Review

Antibiotic Use in Agriculture and Its Consequential Resistance in Environmental Sources: Potential Public Health Implications

Christy Manyi-Loh 1,2,3,*, Sampson Mamphweli 1, Edson Meyer 1 and Anthony Okoh 2,3

1 Fort Hare Institute of Technology, University of Fort Hare, Alice Campus, Alice 5700, Eastern Cape, South Africa; smamphweli@ufh.ac.za (S.M.); emeyer@ufh.ac.za (E.M.)
2 Applied and Environmental Microbiology Research Group (AEMREG), Department of Biochemistry and Microbiology, University of Fort Hare, Alice Campus, Alice 5700, Eastern Cape, South Africa; aokoh@ufh.ac.za
3 SAMRC Microbial Water Quality Monitoring Centre, University of Fort Hare, Alice Campus, Alice 5700, Eastern Cape, South Africa
* Correspondence: cmanyi-loh@ufh.ac.za; Tel.: +27-738-324-268

Received: 16 November 2017; Accepted: 2 March 2018; Published: 30 March 2018

Abstract: Due to the increased demand of animal protein in developing countries, intensive farming is instigated, which results in antibiotic residues in animal-derived products, and eventually, antibiotic resistance. Antibiotic resistance is of great public health concern because the antibiotic-resistant bacteria associated with the animals may be pathogenic to humans, easily transmitted to humans via food chains, and widely disseminated in the environment via animal wastes. These may cause complicated, untreatable, and prolonged infections in humans, leading to higher healthcare cost and sometimes death. In the said countries, antibiotic resistance is so complex and difficult, due to irrational use of antibiotics both in the clinical and agriculture settings, low socioeconomic status, poor sanitation and hygienic status, as well as that zoonotic bacterial pathogens are not regularly cultured, and their resistance to commonly used antibiotics are scarcely investigated (poor surveillance systems). The challenges that follow are of local, national, regional, and international dimensions, as there are no geographic boundaries to impede the spread of antibiotic resistance. In addition, the information assembled in this study through a thorough review of published findings, emphasized the presence of antibiotics in animal-derived products and the phenomenon of multidrug resistance in environmental samples. This therefore calls for strengthening of regulations that direct antibiotic manufacture, distribution, dispensing, and prescription, hence fostering antibiotic stewardship. Joint collaboration across the world with international bodies is needed to assist the developing countries to implement good surveillance of antibiotic use and antibiotic resistance.

Keywords: antibiotics; agriculture; antibiotic resistance; environmental sources; developing countries

1. Introduction

The term antibiotics encompass a wide range of chemical substances that are produced naturally, semi-synthetically, and synthetically, and are used to inhibit (bacteriostatic) bacterial growth or kill them (bactericidal) [1–3]. They are categorized based on their effects as either bacteriostatic or bactericidal, and on their series of efficacy, as narrow or broad-spectrum antibiotics. Furthermore, the classes of drugs that are more widely used in agriculture at the global level, which are of growing scientific concern with regards to their potential adverse effects and risk management steps, include the tetracyclines, aminoglycosides, β-lactams, lincosamides, macrolides, pleuromutilins, and sulphonamides [4–7]. Gelband et al. [8] noted that these antibiotics have the same mode of actions or belong to the same general classes.
as those used for humans; a situation that demands the judicious use of these drugs in animal farming, as there is bound to be a degree of interaction between animals and humans.

Markedly, the antibiotic consumption patterns in agriculture vary across regions and countries in the developing world, and even antibiotics that have been banned in other countries, including the developed countries, are still being used in most developing countries [9,10]. However, the antibiotic consumption profiles in developing countries are greatly influenced by the gross abuse and misuse of antibiotics due to their availability over the counter, through unregulated supply chains as well as the purchase without prescriptions [11]. Also, Van Boeckel et al. [12] projected that the antibiotic consumption will approximately double in the BRICS countries consisting of Brazil, Russia, India, China, and South Africa. The forecast is propelled by a shift to large-scale farms requiring the routine use of antibiotics to maintain the health of animals and productivity. The shift is caused by the progress in consumer demand for animal products. Resistance to antibiotics is an inherent side effect associated with the overuse, abuse, or substantial use of antibiotics [13,14].

The antibiotic resistance pattern varies between regions and countries corresponding to the degree of antibiotic consumption, which is guided and regulated by the antibiotic policies of a particular country [15,16]. Nevertheless, China has been registered as the world’s leading producer and consumer of both animals and human antibiotics. Antibiotic-related crisis is ascribed to the misuse of antibiotics that are, ultimately, discharged into the environment, the presence of antibiotic residues (parent antibiotic or its metabolites or both found in animal derived products) in livestock products and wastes, and lastly, the lack of stringent and effective supervision and control over antibiotics production, use, and disposal [17]. Human activities in response to industrialization drastically heightened the availability of antibiotic residues in food and the environment, and the development and distribution of antibiotic resistant bacteria along with their resistance genes, thus causing an increase in the abundance of resistant bacteria and genes [4].

The antibiotic residues, and antibiotic-resistant bacteria and resistance genes are considered as environmental pollutants and responsible for a tenacious public health crisis throughout the globe [18]. The health challenges linked to antibiotic-resistant microorganisms are more about restricted therapeutic remedies in most developing countries that lack access to good quality treatment, thus, accentuating infection as an important root of morbidity and mortality [19]. However, the soil and water environment have been regarded as vital reservoirs and sources of antibiotic resistance [20,21]; more so, as they are affected by agriculture [22]. Not only does the administration of antibiotics in food-producing animals facilitate antibiotic resistance, but it may also result in the presence of antibiotic residues (including the parent compounds or its metabolites, or both) in animal-derived products (muscles, kidney, liver, fat, milk, and egg) available for human consumption. However, these antibiotic residues have been reported to exert a huge and negative impact on public health and food safety with regards to drug toxicity, immunopathological diseases, carcinogenicity, allergic reactions, and drug sensitization, amongst others [7,23–25]. These adverse impacts tend to be influenced by land use, contaminated water sources, national policies (that symbolize production, trade, animal health, and food security), national and international trade, animal demography, and interactions between the human populations as well, as they are reported to vary considerably between regions and countries [26].

In a nutshell, antibiotic resistance is observed as a “One Health subject”, both as a cause and solution encompassing the interactions between humans, animals, and the environment [27]. Accordingly, in an attempt to contain antibiotic resistance, the World Health Organisation instituted a Global Action Plan (GAP) which demands that each country should develop national action plans in line with the key actions of the GAP, but with respect to its financial resources and extent of its problems [28]. Surveillance and monitoring of antibiotic use and antibiotic resistance is one facet of the strategies against antibiotic resistance. However, developing countries encounter challenges regarding surveillance systems because of lack of capacity and integration [29].

This paper assembles information about antibiotic and antibiotic resistance in animals, animal-derived products, and the agriculture-impacted environment. Basically, it covers antibiotics used
in agriculture, ways through which they end up in the environment causing antibiotic pollution, and on
the other hand, the consequential effects of antibiotic residues on public health. In depth, the consequential
and devastating effect of antibiotic use, known as antibiotic resistance, has been deliberated on to include
salient aspects, such as the determination of antibiotic resistance, antibiotic resistance in livestock farming,
as well as antibiotic resistance in manure-impacted environment (soil and water).

2. Antibiotics in Agriculture

The use of antibiotics is not only constrained to the clinical settings, as prescriptions involved in
the therapeutic regimens for the eradication of diseases in humans. It is also employed in livestock
farming, where antibiotics can be used for disease treatment of animals, and in sub-therapeutic levels
in concentrated animal feed for growth promotion, improved feed conversion efficiency, and for
the prevention of diseases [22,30,31]. Of great concern, the uses, types, and mode of actions of the
antibiotics employed in agriculture and veterinary practice are closely related or the same (that may
belong to the same general classes, function and act in similar ways) to those prescribed to humans [32].
Clearly, the choice of antibiotics and the antimicrobial consumption pattern demonstrates geographical
variation across the continents being influenced by the food animal species, regional production patterns
and types of production system, intensive or extensive farming, purpose of farming (commercial or
industrial or domestic), lack of clear legislative framework or policies on the use of antibiotics, as well as
the size and socioeconomic status of the population, and the farmers in particular [12,33].

The inclusion of nonessential antibiotics in animal feed for growth promotion purposes remains
largely unregulated in the underdeveloped countries [34]. The persistent use of these nonessential
antibiotics in livestock farming can be attributed to the expansion and greater concentration of farmlands,
inadequate governmental policies, and control over the use and sales of antibiotics, reduced use of
infection control measures, and the unwillingness of farmers to execute delegated changes in farm
practices [35]. Developing countries continue to employ the antimicrobial agent for growth promotion to
maintain the healthy state of the animals, to increase productivity, and raise incomes for the farmers [36,37].
However, these are contradictory to the Swedish agricultural data, as it recorded no loss of production
after the ban exercise [36].

Altogether, Boeckel et al. [12] noted that on a global scale, the average antimicrobial agent consumed
per annum of animal produced (per kg) varied across the animal species with values of 45 mg/kg, 148 mg/kg,
and 172 mg/kg associated with cattle, chicken, and pigs, respectively. Equally, their mode of
administration differs with the animal types. In this light, Apata [38] noted that antibiotics were added to
water and feed for chicken in sub-therapeutic levels for growth promotion and prophylaxis. This had
a devastating effect, as even healthy birds were unnecessarily exposed to antibiotics. Moreover, as these
birds compete for food sources, eventually, there exists a difference in the doses consumed between
the individuals, with one receiving a higher dose than others. This introduces another differential in
the selective pressure on commensals, which could lead to the selection of resistant commensals that
would eventually end up in the environment [39]. Singer et al. [40] accorded the administration of
antibiotics in animal feed or water, in which the animals are reared in groups, making it difficult to
isolate only the infected animals, as well as that the isolation process could be stressful to the animals and
dangerous to the veterinarian who has to administer the antibiotic process.

Contrarily, Sekyere [41], in their study, demonstrated the administration of antibiotics to pigs
via the intravenous route for treatment, and in this case, shunned the exposure of healthy animals
to antibiotics. However, this mode of administration might cause the accumulation of these drugs
in adipose tissues, thereby posing a health risk to consumers of pork fat. In addition, Cromwell [42]
mentioned that varying quantities of antibiotics are being employed at the different stages of livestock
production, especially in pig farming, that incorporates four stages viz. gestation, farrowing, weaning,
and finishing. Kim et al. [43] emphasized the significant difference in the use of antibiotics amongst
piglets, fattening pigs, and sows during therapy and growth promotion; antibiotics are employed in
pig farming for treatment, metaphylaxis, prophylaxis, and growth promotion. The authors further
recorded a significant difference in the use of antibiotics between the three production systems in poultry farming, including breeding poultry, broilers, and laying hens. Accordingly, these may release different masses of remnant antibiotics into the environment [30].

Generally, in the developing countries, the level and rate of antibiotic utilization in the farming sector might be influenced by the manner in which the farmers acquire (over the counters) and use these antibiotics (multidrug practices), and also, the presence of existing factors. The existing factors include a high prevalence or level of infections, profound scarcity of state management and development strategies, shortfall in husbandry zone planning, negligible hygienic practices in livestock husbandry in conjunction with the presence of an integrated agricultural system [32,44]. Specifically, in Vietnam, there has been reported cases of frequent and uncontrolled epidemic diseases, such as the porcine reproductive and respiratory syndrome (PRRS), foot and mouth disease, and digestive tract infections and reproductive disorders in piglets and exotic sows, respectively. The disease conditions necessitate the wide use of antibiotics by producers in livestock for the prevention and therapy of diseases as one of the most likely approaches to combat diseases [45]. Moreover, the country practices an integrated agriculture–aquaculture farming system, whereby the aquaculture is being sustained via livestock and human wastes. This further strengthens the risk of exposure of humans, animals, and environment to available antibiotics [43].

Similarly, Guetiya Wadoum et al. [25] noted the multidrug practices by farmers in addition to the use of formulations with low doses of antibiotics that do not indicate the active ingredients, or the withdrawal periods in poultry farming, in Cameroon. As a result, they diagnosed the diseases that occurred or threatened the chickens and decided on the types of antibiotics and dosage to employ, as well, the veterinarians even gave wrong diagnosis about the diseases amongst the birds to encourage and promote the sales of their drugs. What a bizarre situation that creates chances for the abuse of antibiotics? Several authors have demonstrated the indiscriminate use of antibiotics by farmers, and attributed it to lack of knowledge on the prudent use of these drugs, and the possible adverse effects associated with their abuse, non-adherence to manufacturer’s instructions, and the antibiotic withdrawal periods, unavailability of veterinarians and their services. Furthermore, inexperienced farmers relied on the knowledge and advice of experienced farmers and local drug sellers for drug administration, and above all, wealthy farmers tended to employ multiple antibiotics, since they have the potential to acquire the drugs. Also, very few animals are referred to the laboratory for diagnosis to identify the causative agent and to assess the antibiotic susceptibility testing prior to antibiotic application [10,32,37,41,46].

As a consequence, some of these underdeveloped countries still employ some antibiotics, such as chloramphenicol, tylosin, and TCN (a powder mixture that consisted of oxytetracycline, chloramphenicol, and neomycin) which have been banned for use in the developed countries. Accordingly, these drugs have been associated with aggravation of kidney disease (neomycin), carcinogenicity, mutagenicity, and development of aplastic anemia in humans (chloramphenicol) [47,48]. In addition, Guetiya Wadoum et al. [25] mentioned that TCN and tylosin had to be withdrawn for 21 days and 10 days respectively, before the sales of eggs or meat; a situation which is quite difficult for the farmers to implement and respect. This expedites the consumption, by humans, of poultry products harbouring antibiotic residues.

Notwithstanding, the available limited data on antimicrobial utilization in livestock farming ensues the partial reports of antimicrobial consumption and sales. This is due to the lack of surveillance systems subsidized by the government to monitor antimicrobial use and resistance, the lack of knowledge and the reluctance of food animal producers, animal feed producers, public health and veterinary officers and veterinary pharmaceutical companies to provide such in-depth measurements [49,50]. In conclusion, the information presented herein is deduced from the findings obtained by several authors who have previously conducted investigations on antibiotic use and antibiotic resistance, yet the rate of antibiotic usage and antibiotic resistance is alarming; imagine the scenario in which the real/actual data has to be presented. Seemingly, there is a need to call for cooperation or team collaboration from individuals, farmers, veterinarians, consumers, and local vendors of pharmaceutical products for the prudent use of antibiotics both in the clinical
and agricultural settings across the nations or countries, in a bid to circumvent the rising antibiotic resistance of bacteria [51].

2.1. Antibiotics’ Introduction into the Environment

The indiscriminate and abusive use of antibiotics can result in higher concentrations of antibiotics in the environment, which can be termed as antibiotic pollution. The sources via which antibiotics can be released into the environment are diverse, including the human waste streams, and wastes from veterinary use and livestock farming [3]. Antibiotics used for prophylaxis or therapy in humans contaminate the human waste streams, likewise, the antibiotics used in animals for growth promotion, prevention, and treatment equally contaminate the animals’ waste streams. Thus, these are considered as prime sources of antibiotic release into the environment [52]. This is because the administered antibiotics are not fully metabolized, and are released unchanged into the environment, i.e., water, manure or soils. The amount and rate at which the antibiotics are being released into the environments depends on the specific antibiotic and its administered dosage, as well as the species and the age of the animals [51]. Nevertheless, these waste streams will contain both the antibiotics and resistance genes; both considered as pollutants, and their fate in the environment differ [49].

Furthermore, antibiotics and their metabolites contained in stockpiled animal manure may seep through the pile to surface and groundwater, and also into the soil. This is especially so for antibiotics with high water affinity or which are water soluble, thus making their spread and ecotoxicity in the environment faster, and widely with the aid of water fluidity [53]. In the same view, antibiotics can be introduced into the environment via soil fertilization with raw animal manure, irrigation with wastewater generated from farm activities, or via accidental release by runoffs from farms [54]. Interestingly, Hamscher et al. [55] noted that dust contaminated with antibiotics from farms could equally serve as another route of environmental release of these drugs. Chee-Sanford et al. [56] also emphasized the release of antibiotics into the environment via the dispersal of feed and accidental spill of products, as well as discharges.

In addition, Sekyere [41] noted that pig farmers in some different districts in the Ashanti Region of Ghana do not secure their antibiotics, thereby making them freely accessible for use and abuse by unauthorized persons and children. Also, the farmers disposed of their used antibiotic containers by merely throwing them into drains, refuse dumps, or onto bare ground, instead of burying them as recommended. The author further mentioned that these antibiotics were stored under suboptimal environmental conditions, vulnerable to temperature fluctuations that could accelerate their decomposition, thereby causing a reduction in their concentration and efficacy during administration. Such circumstances promote antibiotic resistance of bacteria living in the gastrointestinal tracts of the animals, due to constant exposure to sublethal levels of these antibiotics, or could even cause prompt administration of an overdose of the antibiotics which is noted to be inefficient. More especially, in commercial and intensive poultry farming, antibiotics may be administered to the entire animal population in feed or water, rather than targeting only the diseased animals. Thus, resistance becomes unavoidable [57]. Interestingly, antibiotics produced naturally by environmental microorganisms, to deter competitors from living space and food, are gradually accumulating in the environment [58]. Seemingly, antibiotics are released from their production facilities in high concentrations into the environment [59]. Also, Sahoo and colleagues [60] noted that antibiotics could be found in the natural environment via improper disposal of out-of-date drugs from pharmaceutical shops, and unwanted, expired household pharmaceuticals.

Accordingly, these antibiotics released usually consist of different types, and consequently, they do not degrade, all at the same time, i.e., they degrade at different rates in the environment over time by the main elimination processes, including sorption, photo degradation, biodegradation, and oxidation [61,62]. Albeit, other applied methods, such as adsorption, filtration, coagulation, sedimentation, advanced oxidation processes have been implemented [63]. Specifically, several findings have demonstrated the use of composting, and anaerobic and aerobic digestion to cause the reduction
of the antibiotic’s level in manure, wastewater, and sludge, but these processes vary in efficiency with
the category of the antibiotics, the conditions employed for composting, as well as the type of livestock
manure [53,64]. Nonetheless, the presence of these antibiotics in the environment may create selective
pressure resulting in antibiotic resistance and also the removal processes, reduce the concentrations of
these antibiotics, allowing time for the exposed bacteria to develop resistance which may be presented
as stress adaptation, co-selection, cross-resistance, and cross-protection.

Moreover, the use of antibiotics urges susceptible bacteria to these antibiotics to develop resistance in
a bid to survive. In this view, bacteria prevaricate the inhibitory or bactericidal activities of the antibiotics,
and execute resistance by either modifying or altering the target sites (ribosomes) for binding by antibiotics,
with the help of ribosomal protection proteins which bind to the ribosomes, thereby preventing the binding
and interference of protein synthesis [65,66] or neutralizing antibiotics via enzymes produced by adding
acetyl or phosphate groups to the precise site on the antibiotics [67], or finally, via changing of membrane
permeability due to the presence of efflux pumps on the cell membrane [68,69]. Furthermore, the sensitive
bacteria tend to survive in an antibiotic polluted environment by acquiring antibiotic resistance genes
from other bacteria or phages (lateral gene transfer), undergo mutations in specific antibiotic gene targets,
and by altering of the bacterial surfaces [70].

2.2. Animal-Derived Products and Antibiotic Pollution vs Public Health

In developing countries, food prepared and sold by street vendors is in vogue, and it is still emerging
hastily in some countries, notably Indonesia, Cameroon, and Democratic Republic of Congo [71,72].
These foods usually comprise of meat (beef, pork, snails) either raw, roasted, or cooked in sauce/stew,
starchy foods and snacks, which are sold in restaurants located in public places (markets, schools,
hospitals), on the ground in the streets, and along main roads [73]. It is for this reason that foodborne
outbreaks are highest in developing countries, and dawdles as an issue of public health concern
worldwide, because it is indicated as one of the significant food safety hazards concomitant with
animal-derived foods [74]. Cooked foods sold on the street have a great socioeconomic impact; they create
jobs and provide income to low or unskilled men and women, as well as serve as a major channel for
the supply of food to financially handicapped individuals or poor and less privileged individuals [75].
However, there is increased meat consumption to meet the protein demand of the population [72].

Antibiotics have been reported to accumulate and form residues at varying concentrations in
the tissues and organs of food animals, as presented in Table 1. Billah et al. [24] referred to these
antibiotic residues as chemical residues or pharmacologically active substances representing either
the parent compound or its degraded products, which are released, gathered, or stored in the edible
tissues of the animal, due to their use in the prevention, treatment, and control of animal diseases.
Undoubtedly, in Cameroon, Guetiya Wadoum et al. [25] demonstrated the presence of chloramphenicol
and tetracycline residues in concentrations above the maximum residue limit (MRL) recommended
by the European Union in 2010, in edible chicken tissues (muscle, gizzards, heart, liver, kidney) and
eggs. Similarly, Billah et al. [24] detected ciprofloxacin in higher concentration in egg white, but in
lower concentration in egg yolk during treatment of the birds. Also, Olufemi and Agboola [76] reported
a high oxytetracycline residue in edible beef tissues of cattle slaughtered at Akure, in Nigeria, at violating
levels beyond the MRL stipulated by WHO. However, of profound concern are circumstances in which
diseased animals and animals undergoing therapy could be sold quickly to save funds, or could be
slaughtered and used as food or feed for other animals [43]. This causes difficulties in the prophylactic
approach to handling epidemic diseases and health risks to consumers, as well as a negative influence on
the environment. Van Ryssen [77] reported the use of poultry litter as a feed to farm animals in South
Africa, since it is considered as a bulky protein supplement.

Ideally, no animal derived product should be consumed unless there is a complete absence of
residual amounts of administered drugs. Nevertheless, the intriguing fact is that there are constant
detectable levels of residues, identified via the help of markedly improved analytical methods.
Therefore, the world regulatory authorities have set the MRL for various veterinary drugs that should
be expected and considered safe in foods for human consumption [78,79]. According to Beyene [80],
the diet, age and disease status of the animal added to the absorption, distribution, metabolism, and
excretion of the drugs, the extra-label drug use and the improper withdrawal times, amongst others,
are the risk factors responsible for the development of residues. In this light, farmers are supposed to
adhere and implement the right dosages of the antibiotics, as well as observed their withdrawal periods
prior to slaughter and market, in a bid to avoid illegal concentrations of drug residues in the animal
products. The withdrawal period (clearance or depletion time) defines the length of time required
for an animal to metabolize the administered antibiotics under normal conditions, and also, the time
needed for the antibiotic concentration in the tissues to reduce to a safe and acceptable level described
as tolerance. It can equally be referred to, the time interval necessary between the last administration
of the drug under normal conditions of use to animals and the time when treated animals can be
slaughtered to produce foodstuff safe for public consumption. Depending on the drug product, route of
administration, and dosage form (even with the same active ingredients), the withdrawal periods vary
from a day to several days or weeks, and according to the target animals [81].

