Review

Impact of Anthropogenic Activities on the Dissemination of ARGs in the Environment—A Review

Małgorzata Czatzkowska, Izabela Wolak, Monika Harnisz and Ewa Korzeniewska *

Department of Water Protection Engineering and Environmental Microbiology, Faculty of Geoengineering, University of Warmia and Mazury in Olsztyn, Pravocheńskiego 1, 10-720 Olsztyn, Poland
* Correspondence: ewa.korzeniewska@uwm.edu.pl

Abstract: Over the past few decades, due to the excessive consumption of drugs in human and veterinary medicine, the antimicrobial resistance (AR) of microorganisms has risen considerably across the world, and this trend is predicted to intensify. Many worrying research results indicate the occurrence of pools of AR, both directly related to human activity and environmental factors. The increase of AR in the natural environment is mainly associated with the anthropogenic activity. The dissemination of AR is significantly stimulated by the operation of municipal facilities, such as wastewater treatment plants (WWTPs) or landfills, as well as biogas plants, agriculture and farming practices, including animal production and land application of manure. These activities entail a risk to public health by spreading bacteria resistant to antimicrobial products (ARB) and antibiotic resistance genes (ARGs). Furthermore, subinhibitory concentrations of antimicrobial substances additionally predispose microbial consortia and resistomes to changes in particular environments that are permeated by these micropolllutants. The current state of knowledge on the fate of ARGs, their dissemination and the complexity of the AR phenomenon in relation to anthropogenic activity is inadequate. This review summarizes the state-of-the-art knowledge on AR in the environment, in particular focusing on AR spread in an anthropogenically altered environment and related environmental consequences.

Keywords: antibiotics; antimicrobial resistance; anthropogenic pressure; wastewater; sewage sludge; landfills; biogas plants; animal husbandry; agriculture

1. Introduction

Antibiotics have been used for decades in the pharmacotherapy of bacterial and fungal infections. The discovery of antibiotics is counted among the most important achievements in the history of medicine [1]. Pharmaceuticals are broadly used in human and veterinary medicine. However, their frequent and unwarranted consumption raises a serious concern, compounded by the lack of social awareness of the consequences of excessive administration of drugs [2]. Klein et al. [3] informed that the global consumption of antibiotics increased by 65% in the years 2000–2015, and the predicted rise in drug consumption by 2030 peaks at 200% relative to the year 2015. Based on the data collected by the World Health Organization (WHO) in 65 countries around the world, the average highest antibiotic consumption was noted in the Eastern Mediterranean Region, while the lowest one was in the African Region and the Region of the Americans [4]. The daily defined dose (DDD) in Mongolia, over the whole period analyzed, soared to 64.41 per day (Figure 1). Antibiotics can be excreted by both humans and animals in an unchanged form or as products of their metabolism, regardless of the dose taken; therefore intensive drug consumption in the world increases the pool of released drugs in the environment [5].
Unused antibiotics, which are supposed to be returned for safe disposal, are often mixed with other waste and reach landfills so that their presence is detected in landfill leachate (LL) [11,12]. The management of LL generated in landfills often consists of the purification of LL together with municipal wastewater at wastewater treatment plants (WWTPs) [13]. Moreover, the wastewater delivered to WWTPs is also found to contain antimicrobial substances, used in the treatment of people and animals, and most often discharged to the environment in an unchanged form [14]. After the wastewater treatment process is completed, wastewater is delivered to water receivers, such as rivers and other surface water bodies, that are directly tied to the natural environment. The presence of antibiotics in wastewater is a serious problem and an environmental threat in the circular wastewater economy [15]. In turn, the high supply of antibiotics in veterinary medicine contributes to the presence of antimicrobial substances in the waste generated by intensive animal breeding, for example, in slurry. Slurry, with the antibiotics and antibiotic metabolites it contains, most often undergoes stabilization, after which it can be discharged into soil environment [16], and then, with run-offs from farmland, it can pollute water bodies. A popular slurry stabilization method is anaerobic digestion (AD) with the generation of biogas. The digestate obtained by AD is also used as fertilizer, and the micropollutants it may contain permeate into the soil environment, groundwater and surface waters [1], thereby increasing the pool of pollutants in the soil and water environments, as well as enabling the circulation of antibiotics in these ecosystems.

Depending on the class of pharmaceuticals, it is estimated that from 40 to 80% of a dose of a drug taken by people or animals are excreted with stool and urine in an unchanged, that is active form [17,18]. The most popular antibiotics used globally belong to the classes of quinolones, macrolides, beta-lactams, and aminoglycosides [19]. Pharmaceuticals from the classes of tetracyclines and sulfonamides are the antibiotics broadly used in veterinary medicine, whereas macrolides, penicillin and fluoroquinolones are most often administered in human medicine [20]. Drugs not metabolized in human or animal organisms enter the environment and threaten soil and water ecosystems and plants. The presence of antibiotics in different ecosystems, even in small concentrations, can cause a series of consequences adverse to the environment. These medications can influence the biodiversity of microorganisms and, most importantly, the pool of antimicrobial resistance genes (ARGs) found in microbiomes settled in a given ecosystem, which can be associated with a direct or indirect risk to public health [21]. Antimicrobial resistance (AR) relates to elevated hospitalization and mortality rates, and new zoonotic diseases caused by antibiotic-resistant bacteria (ARB). This is a serious problem concerning the health of people and the welfare
of animals [22]. Health care authorities from the United States of America [23] and the European Union [24] estimate that at least 35,000 and 33,000 premature deaths per year due to infections caused by ARB occur in the USA and Europe, respectively. Uncontrolled exposure of many environments to antibiotics leads to the persistent selective pressure on microorganisms inhabiting these ecosystems. Moreover, ARB and ARGs can be spread with air, water and through links of trophic chains [25–27].

Drug resistance is a well-described global phenomenon with grievous environmental and epidemiological consequences [28]. Human activity largely contributes to the anthropologically shaped environment becoming a reservoir of ARB and ARGs [29]. The dissemination of AR in the environment is mainly due to the operation of municipal facilities, such as WWTPs [30,31] and landfills [13,32], as well as the sector of agriculture [33,34], animal rearing [35,36] and biogas plants [37]. These areas have a considerable accumulation of ARB, which can transfer ARGs between each other (Figure 2).

![Figure 2. The potential origin and fate of ARGs in the environment.](image)

Antibiotics, ARB and ARGs raise a growing concern among researchers and institutions dealing with protecting public health and the environment, and there has been a global discussion on AR for years. The extent of environmental pollution caused by the excessive consumption of drugs, both in human and veterinary medicine, is enormous and therefore gives rise to serious worries [38–41]. In 2006, based on the information about AR determinants, the concept of resistome was developed, understood as a set of all ARGs among pathogenic and commensal microorganisms inhabiting a given ecological niche [42]. It was also concluded that anthropogenic activities directly shape or indirectly affect the environmental AR, while ARGs can be transmitted between people, animals and the environment. In 2016, during the General Assembly of the United Nations, heads of the UN member states admitted that it was necessary to reinforce systems to monitor infections caused by ARB and amounts of antimicrobial medications used in medicine, veterinary medicine and plant production [43].

Numerous research papers dedicated to the spread of AR have laid the foundation for further studies under the program called ‘One Health’, to gain insight into this issue in the context of human medicine, veterinary medicine and the broadly understood environment in a holistic approach. Reduction of the dissemination of AR is one of the principal assumptions of the ‘One Health’ strategy. Another objective is to promote the monitoring of the environment and conduct joint research by scholars from many fields of science, such as public health, veterinary medicine and environmental protection. This strategy
also highlights the strong dependence between the health state of animals and people and the condition of the environment they occupy together.

Importantly, in 2019, the European Commission launched the European Green Deal [44], which promotes measures ‘to increase the efficient use of resources in order to achieve a clean and circular economy, to restore biodiversity, and to reduce pollution.’ In the coming years, it is therefore expected that the consumption of chemical fertilizers will decrease while the use of organic fertilizers, based on livestock and poultry manure, will increase [45]. Meanwhile, monitoring the microbiological contamination of natural fertilizers by ARB and ARGs is insufficient. It is expected that the ongoing international programs devoted to the reduction of AR will enable the implementation of information and research programs and the legal regulations serve to strengthen the control measures and prevent the spread of AR.

The main objective of this study has been to review the current state of knowledge on the impact of anthropogenic activities on the presence of antibiotics and the spread of ARB and ARGs in the environment. The paper describes key reservoirs of antibiotics, ARB and ARGs in the environment and the hotspots involved in their release due to human activity. In addition, the current knowledge on the effects of antibiotic residues on the environment has been reviewed, and the broad consequences of environmental pollution with pharmaceuticals and ARGs have been described to gain a better insight into these issues and support future research.

2. Materials and Methods

This study has developed a protocol to specify the research questions, criteria for inclusion/exclusion, data sources and scientific literature search engines. The authors adhered to the checklist of the Preferred Reporting Items for Systematic Review and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) to carry out the review.

2.1. Data Sources

In compliance with the PRISMA guidelines, the articles were selected according to the four criteria: (i) identification, (ii) screening studies, (iii) eligibility, and (iv) inclusion. The SCOPUS, PubMed, and Google Scholar scientific literature databases were surveyed to find reviewed papers published from 1 January 2010 to 27 September 2022.

2.2. Search Strategy

The strategy employed in the search is illustrated Supplementary Materials Figure S1. The keywords used in the search strategy were: (“Antibiotic Resistance” OR “antibiotic resistance genes” OR “anthropogenic”) AND (“antibiotic resistance genes” OR “antibiotic resistance” OR “co-selection” OR “heavy metals” OR “microplastic”). These were tailored to each database.

A preliminary search was conducted of the published scientific literature related to the subject of this study to identify the keywords to be employed in the advanced search. The keywords for the search are presented in Figure 3. Complementary searches (including forward and backward citation searches of included articles) were conducted to further locate eligible articles that were not identified in the databases search. In addition, a reference list of articles was checked manually so as to find adequate scientific publications for this review of literature data. After filtering the literature, 225 scientific publications were selected for this review article. Figure S2 shows the publications used for this review, grouped by publication year.
Figure 3. A keyword co-occurrence map, considering papers containing “antibiotic resistance” as a keyword. Circle size is proportional to the number of co-occurrences of a particular keyword and clustering by color is based on patterns of co-occurrence among multiple keywords in the published articles. The map was created with VOSviewer (v1.6.16; 2020, Centre for Science and Technology Studies, Leiden University, The Netherlands).

The references identified through the searched terms were imported into Mendeley (Copyright © 2021 Mendeley Ltd., Amsterdam, The Netherlands), and duplicates were removed. The articles were analyzed by reviewing the titles and abstracts in line with our inclusion and exclusion criteria, and the articles selected for this review were read in full text.

3. Results

3.1. Municipal Facilities as Reservoirs of ARGs

The growing global human population and the continual development of local communities are associated with the need to manage huge amounts of wastewater and solid waste. The municipal amenities responsible for this task, such as WWTPs, waste sorting facilities and disposal sites, are an important source of ARB, ARGs and residues of antimicrobial substances, which can further permeate the environment. Based on the review of the literature data, we identified three main reservoirs of ARGs associated with the municipal economy: WWTPs, landfills and biogas plants.

3.1.1. WWTPs

High usage of water by medical care institutions leads to the generation of large quantities of hospital wastewater and sewage. In developed countries, hospitals generate from 400 to 1200 L of wastewater per patient, while in developing countries, this amount ranges between 200 and 400 L [46]. Wastewater from the health care sector is characterized by the presence of a wide array of microorganisms of special clinical importance, including ARB-carrying ARGs. In addition, hospital wastewater also contains antimicrobial substances used in the treatment of patients [47,48]. In view of the ever-growing consumption of drugs and the development of the health care system, the generation of large amounts of hospi-
tal wastewater and its proper management are an enormous challenge in environmental engineering [46].

According to the literature data, although hospital wastewater is treated in hospital wastewater treatment plants (HWWTPs), it is still a reservoir of antibiotics, ARB and ARGs. The subsequent delivery of hospital wastewater to municipal WWTPs is an additional source of promoting the exchange of genetic structures between microorganisms, i.e., horizontal gene transfer (HGT). The process of HGT plays a major role in the dissemination of AR among bacteria [49] and can be realized by three well-studied mechanisms; (1) transduction (transfer of genetic material between bacteria via bacteriophages) [50], (2) transformation (changing the bacterial genotype through extracellular DNA acquire) [51] or (3) conjugation (exchange of conjugative plasmids between physically attached bacteria). Conjugation is commonly observed in nature, even among distantly related microorganisms [19].

The bacteria present in hospital wastewater are particularly predisposed to HGT processes [52]. Yao et al. [53] analyzed the occurrence of antibiotics, ARB and ARGs in wastewater from three hospitals, each using different wastewater treatment processes, including disinfection. These authors noted an incomplete effectiveness in the removal of antibiotics through the processes carried out in HWWTPs, as well as a relatively high abundance of ARGs in treated wastewater, which is then conveyed to WWTPs. Moreover, concentrations of some ARGs encoding the resistance to beta-lactams increased after the treatment in HWWTPs (\( \text{bla}_{\text{OXA-1}} \), \( \text{bla}_{\text{OXA-10}} \) and \( \text{bla}_{\text{TEM-1}} \)). The wastewater treated in HWWTPs was also distinguished by the high counts of pathogenic or opportunistic bacteria of the genera \textit{Acinetobacter}, \textit{Klebsiella}, \textit{Aeromonas} and \textit{Pseudomonas}. These results confirmed the co-occurrence of antibiotics, ARB and ARGs in treated hospital wastewater. When such wastewater is delivered to WWTPs, it enriches the pool of ARB and ARGs in incoming wastewater. As reported in literature references, ARB and ARGs in wastewater from hospitals can be two to nine orders of magnitude higher than in typical municipal wastewater [54].

The main goal of the processes carried out in WWTPs is to lower organic matter content in wastewater and reduce the counts of microorganisms, including pathogenic ones. The structure of the microbiota in influent wastewater can vary and the wastewater treatment processes induce changes in the number and biodiversity of microorganisms, which may contain ARGs. Differences in the structure of the microbiotas characteristic for the wastewater delivered to WWTPs and for treated wastewater are presented in Table 1.

| Type of Wastewater | Country of Research | Dominant Bacterial Phyla (Percentage) | Reference |
|-------------------|---------------------|--------------------------------------|-----------|
| influent          | Germany             | \textit{Firmicutes} (52.2%), \textit{Proteobacteria} (37.8%), \textit{Bacteroidetes} (4.9%), \textit{Actinobacteria} (2.2%) | [55]      |
| effluent          |                     | \textit{Proteobacteria} (54.8%), \textit{Bacteroidetes} (15.7%), \textit{Firmicutes} (14.3%), \textit{Planctomycetes} (2.9%), \textit{Actinobacteria} (2.6%), \textit{Verrucomicrobia} (2.1%) |           |
| influent          | China               | \textit{Firmicutes} (54%), \textit{Proteobacteria} (34%), \textit{Actinobacteria} (7%), \textit{Bacteroidetes} (2%) | [56]      |
| effluent          |                     | \textit{Proteobacteria} (44%), \textit{Actinobacteria} (13%), \textit{Bacteroidetes} (12%), \textit{Firmicutes} (6%) |           |
| influent          | China               | \textit{Proteobacteria} (51.3%), \textit{Firmicutes} (16.4%), \textit{Actinobacteria} (4.7%), \textit{Verrucomicrobia} (1.8%) | [57]      |
| effluent          |                     | \textit{Proteobacteria} (31.2%), \textit{Firmicutes} (1.1%), \textit{Actinobacteria} (8.1%), \textit{Verrucomicrobia} (2.5%) |           |
| influent          | Poland              | \textit{Proteobacteria} (55.13%), \textit{Firmicutes} (25.6%), \textit{Bacteroidetes} (6.3%), \textit{Actinobacteria} (10.65%) | [58]      |
| effluent          |                     | \textit{Proteobacteria} (39.06%), \textit{Firmicutes} (10.1%), \textit{Bacteroidetes} (19.62%), \textit{Actinobacteria} (26.26%), \textit{Verrucomicrobia} (2.54%) |           |
Antibiotics are mentioned among the micropollutants present in wastewater entering WWTPs (Table 2). It has been confirmed that there are effective, chemical and physico-chemical methods for potentially eliminating antibiotics and other AR determinants from wastewater but because of the operating costs, these methods are not widely used [59,60]. As the technological processes most often employed in WWTPs do not unfortunately include technologies specifically designed to remove pharmaceuticals from wastewater, these pollutants eventually end up in surface water bodies together with treated wastewater. Effluent wastewater from WWTPs can be, therefore, one of the major sources of ARB and ARGs in water ecosystems [61–64].

