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Pharmaceutical Antibiotics at a Significant Level in Nature: From Hospitals, Livestock, and Plants to Soil, Water, and Sea

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Abstract

Antibiotics were the world's great therapeutic hope after the Second World War, but today, unmonitored use has become one of the greatest risks for humanity. Without overestimation, one of the last scientific books on antibiotics was entitled: Antibiotics, the perfect storm. Before to environmental contamination by antibiotics, the pathogens got resistant to them. Because of the radical changes that antibiotics have brought about, they can generate new resistant bacteria in the environment that were previously harmless. These microorganisms will be exposed to concentrations of antibiotics never reached or will be exposed to unknown molecules that, for many of them, in certain environments, have never been exposed before. Initially, many of these antibiotics did not penetrate soils with high agricultural production, but in the following decades, they were even interspersed into crops. Nowadays, hundreds of tons of antibiotics are dumped into rivers and the sea. Many hospitals have water treatment facilities to prevent significant contamination, but not all companies, farms, and hospitals in developed, emerging, or poor countries apply wastewater treatment. Antibiotics are incorporated into wild microorganisms and plants, triggering a broad "unnatural" resistance, which will rapidly incorporate this information into the genome of other pathogenic microorganisms by horizontal transfer. On the other hand, antibiotics could be incorporated into drinking water and water intended for human or agricultural consumption that travels without being detected or monitored. This review covers the most important aspects of environmental pollution by antibiotics.

Keywords: antibiotics, water, hospitals, farms, livestock, soil, sea

1. Introduction

Antibiotics exist in normal (low) concentration in nature [1–3]. Bacteria, fungi in general all organisms develop and metabolize these molecules to survive [4]. The discovery of penicillin split the history of humanity in two and that magnificent discovery is only comparable to the handling of electricity, atomic energy, space travel, and anesthesia, among others [5]. The penicillin and antibiotics brought about the saving of millions of lives, but their use and application were exaggerated and misguided to the point that antibiotics are used as food supplements in the

livestock, poultry, swine, and crop industries [6–9]. However, pharmaceutical antibiotics at a significant level in nature and different environments has been detected in previous studies and monitoring in plains, valleys, coast, and mountains, when were monitored in hospital wastewater, farms, rivers, and coastal water [10–13]. Antibiotics emerge as new environment contaminants as plastics, pesticides, among others. The main risk and concern as the pesticides are microbial antibiotics and multidrug resistance. The human being is developing little Frankenstein, likely by carelessness and naivety, contrary to genetically modified organisms (GMOs) opinion, the scare of gene manipulation, and its ethical reflection by the Scientifics and public [14, 15]. The consumer has scary to GMOs, but without laboratory use, the human being is making GMOs resistant to antibiotics. The controversy is rising, why the public is concerned by artificial experiments but carefree by antibiotics pollutants? This environmental risk goes in the same way as global warming.

Probably some natural antibiotic-resistant bacteria in soil gain multidrug resistance consequence by human practices as livestock or water activities. However, antibiotics come to the soil by wastewater from human or animal feces together with the selection of antibiotic-resistant microbiome [16]. Antibiotics and bacteria remain in the soil until water carries them to stream or rivers or are transferred by

Figure 1.

Water carries on antibiotics. Water from hospitals and farms could pass through sewage treatment, but in many countries, those health and environmental rules are not applied or respected, especially in developing countries by poor investment and low budget. Water is used for human consumption, livestock, poultry, swine, and soil irrigation to crop grass and agriculture plants. But lockdown animals, cattle, and others get sick and must be under antibiotic treatment. Then, this sanitary water passes directly to the sewer rarely treated and directly deposited in the streams and rivers. Antibiotics are used in some countries to yield more muscular biomass of livestock, poultry, and swine. This practice increases the level of antibiotics in soil, humans, flora, and fauna. Likely, some soils intersperse antibiotics in roots, stems, leaves, and fruits for human consumption. Even, antibiotics in the soil are absorbed by bacteria, fungi, protists, and invertebrates. Soils stock, pick up, and pour antibiotics in streams, then to rivers and finally to the sea. The pharmaceutical antibiotics were poured into the sea for 70 years. Surely the antibiotics levels in nature and water were not the same before the pharmaceutical antibiotic revolution and production. This image is an actual case in South America, where some hospitals lack the budget to invest in the sewage treatment plant. Near this real example, there are other little villages where its hospital has two water treatment plants, one for human consumption and the other for sewage. In that case, contaminated hospital water never goes back to flow, however, many farms invest weakly in the water treatment process, ejecting polluted water to the environment with antibiotics and pesticides.

roots in plants reaching leaves, which will be consumed by insects, incorporating new molecular information to wild species (Figure 1).

2. Antibiotics real state consummation and biodegradability

Tons of pharmaceutical antibiotics have been produced by the industry. The worldwide production of antibiotics is estimated to be in the order of 100.000 tons per year [17], and 73% in the world and 80% in the United States is used for live-stock consummation [18]. Different from the European Union, where the amount of antibiotic used is 60% for humans and 40% for animals and crops [19]. The great threat as warned by the WHO is to increase the resistance to antibiotics not only by pathogens but also by environmental organisms, which can lead to possible environmental damage (<https://www.who.int/news/item/07-11-2017-stop-using-antibiotics-in-healthy-animals-to-prevent-the-spread-of-antibiotic-resistance>). Now WHO is recommending avoiding the use of antibiotics in healthy animals.