It has been reported that the health of humans correlates directly with the environment
(i.e., their habitat and its components, including plants, animals, microorganisms, and other human
beings) and the quality of food that they consume [60,82]. Taking into consideration the growing human
population, the changing standard of living conditions, the food shortages, and the greater demands
for the intensified production of animal proteins for human consumption across the globe, essential
practices to improve on the agricultural and industrial productivity are needed [83]. Of interest is
the critical use of antibiotics in agriculture to meet the demands of the rising human population,
as the use of antibiotics in this setting has been associated with several benefits. It is therefore
anticipated that, in the future, almost all the animals slaughtered and consumed as food must have
received a chemotherapeutic or a prophylactic agent of some sort [81]. However, the consumption of
these meats, milk, and eggs contaminated with antibiotic residues usually has tremendous impacts on
the health of humans. These effects may be direct or indirect, owing to the high dose of the residues,
which must have accrued over a prolonged period [81]. They can be exhibited as drug hypersensitivity
reactions, aplastic anemia, carcinogenic, mutagenic, immunologic and teratogenic effects, nephropathy,
hepatotoxicity, disruption of the normal flora of the intestines, a reproductive disorder, as well as
the development of antibiotic-resistant bacteria in the gut [80,81,84].
Table 1. Presence of varying concentrations of antibiotic residues in the different animal-derived products in some developing countries.

| Antibiotic Residue | Concentration | Sample | Consequences in Humans/Animals | Country | Literature |
|-------------------|--------------|--------|--------------------------------|---------|------------|
| Oxytetracycline   | 2634.1 ± 703.7 µg/kg | Chicken | Carcinogenicity, cytotoxicity in the bones of broiler chickens. Presence of residues cause technological challenges during milk processing. | Tanzania | Kimeria et al. [85] |
|                   | 3434.4 ± 604.4 µg/kg | Muscle |                                |         |            |
|                   | 3533.1 ± 803.6 µg/kg | Liver |                                |         |            |
|                   | 51.8 ± 90.53 µg/kg | Beef |                                | Nigeria | Olufemi and Agboola [76] |
|                   | 372.7 ± 366.8 µg/kg | Muscle |                                |         |            |
|                   | 1197.7 ± 718.9 µg/kg | Kidney |                                |         |            |
|                   | 15.92 to 108.34 µg/kg | Cattle |                                | Ethiopia | Bedada et al. [86] |
|                   | 99.02 to 112.53 µg/kg | Muscle |                                |         |            |
| Enrofloxacin      | 0.73 and 2.57 µg/kg | Chicken tissues | Allergic hypersensitivity reactions or toxic effects, phototoxic skin reactions, chondrotoxic, and tendon rupture | Iran | Tavakoli et al. [87] |
| Chloramphenicol   | 1.34 and 13.9 µg/kg | Bone marrow toxicity, optic neuropathy, brain abscess |            |         |            |
| Penicillin        | 0.87 and 1.3 µg/kg | Calves muscles | Allergy, affect starter cultures to produce fermented milk product | Ethiopia | Bedada et al. [86] |
| Oxytetracycline   | 3.5 and 4.61 µg/kg | Chicken | Carcinogenicity, cytotoxicity in the bones of broiler chickens |         |            |
| Quinolones        | 30.81 ± 0.45 µg/kg | Beef | Allergic hypersensitivity reactions or toxic effects (phototoxic skin reactions, chondrotoxic) and tendon rupture | Turkey | Er et al. [88] |
|                   | 6.64 ± 1.11 µg/kg |               |                                |         |            |
| Tetracyclines     | 124 to 5812 µg/kg | Chicken | Primary and permanent teeth discoloration in children and infants, allergic reactions and teratogenicity during the first trimester of pregnancy, nephrotoxicity, carcinogenic, hepatotoxicity, and disturbance of the normal microflora of the intestines. | Egypt | Salama et al. [89] |
|                   | 107-6010 µg/kg | Breast |                                |         |            |
|                   | 103 to 8148 µg/kg | Thigh |                                |         |            |
|                   | 150 ± 30 µg/g | Chicken |                                | Cameroon | Gaetiti-Wadoum et al. [25] |
|                   | 62.4 ± 15.3 µg/g | Liver |                                |         |            |
|                   | 50 to 845 µg/kg | Beef |                                | Kenya | Murtuki et al. [90] |
|                   | 50 to 573 µg/kg | Kidney |                                |         |            |
|                   | 25–560 µg/kg | Liver |                                |         |            |
|                   | 107 to 6010 µg/kg | muscles |                                |         |            |
| Aminocillin       | 9.8 to 56.16 µg/mL | Milk | Carcinogenic, teratogenic, and mutagenic effects | Bangladesh | Chowdhury et al. [91] |
| Sulfonamides      | 16.28 µg/kg | Raw milk | Carcinogenic, allergic reactions | China | Zheng et al. [92] |
| Quinolones        | 23.25 µg/kg | Beef | Allergic hypersensitivity reactions or toxic effects (phototoxic skin reactions, chondrotoxic) and tendon rupture | Zambia | Nchima et al. [93] |
| Oxytetracycline   | 199.6 ± 46 ng/g | Beef | Carcinogenicity, allergic reactions |         |            |
| Sulphonamethazine | 86.5 ± 8.7 ng/g |               |                                |         |            |
| Penicillin G      | 15.22 ± 0.61 µg/L | Fresh milk | Allergy (hypersensitivity reaction) ranging from mild skin rash to life-threatening anaphylaxis | Nigeria | Olatuyi et al. [94] |
|                   | 7.60 ± 0.60 µg/L | Cheese (wara) |                                |         |            |
|                   | 8.24 ± 0.50 µg/L | Fermented milk (mono) |                                |         |            |
| Sulfonamides      | 0.08–0.193 µg/g | Chicken | Carcinogenic potential and mild skin rash to severe toxiderma, epidermal toxic necrolysis, blood dyscrasias | Malaysia | Cheong et al. [95] |
|                   | 0.006–0.062 µg/g | Liver |                                |         |            |
|                   | 0.006–0.062 µg/g | Breast |                                |         |            |
| Antibiotic Residue | Concentration | Sample     | Consequences in Humans/Animals                                                                 | Country | Literature          |
|--------------------|---------------|------------|------------------------------------------------------------------------------------------------|---------|---------------------|
| Tetracycline       | >0.1 µg/mL    | Raw milk   | Primary and permanent discoloration of teeth in children and infants, teratogenicity during the first trimester in pregnancy, etc. | India   | Nirala et al. [96]  |
| Oxytetracycline    | >0.1 µg/mL    |            | Carcinogenicity and cytotoxicity in bone marrow of broiler chickens                              |         |                     |
| Sulfadimidine      |               |            | Carcinogenicity and allergic reactions                                                           |         |                     |
| Sulfamethoxazole   |               |            |                                                                                                 |         |                     |
3. The Great Challenge: Antibiotics Resistance

The routine employment of antibiotics, for prevention and growth promotion purposes in livestock farming, selects for antibiotic resistance among commensal and pathogenic bacteria. Owing to the fact that most of these antibiotics are not fully metabolized but released into the environment as waste products, antibiotic resistance has an ecological impact, since these waste products still have the potential to influence the bacteria population and promote antibiotic resistance. Cogliani et al. [36] pointed out that the low concentrations of these antibiotics in the environment bring about random and spontaneous mutagenesis. Therefore, the environment has been viewed as a plausible reservoir or pool of antibiotics and antibiotic-resistant bacteria, as well as their resistance genes [97]. It is a situation of great concern to public health facilities worldwide, as bacteria have the capability to transfer resistance genes between strains of the same species and between different species [98]. This is, however, possible due to the fact that the antibiotic resistance genes are located on elements, including transposons, integrons, and plasmids, that can be immobilized [99]. The transmission of these resistance genes is termed horizontal gene transfer (HGT) or lateral gene transfer (LGT), and it does occur via transformation, conjugation, and transduction processes [100,101]. These processes are responsible for the increasing antibiotic resistance worldwide (because of gene transfers between different bacteria species). LGT has been implicated in the distribution of numerous antimicrobial-resistance determinants, and as the cause of an epidemic in nosocomial and community infections, by conferring resistance to many classes of antimicrobials, which leads to multidrug resistance [102,103]. Moreover, the employment of broad-spectrum antibiotics creates selective pressure on the bacterial flora, thus increasing the advent of multidrug-resistant bacteria which results in the production of new antibiotic-resistant bacteria with cycles of unpleasant treatments [70].

(a) Prevalence of antibiotic resistance in some environmental sources

Several authors have investigated the prevalence of antibiotic resistance of some bacteria in different environmental samples. These include the following: Ejo et al. [104] in their findings observed an overall prevalence rate of 5.5% of *Salmonella* isolates identified from raw meat, eggs, milk, and minced meat and burger samples in Ethiopia. The isolates demonstrated relative resistance to ampicillin, tetracycline, and sulphamethoxazole–trimethoprim, with a prevalence of 47.6%. Rasheed et al. [105] equally noted an overall incidence of 14.7% of drug-resistant *E. coli* obtained from vegetable salad, unpasteurized milk, raw chicken, raw meat, and raw egg surface, with 4% of these isolates exhibiting the extended-spectrum β-lactamase activity. In addition, Carballo et al. [106] recovered three tetracycline residues and sixty-three antibiotic-resistant Gram-negative bacteria that presented with percentage resistance between 33.3% and 66.7% to five well-known antibiotics employed in livestock farming, viz. tetracycline, chloramphenicol, nalidixic acid, sulphamethoxazole, and ampicillin.

Similarly, Zhu and colleagues [107], in their findings, noted the high levels of tetracycline concentration in manure and soil samples procured from three large commercial swine farms, from three different regions in China. The authors further revealed a great diversity of antibiotic resistance genes (149 unique ARGs), and emphasized the absolute abundance of 43% of the aminoglycoside phosphorylation gene *aphA3* in all the manure samples. In the same country, Gao and co-workers [108] equally unravelled the cefotaxime (CTX)-M gene as the most prevalent extended-spectrum beta-lactamase (ESBL) gene found in *E. coli* isolates recovered from both pig farm and soil samples. Apparently, Xiao et al. [21], in a metagenomics analysis of paddy soils from China, provided a broad spectrum profile of antibiotic resistance genes, with multidrug resistance being the most dominant at a level of 38–47.5% of all the samples collected.

Furthermore, Lin et al. [109] isolated and characterized one hundred and thirteen enteric bacteria from the Mhlathuze River, KwaZulu-Natal province, South Africa. Of these bacteria, 75.2% were multidrug resistant, and the enteric isolates obtained from downstream (urban and industrial regions) exhibited greater antibiotic resistance, unlike those from upstream (rural vicinity). This suggests that environmental, industrial, and human activities have a huge impact on the level of...
environmental antibiotic resistance. Wahome [110] noted the microbial contamination of groundwater samples obtained in Ongata Rongai, Kajiado North County, Kenya, with enteric pathogens including *Pseudomonas aeruginosa*, *Shigella* and *Vibrio* species, *E. coli*, and *Salmonella*. The enteric pathogens exhibited high resistance, between 87.5% and 98.5%, to ampicillin, kanamycin, and sulfamethoxazole.

(b) Methods of determining antibiotic resistance of bacterial isolates

The antibiotic resistance profile of bacterial isolates to available antibiotics can be determined by using multiple culture-based methods, with the key feature to isolate the target organism through growth on general multipurpose or selective and/or enriched microbiological media, and subsequent evaluation of their growth in response to specific antibiotic concentrations. The culture-based methods offer a link between antibiotic resistance measurement both in the environment and human clinical setting [111]. These cultured-based techniques are designed as susceptibility tests, and the resistance of the bacterium can be deduced directly from the susceptibility testing. The antibiotic susceptibility test involves both qualitative diffusion and quantitative dilution methods, amongst which is the Kirby–Bauer disc diffusion technique that implements the guidelines adopted from Clinical Laboratory Standards Institute (CLSI) [112]. In this methodology, the size (diameter) of the zone of inhibition developed around each disc placed on plates of microbiological medium inoculated with the pure culture of bacteria isolate is considered as the degree of sensitivity [113]. The antibiotic susceptibility test with disc diffusion test is, however, regarded as a qualitative test to classify an organism as being susceptible or resistant, and paves the way for the better quantitative tests.

Determining the minimum inhibitory concentration (MIC) of an antibiotic against a bacterial isolate ensures the best quantitative estimate of susceptibility. The MIC describes the lowest or least concentration of a drug that is required to inhibit visible bacterial growth after overnight incubation [114]. The MIC value gives an insight into the degree of resistance, the resistance mechanisms, as well as the resistance genes. It can be determined both by micro broth dilution in microplates [115], and agar dilution [116]. In between, the E-test (Epsilometer test) combines the diffusion and dilution theories in susceptibility testing, whereby it determines whether the isolate is resistant or susceptible, based on the clear zone of inhibition. At the same time, it quantifies the sensitivity of the isolate by giving a discrete MIC value at the point where the clear zone of inhibition intersects on the test strip that harbours a predefined gradient of continuous antibiotic concentration ranges [117]. Nevertheless, owing to the inherent ability of microbiological agars to detect contamination of inoculum, Jenkins and Schuetz [116] suggested that agar-based methods are more reliable for the detection of antibiotic resistance, unlike the broth dilution methods. In general, both the agar-based and broth dilution methods are faced with challenges, including cost, and that they are time-consuming and labour intensive [111]. It is worth mentioning that the resistance level of a bacterium greatly depends on the type of test and test conditions applied for the determination of resistance, as well as the kind of antibiotics and its mode of action [118]. It is necessary to conduct continuous surveillance of the antibiotic resistance profile of bacteria, since bacteria are vulnerable to develop unpredictable resistance patterns, based on their genetic plasticity. In addition, the susceptibility patterns of a particular bacteria changes with time, geographical location, country, and the prevailing environmental conditions [16,119]. The recovered information gives knowledge and serves as guidelines in antibiotic selection for treatment, to reduce the use of broad-spectrum antibiotics, and also to slow down resistance development, hence predict future resistance in bacterial isolates [113,120].

(c) Zoonoses and agriculture versus clinical setting

Taking into consideration the routine use of the same antibiotics with similar modes of action both for animal and human purposes, added to the report of zoonoses, which are bacterial infections in humans caused by animal pathogens, including *Salmonella* spp., *Yersinia enterocolitica*, *Listeria monocytogenes*, *Staphylococcus* spp., *Campylobacter jejuni*, *Enterococcus* spp., and *Escherichia coli*, it is somewhat obvious that antibiotic resistance can be transferred from animals to humans [121]. These bacterial pathogens are
of prime importance due to their public health implications, are easily detectable indicator organisms which signify the presence of fecal contamination of the environment, have the potential to acquire resistance genes via lateral gene transfer, and lastly, they can develop resistance to a broad spectrum of last-resort antibiotics [122]. Wegener [123] affirmed that the public health consequences perpetrated by zoonotic pathogens are ever-challenging to evaluate. The consequences involve complex production and distribution systems of food and animals, dissemination of resistance genes and bacterial clones, increased mortality and morbidity, and higher cost in the treatment of disease as well as infections that would have otherwise not have occurred.

These zoonotic pathogens develop resistance in response to the antibiotics used in food animals, and the same strains colonize both animals and humans, and the antibiotic resistance genes can easily spread among the bacterial species or clones that are phylogenetically related [124]. Therefore, these zoonotic bacteria can serve as vectors of antibiotic resistance genes. The resistance can be transferred from animal to animal, or animals to humans, either directly via contact, or indirectly through the food chain, water, sludge-fertilized soils and manure [125]. More specifically, humans can come into contact with antibiotic-resistant bacteria and resistance genes either directly via immediate exposure to animals and biological substances, including urine, feces, milk, semen, and saliva, or indirectly via contact or ingestion of contaminated animal-derived food products [126]. This is, however, the main route for the cause of enteric infections in humans with the zoonotic bacterial pathogens listed above. On the other hand, antibiotic-resistant bacterial strains can be transmitted from humans, including the workers on the farm and their families, to food animals, since it is noted that the digestive tract and the skin of these humans harbour high numbers of commensals, notably *Staphylococcus aureus* [127]. Notwithstanding, the feasibility of transmission is reliant on geographical location, ethnic/cultural practices, religion, hygienic status, farm size, and the type of integrated farming [128]. However, this status quo is true in the rural settings in developing countries, where there is close contact between the animals (specifically, poultry) and humans. Since farming of indigenous-species animals in small numbers appears to be the most common practice of poultry production systems, in this regard, the animals depend on scavenging as a source of food [37,129]. Also, in the developing world, biosecurity and food safety measures are inadequate, thus facilitating the direct and indirect mode of acquiring antibiotic-resistant bacterial strains and their resistance genes. Kagambéga et al. [130] isolated and characterized *S. typhimurium* from poultry and humans that were resistant to the same antibiotics, and harboured the same phage, DT 56, which demonstrated close-relatedness as revealed by pulse field gel electrophoresis.

Lipsitch et al. [131] presented three mechanisms through which antibiotic resistance originating from agriculture can threaten human health, as follows: an individual might be infected by a resistant bacterial pathogen via direct contact or via ingestion of contaminated meat, milk, eggs, or water, and not transmit to other humans. In another scenario, a person might be infected with a resistant pathogen via the aforementioned pathways, with ongoing transmission to other humans and causing infections in some of the individuals. Thirdly, resistance genes derived from the agricultural settings are being introduced into human pathogens by lateral gene transfer. Apart from acquiring resistance by these bacteria, they can equally receive additional virulent genetic elements, leading to an increase in pathogenicity or virulence [39,132].

Wegener et al. [133] emphasized that the observed level of antibiotic resistance is closely associated with the amount that is being consumed. Apparently, the level of antibiotic resistance of these bacteria relies on the quantity and the effects of antibiotics in the natural environment originating from antibiotic management within the agricultural and healthcare settings, as well as the antibiotic prescription guidelines. According to Sahoo et al. [16], the antibiotic prescription is influenced by geographical and climatic factors, socioeconomic conditions, local population density, the behaviour of a particular community towards antibiotic prescription or consumption, and supplier incentives to the prescribers in conjunction to the type of pathogen.

All the same, antibiotic resistance has adverse effects on patients, healthcare systems, and society [134]. More specifically, patients witness a more severe underlying infection, are administered
less efficacious but more toxic antibacterial agents, and receive broad-spectrum antibacterial agents, which are so-called reserved or last resorts as an empirical antibiotic regimen [132]. These might result in treatment failure, as well as an increase in the cost of human therapies, due to the severity and persistence of the diseases, added to long hospital stay and prolonged therapy, respectively [135,136]. Antibiotic resistance equally limits the choice of antibiotics to be implemented in therapy and jeopardizes the chances of the effectiveness of the existing potent antibiotics in treatment regimens used for the eradication of serious but common diseases in the future [137]. The rising level of antibiotic-resistant bacterial pathogens will eventually hamper future treatment and the prevention of infectious diseases in both animals and humans [138]. Also, the incidence of antibiotic resistance is very critical to the immunocompromised population, since these individuals rely solely on the use of antimicrobials as a defense against pathogens [139]. Unfavourably, the rise in antibiotic resistance presents a potential threat to surgical and advanced therapeutic procedures, including transplantation or anticancer therapy that involve immunosuppression. Therefore, these medical procedures need vigorous anti-infective preventive therapies [2,134]. However, antibiotic resistance can cause the death of individuals which is the most severe outcome [134].

(d) Principles of antibiotic use and antibiotic resistance in the clinical and agricultural sectors in both developing and developed countries

The principles or standards established to guide antibiotic use in both agricultural and clinical settings vary between the developed and developing countries, as well as differs from one country to the other. This is visualised from the variation in the antibiotic consumption pattern across the globe, highlighted by Van Boeckel et al. [12]. It is greatly influenced by the antibiotic policies which govern antibiotic use concerning the antibiotic manufacture, antibiotic dispensation, and antibiotic prescription (inappropriate choice and dosing of drugs) of a particular country [140]. However, antibiotic policies are negatively affected by the socioeconomic level (infectious disease burden, income level, educational status, etc.), large population size, and heterogeneity disparity in the healthcare systems in developing countries [11].

The dearth of functioning antibiotic policies has culminated in the inappropriate use of antibiotics. Van Boeckel et al. [12] stated that about 50% of antimicrobials are used incongruously, regardless of the setting owing to lack of antimicrobial stewardship. Antimicrobial stewardship (formerly called antibiotic policy) entails the choice, dosing, route, and duration of administration of a particular antimicrobial agent. It is defined as the administration of the right drug at the right dose, through the right route, at the right time, to the right patient, to ensure the best clinical outcome for treatment or prevention, thereby causing least harm or toxicity in the patient and future patients [141]. The leading goal of antimicrobial stewardship is to optimize clinical outcomes, to maximize clinical cure or prevention, and to limit the unintended penalties of antibiotic use, including toxicity and the emergence of antibiotic-resistant bacteria [141,142].

From the clinical perspective, antibiotics are the most widely used therapeutic agents worldwide. To avoid the irrational and unnecessary use of antibiotics, it is imperative that antimicrobial stewardship is implemented regarding prescriptions guided by appropriate principles based on the patient’s characteristics, the characteristics of the disease-causing agent, and the colonizing microflora [142]. More specifically, that the pharmacokinetics and pharmacodynamics of the drug, as well as host factors are not left out, in an appropriate antibiotic therapy. The microbiological diagnosis presents as the key procedure in any therapeutic process, where the etiologic agent and the antimicrobial susceptibility patterns, as well as surveillance of the resistance of the pathogen are conducted. Appropriate specimens are collected and submitted to the microbiology laboratory for diagnosis. Diagnosis, in most cases, often relies on culture-based methods which are time-consuming and take several days for a positive result to be obtained. As a consequence, other rapid microbiological methods, including rapid polymerase chain reaction and mass spectrometry have been adopted, and stand a better chance for the future [143].
In addition, new and rapid molecular tests, including peptide nucleic acid and matrix-assisted laser desorption/ionization technologies have been introduced, that identify common organisms from positive cultures within several minutes [141]. However, especially in critically ill patients (e.g., endocarditis, bacterial meningitis) that are hospitalised, an empirical therapy is decided guided by the clinical presentation of the patients and the site of the infection, in order to reduce the morbidity and mortality rate. Broad-spectrum antibiotics are used that cover a broad spectrum of suspected and non-susceptible pathogens responsible for the clinical presentation [144]. Usually, the combination therapy relies on the synergistic action of the recommended drugs to clear, more rapidly, the infecting microorganism or infection caused by resistant bacteria to multiple antibiotics, or infections caused by more than one organism, as well as to truncate antibiotic therapy [143]. On the other hand, a definitive therapy is employed following the release of the laboratory results on the specific etiologic agent, with the critical opinion to narrow the antibiotic spectrum. Disapprovingly, the definitive therapy is described as the most important component of the antibiotic therapy, as it optimises treatment, reduces costs and toxicity, added to its great possibility of preventing the development of antibiotic resistance [145]. Also, very important at this junction, the clinician consults the modes of action of these drugs, whether they are bacteriostatic or bactericidal, but in more serious infections, bactericidal antibiotics are preferred. In summary, antibiotics maybe consumed in therapies/treatments as first, second, and third line antibiotics. First line drugs are administered to patients guided by the clinical presentation and antibiotic susceptibility results, and are based on their broad availability, relatively low cost, and tolerance. However, if a patient fails to respond to the initial drugs or develops intolerance to drugs and/or relapse of infection occurs, other drugs, known as the second line, are added to the treatment. Also, if resistance to the second line drugs is observed, third line drugs are included in the treatment, even though these drugs are associated with higher risk of toxicity and other side effects, unlike the first and second line drugs [144].

As indicated above, the use of antibiotics in agricultural settings is not only for therapeutic purposes. The employment of antibiotics in different applications in food animals is described as therapeutic use, prophylactic use, and sub-therapeutic use [146]. Ideally, the use of antibiotics in food animals for therapeutic purposes should be accompanied by antibiotic susceptibility testing (AST). Altogether, the results, the age and immune status of the animal, attributes of the drug (pharmacokinetics and pharmacodynamics), and the cost of the drug, are considered in order to decide on the appropriate drug to be used. As in human medicine, the antibiotics during therapy can be categorized into first, second, and third line drugs [147]. However, with respect to the different animal type and practice, the antibiotics vary in the classification, but the principle still remains that the first line drugs are often used in the treatment of most bacterial infections, and the second and third line options are rarely needed.

However, there is an obvious link between antibiotic use and resistance, both on an individual and population level. The high disease burden, poor hygienic and sanitation conditions, limited access to available antibiotics (due to poverty), disparity in healthcare systems and personals, over-the-counter purchase of drugs, lack of stringent antibiotic policies (that affect the quality and potency of drugs produced), unregulated prescription principles (that lead to self-mediation and prescription by untrained persons), patient expectations, financial incentives to healthcare providers to prescribe antibiotics in developing countries, cause inappropriate use of antibiotics, resulting in antibiotic resistance [140,148,149]. Thus, there exists differences in the antibiotic resistance levels between and within countries. For instance, Gebeeyehu et al. [150] gave an insight into the inappropriate use of antibiotics in the rural (29.2%) and urban (31.1%) communities in North West Ethiopia, and attributed the practice to younger age, involvement with a job, paucity of knowledge on the use of antibiotic preparations of humans to animals, and dissatisfaction with the healthcare services.

(e) Containment of antibiotic resistance or strategies implemented to maintain appropriate use of antibiotics
Nevertheless, across the globe, countries, states, and regions within the countries have implemented several procedures to regulate and reinforce rational and prudent use of antibiotics in both the clinical and agricultural sectors, in order to contain antibiotic resistance. All these procedures are necessary to conserve the available antibiotics and to maintain their effectiveness. Antimicrobial stewardship occupies a central role in the endeavour to avoid misuse, overuse, or abuse of antibiotics in both settings.

I. Clinical sector

In the clinical sector, the front-end or preprescription, and the back-end or postprescription approach are implemented with different techniques/strategies to optimize the use of antibiotics. These techniques include formulary restrictions, order sets and treatment algorithms, clinical guidelines, education, pharmacodynamic dose optimization, computer-assisted decision support system, pharmacist-driven intravenous to oral switch programs, pharmacy dosing programs, and antibiotic cycling [141]. The back-end approach offers as a better option because it uses prospective review and feedback, and focuses on de-escalation, which permits the modification (a change, adjustment/reduction, discontinuation) of initial empirical antibiotic therapy relying on the culture data, clinical status of the patient, as well as the other laboratory results [151]. The antibiotic de-escalation therapy is the key component within antimicrobial stewardship [152].

Apparently, McKenzie et al. [153] demonstrated that antibiotic restriction, education of prescribers and patients, and prescription feedbacks as antimicrobial stewardship strategies have improved with the prudent use of antibiotics in Australian hospitals. In addition, the California state in the United States has instituted antimicrobial stewardship in its state legislation [154]. In addition, some countries (e.g., Brazil and Mexico) have implemented policies to regulate and prohibit the sales of over-the-counter antibiotics without prescription [155]. Also, the Central Drugs Standard Control Organization (CDSCO) in India instigated Schedule H1, a stricter regulation, unlike Schedule 1, in a bid to prohibit the sales of over-the-counter antibiotics. According to Laxminarayan and Chaudhury [156], Schedule 1 harbours antibiotics that must be sold with a valid prescription issued by a registered medical practitioner, and the pharmacist is required to retain a separate register that carries the contact details of the prescribing doctor, the name of the patient, as well as the name and quantity of the drug that is dispensed. The register is kept for three years, and the information contained therein is subject to audit by the government.

