Abstract: The usage of antibiotics has been, and remains, a topic of utmost importance; on the one hand, for animal breeders, and on the other hand, for food safety. Although many countries have established strict rules for using antibiotics in animal husbandry for the food industry, their misuse and irregularities in compliance with withdrawal periods are still identified. In addition to animal-origin foods that may cause antibiotic residue problems, more and more non-animal-origin foods with this type of non-compliance are identified. In this context, we aim to summarize the available information regarding the presence of antibiotic residues in food products, obtained in various parts of the world, as well as the impact of consumption of food with antibiotic residues on consumer health. We also aim to present the methods of analysis that are currently used to determine antibiotic residues in food, as well as methods that are characterized by the speed of obtaining results or by the possibility of identifying very small amounts of residues.

Keywords: antibiotic residues; food safety; antimicrobial resistance; public health

1. Introduction

Antibiotics are produced by living organisms or in the laboratory and have the capacity to kill or inhibit the growth of microorganisms [1]. Even if antibiotics represent a positive aspect for both animals and humans, because of their great impact on their health status, their abusive use can lead to harmful consequences, and especially to the appearance of resistant germs [2–4].

The practice of using antibiotics is still widespread for prophylactic and curative purposes, and the problem of their remnants in animal products, groundwater, soil, and feed has caused (and is still causing) worldwide concern, generating vast costs to combat antibiotic resistance [5]. In order to reduce this effect, a number of developed countries have enforced laws in order to decrease the excessive use of antibiotics as a means to prevent diseases or as an acceleration tool in animals [6]. A number of monitoring programs regarding the use of antibiotics in animal breeding have been implemented over the last 30 years, starting with the Danish Integrated Antimicrobial Resistance Monitoring and Research Program in 1995 [7]. Nowadays, a number of research projects have been developed in this area; as an example, the Disseminating Innovative Solutions for Antibiotic Resistance Management project (DISARM), in which nine European countries are involved [8]. As a counterbalance, in less developed countries in Asia or Africa, the use of antibiotics is still very high due to the great demand for animal products, and this leads to the uncontrolled use of these substances in the breeding systems [9].
Most antibiotic residues can be found in a large range of food products, both animal and vegetal [10]. Although meat consumption is decreasing in developed countries, especially in Europe, in less developed countries it is very high, so meat represents the most important source of antibiotics. Primarily, the main source of antibiotics in food is abusive use (overdosing, non-compliance with the withdrawal period) and the use of antibiotic-contaminated water, or inappropriate disposal of animal dung.

The sources of antibiotics in humans are two-fold: first, prescriptions for people (most commonly penicillins, macrolides, and fluoroquinolones), and, second, the substances used in animal breeding (tetracyclines and sulfonamides). Antibiotics can cause serious effects on human health that have led to the introduction of maximum residue limits (MRL) in food safety legislation [11,12]. Long-term exposure is linked to impairment of the immune system, digestive problems caused by the destruction of the intestinal flora, renal problems, and even carcinogenic effects [13].

Yang et al. (2021) and Huang et al. (2020) mentioned that antibiotics have become widespread in the environment due to their extensive and long-term use, influencing both human health and the system, due to the emergence of antibiotic resistance [14,15]. Saeed et al. (2020) addressed the contamination of food with antibiotic residues, mentioning that it is a global problem, due to the improper use of antibiotics. The authors of the current paper also mentioned methods of analysis to identify antibiotics in food [16].

This review focuses on three aspects: (1) antibiotic use in livestock; (2) antibiotic residues in food and methods of detection; and (3) the impact of consumption of food with antibiotic residues on consumer health.

2. Antibiotic Use in Livestock

Livestock farming plays a very important role in the agriculture of the European Community. Achieving the best results largely depends on the use of safe and good quality feed. Free movement of safe and good quality food and feed is a key aspect of the internal market, and contributes significantly to the health and well-being of consumers [17].