Antibiotics were approved in the USA in the next order: sulfonamides in 1935, penicillin in 1941, aminoglycosides in 1944, cephalosporins in 1945, chloramphenicol in 1949, tetracyclines in 1950, macrolides/lincosamides/streptogramins in 1952, glycopeptides in 1956, rifamycins in 1957, nitroimidazoles in 1959, quinolones in 1962, trimethoprim in 1968, oxazolidinones in 2000, lipopeptides in 2003 [20]. Table 1 relates the antibiotics with their molecular functional group and in the last column their resistance model in microorganisms. Another problem is that antibiotics are not used alone and come with stimulators and enhancers, such as clavulanic acid which helps overcome β -lactam resistance.

Class	Example(s)	Functional group or whole molecule	Model(s) of resistance
β -Lactams	Penicillins (ampicillin), cephalosporins (cephamycin), penems (meropenem), monobactams (aztreonam)		Hydrolysis, efflux, altered target
Aminoglycosides	Gentamicin, streptomycin, spectinomycin		Phosphorylation, acetylation, nucleotidylation, efflux, altered target
Glycopeptides	Vancomycin, teicoplanin		Reprogramming peptidoglycan biosynthesis

Class	Example(s)	Functional group or whole molecule	Model(s) of resistance
Tetracyclines	Minocycline, tigecycline		Monooxygenation, efflux, altered target
Macrolides	Erythromycin, azithromycin		Hydrolysis, glycosylation, phosphorylation, efflux, altered target
Lincosamides	Clindamycin		Nucleotidylation, efflux, altered target
Streptogramins	Synercid		C-O lyase (type B streptogramins), acetylation (type A streptogramins), efflux, altered target
Oxazolidinones	Linezolid		Efflux, altered target
Phenicol	Chloramphenicol		Acetylation, efflux, altered target
Quinolones	Ciprofloxacin		Acetylation, efflux, altered target
Pyrimidines	Trimethoprim		Efflux, altered target

Class	Example(s)	Functional group or whole molecule	Model(s) of resistance
Sulfonamides	Sulfamethoxazole		Efflux, altered target
Rifamycins	Rifampin		ADP-ribosylation, efflux, altered target
Lipopeptides	Daptomycin		Altered target
Cationic	Colistin		Altered target, efflux
Nystatin	Mycostatin		Ergosterol pathway Efflux

The most used pharmaceutical antibiotics, showing class, examples, functional group or whole molecule and models of resistance. Base on from the Gartiser et al. [21], Davies and Davies [22], Li & Zhang [23] and Zhi et al. [24].

Table 1.
Biodegradability and resistance.

Currently, animal production practices are linked with the routine use of antibiotics, and the selection pressure on bacteria is increasing the potential resistance [18]. For example, at the United States, the antibiotics use is broadly applied for animals and crops. This has been a controversial topic for over 30 years. A 1998 report from the prestigious Institute of Medicine of the National Academy of Sciences noted that about 4 million pounds (2000 tons) of antibiotics were used to treat sick farm animals and another 16 million pounds (8000 tons) were used as growth promotions (low doses of antibiotics usually included in animal feed) for animals every year [3]. Worldwide, in 2010, livestock consumed at least 63,200 tons of antibiotics, more than all human consumption [18].

Many investigations pointed out to de biodegradation of antibiotics, but some ones are biodegradable and other ones are accumulative in soil and water [21, 23, 24]. However, this concern is poorly studied today, for example Erythromycin, nystatin and sulfomethoxazole,

Figure 2.

Level of some antibiotic's detection. The detection level of certain antibiotics in ng/L evaluated in soil by [19] work. The data from [29] report is not diagrammed, only penicillin and macrolides were in the highest concentration for the detection, which would leave [19]'s data almost at baseline.

3. Level detection in water and soil and new antibiotics

Various studies have evaluated the presence of antibiotics in soil and water [21, 25–27], as it will see below. Some authors have measured bacterial activity, through the bacterial resistance causes by them or evaluating its concentration in fruits or leaves caused by plants translocation [25, 28]. Besides, others have used direct methods to assess their presence in the environment, using techniques such as HPLC, LCMS, or gas chromatography. As a reference work, we will mention the research of Christian et al., (2003), who evaluated many antibiotics, among which the following stand out 11 β -lactams, 8 macrolides, 3 Sulfonamides, 2 fluoroquinolones, and 4 tetracyclines.

A remarkable review of the last decade with data from the last century is the work of Thiele-Bruhn, [29], but Cristian et al. [19] publish laboratory data in the same year. However, [29], summarized chemistry data such as solubility, molecular weight, polarity or not, etc., as follows. We plotted the data from both European outstanding publish, see **Figure 2**.

4. New antibiotics synthetic molecules

In the race for the discovery of antibiotics some molecules paid a high price since they never reached the consumer, others on the contrary were the panacea to fight hundreds of pathogens [30]. However, the development of resistance from pathogens to antibiotics and their irresponsible use have led to the discouragement of production by pharmaceutical companies [31], while bioaccumulation and biodegradation are the new challenges added to new antibiotics [32]. In addition to fighting the same pathogens, new antibiotics shall aim to preserve soil and water quality and will prevent their accumulation and bioaccumulation. It is likely that the same active principle is used [33], perhaps better than synthesizing new molecules that are more complex to degrade. Anyway, new antibiotics must also fight against the same pathogens; nonetheless, they must also preserve soil and water quality, avoiding its accumulation and bioaccumulation, and perhaps that will be the hardest task, but it is worth it. “Even with more appropriate prescribing, it seems likely that

antibacterial resistance will continue to accumulate in many pathogens and settings, especially in hospitals” [34].