Furthermore, the Medicine Control Council (MCC) as part of the National Drug Policy in South Africa subscribes to the World Health Organization Certification scheme. It is mandated to register and relicense, conduct dossier-based medicine evaluation and laboratory-based testing of all medicines utilized in the country in conformity to the criteria for medical evaluation and good manufacturing practice. Moreover, Essential Drug Lists (EDLs) and Standard Treatment Guidelines (STGs) are developed as part of the strategy of National Health policy (NHP) in South Africa, so as to ensure that drugs are readily available and accessible at primary care and at the hospital level, in addition to limiting the choice of antibiotics use via replacement with formularies in the public sector. Thus, the practice results rational prescribing [157]. Gelband and Duse [158] highlighted that as a regulatory strategy in South Africa, only licensed practitioners might prescribe and/or dispense antibiotics, and the antibiotics are available only on prescription, but not bought over the counter like in other developing countries. In the same way, antibiotic use was substantially decreased at the primary care in Thailand, as well as nationwide actions were demonstrated to address the problem of inappropriate antibiotic use through strengthening of hospital drug and therapeutics committee, engagement in a project based on multifaceted behavioural change intervention, and updating of its essential medicine lists on a regular basis [159].

Surveillance is the pivot in any control strategy directed against infections in a clinical setting and antimicrobial resistance. Antibiotic surveillance is regarded as the keystone in endorsing antibiotic stewardship, and eases the control of antibiotic resistance. It is also considered as the force behind the programmes geared towards antimicrobial resistance, since it generates reliable and crucial data
that can be used to formulate policies on antibiotic use to promote accurate prescriptions of drugs [160]. According to the Global Antibiotic Resistance Partnership—India [161], real changes in antibiotic consumption or dissemination of resistant bacteria can only be appreciated and/or supported when the resistance level is known and tracked over time, unlike undergoing any type of surveillance. Hence, surveillance of antibiotic resistance complements the surveillance of antibiotic use, and obtained data can be implemented to evaluate the success of intervention programmes. Therefore, salient data required for clinical decision making and national policies can be assembled via surveillance of antibiotic use and antibiotic resistance [162].

According to Lowmann [163], the clinical microbiology laboratory undertakes a central role in achieving the key motives of antibiotic stewardship by providing data on culture and susceptibility of the specific patient, and insights for surveillance activities that guides the selection of antibiotics for empirical therapy. Monitoring the consumption of antibiotics is inevitable, as it generates data that can assist in the design and evaluation of interventions aimed at optimizing the use of these antibiotics and prevent rising resistance [155]. The World Health Organisation [164] and the Global Action Plan [165] advocated that the quantity and pattern of antibiotics consumed should be monitored as part of surveillance. Pereko and colleagues [160] analyzed prescription claims data and sales data from 2008 to 2011 in the private sector in Namibia to obtain the number of prescriptions that contained antibiotics and the volume of units sold. The findings highlighted the highest antibiotic consumption by females (53%), followed by individuals of age, 18–45 years (41%) and 34% in Windhoek, with combined therapy of amoxicillin/clavulanic acid as the post prevalent agents used which belong to the family of penicillins.

On the other hand, surveillance of antimicrobial resistance is equally paramount, and should be conducted continuously in order to gain insight into the problem on time, because resistance is evolving. It is defined as the continuous, systematic gathering, analysis, and interpretation of health-related data to monitor and describe an event [166]. Surveillance provides current and salient information needed to develop and monitor antibiotic stewardship programmes, antibiotic formularies, infection control policies, public health interventions, novel antimicrobials, and antibiotic therapy guidelines [167]. It can be executed at the local, regional, national or international level, involving the monitoring of a single bacterial infection or the organism, as well as it can be effected based on funds offered by companies or non-profitable organizations [168,169]. The procedure provides data on the antibiotic-resistant bacteria, resistance genes, and predict the rise of antibiotic resistance as depicted from the trend in the antibiotic resistance profiles. Surveillance represents an early-warning system which performs fast distribution of crucial information to public health and regulatory authorities regarding trends and possibility of outbreaks, to bring about timely response measures [170]. Also, Essack [168] reiterated that antibiotic resistance surveillance data are critically needed to update national infection control policies, essential drug lists, and standard treatment guidelines. In addition, Critchley and Karlowsky [170] further emphasized that the data obtained from surveillance and clinical trial can be employed in association to determine breakpoints. Moreover, new medical needs, as well as notorious isolates for the screening of new agents, can be identified from the information contained in surveillance of antibiotic resistance.

In Africa, South Africa is viewed as the only country with the most active surveillance system. The system comprises of two main active groups, namely; the Group for Enteric, Respiratory and Meningeal Disease Surveillance (GERMS) which focuses on obtaining data centered on AIDS-related opportunistic infections, epidemic-prone diseases, and vaccine-preventable diseases. On the other hand, the South African Society for Clinical Microbiology (SASCM) assembles data from the academic hospital on preferred invasive pathogens secluded from the cerebrospinal fluid samples [171]. Aside from these two groups, extra contributions in the collection of data on antibiotic resistance are given by other groups, including the Sexually Transmitted Infection (STI) Reference Centre in alliance with the National Department of Health, the Enteric Diseases Reference United (EDRU) etc. during surveys. It is worth mentioning that the Gonococcal Antimicrobial Surveillance Programme (GASP) co-ordinated by WHO in Africa was accomplished, owing to the principal role performed by the STI
Reference Centre. The STI Reference Centre has provided training and technical assistance in isolate collection and laboratories in Madagascar, Tanzania, Zimbabwe, and Namibia [158].

Furthermore, in Nigeria, the surveillance system for antibiotic resistance in pulmonary tuberculosis referred to as the National Tuberculosis and Leprosy Control Programme (NTBLCP) is commended by Nasir and co-authors [169] as the only functioning system in which services for drug-resistant TB is provided by four reference laboratories of the country. Also, WHO [172] has introduced the nested PCR equipment in numerous healthcare facilities in Nigeria, therefore, facilitating the molecular-based anti-TB resistance testing regarding rifampicin resistance. Xiao and Li [173] also noted that the Chinese government embarked on a three-year special campaign with the theme “Administrative regulations for the clinical use of antibiotics” to enhance the rational use of antibiotics in 2011. The outcomes of a survey conducted at the tertiary hospitals from 2010 to 2012 involved reductions in antibiotic consumption during prophylaxis in surgical processes (95% to 44.6%), as well as in antibiotic prescriptions to outpatients (22% to 14.7%) and inpatients (68.9% to 54%).

II. Agricultural sector

Antibiotic use for essentially non-medical or non-therapeutic purposes in agricultural settings that are at subtherapeutic levels over an extended period is observed as a major route for the advent of antibiotic resistance and antibiotic-resistant bacteria, and resistance genes have been reported to be transferred to humans [174]. Irrational or non-prudent use of antibiotics in food-producing animals have resulted in antibiotic residues in animal-derived products. Therefore, antimicrobial stewardship is equally implemented to ensure prudent antibiotic use in agriculture, in order to conserve and maintain the effectiveness of available antibiotics, as well as curb the problem of antibiotic resistance and residues in food products derived from animal [175]. Sadly, stewardship interventions in developing countries have often been weakened by the attitude of poorly paid veterinarians who seek supplementary incomes from drug sales, plus the existence of inadequate regulations [25,176]. Summarily, all stakeholders involved in the fight against antibiotic resistance must address it from the standpoint of regulations, surveillance, research, treatment guidelines, infection control, education, and awareness [177]. The National Farmed Animal Health and Welfare Council [178] pointed out that the implementation of antimicrobial stewardship in agriculture can be approached from the following perspectives, including clinical microbiology, infection control (biosecurity), regulations, surveillance on antibiotic use and resistance, animal management, husbandry, and alternatives to antibiotics. A coordinated network of actions from the veterinarians, livestock producers, pharmacists, veterinary pharmaceutical industries, and regulatory authorities are relevant to enforce prudent antibiotic use [179].

Following the Global Action Plan on antimicrobial resistance [28] and the Global principles for the containment of antibiotic resistance in animals intended for food presented by WHO [180], nations are expected to implement measures that are in line with the key actions highlighted for the combat of antimicrobial resistance. Accordingly, Walsh and Wu [181] expressed the interdict on the use of colistin (an antibiotic critical for the treatment of infections caused by highly resistant Gram-negative bacteria in humans) as a feed additive for animals in China. More elaborately, some European countries, including Sweden, Denmark, United Kingdom, Netherlands, etc. introduced bans on the use of antimicrobial growth promoters [36], while Australia and New Zealand implemented a partial ban. Seemingly, in the United States, the restraint on antimicrobial growth promoters is voluntary. In addition, a tripartite alliance involving WHO, World Organisation of Animal Health (OIE), and Food and Agricultural Organisation of the United Nations (FAO) was formed in 2003, which led to the categorization of veterinary medicines into critically important, highly important, and important drugs for human health. This differentiation is to guide their use in animal agriculture across the globe, hence, combating antimicrobial resistance.

Also, some developing countries do not have national limits for antibiotic residues found in animal-derived food, and thus, rely on international maximum residue limits (MRLs). Therefore, in this continuous fight against antibiotic resistance, the joint FAO/WHO expert committee and
Codex Alimentarius Commission updated the MRLs of veterinary drugs in foods of animal origin [79]. Likewise, the Ministry of Health and Family Welfare in India amended the Drugs and Cosmetics regulations, 1945, and set withdrawal limits for drugs used in animal farming. The ministry further emphasized that drug producing companies should equally imprint the withdrawal periods on the containers of drugs meant for animal consumption; however, if not provided, a withdrawal period of not less than 28 days should be considered [182].

It is worth mentioning that the drug delivery system and the priorities and demands of a country vary from one country to another across the world, thereby causing governments to outline regulations or policies or measures according to their local scheme [183]. Mehrotra et al. [184] found that Health Canada has strengthened the veterinary drug regulatory framework in a bid to enhance antibiotic stewardship. These were accomplished via increased control over imported veterinary drugs and active pharmaceutical ingredients (API), a compulsory annual compilation of veterinary antibiotic sales by manufacturers, importers, and compounders. Lastly, it created easy access to low-risk veterinary health products (e.g., vitamins, botanicals, traditional medicines, minerals) which serve as alternatives to antibiotics.

Also, antibiotic prescription and administration to farm animals are supervised by veterinarians, and several behavioral studies have proven that the attitude of farmers to antibiotic use is greatly influenced by the veterinarians. Therefore, interventions geared toward the change of prescribing behaviour of the veterinary could go a long way to optimize antibiotic use by farmers. However, the determinant factors, including a personal opinion regarding the contribution of veterinary medicines in antibiotic resistance, professional ethics to alleviate animal suffering, financial dependence on clients, amongst others, have been noted to influence the prescribing behaviour of the veterinarian [185]. Also, Henton et al. [186] emphasized that the registration of over-the-counter drugs for sales is not optional in South Africa, and the drugs are distributed by the manufacturers to veterinary wholesalers, farmers’ cooperatives, distributors, and feed mix companies.

Also, Lee et al. [187] affirmed that educational programs should be conducted for undergraduate medical and non-medical students in line with generic medicines, mechanism of antibiotic resistance, and prudent use of antibiotics.

Strategies to reduce or limit the therapeutic use of antibiotics in animals via improved animal nutrition, improved living conditions and waste management, biosecurity measures, and improvement in animals’ natural immunity can result in infection prevention and control. These strategies, however, will reduce the level and type of antibiotic needed for treatment, because once the animal is exposed to infection, its immune system can fight seriously against the agent, resulting in less severe manifestations [176]. Moreover, reductions in antibiotic consumption can be achieved by using non-antibiotic alternatives, including prebiotics, probiotics, bacteriocins, vaccines, innate immune system potentiators, bacteriophages, and competitive exclusion cultures for non-specific and specific control of enteric pathogens in animals [188]. Nevertheless, guided interventions, such as vaccination, antihelminthic therapy, optimized herd management, improved biosecurity measures, prudent antibiotic use, performed as teamwork involving the farmers and veterinarians, have led to a marked curtail in antibiotic use, especially the critically important antibiotics, with a decrease of 52% and 32% of the pigs from birth to slaughter and breeding animals, respectively [189].

According to Silbergeld et al. [190], the largest consumption of antibiotics is found in the production of food animals. The documentation of resistant and multidrug-resistant pathogens in food animals poses threats to public health and food security [191]. Also, the findings of the investigation conducted by Chantziaras et al. [192] revealed a strong correlation between the level of specific antibiotics used and the level of resistance in E. coli strains recovered from pigs, cattle, and poultry of seven European countries. Therefore, data collection of antibiotic use is necessary to understand and counteract antibiotic resistance. The monitoring of antibiotic use is crucial in determining the appropriateness of the drugs in use, detect compliance with prudent drug practice, programmes, or regulations [193]. It can equally contribute in the process of optimizing antibiotic use by identifying the most efficient interventions. In addition, monitoring of antibiotic use creates
tolerance in analyzing the temporal trend of antibiotic consumption, and of remarkable interest is the data collected on antibiotic use per animal species. For instance, Schaekel et al. [194] investigated the distribution of antibiotic use per pig age group and active substances (in percentages) used in overall treatment in pig holdings in Germany over a two-year period. The authors found that the types or combination of antibiotics employed varied between the age groups, and the fattening pig experienced a decreasing trend in treatment, but no distinct temporal trend was obtained for the weaners and sucklers. The quantification of antibiotic use in conjunction with data on antibiotic resistance can pave the way for targeted research and development. This is because the data can be used to describe temporal associations between antibiotic use and antibiotic resistance, as well as offer evidence for their links to researchers and policy/decision makers [195].

Surveillance produces reliable data, and it can be approached from various angles; the antibiotic resistance of pathogens or commensal bacteria, antibiotic use in the treatment of diseases and non-therapeutic uses [196]. The surveillance systems for antibiotic consumption are not standardized and differ from one country to the next. These systems may include; DANMAP (Danish Integrated Antimicrobial Monitoring and Resistance programme, Kongens Lyngby, Denmark), MARAN (Monitoring of Antimicrobial Resistance and Antibiotic usage in Animals in Wageningen, The Netherlands), and SANVAD (South African National Veterinary Surveillance and Monitoring Programme for Resistance to Antimicrobial Drugs, Pretoria, South Africa). Systems designed for antibiotic consumption can be automated systems or randomized field studies, as well as nationwide or cross-sectional or longitudinal studies, which focus on analyzing the sample population of farms [194]. On the other hand, the cross-sectional studies can be differentiated into national or regional studies. Overall, these studies are heterogenous, and cannot be compared as they consist of differences, including the duration of data collection (yearly, half a year, or even days), different calculation and reporting methods, along with the stratification in the production systems and farm types [194]. Furthermore, some systems monitor and collect data only at the farm level, making it possible for the implementation of benchmarking approaches, whereby farmers or veterinarians are compared and ranked as stated by their level of antibiotic use. By so doing, measures that are relevant to reduce consumption in the top antibiotic users are introduced or implemented [197].

In addition, Adesokan et al. [198] surveyed the different classes of antimicrobials administered to food animals in South Western Nigeria, and noted that tetracyclines, fluoroquinolones, and followed by beta-lactam/aminoglycosides, were consumed in order of decreasing volume, and mostly in rainy season than dry season. In addition, World Organisation for Animal Health highlighted that 94% of African Countries lack an official surveillance system on the use of antimicrobials in animals [199]. However, though the survey of antimicrobial use in developing countries is inadequate, it demonstrates a high level of farmer prescription, purchase of over-the-counter antibiotics, non-compliance to antibiotic withdrawal periods, and drug counterfeiting [25,167,175].

Surveillance of antibiotic resistance is a vital tool for microbial risk assessment, and the data generated enlighten the understanding of resistance epidemiology, as well as calls for prompt, effective, and early control actions from the government, and also monitor and evaluate the effectiveness of policies implemented by the government [200]. According to Dar et al. [201], and Gelband and Duse [158], only a few national, cross-sectional studies on antibiotic resistance of animal-recovered isolates have been carried out in low- and middle-income countries and South Africa, respectively. However, the surveillance systems differ between countries and/or agencies, due to variation in agricultural practices, monitoring needs, and available guidelines [177]. Furthermore, an integrated surveillance of drug-resistant bacteria obtained from humans, food-producing animals, food and other environmental sites, synchronized with the monitoring system for antibiotic use, can assist in the containment of antibiotic resistance. This is described as the “One Health Approach” intended to attain optimal health for humans, domesticated animals, wildlife, plants, and our environment [29,196]. The first ever integrated animal–human surveillance system was created in Denmark, known as
DANMAP (Danish Integrated Antimicrobial Monitoring and Resistance Programme) which addresses the problem of antibiotic resistance with bacteria of food, animal, and human origin [201].

III. Challenges Faced by Developing Countries Regarding Surveillance Systems

A satisfactory and comprehensive survey is needed to understand the epidemiology of antibiotic resistance in both animals and humans. Even though the global action plan by WHO/OIE/FAO to contain antimicrobial resistance requires each nation or country to implement national action plans, developing countries are still to develop a sustainable surveillance system of antibiotic use and antibiotic resistance [202]. The challenges regarding the surveillance system include:

1. The countries have just a few laboratories with the potential to conduct quality-assured microbiology and drug sensitivity testing. Årdal et al. [203] strongly affirmed that collection and reporting of data and the strengthening of laboratory capacity are the two related issues in surveillance.

2. Due to the high burden of infectious diseases and low socioeconomic status of these countries, there is a lack of available resources [204]. According to Nasir et al. [169], the developing countries lack the funds to purchase reagents and consumables essential for testing antibiotic resistance, thus lack necessary plans for the surveillance of antibiotic-resistant bacteria. The cost necessary for the adequate surveillance, together with the small margin profits in the veterinary sector presents a financial drawback to support surveillance in the veterinary and agricultural sector [166].

3. There is a discrepancy in the selection of isolates. Most of the isolates are from clinical cases that are sick individuals (human or animals). Therefore, the sample of isolates is biased toward a more resistant isolate, owing to the previous antibiotic therapy administered. Also, only a few isolates are involved, since the veterinarian decides on the individual animals to refer to the laboratory. Consequently, the proportion of the isolates is not a representative of the bacteria strains under survey taken from animals [200].

4. Also, relatively few studies have been conducted on animal-recovered isolates, as well as the criteria for testing isolates differ between countries, likewise, the antibiotics that are tested [158,201].

5. Either at the regional, national, and local levels, there exists variation in obtaining data, owing to differences in laboratory protocols, conditions employed for testing, personnel conducting the drug sensitivity assay, antibiotic policies, quality control and assurance of the laboratory, and considerations regarding breakpoints. In reality, there are no well-known breakpoints for the animal, which results in the adoption of breakpoints values from human medicines. Nevertheless, the standard protocols and breakpoints from the Clinical Laboratory Standard Institute (CLSI) have been adopted by most countries [200].

6. These countries also lack stringent and comprehensive policies and plans to circumvent antibiotic resistance. They lack enforcement of regulations regarding prudent antibiotic use, since many are still faced with the problem of purchasing drugs over the counter or without a prescription [161], and the presence of counterfeit drugs [158,196]. Nevertheless, even if some data are collected, they fail to translate the surveillance data into policy, especially in South Africa [9].

7. At the national level, there is a lack of collaborative measures between the different laboratories regarding surveillance of antibiotic resistance, which might hamper efforts to track emerging resistance and also limit the chances of systematic comparison and evaluation of national activities directed toward the containment of antibiotic resistance.

3.1. Antibiotic Resistance in Livestock Farming

According to Woolhouse et al. [205], antibiotic resistance in livestock farming can be looked at from four different viewpoints, i.e., the animals (cattle, pigs, poultry, sheep) and animal-derived products, farm workers, and farm environmental sites (water, soil, feeds, wastewater, sewage, lagoon,
manure, and sludge after treatment). All these constitute the several compartments and different niches in the farm described as an ecosystem [127]. Undoubtedly, farm animals are a very important component in understanding the interplay between humans, animals, and the environment regarding bacteria, antibiotics, and antibiotic resistance gene movement [205]. The digestive tract of animals, like humans (farm workers), is colonized with diverse microorganisms, including commensals and resistant bacteria. Thus, it serves as the most important reservoir of microorganisms. Therefore, it can play a vital role in the dissemination and acquisition of resistant bacteria and their resistance genes [127].

Shobrak and Abo-Amer [206] noted the occurrence of multidrug-resistant *E. coli* and *E. vulneris* in cloacal samples of both migrating and non-migrating birds which served as carriers. Through the release of their fecal residues into water bodies and other environmental sources, it could enable the spread of these resistant bacterial strains and their resistance determinants even to remote areas by means of migration. The anatomical feature of the gut varies between poultry and the other mammalian animals, which in turn influences the intestinal microbiome [207]. The intestinal microbiome changes with age, the type of diet fed, antibiotics ingested, infection with pathogens, amongst other life events [208]. It has been reported that microorganisms in the gut interact extensively with the host, diet, and the intestinal gut microbes, and exert a huge impact on the animal’s immunity and physiology, and ultimately affects the health of the animal and its production [209].

The continuous antibiotic exposure to animals via oral administration creates selective pressure for the development of resistance, and resistant bacteria associated with animals can then enter into the food chain through the consumption of meat (contaminated during slaughter or processing of carcass, if the gut is accidentally cut or intestine empties its contents into the thoracic and abdominal cavities when the carcass of poultry is gutted during processing) or other animal-derived products, through farm runoff water and other means. However, the greater the quantity of antibiotic used, the higher the selective pressure. Van et al. [210] reiterated that food contaminated with antibiotic-resistant bacteria could cause amplification of resistance genes and facilitate the transfer of the antibiotic resistance determinants to other bacteria of clinical importance found in humans, and can be further transferred within humans to more pathogenic bacteria. Therefore, food or animal-derived products, including meat, milk, and eggs, may represent an active and key medium through which antibiotic resistance determinants are continually being transferred between bacteria, and from animals to humans [123]. Bosco et al. [211] clearly documented the multidrug resistance of *Salmonella* isolates recovered from cattle, pigs, chickens, eggs, and animal-derived products, as well as cross-species transmission of plasmids between animal and humans in Uganda.

Also, the farm environment is composed of environmental sites, such as manure, wastewater, soils, effluent, and sewage, which serve as hotspots for antibiotic resistance pollution. More specifically, Bester and Essack [39] indicated that animals are very exposed at a high degree to their environment, making it easier for them to be infected with bacteria harboring problematic genetic material, especially from the soil environment. In the same light, animal urine and feces containing antibiotic residues, antibiotic-resistant bacteria, and resistance genes may be released into manure, and animals might, in turn, be allowed to graze on pasture grown on soil fertilized with this raw manure. This, therefore, creates the likelihood of bringing back these xenobiotics to animals and humans [127].

Nevertheless, manure, which has been described as a hotspot for antibiotic resistance bacteria and antibiotic resistance genes, can serve as a plausible route of transmission of these resistant bacteria and their genes into the soil and water via deliberate or accidental processes [212]. Therefore, it is advised that manure should be treated before land application via biological methods, including anaerobic digestion. However, Resende et al. [213] in their findings noted the prevalence and persistence of potentially pathogenic bacteria which demonstrated multidrug resistance against oxacillin, ampicillin, and levofloxacin, amongst other antibiotics, both in the influent (cattle manure) and effluent (digestate) released from an anaerobic biodigester. The authors suggested that the rate of survival of these bacteria depended on the temperature of the operating process in association with the duration of the fermentation process and the microbial composition. Ostensibly, Maynaud et al. [214] further
confirmed the occurrence of enteric pathogenic bacteria in the digestate obtained from the anaerobic biodigester. The authors emphasized the potential of the viable, but non-cultural state of bacteria, which might cause the regrowth of pathogens during digestate storage, prior to land spreading. Consequently, the need of post treatment of digestate via mechanical, chemical, physical, and biological methods is very vital [215]. In addition, the sanitary risk and microbiological safety of digestate should be evaluated before land application of digestate, in a bid to dodge the ecological, human, animal, and environmental health implications. Nevertheless, it is a call for concern when pathogenic bacteria are present alongside with antibiotic-resistant bacteria in untreated or treated animal manure.

Alternatively, the very common and economic approach to manage manure generated from livestock farming is by application on nearby agricultural fields. However, raw manure can be flushed by heavy rainfall or runoffs from the surface of manure-amended soils into nearby water bodies used by humans for sanitation and domestic purposes [216]. Moreover, due to the constraints on available freshwater resources in developing countries, wastewater serves as a vital source of water and nutrients for irrigation of agricultural fields, in a bid to circumvent the problem of food insecurity in these countries [217]. However, wastewater may infiltrate into groundwater, causing pollution and contamination with toxic chemicals, antibiotics, and organic matter. In addition, owing to the lack of or inefficient wastewater treatment plants, wastewater or improperly treated wastewater is mostly released into surface water bodies that act as reservoirs for domestic and industrial wastes, causing pollution [218].