Table 2. Antimicrobial substances most frequently detected in the influent wastewater collected from the WWTPs.

| Antimicrobial Class | Antimicrobial Substance | Concentration [ng L\(^{-1}\)] | Reference |
|---------------------|-------------------------|-------------------------------|-----------|
| beta-lactam         | amoxicillin             | 232–5698                      | [65]      |
|                     | ampicillin              | 306–4120                      | [65]      |
|                     | penicillin G            | 120–2230                      | [66]      |
| fluoroquinolone     | ciprofloxacin           | 475–913                       | [67,68]   |
| imidazole           | ofloxacin               | 130–730                       | [66,69]   |
| macrolide           | clarithromycin          | 904–7.3 × 10\(^6\)           | [67,68,71]|
| macrolide           | erythromycin            | 5–2300                        | [71,72]   |
| sulfonamide         | sulfamethoxazole        | 387–5.3 × 10\(^6\)           | [67,68,71]|
| tetracycline        | sulfadiazine            | 326–1072                      | [71]      |
| tetracycline        | tetracycline            | 26.23–4160                    | [66,70]   |
| tetracycline        | doxycycline             | 16.44–97.911                  | [70]      |

Wastewater treatment plants are among the human-made facilities that create conditions particularly suitable for the occurrence of processes of exchange of genetic structures, including ARGs, between microorganisms dwelling in wastewater being treated in these facilities. At the same time, WWTPs promote the increased selection of bacteria possessing specific ARGs [73]. High counts of microorganisms and subinhibitory concentrations of antimicrobials present in influent wastewater contribute to the transfer of ARGs between microorganisms due to the so-called selection pressure and, consequently, to their spreading in wastewater on an enormous scale [74]. Dissemination of ARGs among microorganisms is also associated with mobile genetic elements (MGEs), such as plasmids, conjugation transposons and integrons. Mobile genetic elements allow the capture and expression of exogenous genes [75]. MGEs also facilitate the transfer of ARGs between microorganisms. Moreover, this transfer can also be stimulated by the presence in the ecosystem of such antibiotics as beta-lactams or tetracyclines, popular in human and veterinary medicine [76]. Of particular concern is the fact that even when selective pressure is absent or weak, MGEs can be transferred between microorganisms [77].

Many researchers have analyzed ARB and ARGs in wastewater sampled at WWTPs [74,78–87]. It has been confirmed that the general population’s seasonal intensity of drug consumption affects both the concentrations of ARGs in wastewater and the extent of their further transmission to the environment [78]. Wastewater has been observed to contain clinically significant strains of bacteria characterized by drug resistance [79,80]. It has also been found that despite the high percent reduction of ARB and ARGs resulting from wastewater treatment, considerable amounts of these micropollutants are still discharged into the environment together with treated wastewater [78,79]. Furthermore, it has been determined that ARB and ARGs can be transferred in bioaerosol from wastewater to the mucus membrane of the upper respiratory tract among the WWTP’s employees, thereby increasing their exposure to infectious agents [80]. The types of ARGs whose presence has been detected in influent and effluent wastewater sampled at WWTPs and HWWTPs are summarized in Table 3.
| Type of Wastewater | Type of Samples | ARGs | The Relative Abundance of ARGs (Number of Copies Normalized against 1 mL of Sample or Gene 16S rRNA) | Ref. |
|-------------------|-----------------|------|-------------------------------------------------------------------------------------------------|-----|
| Municipal wastewater | Effluent | blaGES-1, blaTEM-1, blaOXA-1, qnrS, qnrA, blagCIS-1, blaTEM-1, blagOXA-1, blaTEM-1 | from $4.6 \times 10^{-1}$ to $1.4 \times 10^{-3}$ | [53] |
| Hospital wastewater | Effluent | blaTEM, ermB, qnrS, sul1, tetW, blagTEM, blagCIS, blagOXA, | gene copies in 1 mL of sample range from $10^6$ to $10^7$ | [81] |
| | Effluent | blagTEM, blagCIS, blagOXA, sul1, tetA, tetB, tetC, tetD, TEM, sul1, tet2, sul2, sul2, sul2 | from $1.0 \times 10^4$ to $1.7 \times 10^6$ | [78] |
| | Effluent | blagTEM, blagCIS, blagOXA, sul1, tetA, tetB, tetC, tetD, TEM, sul1, tet2, sul2, sul2 | from $1.0 \times 10^4$ to $1.7 \times 10^6$ | [85] |
| | Effluent | blagTEM, blagCIS, blagOXA, sul1, tetA, tetB, tetC, tetD, TEM, sul1, tet2, sul2, sul2 | from $1.0 \times 10^4$ to $1.7 \times 10^6$ | [84] |
| | Effluent | blagTEM, blagCIS, blagOXA, sul1, tetA, tetB, tetC, tetD, TEM, sul1, tet2, sul2, sul2 | from $1.0 \times 10^4$ to $1.7 \times 10^6$ | [74] |
| | Effluent | blagTEM, blagCIS, blagOXA, sul1, tetA, tetB, tetC, tetD, TEM, sul1, tet2, sul2, sul2 | from $1.0 \times 10^4$ to $1.7 \times 10^6$ | [85] |
| | Effluent | blagTEM, blagCIS, blagOXA, sul1, tetA, tetB, tetC, tetD, TEM, sul1, tet2, sul2, sul2 | from $1.0 \times 10^4$ to $1.7 \times 10^6$ | [86] |
| | Effluent | blagTEM, blagCIS, blagOXA, sul1, tetA, tetB, tetC, tetD, TEM, sul1, tet2, sul2, sul2 | from $1.0 \times 10^4$ to $1.7 \times 10^6$ | [87] |
| | Effluent | blagTEM, blagCIS, blagOXA, sul1, tetA, tetB, tetC, tetD, TEM, sul1, tet2, sul2, sul2 | from $1.0 \times 10^4$ to $1.7 \times 10^6$ | [81] |

* na—data not available.
Wastewater treatment plants can receive thousands of m$^3$ daily of wastewater, which can carry an immense load of various kinds of pollutants. The processes carried out in WWTPs aiming to remove impurities from wastewater typically comprise the pre-treatment stage, where most of the suspended solids should be removed. The next stage is the biological treatment of wastewater, where primarily the activated sludge technology is worth noting. Wastewater is then conveyed from biological treatment chambers to a secondary sedimentation tank, where it is separated from activated sludge. Some of the sludge is recirculated back to the bioreactors, while the remaining amounts are removed [90]. The initial sludge generated in the early stage of wastewater treatment and the excess sludge from bioreactors compose a pool of sewage sludge that requires proper disposal and management.

Impurities present in influent wastewater reaching WWTPs, including microbiological pollutants and residues of antimicrobial substances, accumulate in sewage sludge. There are many reports [73,83] confirming that as a result of the presence of antibiotics as well as ARB and ARGs in effluent wastewater from WWTPs, their occurrence is also observed in sewage sludge. The types and concentrations of antibiotics and ARGs, in addition to the abundance and composition of microbial assemblages present in sewage sludge, can vary and is directly dependent on the quality of wastewater received by WWTPs, and on the type of processes involved in the wastewater treatment. Data concerning the occurrence of particular micropollutants in sewage sludge are collated in Table 4.

### Table 4. Antimicrobials, microorganisms and ARGs detected in sewage sludge.

| Antimicrobial Class and Antimicrobial Substances | Ref. | Dominant Bacterial Phyla and Genera | Ref. | ARGs | Ref. |
|-----------------------------------------------|------|------------------------------------|------|------|------|
| Fluoroquinolone:                              |      |                                    |      |      |      |
| ofloxacin [0.5–7950 µg kg$^{-1}$].            |      | Proteobacteria                     |      |      |      |
| norfloxacin [75.5–21,335 µg kg$^{-1}$].       |      | (Acinetobacter, Aeromonas,         |      |      |      |
| ciprofloxacin [≤1–4720 µg kg$^{-1}$].         |      | Alcaligenes, Comamonas,            |      |      |      |
|   roxithromycin [≤17 µg kg$^{-1}$].           |      | Brevedundomonas,                   |      |      |      |
|   tetracycline:                              |      | Methylobacterium,                  |      |      |      |
|      oxytetracycline [1742–36,650 µg kg$^{-1}$] | 96–100 | Sulfonamide:                       |      |      |      |
|      tetracycline [101–2943 µg kg$^{-1}$].     | 96–100 | (Bacteroides, Cloacibacterium,      |      |      |      |
|                          | 96–100 | Paludibacter, Stephiscobacterium,   |      |      |      |
|                          | 96–100 | Flavobacterium).                   |      |      |      |
|                          | 96–100 | Firmicutes                         |      |      |      |
|                          | 96–100 | (Clostridium, Bacillus)            |      |      |      |
|                          | 96–100 | Actinobacteria                     |      |      |      |
|                          | 96–100 | (Propionibacterium, Mycobacterium),|      |      |      |
|                          | 96–100 | Acidobacteria                      |      |      |      |
|                          | 96–100 | Saccharibacteria                   |      |      |      |
|                          | 96–100 | Spirochaetes                       |      |      |      |
|                          | 96–100 | (Treponema)                        |      |      |      |
| Tetracycline:                               |      |                                    |      |      |      |
| chlorotetracycline [5.95–3843.7 µg kg$^{-1}$]|      |                                    |      |      |      |
| doxycycline [127.45–2104.2 µg kg$^{-1}$]      |      |                                    |      |      |      |

Considering the ongoing dissemination of AR in the environment, it is significant to acknowledge the fact that quantities of sewage sludge produced by WWTPs are growing constantly, reaching hundreds of millions of Mg annually across the whole world. However, not all countries keep statistics on the production of wastewater and sewage sludge. For example, in India, the second country in the world in terms of population (18.04%) and the seventh in size, the data concerning this subject are very limited or fragmentary. It is known that the production of wastewater in India in 2014–2015 was 62,000 million m$^3$ a day, while the wastewater treatment capacity in the same time period was slightly over 23,000 million m$^3$ a day [104]. There are no available data on the production and handling of sewage sludge in that country.

Another Asian country, China, is one of the leading producers of sewage sludge, generating an amount of 11 × 10$^9$ Mg annually [105]. Less than 30% of this amount is used as fertilizer, 26.7% is incinerated, and 20% is deposited on landfills [106]. In 2019,
around 317 thousand Mg of dry matter of sewage sludge was produced in Australia; 70% of this mass fertilizes agricultural land, and 26% is used for soil reclamation purposes. The remaining 6% is deposited in landfills or discharged into the ocean [107].

In the USA, the annual output of sewage sludge in 2019 reached $4.7 \times 10^6$ Mg, of which more than half ended up in landfills [108]. On the other hand, data pertaining to sewage sludge production in South America are scanty. In Brazil, the largest and most populous country on this continent, many municipalities do not possess adequate technologies for wastewater treatment, as a result of which untreated wastewater is discharged to surface water bodies, posing a direct threat to the environment [109]. In 2015, Brazil was inhabited by over 204.5 million people, but only 98 million had access to sewers [110].

In the European Union, the largest sewage sludge is produced by Germany, Spain, Italy and France. Table 5 shows data on sewage sludge production in the EU member states, according to the information provided on the Eurostat website [111]. However, these data are fragmentary because they do not illustrate the whole scale of sewage sludge generation each year by all the EU member states. In the last set of data for the year 2019, some of the largest sewage sludge producers, such as Spain and Italy, are missing [111]. Nearly half of the sewage sludge produced in the EU is used in agriculture and enters soils. Slightly less than 13% are applied for soil reclamation, and almost 9% are deposited in landfills [112].

Table 5. Sewage sludge production and disposal in selected countries in 2019. Based on data from Eurostat, 2022.

| Country             | Production of Sewage Sludge (Thousand Mg) |
|---------------------|------------------------------------------|
| Germany             | 1749.86                                   |
| Poland              | 574.64                                    |
| Austria             | 233.56                                    |
| Romania             | 230.59                                    |
| Hungary             | 227.89                                    |
| Czech Republic      | 221.09                                    |
| Norway              | 141.35                                    |
| Albania             | 96.20                                     |
| Ireland             | 58.63                                     |
| Slovakia            | 54.83                                     |
| Lithuania           | 39.94                                     |
| Slovenia            | 34.80                                     |
| Estonia             | 24.94                                     |
| Latvia              | 24.18                                     |
| Croatia             | 20.65                                     |
| Malta               | 9.69                                      |
| Serbia              | 9.60                                      |
| Bosnia and Herzegovina | 9.50                                  |
| Luxembourg          | 8.89 (e)                                  |

—a—estimated.

Because of the content of organic substances and nutrients, the agricultural use of sewage sludge is a preferred option in many countries [112,113]. Using sewage sludge as a fertilizer is a solution to the problem of its utilization but considering the risk of spreading AR that it involves, this practice creates a real threat to the environment and public health.

Due to the legal restriction on depositing sewage sludge binding in many countries, to manage this type of waste, it is first submitted to stabilization and then used in agriculture as a valuable source of nitrogen and phosphorus, for making compost and for reclamation of degraded land [114]. Disposal of sewage sludge is most often achieved by composting or AD. However, the application of aerobically or anaerobically treated sewage sludge for soil fertilization may trigger serious ecological problems, especially in the context of polluting soil with antibiotics [45]. Antibiotic residues in sewage sludge can appear in a wide range from ng to 100 mg kg$^{-1}$ of the dry matter of sewage sludge [39]. Analysis of the efficiency of sewage sludge stabilization does not include checking the presence of
drugs or the counts of ARB and ARGs. Thus, the pollutants contained in sewage sludge eventually enter the soil environment, which creates a risk of an adverse impact on the physical, chemical and biological properties of soils [15]. Among the consequences of soil fertilization with stabilized sewage sludge containing residues of pharmaceuticals, there are changes in the structure of the soil’s microbiome and resistome, and possible transmission of ARGs between microorganisms inhabiting a given ecosystem.