5. Antibiotics in wastewater from hospital

As emphasized in **Figure 1**, some hospitals around the world have their wastewater treatment plant (WWTP). However, the vast majority in the world in both developed [35] and developing countries [36] or in poor countries [37], hospitals water goes directly into the sewers, which in many cases reach the rivers and the sea carrying a huge load of antibiotics. Even, the larger hospitals in many towns dumped antibiotics are into the sewers. Recently, Bansal [38] published an excellent review about hospital effluents, proposing finally bioremediation for control and lowering the multidrug-resistant bacteria, and author concludes with the sentence: “Antibiotic compounds have a suspicious reputation among the class of pollutants referred to as ‘emerging contaminants’ as the biological activity of antibiotics is an intrinsic characteristic of their functional design”. Then actually, there are two concerns: first the resistant bacteria [39] and second the antibiotic pollutant. Consequently, both problems would be repaired by not throwing more antibiotics into the environment.

The Antibiotics’ ecotoxicological risks over the effluent discharge on the aquatic ecosystem is the main concern. Aydin et al. [36] found azithromycin, clarithromycin, and ciprofloxacin as most abundant in WWTP with seasonal differences ranged from 21.2 ± 0.13 to 4886 ± 3.80 ng/L in summer and from 497 ± 3.66 to $322,735 \pm 4.58$ ng/L in winter analyzing WWTP from some hospitals in Turkey. The total antibiotic load to the influent in those WWTP was 3.46 g/day in summer and 303.2 g/day in winter.

Hocquet et al. [40] say that in France and worldwide a few countries demand or recommend previous treatment of hospital effluents before discharge into the main wastewater stream for treatment at municipal WWTP. There are well-known cases such as those of the city of Montreal related at the St. Lawrence River [41]. In Norway Langford & Thomas [42] study by LCMS two antibiotics (clotrimazole and other not specified) among 38 pharmaceutical compounds, showing that perhaps the use of antibiotics in that country has already begun to be discouraged or used with responsibly in hospitals, not being the case for most of the remaining compounds. Santos et al. [43] made a biggest elaborated work where they found in WWTP 4 antibiotics as follow: fluoroquinolone, macrolide, sulfamethoxazole, trimethoprim calculated by mg per day per 1000 inhabitant were ranged between 19 and 1337, 24–53, 75–199, and n.d.–43 respectively. The total antibiotics calculated by mg per day per 1000 inhabitant was ranged between 174 and 1612 and other antibiotics were ranged between 2 and 67.

6. Antibiotics in drinking water, farm water, and aquifers

Perhaps one of the most worrisome issues with non-treatment of hospital water is that water with antibiotics can reach farms and/or water for human or animal consumption and even plant irrigation. In Kumasi, a big city in Ghana, the hospital wastewater and effluents from waste stabilization ponds, are directly discharged as low-quality water into nearby streams which are eventually used to irrigate vegetables. The presence of 12 commonly used antibiotics was detected: metronidazole, ciprofloxacin, erythromycin, trimethoprim, ampicillin, cefuroxime, sulfamethoxazole, amoxicillin, tetracycline, oxytetracycline, chlortetracycline,

and doxycycline [44]. The authors reported 15 µg/L for ciprofloxacin in hospital wastewater, and after the antibiotic concentration in irrigation water was up from 0.2 µg/L to 200 ng/L; these quantities lead us to think or almost elucubrating a refined method to purify and reuse those antibiotic as the recycling urine to purify drink water at International Station at the space. Seriously, we imagine that astronauts did not consume antibiotics before (<https://asgardia.space/en/news/Drugs-in-Space-What-Can-Get-an-Astronaut-High>) [45]. Peculiar because everybody on the Earth consumes antibiotics without prescription, for instance in one preschool in Hong Kong, 31 children were detected veterinary antibiotics in urine, not human antibiotics. Norfloxacin and penicillin were the main antibiotics detected (48.4% and 35.5%, respectively), with median concentrations of 0.037 and 0.13 ng/mL, respectively [46]. In the same study enrofloxacin, penicillin, and erythromycin were the most detected veterinary antibiotics in raw and cooked food.

In many countries, farm irrigation water is already a vehicle for various antibiotics causing bioaccumulation in crop plants such as tomatoes and wheat crops [25, 47]. However, the bioaccumulation of antibiotics on tomatoes irrigated with wastewater is no consistent and depends on the high concentration of antibiotics on soil [25]. But researches reveal that hazardous quotidian (HQ) values show that the consumption of fruits harvested from tomato plants irrigated for long period with the wastewater applied for irrigation under field conditions in this study represents a low risk to human health [25]. On the other hand, in wheat plants that were spray-irrigated with wastewater treatment plant effluent, ofloxacin was found throughout the plant, with higher concentrations in the straw (10.2 ± 7.05 ng/g) and lower concentrations in the grain (2.28 ± 0.89 ng/g). Trimethoprim was found only on grain or straw surfaces, whereas carbamazepine and sulfamethoxazole were concentrated within the grain (1.88 ± 2.11 and 0.64 ± 0.37 ng/g, respectively). These findings demonstrate that pharmaceuticals and personal care products (PPCPs) can be taken up into wheat plants and adhere to plant surfaces when WWTP effluent is spray-irrigated [47].

Identical to what happened with pesticides, cyanide, and mercury, one of the biggest pollution problems today is that of aquifers. Wang et al. [48] evaluated the presence of antibiotics in groundwater up to 50 meters of aquifers, finding seasonal differences in spring, summer, and winter an average value of 1.60 µg/L, 0.772 µg/L, and 0.546 µg/L respectively. The predominant antibiotics were fluoroquinolones and tetracyclines, but the highest risk probably will be erythromycin for algae in surface waters and in deep waters, where ciprofloxacin would be the most concentrated among the 14 antibiotics.