3.2. Antibiotic Resistance in the Soil Environment

The soil is an ecosystem and a natural resource with unique biodiversity, taking into consideration abundance, quantities of species, and functions of organisms [218,219]. With respect to total biomass, microorganisms are considered as the principal part of the soil community, and are basically responsible for decomposition of organic matter, degradation of toxic compounds, and nutrient transformation [218]. Interestingly, the soil is composed of microorganisms that produce antibiotic by so doing; it can equally serve as a reservoir of antibiotic-resistant bacteria and resistance genes [220,221]. The soil serves as a hub to establish connections between the air, water, rocks, and organisms, and it is involved in many different functions termed ecosystem services in the natural world [222]. Thus, it can be described as quite a large reservoir of antibiotic resistance determinants, since it includes the antibiotic resistance determinants found in all plants, fungi, soil bacteria, small animals, and protists [222]. In addition, Reisenfeld et al. [20] indicated that uncultured soil bacteria are a possible reservoir of antibiotic resistance genes with greater diversity as compared to previous findings, and such diversity can be ascertained and fathomed using culture-independent methods. Furthermore, vegetables grown in unfertilized soil were equally shown to harbour antibiotic-resistant bacteria and resistance determinants that naturally occur in soils [97].

It is somewhat obvious that the abundance and the mobility of antibiotic-resistant bacteria and resistance determinants in the soil can be greatly influenced by the application of manure (containing antibiotic residues, antibiotic-resistant bacteria, and their resistance genes on mobile elements) during fertilization of the soil, the use of wastewater (black or grey water) for the irrigation of agricultural lands, and the use of antibiotics to treat crop diseases [4,223]. More specifically, when soils are treated or amended, antibiotics and their degraded metabolites, as well as antibiotic-resistant bacteria and their corresponding resistance genes, are introduced into the soil environment. Therefore, transfer of antibiotic resistance genes becomes inevitably fast, owing to the rapid growth of bacteria and HGT [224]. However, the persistence and the rate of dissipation of the antibiotic resistance genes is dependent on the VGT/HGT of ARG, the transport and viability of the bacteria harbouring the genes, whether the free DNA obtained from cell lysis will be degraded, adsorbed to soil or organic matter, or acquired by new cells, as well as the transportation of the extracellular ARG [56]. However, the introduction into the soil environment via manure fertilization has been reported to cause an alteration in phylogenetic
structure, amplification in resistance level, and disturbance in ecological function (e.g., nutrient cycling) in the microenvironment [49,212,225].

Also, the degree or extent of the changes impacted on the soil will depend on the type of manure. In details, varying quantities of antibiotics are employed in livestock, and the quantity depends on the species of animals and the kind of farming system. The level of antibiotics found in manure available for a land application depends on manure management practices, which equally vary depending on the size of the herd, the type of livestock and farm operations, as well as the production stage of the animals [56]. According to Chee-Sanford et al. [56], the introduction of antibiotics in the soil may give a selective advantage to commensal bacteria harbouring resistance genes, or may create selective pressure, necessitating the acquisition of resistance genes in the commensal population.

Numerous authors have characterized antibiotic-resistant bacteria and resistance genes from vegetables, including lettuce, cabbage, radish, green corn, onion, carrot, and fluted pumpkins grown on manure fertilized soils and irrigated with wastewater [97,223,226]. Specifically, Bonyadian et al. [227], in a study in Iran, demonstrated the presence of antibiotic-resistant verotoxigenic \(E.\ coli\) on vegetable samples collected randomly from retail shops. However, Kumar et al. [228] indicated that these vegetables absorb antibiotic contained in the manure. Therefore, the direct consumption by humans (uncooked or raw) of vegetables might lead to the transfer of antibiotic-resistant bacteria and their resistance genes, which may cause bacterial infections. Notwithstanding, Beuchat [229] and Johannessen et al. [230] suggested that the contamination of vegetable leaves may arise from diverse sources, such as manure, soil, water (for irrigation and cleaning), the handling equipment for product harvesting and processing, the mode of transportation, in addition to animals at both the pre- and post-harvest process.

3.3. Antibiotic Resistance in the Water Environment

Microorganisms (specifically, bacteria) do not live in isolation [4], but are found in milieu/medium (humans, air, water, plants, and soil) known as their habitat (aquatic ecosystem), which offers them with the appropriate nutritional and growth requirements necessary for survival. Consequently, water represents one of the most important habitats for bacteria on the planet earth, and serves as a main natural route for the dissemination of microorganisms between different environmental compartments and/or aquatic ecosystems, humans, and other animals [231,232]. According to Taylor et al. [233], the aquatic environment is considered as a fundamental setting for environmental release, transformation, mixing, and persistence of antibiotic residues, antibiotic-resistant bacteria, and antibiotic resistance genes. The water (aquatic) environment can be subdivided into marine and fresh water based on salinity, average temperature, depth, and nutrient content [234]. More elaborately, the microbial aquatic environment includes surface and ground waters, drinking water, tap water, and wastewater. These waters have dynamic and distinct bacterial composition patterns influenced by temporal and spatial unevenness in physicochemical and biotic factors, including environmental stresses and nutrient composition [232,235]. Nevertheless, some known waterborne bacteria include \(E.\ coli\), \(Vibrio\), \(Shigella\), and \(Salmonella\) species [236]. The aquatic environment has been reported to be the origin and reservoir of antibiotic-resistant bacteria and resistance genes [231,237].

Microbial communities respond to drastic changes in the ecosystem functioning, species composition and abundance, due to pollution [238,239], resulting in hypoxia, eutrophication, bioaccumulation and dissemination of pathogens [240]. Consequently, the abundance of antibiotic residues and pool of antibiotic-resistant bacteria and their resistance genes in aquatic ecosystems can be influenced or altered or amplified by the discharge of wastewaters from industrial and municipal wastewater treatment plants, runoff from manure-fertilized agricultural land, leakage from septic tanks and broken sewage pipes, and feces from wildlife, into water bodies [97,118,223,241].

Furthermore, the aquatic environments offer ecological and economic benefits [240]. Rivers serve as predominant sources of renewable water for freshwater ecosystems and humans, wherein they perform functions such as in irrigation, and are used as drinking water and for recreation [242]. Water is
indispensable to life. Therefore, humans need clean and safe drinking water to protect their health from waterborne bacterial infections [236]. Water safe for human consumption needs to be free of pathogenic bacteria, although, the existence of pathogenic bacteria in water is intermittent, changeable, and at low levels, coupled with the fact that the isolation and cultivation of pathogenic bacteria from water sources are not straightforward. Therefore, routine microbiological water analysis does not involve the detection of pathogenic bacteria [236]. Interestingly, Enterococci and E. coli have been used in monitoring the fecal contamination of drinking and recreational water [235]. Nevertheless, fecal pollution of water sources is an increasing problem both in the developed and developing countries. In the latter countries, there may be an increase in the occurrence of pathogenic bacteria in river water near large urban populations, due to inept sewage treatment, fast-growing population, low income, and severe water stress. Hence, infection rates tend to be high, with waterborne pathogens [243]. Mulamattathil et al. [243] recovered coliforms and heterotrophic bacteria, as well as antibiotic-resistant Aeromonas and Pseudomonas species from surface and drinking water in Mafikeng, South Africa. The occurrence of these pathogens in drinking water might indicate serious health implications, especially among the immunocompromised individuals [244,245].

(a) Recreational waters and antibiotic resistance

Recreation has a pertinent role in the life of the human population, who always tend to couple the scene with water, be it man-made or natural. It has been reported that antibiotic resistant bacteria can equally be transmitted to humans during recreational use of fresh or marine water, which are natural aquatic habitats [246]. The natural aquatic environment, e.g., the surface waters, such as rivers and sea, serve as a receiving body of runoff water from farmlands fertilized with sewage sludge and animal manure, and wastewater discharged from treatment plants, which contain obvious concentrations of antibiotic resistant bacteria and their resistance determinants, along with biologically active metabolites of antibiotics or the parent compounds [247]. This causes great environmental damage and eutrophication, which might result in serious degradation of the water quality owing to the influx of high nutrients [248]. The quality of recreational water can be evaluated using fecal indicator bacteria, including E. coli and Enterococcus. Restricted to these two bacteria, the prevalence of antibiotic-resistant bacteria in the natural aquatic environment is always underestimated, because all the studies are geared towards measuring antibiotic resistance in the aforementioned culturable bacteria. However, other bacteria are present in the natural habitat, and might harbour antibiotic resistance genes which may equally contribute in the pool of resistance genes found in the habitat, thus, have the potential to disseminate bacterial resistance [249]. This is affirmed by the findings of Lihan et al. [250], who through culture-based methods and DNA fingerprinting unraveled the presence of single and multiple antibiotic-resistant Enterobacter, Serratia, Pantoea, Klebsiella, and Citrobacter in water samples obtained from a recreational river located in a resort community in Malaysia Borneo. Besides, the marine settings are special areas desired for recreational purposes and resting, and as such, are exposed to waste from residences, ships, and industries, as well as coastal areas which are site for highly populated cities, extensive fish farming, and recreational areas [251,252]. The transmission of the resistant bacteria and the resistance genes to humans depends on the type of water sport undertaken, as well as the density of the antibiotic-resistant bacteria in the water [249]. The concentration/magnitude of these resistant bacteria in the recreational waters is determined by the local landscape (e.g., coastal waters), wind speed, ultraviolet radiation, temperature, rainfall, and the source and level of pollution [253]. In a study conducted by Overbey and colleagues [247], higher levels of E. coli and Enterococcus were enumerated in recreational water samples collected from sewage-impacted sites in five beaches in Galápagos Island, Ecuador. In addition, Fernandes Cardoso de Oliveira et al. [254] revealed a higher level of multiple antibiotic resistance in heterotrophic marine bacteria recovered from sea water and sand in Gonzaguinha, the most organic polluted recreational beach, amongst Ilha Porchat and Guaraú beaches located in Southeast Brazil.

Also, Alipour et al. [255] noted the presence of multiple antibiotic-resistant Enterococcus species characterized from the river and coastal water samples in the Northern part of Iran, therefore, these habitats are not suitable for swimming, as they would increase the risk of human exposure
to antibiotic-resistant bacteria and resistance genes. Furthermore, Akanbi et al. [256] demonstrated the multiple antibiotic resistance patterns of *Staphylococcus aureus* isolated from recreational waters and beach sand identified by the occurrence of *mec A*, *fem A*, *rpo B*, *bla Z*, *erm B*, and *tet M* genes, in the Eastern Cape Province of South Africa. The beach water and sand can act as a plausible pool for antibiotic-resistant bacteria and resistance genes, and hence facilitate transmission via the direct ingestion of the seawater and/or direct contact with sea water during recreational activities undertaken in these waters [249]. In recent times, the awareness and involvement of many people in water sports have greatly increased [257], due to an increase in the local population and income earners, as well as tourism.

(b) Drinking water and antibiotic resistance

Most of the population in rural settings and urban settlements rely on untreated groundwater as a source of drinking water, due to the scarcity of fresh surface waters [258]. Untreated groundwater is considered safe for drinking, because it originates from the ground. Therefore, it is described as a natural water habitat protected from human intervention. Apparently, its microbiota reflects the natural population of the habitat [259]. Nevertheless, depending on the location/environment, groundwater becomes vulnerable to contamination with antibiotic residues, antibiotic resistant bacteria, and resistance genes from surface runoff of animal feces deposited on the ground in concentrated animal feeding operations, seepage of liquid/solid manure from storage sites (lagoons), leachate from landfill sites, spillage from broken sewage pipes, and leakage from septic tanks [56,118]. Also, in the North West province of South Africa, a study conducted by Carsten [260] revealed a very poor physicochemical and microbiological quality of water samples obtained from boreholes in the Mooi River and Harts River catchment areas. The authors attributed the results to the fecal contamination of groundwater with fecal bacteria and opportunistic bacteria that displayed different levels of antibiotic resistance.

Surprisingly, Kümmnerer [118] reported that antibacterial agents found in groundwater are of considerable low concentration. In accordance with this, Li et al. [261] mentioned that the microbial concentration in groundwater is closely associated with its depth, season, weather conditions, and the type of adjacent land used in the concentrated animal feeding operations.

Wastewater constitutes “black water and grey water”. It describes all water with adversely affected quality due to influences from human activities [262]. Wastewater embodies water from livestock and poultry farms, aquaculture farms, and municipality that is sometimes released into the environment without treatment or used for irrigation by farmers involved in urban agriculture, since it contains significant amounts of micronutrients and organic matter, and provides water [263,264]. Due to the unavailability of good quality water worldwide, farmers resort to employing wastewater for irrigation, thereby promoting plant growth, water conservation, nutrient recycling, and reductions in inorganic fertilizer applied to the soil, and polluted water being discharged into the surroundings [265,266]. Owing to its numerous sources of water collection, wastewater contains diverse elements, inorganic mineral, antibiotic residues, antibiotic-resistant bacteria and resistance genes, human and animal feces and urine, etc. [267]. The sewage or wastewater treatment plant receives the wastewater, and partially treats or treats it, before discharge of its effluents into the environment. Therefore, the wastewater treatment plant serves as a link between human activities and the environment, and serves as a potential reservoir and release channel of antibiotic-resistant bacteria and resistance genes, giving a perfect opportunity for the transfer of antibiotic resistance genes [14,268,269]. The biological processes at the wastewater treatment plant might cause a reduction in the volume of antibiotics to varying degrees [267]. However, across the different regions of the world utilizing distinct types of wastewater treatment, these plants have been reported to be responsible for the discharge of about one billion cultivable coliform bacteria into the environment, indicating their inefficiency to reduce antibiotic-resistant bacteria and their resistance genes [270]. Clearly, Adefisoye and Okoh [268] demonstrated the occurrence of multidrug-resistant *E. coli* from the final discharged effluents of two wastewater treatment plants situated in the Eastern Cape Province, South Africa.

(c) Waterborne disease outbreaks caused by recreational/drinking waters versus antibiotic resistance
Outbreaks of diseases implicating water as a vehicle of transmission are termed waterborne disease outbreaks, because two or more persons are affected by a similar illness after being exposed to water, and are epidemiologically linked by time and by location of the water [271,272]. Humans become vulnerable to infections when exposed to the beaches when the waters are turbid and experiencing high waves, as well as after heavy rainfall; these cause the waters to be contaminated and unsafe [273]. Depending on the environmental conditions (climactic factors) and the characteristics of the pathogens, the waterborne pathogen grows in the aquatic habitat, however, its number, type, infectivity, and virulence is greatly influenced by the temperature, UV radiation, precipitation patterns, and water availability in the recreational waters [274].

According to Schets et al. [275], the waterborne illnesses in humans associated with the use of untreated or contaminated recreational water mainly comprise of gastroenteritis and skin infections. The authors further revealed that the bathing sites were predisposed to fecal contamination and environmental conditions that favoured the growth of naturally occurring pathogens. Children are viewed to be at a higher risk of gastroenteritis from recreational waters, because they last longer and swallow more water during swimming, as well as they play in shallow water and sand which are most contaminated, and experience a high tendency of hand to mouth exposure [273].

However, waterborne infections associated with exposure to drinking water include acute gastroenteritis, typhoid, diarrhoea, acute respiratory and neurological illness, and skin infections [272,276]. Between 2000 and 2001, South Africa witnessed a surprising and the biggest cholera outbreak in Africa, which involved 114,000 cases across nine provinces and caused 260 deaths, although it originated from KwaZulu Natal province [277]. Equally, Allam et al. [278] reported an outbreak of cholera involving 218 persons, which attacked a greater number of children (aged 5–14 years), males, and individuals greater than or equal to 60 years in Andhra Pradesh, India, and was caused by the contamination of reservoir water with *Vibrio cholerae*. This outbreak claimed three human lives. Even Biswas and colleagues [279] investigated an outbreak of cholera in Haibatpur village, India, caused by pond water contaminated with *Vibrio cholerae*. Ramurmutty and Sharma [280] suggested that the recurrent outbreaks of cholera in India are due to the presence of short-term carriers of *Vibro cholerae* in the communities, the constant change in biotypes and serotypes of this strain, development of resistance to the previous multiple antimicrobial agents used in the treatment of cholera- as well as poor water quality, unhygienic sanitation- and overcrowding.

A shigellosis outbreak among 533 students in a rural elementary school in China was investigated, and findings were linked to the presence of *Shigella flexneri* 2b in untreated well water [281]. A diarrhoea outbreak in China caused by enteropathogenic and enterotoxigenic *E. coli* was noted among 131 individuals exposed to well water contaminated by river water [282]. Between May and August 2010 in Southern Vietnam, Nguyen and co-authors [283] documented an outbreak of diarrhea that infected seventy-one persons through the consumption of iced tea contaminated with *V. cholerae* O1, altered El Tor strains. Also, Ali et al. [284] noted a typhoid fever outbreak that affected 1430 individuals, originating from the consumption of fecally contaminated tap water both in military camps and the general population located in Kikwit, Democratic Republic of Congo, in 2011. In a Croatian study, Kovačić et al. [285] reported an outbreak of gastroenteritis, which affected 68 persons in a County Centre of Šibenik, caused by the pollution of groundwater used for drinking with *Salmonella enterica* subsp. *enterica* serovar *Enteritidis*. Fortunately, the isolates of the bacterium were susceptible to a range of antibiotics.

Furthermore, Farooqui et al. [286] documented an outbreak of typhoid fever caused in Nek Muhammad village, Karachi—Pakistan, which involved over 300 hundred people, and resulted in the deaths of three humans in 2004. The findings in this study associated the outbreak to multidrug-resistant *Salmonella enterica* serovar Typhi ingested through well water that served as the sole source of drinking water in the community, but was unacceptably polluted with dead and decaying bodies of animal, fecal material, and garbage. Similarly, Ma et al. [287] reported the waterborne outbreak of shigellosis in China caused by *Shigella sonnei* with resistance to azithromycin, and third class cephalosporins, due to *mph (A)* and *blaCTX-M-14*-harboring IncB/O/K/Z group transmissible
plasmid. In addition, Akoachere et al. [288] unravelled the persistence of multidrug-resistant toxigenic *Vibrio cholerae* O1 in water samples (taps, dug wells, and streams) collected from New Bell—Doula, and associated these bacteria strains with the 2010–2011 cholera epidemic that recorded the highest number of death cases in the Littoral province of Cameroon.

In a nutshell, in developing countries, antibiotic-resistant bacteria are mostly found in animals, animal-derived food products, and agro-food environments [289]. Consequently, most of the gastrointestinal diseases of humans of public health concern including gastroenteritis, salmonellosis, shigellosis, cholera, listeriosis, campylobacteriosis, and yersiniosis are caused by pathogenic bacteria of public health and environmental importance via water and/or food contaminated with feces of animals or patients [236]. These diseases even become more complicated and severe with the presence of the antibiotic-resistant strains of the causative pathogens harbouring antibiotic resistance genes. As a result, Table 2 compiles information on the notorious environmental pathogens causing gastrointestinal and other diseases in humans/animals through the consumption of fecally-contaminated water and/or food, their resistance to antibiotics typical of human, veterinary and agricultural use, and the implicated antibiotic resistance genes occurring in some countries.
Table 2. Notorious pathogens, antibiotic resistance, and implicated resistance genes from environmental samples in some developing countries.

| Pathogens                  | Antibiotic Resistance | Resistance Genes | Source                              | Diseases Caused/Symptoms                                                                 | Country  | Literature             |
|---------------------------|-----------------------|------------------|-------------------------------------|-----------------------------------------------------------------------------------------|----------|------------------------|
| **Escherichia coli**      | Multidrug resistance  | β-lactam, β-lactam-β-lactamase, aminoglycoside resistance | Drinking water, vegetables, raw eggs, raw chicken, unpasteurized milk, raw meat | Diarrhoea, septicaemia, urinary tract infections, neonatal meningitis, abdominal pain, fever, pneumonia, hemolytic uraemic syndrome, nosocomial bacteraemia | India    | Purohit et al. [290]   |
|                           |                       | β-lactam, β-lactam-β-lactamase, aminoglycoside resistance | Household water supply |                                                                                         | Bangladesh | Talukdah et al. [291] |
|                           |                       | β-lactam, β-lactam-β-lactamase, aminoglycoside resistance | Drinking water |                                                                                         | Saudi Arabia | Shobarak and Abo-Amer [296] |
| **Salmonella enteritidis** | Multidrug resistance  | β-lactam, β-lactam-β-lactamase, aminoglycoside resistance | Chicken and turkey meat | Diarrhoea, septicaemia, urinary tract infections, neonatal meningitis, abdominal pain, fever, pneumonia, hemolytic uraemic syndrome, nosocomial bacteraemia | Tunisia   | Soufi et al. [298]    |
| **Salmonella typhimurium** | Multidrug resistance  | β-lactam, β-lactam-β-lactamase, aminoglycoside resistance | Raw food, soil |                                                                                         | Burkina Faso | Bagné et al. [299] |
|                           |                       | β-lactam, β-lactam-β-lactamase, aminoglycoside resistance | Retail food |                                                                                         | Tanzania   | Lyimo et al. [300]    |
|                           |                       | β-lactam, β-lactam-β-lactamase, aminoglycoside resistance | Effluent from wastewater treatment facilities |                                                                                         | Nigeria    | Adewole et al. [301]  |
|                           |                       | β-lactam, β-lactam-β-lactamase, aminoglycoside resistance | Effluent from wastewater treatment facilities |                                                                                         | Iran      | Bonyadidian et al. [227] |
|                           |                       | β-lactam, β-lactam-β-lactamase, aminoglycoside resistance | Waste, litter, soil and water samples from poultry farms |                                                                                         | China      | Gao et al. [108]      |
|                           |                       | β-lactam, β-lactam-β-lactamase, aminoglycoside resistance | Drinking water |                                                                                         | South Africa | Adefisoye and Okoh [268] |
| **Escherichia coli**      | Multidrug resistance  | β-lactam, β-lactam-β-lactamase, aminoglycoside resistance | Drinking water, vegetables, dry foods | Salmonellosis (diarrheal disease), bacteraemia | Kenya    | Christabel et al. [303] |
| **Shigella sp.**          | Multidrug resistance  | β-lactam, β-lactam-β-lactamase, aminoglycoside resistance | Food | Shigellosis (bacillary dysentery) | Brazil | Oliveira et al. [304] |

**Notes:**
- Source: Drinking water, vegetables, raw eggs, raw chicken, unpasteurized milk, raw meat.
- Diseases Caused/Symptoms: Diarrhoea, septicaemia, urinary tract infections, neonatal meningitis, abdominal pain, fever, pneumonia, hemolytic uraemic syndrome, nosocomial bacteraemia.
Table 2. Cont.

| Pathogens                   | Antibiotic Resistance | Resistance Genes | Source                                      | Diseases Caused/Symptoms                                                                 | Country        | Literature                        |
|-----------------------------|-----------------------|------------------|---------------------------------------------|----------------------------------------------------------------------------------------|----------------|-----------------------------------|
| Staphylococcus aureus       | Multidrug resistance  | mec A, bla Z, tet K | Broiler chicken (ecaucum, feces, retail meat) | Bovine mastitis, endocarditis, osteomyelitis, furunculosis, necrotizing pneumonia, toxin syndromes, gastroenteritis, abscess formation | South Africa  | Mkize et al. [306]                |
|                             |                       | NA               | Milk                                        |                                                                                        | Namibia        | Aleba et al. [307]                |
| Salmonella enterica         | Multidrug resistance  | NA               | Feces of poultry, swine and hedgegode        | Salmonellosis (diarrhoeal disease), bacteraemia                                        | Burkina Faso  | Kagambéga et al. [130]            |
| Salmonella enterica subsp. enterica | Multidrug resistance  | NA               | Food, water, and animal                      |                                                                                        | Sudan          | Elmadiena et al. [308]            |
| Enterococcus faecium        | Multidrug resistance  | Tet M, tet L, erm B | Chicken feces and residual water             | Neonatal meningitis, vancomycin-resistant enterococci (VRE) infections, nosocomial infections | Angola         | Martins et al. [309]              |
| Vibrio species              | Multidrug resistance  | bla R1, dfr A15,aad A2 cassettes | Surface urban water, shell fish             | Diarrhoea, cholera/profuse watery stool (rice water stool)                             | Mozambique     | Taviani et al. [310]              |
| Entereococcus species       | Multidrug resistance  | van A, van C1, van C2 | Meat, fish, vegetables, pasteurized milk, cheese |                                                                                        | Egypt          | Raafat et al. [311]               |
|                             |                       | erm B, tet M-terK, aph(3’)-III, ant(6), van C2, aac(6’)-aph(2’)-2 | Vegetables                                  | Nosocomial infections, neonatal meningitis, urinary and wound infections               | Said et al.    | [312]                             |
|                             |                       | tet M, tet L, erm B, cat gene, aph(3’)-I1a gene, aac(6’)-aph(2’)-I1a | Seafoods                                    |                                                                                        | Said et al.    | [313]                             |
| Staphylococcus sp.          | Multidrug resistance  | NA               | Starch, meat, salad, vegetables              | Skin infections, bovine mastitis, infections associated with prosthetic devices and catheters, gastroenteritis, abscess formation | Botswana       | Loeto et al. [314]                |
|                             |                       | bla Z, tet M     | Milk and traditional cheese and kashk        |                                                                                        | Iran           | Jamal et al. [315]                |
| Campylobacter sp.           | Multidrug resistance  | NA               | Chickens                                     | Campylobacteriosis, post infectious irritable bowel syndrome                            | South Africa   | Bester and Essack [33]            |
| Pseudomonas sp.             | Multidrug resistance  | tet A, Sul 1, bla TEM1, aadA2, aadA1, dfr A15, dfr 1 | Treated and untreated water                  | Infections of the blood, bone, urinary tract, central nervous system, and wounds endocarditis, pneumonia (nosocomial infections) | Nigeria        | Adestoi et al. [316]              |
|                             |                       | NA               | Abattoir environment                         |                                                                                        |                | Ighinosa and Obuekwe [317]        |
| P. aeruginosa               | Multidrug resistance  | pse-1, tet A, ant(3’)-I1a, tet B | Meat, meat product                           |                                                                                        | Uganda         | Bosco et al. [211]                |
|                             |                       | NA               | Broiler’s chicken (South Africa)             |                                                                                        | Namibia        | Zishiri et al. [318]              |
|                             |                       | pse-1, tet A, ant(3’)I1a, tet B | Broiler’s chicken (Brazil)                   |                                                                                        | Ethiopia       | Ejo et al. [104]                  |
|                             |                       | NA               | Raw meat, minced meat, burger samples, raw eggs, raw milk | Salmonellosis (diarrhoeal disease), bacteraemia                                       | Thailand & Laos| Sirwat et al. [319]              |
|                             |                       | dfrA12-aadA2, aadA2-his G, qnr S | Pigs, retail pork                            |                                                                                        | Senegal        | Bada-Alamebdji et al. [320]       |
|                             |                       | NA               | Raw chicken                                  |                                                                                        | Namibia        | Shilangale [321]                  |
|                             |                       | NA               | Beef                                        |                                                                                        | Benin Republic | Siria et al. [322]                |
| Salmonella sp.              | Multidrug resistance  | NA               | Street foods including macaroni, salad, bean cooked in sauce, rice in sauce | As indicated above                                                               |                |                                   |
| Staphylococcus aureus       | Multidrug resistance  | NA               | Street foods including macaroni, salad, bean cooked in sauce, rice in sauce | As indicated above                                                               |                |                                   |
Table 2. Cont.