3.1.2. Landfills

Depositing waste on landfills is a widespread, global practice to dispose of and stabilize the solid fraction of municipal waste, known as MSW (Municipal Solid Waste) [115]. The total amount of MSW gathered in landfills reaches hundreds of millions of Mg annually. The method of landfilling MSW is economically competitive relative to other waste management methods, which is why it is the most common solution used in developing countries [116]. Nevertheless, landfilling makes an important contribution to waste management even in highly developed countries. For instance, 20, 104, 19, 55 and 330,000 Mg of waste daily were deposited in Australia, Denmark, Spain, Sweden and China, respectively, in 2017 [117]. Although, in some countries, the number of active municipal landfills is on the decrease, there are still thousands of active landfills which are planned to be closed in a decade or a few decades. The major problem in waste management, however, is not the quantities of landfilled MSW but the inadequate handling thereof. Particularly in developing countries, nearly 90% of the solid fraction of municipal waste is landfilled without any pretreatment [116].

Landfills contain a wide array of pollutants, including heavy metals or complex organic and inorganic compounds [116]. Moreover, the lack of social awareness concerning risks due to environmental pollution with antibiotics contributes to the wrong handling of unused or expired medicines, which may directly stimulate the increasing content of these contaminants in landfills. Landfills are generally considered to be the site for storing both medicines and illegal clinical waste, used nappies and pet excreta. Antibiotics, like any pharmaceuticals, should be stored properly, and when expired or not used completely, they should be disposed of correctly. However, insufficient social awareness often leads to the incorrect handling of antibiotics, which means that many unused antibiotics end up in landfills. The presence of antibiotics can exert pressure on communities of bacteria, affecting the occurrence of ARB and ARGs [118]. The widespread, excessive and improper use of antibiotics observed nowadays raises serious concerns about the prevalence of ARGs, which are frequently detected in landfills and in LL.

The main problem with landfills is that antibiotics, ARB and ARGs can be transferred to the environment via LL [119]. Water seepage through waste deposited in landfills leads to the leaching of various types of pollutants. The following can be distinguished: suspended substances, dissolved substances and substances originating from the decomposition of waste, as well as microorganisms, including pathogens. One of the biggest challenges connected with the operation of waste disposal plants is to handle LL generated in landfills in an environmentally sound manner [120]. A popular solution is the treatment of LL together with municipal wastewater at WWTPs [121], which results in the additional enrichment of municipal waste with antibiotics, ARB and ARGs [61]. Table 6 presents the specification of antibiotics detected in LL.
Table 6. Summary of antimicrobial substances and their concentration in landfill leachates, based on data collected by Yu et al. [122].

| Antimicrobial Class | Antimicrobial Substance | Concentration [ng L$^{-1}$] |
|---------------------|-------------------------|----------------------------|
| Macrolide           | azithromycin            | from 13.5 to 50.2          |
|                     | erythromycin             | from 12.0 to 39,800.5      |
|                     | roxithromycin            | from 7.8 to 4745.8         |
|                     | cefoxitin                | from 3.1 to 72.3           |
|                     | cefotaxime               | from 11.77 to 537          |
| Beta-lactam         | cephalosporin            | from 22 to 160             |
|                     | penicillin G             | from 4.9 to 4482.5         |
| Flouroquinolone     | norfloxacin              | from 25.9 to 21,033.33     |
|                     | ofloxacin                | from 8.7 to 190,000        |
|                     | sulfadiazine             | from 15.3 to 29,208        |
| Sulfonamide         | sulfamethoxazole         | from 0.7 to 8488           |
|                     | sulfmonomethoxine        | from 9.8 to 2750           |
|                     | doxycycline              | <228                       |
| Tetracycline        | oxytetracycline          | <3245.0                    |
|                     | tetracycline             | from 0.2 to 19,000         |

Many research papers have analyzed the presence of antibiotics, ARB and ARGs in LL. It has been noted that the occurrence of some classes of antibiotics in LL can correlate with the abundance of a local population [116]. It has been observed that concentrations of particular antibiotics in LL from landfills disused for years can remain very high, in excess of the Predicted No Effect Concentrations (PNEC) relative to the AR selection [123]. It has also been demonstrated that LL can be a substantial reservoir of ARGs and MGEs [13,116,124]. The presence of MGEs can be closely correlated with the abundance of ARGs, and the frequency of ARGs and MGEs can correlate additionally with the concentration of particular elements, including heavy metals [116]. Moreover, while some authors have observed significant differences in the distribution of ARGs in LL samples from different landfills [116], others have not noticed any evident regional pattern of distribution of these micropollutants [124]. Wang et al. [13] noted that the process of LL treatment is effective in the removal of ARGs. The research results provided by these scholars confirmed the effect of LL on the water resistome in a river to which treated LL was discharged. This suggests the risk of spreading AR determinants in the environment due to the discharge of treated LL to surface water bodies.

The literature data show that both landfills and LL play a role in the significant pools of antimicrobial substances (Table 6), and ARGs (Table 7) in the environment, thus predisposing AR to uncontrolled development in the environment.

Table 7. Types of ARGs detected in landfill leachate.

| Dominant Microorganisms | ARGs          | The Relative Abundance of ARGs (Number of Copies Normalized against 16S rRNA or ngDNA) | Ref. |
|-------------------------|---------------|--------------------------------------------------------------------------------------|-----|
| Genera: Acholeplasma,  | sul1, sul2,   | >1.0 × 10$^{-1}$/16S rRNA                                                           | [124] |
| Aminicibrio, Candidatus | ermF, adaA,  bacA, |                                                                                  |     |
| Cloacomonas, Petrimonas |               |                                                                                  |     |
| Sedimentibacter, Tissierella |          |                                                                                  |     |
| na a                    | qnrA          | 1.1/165 rRNA                                                                         | [116] |
|                         | qnrB          | 1.13 × 10$^{-2}$/165 rRNA                                                            |     |
|                         | qnrD          | 4.95 × 10$^{-6}$/165 rRNA                                                            |     |
|                         | blaoXa10      | 3.86 × 10$^{-4}$/165 rRNA                                                            |     |
|                         | penA          | 10$^{-6}$–10$^{-5}$/165 rRNA                                                         |     |
Table 7. Cont.

| Dominant Microorganisms | ARGs | The Relative Abundance of ARGs (Number of Copies Normalized against 16S rRNA or ngDNA) | Ref. |
|-------------------------|------|----------------------------------------------------------------------------------|------|
| na                      | tetO | from $4.1 \times 10^{-5}$ to $4.2 \times 10^{-2}$/16S rRNA                    |      |
|                         | tetW | from $5.7 \times 10^{-5}$ to $4.9 \times 10^{-3}$/16S rRNA                    |      |
|                         | blaTEM | from $3.7 \times 10^{-5}$ to $3.9 \times 10^{-2}$/16S rRNA                    | [125]|
|                         | sul1 | from $4.5 \times 10^{-5}$ to $3.1 \times 10^{-2}$/16S rRNA                    |      |
|                         | sul2 | from $1.4 \times 10^{-4}$ to $6.2 \times 10^{-2}$/16S rRNA                    |      |
| Phyla: Proteobacteria, Firmicutes, Chloroflexi, Actinobacteria, Bacteroidetes, Acidobacteria | sul1 | 5.6 ± 0.9 log10/ng DNA                                                         |      |
|                         | sul2 | 5.5 ± 0.8 log10/ng DNA                                                         | [126]|
|                         | aadA1 | 4.1 ± 0.7 log10/ng DNA                                                         |      |
|                         | blaCTX-M |                                 |      |
|                         | tetM |                                 |      |
|                         | tetX | from $2.99 \times 10^{-3}$ to $2.16 \times 10^{-2}$/16S rRNA                  | [127]|

* na—data not available.

3.1.3. Biogas Plants

Due to the human population growth, progressing urbanization and intensification of agriculture, the amounts of organic waste generated worldwide have turned into a huge burden on the natural environment. In order to produce alternative, eco-friendly energy and to reduce quantities of landfilled waste, many biogas plants, both agricultural ones and operating at WWTPs and landfills, have been launched in recent years. Nowadays, there are about 50 million micro-bioreactors and a total of 132,000 small, medium and large bioreactors operating worldwide. This number is continually increasing, and the potential for the further development of the biogas plant sector is immense and found in every country [128,129]. Anaerobic digestion (AD) has become an attractive technology for the stabilization of organic residues, in which waste is ‘a renewable resource’ as it can be reused for generating new products and biofuels [130]. Methane fermentation creates great potential for the production of an environmentally friendly fuel such as biogas [131]. Biogas produced by AD can be converted into a more efficient biofuel, such as biomethane [132]. The data collected by the European Biogas Association show that the number of biogas plants producing biomethane in Europe increased in two years from 483 (in 2018) to 729 (in 2020). At present, biomethane is produced in 18 European countries, and the largest producers are Germany (232 biogas plants), France (131) and the United Kingdom (80) [133].

Different types of organic waste can be submitted to AD, for example, animal feces [128], by-products from the food processing industry [134] and the animal feed industry [135], sludge from WWTPs [136], or post-harvest residues [137], which are degraded and converted into biogas and the process’s by-product called digestate [138]. Because of its high content of valuable nutrients, digestate can be used as a fertilizer in plant production [139]. However, to ensure sanitary, environmental and food safety, prior to using digestate for agricultural purposes, it must achieve proper quality in terms of both the concentrations of nutrients and the content of pollutants, e.g., heavy metals and pathogens. Digestate obtained by AD is especially hazardous in this regard, as it may contain antibiotics, ARB and ARGs, thus contributing to the dissemination of AR in the environment [96,140,141] (Table 8).
Table 8. Data on the presence of antibiotics, ARB and ARGs in various digestate materials from AD process.

| Source                                      | Country        | ARB * in Samples          | AAs of ARGs b (in 1 g d<sup>c</sup>−1)                                                                 | Antibiotics Persistent in Sample (µg g<sup>d</sup>−1) | Ref. |
|---------------------------------------------|----------------|---------------------------|------------------------------------------------------------------------------------------------------|-----------------------------------------------|------|
| sewage sludge digestate                     | Poland         | na d                      | bla<sub>OXA</sub> and bla<sub>TEM</sub> from 10<sup>4</sup> to 10<sup>7</sup>; tetA, tetM and tetQ from 10<sup>3</sup> to 10<sup>7</sup>; sul1 10<sup>7</sup>−10<sup>10</sup>; ermF, linA and mef A from 10<sup>3</sup> to 10<sup>8</sup> | 0.26 of MET<sup>e</sup>; 2.91 of SMX<sup>f</sup>; 1.25 of CEF<sup>g</sup>; 4.55 of DOC<sup>h</sup>; 1.25 of OXY<sup>i</sup>; 1.74 of CIP<sup>j</sup>; 2.07 of NA<sup>k</sup> | [96] |
| corn shredded, triticale, soya, cotton seeds, corn flour and fresh zoological waste digestate | Italy           | na                        | aac-(6<sup>′</sup>)-Ib-cr up to 10<sup>5</sup>; qnrS up to 10<sup>7</sup>; qepA up to 10<sup>6</sup> | 7.5 of CIP; 0.25 of SMX | [139] |
| sewage sludge digestate                     | Türkiye         | na                        |                                                                                                     | 1.49 of CLAR<sup>i</sup>; 1.49 of AZYT<sup>m</sup>; 5.03 of CIP; 5.35 of DOXY; from 0.22 to 3.63 of OXY; 2.57 of SMX; 0.07−2.52 of CHLOR<sup>n</sup>; 0.03−1.30 of ERY<sup>o</sup>; 6.63 of SMX; 4.34 of TRIM<sup>p</sup> | [142] |
| cattle manure digestate                     | Poland          | na                        | from 10<sup>4</sup> to 10<sup>7</sup> of bla<sub>TEM</sub> and bla<sub>OXA</sub>; from 10<sup>3</sup> to 10<sup>7</sup> of cfxA; from 10<sup>3</sup> to 10<sup>8</sup> of tetA, from 10<sup>3</sup> to 10<sup>7</sup> of tetM; from 10<sup>3</sup> to 10<sup>9</sup> of tetQ; from 10<sup>5</sup> to 10<sup>7</sup> of ermF; from 10<sup>6</sup> to 10<sup>8</sup> of sul1; from 10<sup>5</sup> to 10<sup>7</sup> of aac(6<sup>′</sup>)-Ib-cr; from 10<sup>5</sup> of 10<sup>9</sup> of qepA; from 10<sup>5</sup> of 10<sup>5</sup> of intI1; from 10<sup>5</sup> to 10<sup>7</sup> of intI2 | 0.02 of MET; 4.35 of ENR; 0.24 of SMX; 9.62 of OXY; 1.63 of CHLOR; 5.07 of TET<sup>r</sup> | [143] |
| food waste and slurry digestate             | China           | Pedobacter, Fluviicola, Devosia, and Desulfatiglans | from 10<sup>1</sup> to 10<sup>3</sup> of ermB, tetM, tetW and intI1; from 10<sup>4</sup> to 10<sup>6</sup> of bla<sub>TEM</sub>, ermB, tetW, and ermF tetW, sul2 and intI2 > 10<sup>9</sup> copies g<sup>d</sup> dry solid<sup>−1</sup>; tetC, tetM, tetQ and tetX > 10<sup>7</sup> copies g<sup>d</sup> dry solid<sup>−1</sup> | na | [144] |
| dairy manure digestate                      | China           | na                        | tetC, tetM, tetQ and tetX > 10<sup>7</sup> copies g<sup>d</sup> dry solid<sup>−1</sup> from 10<sup>10</sup> to 10<sup>13</sup> of intI1, sul1 and tetM; lower than 0.1% of bla<sub>TEM</sub>, bla<sub>CTX-M-32</sub>, bla<sub>OXA-58</sub>, qnrS and mefA. | na | [145] |
| swine slurries and their digestates         | Spain           | na                        |                                                                                                     | na | [146] |
| dairy manure and effluent digestate         | USA             | na                        | from 10<sup>9</sup> to 10<sup>14</sup> sul1, sul2, tetM and tetG | na | [147] |

*—antibiotic resistance bacteria, b—antibiotic resistance genes, c—amount of ARGs per 1 g of digestate, d—data not available, e—metronidazole, f—sulfamethoxazole, g—cefuroxime, h—doxycycline, i—oxtetracycline, j—ciprofloxacin, k—nalidixic acid, l—clarithromycin, m—azithromycin, n—chlorotetracycline, o—erythromycin, p—trimethoprim, r—tetracycline.
There are many studies attesting to the fact that the intensive use of antibiotics makes antimicrobial substances enter organic substrates converted by AD, as a result of which such substances then appear in digestate [96,103,143,148,149]. The presence of drugs from the classes of tetracyclines, sulfonamides, and fluoroquinolones has been detected in digestate from poultry litter [125], sewage sludge [96], and bovine slurry [147]. What is more, antibiotics present in AD processed substrates, especially ciprofloxacin, norfloxacin [150], and tetracycline, can demonstrate high resistance [146]. The occurrence of drugs in digestate can exert selective pressure on microorganisms, which creates a potential pathway for acquiring and spreading ARGs, which have been detected in digestate in many studies [45,147]. The scientific literature also confirms that bacteria from the phyla Firmicutes, Bacteroidetes, and Proteobacteria are the major ARGs carriers, hence when there is no selective pressure, the succession of the mentioned microorganisms may affect the transfer and dissemination of ARGs between microorganisms [96,151,152].