In terms of animals of economic interest and poultry farms, various active substances are used, including antibiotics, in order to maintain the health of the animals and to have a better yield for breeding. Antibiotics can be administered via feed or by intramuscular injection [18,19]. Medicated feed is an oral route of veterinary medicinal product administration. Medicated feed is a homogeneous mixture of feed and veterinary medicinal products [20].

Regulation (EU) 6/2019 establish rules for the authorization of use of veterinary medicinal products in feeding stuffs, including the manufacture, distribution, advertising, and surveillance of such products [12]. Feed business operators, which handle manufacturing, storing, transporting, or placing medicated feed and intermediate products on the market, must be authorized by the competent authority, in accordance with the authorization system, to ensure both the safety of the feed and the traceability of the products. The labeling of medicated feed stuffs must comply with the general principles set out in Regulation (EC) 767/2009, and are subject to specific labeling requirements, in order to provide users with the information necessary for the correct administration of medicated feed [21]. Such administration must be adequately described in the product information to ensure correct administration and proper dosing of certain veterinary medicinal products, to be administered orally to animals, in feed, or in drinking water, especially in the case of treating groups of animals. The relevant legislation provides the establishment of additional instructions for cleaning of the equipment used in the administration of respective medicinal products, in order to avoid cross-contamination and to reduce resistance to antimicrobials [12]. A large range of synthetic feed additives are included in this category of antibiotics and are used in animal feeding to increase production efficiency and to control different diseases [8].

Recent studies have shown that a significant percentage of all manufacturers add antibiotics to healthy animals’ feed to prevent, rather than cure, diseases [22–25]. According to Erofeeva et al., livestock accounts for approximately 50% of all antibiotics produced in the world. During the life of an animal, the use of antibiotics can significantly increase a gain in
weight by increasing the use of nutrients in the diet, which, in the end, makes it possible to reduce feed costs and shorten the feeding period [25]. Feed manufacturers and authorities establish procedures and instructions for the effective and safe use of authorized and prescribed veterinary medicinal products, for oral administration, other than medicated feeding stuff, such as mixing drinking water with veterinary medicinal products or manually mixing a veterinary medicinal product in feed, which are administered by farmers to food-producing animals. These instructions take into account the scientific recommendations of the European Medicines Agency, established by Regulation (EC) No. 726/2004, on measures to minimize over dosage or under dosage, unintended administration to animals other than those targeted, the risk of cross-contamination, and the release of these products into the environment [12,26]. Homogeneous dispersion of veterinary medicinal product in feed is also essential for the manufacture of safe and effective medicated feed [20].

According to different researchers, reliable data regarding the quantity and patterns of use, dose, and frequency, are not very accurate [27–29]. Disease prevention is more effective than treating it. Drug treatment, with antimicrobials in particular, should in no way replace good animal husbandry, biosecurity, and management practices [20]. Excessive weight loss at the beginning of the lactation period leads to the appearance of stress, increasing the susceptibility of animals to diseases, which is why medicated feed has been used for animals for curative and preventive purposes [30]. The US Department of Agriculture noted that approximately 88% of growing swine receive antibiotics in their feed for disease prevention and growth promotion purposes, commonly tetracyclines or tylosin [22]. Some of the most frequently used antibiotics in ruminants are ionophores, a distinctive class of antibiotics that can influence intestinal flora to achieve increased energy and amino acid availability and improved nutrient utilization [22]. Most beef calves in feed lots and some dairy heifers receive this drug routinely in their feed. Ionophores have never been used in humans or therapeutically in animals, because of their specific mode of action. The impact that medicated food has on human health, and implicitly how antibiotic resistance is installed after ingesting food with antibiotics residues, is a topic that we will detail in a later section, but it is worth mentioning that while some bacteria are intrinsically resistant to these drugs, there is currently no evidence to suggest that ionophore resistance is transferable [22,28].

The presence of antibiotics in feed is not desirable due to the antibiotic resistance that the bodies can later acquire. Therefore, the elimination of antibiotics from feed, but improvements in the productivity of pigs and poultry, has been achieved through the use of feed additives, such as omega 3, immunoglobulin, organic and inorganic acids, zinc oxide, yeast derived β glucans, essential oils, prebiotics, probiotics, threonine, cysteine, and herbs and spices [31,32]. On the other hand, the conclusion of another study was that the elimination of prophylactic in-feed antibiotics leads to minor reductions in productive performance and animal health [29].