| Pathogens                  | Antibiotic Resistance | Resistance Genes | Source                                         | Diseases Caused/Symptoms                                           | Country            | Literature                |
|---------------------------|-----------------------|------------------|------------------------------------------------|-------------------------------------------------------------------|--------------------|---------------------------|
| *Escherichia coli*        | Multidrug resistance  | NA               | Turkey meat                                    | As indicated above                                                | Morocco            | Abdellah et al. [323]     |
| *Staphylococcus aureus*   | Multidrug resistance  | NA               | Surface water, wastewater effluent            | Gastroenteritis and wound infections                              | South Africa       | Olaniran et al. [324]     |
| *Listeria sp.*            | Multidrug resistance  | NA               | Surface water, drinking water                 | As indicated above                                                | As indicated above | Mulamattathil et al. [243]|
| *Aeromonas sp.*           | Multidrug resistance  | NA               | Surface water, wastewater effluent            | As indicated above                                                | As indicated above | Mulamattathil et al. [243]|
| *Salmonella typhimurium*  | Multidrug resistance  | NA               | Animal feces, eggs                            | Salmonellosis(diarrheal disease), bacteraemia                     | Kenya              | Nyabundi et al. [325]     |
| *Salmonella enteritidis*  | Multidrug resistance  | NA               | Hospital effluent, wastewater, urban rivers   | As indicated above                                                | Democratic Republic of Congo | Laffite et al. [326]      |
| *Escherichia coli*        | Multidrug resistance  | bla*TEM*,aadA, bla*CTX-M, bla*SHV | Hospital effluent, wastewater, urban rivers | As indicated above                                                | Democratic Republic of Congo | Laffite et al. [326]      |
| *Enterococcus sp.*        | Multidrug resistance  | NA               | Oluwa river                                    | Meningitis, anthrax, pneumonia, food poisoning                    | Nigeria            | Ayandiran et al. [327]    |
| *Pseudomonas sp.*         | Multidrug resistance  | NA               | Drinking water                                 | As indicated above                                                | Intrabdominal tract infections, septic arthritis, ophthalmic infections, bacteraemia, UTI | Nigeria            | Ayandiran et al. [327]    |
| *Klebsiella oxytoca*      | Multidrug resistance  | NA               | Surface water                                  | Septic shock, urinary tract infection                            | Mexico             | Delgado-Gardéa et al. [328]|
| *Escherichia coli*        | Multidrug resistance  | NA               | Surface water                                  | As indicated above                                                | Intra-abdominal tract infections, septic arthritis, ophthalmic infections, bacteraemia, UTI | Mexico             | Delgado-Gardéa et al. [328]|
| *Citrobacter freundii*    | Multidrug resistance  | dfd A1, dfd A5, dfd A7, dfd A12, dfd A15, dfd A17, dfd A25, aad A1, aad A2, aad A5, aad A7, aad A12, and A22, aac(3)-Id, cml A, re A2, aap, IM*TEM*, IM*SHV, IM*CTX-M, IM*SHV, flo R, qnr S, aac(6)-Id-cr | Milk               | Bovine mastitis, pulmonary pneumonia, septicaemia, wound infections, septic arthritis, ophthalmic infections, bacteraemia, hepatic, pancreatic and biliary disease, nosocomial infections (UTI, wounds, blood and lower respiratory tract infections) | Egypt              | Ahmed and Shimamoto [329] |
| *Providencia rettgeri*    | Multidrug resistance  | NA               | Drinking water                                  | Variety of nosocomial infections                                 | As indicated above | Uganda                    | Soge et al. [330]          |
| *Escherichia coli*        | Multidrug resistance  | bla*TEM*, int A, mnf A, erm B, Sav 1, int 1 | Drinking water                                  | Neonatal sepsis, arthritis, UTI                                  | Uganda             | Soge et al. [330]          |
| *Klebsiella sp.*          | Multidrug resistance  | NA               | Drinking water                                  | UTI and formation of stones                                      | As indicated above | Uganda                    | Soge et al. [330]          |
| *Proteus spp.*            | Multidrug resistance  | NA               | Drinking water                                  | UTI and formation of stones                                      | As indicated above | Uganda                    | Soge et al. [330]          |
| *Providencia rettgeri*    | Multidrug resistance  | NA               | Drinking water                                  | Cystitis, complicated UTI                                        | As indicated above | Uganda                    | Soge et al. [330]          |
| *Pseudomonas sp.*         | Multidrug resistance  | NA               | Drinking water                                  | Not involved in any invasive disease                              | As indicated above | Uganda                    | Soge et al. [330]          |
| *Salmonella sp.*          | Multidrug resistance  | NA               | Drinking water                                  | Not involved in any invasive disease                              | As indicated above | Uganda                    | Soge et al. [330]          |
| *Serratia odorifera*      | Multidrug resistance  | NA               | Drinking water                                  | Not involved in any invasive disease                              | As indicated above | Uganda                    | Soge et al. [330]          |
The data in the tables represent the findings obtained from several studies conducted by different researchers across the world in their quest to determine antibiotic resistance genes in environmental sources, in a bid to strategically fight against the problem of rising antibiotic resistance. These findings were retrieved from published articles found in Science Direct, Pubmed, Medline databases, etc., using Google search engine. The search was done in a systematic way, and the search query term was modified using related terms to maximize accuracy. It can be depicted from Table 2, that antibiotic resistance is a global challenge, and needs to be addressed by the joint efforts from all the countries across the world, as we can never stop international travel and trade. Second, antibiotic resistant bacteria and resistance genes do not originate only from humans relating to clinical settings, but they are available and prevalent in the environment, food, and water that we consume. In addition, the table emphasises the presence of multidrug resistance in the respective countries, which is an uglier scenario, as the antibiotic resistance genes can be disseminated via food, water, and other environmental sources to clinical pathogens, thereby causing health threats to the public (especially the immunocompromised individuals who depend on antibiotics to boost their immune system). Consequently, owing to the high infectious disease burden in developing countries, alongside the poor sanitation and hygienic conditions, data in the tables create more awareness in the population about environmental antibiotic resistance, such that intervention measures be reinforced, to ensure prudent use of antibiotics, in a bid to contain antibiotic resistance. Furthermore, there is a clear need for continuous surveillance to monitor antibiotic resistance.

4. Conclusions

Antibiotics, naturally or semi-synthetically or synthetically produced substances, are very vital in the agricultural, veterinary, and clinical settings. These substances are endowed with bacteriostatic (inhibitory) or bactericidal activities necessary for prophylactic and therapeutic purposes in the lives of humans and animals, to prevent and treat diseases. Regardless of these beneficial roles, associated with antibiotics use are also hostile effects, in addition to their implementation at a sub-therapeutic level as growth promoters in feed and water consumed by livestock over an extended period. These may lead to antibiotic pollution, resulting in antibiotic residues in animal-derived products, including meat, milk, eggs, and edible tissues, and when consumed by humans, can cause direct toxicity, the development and emergence of antibiotic-resistant strains of bacteria, as well as therapeutic failure in clinical cases [136].

Of great concern are the food/waterborne pathogens responsible for life-threatening and difficult-to-treat gastrointestinal infections in humans, thus, of great concern to public healthcare systems worldwide. Nevertheless, following the chronicles of multidrug resistance of these pathogens in the developing countries, we hereby conclude that continuous surveillance of the antibiotic resistance profiles of bacterial pathogens (obtained from humans, animals, food, and other environmental sites) of public and environmental significance be implemented because of the high burden of infectious diseases. Also, patients harboring antibiotic-resistant infections might be unable to secure or afford effective second and third line antibiotic treatments. The situation is further compounded in these regions due to pollution of available water sources, poor hygienic measures, civil conflicts, increased population of immunocompromised individuals, lack of adequate laboratory infrastructures and personnel for the diagnosis of the disease-causing agents and surveillance of their antibiogram patterns, added to the deficiency in knowledge on prudent antibiotic use and antibiotic resistance [331].

5. Recommendations on Ways to Reduce the Overall Level of Antibiotic Resistance in Agricultural Settings

The unscrupulous use of antibiotics in farm animals has further compounded the problems of antibiotic resistance. Taking this into consideration, implementing measures that will help to reduce the abuse of antibiotics in livestock farming will, therefore, go a long way to further affect the level of antibiotic resistance. This is because there is an interrelationship between the
environment and animals, which ultimately influences public health (humans). Altogether, the following recommendations are set forth; following the chronicles of the information studied, there is a general weakness among farmers regarding the lack of knowledge on antibiotic use and storage, its abuse, and consequent hazards to public health and the environment [32]. Accordingly, a sensitization campaign is inevitable to educate both the farmers and the general population on the dangers of the imprudent use of antibiotics, improper storage of antibiotics, and the resulting antibiotic resistance, with its consequences on public health. Also, veterinary activities and therapy are mostly assumed and performed by owners in industrial and semi-industrial production systems, regardless of whether they are qualified or trained [43]. Sekyere [41] equally highlighted that the veterinarian services are lacking due to the locations of the farms and/or the veterinarians are limited in number and their facilities. Notwithstanding, livestock farming contributes to the economy of the country, therefore, at this juncture, we hereby propose that the government and well renowned and financially viable private companies that are interested in the economic development of the country should encourage the employment of regular, proper, and efficient veterinarian services via subsidies to farmers, especially to lower-income farmers in the rural and remote settings of the country.

Furthermore, the indiscriminate use of antibiotics (that is, without prescription, supervision, and guidance from veterinarians) in animal farming should be avoided. Veterinary officers and pharmacists should adhere strictly to the policies governing prescriptions of antibiotics used in animal farming. They should equally ensure (via sensitization and consultation) that the farmers adhere to the dosage, length, and administration of treatment and withdrawal periods of antibiotics prescribed for a purpose, as well as the causative agent of the disease be diagnosed and antibiotic susceptibility testing conducted against the disease causative agent prior to prescription and employment of the antibiotics [41,43]. Moreover, routine surveillance and detailed analysis of antibiotic residues present in foods of animal origin should be conducted before being dispatched or delivered for human consumption. Owing to the variations in antibiotic consumption patterns and differences in animal production systems between countries [12,43], we therefore advise that based on the country, stringent control and/or regulations should be implemented by policy makers to enforce the legitimate purchase and employment of antibiotics in animal farming.

Nonetheless, farmers should be educated on the need of good and proper hygienic/sanitation conditions and facilities which nurture healthy living in the animals and preclude the opportunities for the emergence of disease conditions and infections, thus evading therapeutic antibiotic regimens. Ultimately, the use of antibiotics in food-producing animals should be limited by incorporating possible alternative substances, including probiotics, prebiotics, and plant-derived or crude plant extracts for the treatment and prevention of diseases [9,25]. Consequently, persistent and extensive surveillance should be conducted by the government in collaboration with the public health authorities to monitor antibiotic consumption in animal farming, in addition to the antibiotic resistance profiles of notorious foodborne pathogens to well-known drugs used in animal farming. Furthermore, the government and public health sector should make available, services for research and analysis of data obtained via the surveillance studies in order to track the drug and its residue level in most environmental samples.

Acknowledgments: We are grateful to National Research Foundation (Grant No. 98031), the South Africa Medical Research Council, the Department of Science and Technology, South Africa, and the University of Fort Hare for financial support (C114 & C702).

Author Contributions: C.M.-L. conceptualised and designed the study as well as drafted the manuscript making sure that relevant and concise information were not excluded; S.M., E.M. and A.O. proof read and approved the final version of the manuscript for submission and subsequent publication.

Conflicts of Interest: The authors declare no conflict of interest.
References

1. Milić, N.; Milanovic, M.; Letić, N.G.; Sekulić, M.T.; Radonić, J.; Mihajlović, I.; Miloradov, V. Occurrence of antibiotics as emerging contaminant substances in the aquatic environment. *Int. J. Environ. Health Res.* 2013, 23, 296–310. [CrossRef] [PubMed]

2. Martínez, J.L. Natural antibiotic resistance and contamination by antibiotic resistance determinants: The two ages in the evolution of resistance to antimicrobials. *Front. Microbiol.* 2012, 3. [CrossRef] [PubMed]

3. Gillings, M.R. Evolutionary consequences of antibiotic use for the resistome, mobilome, and microbial pangenome. *Front. Microbiol.* 2013, 4. [CrossRef] [PubMed]

4. Finley, R.L.; Collignon, P.; Joakim Larsson, D.G.; McEwen, S.A.; Xian-Zhi, L.; Gaze, W.H.; Reid-Smith, R.; Timinouni, M.; Graham, D.W.; Topp, E. The Scourge of Antibiotic Resistance: The Important Role of the Environment. *Clin. Infect. Dis.* 2013, 57, 704–710. [CrossRef] [PubMed]

5. Abou-Rayaa, S.H.; Shalaby, A.R.; Salama, N.A.; Emam, W.H.; Mehaya, F.M. Effects of ordinary cooking procedures on tetracycline residues in chicken meat. *J. Food Drug Anal.* 2013, 21, 80–86.

6. De Brierio, N.; Atkinson, J.; Borriello, S.P.; Pokludova, L. Antibiotics used most commonly to treat animals in Europe. *Vet. Rec.* 2014, 175, 325. [CrossRef] [PubMed]

7. Baynes, R.E.; Dedonder, K.; Kissell, L.; Mzyk, D.; Marmulak, T.; Smith, G.; Tell, L.; Gehring, R.; Davis, J.; Riviere, J.E. Health concerns and management of select veterinary drug residues. *Food Chem. Toxicol.* 2016, 88, 112–122. [CrossRef] [PubMed]

8. Gelband, H.; Miller-Petrie, M.; Pant, S.; Gandra, G.; Levinson, J.; Barter, D.; White, W.; Laxminarayan, R. *The State of the World’s Antibiotics, 2015*; Centre for Disease Dynamics, Economics and Policy: Washington, DC, USA, 2015.

9. Moyane, J.N.; Jideani, A.I.O.; Aiyegoro, O.A. Antibiotics usage in food-producing animals in South Africa and impact on human: Antibiotic resistance. *Afr. J. Microbiol. Res.* 2013, 7, 2990–2997.

10. Adebowale, O.O.; Adeyemo, O.K.; Awoyomi, O.; Dada, R.; Adebowale, O. Antibiotic use and practices in commercial poultry laying hens in Ogun State Nigeria. *Rev. Elev. Med. Vet. Pays Trop.* 2016, 69, 41–45. [CrossRef]

11. Ayukekong, J.A.; Ntemgwa, M.; Atabe, A.N. The threat of antimicrobial resistance in developing countries: Causes and control strategies. *Antimicrob. Resist. Infect. Control* 2017, 6, 47. [CrossRef] [PubMed]

12. Van Boeckel, T.P.; Brower, C.; Gilbert, M.; Grenfell, B.T.; Levin, S.A.; Robinson, T.P.; Teillant, A.; Laxminarayan, R. Global trends in antimicrobial use in food animals. *Proc. Natl. Acad. Sci. USA* 2015, 112, 5649–5654. [CrossRef] [PubMed]

13. Williams-Nguyen, J.; Sallach, J.B.; Bartelt-Hunt, S.; Boxall, A.B.; Durso, L.M.; McLain, J.E.; Singer, R.S.; Snow, D.D.; Zilles, J.L. Antibiotics and Antibiotic Resistance in Agroecosystems: State of the Science. *J. Environ. Qual.* 2016, 45, 394–406. [CrossRef] [PubMed]

14. Zhang, Y.; Marrs, C.F.; Simon, C.; Xi, C. Wastewater treatment contributes to selective increase in antibiotic resistance among *Acinetobacter* spp. *Sci. Total Environ.* 2009, 407, 3702–3706. [CrossRef] [PubMed]

15. Benbachir, M.; Benredjeb, S.; Boye, C.S.; Dosso, M.; Belabbes, H.; Kamoun, A.; Kair, O.; Elmdaghri, N. Two-year surveillance of antibiotic resistance in *Streptococcus pneumoniae* in four African cities. *Antimicrob. Agents Chemother.* 2001, 45, 627–629. [CrossRef] [PubMed]

16. Sahoo, K.C.; Tamhankar, A.J.; Sahoo, S.; Sahu, P.S.; Klintz, S.R.; Lindborg, C.S. Geographical Variation in Antibiotic-Resistant *Escherichia coli* Isolates from Stool, Cow-Dung and Drinking Water. *Int. J. Environ. Res. Public Health* 2012, 9, 746–759. [CrossRef] [PubMed]

17. Zhang, Y.; Marrs, C.F.; Ye, W.; Simon, C.; Foxman, B.; Nriagu, J. Prevalence of Antibiotic Resistance in Drinking Water Treatment and Distribution Systems. *Appl. Environ. Microbiol.* 2009, 75, 5714–5718. [CrossRef] [PubMed]

18. Samie, A.; Guerrant, R.L.; Barrett, L.; Bessong, P.O.; Igumbar, E.O.; Obi, C.I. Prevalence of intestinal parasitic and bacterial pathogens in diarrhoeal and non-diarrhoeal human stools from Vhembe district, South Africa. *J. Health Popul. Nutr.* 2012, 27, 739–745. [CrossRef]

19. Riesenfeld, C.S.; Goodman, R.M.; Handelsman, J. Uncultured soil bacteria are a reservoir of new antibiotic resistance genes. *Environ. Microbiol.* 2004, 6, 981–989. [CrossRef] [PubMed]
21. Xiao, K.-Q.; Li, B.; Ma, L.; Bao, P.; Zhou, X.; Zhang, T.; Zhu, Y.-G. Metagenomic profiles of antibiotic resistance genes in paddy soils from South China. *FEMS Microbiol. Ecol.* 2016, 92, fiw023. [CrossRef] [PubMed]

22. You, Y.; Silbergeld, E.K. Learning from agriculture: Understanding low-dose antimicrobials as drivers of resistome expansion. *Front Microbiol.* 2014, 5, 284. [PubMed]

23. Alhendi, A.B.; Homeida, A.-A.M.; Gaili, E.S. Drug residues in broiler chickens fed with antibiotics in ration. *Vet. Arhiv* 2000, 70, 199–205.

24. Billah, M.D.M.; Rana, S.M.M.; Hossain, M.S.; Ahamed, S.K.; Banik, S.; Hasan, M. Ciprofloxacin residue and their impact on biomolecules in eggs of laying hens following oral administration. *Int. J. Food Contam.* 2015, 2, 13. [CrossRef]

25. Guetiya-Wadoum, R.E.; Zambou, N.F.; Anyangwe, F.F.; Njimou, J.R.; Coman, M.M.; Verdenelli, M.C.; Cecchini, C.; Silvi, S.; Orpianesi, C.; Cresci, A.; et al. Abusive use of antibiotics in poultry farming in Cameroon and the public health implications. *Br. Poult. Sci.* 2016, 57, 485–493. [CrossRef] [PubMed]

26. World Health Organization (WHO). *The Evolving Threat of Antimicrobial Resistance: Options for Action; World Health Organization: Geneva, Switzerland*, 2012; ISBN 978 92 4 150976 3.

27. Bhusan, C.; Khurana, A.; Sinha, R.; Nagaraju, M. *Antibiotic Resistance in Poultry Environment: Spread of Resistance from Poultry Farm to Agricultural Field; Centre for Science and Environment*: New Delhi, India, 2017.

28. World Health Organisation. *Global Action Plan on Antimicrobial Resistance; World Health Organization: Geneva, Switzerland*, 2015; ISBN 978 924 150976 3.

29. Queenan, K.; Häsler, B.; Rushton, J. A One Health approach to antimicrobial resistance surveillance: Is there a business case for it? *Int. J. Antimicrob. Agents* 2016, 48, 422–427. [CrossRef] [PubMed]

30. Hong, P.-Y.; Al-Jassim, N.; Ansari, M.I.; Mackie, R.I. Environmental and public health implications of water reuse: Antibiotics, antibiotic resistant bacteria and antibiotic resistance genes. *Antibiotics* 2013, 2, 367–399. [CrossRef] [PubMed]

31. Hao, H.; Cheng, G.; Iqbal, Z.; Ai, X.; Hussain, H.I.; Huang, L.; Dai, M.; Wang, Y.; Liu, Z.; Yuan, Z. Benefits and risks of antimicrobial use in food-producing animals. *Front. Microbiol.* 2014, 5, 288. [CrossRef] [PubMed]

32. Saiful Islam, K.B.M.; Shiraj-Um-Mahmuda, S.; Hazzaz-Bin-Kabir, M. Antibiotic usage patterns in selected poultry production systems in KwaZulu-Natal, South Africa. *J. Food Prot.* 2012, 75, 154–159. [CrossRef] [PubMed]

33. Bester, L.A.; Essack, S.Y. Observational study of the prevalence and antibiotic resistance of *Campylobacter spp.* From different poultry production systems in KwaZulu-Natal, South Africa. *J. Food Prot.* 2012, 75, 154–159. [CrossRef] [PubMed]

34. Kaplan, J.; Bowman, M.; Cordova, C.; Kar, A. Pharming Chickens: It’s Time for the US Poultry Industry to Demonstrate Antibiotic Stewardship; Natural Resources Defence Council: New York, NY, USA, 2014.

35. Cogliani, C.; Goosens, H.; Greko, C. Restricting antimicrobial use in food animals: Lessons from Europe. *Microbe* 2011, 6, 274–279. [CrossRef]

36. Braykov, N.P.; Eisenberg, J.N.S.; Grossman, M.; Zhang, L.; Vasco, K.; Cevallos, W.; Muñoz, D.; Acevedo, A.; Moser, K.A.; Marrs, C.F.; et al. Antibiotic resistance in animal and environmental samples associated with small-scale poultry farming in Northwestern Ecuador. *mSphere* 2016, 1, e00021-15. [CrossRef] [PubMed]

37. Apata, D.F. Antibiotic resistance in poultry. *Int. J. Poult. Sci.* 2009, 8, 404–408. [CrossRef]

38. Founou, L.L.; Essack, S.Y. Antibiotic resistance via the food chain: Fact or fiction? *S. Afr. J. Sci.* 2010, 106, 1–5. [CrossRef]

39. Singer, A.C.; Shaw, H.; Rhodes, V.; Hart, A. Review of antimicrobial resistance in the environment and its relevance to environmental regulators. *Front. Microbiol.* 2016, 7, 1728. [CrossRef] [PubMed]

40. Sekyere, J.O. Antibiotic types and handling practices in disease management among pig farms in Ashanti region, Ghana. *J. Vet. Med. 2014, 2014, 531952. [CrossRef] [PubMed]

41. Cromwell, G.L. Why and how antibiotics are used in swine production. *Anim. Biotechnol.* 2002, 13, 7–27. [CrossRef] [PubMed]

42. Kim, D.P.; Rman, C.S.; Douny, C.; Dinh, T.V.; Xuan, B.H.; Vu, B.D.; Hong, N.P.; Scippo, M.L. First survey on the use of antibiotics in pig and poultry production in the Red river Delta region of Vietnam. *Food Public Health* 2013, 3, 247–256.