The AD process conducted in line with the current technological possibilities does not guarantee complete removal of antibiotics, ARB or ARGs. Furthermore, the risk of ARGs emission to the environment is also affected by the storage time of digestate before it is used in agriculture. It has been found that a 30-day storage time of digestate decreased the total relative number of ARGs, while resulting in an increase in the counts of particular ARGs sub-types, including \textit{tetM}, \textit{tetX}, \textit{tetQ}, \textit{tetS}, \textit{ermE}, and \textit{sul2} [149].

The release of antibiotics, ARB, and ARGs present in digestate to the environment threatens the public health and distorts the microbiological balance in soils and waters. The challenge technology engineers are facing is to develop new, more efficient technologies and strategies for intensive management in order to enhance the removal of ARGs at all stages of AD.

3.2. The Impact of Agriculture and Animal Husbandry on the Presence of Drugs, ARB and ARGs in the Environment

Processes of obtaining plant and animal products by plant breeding and growing and by animal breeding and rearing are closely related to circular economy. The animal excreta from animal production are the main type of waste generated in agriculture. The biggest challenge concerning the handling of this waste arises from its content of veterinary antimicrobial drugs. Antibiotics found in farm animal feces determine the patterns of resistance to pharmaceuticals among the microorganisms present in manure. Because the most popular way of managing such waste as manure is to use it for fertilization, antibiotics, ARB, and ARGs can accumulate in soil and in crops. The exposure of the soil environment to manure containing antimicrobial substances leads to a selective advantage of ARB in the environment. Moreover, antibiotic therapy used in animal production can have a significant influence on the occurrence of antimicrobial substances, ARB and ARGs in food offered to consumers.

3.2.1. Agriculture

As mentioned in Section 3.1.3, drugs used in agriculture enter the environment mainly with manure, commonly used all over the world for fertilization of soils. Degradation of antibiotics in an animal organism depends on the type of an antimicrobial substance. As much as over 80% of the dose of an antibiotic administered to an animal can be excreted with urine and stool in an unchanged form or as metabolites [18]. It has been demonstrated that antibiotics show strong inclination towards adsorption to manure, and the degree of adsorption depends on the state of matter [153]. Ezzariai et al. [154] noted that residues of antibiotics in animal feces reached amounts as high as 136 mg kg$^{-1}$ of dry matter. Other researchers recorded high concentrations of sulfamethazine and tetracycline in manure-based fertilizer samples, which were 5650 and 1920 mg kg$^{-1}$, respectively [155].

Antibiotics, ARB, and ARGs can also be spread in the environment with wastewater from animal farms and with runoffs from agricultural lands, which is a source of hazard. Areas in the vicinity of rivers and other surface water bodies are often used as agricultural
Int. J. Environ. Res. Public Health 2022, 19, 12853

land, where vegetables, cereals and other crops are grown. They are also used by livestock for grazing or drinking water. Moreover, irrigating arable fields with treated wastewater is a common practice, although it adds to the dissemination of micropollutants in agricultural habitats [156]. In liquid matrices, drugs often appear in amounts below the level of detectability, which means that the actual amounts of antibiotics in the soil and water environment may be underestimated. Even despite their low concentrations, antibiotics continue to be bioavailable and their influence on the environment and on AR can be substantial. Agricultural activity contributes to the spread of antibiotics, the acquisition of ARGs by microorganisms, and the dissemination of ARB and ARGs on a broad scale, also through the food chain. The presence of ARGs has been recorded in plantations of crops grown for human consumption [18,157,158]. Consumption of many unprocessed, raw leafy and non-leafy vegetables, root vegetables, sprouts or fruits could be the cause of human exposure to microorganisms, including ARB, inhabiting such types of food [21,159]. Scientific research completed in recent years has shown the presence of antibiotics, ARB and ARGs in agricultural products, for example seeds [160], parsley roots [158], or lettuce [156,161] (Table 9).

Table 9. Antimicrobials, ARB and ARGs detected in selected food samples of plant origin.

| Source | Country of Research | ARB a in Samples | AAs b of ARGs c (in 1 g d−1) | Antibiotics Persistent in Sample | Ref. |
|--------|---------------------|-----------------|------------------------------|---------------------------------|------|
| Soil and lettuce | Australia | na a | 144 different ARGs to beta-lactam, aminoglycoside, macrolide-lincoside-streptogramine B (MLSb) and tetracycline from 4.37 × 10^6 to 2.02 × 10^10 g−1 (soil); from 7.45 × 10^6 to 8.24 × 10^8 g−1 (lettuce) | na | [21] |
| Groundwater | Poland | na | sul2 6.54 × 10^3; tetA 1.94 × 10^11; tetM 2.80 × 10^3; sul1 3.10 × 10^3 | na | [18] |
| Crops cultivated on manure-amended plots | China | Antibiotic-resistant endophytic bacteria 10^5 CFU g−1 | sul2-10^−4 copies per 16S rRNA | na | [160] |
| Seeds of Pakchoi—vegetable endophytic systems lettuce leaves, roots, and soil | China | na | intI1, tetW, ermF, ermX, and sul1 ranged from 10^3 to 10^6 | na | [161] |
| soil, rhizospheric soil, bread beans, lettuce Lactuca sativa L. cv. Batavia, roots, leaves and beans in tomatoes Lycopersicon esculentum Mill. | Spain | na | sul1, tetM, qnrS1, blaCTX-M-32, blaVIM-9, meCA (except broad beans), blaTEM ranged from 1 to 10^6 | na | [162] |
| carrot tuber fertilized with pig manure | China | na | mdhF-2 10^6; blupX-Y-Z, vanA,B, sul2, intI1-ch, mecF, catB8, floR, tetT, aac6 (6)-Ib, and SL-3-4.8 × 10^4 | na | [163] |

a—antibiotic resistance bacteria, b—absolute abundances, c—antibiotic resistance genes, d—amount of ARGs per 1 g of digestate, e—not available, f—sulfamethoxazole, g—dry mass, h—doxycycline, i—colony forming unit.

Endophytic bacteria colonizing plant tissues may possess ARGs and be present in different plant organs: roots, stems, leaves or fruits. The most diverse microbiome of plants is found in the roots, which is a consequence of their immediate contact with soil [164,165]. It has been demonstrated that the exposure of crops to antibiotics may promote their growth with the simultaneous accumulation of antimicrobials in plant tissues [160]. The degree to which plants absorb antibiotics depends on various biotic and abiotic factors and on the type of crop. Cereals and fruits are less prone to absorbing pollutants than leafy and root vegetables [166]. Moreover, the presence of antibiotics induces an increased frequency of ARB among the total endophytic bacteria [160]. Additionally, fresh plant
products can contain opportunistic microorganisms, including ones of the genera *Klebsiella* and *Enterobacter*, whose presence has been detected on such vegetables as cabbage, pepper or tomatoes [159,167,168]. Furthermore, some ARB determined in soil and manure show phylogenetic similarity to human pathogens (e.g., of the genus *Acinetobacter*), thereby raising the probability of genetic exchange between microorganisms [169]. In order to constrain the effect of soil fertilization on increasing the diversity of the resistome of both the soil and crops, there is no doubt that specific legal regulations must enter into force, especially in developing countries.

### 3.2.2. Animal Husbandry

In order to meet the demand for animal-origin food, antibiotics have become an indispensable element of livestock rearing. Models of using antibiotics in animal production differ depending on the world’s region, country’s policy and type of production. In industrial countries, meat consumption has been slightly decreasing in recent years while growing rapidly in developing countries, where access to veterinary antibiotics is not regulated, and the knowledge on AR is insufficient [20]. Some antimicrobial drugs are forbidden in developed countries but can still be used in most developing states [170]. Although some countries have limited the use of antibiotics in livestock exclusively to medical purposes (including some EU member states, in compliance with 1831/2003/EC of 2016), these pharmaceuticals continue to be used in excess in many regions around the world, where intensive animal production is carried out (the USA, China, Russia, India and Republic of South Africa). It is estimated that antibiotic therapy in livestock production in the USA corresponds to around 80% of the total consumption of antimicrobial substances in this country. Moreover, most of the antimicrobials used for this purpose are also administered in human medicine [171,172].

At present, approximately 30 different antimicrobial classes are used in livestock production across the world. Among the drugs administered to farm animals, there are mainly macrolides, beta-lactams and tetracyclines [173]. In European countries, the total quantity of applied antibiotics converted per kg of animal body is no less than 20 up to 188 mg. Most antibiotics are used in the breeding and rearing of swine and poultry, and the average dose in the world is 172 and 148 mg, respectively, per kg of animal body weight. In turn, the same dose for cattle is around 45 mg per kg of body weight [171]. In 2013, the use of antimicrobials in animal production administered in order to treat diseases and as growth stimulants reached 420 mg annually in the United Kingdom and 14,600 mg annually in the United States. For comparison, in the same year, 2013, the consumption of antibiotics in livestock production in China peaked at 84,500 mg [174]. Unfortunately, the administration of drugs to animals is inevitably associated with the risk of their presence in food products of animal origin.

Thermal treatment of products of animal origin can reduce the risk of consuming antibiotics these products may contain, such as sulfonamides, fluoroquinolones and tetracyclines, but cannot eliminate drugs from the class of beta-lactams. The persistence of the latter class of antibiotics can lead to a situation where residues of these antibiotics are found in thermally treated milk and in dairy products made from such milk, being a threat to the health of consumers [20]. Antimicrobial substances have been detected in milk [20], sheep meat [175], poultry meat [176] and beef [177] (Table 10).
Table 10. The presence and concentration of various antibiotics in selected food samples of animal origin.

| Source                          | Country of Research     | ARB a in Samples | Antibiotics Persistent in Sample                                      | References |
|---------------------------------|-------------------------|------------------|------------------------------------------------------------------------|------------|
| Milk                            | Bangladesh              | na b             | 61.2 and 124 µg L⁻¹ respectively for OXY c and AMO d, 20.7–82.1, 41.8–320.8, and 32.8–95.6 µg kg⁻¹, respectively, for SUL e, TET f, STREP g and CIP h | [178]      |
| Chicken, beef and pork          | Republic of South Africa| na               | 508.4 mg kg⁻¹ AMO (chicken) 515.4 mg kg⁻¹ AMO (fish) up to 275 ng g⁻¹ CIP up to 242 ng g⁻¹ ENRO i | [178]      |
| Chicken and fish                | Bangladesh              | na               | 10–155; 25–135 and 50–115 µg kg⁻¹, respectively, for OXY, CIP and ENRO | [177]      |
| Chicken                         | Indonesia               | na               | 4.25 ng kg⁻¹ CHLOR i                                                    | [180]      |
| Broiler meat and liver          | Bangladesh              | Campylobacter jejuni i Campylobacter coli |                                                                                  |            |
| Meat of the sea bream            | Türküye                 | na               | 4.25 ng kg⁻¹ CHLOR i                                                    | [181]      |
| (Sparus aurata) and sea brass fish|(Dicentrarchus labrax)   |                  | 4.25 ng kg⁻¹ CHLOR i                                                    | [181]      |

| Source                          | Country of Research     | ARB a in Samples | Antibiotics Persistent in Sample                                      | References |
|---------------------------------|-------------------------|------------------|------------------------------------------------------------------------|------------|
| Milk                            | Bangladesh              | na b             | 61.2 and 124 µg L⁻¹ respectively for OXY c and AMO d, 20.7–82.1, 41.8–320.8, and 32.8–95.6 µg kg⁻¹, respectively, for SUL e, TET f, STREP g and CIP h | [178]      |
| Chicken, beef and pork          | Republic of South Africa| na               | 508.4 mg kg⁻¹ AMO (chicken) 515.4 mg kg⁻¹ AMO (fish) up to 275 ng g⁻¹ CIP up to 242 ng g⁻¹ ENRO i | [178]      |
| Chicken and fish                | Bangladesh              | na               | 10–155; 25–135 and 50–115 µg kg⁻¹, respectively, for OXY, CIP and ENRO | [177]      |
| Chicken                         | Indonesia               | na               | 4.25 ng kg⁻¹ CHLOR i                                                    | [180]      |
| Broiler meat and liver          | Bangladesh              | Campylobacter jejuni i Campylobacter coli |                                                                                  |            |
| Meat of the sea bream            | Türküye                 | na               | 4.25 ng kg⁻¹ CHLOR i                                                    | [181]      |
| (Sparus aurata) and sea brass fish|(Dicentrarchus labrax)   |                  | 4.25 ng kg⁻¹ CHLOR i                                                    | [181]      |

a—antibiotic resistance bacteria, b—data not available, c—oxytetracycline, d—amoxicillin, e—sulfanilamide, f—tetracycline, g—streptomycin, h—ciprofloxacin i—enrofloxacin, i—chlortetracycline.

The lack of adequate veterinary supervision and the administration of subtherapeutic doses of antibiotics are the major factors contributing to the spread of AR in livestock populations. Contemporary animal husbandry is often characterized by high livestock density and routine administration of antibiotics, which may predispose it to the emergence of new zoonotic pathogens resistant to antibiotics. The presence of ARB in animals reared for meat and in food products made from such animals has been documented all over the world. Methicillin-resistant Staphylococcus aureus (MRSA) and strains of Escherichia coli resistant to colistin, as well as E. coli resistant to carbapenems, have been detected in swine. Species of Campylobacter jejuni and Campylobacter coli resistant to ampicillin, streptomycin and tetracycline have been isolated from chickens, while multidrug-resistant strains of Pseudomonas aeruginosa and Acinetobacter baumannii have been isolated from swine, poultry and cattle [182–186].

Antibiotic-resistant bacteria can be transferred from farm animals to humans directly via food, such as meat, fish, eggs and dairy products [187]. Numerous outbreaks of food infections caused by ARB, including strains of Staphylococcus aureus and Escherichia coli and various species of the genera Enterococcus, Aeromonas and Salmonella, are linked to food made from farm animals have been reported worldwide [188,189]. Moreover, the transmission of resistant strains can occur via different routes, also between animals of different species, through direct contact with other animals, or their saliva, feces or blood, which contain ARB [170]. This creates a risk of transmitting ARB and ARGs from animals to humans and of human pathogens acquiring resistance to the classes of antibiotics used in both veterinary and human medicine.

A way to decelerate the spread of AR in animal production is to reduce or optimize the use of antibiotics in animal husbandry. Additionally, it is recommended to improve the hygiene and animal housing conditions as well as the quality of feeds, which will have a direct influence on the welfare and health of animal herds and flocks, thus eliminating superfluous antibiotic treatments. Moreover, other prophylactic measures are recommended, such as inoculations and supplementation of feeds with pro- and prebiotics as well as bioactive compounds (e.g., antimicrobial peptides) [190].
3.3. Co-Selection of ARGs by Other Anthropogenic Pollutants

3.3.1. Heavy Metals

Heavy metals (HMs), the most common of which are lead (Pb), zinc (Zn), mercury (Hg), nickel (Ni), cadmium (Cd), copper (Cu), chromium (Cr) and arsenic (As), are widely distributed in the environment. These pollutants are detected in wastewater [191], sewage sludge [92,192], LL [193], manure [18,194] and in fertilized soil [195]. Heavy metals are not biodegradable, can be toxic and carcinogenic, and pose a serious threat to life-forms and the environment. Some of the HMs detected, even in scant amounts, may be dangerous [191,196].