Advertising for medicated feeding stuffs addressed persons who cannot properly assess the risks associated with their use, and may lead to improper or excessive use of the medicinal product, which may harm public or animal health or the environment [20].

Animal health management is mainly based on disease prevention, compliance with hygiene conditions, and the correct application of disinfection actions. Preventive use of synthetic chemical allopathic medicines is forbidden in order to obtain organic products. In case antibiotics are compulsory, treatment should be carefully managed through minimal use with a high efficiency. In such cases, in order to ensure the integrity of organic production for consumers, an official withdrawal period after the use of such medicinal products requires a longer period of time. In organic production, the use of antibiotics as growth or production stimulants, coccidiostats, hormones, etc., is not permitted [33].

3. Antibiotic Residues in Food

Dozens of scientific papers have been published over the years, focusing on antibiotic residues in food and feed. Antibiotics can be naturally produced by living organisms or
they can be synthetically produced in a laboratory. The main role of antibiotics is to inhibit or kill microorganism growth [1,34]. Antibiotics can be used as feed additives in livestock in order to maintain animal health; lately, however, there is an increasing attempt to stop this phenomenon as antibiotic residues can be consumed by humans with food of animal origin (meat, milk, eggs, fish, honey, etc.). It should be noted that, not only may food from animal origin have antibiotic residues, but also plant foods, which can be contaminated by soil and water [35,36]. From Table 1, it can be seen that antibiotic residues are found in all foods intended for human consumption, whether they are of animal or non-animal origin. It can be seen that most studies were performed to determine the presence of antibiotic residues in milk, followed by meat, and then by honey. Another thing to note is that research on antibiotic residues started in the 1980s, but the largest number of works in this field appeared in the last 5 years.

Table 1. Bibliometric analysis according with “Web of Science” database.

| Field of Research                                      | Number of Scientific Publications |
|-------------------------------------------------------|-----------------------------------|
| Antibiotic residues in food                           | 67                                |
| Antibiotic residues in feed                           | 17                                |
| Antibiotic residues in animal origin food             | 12                                |
| Antibiotic residues in non-animal origin food         | 6                                 |
| Antibiotic residues in meat                           | 54                                |
| Antibiotic residues in meat products                  | 4                                 |
| Antibiotic residues in fish                           | 12                                |
| Antibiotic residues in milk                           | 292                               |
| Antibiotic residues in eggs                           | 21                                |
| Antibiotic residues in honey                          | 45                                |

In order to ensure food safety for consumers, more and more studies have attempted to find effective and rapid methods for the detection antibiotic residues in feed and food [36]. Consumers are also increasingly interested in consuming quality food, and are increasingly turning to organic products, which provide them with more safety relative to conventional products.

Several studies have shown the presence of antibiotic residues in various types of food (Table 2).

Table 2. Presence of varying concentrations of antibiotic residues in the different animal-derived products in some developing countries. Reprinted from [37].

| Antibiotic Residue | Concentration | Sample | Country   | Literature               |
|--------------------|---------------|--------|-----------|--------------------------|
| Oxytetracycline    | 2604.1 ± 703.7 µg/kg 3434.4 ± 604.4 µg/kg 3533.1 ± 803.6 µg/kg | Chicken Muscle Liver Kidney | Tanzania | Kimeria et al. [38] |
|                    | 51.8 ± 90.53 µg/kg 372.7 ± 366.8 µg/kg 1197.7 ± 718.9 µg/kg | Beef Muscle Kidney Liver | Nigeria | Olufemi and Agboola [39] |
|                    | 15.92 to 108.34 µg/kg 9.02 to 112.53 µg/kg | Cattle Muscle Kidney | Ethiopia | Bedada et al. [40] |
| Enrofloxacin       | 0.73 and 2.57 µg/kg | Chicken tissues | Iran | Tavakoli et al. [41] |
| Chloramphenicol    | 1.34 and 13.9 µg/kg | | | |
| Penicillin         | 0.87 and 1.3 µg/kg | | | |
| Oxytetracycline    | 3.5 and 4.61 µg/kg | Calves muscles | | |
Table 2. Cont.