43. Bashahun, D.G.M.; Odoch, T.A. Assessment of antibiotic usage in intensive poultry farms in Wakiso District, Uganda. *Livest. Res. Rural Dev.* 2015, 27, 247.
45. Porphyre, V.; Nguyen, N.S.; Ha, M.T.; Geneve, S.; Henry, C. Local epidemiosurveillance in swine diseases in Northern Vietnam: Description and preliminary results. *Ann. N. Y. Acad. Sci.* 2006, 1081, 528–530. [CrossRef] [PubMed]

46. Kim, J.; Kang, C.-I.; Joo, E.-J.; Ha, Y.E.; Cho, S.Y.; Gwak, G.-Y.; Chung, D.R.; Peck, K.R.; Song, J.H. Risk factors of community-onset spontaneous bacterial peritonitis caused by fluoroquinolone-resistant Escherichia coli in patients with cirrhosis. *Liver Int.* 2014, 34, 695–699. [CrossRef] [PubMed]

47. Wongtavatchai, J.; McLean, I.G.; Ramos, F.; Arnold, D. *WHO Food Additives Series 53: Chloramphenicol* JECFA (WHO: Joint FAO/WHO Expert Committee on Food Additives), IPCS (International Programme on Chemical Safety), INCHEM; WHO: Geneva, Switzerland, 2004; pp. 7–85.

48. Berendsen, B.; Stolker, L.; De Jong, J.; Nielsen, M.; Tserendorj, J.E.; Sodnomdarjaa, R.; Elliot, T.C. Evidence of natural occurrence of banned antibiotic chloramphenicol in herds and grass. *Anal. Bioanal. Chem.* 2010, 397, 1955–1963. [CrossRef] [PubMed]

49. Martínez, J.L. Environmental pollution by antibiotics and by antibiotic resistance determinants. *Environ. Pollut.* 2009, 157, 2893–2902. [CrossRef] [PubMed]

50. Eagar, H.; Swan, G.; van Vuuren, M. A survey of antimicrobials usage in animals in South Africa with specific reference to food animals. *J. S. Afr. Vet. Assoc.* 2012, 83, 16. [CrossRef] [PubMed]

51. Zhao, L.; Dong, Y.H.; Wang, H. Occurrence and fate of antibiotics in manures from feedlot livestock in eight provinces of China. *Sci. Total Environ.* 2010, 408, 1069–1075. [CrossRef] [PubMed]

52. Dolliver, H.; Gupta, S. Antibiotic losses in leaching and surface runoff from manure-amended agricultural land. *J. Environ. Qual.* 2008, 37, 1227–1237. [CrossRef] [PubMed]

53. Du, L.; Liu, W. Occurrence, fate, and ecotoxicity of antibiotics in agro-ecosystems. A review. *Agron. Sustain. Dev.* 2002, 32, 309–327. [CrossRef] [PubMed]

54. Spiels, M.; Goyal, S. *Best Management Practices for Pathogen Control in Manure Management Systems*; University of Minnesota: Minneapolis, MN, USA, 2007; Available online: http://www.extension.umn.edu/agriculture/manure-management-and-air-quality/manure-pathogens/best-management-practices/ (accessed on 27 August 2017).

55. Hamscher, G.; Pawelzick, H.T.; Szcesny, S.; Nau, H.; Hartung, J. Antibiotics in dust originating from as pig-fattening farm: A new source of health hazard for farmers. *Environ. Health Perspect.* 2009, 117, 1590–1594. [CrossRef] [PubMed]

56. Chee-Sanford, J.C.; Mackie, R.I.; Koike, S.; Krapac, I.G.; Lin, Y.-F.; Yannarell, A.C.; Maxwell, S.; Aminov, R.I. Fate and transport of antibiotic residues and antibiotic resistance genes following land application of manure waste. *J. Environ. Qual.* 2009, 38, 1086–1108. [CrossRef] [PubMed]

57. Van den Bogaard, A.E.; London, N.; Driessen, C.; Stobberingh, E.E. Antibiotic resistance of faecal *Escherichia coli* in poultry, poultry framers and poultry slaughterers. *J. Antimicrob. Chemother.* 2001, 47, 763–771. [CrossRef] [PubMed]

58. Criswell, D. *The Evolution of Antibiotic Resistance*; Institute for Creation Research: Dallas, TX, USA, 2004.

59. Li, D.; Yu, T.; Zhang, Y.; Yang, M.; Li, Z.; Liu, M.; Qi, R. Antibiotic resistance characteristics of environmental bacteria from an oxytetracycline production wastewater treatment plant and the receiving river. *J. Environ. Qual.* 2010, 39, 3444. [CrossRef] [PubMed]

60. Sahoo, K.C.; Tamhankar, A.J.; Johansson, E.; Lundborg, C.S. Antibiotic use, resistance development and environmental factors: A qualitative study among healthcare professionals in Orissa, India. *BMC Public Health* 2010, 10, 629. [CrossRef] [PubMed]

61. Li, X.; Shi, H.; Li, K.; Zhang, L.; Gan, Y. Occurrence and fate of antibiotics in advanced wastewater treatment facilities and receiving rivers in Beijing, China. *Front. Environ. Sci. Eng.* 2014, 8, 888–894. [CrossRef]

62. Liu, C.-H.; Chuang, Y.-H.; Li, H.; Teppen, B.J.; Boyd, S.A.; Gonzalez, J.M.; Johnson, C.T.; Lehmann, J.; Zhang, W. Sorption of lincomycin by manure-derived biochars from water. *J. Environ. Qual.* 2016, 45, 519–527. [CrossRef] [PubMed]

63. Homem, V.; Santos, L. Degradation and removal methods of antibiotics from aqueous matrices: A review. *J. Environ. Manag.* 2011, 92, 2304–2347. [CrossRef] [PubMed]

64. Bao, Y.; Zhou, Q.X.; Guan, L.; Wang, Y. Depletion of chlortetracycline during composting of aged and spiked manures. *Water Manag.* 2009, 29, 1416–1423. [CrossRef] [PubMed]

65. Dever, L.A.; Dermody, T.S. Mechanisms of bacteria resistance to antibiotics. *Arch. Intern. Med.* 1991, 151, 886–895. [CrossRef] [PubMed]
66. Lambert, P.A. Bacterial resistance to antibiotics: Modified target sites. *Adv. Drug Deliv. Rev.* 2005, 57, 1471–1485. [CrossRef] [PubMed]

67. Munita, J.M.; Arias, C.A. Mechanisms of Antibiotic Resistance. *Microbiol. Spectr.* 2016, 4. [CrossRef]

68. Soto, S.M. Role of efflux pumps in the antibiotic resistance of bacteria embedded in a biofilm. *Virulence* 2013, 4, 223–229. [CrossRef] [PubMed]

69. Blanco, P.; Hernando-Amado, S.; Reales-Calderon, J.A.; Corona, F.; Lira, F.; Alcalde-Rico, M.; Bernardini, A.; Sanchez, M.B.; Martinez, J.L. Bacterial Multidrug Efflux Pumps: Much More Than Antibiotic Resistance Determinants. *Microorganisms* 2016, 4, 14. [CrossRef] [PubMed]

70. Schjørring, S.; Krogfelt, K.A. Assessment of Bacterial Antibiotic Resistance Transfer in the Gut. *Int. J. Microbiol.* 2011, 2011, 312956. [CrossRef] [PubMed]

71. Muyanja, C.; Naviga, L.; Brenda, N.; Nasinyama, G. Practices, knowledge and risk factors of street food vendors in Uganda. *Food Control* 2011, 22, 1551–1558. [CrossRef]

72. Mahangaiko, M.; Mabi, N.; Bakana, M.; Nyongombe, U. Food contamination with salmonella and human health in Kinshasa city, Democratic Republic of Congo (DRC). *J. Appl. Biosci.* 2015, 94, 8809–8814. [CrossRef]

73. Makelele, L.K.; Kazadi, Z.A.; oleko, R.; Foma, R.; Mpalang, R.K.A.; Ngbolua, K.T.N.; Gédeon, B.N. Microbiological quality of food sold by street vendors in Kisangani, Democratic Republic of Congo. *Afr. J. Food Sci.* 2015, 9, 285–290.

74. Maripandi, A.; Al-Salamah, A.A. Multiple antibiotic resistance and plasmid profiles of Salmonella enteritidis isolated from retail chicken meats. *Am. J. Food Technol.* 2010, 5, 260–268. [CrossRef]

75. FAO. The State of Food Insecurity in the World; FAO: Rome, Italy, 2014; Available online: http://www.fao.org/docrep/013/i1683e/i1683e.pdf (accessed on 26 November 2014).

76. Olufemi, O.I.; Agboola, E.A. Oxytetracycline Residues in Edible Tissues of Cattle Slaughtered in Akure, Nigeria. *Internet J. Food Saf.* 2009, 11, 62–66.

77. Van Ryssen, J.B.J. Poultry litter as a feedstuff for ruminants: A South African scene. *S. Afr. J. Anim. Sci.* 2001, 93, 1256–1264. [PubMed]

78. Regulation, H. The Council of the European Communities: Council Regulation (EEC) No. 2377/90. *Official J. L.* 1990, 224, 1–8.

79. Codex Alimentarius Commission. *Maximum Residue Limits for Veterinary Drugs in Foods; Updated as at the 35th Session of the Codex Alimentarius Commission, CAC/MRL; Codex Alimentarius Commission:* Fribourg, Switzerland, 2012; Volume 2, pp. 1–40.

80. Beyene, T. Veterinary Drug Residues in Food-animal Products: Its Risk Factors and Potential Effects on Public Health. *J. Vet. Sci. Technol.* 2016, 7, 285. [CrossRef]

81. Lee, M.H.; Lee, H.J.; Ryu, P.D. Public health risks: Chemical and antibiotics residues. *Asian-Aust. J. Anim. Sci.* 2001, 14, 402–413. [CrossRef]

82. Ames, B.N. Dietary carcinogens and anticarcinogens. Oxygen radicals and degenerative diseases. *Science* 1983, 221, 1256–1264. [CrossRef] [PubMed]

83. Padol, A.R.; Malapure, C.D.; Dompie, V.D.; Kamdi, B.P. Occurrence, Public Health Implications and Detection of Antibacterial Drug Residues in Cow Milk. *Environ. We Int. J. Sci. Technol.* 2015, 5, 7–28. [CrossRef]

84. Nisha, A.R. Antibiotic residues-A global health hazard. *Vet. World* 2008, 12, 375–377. [CrossRef]

85. Kimera, Z.I.; Mdegela, R.H.; Mhaiki, C.J.N.; Karimuribo, E.D.; Mabiki, F.; Nonga, H.E.; Mwesongo, J. Determination of oxytetracycline residues in cattle meat marketed in the Kilosa district, Tanzania. *Onderstepoort J. Vet. Res.* 2015, 82. [CrossRef] [PubMed]

86. Bedada, A.H.; Zewde, B.M.; Molla Zewde, B.M. Tetracycline residue levels in slaughtered beef cattle from three slaughterhouses in Central Ethiopia. *Glob. Vet.* 2012, 8, 546–554.

87. Tavakoli, H.R.; Saeaeefrouzabad, M.S.; Afsharfarimia, S.; Joneidijafari, F.; Saadat, S. Detecting antibiotic residues by HPLC method in chicken and calves meat in diet of a Military Center in Tehran. *Acta Med. Mediterr.* 2015, 31, 1427–1433.

88. Er, B.; Onurdağ, F.K.; Demirhan, B.; Özgarcı, S.O.; Öktener, A.B.; Abbasoğlu, U. Screening of quinolone antibiotic residues in chicken meat and beef sold in the markets of Ankara, Turkey. *Poult. Sci.* 2013, 92, 2212–2215. [CrossRef] [PubMed]

89. Salama, N.A.; Abou-Raya, S.H.; Shalaby, A.R.; Enam, W.H.; Mehaya, F.M. Incidence of tetracycline residues in chicken meat and liver retailed to consumers. *Food Addit. Contam. Part B* 2011, 4, 88–93. [CrossRef] [PubMed]

90. Muriuki, F.K.; Ogar, W.O.; Njeruh, F.M.; Mitema, E.S. Tetracycline residue levels in cattle meat from Nairobi slaughter house in Kenya. *J. Vet. Sci.* 2001, 2, 97–101. [PubMed]
91. Chowdhury, S.; Hassan, M.M.; Alam, M.; Sattar, S.; Bari, M.D.S.; Saifuddin, A.K.M.; Hoque, M.D.A. Antibiotic residues in milk and eggs of commercial and local farms at Chittagong, Bangladesh. *Vet. World* 2015, 8, 467–471. [CrossRef] [PubMed]

92. Zheng, N.; Wang, J.; Han, R.; Xu, X.; Zhen, Y.; Qu, X.; Sun, P.; Li, S.; Yu, Z. Occurrence of several main antibiotic residues in raw milk in 10 provinces of China. *Food Addit. Contam. Part B* 2013, 6, 84–89. [CrossRef] [PubMed]

93. Nchima, G.; Choongo, K.; Muzandu, K.; Nalubamba, K.; Muma, J.; Bumbang, F.; Monga, G.; Kangwa, H. Determination of oxytetracycline and sulphamethazine residues in marketed beef from selected parts of Zambia to assess compliance with maximum residual limits. *Am. J. Res. Commun.* 2017, 5, 42–64.

94. Olatoye, I.O.; Daniel, O.F.; Ishola, S.; Sun, P.; Li, S.; Yu, Z. Screening of antibiotics and chemical analysis of penicillin residue in fresh milk and traditional dairy products in Oyo state, Nigeria. *Vet. World* 2016, 9, 948–954. [CrossRef] [PubMed]

95. Cheong, C.K.; Hajeb, P.; Jinap, S.; Ismail-Fitry, M.R. Sulfonamides determination in chicken meat products from Malaysia. *Int. Food Res. J.* 2010, 17, 885–892.

96. Nirala, R.K.; Anjana, K.; Mandal, K.G.; Jayachandran, C. Persistence of Antibiotic Residue in Milk under Region of Bihar, India. *Int. J. Curr. Microbiol. Appl. Sci.* 2017, 6, 2296–2299.

97. Marti, R.; Scott, A.; Tien, Y.-C.; Murray, R.; Sabourin, L.; Zhang, Y.; Toppa, E. Impact of Manure Fertilization on the Abundance of Antibiotic Resistant Bacteria and Frequency of Detection of Antibiotic Resistance Genes in Soil and on Vegetables at Harvest. *Appl. Environ. Microbiol.* 2013, 79, 5701–5709. [CrossRef] [PubMed]

98. Chang, Q.; Wang, W.; Regev-Yochay, G.; Lipsitch, M.; Hanage, W.P. Antibiotics in agriculture and the risk to human health: How worried should we be? *Evol. Appl.* 2015, 8, 240–245. [CrossRef] [PubMed]

99. Allen, H.K.; Donato, J.; Wang, H.H.; Cloud-Hansen, K.A.; Davies, J.; Handelsman, J. Call of the wild: Antibiotic resistance genes in natural environments. *Nat. Rev. Microbiol.* 2010, 8, 251–259. [CrossRef] [PubMed]

100. Summers, A.O. Genetic linkage and horizontal gene transfer, the roots of the antibiotic multi-resistance problem. *Anim. Biotechnol.* 2006, 17, 125–135. [CrossRef] [PubMed]

101. Landecker, H. Antibiotic Resistance and the Biology of History. *Body Soc.* 2016, 22, 19–52. [CrossRef] [PubMed]

102. Barlow, R.S.; Fegan, N.; Gobius, K.S. A comparison of antibiotics resistance integrons in cattle from separate beef meat production systems at slaughter. *J. Appl. Microbiol.* 2008, 104, 651–658. [CrossRef] [PubMed]

103. Warnes, S.L.; Highmore, C.J.; Keevil, C.W. Horizontal Transfer of Antibiotic Resistance Genes on Abiotic Touch Surfaces: Implications for Public Health. *mBio* 2012, 3, e0048912. [CrossRef] [PubMed]

104. Ejo, M.; Garedew, L.; Alebachew, Z.; Worku, W. Prevalence and Antimicrobial Resistance of Salmonella Isolated from Animal-Origin Food Items in Gondar, Ethiopia. *BioMed Res. Int.* 2016, 2016, 4290506. [CrossRef] [PubMed]

105. Rasheed, M.U.; Thajuddin, N.; Ahamed, P.; Teklemariam, Z.; Jamil, K. Antimicrobial drug resistance in strains of *Escherichia coli* isolated from food sources. *Rev. Inst. Med. Trop. Sao Paulo* 2014, 56, 341–346. [CrossRef] [PubMed]

106. Carbollo, M.; Esperón, F.; Sacristán, C.; González, M.; Vázquez, B.; Aguayo, S.; de la Torre, A. Occurrence of tetracycline residues and antimicrobial resistance in gram negative bacteria isolates from cattle farms in Spain. *Adv. Biosci. Biotechnol.* 2013, 4, 295–303. [CrossRef]

107. Zhu, Y.-G.; Johnsonc, T.A.; Su, J.-G.; Qiao, M.; Guo, G.-X.; Stedtfeld, R.D.; Hashsham, S.A.; Tiedje, J.M. Diverse and abundant antibiotic resistance genes in Chinese swine farms. *Prot. Natl. Acad. Sci. USA* 2012, 110, 3435–3440. [CrossRef] [PubMed]

108. Gao, L.; Hu, J.; Zhang, X.; Wei, L.; Li, S.; Miao, Z.; Chai, T. Application of swine manure on agricultural fields contributes to extended-spectrum β-lactamase-producing *Escherichia coli* spread in Tai’an, China. *Front. Microbiol.* 2015, 6, 313. [CrossRef] [PubMed]

109. Lin, J.; Biyela, P.T.; Puckree, T. Antibiotic resistance profiles of environmental isolates from Mhlathuze River, KwaZulu-Natal (RSA). *Water SA* 2004, 30, 23–28. [CrossRef]

110. Wahome, C.N. Contamination Levels of Groundwater, Antimicrobial Resistance PATTERNS, Plasmid Profiles and Chlorination Efficacy in Ongata Rongai, Kajiado North County, Kenya. Master’s Thesis, Kenyatta University, Nairobi City, Kenya, 2013.

111. McLain, J.E.; Cytryn, E.; Durso, L.M.; Youn, S. Culture-based Methods for Detection of Antibiotic Resistance in Agroecosystems: Advantages, Challenges, and Gaps in Knowledge. *J. Environ. Qual.* 2016, 45, 432–440. [CrossRef] [PubMed]
112. Bauer, A.W.; Kirby, W.M.M.; Sherris, J.C.; Turck, M. Antibiotic susceptibility testing by a standardized single disk method. *Am. J. Clin. Pathol.* 1966, 36, 493–496. [CrossRef]

113. Motamedi, H.; Mirzabeigi, H.; Shirali, T. Determining of antibiotic resistance profile in *Staphylococcus aureus* isolates. *Asian Pac. J. Trop. Med.* 2010, 3, 734–737. [CrossRef]

114. Andrews, J.M. Determination of minimum inhibitory concentrations. *J. Antimicrob. Chemother.* 2001, 48, 5–16. [CrossRef] [PubMed]

115. Wiegand, J.K.; Hilpert, K.; Hancock, R.E.W. Agar and broth dilution methods to determine the minimal inhibitory concentration (MIC) of antimicrobial substances. *Nat. Protoc.* 2008, 3, 163–175. [CrossRef] [PubMed]

116. Jenkins, S.G.; Schuetz, A.N. Current concepts in laboratory testing to guide antimicrobial therapy. *Mayo Clin. Proc.* 2012, 87, 290–308. [CrossRef] [PubMed]

117. Brown, D.F.J.; Brown, L. Evaluation of the E test, a novel method of quantifying antimicrobial activity. *J. Antimicrob. Chemother.* 1991, 27, 185–190. [CrossRef] [PubMed]

118. Kümmerer, K. Antibiotics in the aquatic environment— A Review—Part 1. *Chemosphere* 2009, 75, 417–434. [CrossRef] [PubMed]

119. Philips, I.; Casewell, M.; Cox, T.; De Groot, B.; Friis, C.; Jones, R.; Nightingale, C.; Preston, R.; Waddell, J. Does the use of antibiotics in food animals pose a risk to human health? A critical review of published data. *J. Antimicrob. Chemother.* 2004, 53, 28–52. [CrossRef] [PubMed]

120. Mezger, A.; Gullberg, E.; Göransson, J.; Zorzet, A.; Herthnek, D.; Tano, E.; Nilsson, M.; Andersson, D.I. A General Method for Rapid Determination of Antibiotic Susceptibility and Species in Bacterial Infections. *J. Clin. Microbiol.* 2015, 53, 425–432. [CrossRef] [PubMed]

121. Davies, J.; Davies, D. Origins and evolution of antibiotic resistance. *Clin. Microbiol. Infect.* 2016, 22, 416–422. [CrossRef] [PubMed]

122. Davies, J.; Davies, D. Origins and evolution of antibiotic resistance. *Clin. Microbiol. Infect.* 2016, 22, 416–422. [CrossRef] [PubMed]

123. Wegener, H.C. Antibiotic Resistance: Linking Humans and Animal Health: IMPROVING Food Safety through a One Health Approach: Workshop Summary. Institute of Medicine, National Academic Press: Washington, DC, USA, 2012.

124. Sundsfjord, A.; Simonsen, G.S.; Courvalin, P. Human infections caused by glycopeptide-resistant *Enterococcus* spp. Are they a zoonosis? *Clin. Microbiol. Infect.* 2001, 7, 17–33. [CrossRef]

125. Marshall, B.M.; Levy, S.B. Food Animals and Antimicrobials: Impacts on Human Health. *Clin. Microbiol. Rev.* 2011, 24, 718–733. [CrossRef] [PubMed]

126. Founou, L.L.; Founou, R.C.; Essack, S.Y. Antibiotic resistance in the food chain: A developing-country perspective. *Front. Microbiol.* 2016, 7, 1881. [CrossRef] [PubMed]

127. Acar, J.F.; Moulin, G. Antimicrobial resistance at farm level. *Rev. Sci. Tech.* 2006, 25, 775–792. [CrossRef] [PubMed]

128. Kitalyi, A.J. Village chicken production systems in developing countries: What does the future hold? *World Anim. Rev.* 1997, 89, 48–53.

129. Kitalyi, A.J. Village chicken production systems in developing countries: What does the future hold? *World Anim. Rev.* 1997, 89, 48–53.

130. Kagambega, A.; Lienemann, T.; Aulu, L.; Traoré, A.S.; Barro, N.; Siitonen, A.; Haukka, K. Prevalence and characterization of *Salmonella enterica* from faeces of cattle, poultry, swine and hedgehogs in Burkina Faso and their comparison to human *Salmonella* isolates. *BMC Microbiol.* 2013, 13, 253. [CrossRef] [PubMed]

131. Lipsitch, M.; Singer, R.S.; Levin, B.R. Antibiotics in agriculture: When is it time to close the barn door? *Proc. Natl. Acad. Sci. USA* 2002, 99, 5752–5754. [CrossRef] [PubMed]

132. Cosgrove, S.E.; Yehuda Carmeli, Y. The Impact of Antimicrobial Resistance on Health and Economic Outcomes. *Clin. Infect. Dis.* 2003, 36, 1433–1437. [PubMed]

133. Wegener, H. The consequences for food safety of the use of fluoroquinolones in food animals. *N. Engl. J. Med.* 1999, 340, 1581–1582. [CrossRef] [PubMed]

134. Friedman, N.D.; Temkin, E.; Carmeli, Y. The negative impact of antibiotic resistance. *Clin. Microbiol. Infect.* 2016, 22, 416–422. [CrossRef] [PubMed]

135. Lutful Kabir, S.M. Avian colibacillosis and salmonellosis: A closer look at epidemiology, pathogenesis, diagnosis, control and public health concerns. *Int. J. Environ. Res. Public Health* 2010, 7, 89–114. [CrossRef] [PubMed]
136. Vishnuraj, M.R.; Kandepan, G.; Rao, K.H.; Chand, S.; Kumbhar, V. Occurrence, public health hazards and detection methods of antibiotic residues in foods of animal origin: A comprehensive review. Cogent Food Agric. 2016, 2, 1235458. [CrossRef]

137. Da Costa, P.M.; Loureiro, L.; Matos, A.J.F. Transfer of Multidrug-Resistant Bacteria Between Intermingled Ecological Niches: The Interface Between Humans, Animals and the Environment. Int. J. Environ. Res. Public Health 2013, 10, 278–294. [CrossRef] [PubMed]

138. Shanks, C.R.; Peteroy-Kelly, M.A. Analysis of antimicrobial resistance in bacteria found at various sites on surfaces in an urban university. BIOS 2009, 80, 105–113. [CrossRef]

139. White, D.G.; Zhao, S.; Simjee, S.; Wagner, D.D.; McDermot, P.F. Antimicrobial resistance resistance of foodborne pathogens. Microbes Infect. 2002, 4, 405–412. [CrossRef]

140. Gebeheyu, E.; Bantie, L.; Azage, M. Inappropriat use of antibiotics and its associated factors among Urban and rural communities of Bahir Dar City administration, NorthWest Ethiopia. PLoS ONE 2015, 10, e0138179. [CrossRef]

141. Garnacho-Montero, J.; Escoresca-Ortega, A.; Fernández-Delgado, E. Antibiotic de-escalation in the ICU: How is it done? Curr. Opin. Infect. Dis. 2015, 28, 193–198. [CrossRef] [PubMed]

142. Masterton, R.G. Antibiotic de-escalation. Crit. Care Clin. 2011, 27, 149–162. [CrossRef] [PubMed]

143. McKenzie, D.; Rawlins, M.; Pople, T.; van der Merwe, L. Part III. Antibiotic supply chain and management in South East Asia Manish Kakkar and colleague. BMJ 2017, 358, j3760. [CrossRef] [PubMed]

144. Leekha, S.; Terrell, C.L.; Edson, R.S. General Principles of Antimicrobial Therapy. Mayo Clin. Proc. 2011, 86, 156–167. [CrossRef] [PubMed]

145. Santon, S.; Davidson, L.E. Antimicrobial Stewardship. Mayo Clin. Proc. 2011, 86, 1113–1123. [CrossRef] [PubMed]

146. Laxminarayan, R.; Bhutta, Z.; Duse, A.; Jenkins, P.; O’Brien, T.; Okeke, I.N.; Pablo-Mendez, A.; Klugman, K.P. Poverty related and neglected diseases—An economic and epidemiological analysis of poverty relatedness and neglect in research and development. Glob. Health Action 2015, 25, 25818. [CrossRef] [PubMed]

147. Vincent, J.-L.; Bassetti, M.; François, B.; Karam, G.; Chastre, J.; Torres, A.; Roberts, J.A.; Taccone, F.S.; Rello, J.; Calandra, T.; et al. Advances in antibiotic therapy in the critically ill. Crit. Care 2016, 20, 133. [CrossRef] [PubMed]

148. White, D.G.; Zhao, S.; Simjee, S.; Wagner, D.D.; McDermot, P.F. Antimicrobial resistance resistance of foodborne pathogens. Microbes Infect. 2002, 4, 405–412. [CrossRef]

149. Kakkar, M.; Sharma, A.; Vong, S. Developing a situation analysis tool to assess containment of antimicrobial resistance. Pharmacol. J. 2018, 13, 57.