The half-lives of HMs are estimated to be hundreds or even thousands of years. One of the longest half-lives characterizes copper, which is widely used in various industrial sectors [197]. The presence of HMs in wastewater shows an increasing tendency with the development of human and industrial activities. These pollutants accumulate in sewage sludge, and wastewater loaded with the presence of HMs continues to the aquatic environment, threatening the ecosystem and human health [191,198]. The occurrence of these micropollutants in the waste stream at the landfill, as well as in LL, creates a risk that they enter soil and surface waters [199]. The presence of HMs is also found in provender for cattle, pigs, and poultry [200]. Moreover, some studies showed that pig feces had higher concentrations of zinc (941.1 mg kg\(^{-1}\)) and copper (137.6 mg kg\(^{-1}\)) compared to their provender (139.8 and 31.5 mg kg\(^{-1}\), respectively). The use of fertilizers based on sewage sludge and manure containing HMs leads to their accumulation in the soil and creates an additional, long-term selection pressure on microorganisms [201].

The presence of HMs and antibiotics in water and soil environments, as a result of various anthropogenic activities, leads to the exposure of microorganisms to both kinds of pollutants [197]. The connection between HMs and AR proliferation has been analyzed in wastewater and solid waste [202–204], agriculture [194,205,206] and industrially contaminated environments [207,208]. Significant incidence of ARB and ARGs from HMs and antimicrobial co-contaminated environments suggests that exposure of microorganisms to HMs pollution co-selects AR [209]. The co-selection of AR occurs when microorganisms harbor two different resistance genes towards antimicrobials and HMs (co-resistance) or one gene which is responsible for tolerance to antibiotics and HMs (cross-resistance) [209–211]. A variety of HMs at concentrations found in different environments have the ability to co-select ARB and resistance plasmids. If resistance genes for both types of compounds are located on the same plasmid, exposure to HMs can also promote the HGT of AR [210]. Horizontal gene transfer impacts microbial evolution and leads to the dissimilation of ARGs among both environmental and clinical microorganisms [212]. Long-term exposure of microorganisms to HMs can lead to changes in biodiversity and abundance of ARGs, and the co-selection of ARGs caused by the presence of these micropollutants is perceived as another threat to the environment [208,210,213].

3.3.2. Microplastics

The continuously growing production and use of plastics have resulted in an increase in the stream of this fraction of waste all over the world. Pollution of the environment from microplastics (MP), which are plastic debris smaller than 5 mm in diameter, is a common and global problem that will aggravate in the future [212]. Concerns about the presence of MP in various environments are compounded by their ability to adsorb many chemicals, including antibiotics and HMs. Moreover, microplastic debris provides a hydrophobic surface to support the formation of biofilms by microorganisms. For this reason, MP is an anthropogenic vector for the large-scale transport of ARB and ARGs [209,212,214,215]. Particles of MP, together with ARB and ARGs, have been identified in both wastewater [216] and LL [217], as well as in the air [218], soil [219] and river and sea water [220].

Municipal facilities, such as WWTPs and landfills, are considered hotspots for antibiotics, ARB, and ARGs, as well as MP [216]. Municipal wastewater contains MP from clothing and personal care products [221,222]. It is estimated that 80–90% of MP in wastew-
ater is retained in the sludge, but the remainder enters the aquatic environment along with the treated wastewater and permeates the soil with soil-applied stabilized sewage sludge [223]. Microplastics present in the waste fraction in a landfill and in LL may further infiltrate into the soil and water environment [216]. Microplastics migrating into the environment, carrying antibiotics, ARB, and ARGs, affect changes in microbial communities and resistomes. Interestingly, the type of polymer plays a role in the transfer of AR determinants; some studies have shown that polyethylene (PE) has greater transport potential compared to polypropylene (PP) [217]. Moreover, the presence of additional micropollutants such as antibiotics or HMs may increase the pool of ARGs carried on MP [216]. It is worrying that both antibiotics and HMs, as well as MP, can intensify the development of AR among microorganisms and stimulate HGT [224,225]. The particles of MP constitute a vector for many micropollutants, additionally supporting the co-selection of ARGs based on the presence of HMs [209].

4. Conclusions

In sum, it should be concluded that the anthropogenic environment and all objects it contains have a direct influence on the presence of antibiotics and the spread of ARB and ARGs in the environment. The facilities associated with municipal infrastructures, such as WWTPs and landfills, but also biogas plants and agriculture, including plant and animal production, are key reservoirs of antibiotics, ARB and ARGs. The anthropogenic activity enables a huge pool of antimicrobials to enter the environment, which leads to their uncontrolled consumption by people and animals, also due to the improper disposal of unused drugs. An incomplete metabolism of antibiotics and the fact that antibiotics permeate various environments contribute to the selective pressure, hereby facilitating an increase of the ARGs pool among microorganisms. Many scientific reports indicate that ARGs are omnipresent in a variety of anthropogenic environments, and their range of occurrence is very wide. A significant role in the dissemination of ARGs is played by MGEs and HGT processes, which take place in various environments, especially the ones at WWTPs. Both antibiotics and ARB and ARGs are released to the water environment together with discharged treated wastewater and with LL, as well as via surface runoffs from arable fields and farm buildings. Furthermore, the soil environment is most often enriched with these micropollutants as a consequence of the fertilization of fields with stabilized waste from municipal facilities and the agricultural sector.

The information collated in this review proves that further research is needed to answer the question of how to prevent the proliferation of ARGs in the environment in order to reduce the risk of AR acquisition by microorganisms. Moreover, the important role of other anthropogenic pollutants such as HMs and MP, which can additionally co-select AR and intensify its development among microorganisms, was highlighted. A better insight into the role of anthropogenically transformed environments in the dissemination of AR is necessary for undertaking specific legislative initiatives and effectively reducing the mentioned phenomenon.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijerph191912853/s1, Figure S1: SCOPUS PRISMA flowchart showing the results of the publication’s search and screening process for this review; Figure S2: The number and date of publications used to develop this review.

Author Contributions: Conceptualization, M.C. and I.W.; methodology, M.C. and I.W.; software, M.C.; validation, M.C. and I.W.; formal analysis, M.C. and I.W.; investigation, M.C. and I.W.; resources, M.C. and I.W.; data curation, M.C.; writing—original draft preparation, M.C. and I.W.; writing—review and editing, M.H. and E.K.; visualization, M.C. and I.W.; supervision, E.K. and M.H.; project administration, M.C. and I.W.; funding acquisition, M.C. and I.W. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the National Science Centre (Poland), grant numbers 2020/37/N/NZ9/00343 and 2020/37/N/NZ9/00431.
Institutional Review Board Statement: Not applicable.
Informed Consent Statement: Not applicable.
Data Availability Statement: Not applicable.
Conflicts of Interest: The authors declare no conflict of interest.

References
1. Caracciolo, A.B.; Visca, A.; Massini, G.; Patrolecco, L.; Miritana, V.M.; Grenni, P. Environmental Fate of Antibiotics and Resistance Genes in Livestock Waste and Digestate from Biogas Plants. *Environ. Sci. Pollut. Res. Manag.* **2020**, *2020*, 1–9. [CrossRef]
2. Tian, M.; He, X.; Feng, Y.; Wang, W.; Chen, H.; Gong, M.; Liu, D.; Clarke, J.L.; Van Eerde, A. Pollution by antibiotics and antimicrobial resistance in livestock and poultry manure in China, and countermeasures. *Antibiotics* **2021**, *10*, 539. [CrossRef]
3. Klein, E.Y.; Van Boeckel, T.P.; Martinez, E.M.; Pant, S.; Gandra, S.; Levin, S.A.; Goossens, H.; Laxminarayan, R. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E3463–E3470. [CrossRef] [PubMed]
4. WHO Report on Surveillance of Antibiotic Consumption 2016–2018 Early Implementation. 2018. Available online: https://medbox.org/document/who-report-on-surveillance-of-antibiotic-consumption#GO (accessed on 10 February 2022).
5. aus der Beek, T.; Weber, F.A.; Bergmann, A.; Hickmann, S.; Ebert, I.; Hein, A.; Küster, A. Pharmaceuticals in the environment—Global occurrences and perspectives. *Environ. Toxicol. Chem.* **2016**, *35*, 823–835. [CrossRef]
6. Dameh, M.; Green, J.; Norris, P. Over-the-counter sales of antibiotics from community pharmacies in Abu Dhabi. *Pharm. World Sci.* **2010**, *32*, 643–650. [CrossRef]
7. Băhța, M.; Tesfamariam, S.; Weldemariam, D.G.; Yemane, H.; Tesfamariam, E.H.; Alem, T.; Russom, M. Dispensing of antibiotics without prescription and associated factors in drug retail outlets of Eritrea: A simulated client method. *PLoS ONE* **2020**, *24*, e0228013. [CrossRef]
8. Belachew, S.A.; Hall, L.; Selvey, L.A. Non-prescription dispensing of antibiotic agents among community drug retail outlets in Sub-Saharan African countries: A systematic review and meta-analysis. *Antimicrob. Resist. Infect. Control* **2021**, *10*, 13. [CrossRef]
9. Sulis, G.; Gandra, S. Access to antibiotics: Not a problem in some LMICs. *Environ. Int.* **2019**, *130*, 104912. [CrossRef] [PubMed]
10. Auta, A.; Hadi, M.A.; Oga, E.; Adewuyi, E.O.; Abdu-Aguye, S.N.; Adeloye, D.; Morgan, D.J. Global access to antibiotics without prescription in community pharmacies: A systematic review and meta-analysis. *J. Infect. Prev.* **2018**, *78*, 8–18. [CrossRef] [PubMed]
11. Wang, Y.; Zhang, R.; Lei, Y.; Song, L. Antibiotic resistance genes in landfill leachates from seven municipal solid waste landfills: Seasonal variations, hosts, and risk assessment. *Sci. Total Environ.* **2022**, *853*, 158677. [CrossRef] [PubMed]
12. Wu, D.; Su, Y.; Wang, P.; Zhao, J.; Xie, J.; Xie, B. Uncover landfilled antimicrobial resistance: A critical review of antibiotics flux, resistome dynamics and risk assessment. *Natl. Sci. Open* **2022**, *1*, 20220012. [CrossRef]
13. Wang, J.Y.; An, X.L.; Huang, F.Y.; Su, J.Q. Antibiotic resistome in a landfill leachate treatment plant and effluent-receiving river. *Chemosphere* **2020**, *242*, 125207. [CrossRef]
14. Chen, Y.; Shen, W.; Wang, B.; Zhao, X.; Su, L.; Kong, M.; Li, H.; Zhang, S.; Li, J. Occurrence and fate of antibiotics, antimicrobial resistance determinants and potential human pathogens in a wastewater treatment plant and their effects on receiving waters in Nanjing, China. *Ecotoxicol. Environ. Saf.* **2020**, *206*, 111371. [CrossRef]
15. Amarasiri, M.; Sano, D.; Suzuki, S. Understanding human health risks caused by antibiotic resistant bacteria (ARB) and antibiotic resistance genes (ARG) in water environments: Current knowledge and questions to be answered. *Crit. Rev. Environ. Sci. Technol.* **2020**, *50*, 2016–2059. [CrossRef]
16. Berendsen, B.J.A.; Wegh, R.S.; Memelink, J.; Zuidema, T.; Stolker, L.A.M. The analysis of animal faeces as a tool to monitor antibiotic usage. *Talanta* **2015**, *132*, 258–268. [CrossRef]
17. Kies, F.K.; Bouchtebak, S.; Bendaidia, N. Soil Contamination by Pharmaceutical Pollutants: Adsorption of an Antibiotic (Amoxicillin) on an Agricultural Land. *Proceedings 2020*, *30*, 60. [CrossRef]
18. Buta, M.; Korzeniewska, E.; Harnisz, M.; Hubeny, J.; Zielirski, W.; Rolbiecki, D.; Bajkacz, S.; Felis, E.; Kokoszka, K. Microbial and chemical pollutants on the manure-crops pathway in the perspective of “One Health” holistic approach. *Sci. Total Environ.* **2021**, *785*, 147411. [CrossRef] [PubMed]
19. Dechêne-Tempier, M.; Marois-Crèhan, C.; Libante, V.; Jouy, E.; Leblond-Bourget, N., Payot, S. Update on the mechanisms of antibiotic resistance and the mobile resistome in the emerging zoonotic pathogen *Streptococcus suis*. *Microorganisms* **2021**, *9*, 1765. [CrossRef]
20. Treiber, F.M.; Beranek-Knauer, H. Antimicrobial residues in food from animal origin—a review of the literature focusing on products collected in stores and markets worldwide. *Antibiotics* **2021**, *10*, 534. [CrossRef]
21. Zhang, Y.J.; Hu, H.W.; Chen, Q.L.; Singh, B.K.; Yan, H.; Chen, D.; He, J.Z. Transfer of antibiotic resistance from manure-amended soils to vegetable microbiomes. *Environ. Int.* **2019**, *130*, 104912. [CrossRef] [PubMed]
22. Wang, P.; Wu, D.; You, X.; Li, W.; Xie, B. Distribution of antibiotics, metals and antibiotic resistance genes during landfilling process in major municipal solid waste landfills. *Environ. Pollut.* **2019**, *255*, 113222. [CrossRef]
23. Centers for Disease Control and Prevention. 2019. Available online: https://www.cdc.gov/drugresistance/ (accessed on 10 February 2022).
24. European Health Union. EU Action on Antimicrobial Resistance. 2019. Available online: https://ec.europa.eu/health/antimicrobial-resistance/eu-action-antimicrobial-resistance_en (accessed on 10 February 2022).