| Antibiotic Residue | Concentration | Sample       | Country  | Literature          |
|---------------------|---------------|--------------|----------|---------------------|
| Quinolones          | 30.81 ± 0.45 µg/kg 6.64 ± 1.11 µg/kg | Chicken Beef | Turkey   | Er et al. [42]      |
| Tetracyclines       | 124 to 5812 µg/kg 107–6010 µg/kg 103 to 8148 µg/kg | Chicken Breast Thigh Livers | Egypt    | Salama et al. [43]  |
|                     | 150 ± 30 µg/g 62.4 ± 15.3 µg/g | Chicken Liver Muscle | Cameroon | Guetiya-Wadoum et al. [44] |
|                     | 50 to 845 µg/kg 50 to 573 µg/kg 23–560 µg/kg | Beef Kidney Liver Muscle | Kenya    | Muriuki et al. [45] |
| Amoxicillin         | 9.8 to 56.16 µg/mL 10.46 to 48.8 µg/g | Milk Eggs | Bangladesh | Chowdhury et al. [46] |
| Sulfonamides Quinolones | 16.28 µg/kg 23.25 µg/kg | Raw milk | China    | Zheng et al. [47]   |
| Oxytetracycline     | 199.6 ± 46 ng/g 86.5 ± 8.7 ng/g | Beef         | Zambia   | Nchima et al. [48] |
| Sulphamethazine     | 15.22 ± 0.61 µg/L 7.60 ± 0.60 µg/L 8.24 ± 0.50 µg/L | Fresh milk Cheese (wara) Fermented milk (nono) | Nigeria | Olatoye et al. [49] |
| Penicillin G        | 0.08–0.193 µg/g 0.006–0.062 µg/g | Chicken Liver Breast | Malaysia | Cheong et al. [50] |
| Tetracycline        | >0.1 µg/mL | Raw milk | India    | Kumari Anjana et al. [51] |

3.1. Products of Non-Animal Origin

Although food products of animal origin are considered to be the major source of antibiotic residues, studies in the literature have shown that even non-animal origin products represent an important problem regarding this type of contamination. The main sources of these compounds in agriculture are irrigation water with antibiotics traces due to inappropriate recycling processes or the use of manure as soil amendments, which leads to spreading antibiotics through the food chain [52]. As a result of these agricultural practices, antibiotics in soil can be taken up by plants, entering the food chain. Due to the fact that plants are considered to be a minor source of antibiotic residues, studies have focused on few compounds [29–31]. The most common vegetables that accumulate antibiotics are considered to be cereals, such as wheat, rice, and oat, and coarse grains, such as maize and barley. In this field, studies have focused on antibiotic detection in different matrices or were conducted as experiments in a hydroponic environment [53–57].

In recent years, research has been conducted in order to study the relation between intake of antibiotics in edible crops due to poorly management of wastewater used in irrigations and from manure [53,55,58–61]. Pan and Chu (2017) studied the influence of some antibiotics (tetracycline, sulfamethazine, norfloxacin, erythromycin, and chloramphenicol) on crops in relation to two types of contamination, irrigation with wastewater and soil amendment with animal manure. Findings showed that the distribution of tetracycline, norfloxacin, and chloramphenicol in crop tissues were as follows: fruit > leaf/shoot > root;
an opposite order was found for sulfamethazine (SMZ) and erythromycin (ERY), i.e., root > leaf/shoot > fruit [58]. Research also revealed that the uptake of antibiotics in crops was higher in the case of wastewater use and it was lower in the case of manure fertilization, argued by the fact that crops are more likely to absorb residues during the continuous process of irrigation. However, the levels of antibiotics ingested through the consumption of edible crops under the different treatments were much lower than acceptable daily intake (ADI) levels.