7. Antibiotics in agricultural practices in farms

A disturbing issue today in farms and ranches as industry type is that in these places the handling of antibiotics is on a large scale even in higher quantities than in hospitals. There is overestimation since we mention before that in the United States the 80% of antibiotics are used for livestock consummation [18], which must be very similar in many countries in which these levels are allowed, or where there is not even a single rule about it. We previously mentioned the irrigation of tomato and wheat with water contaminated with antibiotics [25, 47], that is, in an indirect relationship to antibiotic management. We will now talk about the direct handling of antibiotics by the farms and what consequences this has brought to their soil and water. No, the issue is another, for example, many farms have their aqueducts or crop irrigation systems. There are very few studies on pesticide and antibiotic composition, and except for supported studies, where health and environment are the

concerns and priority. From those studies is possible to collect valuable information. It is important to emphasize that some veterinary antibiotics have been handled as dietary supplements or as a supplement for spraying crops. This is the case of Chung et al. [49], who investigates veterinary antibiotics in soil experimentally contaminated by chlortetracycline, enrofloxacin, and sulphathiazole and translocated and bioaccumulates in roots and leaves of radish. They established that the concentration of chlortetracycline was lower than 2.73%, for enrofloxacin ranged 0.08–3.90%, and sulphathiazole lower than 1.64%. In another study in north China [50], the authors look at antibiotics in manure, soil, vegetables, and groundwater. This interesting work mentioned the complex antibiotic translocation from manure to the soil, establishing residual rate (RR) of antibiotics (mg/kg ha yr). The antibiotics used were sulfamethoxazole (SMZ), sulfadoxine (SDO), sulfachlorpyridazine (SCP) and chloramphenicol (CAP), oxytetracycline (OTC), tetracycline (TC), chlortetracycline (CTC), lincomycin (LIN), ofloxacin (OFL), ciprofloxacin (CIP). They conclude that with the application of manure containing antibiotics to organic vegetable bases, the residues of antibiotics in soil, vegetables, and groundwater were widely detected, mainly OTC, TC, CTC, and SCP with RR from 1,6 to 43% and the range of antibiotics in vegetable was 0.1–532 mg/kg using radish, rape, celery, coriander, which not all antibiotics were detectable. An interesting large study in northeastern China [51] using feces from chicken, pig, and dairy cow, 14 veterinary antibiotics such as tetracycline, oxytetracycline, chlortetracycline, ciprofloxacin, sulfaguanidine (SG), sulfanilamide (SA), sulfamethoxazole, sulfamonomethoxine (SMM), sulfamerazine (SMR), sulfachlorpyridazine (SCP), norfloxacin (NOR), enrofloxacin (ENR), difloxacin (DIF), and tylosin (TYL) were detected by HPLC, which six antibiotics (OTC, CTC, TC, TYL, SCP, and SMZ) were assessed using the hazard quotient (HQ). The 14 veterinary antibiotics detected in three types of animal feces the authors found that antibiotics occurred 7,41 to 57,41% inside 54 samples, and the levels ranged from 0,08 to 56.81 mg/kg. TCs were predominant with a maximum level of 56.81 mg/kg mostly detected in pig feces. SAs were common and detected with the highest concentration of 7.11 mg/kg. Fluoroquinolones were more widely detected in chicken feces rather than in pig or dairy cow manure, which contained the dominant antibiotic ENR [51].

Other interesting studies in Waseca and Staples, Minnesota USA, used chlortetracycline, monensin, sulfamethazine, tylosin, and virginiamycin evaluated in 11 vegetable crops in two different soils fertilized with raw versus composted turkey and hog manure or inorganic fertilizer [52], the authors conclude that all antibiotics in vegetable tissues were generally less than the limits of quantification were less than 10 µg/kg, and radish peel and spinach leaf were the vegetables that bioaccumulated more antibiotics than others ranging from 4 to 6 µg/kg. In other research, the authors evaluated the transfer of five different antibiotics such as tetracycline, sulfamethazine, norfloxacin, erythromycin, and chloramphenicol (CAP) evaluated in carrot, tomato, and lettuce under two levels of antibiotic-contaminated wastewater irrigation and animal manure fertilization [53]. TC, NOR, and CAP were accumulated at higher levels in the shoots/leaves than the other two compounds, except for CAP in carrot. Likewise, this work concludes that the levels of antibiotics are in acceptable daily intake (ADI), indicating that the main problem is not bioaccumulation in plants or animals, but bioaccumulation in multi-drug resistant bacteria related to environmental contamination.

As it was previously mentioned, Sulfonamides (SAs) are one of the most persistent antibiotics in soil and water, but especially bioaccumulate, and more than three tons of SM are used annually in Europe for swine production [54]. Li et al. [54] evaluated SAs in pakchoi cabbage such as sulfadiazine (SDZ), sulfamethazine (SM₂), and SMZ. The three antibiotics are spiked in soil could be taken up by

pakchoi cabbage. SM₂ and SMZ were accumulated more easily by pakchoi cabbage than SDZ. The dissipation half-lives of SMZ (16.8 d) and SM₂ (16.7 d) in soil were significantly longer than SDZ (10.8 d).

In a study in an agricultural-livestock region of Japan, loads of veterinary antibiotic oxytetracycline (OTC) in stream waters were investigated [55]. OTC was detected in the concentration range of 2 ng/L to 68 µg/L. An increase in daily OTC loads was observed during the winter as a result of the common veterinary practice of using higher doses of antibiotics as prophylaxis in the prevention of winter diseases. Also, OTC concentrations were observed in stream water near one of the cattle farms. According to the authors, the daily OTC load rate was in a reasonable range to the number of animals, but it was not looked at the antibiotic loads in soil or the associated resistant bacteria.