150. Laxminarayan, R.; Chaudhury, R.R. Antibiotic policy. Public Health Rep. 2012, 127, 4–22. [CrossRef] [PubMed]

151. Economou, V.; Gousia, P. Agriculture and food animals as a source of antimicrobial-resistant bacteria. Infect. Drug Resist. 2015, 8, 49–61. [CrossRef] [PubMed]

152. Gyssens, I.C. Antibiotic policy. Mayo Clin. Proc. 2011, 86, 1113–1123. [CrossRef] [PubMed]

153. Mustard, P. Over-the-Counter Restrictions on Antibiotic Consumption in Brazil and Mexico. PLoS ONE 2013, 8, e75550. [CrossRef] [PubMed]

154. Economou, V.; Gousia, P. Agriculture and food animals as a source of antimicrobial-resistant bacteria. Infect. Drug Resist. 2015, 8, 49–61. [CrossRef] [PubMed]

155. Da Costa, P.M.; Loureiro, L.; Matos, A.J.F. Transfer of Multidrug-Resistant Bacteria Between Intermingled Ecological Niches: The Interface Between Humans, Animals and the Environment. Int. J. Environ. Res. Public Health 2013, 10, 278–294. [CrossRef] [PubMed]

156. Gelband, H.; Duse, A.G. Executive summary. S. Afr. Med. J. 2011, 101, 552–555. [CrossRef] [PubMed]

157. Santon, S.; Davidson, L.E. Antimicrobial Stewardship. Mayo Clin. Proc. 2011, 86, 1113–1123. [CrossRef] [PubMed]

158. Gelband, H.; Duse, A.G. Executive summary. S. Afr. Med. J. 2011, 101, 552–555. [CrossRef] [PubMed]

159. Holloway, K.A.; Kotwani, A.; Puri, M.; Tisocki, K. Antibiotic use in South East Asia and policies to promote appropriate use: Reports from country situational analyses. BMJ 2017, 358, 9–13. [CrossRef] [PubMed]

160. Pereko, D.D.; Lubbe, M.S.; Essack, S.Y. Surveillance of antibiotic use in the private sector in Namibia using sales and claims data. J. Infect. Dev. Ctries. 2016, 10, 1243–1249. [CrossRef] [PubMed]
161. Global Antibiotic Resistance Partnership (GARP)—India. Rationalizing antibiotic use to limit antibiotic resistance in India. *Indian J. Med. Res.* 2011, 134, 281–294.

162. Uchil, R.R.; Kohli, G.S.; Katekhay, V.M.; Swami, O.C. Strategies to Combat Antimicrobial Resistance. *J. Clin. Diagn. Res.* 2014, 8, ME01–ME04. [CrossRef] [PubMed]

163. Lowman, W. Key to antimicrobial stewardship success: Surveillance by diagnostic microbiology laboratories. *S. Afr. Med. J.* 2015, 105, 359–360. [CrossRef] [PubMed]

164. World Health Organization. Draft Global Action Plan on Antimicrobial Resistance. Draft for Consultation with Member States, October 2014. Available online: http://www.who.int/drugresistance/AMR_DRAFT_GAP_1_Oct_2014_for_MS_consultation.pdf (accessed on 28 November 2017).

165. Leung, E.; Weil, D.; Raviglione, M.; Nakatani, H. Policy package to combat antimicrobial resistance. *Bull. World Health Organ.* 2011, 89, 390–392. [CrossRef] [PubMed]

166. Fluit, A.C.; van der Bruggen, J.T.; Aarestrup, F.M.; Verhoef, J.; Jansen, W.T.M. Priorities for antibiotic resistance surveillance in Europe. *Clin. Microbiol. Infect.* 2006, 12, 410–417. [CrossRef] [PubMed]

167. Tacconelli, E.; Sifakis, F.; Harbarth, S.; Schrijver, R.; van Mourik, M.; Voss, A.; Sharland, M.; Rajendran, N.B.; Rodriguez-Baño, J. Surveillance for control of antimicrobial resistance. *Lancet* 2017. [CrossRef]

168. Essack, S.Y. Strategies for the Prevention and Containment of Antibiotic Resistance. *S. Afr. Fam. Pract.* 2006, 48, 51. [CrossRef]

169. Nasir, I.A.; Babyo, A.; Emeribe, A.U.; Sani, N.O. Surveillance for antibiotic resistance in Nigeria: Challenges and possible solutions. *Trends Med. Res.* 2015, 10, 106–113. [CrossRef]

170. Critchley, I.A.; Karlowsky, J.A. Optimal use of antibiotic resistance surveillance systems. *Clin. Microbiol. Infect.* 2004, 10, 502–511. [CrossRef] [PubMed]

171. Bamford, C.; Brink, A.; Govender, N.; Lewis, D.A.; Perovic, O.; Botha, M.; Harris, B.; Keddy, K.H.; Gelband, H.; Duse, A.G. Part V. Surveillance activities. *S. Afr. Med. J.* 2011, 101, 579–582. [PubMed]

172. World Health Organisation. *Global Report on Surveillance*; World Health Organisation: Geneva, Switzerland, 2014; Available online: http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf (accessed on 18 January 2018).

173. Xiao, Y.; Li, L. The actions of china in containing antimicrobial resistance. *AMR Control* 2015, 46–53.

174. Duro, L.M.; Cook, K.L. Impact of antibiotics use in JN agriculture. What are the benefits and risks? *Curr. Opin. Microbiol.* 2014, 19, 37–44. [CrossRef] [PubMed]

175. Moudgil, P.; Bedi, J.S.; Moudgil, A.D.; Gill, J.P.S.; Aulakh, R.S. Emerging issue of antibiotic resistance from food producing animals in India: Perspective and legal framework. *Food Rev. Int.* 2017. [CrossRef]

176. Ying, G.-G.; He, L.-Y.; Ying, A.J.; Zhang, Q.-Q.; Liu, Y.-S.; Zhao, J.-L. China Must Reduce Its Antibiotic Use. *Indian J. Med. Res.* 2011, 89, 359–360. [CrossRef] [PubMed]

177. Sharma, C.; Rokana, N.; Chandra, M.; Singh, B.P.; Gulhane, R.D.; Gill, J.P.S.; Ray, P.; Punia, A.K.; Panwar, H. Antimicrobial Resistance: Its Surveillance, impact, and Alternative Management Strategies in Dairy Animals. *Front. Vet. Sci.* 2018, 4, 237. [CrossRef] [PubMed]

178. National Farmed Animal Health and Welfare Council. *Antimicrobial Stewardship in Food Animals in Canada*; National Farmed Animal Health and Welfare Council: Bluevale, ON, Canada, 2016.

179. Van Vuuren, M. Appropriate use of antimicrobials in animal health. In *Proceedings of the Antimicrobial Resistance Summit*, Birchwood Hotel, Sandton, South Africa, 16 October 2014.

180. World Health Organisation. *WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food*; WHO/CDS/CSR/APH/2000.4; World Health Organisation: Geneva, Switzerland, 2000.

181. Walsh, T.R.; Wu, Y. China bans colistin as a feed additive for animals. *Lancet* 2016, 16, 1102–1103. [CrossRef]

182. FSSAI. Food Safety Standards (Contaminants, Toxins and Residues) Regulations. Ministry of Health and Family Welfare. Govt. of India. 2011. Available online: https://www.suratmunicipal.gov.in/Content/Documents/Downloads/FssAct/FssAct1.pdf (accessed on 6 June 2015).

183. Lhermie, G.; Gröhn, Y.T.; Raboisson, D. Addressing Antimicrobial Resistance: An Overview of Priority Actions to Prevent Suboptimal Antimicrobial Use in Food-Animal Production. *Front. Microbiol.* 2017, 7, 2114. [CrossRef] [PubMed]

184. Mehrotra, M.; Li, X.-Z.; Ireland, M.J. Enhancing antimicrobial stewardship by strengthening the veterinary drug regulatory framework. *Can. Commun. Dis. Rep.* 2017, 43, 220–223. [CrossRef]
185. Speksnijder, D.C.; Jaarsma, A.D.C.; van der Gugten, A.C.; Verheij, T.J.M.; Wagenaar, J.A. Determinants Associated with Veterinary Antimicrobial Prescribing in Farm Animals in The Netherlands: A qualitative study. *Zoonoses Public Health* 2015, 62, 39–51. [CrossRef] [PubMed]

186. Henton, M.M.; Eagar, H.A.; Swan, G.E.; van Vuuren, M. Part VI. Antibiotic management and resistance in livestock production. *S. Afr. Med. J.* 2011, 101, 583–586. [PubMed]

187. Lee, C.-R.; Lee, J.H.; Kang, L.-W.; Jeong, B.C.; Lee, S.H. Educational Effectiveness, Target, and Content for Prudent Antibiotic Use. *BioMed Res. Int.* 2015, 2015. [CrossRef] [PubMed]

188. Bischoff, K.M.; Callaway, T.R.; Edrington, T.S.; Cunovese, K.J.; Crippen, T.I.; Nisbert, D. Antimicrobial use in food animals: Potential alternatives. In *Encyclopedia of Animal Science*; Pond, W.S., Bell, A.W., Eds.; CRC Press: Boca Raton, FL, USA, 2005; pp. 45–47.

189. Postma, M.; Vanderhaeghen, W.; Sarrazin, S.; Maes, D.; Dewulf, J. Reducing antimicrobial usage in pig production without jeopardizing production parameters. *Zoonoses Public Health* 2016. [CrossRef] [PubMed]

190. Silbergeld, E.; Graham, J.; Price, B.L. Industrial food animal production, antimicrobial resistance, and human health. *Ann. Rev. Public Health* 2008, 29, 151–169. [CrossRef] [PubMed]

191. John, O.S. Surveillance of antimicrobial resistance in pigs using escherichia coli faecal isolates. *CIB Technol.* 2014, 3, 78–83.

192. Chantziaras, I.; Boyen, F.; Callens, B.; Dewulf, J. Correlation between veterinary antimicrobial use and antimicrobial resistance in food-producing animals: A report on seven countries. *J. Antimicrob. Chemother.* 2014, 69, 827–834. [CrossRef] [PubMed]

193. Van Vuuren, M. Principles of responsible use of antimicrobial drugs in production animals. In Proceedings of the AVCA Congres, Kopanong Conference Centre, Benoni, South Africa, 8–9 September 2015.

194. Schaekel, F.; May, T.; Seiler, J.; Hartmann, M.; Kreienbrock, L. Antibiotic drug usage in pigs in Germany- Are the class profiles changing? *PloS ONE* 2017, 12, e0182661. [CrossRef] [PubMed]

195. Magouras, I.; Carmo, L.P.; Stärk, K.D.C.; Schüpbach-Regula, G. Antimicrobial usage and -resistance in Livestock: Where should we focus? *Front. Vet. Sci.* 2017, 4, 148. [CrossRef] [PubMed]

196. Goutard, F.; Bordier, M.; Calba, C.; Erlacher-Vindel, E.; Góchez, D.; de Balogh, K.; Benigno, C.; Kalpravidh, W.; Roger, F.; Vong, S. Antimicrobial policy interventions in food animal production in South East Asia. *BMJ* 2017, 358, j3544. [CrossRef] [PubMed]

197. Mevius, D.; Dick Heederik, D. Reduction of antibiotic use in animals “let’s go Dutch”. *J. Verbr. Lebensm.* 2014, 9, 177–181. [CrossRef]

198. Adesokan, H.K.; Akanbi, I.O.; Akanbi, I.M.; Obaweda, R.A. Pattern of antimicrobial usage in livestock animals in south-western Nigeria: The need for alternative plans. *Onderstepoort J. Vet. Res.* 2015, 82. [CrossRef] [PubMed]

199. Nisi, R.; Brink, N.; Diaz, F.; Moulin, G. Antimicrobial Use in Animals: Analysis of the OIE Survey on Monitoring of the Quantities of Antimicrobial Agents Used in Animals; World Organisation for Animal Health: Paris, France, 2013; Available online: http://www.oie.int/eng/A_AMR2013/Presentations/S2_4_Fran%C3%A7oisDiaz.pdf (accessed on 30 September 2015).

200. Bywater, R.J. Identification and Surveillance of Antimicrobial Resistance Dissemination in Animal Production. *Poult. Sci.* 2005, 84, 644–648. [CrossRef] [PubMed]

201. Dar, O.A.; Hasan, R.; Schlundt, J.; Harbarth, S.; Caleo, G.; Dar, F.K.; Littmann, J.; Rwėyemamu, M.; Buckley, E.J.; Shahid, M.; et al. Antimicrobials: Access and sustainable eff ectiveness 4. Exploring the evidence base for national and regional policy interventions to combat resistance. *Lancet* 2016, 387, 285–295. [CrossRef]

202. Tangcharoensathien, V.; Sommanustweechai, A.; Chanthong, B.; Sumpradit, N.; Sakulbumrungsil, R.; Jaroenpaj, S.; Sermsinsiri, V. Surveillance of antimicrobial consumption: Methodological review for systems development in Thailand. *Viewpoints* 2017, 7. [CrossRef]

203. Årdal, C.; Outterson, K.; Hoffman, S.J.; Ghafur, A.; Sharland, M.; Ranganathan, N.; Smith, R.; Zorzet, A.; Cohn, J.; Pittet, D.; et al. Antimicrobials: Access and sustainable eff ectiveness 5 International cooperation to improve access to and sustain eff ectiveness of antimicrobials. *Lancet* 2016, 387, 296–307. [CrossRef]

204. Seale, A.C.; Gordon, N.C.; Islam, J.; Peacock, S.J.; Scott, J.A.G. AMR Surveillance in low and middle-income settings—A roadmap for Global Antimicrobial Surveillance System (GLASS). *Wellcome Open Res.* 2017, 2, 92. [CrossRef] [PubMed]
205. Woolhouse, M.; Ward, M.; van Bunnik, B.; Farrar, J. Antimicrobial resistance in humans, livestock and the wider environment. *Philos. Trans. R. Soc. B* **2015**, *370*, 20140083. [CrossRef] [PubMed]

206. Shobrak, M.Y.; Abo-Amer, A.E. Role of wild birds as carriers of multi-drug resistant *Escherichia coli* and *Escherichia vulneris*. *Braz. J. Microbiol.* **2014**, *45*, 1199-1209. [CrossRef] [PubMed]

207. Pan, D.; Yu, Z. Intestinal microbiome of poultry and its interaction with host and die. *Gut Microbes* **2014**, *5*, 108-119. [CrossRef] [PubMed]

208. Téllez, G.; Laukova, A.; Latorre, J.D.; Hernandez-Velasco, X.; Hargis, B.M.; Callaway, T. Food-producing animals and their health in relation to human. *Microb. Ecol. Health Dis.* **2015**, *26*, 25876. [CrossRef] [PubMed]

209. Kogut, M.H.; Ryan, J.; Arsenault, R.J. Editorial: Gut Health: The new paradigm in food animal production. *Front. Vet. Sci.* **2016**, *3*, 71. [CrossRef] [PubMed]

210. Van, T.T.H.; Moutafis, G.; Tran, L.T.; Coloe, P.J. Antibiotic Resistance in Food-Borne Bacterial Contaminants in Vietnam. *Appl. Environ. Microbiol.* **2007**, *73*, 7906-7911. [CrossRef] [PubMed]

211. Bosco, K.J.; Kaddu-Mulindwa, D.H.; Assimwe, B.B. Antimicrobial Drug Resistance and Plasmid Profiles of Salmonella isolates from Humans and Foods of Animal Origin in Uganda. *Adv. Infect. Dis.* **2012**, *2*, 151-155. [CrossRef]

212. Franklin, A.M.; Aga, D.S.; Cytryn, E.; Durso, L.M.; McLai, J.E.; Pruden, A.; Roberts, M.C.; Rothrock, M.J., Jr.; Snow, D.D.; Watson, J.E.; et al. Antibiotics in Agroecosystems: Introduction to the Special Section. *J. Environ. Qual.* **2016**, *45*, 377-393. [CrossRef] [PubMed]

213. Resende, J.A.; Silva, V.L.; de Oliveira, T.L.R.; Fortunato, S.D.O.; Carneiro, J.D.C.; Otenio, M.H.; Diniza, C.G. Prevalence and persistence of potentially pathogenic and antibiotic resistant bacteria during anaerobic digestion treatment of cattle manure. *Bioresour. Technol.* **2014**, *153*, 284-291. [CrossRef] [PubMed]

214. Maynaud, G.; Pourche, R.A.-M.; Ziebal, C.; Cuny, A.; Druilhe, C.; Steyer, J.-P.; Wéry, N. Persistence and Potential Viable but Non-culturatable State of Pathogenic Bacteria during Storage of Digestates from Agricultural Biogas Plants. *Front. Microbiol.* **2016**, *7*, 1469. [CrossRef] [PubMed]

215. Amin, F.R.; Khalid, H.; Zhang, H.; Rahman, S.U.; Zhang, R.; Lui, G.; Chen, C. Pre-treatment methods of lignocellulosic biomass for anaerobic digestion. *AMB Exp.* **2017**, *7*, 72. [CrossRef] [PubMed]

216. Pollard, A.T.; Morra, M.J. Estrogen: Properties, behaviour and fate in dairy manure amended soils. *Environ. Rev.* **2017**, *25*, 452-462. [CrossRef]

217. Jiménez, B. Irrigation in Developing countries using wastewater. *Int. Rev. Environ. Strateg.* **2006**, *6*, 229-250.

218. Edokpayi, J.N.; Odiyo, J.O.; Durowoju, O.S. Impact of Wastewater on Surface Water Quality in Developing Countries: A Case Study of South Africa. In *Water Quality*; INTECH: Vienna, Austria, 2017; pp. 401-416.

219. Comerford, N.B.; Franzluebbers, A.J.; Stromberger, M.E.; Morris, L.; Markewitz, D.; Moore, R. Assessment and Evaluation of Soil Ecosystem Services. *Soil Horiz.* **2013**. [CrossRef]

220. Sethi, S.; Kumar, R.; Gupta, S. Antibiotic production by microbes isolated from soil. *Int. J. Pharm. Sci. Res.* **2013**, *4*, 2967-2973. [CrossRef]

221. Nesme, J.O.; Simonet, P.P. The soil resistome: A critical review on antibiotic resistance origins, ecology and dissemination potential in telluric bacteria. *Environ. Microbiol.* **2015**, *17*, 913-930. [CrossRef] [PubMed]

222. Monier, J.M.; Deman, A.; Lebreton, B.; Stoops, S.; Grassé, S. Ecological factors influencing survival and growth of human pathogens on raw fruits and vegetables. *Molecules* **2018**, *23*, 795. [CrossRef] [PubMed]
230. Johannessen, G.S.; Loncarevic, S.; Kruse, H. Bacteriological analysis of fresh produce in Norway. *Int. J. Food Microbiol.* 2002, 77, 199–204. [CrossRef]

231. Baquero, F.; Martínez, J.-L.; Cantón, R. Antibiotics and antibiotic resistance in water environments. *Curr. Opin. Biotechnol.* 2008, 19, 260–265. [CrossRef] [PubMed]

232. Vaz-Moreira, I.; Nunes, O.C.; Manaia, C.M. Bacterial diversity and antibiotic resistance in water habitats: Searching the links with the human microbiome. *FEMS Microbiol. Rev.* 2014, 38, 761–778. [CrossRef] [PubMed]

233. Biyela, P.T.; Lin, J.; Bezuidenhout, C.C. The role of aquatic ecosystems as reservoirs of antibiotic resistant bacteria and antibiotic resistance genes. *Water Sci. Technol.* 2004, 50, 45–50. [PubMed]

234. Aryal, S.; Karki, G.; Pandey, S. Microbial diversity in freshwater and marine environment. *Nepal J. Biotechnol.* 2015, 3, 68–70. [CrossRef]

235. Ibegwe, A.M.; Ma, J.; Murinda, S.E. Bacterial community composition and structure in an urban river impacted by different pollutant sources. *Sci. Total Environ.* 2016, 566–567, 1176–1185. [CrossRef] [PubMed]

236. Cabral, J.P.S. Water Microbiology. Bacterial Pathogens and Water. *Int. J. Environ. Res. Public Health* 2010, 7, 3657–3703. [CrossRef]

237. Biyela, P.T.; Lin, J.; Bezuidenhout, C.C. The role of aquatic ecosystems as reservoirs of antibiotic resistant bacteria and antibiotic resistance genes. *Water Sci. Technol.* 2004, 50, 45–50. [PubMed]

238. Nogales, B.; Lanfranconi, M.P.; Piña-villalonga, J.M.; Bosch, R. Anthropogenic perturbations in marine microbial communities. *FEMS Microbiol. Rev.* 2011, 35, 275–298. [CrossRef] [PubMed]

239. Igbinosa, E.O.; Odjadjare, E.E. Antibiotics and Antibiotic resistance determinants: An undesired element in the environment. *Front. Microbiol.* 2015, 2, 858–866.

240. Coutinho, F.H.; Pinto, L.H.; Vieira, R.P.; Martins, O.B.; Salloto, G.R.B.; Santoro, D.D.O.; Clementino, M.M.; Cardoso, A.M. Antibiotic resistance in aquatic environments of Rio de Janeiro, Brazil. In *Perspectives in Water Pollution*; INTECH: Vienna, Austria, 2013.

241. Kemper, N. Veterinary antibiotics in the aquatic and terrestrial environment. *Ecol. Indic.* 2008, 8, 1–132. [CrossRef]

242. Xiong, W.; Sun, Y.; Ding, X.; Zhang, Y.; Zeng, Z. Antibiotic resistance genes occurrence and bacterial community composition in the Liuxi River. *Front. Environ. Sci.* 2014, 2, 61. [CrossRef]

243. Mulamattathil, S.G.; Bezuidenhout, C.; Mbewe, M.; Ateba, C.N. Isolation of Environmental Bacteria from Surface and Drinking Water in Mafikeng, South Africa, and Characterization Using Their Antibiotic Resistance Profiles. *J. Pathogens* 2014, 2014, 371208. [CrossRef] [PubMed]

244. Dumontet, S.; Krovacek, K.; Svenson, S.B.; Pasquale, V.; Baloda, S.B.; Figliuolo, G. Prevalence and diversity of *Aeromonas* and *Vibrio* species in coastal waters of Southern Italy. *Comp. Immunol. Microbiol. Infect. Dis.* 2000, 23, 53–72. [CrossRef]

245. Pavlov, D.; de Wet, C.M.E.; Grabow, W.O.K.; Ehlers, M.M. Potentially pathogenic features of heterotrophic plate count bacteria isolated from treated and untreated drinking water. *Int. J. Food Microbiol.* 2004, 92, 275–287. [CrossRef] [PubMed]

246. Santiago-Rodriguez, T.M.; Rivera, J.F.; Toranzos, G.A. Antibiotic-resistance and virulence genes in Enterococcus isolated from tropical recreational waters. *J. Water Health* 2013, 11, 387–398. [CrossRef] [PubMed]

247. Ovechey, K.N.; Hatcher, S.M.; Stewart, J.R. Water quality and antibiotic resistance at beaches of the Galápagos Islands. *Front. Environ. Sci.* 2015, 3, 64. [CrossRef]

248. Dwight, R.H.; Baker, D.B.; Semenza, J.C.; Olson, B.H. Health effects associated with recreational coastal water use: Urban versus rural California. *Am. J. Public Health* 2004, 94, 565–567. [CrossRef] [PubMed]

249. Leonard, A.F.C.; Zhang, L.; Balfour, A.J.; Garside, R.; Gaze, W.H. Human recreational exposure to antibiotic resistant bacteria in coastal bathing waters. *Environ. Int.* 2015. [CrossRef] [PubMed]

250. Lihan, S.; Tian, P.K.; Chiew, T.S.; Ching, C.L.; Shahbudin, A.; Hussain, H.; Mohd-Azlan, J. The distribution and characteristics of bacteria in recreational river water of a community resort in Baram, Sarawak, Malaysian Borneo. *Int. Food Res. J.* 2017, 24, 2238–2245.