25. Sun, J.; Jin, L.; He, T.; Wei, Z.; Liu, X.; Zhu, L.; Li, X. Antibiotic resistance genes (ARGs) in agricultural soils from the Yangtze River Delta, China. Sci. Total Environ. 2020, 740, 140001. [CrossRef] [PubMed]

26. Keenum, I.; Williams, R.K.; Ray, P.; Garner, E.D.; Knowlton, K.F.; Pruden, A. Combined effects of composting and antibiotic administration on cattle manure–borne antibiotic resistance genes. Microbiome 2021, 9, 81. [CrossRef] [PubMed]

27. Korzeniewska, E.; Harnisz, M. Extended-spectrum beta-lactamase (ESBL)-positive Enterobacteriaceae in municipal sewage and their emission to the environment. J. Environ. Manage. 2013, 128, 904–911. [CrossRef] [PubMed]

28. Gao, H.; Zhang, L.; Lu, Z.; He, C.; Li, Q.; Na, G. Complex migration of antibiotic resistance in natural aquatic environments. Environ. Pollut. 2018, 232, 1–9. [CrossRef] [PubMed]

29. Sánchez-Baena, A.M.; Caicedo-Bejarano, L.D.; Chávez-Vivas, M. Structure of bacterial community with resistance to antibiotics in aquatic environments. A systematic review. Int. J. Environ. Res. Public Health 2021, 18, 2348. [CrossRef] [PubMed]

30. Rolbiecki, D.; Harnisz, M.; Korzeniewska, E.; Jalowiecki, L.; Plaza, G. Occurrence of fluoroquinolones and sulfonamides resistance genes in wastewater and sludge at different stages of wastewater treatment: A preliminary case study. Appl. Sci. 2020, 10, 5816. [CrossRef]

31. Harnisz, M.; Kiedrzyńska, E.; Kiedrzyński, M.; Korzeniewska, E.; Czatzkowska, M.; Koniuszewska, I.; Jóźwik, A.; Szklarek, S.; Nięstypska, S.; Zalewski, M. The impact of WWTP size and sampling season on the prevalence of antibiotic resistance genes in wastewater and the river system. Sci. Total Environ. 2020, 740, 140466. [CrossRef] [PubMed]

32. Zainab, S.M.; Junaid, M.; Xu, N.; Malik, R.N. Antibiotics and antibiotic resistant genes (ARGs) in groundwater: A global review on dissemination, sources, interactions, environmental and human health risks. Water Res. 2020, 187, 116455. [CrossRef]

33. Zhou, Z.; Yao, H. Effects of composting different types of organic fertilizer on the microbial community structure and antibiotic resistance genes. Microorganisms 2020, 8, 268. [CrossRef] [PubMed]

34. Zhou, X.; Qiao, M.; Wang, F.H.; Zhu, Y.G. Use of commercial organic fertilizer increases the abundance of antibiotic resistance genes and antibiotics in soil. Environ. Sci. Pollut. Res. 2017, 24, 701–710. [CrossRef] [PubMed]

35. Fouz, N.; Pangesti, K.N.A.; Yasir, M.; Al-Malki, A.L.; Azhar, E.I.; Hill-Cawthorne, G.A.; El Ghany, M.A. The contribution of wastewater to the transmission of antimicrobial resistance in the environment: Implications of mass gathering settings. Trop. Med. Infect. Dis. 2020, 5, 33. [CrossRef] [PubMed]

36. Sazykin, I.S.; Khmelevtsova, L.E.; Seliverstova, E.Y.; Sazykina, M.A. Effect of Antibiotics Used in Animal Husbandry on the Distribution of Bacterial Drug Resistance (Review). Appl. Biochem. Microbiol. 2021, 57, 20–30. [CrossRef]

37. Sun, H. Antibiotic Resistance in Biogas Processes. Ph.D. Thesis, Swedish University of Agricultural Sciences, Uppsala, Sweden, 2021; pp. 1652–6880, ISBN 9789177608479. Available online: https://pub.epsilon.slu.se/26327/ (accessed on 10 February 2022).

38. Bouki, C.; Venieri, D.; Diamadopoulos, E. Detection and fate of antibiotic resistant bacteria in wastewater treatment plants: A review. Ecotoxicol. Environ. Saf. 2013, 91, 1–9. [CrossRef] [PubMed]

39. Zhu, Z.; Yao, H. Combined effects of composting and antibiotic administration on cattle manure–borne antibiotic resistance genes. Microbiome 2021, 9, 81. [CrossRef] [PubMed]

40. Xie, S.; Wu, N.; Tian, J.; Liu, X.; Wu, S.; Mo, Q.; Lu, S. Review on the removal of antibiotic resistance genes from livestock manure by composting. IOP Conf. Ser. Earth Environ. Sci. 2019, 2019, 1–9. [CrossRef] [PubMed]

41. Marano, R.B.M.; Gupta, C.L.; Cozer, T.; Jurkevitch, E.; Cytryn, E. Hidden Resistor: Enrichment Reveals the Presence of Clinically Relevant Antibiotic Resistance Determinants in Treated Wastewater-Irrigated Soils. Environ. Sci. Technol. 2021, 55, 6814–6827. [CrossRef]

42. Kim, D.W.; Cha, C.J. Antibiotic resistance from the One-Health perspective: Understanding and controlling antimicrobial resistance transmission. Exp. Mol. Med. 2021, 53, 301–309. [CrossRef]

43. United Nations. Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance: Draft Resolution/Submitted by the President of the General Assembly; United Nations: New York, NY, USA, 2016; Available online: https://digitallibrary.un.org/record/842813? (accessed on 15 February 2022).

44. European Commission. A European Green Deal. 2019. Available online: https://ec.europa.eu/info/strategy/priorities-2019-2024/european-green-deal_en (accessed on 10 February 2022).

45. Visca, A.; Rauseo, J.; Spataro, F.; Patrolocco, L.; Gennari, P.; Massini, G.; Mazzurco Miriana, V.; Barra Caracciolo, A. Antibiotics and antibiotic resistant genes in anaerobic digesters and predicted concentrations in agroecosystems. J. Environ. Manage. 2022, 301, 113891. [CrossRef]

46. Lien, L.T.Q.; Hoa, N.Q.; Chuc, N.T.K.; Thoa, N.T.M.; Phuc, H.D.; Diwan, V.; Dat, N.T.; Tamhankar, A.J.; Lundborg, C.S. Antibiotics in wastewater of a rural and an urban hospital before and after wastewater treatment, and the relationship with antibiotic use—a one year study from Vietnam. Int. J. Environ. Res. Public Health 2016, 13, 588. [CrossRef] [PubMed]
71. Kortesmäki, E.; Östman, J.R.; Meierjohann, A.; Brozinick, J.M.; Eklund, P.; Kronberg, L. Occurrence of Antibiotics in Influent and Effluent from 3 Major Wastewater-Treatment Plants in Finland. Environ. Toxicol. Chem. 2020, 39, 1774–1789. [CrossRef]

72. de Jesus Gaffney, V.; Cardoso, V.V.; Cardoso, E.; Teixeira, A.P.; Martins, J.; Benoliel, M.J.; Almeida, C.M.M. Occurrence and behaviour of pharmaceutical compounds in a Portuguese wastewater treatment plant: Removal efficiency through conventional treatment processes. Environ. Sci. Pollut. Res. 2017, 24, 14717–14734. [CrossRef] [PubMed]

73. Sabri, N.A.; Schmitt, H.; Van Der Zaan, B.; Gerritsen, H.W.; Zuidema, T.; Rijnaarts, H.H.M.; Langenhoff, A.A.M. Prevalence of antibiotics and antibiotic resistance genes in a wastewater effluent-receiving river in the Netherlands. J. Environ. Chem. Eng. 2020, 8, 102245. [CrossRef]

74. Pazda, M.; Kumorjka, J.; Stepnowski, P.; Mulkiewicz, E. Antibiotic resistance genes identified in wastewater treatment plant systems—A review. Sci. Total Environ. 2019, 697, 134023. [CrossRef] [PubMed]

75. Han, X.M.; Hu, H.W.; Chen, Q.L.; Yang, L.Y.; Li, H.L.; Zhu, Y.G.; Li, X.Z.; Ma, Y.B. Antibiotic resistance genes and associated bacterial communities in agricultural soils amended with different sources of animal manures. Soil Biol. Biochem. 2018, 126, 91–102. [CrossRef]

76. Yoo, K.; Yoo, H.; Lee, J.; Choi, E.J.; Park, J. Exploring the antibiotic resistome in activated sludge and anaerobic digestion sludge in an urban wastewater treatment plant via metagenomic analysis. J. Microbiol. 2020, 58, 123–130. [CrossRef]

77. Urbaniaik, C.; Grams, T.; Mason, C.E.; Venkateswaran, K. Simulated microgravity promotes horizontal gene transfer of antimicrobial resistance genes between bacterial genera in the absence of antibiotic selective pressure. Life 2021, 11, 960. [CrossRef]

78. Osińska, A.; Korzeniewska, E.; Harnisz, M.; Felis, E.; Bajkacz, S.; Jachimowicz, P.; Niestepski, S.; Konopka, I. Small-scale wastewater treatment plants as a source of the dissemination of antibiotic resistance genes in the aquatic environment. J. Hazard. Mater. 2020, 387, 121221. [CrossRef]

79. Mokracka, J.; Koczurza, R.; Kaznowski, A. Multiresistant Enterobacteriaceae with class 1 and class 2 integrons in a municipal wastewater treatment plant. Water Res. 2012, 46, 3353–3363. [CrossRef]

80. Zielinski, W.; Korzeniewska, E.; Harnisz, M.; Hubeny, J.; Buta, M.; Rolbiecki, D. The prevalence of drug-resistant and virulent Staphylococcus spp. in a municipal wastewater treatment plant and their spread in the environment. Environ. Int. 2020, 143, 109514. [CrossRef]

81. Rodriguez-Mozaz, S.; Chamorro, S.; Marti, E.; Huerta, B.; Gros, M.; Sánchez-Melsiò, A.; Borrego, C.M.; Barceló, D.; Balcázar, J.L. Occurrence of antibiotics and antibiotic resistance genes in hospital wastewater and urban wastewaters and their impact on the receiving river. Water Res. 2015, 69, 234–242. [CrossRef]

82. Korzeniewska, E.; Harnisz, M. Science of the Total Environment Relationship between modified activated sludge wastewater treatment and changes in antibiotic resistance of bacteria. Sci. Total Environ. 2018, 639, 304–315. [CrossRef] [PubMed]

83. Ben, W.; Wang, J.; Cao, R.; Yang, M.; Zhang, Y.; Qiang, Z. Distribution of antibiotic resistance in the effluents of ten municipal wastewater treatment plants in China and the effect of treatment processes. Chemosphere 2017, 172, 392–398. [CrossRef]

84. Pärnänen, K.M.M.; Narciso-Da-Rocha, C.; Kneis, D.; Berendonk, T.U.; Cacace, D.; Do, T.T.; Elpers, C.; Fatta-Kassinos, D.; Henriques, I.; Jaeger, T.; et al. Antibiotic resistance in European wastewater treatment plants mirrors the pattern of clinical antibiotic resistance prevalence. Sci. Adv. 2019, 5, eaau9124. [CrossRef]

85. Raafat, I.D.; Lekunberri, I.; Sánchez-Melsiò, A.; Aouni, M.; Borrego, C.M.; Balcázar, J.L. Abundance of antibiotic resistance genes in five municipal wastewater treatment plants in the Monastir Governorate, Tunisia. Environ. Pollut. 2016, 219, 353–358. [CrossRef] [PubMed]

86. Alygizakis, N.A.; Ürik, J.; Beretsou, V.G.; Kampaouris, I.; Galani, A.; Oswaldowa, M.; Berendonk, T.; Oswald, P.; Thomaidis, N.S.; Slobodnik, J.; et al. Evaluation of chemical and biological contaminants of emerging concern in treated wastewater intended for agricultural reuse. Environ. Int. 2020, 138, 105597. [CrossRef]

87. Wang, R.; Ji, M.; Zhai, H.; Guo, Y.; Liu, Y. Occurrence of antibiotics and antibiotic resistance genes in WWTP effluent-receiving water bodies and reclaimed wastewater treatment plants. Sci. Total Environ. 2021, 796, 148919. [CrossRef]

88. Le, T.H.; Ng, C.; Chen, H.; Yi, X.Z.; Koh, T.H.; Barkham, T.M.S.; Zhou, Z.; Gin, K.Y.H. Occurrences and characterization of antibiotic-resistant bacteria and genetic determinants of hospital wastewater in a tropical country. Antimicrob. Agents Chemother. 2016, 60, 7449–7456. [CrossRef] [PubMed]

89. Le, T.H.; Ng, C.; Chen, H.; Yi, X.Z.; Koh, T.H.; Barkham, T.M.S.; Zhou, Z.; Gin, K.Y.H. Occurrences and characterization of antibiotic-resistant bacteria and genetic determinants of hospital wastewater in a tropical country. Antimicrob. Agents Chemother. 2016, 60, 7449–7456. [CrossRef] [PubMed]

90. Sheng, Y.; Linville, J.L.; Urgun-Demirtas, M.; Mintz, M.M.; Snyder, S.W. An overview of biogas production and utilization at full-scale wastewater treatment plants (WWTPs) in the United States: Challenges and opportunities towards energy-neutral WWTPs. Renew. Sustain. Energy Rev. 2020, 102, 574968. [CrossRef] [PubMed]

91. Li, W.; Shi, Y.; Gao, L.; Liu, J.; Cai, Y. Occurrence, distribution and potential affecting factors of antibiotics in sewage sludge of wastewater treatment plants in China. Sci. Total Environ. 2013, 445, 306–313. [CrossRef]

92. Cheng, M.; Wu, L.; Huang, Y.; Luo, Y.; Christie, P. Total concentrations of heavy metals and occurrence of antibiotics in sewage sludges from cities throughout China. J. Soils Sediments 2014, 14, 1123–1135. [CrossRef]

93. Ashfaq, M.; Khan, K.N.; Rasool, S.; Mustafa, G.; Safi-Ur-Rehman, M.; Nazar, M.F.; Sun, Q.; Yu, C.P. Occurrence and ecological risk assessment of fluoroquinolone antibiotics in hospital wastewater of Lahore, Pakistan. Environ. Toxicol. Pharmacol. 2016, 42, 16–22. [CrossRef]
94. Gao, L.; Shi, Y.; Li, W.; Niu, H.; Liu, J.; Cai, Y. Occurrence of antibiotics in eight sewage treatment plants in Beijing, China. *Chemosphere* 2012, 86, 665–671. [CrossRef]

95. An, J.; Chen, H.; Wei, S.; Gu, J. Antibiotic contamination in animal manure, soil, and sewage sludge in Shenyang, northeast China. *Environ. Earth Sci.* 2015, 74, 5077–5086. [CrossRef]

96. Czatkowska, M.; Harnisz, M.; Korzeniewska, E.; Rusanow ska, P.; Bajkacz, S.; Felis, E.; Jastrzebski, J.P.; Pauksztoto, L.; Koniuszewska, I. The impact of antimicrobials on the efficiency of methane fermentation of sewage sludge, changes in microbial biodiversity and the spread of antibiotic resistance. *J. Hazard. Mater.* 2021, 416, 125773. [CrossRef] [PubMed]

97. Nascimento, A.L.; Souza, A.J.; Andrade, P.A.M.; Andreote, F.D.; Coscione, A.R.; Oliveira, F.C.; Regitano, J.B. Sewage sludge microbial structures and relations to their sources, treatments, and chemical attributes. *Front. Microbiol.* 2018, 9, 1462. [CrossRef] [PubMed]

98. Dominguez, J.; Aira, M.; Crandall, K.A.; Perez-Losada, M. Earthworms drastically change fungal and bacterial communities during vermicomposting of sewage sludge. *Sci. Rep.* 2021, 11, 15556. [CrossRef] [PubMed]

99. Stiborova, H.; Strejcek, M.; Musilova, L.; Demmerova, K.; Ulhlik, O. Diversity and phylogenetic composition of bacterial communities and their association with anthropogenic pollutants in sewage sludge. *Chemosphere* 2020, 238, 124629. [CrossRef] [PubMed]

100. Xu, S.; Lu, W.; Qasim, M.Z. High-throughput characterization of the expressed antibiotic resistance genes in sewage sludge with transcriptional analysis. *Ecotoxicol. Environ. Saf.* 2020, 205, 111377. [CrossRef] [PubMed]

101. Redhead, S.; Nieuwland, J.; Esteves, S.; Lee, D.H.; Kim, D.W.; Mathias, J.; Cha, C.J.; To leman, M.; Dinsdale, R.; Guwy, A.; et al. Fate of antibiotic resistant *E. coli* and antibiotic resistance genes during full scale conventional and advanced anaerobic digestion of sewage sludge. *PLoS ONE* 2020, 15, e0237283. [CrossRef]

102. Qiu, X.; Zhou, G.; Wang, H.; Wu, X. The behavior of antibiotic-resistance genes and their relationships with the bacterial community and heavy metals during sewage sludge composting. *Ecotoxicol. Environ. Saf.* 2021, 216, 112190. [CrossRef]

103. Calero-Cáceres, W.; Melgarejo, A.; Colomer-Lluch, M.; Stoll, C.; Lucena, E.; Jofre, J.; Muniesa, M. Sludge as a potential important source of antibiotic resistance genes in both the bacterial and bacteriophage fractions. *Environ. Sci. Technol.* 2014, 48, 7602–7611. [CrossRef] [PubMed]

104. National Inventory of Sewage Treatment Plants CPCB. 2021. Available online: https://cpcb.nic.in/ (accessed on 17 February 2022).