As we mentioned in the last section the antibiotic accumulation is the second main concern after natural pathogen bacteria. Osterman et al. [56] elaborate one investigation about veterinary antibiotics leached in calcareous Chinese croplands. They found that in daily farm practice, sulfamethazine was constantly detected in the leachate up to 120 ng/L, and conclude that the overall substances were still detected in the soil after 53 days, suggesting that there was no overall rapid and complete dissipation, indicating that strong lixiviation under rainfall does not eliminate the totality of antibiotics and its incomplete dissipation increases risks of their accumulation in soil. Other Chinese work developed antibiotics detection in the agricultural soils from the Yangtze River Delta [57], among which five antibiotics were prevalent in 241 soil samples with a 100% detection rate and total concentration ranging from 4.55 to 2010 ng/g dry weight. The concentrations were as follow: quinolones with mean 48.8 ng/g, tetracyclines with mean 34.9 ng/g, sulfonamides with mean 2.35 ng/g, ciprofloxacin with mean 27.7 ng/g, and oxytetracyclines with a mean of 18.9 ng/g, being the most prevalent the two last ones.

Sarkar et al. [58] did an excellent review of antibiotics in the farm, livestock, aquaculture, and plants, and they concluded that the indiscriminate use of veterinary and human antibiotics not only created multidrug resistant human or animal bacteria, but plant resistant bacteria. Complex and jeopardy manipulation because the human being was transformed the overall bacteria species multidrug-resistant without suspecting. On the other hand, it is not to make the studies unsettling or reassuring that human or livestock antibiotics concentration is an acceptable level when we have to transform rapidly the species and filling the Earth with antibiotics. The most important now is to make clever decisions such as those discussed by Kuppusamy et al. [59]. They comment in their critical review that precisely the veterinary antibiotics are usually poorly sorbed in the animal gut, and the majority is excreted unchanged or as their recalcitrant metabolites in feces and urine.

8. Antibiotics in livestock, poultry, and swine

Antibiotics are very important in the prescription and treatment, to recover the health of the animals. However, there is no logical explanation for antibiotics as a supplementary feed, except to clarify that the animal biomass increases. There is no scientific explanation about the use and human health of the consumption of beef, chicken or pork fed with no antibiotic supplement. There is a valuable review in these topics especially antibiotics in livestock [58, 60, 61].

There are three main concerns about antibiotics in livestock, which could be in poultry and swine: 1- the high antibiotic concentration in treatment [62], 2- the high concentration in supplementary foods [63], and 3- the extra antibiotics pick out by livestock from water or grass [64]. And a final concern will be, what is the

final concentration of antibiotics in the beef after cooking or treatment in the sausage or deli process. However, most of the antibiotics consumed by livestock are found in the feces [65], indicating poor assimilation, overuse, and uselessness, or little control over their management. If the farmer gives to the animal too much or little antibiotics, it will heal and fatten [61]. Therefore, the excessive cost of antibiotics and their great management on farms is almost unjustifiable, saving a lot of money in the decrease of management that could preserve the health of the troop and the environment by eliminating multi-resistant bacteria from its environment decontaminated [66].

There is no difference in antibiotics panorama in poultry and swine [67]. For example, Zheng et al. [68] determined the presence of 15 sulfonamides in livestock and poultry manure standardizing a new technique with UPLC-MS/MS plus Fe₃O₄-MWCNTs. The SAs recovered oscillated from 89 to 119% and the limit of detection of the method was reached 0,5 to 1 µg/kg dry weight, and the limit of quantification was between 1 and 3 µg/kg dry weight. Swine manure contains up to 12 antibiotics, was detected by Rasschaert et al. [69] work. The most frequent antibiotic detected were doxycycline, sulfadiazine, and lincomycin. Doxycycline was found in the highest concentration in manure with a mean of 1476 µg/kg from 8 to 13632 µg/kg, tylosin was found in manure with mean concentrations of 784 µg/kg from 17 to 5599 µg/kg, oxytetracycline was found in manure with mean concentrations of 482 µg/kg from 11 to 3865 µg/kg, lincomycin, was found in manure with mean concentrations of 177 µg/kg manure from 9 to 3154 µg/kg. The remained 18 antibiotics were found in manure with mean concentrations of less than 100 µg/kg.

9. Antibiotics in aquaculture or fish-farming

Aquaculture is another prominent fish and meat business and veterinary antibiotics are also used in aquaculture for the preservation of Salmonidae, and other large-scale cultured species. Currently, aquaculture almost reaches the same level of production as fishing, and likely it will exceed the production of world fisheries in the coming years (FAO) (<http://www.fao.org/faostat/en/#data/CL>). Chen et al. [70], investigate the bioaccumulation of ciprofloxacin and enrofloxacin in some tissues of culture grass carp such as plasma, bile, liver, and muscle tissues, They calculated the mean values of log bioaccumulation factors (Log BAFs) for these antibiotics and main results were for plasma in the range of 0,43-3,70, for bile in the range 0,36-4,75, for liver in the range – 0,31-4,48, and for muscle in the range 0,23-4,33. This work also calculated hazard quotients, human health risk evaluation, however, the authors state that those grass carp do not pose risk for human health and clarifying that very little has been published in this regard.