251. Carvalho, E.M.R.; Costa, R.A.; Araújo, A.J.G.; Carvalho, F.C.T.; Pereira, S.P.; Sousa, O.V.; Vieira, R.H.S.F. Multiple antibiotic resistance of Enterococcus isolated from coastal water near an outfall in Brazil. *Afr. J. Microbiol. Res.* 2014, 8, 1825–1831. [CrossRef]

252. Sivri, N. Antibiotic resistance (AR) among enteric bacteria in Marine environments of Marmara Sea. *Adv. Biotechnol. Microbiol.* 2017, 6, 555694. [CrossRef]
253. World Health Organization (WHO). *Guidelines for Safe Recreational Water Environments*. Vol. 1, Coastal and Fresh Waters; WHO: Geneva, Switzerland, 2003; Available online: http://apps.who.int/iris/bitstream/10665/42591/1/9241545801.pdf (accessed on 18 January 2017).

254. Fernandes Cardoso de Oliveira, A.J.; Ranzani de França, P.T.; Pinto, A.B. Antimicrobial resistance of heterotrophic marine bacteria isolated from seawater and sands of recreational beaches with different organic pollution levels in southeastern Brazil: Evidence of resistance dissemination. *Environ. Monit. Assess.* 2010, 169, 375–384. [CrossRef] [PubMed]

255. Alipour, M.; Hajiesmaili, R.; Talebjannat, M.; Yahyapour, Y. Identification and Antimicrobial Resistance of Enterococcus Sp. Isolated from the River and Coastal Waters in Northern Iran. *Sci. World J.* 2014, [CrossRef] [PubMed]

256. Akanbi, O.E.; Njom, H.A.; Fri, J.; Otigbi, A.C.; Clarke, A.M. Antimicrobial Susceptibility of Staphylococcus aureus Isolated from Recreational Waters and Beach Sand in Eastern Cape Province of South Africa. *Int. J. Environ. Res. Public Health* 2017, 14, 1001. [CrossRef] [PubMed]

257. Pond, K. *WATER recreation and Diseases: Plausibility of Associated Infection: Acute Effects, Sequelae and Mortality;* World Health Organisation: Geneva, Switzerland, 2005.

258. McKeon, D.M.; Calabrese, J.P.; Bissonnette, G.K. Antibiotic resistant gram-negative bacteria in rural groundwater supplies. *Waer. Res.* 1995, 29, 1902–1908. [CrossRef]

259. European Commission. Scientific Committee on Emerging and Newly Identified Health Risks. Assessment of the Antibiotic Resistance Effects of Biocides. 2009. Available online: http://ec.europa.eu/health/phrisk/committees/04scenihr/docs/scenihr021.pdf (accessed on 28 January 2018).

260. Carstens, A.J. Evaluation of Microbiological and Physico-Chemical Quality of Water from Aquifers in the North West Province, South Africa. Master’s Thesis, North West University, Potchefstroom, South Africa, 2012.

261. Li, X.; Atwill, E.R.; Antaki, E.; Applegate, O.; Bergamaschi, B.; Bond, R.F.; Chase, J.; Ransom, K.M.; Samuels, W.; Watanabe, N.; et al. Fecal indicator and pathogenic bacteria and their antibiotic resistance in Alluvial Groundwater of an irrigated agricultural region with dairies. *J. Environ. Qual.* 2015, 44, 1435–1447. [CrossRef] [PubMed]

262. Burton, F.; Stensey, H. *Wastewater Engineering, Treatment and Reuse*, 4th ed.; McGraw Hill: New York, NY, USA, 2003.

263. Palese, A.M.; Pasquale, V.; Celano, G.; Figliuolo, G.; Masi, S.; Xiloyannis, C. Irrigation of olive groves in Southern Italy with treated municipal wastewater: Effects on microbiological quality of soil and fruits. *Agric. Ecosyst. Environ.* 2009, 129, 43–51. [CrossRef]

264. Sou, M.; Yacouba, H.; Mermoud, A. Fertilising value and health risks assessment related to wastewater reuse in irrigation, case study in a Soudano-Sahelian city. Ouagadougou. *J. Sci.* 2011, 6, 4–8.

265. Noori, M.; Mahdiye, M.; Noroz, R. Wastewater irrigation effects on growth parameters of Alyssum longistilum Grossh. (Brassicaceae) a medicinal plant in Iran. In Proceedings of the International Conference on Women in Science and Technology in the Arab Countries, Kuwait City, Kuwait, 21–23 April 2013.

266. Singh, P.K.; Dshehbarat, P.B.; Ramteke, D.S. Effects of sewage wastewater irrigation on soil properties, crop yield and environment. *Agric. Water Manag.* 2011, 103, 100–104. [CrossRef]

267. Lundborg, C.S.; Tamhankar, A. Antibiotic residues in the environment of South East Asia. *BMJ* 2017, 358, 42–45. [CrossRef] [PubMed]

268. Adesiloye, M.A.; Okoh, A.I. Identification and antimicrobial resistance prevalence of pathogenic *Escherichia coli* strains from treated wastewater effluents in Eastern Cape, South Africa. *MicrobiologyOpen* 2016, 5, 143–151. [CrossRef] [PubMed]

269. Manaia, C.M.; Macedo, G.; Fatta-Kassinos, D.; Nunes, O.C. Antibiotic resistance in urban aquatic environments: Can it be controlled? *Appl. Microbiol. Biotechnol.* 2016, 100, 1543–1557. [CrossRef] [PubMed]

270. Heuer, O.E.; Kruse, H.; Grave, K.; Collignon, P.; Karunasagar, I.; Angulo, F.J. Human health consequences of use of antimicrobial agents in aquaculture. *Clin. Infect. Dis.* 2009, 49, 1248–1253. [CrossRef] [PubMed]

271. Craun, M.F.; Craun, G.F.; Calderon, R.L.; Beach, M.J. Waterborne outbreaks reported in the United States. *J. Water Health* 2006, 4, 19–30. [CrossRef] [PubMed]

272. Gunther, F.C.; Brunkard, J.M.; Roy, S.L. Causes of outbreaks associated with drinking water in the United States from 1971–2006. *Clin. Microbiol. Rev.* 2010, 23, 507–528.

273. Sanborn, M.; Takaro, T. Recreational water-related illness Office management and prevention. *Can. Fam. Phys.* 2013, 59, 491–495.
274. De Roda Husman, A.M.; Schets, F.M. *Climate Change and Recreational Water-Related Infectious Diseases*; Report 330400002; RIVM: Bilthoven, The Netherlands, 2010.

275. Schets, F.M.; De Roda Husman, A.M.; Havelaar, A.H. Disease outbreaks associated with untreated recreational water use. *Epidemiol. Infect.* 2011, 39, 1114–1125. [CrossRef] [PubMed]

276. Daud, M.K.; Nafees, M.; Ali, S.; Rizwan, M.; Bajwa, R.A.; Shakoor, M.B.; Arshad, M.U.; Chatha, S.A.S.; Deeba, F.; Murad, W.; et al. Drinking Water Quality Status and Contamination in Pakistan. *BioMed Res. Int.* 2017, 2017. [CrossRef] [PubMed]

277. Hemson, D.; Dube, B. Water services and public health: The 2000–2001 cholera outbreak in KwaZulu-Natal, South Africa. In Proceedings of the 8th World Congress on Environmental Health, Durban, South Africa, 22–27 February 2004.

278. Allam, R.R.; Uthappa, C.K.; Nidini, C.; Udaragudi, P.R.; Tadi, G.P.; Murhekar, M.V. An outbreak of cholera due to contaminated water, Medak district, Andhra Pradesh, India. *Indian Commun. Med.* 2015, 40, 283–285. [CrossRef]

279. Biswas, D.K.; Bhunia, R.; Maji, D.; Das, P. Contaminated Pond Water Favors Cholera Outbreak at Haibatpur Village, Purba Medinipur District, West Bengal, India. *J. Trop. Med.* 2014, 2014. [CrossRef] [PubMed]

280. Ramamurthy, T.; Sharma, N.C. Cholera outbreaks in India. *Curr. Trop. Microbiol. Immunol.* 2014, 379, 49–85. [CrossRef]

281. He, F.; Han, K.; Liu, L.; Sun, W.; Zhang, L.; Zhu, B.; Ma, H. Shigellosis Outbreak Associated with Contaminated Well Water in a Rural Elementary School: Sichuan Province, China, June 7–16, 2009. *PLoS ONE* 2009, 7, e47239. [CrossRef] [PubMed]

282. Zeng, W.; Jiang, S.; Liang, X.; Chen, J.; Dou, F. Investigation of a Community Outbreak of Diarrhea Associated with Drinking Water in Suburb of Chengdu, China. *Open J. Epidemiol.* 2015, 5, 147–154. [CrossRef]

283. Nguyen, T.V.; Pham, Q.D.; Do, Q.K.; Diep, T.T.; Ho, T.V.; Do, H.T.; Phan, L.T.; Tran, H.N. Cholera returns to southern Vietnam in an outbreak associated with consuming unsafe water through iced tea: A matched casecontrol study. *PLoS Negl. Trop. Dis.* 2017, 11, e0005490. [CrossRef] [PubMed]

284. Ali, E.; van den Beigh, R.; H’Dondt, R.; Kuma-Kuma, D.; De Weggeneleire, A.; Baudot, Y.; Lambert, V.; Hunter, P.; Zachariah, R.; Maes, P. Localised transmission hotspots of a typhoid fever outbreak in the Democratic Republic of Congo. *Pan Afr. Med. J.* 2017, 28, 179. [CrossRef]

285. Kovaˇ cic, A.; Huljev, Ž.; Sušic, E. Groundwater as the source of outbreak of *Salmonella Enteritidis*. *J. Epidemiol. Glob. Health* 2017, 7, 181–184. [CrossRef] [PubMed]

286. Farooqui, A.; Khan, A.; Kazmi, S.U. Investigation of a community outbreak of typhoid fever associated with drinking water. *BMC Public Health* 2009, 9, 476. [CrossRef] [PubMed]

287. Ma, Q.; Xu, X.; Luo, M.; Wang, J.; Yang, C.; Hu, X.; Liang, B.; Wu, F.; Yang, X.; Wang, J.; et al. A waterborne outbreak of Shigella sonnei with resistance to azithromycin and third-generation cephalosporins in China in 2015. *Antimicrob. Agents Chemother.* 2015, 61, e00308-17. [CrossRef] [PubMed]

288. Akoachere, J.-F.T.K.; Masalla, T.N.; Njom, H.A. Multidrug resistant toxigenic *Vibrio cholera* O1 is present in water sources in New Bell, Douala, Cameroon. *BMC Infect. Dis.* 2013, 13, 366. [CrossRef] [PubMed]

289. Grace, D. Review of evidence on antimicrobial resistance and animal agriculture in developing countries. *Int. Livest. Inst.* 2015. [CrossRef]

290. Purohit, M.R.; Chandran, S.; Shah, H.; Diwan, V.; Tamhankar, A.J.; Lundborg, C.S. Antibiotic Resistance in an Indian Rural Community: A ‘One-Health’ Observational Study on Commensal Coliform from Humans, Animals, and Water. *Int. J. Environ. Res. Public Health* 2017, 14, 386. [CrossRef]

291. Talukdar, P.K.; Rahman, M.; Rahman, M.; Nabi, A.; Islam, Z.; Hoque, M.M.; Endtz, H.P.; Islam, M.A. Antimicrobial resistance, virulence factors and genetic diversity of *Escherichia coli* isolates from household water supply in Dhaka, Bangladesh. *PLoS ONE* 2013, 8. [CrossRef] [PubMed]

292. Chishimba, K.; Hang’ombe, B.M.; Muzandu, K.; Mshana, S.E.; Matee, M.I.; Nakajima, C.; Suzuki, Y. Detection of Extended-Spectrum Beta-Lactamase-Producing *Escherichia coli* in market-ready chickens in Zambia. *Int. J. Microbiol.* 2016, 2016, 5275724. [CrossRef] [PubMed]

293. Mercat, M.; Clermont, O.; Massot, M.; Ruppe, E.; Garine-Wichatsky, M.D.; Miguel, E.; Fox, H.V.; Cornelis, D.; Andremont, A.; Denamur, E.; et al. *Escherichia coli* Population Structure and Antibiotic Resistance at a Buffalo/Cattle Interface in Southern Africa. *Appl. Environ. Microbiol.* 2016, 82, 1459–1467. [CrossRef] [PubMed]
294. De Faria, A.C.S.; de Godoy, I.; Sanches, A.A.A.; Iglesias, G.A.; Candido, S.L.; da Paz, R.C.R.; Nakazato, L.; Dutra, V. Detection of resistance genes and evaluation of water quality at zoo lakes in Brazil. Ciência Rural 2016, 46, 860–866. [CrossRef]

295. Mainda, G.; Bessell, P.B.; Muma, J.B.; McAteer, S.P.; Chase-Topping, M.E.; Gibbons, J.; Stevens, M.P.; Gally, D.L.; Bronsvoort, B.M.D.C. Prevalence and patterns of antimicrobial resistance among Escherichia coli isolated from Zambian dairy cattle across different production systems. Sci. Rep. 2015, 5, 12439. [CrossRef] [PubMed]

296. Hinthong, W.; Pumipuntu, N.; Santajit, S.; Kulpchanprasit, S.; Buranasinsup, S.; Sookrugn, N.; Chaichumpa, W.; Aiumurai, P.; Indrawattana, N. Detection and drug resistance profile of Escherichia coli from subclinical mastitis cows and water supply in dairy farms in Saraburi Province, Thailand. PeerJ 2017, 5, e3431. [CrossRef] [PubMed]

297. Adzitey, F.; Nafisah, S.; Haruna, A. Antibiotic Susceptibility of Escherichia coli Isolated from some Drinking Water Sources in Tamale Metropolis of Ghana. Curr. Res. Bacteriol. 2015, 8, 34–40. [CrossRef]

298. Soufi, L.; Abbassi, M.S.; Sanz, Y.; Vinué, L.; Somalo, S.; Zarazaga, M.; Abbas, A.; Dbuya, R.; Khanfir, L.; Hassen, A.B.; et al. Prevalence and Diversity of Integrons and Associated Resistance Genes in Escherichia coli Isolates from Poultry Meat in Tunisia. Foodborne Pathog. Dis. 2009, 6, 1067–1073. [CrossRef] [PubMed]

299. Bagré, T.S.; Sambe-Ba, B.; Ibrahim, H.B.; Tchamba, G.B.; Dembélé, R.; Wane, A.A.; Bako, E.; Traoré, A.S.; Barro, N.; Gassama-Sow, A. Isolation and characterization of enteropathogenic and enterotoxigenic Escherichia coli from dairy products consumed in Burkina Faso. Afr. J. Microbiol. Res. 2017, 11, 537–545.

300. Lyimo, B.; Buza, J.; Subbiah, M.; Smith, W.; Call, D.R. Comparison of antibiotic resistant Escherichia coli obtained from drinking water sources in northern Tanzania: A cross-sectional study. BMC Microbiol. 2016, 16, 254. [CrossRef] [PubMed]

301. De Oliveira, F.A.; Brandelli, A.; Tondo, E.C. Antimicrobial resistance in Salmonella Enteritidis from foods involved in human salmonellosis outbreaks in southern Brazil. New Microbiol. 2006, 29, 49–54. [PubMed]

302. El-Sharkawy, H.; Tahoun, A.; El-Gohary, A.B.D.E.G.A.; El-Abasy, M.; El-Khayat, F.; Gillespie, T.; Kitade, Y.; Hafez, H.M.; Neubauer, H.; El-Adawy, H. Epidemiological, molecular characterization and antibiotic resistance of Salmonella enterica serovars isolated from chicken farms in Egypt. Gut Pathog. 2017, 9, 8. [CrossRef] [PubMed]

303. Christabel, M.; Budambula, N.; Kiiru, J.; Kariuki, S. Characterization of antibiotic resistance in environmental enteric pathogens from Kibera slum in Nairobi-Kenya. J. Bacteriol. Res. 2012, 4, 46–54. [CrossRef]

304. El-Sharkawy, H.; Tahoun, A.; El-Gohary, A.B.D.E.G.A.; El-Abasy, M.; El-Khayat, F.; Gillespie, T.; Kitade, Y.; Hafez, H.M.; Neubauer, H.; El-Adawy, H. Epidemiological, molecular characterization and antibiotic resistance of Salmonella enterica serovars isolated from chicken farms in Egypt. Gut Pathog. 2017, 9, 8. [CrossRef] [PubMed]

305. Mkize, N.; Zishiri, O.T.; Mukaratirwa, S. Genetic characterization of antimicrobial resistance and virulence genes in Staphylococcus aureus isolated from commercial broiler chickens in the Durban metropolitan area, South Africa. J. S. Afr. Vet. Assoc. 2017, 88, a1416. [CrossRef] [PubMed]

306. Ateba, C.N.; Mbewe, M.; Moneoang, M.S.; Bezuidenhout, C.C. Antibiotic-resistant Staphylococcus aureus isolated from milk in the Mafikeng Area, North West province, South Africa. S. Afr. J. Sci. 2010, 106. [CrossRef]

307. Elmadiena, M.M.; El Hussein, A.A.; Muckle, C.A.; Cole, L.; Wilkie, E.; Mistry, K.; Perets, A. Antimicrobial susceptibility and multi-drug resistance of Salmonella enterica subspecies enterica serovars in Sudan. Trop. Anim. Health Prod. 2013, 45, 1113–1118. [CrossRef] [PubMed]

308. Martins, E.; Novaïs, C.; Freitas, A.R.; Dias, A.R.; Ribeiro, T.G.; Antunes, P.; Peixe, L. Filling the map for antimicrobial resistance in sub-Saharan Africa: Ampicillin-resistant Enterococcus from non-clinical sources in Angola. J. Antimicrob. Chemother. 2015, 2914–2916. [CrossRef] [PubMed]

309. Taviani, E.; Ceccarelli, D.; Lazzaro, N.; Bani, S.; Cappuccinelli, P.; Colwell, R.R.; Colombo, M.M. Environmental Vibrio spp., isolated in Mozambique, contain a polymorphic group of integrative conjugative elements and class 1 integrons. FEMS Microbiol. Ecol. 2008, 64, 45–54. [CrossRef] [PubMed]

310. Raafat, S.A.; Abo-Elnagd, E.K.; Awad, R.A.; Hassan, E.M.; Alrasheedy, Z.E. Prevalence of Vancomycin Resistant Enterococci in Different Food Samples. Egypt. J. Med. Microbiol. 2016, 25, 47–55.
312. Said, L.B.; Klibi, N.; Dziri, R.; Borgo, F.; Boudabous, A.; Ben Slama, K.B.; Torres, C. Prevalence, antimicrobial resistance and genetic lineages of *Enterococcus* spp. from vegetable food, soil and irrigation water in farm environments in Tunisia. *J. Sci. Food Agric.* 2016, 96, 1627–1633. [CrossRef] [PubMed]

313. Said, L.B.; Hamdoumi, M.; Klibi, A.; Slama, K.B.; Torres, C.; Klibi, N. Diversity of species and antibiotic resistance in enterococci isolated from seafood in Tunisia. *Ann. Microbiol.* 2017, 67, 135–141. [CrossRef]

314. Loeto, D.; Wale, K.; Coetzee, T.; Khare, K.B.; Sigwele, T.C.; Letsholo, B.; Ndabambi, N. Determination of antibiotic resistance and enterotoxigenic potential of *Staphylococcus aureus* strains isolated from foods sold by street vendors in Gaborone, Botswana. *Int. J. Bioassays* 2017, 6, 5334–5339. [CrossRef]

315. Jamali, H.; Paydar, M.; Radmehr, B.; Ismail, S.; Dadrasnia, A. Prevalence and antibiotic resistance of *Staphylococcus aureus* isolated from raw milk and dairy products. *Food Control* 2015, 54, 383–388. [CrossRef]

316. Adesoji, A.T.; Adeniyi, A.O.; Olatoye, I.O. Molecular characterization of selected multidrug resistant *Pseudomonas* from water distribution systems in South western. *Nigeria Ann. Clin. Microbiol. Antimicrob.* 2015, 14, 39. [CrossRef] [PubMed]

317. Igbinosa, E.O.; Obuekwe, I.S. Evaluation of antibiotic resistant gene in abattoir environment: A concern to public health. *J. Appl. Sci. Environ. Manag.* 2014, 18, 165–171. [CrossRef]

318. Zishiri, O.T.; Mkhize, N.; Mukaratirwa, S. Prevalence of virulence and antimicrobial resistance genes in *Salmonella* spp isolated from commercial chickens and human clinical isolates from South Africa and Brazil. *Onderstepoort J. Vet. Res.* 2016, 83, a1067. [CrossRef] [PubMed]

319. Sinwat, N.; Angkititrakul, S.; Coulson, K.F.; Pilapil, F.M.I.R.; Meunsene, D.; Chuanchuen, R. High prevalence and molecular characteristics of multidrug-resistant *Salmonella* in pigs, pork and humans in Thailand and Laos provinces. *J. Med. Microbiol.* 2016, 65, 1182–1193. [CrossRef] [PubMed]

320. Bada-Alambedji, R.; Fofana, A.; Seydi, M.; Akakpo, A.J. Antimicrobial resistance of *Salmonella* isolated from poultry carcasses in Dakar (Senegal). *Braz. J. Microbiol.* 2006, 37, 510–515. [CrossRef]

321. Shilangale, R.P.; Klibi, N.; Boudabous, A.; Slama, K.B.; Torres, C.; Klibi, N. Prevalence, serotypes and antimicrobial resistance of *Salmonella* isolated from beef and irrigation water in farm environments in Tunisia. *J. Sci. Food Agric.* 2016, 96, 1627–1633. [CrossRef] [PubMed]

322. Sina, H.; Baba-Moussa, F.; Kayodé, A.P.; El Baroudi, R.D.; El Magharmouch, S.; Diouf, S.; El Maktouf, N. Antimicrobial resistance and molecular characteristics of multidrug-resistant *Salmonella* in pigs, pork and humans in Thailand and Laos provinces. *J. Med. Microbiol.* 2016, 65, 1182–1193. [CrossRef] [PubMed]

323. Abdellah, E.A.; Fouzia, R.F.; Bouchra, O. Prevalence and antibiogram study of *Escherichia coli* and *Staphylococcus aureus* isolated from turkey meat in Morocco. *Pharmaceut. Anal. Acta* 2013, 4, 270. [CrossRef]

324. Olaraniran, A.O.; Nzimande, S.B.T.; Mkize, N.G. Antimicrobial resistance and virulence signatures of *Listeria* and *Aeromonas* species recovered from treated wastewater effluent and receiving surface water in Durban, South Africa. *BMC Microbiol.* 2015, 15, 234. [CrossRef] [PubMed]

325. Nyabundi, D.; Onkoba, N.; Kimathi, R.; Nyachieo, A.; Juma, G.; Kinyanjui, P.; Kamau, J. Molecular characterization and antibiotic resistance profiles of *Salmonella* isolated from fecal matter of domestic animals and animal products in Nairobi Tropical Diseases. *Travel Med. Vaccines* 2017, 3, 2. [CrossRef] [PubMed]

326. Laffite, A.; Kilunga, P.I.; Kayembe, J.M.; Devarajan, N.; Mulaji, C.K.; Giuliani, G.; Slaveykova, V.I.; Poté, J. Hospital effluents are one of several sources of metal, antibiotic resistance genes, and bacterial markers disseminated in sub-Saharan Urban Rivers. *Front. Microbiol.* 2016, 7, 1128. [CrossRef] [PubMed]

327. Ayandiran, T.A.; Ayandele, A.A.; Dahunsi, S.O.; Ajala, O.O. Microbial assessment and prevalence of antibiotic resistance in polluted Oluwa River Nigeria. *Egypt. J. Aquat. Res.* 2014, 40, 291–299. [CrossRef] [PubMed]

328. Delgado-Gardea, M.C.E.; Tamez-Guerra, P.; Zavala-Mercado, A.; de la Serna, E.; de la Vega, G.E.; Nezábal, G.V.; Pérez-Reocer, M.C.; Sánchez-Ramírez, B.; González-Horta, M.D.C.; Infante-Ramírez, R. Multidrug-Resistant Bacteria Isolated from Surface Water in Bassaseachic Falls National Park, Mexico. *Int. J. Environ. Res. Public Health* 2016, 13, 597. [CrossRef] [PubMed]

329. Ahmed, A.M.; Shimamoto, T. Molecular characterization of antimicrobial resistance in Gram-negative bacteria isolated from bovine mastitis in Egypt. *Microbiol. Immunol.* 2011, 55, 318–327. [CrossRef] [PubMed]
330. Soge, O.O.; Giardino, M.A.; Ivanova, I.C.; Pearson, A.L.; Meschke, J.S.; Roberts, M.C. Low prevalence of antibiotic-resistant gram-negative bacteria isolated from rural south-western Ugandan groundwater. *Water SA* 2009, 35, 343–347. [CrossRef]

331. Kariuki, S.; Dougan, G. Antibacterial resistance in sub-Saharan Africa: An underestimated emergency. *Ann. N. Y. Acad. Sci.* 2014, 1323, 43–55. [CrossRef] [PubMed]

© 2018 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).