105. MOHURD (Ministry of Housing and Urban-Rural Development). China Urban Construction Statistical Yearbook 2018; MOHURD: Beijing, China, 2020. Available online: https://www.mohurd.gov.cn/ (accessed on 17 February 2022).

106. Wei, L.; Zhu, F.; Li, Q.; Xue, C.; Xia, X.; Yu, H.; Zhao, Q.; Jiang, J.; Bai, S. Development, current state and future trends of sludge management in China: Based on exploratory data and CO₂-equivalent emissions analysis. *Environ. Int.* 2020, 144, 106093. [CrossRef]

107. ANZBP. 2019. Available online: https://www.biosolids.com.au/guidelines/australian-biosolids-statistics/ (accessed on 18 February 2022).

108. EPA. 2019. Available online: https://www.epa.gov/biosolids/ (accessed on 19 February 2022).

109. ANA—The Brazilian National Water Agency: Atlas Sewage, Pollution of Watersheds. 2017. Available online: http://atlasesgotos.ana.gov.br/ (accessed on 18 February 2022).

110. Cañote, S.J.B.; Barros, R.M.; Lora, E.E.S.; del Olmo, O.A.; dos Santos, I.F.S.; Piñas, J.A.V.; Ribeiro, E.M.; de Freitas, J.V.R.; de Castro, é Silva, H.L. Energy and Economic Evaluation of the Production of Biogas from Anaerobic and Aerobic Sludge in Brazil. *Waste Biomass Val.* 2021, 12, 947–969. [CrossRef]

111. Eurostat. 2022. Available online: https://ec.europa.eu/eurostat/ (accessed on 18 February 2022).

112. Campo, G.; Cerutti, A.; Lastella, C.; Leo, A.; Panepinto, D.; Zanetti, M.; Ruffino, B. Production and destination of sewage sludge in the piemonte region (Italy): The results of a survey for a future sustainable management. *Int. J. Environ. Res. Public Health* 2021, 18, 3556. [CrossRef]

113. Buta, M.; Hubeny, J.; Zieleński, W.; Harnisz, M.; Korzeniewska, E. Sewage sludge in agriculture—the effects of selected chemical pollutants and emerging genetic resistance determinants on the quality of soil and crops—a review. *Ecotoxicol. Environ. Saf.* 2021, 214, 112070. [CrossRef] [PubMed]

114. Lasaridi, K.E.; Manios, T.; Statmatiadi, S.; Chroni, C.; Kyriacou, A. The evaluation of Hazards to man and the environment during the composting of sewage sludge. *Sustainability* 2018, 10, 2618. [CrossRef]

115. Wu, D.; Wang, L.; Su, Y.; Dolling, J.; Xie, B. Associations between human bacterial pathogens and ARGs are magnified in leachates as landfill ages. *Chemosphere* 2021, 264, 128446. [CrossRef] [PubMed]

116. You, X.; Wu, D.; Wei, H.; Xie, B.; Lu, J. Fluoroquinolones and B-lactam antibiotics and antibiotic resistance genes in autumn leachates of seven major municipal solid waste landfills in China. *Environ. Int.* 2018, 113, 162–169. [CrossRef]

117. Wijekoon, P.; Koliyabandara, P.A.; Cooray, A.T.; Lam, S.S.; Athapattu, B.C.L.; Vithanage, M. Progress and prospects in mitigation of landfill leachate pollution: Risk, pollution potential, treatment and challenges. *J. Hazard. Mater.* 2022, 421, 126627. [CrossRef]

118. Anand, U.; Reddy, B.; Singh, V.K.; Singh, A.K.; Kesari, K.K.; Tripathi, P.; Kumar, P.; Tripathi, V.; Simal-Gandara, J. Potential environmental and human health risks caused by antibiotic-resistant bacteria (ARB), antibiotic resistance genes (ARGs) and emerging contaminants (ECs) from municipal solid waste (MSW) landfill. *Antibiotics* 2021, 10, 374. [CrossRef]

119. Borquaye, L.S.; Ekuadzi, E.; Darko, G.; Ahor, H.S.; Nsiah, S.T.; Sarney, I.A.; Mutala, A.H.; Boamah, V.E.; Woode, E. Occurrence of antibiotics and antibiotic-resistant bacteria in landfill sites in Kumasi, Ghana. *J. Chem.* 2019, 2019, 6934507. [CrossRef]

93. Lasaridi, K.E.; Manios, T.; Statmatiadi, S.; Chroni, C.; Kyriacou, A. The evaluation of Hazards to man and the environment during the composting of sewage sludge. *Sustainability* 2018, 10, 2618. [CrossRef]
120. Raghab, S.M.; Abd El Meguid, A.M.; Hegazi, H.A. Treatment of leachate from municipal solid waste landfill. *HBRC J*. 2013, 9, 187–192. [CrossRef]

121. Wu, D.; Huang, X.-H.; Sun, J.-Z.; Graham, D.W.; Xie, B. Antibiotic Resistance Genes and Associated Microbial Community Conditions in Aging Landfill Systems. *Environ. Sci. Technol.* 2017, 51, 12859–12867. [CrossRef]

122. Yu, X.; Sui, Q.; Lyu, S.; Zhao, W.; Liu, J.; Cai, Z.; Yu, G.; Barcelo, D. Municipal solid waste landfills: An underestimated source of pharmaceutical and personal care products in the water environment. *Environ. Sci. Technol.* 2020, 54, 9757–9768. [CrossRef]

123. Chung, S.S.; Zheng, J.S.; Burket, S.R.; Brooks, B.W. Select antibiotics in leachate from closed and active landfills exceed thresholds for antibiotic resistance development. *Environ. Int.* 2018, 115, 89–96. [CrossRef]

124. Zhao, R.; Feng, J.; Yin, X.; Liu, J.; Fu, W.; Berendonk, T.U.; Zhang, T.; Li, X.; Li, B. Antibiotic resistome in landfill leachate from different cities of China deciphered by metagenomic analysis. *Water Res.* 2018, 134, 126–139. [CrossRef]

125. Wang, Y.; Tang, W.; Qiao, J.; Song, L. Occurrence and prevalence of antibiotic resistance in landfill leachate. *Environ. Sci. Pollut. Res.* 2015, 22, 12525–12533. [CrossRef]

126. Wu, D.; Chen, G.; Zhang, X.; Yang, K.; Xie, B. Change in microbial community in landfill refuse contaminated with antibiotics facilitates denitrification more than the increase in ARG over long-term. *Sci. Rep.* 2017, 7, 41230. [CrossRef]

127. Zhang, X.H.; Xu, Y.B.; Huang, L.; Ling, J.Y.; Zheng, L.; Du, Q.P. Occurrence of antibiotic resistance genes in landfill leachate treatment plant and its effluent-receiving soil and surface water. *Environ. Pollut.* 2016, 218, 1255–1261. [CrossRef]

128. Metson, G.S.; Feiz, R.; Quttineh, N.H.; Tonderski, K. Optimizing transport to maximize nutrient recycling and green energy recovery. *Resour. Conserv. Recycl.* 2020, 9, 100049. [CrossRef]

129. World Biogas Association. Global Potential of Biogas. 2019. Available online: http://www.worldbiogasassociation.org/ (accessed on 25 February 2022).

130. Ryan, N.B.D.; Enright, R.M.A.M. Effect of Co-digestion Ratio and Enzyme Treatment on Biogas Production from Grass Silage and Chicken Litter. *Waste Biomass Val.* 2019, 10, 3271–3277. [CrossRef]

131. Koniuszewska, I.; Korzeniewska, E.; Harnisz, M.; Czatkowska, M. Intensification of biogas production using various technologies: A review. *Int. J. Energy Res.* 2020, 44, 6240–6258. [CrossRef]

132. Bowe, S. Market development and certification schemes for biomethane. In *Woodhead Publishing Series in Energy, The Biogas Handbook*; Wellinger, A., Murphy, J., Baxter, D., Eds.; Woodhead Publishing: Sawston, UK, 2013; ISBN 9780857094988. [CrossRef]

133. European Biogas Association. Available online: https://www.europeanbiogas.eu/the-european-biogas-map-2020-shows-a-51-increase-of-biometane-plants-in-europe-in-two-years/ (accessed on 10 February 2022).

134. Park, M.J.; Jo, J.H.; Park, D.; Lee, D.S.; Park, J.M. Comprehensive study on a two-stage anaerobic digestion process for the sequential production of hydrogen and methane from cost-effective molasses. *Renew. Energy* 2010, 35, 6194–6202. [CrossRef]

135. Styles, D.; Gibbons, J.; Williams, A.P.; Stichnothe, H.; Chadwick, D.R.; Healey, J.R. Cattle feed or bioenergy? Consequential life cycle assessment of biogas feedstock options on dairy farms. *GCB Bioenergy* 2014, 7, 1034–1049. [CrossRef]

136. Xiao, L.; Wang, Y.; Lichtfouse, E.; Li, Z.; Kumar, P.S.; Liu, J.; Feng, D.; Yang, Q.; Liu, F. Effect of Antibiotics on the Microbial Efficiency of Anaerobic Digestion of Wastewater: A Review. *Front. Microbiol.* 2021, 11, 61613. [CrossRef]

137. Reumer, M.; Harnisz, M.; Lee, H.J.; Reim, A.; Grunert, O.; Putikinen, A.; Fritz, H.; Bodeker, P.E.; Ho, A. Impact of peat mining and restoration on methane turnove potential and methane-cycling microorganisms in a northern bog. *Appl. Environ. Microbiol.* 2018, 84, e02218-17. [CrossRef]

138. Vitez, T.; Dokulilova, T.; Vitezova, M.; Elbl, J.; Kintl, A.; Kynicky, J.; Hladky, J.; Brtnicky, M. The Digestion of Waste from Vegetables and Maize Processing. *Waste Biomass Val.* 2020, 11, 2467–2473. [CrossRef]

139. Visca, A.; Caracciolo, A.B.; Genni, P.; Patrolecco, L.; Rauseo, J.; Massini, G.; Miritana, V.M.; Spataro, F. Anaerobic digestion and removal of sulfamethoxazole, enrofloxacin, ciprofloxacin and their antibiotic resistance genes in a full-scale biogas plant. *Antibiotics* 2021, 10, 502. [CrossRef]

140. Koniuszewska, I.; Czatkowska, M.; Harnisz, M.; Korzeniewska, E. The impact of antimicrobial substances on the methanogenic community during methane fermentation of sewage sludge and cattle slurry. *Appl. Sci. 2021*, 11, 369. [CrossRef]

141. Gurmessana, B.; Pedretti, E.F.; Cocco, S.; Cardelli, V.; Corti, G. Manure anaerobic digestion effects and the role of pre- and post-treatments on veterinary antibiotics and antibiotic resistance genes removal efficiency. *Sci. Total Environ.* 2020, 721, 137532. [CrossRef]

142. Aydun, S.; Ulvi, A.; Bedük, F.; Aydin, M.E. Pharmaceutical residues in digested sewage sludge: Occurrence, seasonal variation and risk assessment for soil. *Sci. Total Environ.* 2022, 817, 152864. [CrossRef]

143. Koniuszewska, I.; Harnisz, M.; Korzeniewska, E.; Czatkowska, M.; Jastrzębski, J.P.; Paukszto, Ł.; Bajkacz, S.; Felis, E.; Rusanowska, P. The Effect of Antibiotics on Mesophilic Anaerobic Digestion Process of Cattle Manure. *Energies* 2021, 14, 1125. [CrossRef]

144. Wang, P.; Zheng, Y.; Lin, P.; Chen, X.; Qi, L.; Yang, X.; Ren, L. Characteristics of antibiotic resistance genes in full-scale anaerobic digesters of food waste and the effects of application of biogas slurry on soil antibiotic resistance genes. *Environ. Sci. Pollut. Res.* 2022, 29, 18944–18954. [CrossRef]

145. Sanz, C.; Casado, M.; Navarro-Martin, L.; Tadić, D.; Parera, J.; Tugues, J.; Bayona, J.M.; Piña, B. Antibiotic and antibiotic-resistant gene loads in swine slurries and their digestates: Implications for their use as fertilizers in agriculture. *Environ. Res.* 2021, 194, 110513. [CrossRef][PubMed]
147. Schueler, J.; Lansing, S.; Crosette, E.; Naas, K.; Hurst, J.; Raskin, L.; Wigginton, K.; Agra, D.S. Tetracycline, sulfadimethoxine, and antibiotic resistance gene dynamics during anaerobic digestion of dairy manure. J. Environ. Qual. 2021, 50, 694–705. [CrossRef] [PubMed]

148. Nesse, A.S.; Aanrud, S.G.; Lyche, J.L.; Sogn, T.; Kallenborn, R. Confirming the presence of selected antibiotics and steroids in Norwegian biogas digestate. Environ. Sci. Pollut. Res. Int. 2022, 1–11. [CrossRef] [PubMed]

149. Zhang, Y.; Zheng, Y.; Zhu, Z.; Chen, Y.; Dong, H. Dispersion of Antibiotic Resistance Genes (ARGs) from stored swine manure biogas digestate to the atmosphere. Sci. Total Environ. 2021, 761, 144108. [CrossRef]

150. Wen, Q.; Yang, S.; Chen, Z. Mesophilic and thermophilic anaerobic digestion of swine manure with sulfamethoxazole and norfloxacin: Dynamics of microbial communities and evolution of resistance genes. Front. Environ. Sci. Eng. 2021, 15, 94. [CrossRef]

151. Xu, S.; Qasim, M.Z.; Zhang, T.; Wang, R.; Li, C.; Ge, S. Diversity, abundance and expression of the antibiotic resistance genes in a Chinese landfill: Effect of deposit age. J. Hazard. Mater. 2021, 417, 126027. [CrossRef]

152. Zhang, R.M.; Liu, X.; Wang, S.L.; Fang, L.X.; Sun, J.; Liu, Y.H.; Liao, X.P. Distribution patterns of antibiotic resistance genes and their bacterial hosts in pig farm wastewater treatment systems and soil fertilized with pig manure. Sci. Total Environ. 2021, 758, 143654. [CrossRef]

153. Álvarez, J.A.; Otero, L.; Lema, J.M.; Omil, F. The effect and fate of antibiotics during the anaerobic digestion of pig manure. Bioresour. Technol. 2010, 101, 8581–8586. [CrossRef]

154. Ezzariai, A.; Hafidi, M.; Khadra, A.; Aemig, Q.; El Fels, L.; Barret, M.; Merlina, G.; Patureau, D.; Pinelli, E. Human and veterinary antibiotics during composting of sludge or manure: Global perspectives on persistence, degradation, and resistance genes. J. Hazard. Mater. 2018, 359, 465–481. [CrossRef]

155. Zhou, X.; Wang, J.; Lu, C.; Liao, Q.; Gudda, E.O.; Ling, W. Antibiotics in animal manure and manure-based fertilizers: Occurrence and ecological risk assessment. Chemosphere 2020, 255, 127006. [CrossRef]