Sankar et al. [58] reviewed other previous articles reporting that Kurunasagar et al. [59], published the use and application of cotrimoxazole, chloramphenicol, streptomycin, erythromycin being already a habit in fish aquaculture in India. But as declared Burrige et al. [71], “the use and potential effects of these compounds are herein summarized for the four major salmon producing nations: Norway, Chile, UK and Canada” and state that around 75 percent of the antibiotics fed to fish are excreted into the water. On the other hand, Romero et al. [72], looked the effect of oxytetracycline by HSP70:GFP expression in fish larvae after 48 hours, and how oxytetracycline-triggered the stress and the immune response. In consequence, they believe that is possible new alternative practices for the prevention in aquaculture due to the use, overuse, or abuse of antibiotics, which promote the contamination of the environment and rise resistant bacteria. They consider alternative solutions such as developing strict regulations controlling

the use of antibiotics and having led to only a few antibiotics being licensed for use in aquaculture and preventing the high proportions of antibiotic-resistant bacteria which still persist in sediments and farm surroundings and suggesting the implementation of rearing practices that reduce the level of stress from fish larvae to adult, which could reduce the likelihood of infections requiring antibiotic treatment.

10. Antibiotics in soil

Probably one of the main concerns about antibiotic contamination is their accumulation in soil, by the effect on resistant bacteria and direct consequence in human and animal health. Likely the easier indirect antibiotic detection is to calculate the concentration in crops [73, 74], as was mentioned by Christou et al. [25] reporting antibiotics in tomatoes from the soil. This work elaborated during three years shows that the accumulation of DCF, SMX, and TMP in the soil detected by MeOH-NaOH solution and Chromatography MS/MS, The results show an imminent physical translocation as we shown in **Figure 1**, and show great variability in the accumulation of the three antibiotics during those 3 years, with increases or decreases depending on the irrigation using wastewater and depending on the duration of irrigation and the origin of the wastewater applied. Other authors monitoring sulfonamides and tetracyclines over 18 years from an agricultural field site in Lower Saxony, Germany [75]. SAs and TCs are largely fixed in the upper soil layer. The analysis showed a strong decrease below the sampling depth of 30 cm which is the depth of the plow and below other antibiotics such as SG and SMZ were detected up to 90 cm, TC was shown to persist >100 µg/kg in topsoil, however this antibiotic no leachate in deeper soil segments or groundwater. They conclude that some SAs disappeared, but other veterinary antibiotics are even more persistent than expected.

In Kenia, Africa Yang et al. [76] analyzed four soils in the suburban area of Narok. Over 12 antibiotics analyzed they found that SMX, SMZ, OTC, and ENR were the major antibiotics that polluted those soils among 12 antibiotics monitored and the highest average value was for Narok 43,64 µg/kg dry weight, and the other three average values were Mai Mahiu 26.70 µg/kg dry weight, Juja 24.41 µg/kg dry weight, and Mount Suswa Conservancy 12,21 µg/kg dry weight. They advise more attention to reduce the misuse of SAs. Pan and Chu [27], investigated TC, NOR, SM2, CAP, Erythromycin (EM), antibiotics in agricultural soils, and was probably the first study. The Persistence and environmental risk profile of the five antibiotics were TC > NOR > EM > CAP > SM2, but “the study suggests that the adsorption of antibiotics in soil depends on the physicochemical properties of both antibiotics and soil”. Probably this study was the first to develop a model for predict antibiotic persistence in soil.

11. Antibiotics in crops plants

Antibiotics for plants were used since the 1950s to control certain bacterial diseases the most common used are oxytetracycline and streptomycin. In the United State antibiotics for plants represent 0,5% of total antibiotics used in this country. However, the emergence of antibiotic resistance of *Xanthomonas campestris*, *Erwinia amylovora*, and *Pseudomonas* spp., and has blocked the control of their diseases [77]. Then plants could pick up three kinds of antibiotics: antibiotics plants, human antibiotics [44], and veterinary antibiotics [78].

Some, but not many countries have rules for quality plant irrigation, but that concern is complex because WWTPs have some low load of antibiotics. The other side of the problem is irrigating plants directly with WW [25, 28]. As mentioned above, different antibiotics were detected in crops plant [58, 79, 80], those research emphasize the low risk for human health as daily intake, forgetting the drug charge in the environment and the resistant bacteria even now for control pathogen of the plant.

12. Antibiotics in rivers and sea

Finally, we arrive at the climax where all the antibiotics will finally be deposited if their degradation does not occur or if the increase of antibiotics continues its course as if such substances do not represent a risk for all the species in nature that has learned to fight diseases with evolution as antibiotic resistance [81]. Rivers and the sea are the final deposits of antibiotics and or following studies and many others that we cannot all cite shown that biodegradation, degradation, and bioaccumulation can once again put the health of the planet at risk.

The previous data show that antibiotics degradation is not totally in agreement with antibiotics in soils, farms, and WWTPs. We know today the antibiotic loads in pristine rivers as Amazona, Niger, Congo, Zambezi, Lena, Amour, and Yenisei carrying low concentrations of antibiotics, but the remaining rivers of the world-wide receive greater loads of antibiotics [41, 73, 82]. We could again make the list of antibiotics and see that they follow the same comparison of antibiotics and all effluents from WWTPs [81], the main technical solution will be the degradation of antibiotics before reach the river stream. About this concern, some researchers begin to develop this challenge [48, 83, 84].

As Zang et al., [85], mentioned, "the ocean is an important sink of land-based pollutants", and exactly as crop plants allow detection of antibiotics, marine food will be the best way to follows the study of bioaccumulation of antibiotics [86, 87]. Liu et al. [86], found 9 SAs, TMP, 5 FQ, and 4 ML, which were in gill, muscle, kidney, and liver tissues of seven wild fish species collected from Laizhou Bay, North China. As previous famous works with mercury accumulation of marine fish, now there are antibiotics reports in tissue fish in higher concentrations than aquaculture fish.