In Northern China, studies have shown that oxytetracycline, tetracycline, chlortetracycline, sulfamethoxazole, sulfadoxine, sulfachloropyridazine, chloramphenicol, ofloxacin, pefloxacin, and lincomycin were found in vegetables. In the same geographical area, relatively high concentrations of norfloxacin, ciprofloxacin, and enrofloxacin were found in vegetables, such as tomato, cucumber, pepper, spinach, eggplant, and crown daisy [62]. Other studies have shown that parts of vegetables, such as the roots of carrot and leaves of lettuce, as well as cabbage and spinach, the stem of celery, and fruits of cucumber, bell pepper, and tomato had 64% pharmaceutical residues, including antibiotics, due to the wastewater used for irrigation [63]. Bassil et al. (2013) evaluated the uptake of gentamicin and streptomycin in carrot (Daucus carota), lettuce (Lactuca sativa), and radish (Raphanus sativus) due to the same type of fertilization. The conclusion of the study was that three crops absorbed relatively higher amounts of gentamicin (small molecule) than streptomycin (large molecule), and that the levels of antibiotics in plant tissues increased when increasing the antibiotic concentration in manure [64]. The intake of antibiotics into vegetables seedlings were also studied by Ahmed et al. (2015), who showed that cucumber (Cucumis sativus), cherry tomato (Solanum lycopersicum), and lettuce had relatively high levels of tetracyclines and sulfonamides in the non-edible parts, but lower concentrations in fruit parts and were within acceptable daily intake levels [61].

### 3.2. Products of Animal Origin

The use of antibiotics that may lead to the accumulation of residues in meat, milk, eggs, and honey should not be allowed in foods intended for human consumption. If the use of antibiotics is necessary in the treatment or prevention of various animal diseases, a withholding period must be respected until antibiotic residues are no longer detected [65]. The presence of antibiotic residues in meat from various species of economic interest is considered a significant danger to public health.

The results of the study conducted by Al-Mashhadany in 2020 on sheep meat harvested from supermarkets in Iraq showed that samples contained antibiotic residues at a level higher than the maximum allowed limits. Cooling and freezing, as preservation methods, slightly reduce antibiotic residues in meat. The same study showed that thermal processing of lamb meat (cooking for about 45 min) leads to a transformation of antibiotic residues into inactive residues against bacteria [66].

Another study conducted by Babapour et al. in 2012 on meat samples collected from Iran obtained similar results in terms of the incidence rate of antibiotic residues in meat [67]. A higher incidence of antibiotic residue has been reported in Nigeria in beef samples [68]. In contrast, the lowest incidence rates were reported in sheep samples analyzed in Spain [48]. The presence of fluoroquinolone residues (enrofloxacin and ciprofloxacin) in some Indonesian chicken samples indicated that it were used by farmers in poultry feed [69,70].

Milk with antibiotic residues significantly influences the technological process of obtaining dairy products, which includes the technology used for dairy yeasts. Antibiotics can get into milk from treatments applied to sick animals or (less often and not recommended) through the use of preservatives. Milk with antibiotic residues is considered a rigged food on the market. By consuming unpasteurized milk, antibiotic-resistant bacteria can be transmitted to consumers, especially in areas with a dense population and a lower degree of development, where there is a risk of improper storage of milk and dairy products [71,72]. Milk and dairy products are exposed to contamination by antibiotics and
other drug residues, but also to neutralizing and preserving substances [73–75]. Analysis of antibiotic residues in dairy products (pasteurized drinking milk, yogurt, sour cream, whipped milk, cheese) leads to the identification of the gentamicin/neomycin group, especially in sour cream. Macrolides sometimes appear in cheese, and tetracyclines in sour cream and cheese. Here, we discuss about milk samples subject to confirmatory investigations, used for human consumption. Moghadam et al. (2016) identified that 38.5% of raw milk samples collected from the Iranian province of Khorasan Razavi had penicillin residues, while Ghanavi et al. (2013) reported identification of residues of 11% antibiotics of cow milk samples collected from different regions of Iran [76,77]. Studies conducted by Vinu, (2021) showed that there is a direct correlation between the stage of lactation and the presence of antibiotic residues in milk; 34.3% of positive samples came in the lactation stage of 0–70 days, 20% between 70–140 days of lactation, and 45.7% between 140–305 days of lactation [78]. Additionally, Knappstein et al. (2004) highlighted a direct correlation between milk production and the presence of antibiotic residues (cefquinomas), their level not being influenced by the frequency with which milking was performed [79].