156. Buta-Hubeny, M.; Korzeniewska, E.; Hubeny, J.; Zieliński, W.; Rolbiecki, D.; Harnisz, M.; Paukszto, Ł. Structure of the manure resistome and the associated mobilome for assessing the risk of antimicrobial resistance transmission to crops. Sci. Total Environ. 2022, 808, 152144. [CrossRef] [PubMed]

157. Rahman, M.; Alam, M.U.; Luies, S.K.; Kamal, A.; Ferdous, S.; Lin, A.; Sharior, F.; Khan, R.; Rahman, Z.; Parvez, S.M.; et al. Contamination of fresh produce with antibiotic-resistant bacteria and associated risks to human health: A scoping review. Int. J. Environ. Res. Public Health 2022, 19, 360. [CrossRef] [PubMed]

158. Zhang, H.; Li, X.; Yang, Q.; Sun, L.; Yang, X.; Zhou, M.; Deng, R.; Bi, L. Plant growth, antibiotic uptake, and prevalence of antibiotic resistance in an endophytic system of pakchoi under antibiotic exposure. Int. J. Environ. Res. Public Health 2017, 14, 1336. [CrossRef]

159. Duan, M.; Li, H.; Gu, J.; Tuo, X.; Sun, W.; Qian, X.; Wang, X. Effects of biochar on reducing the abundance of oxytetracycline, antibiotic resistance genes, and human pathogenic bacteria in soil and lettuce. Environ. Pollut. 2017, 224, 787–795. [CrossRef] [PubMed]

160. Cericrea, F.; Matamoros, V.; Bayona, J.M.; Berendonk, T.U.; Elsinga, G.; Hornstra, L.M.; Piña, B. Antibiotic resistance gene distribution in agricultural fields and crops. A soil-to-food analysis. Environ. Res. 2019, 177, 18–26. [CrossRef]

161. Mei, Z.; Xiang, L.; Wang, F.; Xu, M.; Fu, Y.; Wang, Z.; Hashsham, S.A.; Jiang, X.; Tiedje, J.M. Bioaccumulation of Manure-born antibiotic resistance genes in carrot and its exposure assessment. Environ. Int. 2021, 157, 106830. [CrossRef]

162. Pu, C.; Liu, L.; Yao, M.; Liu, H.; Sun, Y. Responses and successions of sulfonamides, tetracyclines and fluoroquinolones resistance genes and bacterial community during the short-term storage of biogas residue and organic manure under the incubator and natural conditions. Environ. Pollut. 2018, 242, 749–759. [CrossRef]

163. Santoyo, G.; Moreno-Hagelsieb, G.; del Carmen Orozco-Mosqueda, M.; Glick, B.R. Plant growth-promoting bacterial endophytes. Microb. Res. 2016, 183, 92–99. [CrossRef]

164. Christou, A.; Papadavid, G.; Dalias, P.; Fotopoulos, V.; Michael, C.; Bayona, J.M.; Piña, B.; Fatta-Kassinos, D. Ranking of crop plants according to their potential to uptake and accumulate contaminants of emerging concern. Environ. Res. 2019, 170, 422–432. [CrossRef]

165. Fatemi, M.; Niyyati, M.; Rouhani, S.; Karamati, S.A.; Mirjalali, H.; Karanis, P. Contamination of fresh vegetables in municipal stores with pathogenic Acanthamoeba genotypes; a public health concern. Int. J. Environ. Health Res. 2022, 1–12. [CrossRef]

166. Elshafei, E.A.; Kadry, M.; Nader, S.M.; Ahmed, Z.S. Extended-spectrum-beta-lactamases and carbapenemase-producing Klebsiella pneumoniae isolated from fresh produce farms in different governorates of Egypt. Vet. World 2022, 15, 1191–1196. [CrossRef]

167. Ezzariai, A.; Hafidi, M.; Khadra, A.; Aemig, Q.; El Fels, L.; Barret, M.; Merlina, G.; Patureau, D.; Pinelli, E. Human and veterinary antibiotics during composting of sludge or manure: Global perspectives on persistence, degradation, and resistance genes. J. Hazard. Mater. 2018, 359, 465–481. [CrossRef]

168. Fatemi, M.; Niyyati, M.; Rouhani, S.; Karamati, S.A.; Mirjalali, H.; Karanis, P. Contamination of fresh vegetables in municipal stores with pathogenic Acanthamoeba genotypes; a public health concern. Int. J. Environ. Health Res. 2022, 1–12. [CrossRef]

169. Elshafei, E.A.; Kadry, M.; Nader, S.M.; Ahmed, Z.S. Extended-spectrum-beta-lactamases and carbapenemase-producing Klebsiella pneumoniae isolated from fresh produce farms in different governorates of Egypt. Vet. World 2022, 15, 1191–1196. [CrossRef]

170. Manyi-Loh, C.; Mamphweli, S.; Meyer, E.; Okoh, A. Antibiotic use in agriculture and its consequential resistance in environmental sources: Potential public health implications. Molecules 2018, 23, 795. [CrossRef]
171. 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]

172. Zalewska, M.; Blażewiejwska, A.; Czapko, A.; Popowska, M. Antibiotics and Antibiotic Resistance Genes in Animal Manure—Consequences of Its Application in Agriculture. *Front. Microbiol.* **2021**, *12*, 610656. [CrossRef] [PubMed]

173. Laxminarayan, R.; Van Boeckel, T.; Teillant, A. The Economic Costs of Withdrawing Antimicrobial Growth Promoters from the Livestock Sector. *OECD Food Agric. Fish. Pap.* **2015**, *78*, 4–41. [CrossRef]

174. Zhang, Q.Q.; Ying, G.G.; Pan, C.G.; Liu, Y.S.; Zhao, J.L. Comprehensive evaluation of antibiotics emission and fate in the river basins of China: Source analysis, multimedia modeling, and linkage to bacterial resistance. *Environ. Sci. Technol.* **2015**, *49*, 6772–6782. [CrossRef]

175. Al-Mashhadany, D.A. Monitoring of antibiotic residues among sheep meats at Erbil city and thermal processing effect on their remnants. *Iraqi J. Vet. Sci.* **2020**, *34*, 217–222. [CrossRef]

176. Widiastuti, R.; Martindah, E.; Anastasia, Y. Detection and Dietary Exposure Assessment of Fluoroquinolones Residues in Chicken Meat from the Districts of Malang and Blitar, Indonesia. *Trop. Anim. Sci.* **2022**, *45*, 98–103. [CrossRef]

177. Ramatla, T.; Ngoma, L.; Adetunji, M.; Mwanza, M. Evaluation of antibiotic residues in raw meat using different analytical methods. *Antibiotics* **2017**, *6*, 34. [CrossRef]

178. Rahman, M.S.; Hassan, M.M.; Chowdhury, S. Determination of antibiotic residues in milk and assessment of human health risk in Bangladesh. *Heligol. 2021*, *7*, e00739. [CrossRef]

179. Ferdous, J.; Bradshaw, A.; Islam, S.K.M.A.; Zamil, S.; Islam, A.; Ahad, A.; Fournie, G.; Anwer, M.S.; Hoque, M.A. Antibiotic Residues in Chicken and Fish, Chittagong, Bangladesh. *Ecohealth* **2019**, *16*, 429–440. [CrossRef]

180. Neogi, S.B.; Islam, M.M.; Islam, S.K.S.; Akhter, A.H.M.T.; Skidder, M.M.H.; Yamashiki, S.; Kabir, S.M.L. Risk of multi-drug resistant *Campylobacter* spp. and residual antimicrobials at poultry farms and live bird markets in Bangladesh. *BMC Infect. Dis.* **2020**, *20*, 278. [CrossRef]

181. Doğan, Y.N.; Pamuk, Ş.; Gürler, Z. Chloramphenicol and sulfonamide residues in sea bream (*Dicentrarchus labrax*) and sea bass (*Sparus aurata*) fish at aquaculture farm. *Environ. Sci. Pollut. Res.* **2020**, *27*, 41248–41252. [CrossRef]

182. Hasman, H.; Moodley, A.; Guardabassi, L.; Stegger, M.; Skov, R.L.; Aarestrup, F.M. Spa type distribution in *Acinetobacter baumannii* in livestock animals in Lebanon. *J. Antimicrob. Chemother.* **2016**, *70*, 950–951. [CrossRef] [PubMed]

183. Ewnetu, D.; Mihret, A. Prevalence and Antimicrobial Resistance of *Staphylococcus aureus* originating from pigs, cattle and poultry. *Vet. Microbiol.* **2010**, *141*, 326–331. [CrossRef]

184. Ewenetu, D.; Mihret, A. Prevalence and Antimicrobial Resistance of *Campylobacter* Isolates from Humans. *Foodborne Pathog. Dis.* **2010**, *7*, 7–10. [CrossRef]

185. Al Bayssari, C.; Dabboussi, F.; Hamze, M.; Rolain, J.M. Emergence of carbapenemase-producing *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in livestock animals in Lebanon. *J. Antimicrob. Chemother.* **2015**, *70*, 950–951. [CrossRef] [PubMed]

186. Walia, K.; Sharma, M.; Vijay, S.; Shome, B.R. Understanding policy dilemmas around antibiotic use in food animals & offering potential solutions. *Indian J. Med. Res.* **2019**, *142*, 101–118. [CrossRef]

187. Chmipeteau, O.M.; Pogurschi, E.N.; Popa, D.C.; Dragomir, N.; Drăgotăiu, T.; Mihai, O.D.; Petcu, C.D. Antibiotic Use in Livestock and Residues in Food—A Public Health Treat: A Review. *Foods* **2022**, *11*, 1430. [CrossRef] [PubMed]

188. 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]

189. Kumar, R.; Yadav, B.R.; Singh, R.S. Antibiotic resistance and pathogenicity factors in *Staphylococcus aureus* isolated from mastitic Sahiwal cattle. *J. Biosci.* **2011**, *36*, 175–188. [CrossRef]

190. Zhao, Y.; Yang, Q.E.; Zhou, X.; Wang, F.H.; Muirinen, J.; Virta, M.P.; Brandt, K.K.; Zhu, Y.G. Antibiotic resistome in the livestock and aquaculture industries: Status and solutions. *Crit. Rev. Environ. Sci. Technol.* **2021**, *51*, 2159–2196. [CrossRef]

191. Qasem, N.A.A.; Mohammed, R.H.; Lawal, D.U. Removal of heavy metal ions from wastewater: A comprehensive and critical review. *NPJ Clean Water* **2021**, *4*, 36. [CrossRef]

192. Shamuyarira, K.; Gumbo, J. Assessment of Heavy Metals in Municipal Sewage Sludge: A Case Study of Limpopo Province, South Africa. *Int. J. Environ. Res. Public Health* **2014**, *11*, 2569–2579. [CrossRef]

193. Hussein, M.; Yoned, K.; Mohd-Zaki, Z.; Amir, A.; Othman, N. Heavy Metals in Leachate, Impacted Soils and Natural Soils of Different Landfills in Malaysia: An Alarming Threat. *Chemosphere* **2021**, *267*, 128874. [CrossRef]

194. Ji, X.; Shen, Q.; Liu, F.; Ma, J.; Xu, G.; Wang, Y.; Wu, M. Antibiotic resistance gene abundances associated with antibiotics and heavy metals in animal manures and agricultural soils adjacent to feedlots in Shanghai; China. *J. Hazard. Mater.* **2012**, *235*, 178–185. [CrossRef]

195. Lehmann, L.; Bloem, E. Antibiotic residues in substrates and output materials from biogas plants—Implications for agriculture. *Chemosphere* **2021**, *278*, 130425. [CrossRef]

196. Martins, V.V.; Zanetti, M.O.B.; Pitondo-Silva, A.; Stehling, E.G. Aquatic environments polluted with antibiotics and heavy metals: A human health hazard. *Environ. Sci. Pollut. Res.* **2014**, *21*, 5873–5878. [CrossRef] [PubMed]

197. Medardus, J.J.; Molla, B.Z.; Nicol, M.; Morrow, W.M.; Rajala-Schultz, P.J.; Kazwala, R.; Gebreyes, W.A. In-feed use of heavy metal micronutrients in U.S. swine production systems and its role in persistence of multidrug-resistant salmonellae. *Appl. Environ. Microbiol.* **2014**, *80*, 2317–2325. [CrossRef] [PubMed]
215. Li, J.; Ma, Y.B.; Hu, H.W.; Wang, J.T.; Li, J.J.; Ma, Y.B.; Chen, D. Field-based Evidence for Copper Contamination Induced Changes of Antibiotic Resistance in Agricultural Soils. *Environ. Microbiol.* 2016, 18, 3896–3909. [CrossRef]

216. Liu, Y.; Liu, W.; Yang, X.; Wang, J.; Lin, H.; Yang, Y. Microplastics are a hotspot for antibiotic resistance genes: Progress and perspective. *Sci. Total Environ.* 2021, 773, 145643. [CrossRef]

217. Su, Y.; Zhang, Z.; Zhu, J.; Shi, J.; Wei, H.; Xie, B.; Shi, H. Microplastics act as vectors for antibiotic resistance genes in landfill leachate: The enhanced roles of the long-term aging process. *Environ. Pollut.* 2021, 270, 116278. [CrossRef] [PubMed]

218. Chen, G.; Feng, Q.; Wang, J. Mini-review of microplastics in the atmosphere and their risks to humans. *Sci. Total Environ.* 2020, 703, 135504. [CrossRef]

219. De Souza MacHado, A.A.; Lau, C.W.; Till, J.; Kloas, W.; Lehmann, A.; Becker, R.; Rillig, M.C. Impacts of Microplastics on the Soil Biophysical Environment. *Environ. Sci. Technol.* 2018, 52, 9656–9665. [CrossRef] [PubMed]

220. Wang, S.; Xue, N.; Li, W.; Zhang, D.; Pan, X.; Luo, Y. Selectively enrichment of antibiotics and ARGs by microplastics in river, estuary and marine waters. *Sci. Total Environ.* 2020, 708, 134594. [CrossRef]

221. Duus, K.; Coors, A. Microplastics in the aquatic and terrestrial environment: Sources (with a specific focus on personal care products), fate and effects. *Environ. Sci. Eur.* 2016, 28, 2. [CrossRef] [PubMed]

222. Hernandez, E.; Nowack, B.; Mitran, D.M. Polyester Textiles as a Source of Microplastics from Households: A Mechanistic Study to Understand Microfiber Release during Washing. *Environ. Sci. Technol.* 2017, 51, 7036–7046. [CrossRef]

223. Xu, X.; Jian, Y.; Xue, Y.; Hou, Q.; Wang, L. Microplastics in the wastewater treatment plants (WWTPs): Occurrence and removal. *Chemosphere* 2019, 235, 1089–1096. [CrossRef]

224. Jutkina, J.; Marathe, N.; Flach, C.-F.; Larsson, D. Antibiotics and common antibacterial biocides stimulate horizontal transfer of resistance at low concentrations. *Sci. Total Environ.* 2018, 616, 172–178. [CrossRef] [PubMed]

225. Zhang, Y.; Gu, A.Z.; Cen, T.; Li, X.; He, M.; Li, D.; Chen, J. Sub-inhibitory concentrations of heavy metals facilitate the horizontal transfer of plasmid-mediated antibiotic resistance genes in water environment. *Environ. Pollut.* 2018, 237, 74–82. [CrossRef]