Alga will be another antibiotic "bio-accumulator" to detect antibiotics in rivers and sea. Seoane et al. [88] developed an experimental evaluation of chloramphenicol (CHL), florfenicol (FLO), and oxytetracycline (OTC) in marine microalga *Tetraselmis suecica*, showing that three antibiotics inhibited the growth after 96 h with IC₅₀. Finally, we think that in the future it will be necessary to look for antibiotics in river and sea sediments. But these first works are already beginning to fill the research data worldwide and to conclude without doubts that antibiotics are the "new emergent pollutants of Earth". Pioneer work from Fernandes et al., [89] in Portugal found azithromycin in Leça river at 2819 ng/g in water but in sediments at 43,2 ng/g.

13. Strategies to change all previous practices, challenges, and hopes

Table 2 is not a summary of this review of all articles. It is a simple exercise to verify that perhaps no antibiotic has disappeared from industrial production and it generates a contradictory taste associated with the fact that pharmaceutical companies are discouraged from manufacturing new antibiotics, but the sale and

Type	Antibiotic	References
Agricultural soil		
Tetracyclines	tetracycline, doxycycline, oxytetracycline	[27]
Fluoroquinolones	ofloxacin, ciprofloxacin, norfloxacin, enrofloxacin	[57]
Sulfonamides	sulfadimethoxine, sulfamethazine, sulfamethizole, sulfamerazine, sulfamethoxazole, sulfadiazine	[74]
Macrolides	erythromycin	[76]
Amphenicols	chloramphenicol	[79]
Aquaculture		
Sulfonamides	sulfamethoxazole, sulfaquinoxaline	[58]
Tetracyclines	oxytetracycline	[70]
Fluoroquinolones	norfloxacin, ofloxacin, ciprofloxacin, enrofloxacin, pefloxacin	[72]
Macrolides	<i>erythromycin-H₂O</i>	
Amphenicols	chloramphenicol, florphenicol,	
Aminoglycosides	streptomycin	
Combination of trimethoprim and sulfamethoxazole	cotrimoxazole	
Sulfonamide/Diaminopyridine	sulfadimethoxine/ormetoprim	
Crops		
Tetracyclines	Tetracycline, oxytetracycline, chlortetracycline, doxycycline	[28]
Sulfonamides	sulfamethoxazole	[58]
Diaminopyrimidines	trimethoprim	[74]
Macrolides	erythromycin	[79]
Azoles	metronidazole	[80]
Cephalosporins	Cefuroxime, second generation	
β -lactams	ampicillin, amoxicillin	
Fluoroquinolones	ciprofloxacin (CIP); norfloxacin (NOR)	
Aminoglycosides	blastidicin S, validamycin	
antibiotics of fungal origin	strobilurin, odemansins.	

Type	Antibiotic	References
In agricultural practices in farms		
Azoles	metronidazole	[25]
Macrolides	erythromycin, norfloxacin, tylosin, spiramycin	[44]
Sulfonamides	sulfamethoxazole, Sulfadiazine: sulfamethazine, sulfamethoxazol sulphathiazole sulfaguanidine, sulfanilamide, sulfamonomethoxine, sulfamerazine, sulfachlorpyridazine, sulphadimethoxine, sulphadimidine, sulfapyridine	[49–54]
Diaminopyrimidines	trimethoprim	[60]
Tetracyclines	tetracycline, oxytetracycline, chlortetracycline, doxycycline	[78]
Cephalosporins (second generation)	cefuroxime	
β -lactams	ampicillin, amoxicillin, benzylpenicillin, cloxacilin, dicloxacillin, oxacillin	
Amphenicols	chloramphenicol	
Lincosamides	lincomycin	
Quinolones	ofloxacin, pefloxacin, ciprofloxacin, enrofloxacin, difloxacin, marbofloxacin	
Aminoglycosides	Streptomycin, apramycin, kanamycin, spectinomycin	
Peptides	virginiamycin	
Ionophores	monensin	
Peptidomimetics	bacitracin	
Diaminopyrimidines	trimethoprim	
Cephalosporins	ceftiofur, cefquinom	
Hospital		
β -lactams	ampicillin amoxicillin	[39]
Sulfonamides	streptomycin; sulfamethoxazole	[44]
Tetracyclines	tetracycline, oxytetracycline chlortetracycline and doxycycline	
Aminoglycosides	streptomycin	
Fluoroquinolones	ciprofloxacin;	
Cephalosporins	cefotaxime;	
Cephamycin (second-generation)	cefoxitin	
Azoles	metronidazole	
Macrolides	erythromycin	
Diaminopyrimidines	trimethoprim	
Cephalosporins (second generation)	cefuroxime	

Type	Antibiotic	References
Livestock, poultry and swine		
Tetracyclines:	Tetracycline, oxytetracycline, chlortetracycline doxycycline	[51]
Sulfonamide Aminoglycoside:	sulfamethazine neomycin	[56]
Ionophore:	monensin	[67]
Macrolide:	tylosin	[69]
β -lactams	amoxicillin	[78]
Cephalosporines	ceftiofur	[90]
Polypeptide	colistin	[91]
Diaminopyrimidines	trimethoprim	
Lincosamides	lincomycin	
Sulfonamides	sulfachlorpyridazine, sulfadiazine, sulfadimethoxine, sulfamerazine, sulfamethazine, sulfamethoxazole, sulfamethoxypyridazine, sulfapyridine, sulfathiazole, sulfaguanidine, sulfanilamide, sulfamonomethoxine, sulfachlorpyridazine	
Quinolones	norfloxacin, ciprofloxacin, enrofloxacin, difloxacin	
Rivers		
β -lactams	amoxicillin	[73]
Sulfonamides	sulfamethoxazole	[79]
Tetracyclines	tetracycline oxytetracycline	[81]
Quinolones	nalidixic acid, fluoroquinolones	
Macrolides		
Diaminopyrimidines	trimethoprim	
Sea		
Sulfonamides		[86]
fluoroquinolones		[88]
Macrolides		
Diaminopyrimidines	trimethoprim	
Amphenicols	chloramphenicol, florphenicol	