In most countries, eggs are the main product generated from backyard poultry production systems due to the fact that they can be quickly consumed or sold to meet essential family needs. In a study by Cornejo et al. (2020), in Chile, the presence of antimicrobial residues in eggs, such as tetracyclines, beta-lactams, aminoglycosides, and macrolides, was analyzed. The survey showed that all samples were positive for at least one of the four antimicrobials tested [80]. Another recent study from China concluded that careful monitoring should be imposed on antibiotic residues in poultry eggs, after detecting 30% positive egg samples for quinolones, tetracyclines, and sulphonamides [81].

The most common contaminations of honey can be explained by treatments in order to control honeybee diseases and contaminants coming from procedures applied in agriculture [82]. The European Union has forbidden the use of antibiotics for bees, this aspect is strictly enforced by recent legislation [83,84]. The most common and important antibiotics found in honey are beta-lactams (penicillin, ampicillin, cloxacillin, amoxicillin for bacterial infections), amphenicols (thiamphenicol, florfenicol, chloramphenicol which are carcinogenic antimicrobials), tetracyclines (oxytetracycline, chlortetracycline, tetracycline for bacterial diseases), macrolides (erythromycin, tylosin, oleandomycin and spiramycin), and aminoglycoside, fluoroquinolones (ciprofloxacin, enrofloxacin, norfloxacin—growth enhancing) [85–87].

3.3. Methods of Analysis

Analytical techniques for determining antibiotics have gradually evolved with the advent of increasingly advanced technology. If, 50 years ago, the usual technique was based on inhibiting the development of known bacterial cultures, the so-called microtest (the principle used in the antibiogram), today we are see the determination of antibiotics using high performance liquid chromatography coupled with mass spectrometry (LC-MS/MS).

Analysis methods can be classified into screening analysis methods and confirmatory analysis methods.

(a) Screening analysis methods list

Screening methods use equipment that is more readily available in terms of price and mode of operation to identify a group of antibiotics or an antibiotic, with or without quantification of that antibiotic. The general rule is that any result obtained by a screening method must be confirmed using a confirmation method. The screening methods used are the most varied, and are based on different principles, such as microbial inhibition, enzyme immunoassay, stick format (lateral flow devices), radioimmunoassay (RIA), chemiluminescence immunoassay (CLIA), fluorescence immunoassay (FIA), and colloidal gold immunoassay (CGIA). Screening methods for antibiotics have proven to be useful and fast tools that provide results with a high accuracy and sensitivity, which can guarantee safe food [17].

1. Microbial Inhibition Test (Microtest)
This test is based on the incubation of environmental plates with a suspension of a known concentration of bacterial strains, which is added to the test sample. If the test sample has an antibiotic, it will not allow the development of specific colonies, thus opening a halo area around the sample to be analyzed [88]. This test is an expensive test that involves specific endowments that are specific to a food microbiology laboratory, as well as specialized personnel; another major disadvantage is the obtaining of results after an average of 18 h of incubation, and not in 1–2 h as in other screening methods.

2. Delvotest

This is a classic test for determining antibiotics in milk and is based on the whole principle of microbial inhibition. In the absence of an antibiotic, the bacterial suspension develops and the opacity of the environment, or the change in color due to the appearance of acid in the bacteria-growing activity, is noted. In the presence of an antibiotic, the bacterial strain does not develop and there is an area of inhibition or a lack of environmental color change [89]. This type of test is very sensitive to β-lactam antibiotics, but can also be used for sulfonamides and other antimicrobials. This type of test requires incubation for several hours before results can be visualized, so this test was modified by borrowing principles from the enzyme immunoassay, thus forming antibody–antibiotic complexes that develop a color reaction in the presence an enzyme. A low intensity usually means positive, while a high intensity is considered negative. These tests are more expensive than conventional tests with microbial inhibitors, but provide a result in minutes. The major disadvantage is that they only detect substances that react immunologically with the receptor.

