of all AA produced in the USA in one year.[16] At the present moment, the FDA is analysing whether to restrict the use of AA in FPA, advising limiting its use only under veterinary supervision or consultation.[17]

The AA most frequently used in animals are tetracyclines, followed by macrolides, pleuromutilins, lincosamides, penicillins, and sulphonamides. The use of cephalosporins and FQ is more limited than in human medicine, although the use of FQ seems to be increasing in the last few years,[13] partly due to its high use in aquaculture. Cephalosporins are almost exclusively used in veterinary therapy and mostly in companion animals.

Current European legislation does not permit the use of antibiotics in plant agriculture. In USA, the AA most commonly used on plants are oxytetracycline and streptomycin, although this use represents less than 0.5% of total antibiotic use. Gentamicin is used for this purpose in some Latin-American countries.

The presence of antimicrobial residues and of antimicrobial resistant bacteria in the environment could result in adverse ecological and public health effects, and they should be considered as environmental pollutants.[18] AA administered to farm animals, and particularly in aquaculture, can be released unaltered in water and soil, and during the period in which they maintain their antimicrobial action, its presence could contribute to the selection of resistant microorganisms. Another potential effect of AA in the environment is the disequilibrium in the microbiota of the natural ecosystems. Some studies conducted in different countries, including Spain, have warned of the presence of antimicrobial residues (sulphonamides, tetracycline, quinolones and others) in rivers,[19] with the public health and ecological consequences that this could represent, arguing about the need for upgrading sewage treatment plants.

The aquatic environment favours the transfer of antimicrobial resistance genes, which sometimes involves the mobilisation of multiresistance plasmids.[19] Rivers can be contaminated with quinolones, drugs in widespread use in aquaculture, and which have a slow biodegradation process that enables them to remain in the environment for long periods of time.[10] This could favour the mobilization of *qnr* genes (associated to quinolone resistance) from the chromosome of aquatic bacteria into plasmids that could be captured by human bacterial pathogens. This phenomenon might favour the first step in the transfer of these genes to human pathogens.[18,20]

Antimicrobial resistance is associated with both human and non-human uses of AA and prudent and rational use of them in all fields is mandatory. Selection and dissemination of antimicrobial resistance mechanisms in the bacterial world is a rapid process, but reversion is complex and occurs very slowly. Thus, it is extremely important to establish correct agreements of antimicrobial uses, both in human and veterinary medicine, to control this problem. We live in a globalized world, and resistant bacteria and genes of resistance do not have boundaries for a worldwide dissemination. Those persons involved in human and animal health should work together and exchange their knowledge to appropriately identify and understand the key factors involved in the emergence and spread of resistance in animals and humans, and to detect the complex transfer routes between different ecosystems.

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