Type	Antibiotic	References
Wastewater treatment plants (WWTPs)		
Quinolones	ofloxacin, ciprofloxacin	[25]
Sulfonamides	sulfamethoxazol	[44]
Diaminopyrimidines	trimethoprim	[47]
Tetracyclines	tetracycline, oxytetracycline, chlortetracycline, doxycycline	
β-lactams	ampicillin, amoxicillin	
Cephalosporins (second generation)	cefuroxime	
Macrolides	erythromycin	
Azoles	metronidazole	
Veterinary and human antibiotics		
B-lactams	emoxycilin	[58]
Macrolides	tylosin, azithromycin	
Aminoglycosides	neomycin, gentamycin	
Fluoroquinolones	enrofloxacin, ciprofloxacin, levofloxacin, ofloxacin	
Tetracyclines	oxytetracycline, chlortetracycline	
Streptogramins	virginiamycin	
Glycopeptide	avoparcin	
Phenicol	florphenicol	
Cephalosporins	cephalexin	
Polypeptides	enramycin	
Pleuromultilin	tiamulin	
Foods		
Fluoroquinolones	Enrofloxacin,	[46]
β-lactams	penicillin	[92]
Macrolides	Erythromycin, tilmicosin	
<i>This table is not a summary of the articles reviewed, and the goal was compared to all human practices with antibiotics used, which it is clear that antibiotics production and release in nature was risen in the last years and the discouragement to discover new antibiotics are not in a relationship with production.</i>		

Table 2.
Some selected antibiotics in the practices were reviewed

large scale production is not a compromise. This alone is one of the most profitable businesses in the pharmaceutical industry with a high cost of sacrifice from nature to our food. The bioaccumulation and accumulation of antibiotics in all our activities is already a risk rather than a fact. We did not do the review of antibiotics in food, but several authors who have reviewed other practices independent of human health have realized that there will be no health if the whole environment is contaminated to our food. We did not do the review of antibiotics in food, but several authors who have reviewed other practices independent of human health have realized that there will be no health if the whole environment is contaminated to our food.

A prime candidate as a bioaccumulator of antibiotics and other contaminants is milk and is perhaps one of the best-monitored foods in the world. In a pioneer study in the north of Italy Chiesa et al. [93] developed the detection by LC-HRMS veterinary antibiotics in milk. The researcher detected Lincomycin 30 samples (17,29 ppm the mean) from 254 raw milk samples and oxytetracycline in three samples and two samples with cefapirin and spiramycin. Part per million is the of an antibiotic is a negligible amount when absorbed by humans, however, the remaining concern

Figure 3.
Practice and management of antibiotics, milk, and lactic acid bacteria. The practice of antibiotics (penicillin molecule example on diagram) treatment of mastitis in cattle has generated problems for the milk elaboration and consumer. Antibiotics were found in the milk in enough concentrations to inhibit dairy starter microorganisms and cause economic losses to the cheese and fermented milk industries from the sixties years [94]. Today this practice is monitored in many farms and countries, however, is not extensively applied in every country or farm, therefore, dairy industries are obliged and encouraged by national health and food institutions to monitoring antibiotics levels in milk. Other interesting studies with lactic acid bacteria [95], show that bacteria had developed important levels of antibiotic resistance. Confinement of cattle and water treatment will prevent new emergent antibiotic-resistant bacteria in soil and water and that will be the first step to lower the level of pharmaceutical antibiotics in nature. Programs for monitoring antibiotic-resistant wild bacteria must rise in each country in the next years.

is whether the trace amount is a stimulator of resistance in lactic acid bacteria. An excellent measure will be to continue monitoring if lactic acid bacteria in milk are developing resistance to antibiotics. Assimilating antibiotic-resistant bacteria from our microbiome may have future consequences that we cannot yet measure. Therefore, the work of Chiesa et al., [93] serves us to predict the possible exposure of lactic acid bacteria to veterinary antibiotics. See **Figure 3**.

14. Conclusions

Perhaps we never imagined that after successful treatment with antibiotics that allowed us to leave the hospital, our true and lasting health was associated with them. The hospital's water will end up watering our food, which will end up on our plates as we have already seen to the satiety. The institutes and ministries of health, agriculture, and the environment, now have the same role and associated with the ministries of economy, education. If we do not realize the damage caused, will continue to save publications to demonstrate that there is no risk with antibiotics, and hospitals and farms will never change their irrational practices of consuming antibiotics as food.

Antibiotics monitoring will be a challenge in the future, and elimination will be a sustainable economic future. We cannot advise: "stopping the use of antibiotics for human or animal disease treatment", never, we do not have a better option. But we are sure that the rational application of good practices goes on to help the rapid elimination or accumulation of antibiotics in every environment as soil or sea. Biodegradation and bioremediation are an excellent opportunity. Firstly, antibiotics are metabolized rapidly by millions of microorganism, while as long as the antibiotic load in nature is reasonable, in other words, an antibiotic load low or close to the natural concentration; secondly the chemical, microbiological and mechanical techniques to eliminate antibiotics in nature will contribute to decontaminate the environments and to lower their indiscriminate use.

Several authors are assuring the risk if we do not stop [96, 97]. New alternatives and innovations will be promising new research since demonstrating a low risk of bioaccumulation will not eliminate practices that have led to the filling of soil and water in the rivers and sea with antibiotics. Many of us believe that detection techniques and new practices will change the future, such as those suggested by Behera et al. [98]. Decreasing antibiotic use will be the only way to decontaminate soil and water and reduce antibiotic-resistant bacteria.

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