3. Enzyme-linked immunosorbent assay (ELISA)

This method is based on the classical antigen–antibody reaction in the presence of a conjugate. The technique of obtaining the antibody is relatively simple and is based on the body’s ability to generate antibodies to a particular antigen, usually using different adjuvants that increase the body’s ability to produce antibodies [90]. This assay represents the most common screening test for detecting of antibiotic residues, especially in food samples [91], and the sensitivity of this method is sometimes superior to confirmatory methods [92]. Depending on the antibiotic detected, different immunoenzymatic techniques have emerged. Thus, for the determination of fluoroquinolones, competitive ELISA methods have been developed using the reaction between the antigen–conjugate (fluoroquinolone)–antibody (bovine serum albumin) and the specific polyclonal antibody [93]. Additionally, for the determination of chloramphenicol and tetracycline, the specific monoclonal antibody is used in most cases [94,95]. ELISA can also assess multiple residues of antibiotics in different foods, so a new colorimetric and dual-colorimetric ELISA test has been developed for simultaneously determination of 13 fluoroquinolone residues and 22 sulfonamides [96,97]. The sensitivity of the ELISA method has been improved by the addition of a biotin-streptavidin compound that allows better catalysis of the substrate [98–100]. Immunoenzymatic analysis techniques have been developed for the determination of antibiotics in both animal products (milk, eggs, meat) and aquaculture products and feed [101,102]. In conclusion, it can be said that the enzyme-linked immunosorbent assay is a fast, sensitive, and easy to implement test [100], but that it also has some disadvantages, including a fairly high percentage of false positive results due to cross-reactions and low reproducibility [95].

4. Radioimmunotest (RIA)

This technique uses isotope-labeled, as well as unlabeled, antigens to react competitively with antibodies. This technique is used to detect antibiotics in various products of animal origin, as well as in various products in the aquatic environment [103].

5. Chemiluminescence Immunoassay (CLIA)

This test is widely used due to the fact that it is an easy, fast, sensitive, and selective test [104]. CLIA is based on the combination of two systems, namely the immune response and actual chemiluminescence analysis. Due to its high specificity and sensitivity, CLIA is
used in many fields, but it has limitations due to the compounds used such as acridinium derivatives and the immediate emission of light is a disadvantage due to its measurement problems [105].

6. Colloidal gold immunochromatographic assay (CGIA)

This new test uses colloidal gold as a tracer in an alkaline environment, which interacts with negatively and positively charged groups and antibody protein molecules [106]. This technique has been developed for the rapid determination of chloramphenicol [107]. Another CGIA technique was developed for the simultaneous determination of quinolones, tetracycline, and sulfonamide in milk, thus allowing the concomitant determination of 36 different antibiotics in less than 10 min [108]. A high-sensitivity CGIA test was developed for the determination of streptomycin in pig milk and urine, with a very low limit of detection of 2.0 ng/mL for milk and 1.9 ng/mL in urine [99].

7. Fluorescence Polarization Assay (FPIA)

The principle of the test is competitive and is based on the binding of fluoroflora to a specific antigen and highlights the fluorescent compound as a standard compound needed to detect and identify an unknown antigen. If the antibiotic sought is not in the sample, a tracer will be bound to the antibody and the signal will be high [109]. Various FIA techniques have been developed for the simultaneous determination of several fluoroquinolones in food; these techniques are based on the use of monoclonal antibodies. Other FPIA techniques have been developed for the simultaneous determination of cephalexin and cefadroxil in milk samples, gentamicin in goat’s milk, as well as other antibiotic [99,110]. FIA is an easy-to-implement screening method that allows the simultaneous detection of various antibiotics in a short period of time. As a disadvantage, this test requires a sample preparation step to extract the antibiotic from the sample, as well as a filtering step to obtain a colorless sample that does not affect the reading of the sample relative to the fluorescence points [111].

8. Lateral flow immunoassay (LFIA)

Until a few years ago, this type of test had applications only in areas such as the diagnosis of various diseases, pregnancy, and identification of various toxins in the environment. However, recently, there have been applications for the use of LFIA for the simultaneous detection of beta-lactams, quinolones, sulfonamides, and tetracyclines in food [112]. The advantages of using this test include its ease of use, increased shelf life—up to 2 years, and use at room temperature. Like any very simple test, it has many disadvantages: many false positive or false negative results, low reproducibility, etc. [113].

(b) Confirmatory analysis methods

Analysis techniques have evolved gradually and the need for more and more advanced methods has been a natural consequence. While screening methods, with the exception of microtest, do not involve major costs or specialized personnel, confirmation methods involve the use of expensive equipment (LCMSMS, GCMSMS) and highly qualified personnel. Depending on the antibiotics of interest, the equipment and extraction steps are different. A mass spectrometer (MS) is an equipment with an operating principle that is the production of ions, their sorting according to the specific mass-to-load ratio (m/z), and the analysis of the obtained signals. Each compound is characterized by a specific m/z ratio, with data present in the literature, as well as in the software of the latest generation of equipment, which comes equipped with data libraries that allow the identification of compounds against reference values [114]. The use of MS is very common in the analysis of antibiotic residues because it has a much higher specificity than screening methods and allows the simultaneous determination of many classes of antibiotics. GCMS/MS has previously been used, but due to the fact that the processing of samples for gas chromatography is more cumbersome and often requires derivatization steps for signal amplification, the development of methods of analysis for the simultaneous determination of antibiotics of several classes is more difficult [115].
1. Liquid chromatography coupled with mass spectrometry (LC/MS/MS)

Liquid chromatography coupled with mass spectrometry is a commonly used technique for determining antibiotic residues in food. This technique is used by both official laboratories for routine analyses as well as by national reference laboratories and European reference laboratories. With liquid chromatography coupled with mass spectrometry, determining seven classes of antibiotics was possible, totaling 30 antibiotics in less than 8 min. The preparation of a sample involves the weighing of 1 g of sample of a meat obtained and is evaporated and then taken up again with 1 mL of ultrapure and used for introduction into the LC/MS/MS. LC/MS/MS equipment which is optimized for the identification and quantification of each compound of interest [114]. Another method of determining antibiotics allows the determination of 46 antibiotics from different classes. This method was developed for the determination of cows from cow’s milk, beef, sheep, pigs, equines, and birds, as well as fish and shrimp [116]. As a general principle, a sample is extracted with a mixture of solvents, purified by passing through an SPE column, and then injected into the LC/MS/MS. For antibiotic residues, the method of analysis must meet the performance criteria of European Commission Decision No. 2002/657 [117]. In general, regardless of the laboratory in which antibiotic residues are determined by LC/MS/MS, the extraction protocol is generally the same; namely, extraction of the sample with an organic solvent, purification by passing through an SPE column, injection into LC/MS/MS, and the criteria for performance must comply with European Commission.

2. Gas chromatography coupled with mass spectrometry (GC/MS/MS)

Using gas chromatography coupled with mass spectrometry, there are fewer applications because the derivatization stage is cumbersome and affects the long-term life of the equipment, so applications are restricted to 1–2 classes of antibiotics that can be determined simultaneously. The sample preparation protocol is generally the same as for LCMS/MS; namely, sample extraction with organic solvent, purification by passing through an SPE column, specific sample derivatization, injection into GC/MS/MS, and performance criteria must meet European Commission Decision No. 2002/657.

Official laboratories in Romania use methods that use LC/MS/MS equipment and analyzed compounds are those provided by the Surveillance and Control Program in the field of food safety; the developed methods are based on standardized methods or are provided by European reference laboratories. Thus, in Romania a method for determining 14 classes of antibiotics totaling 83 antibiotics is used, and tissue samples for milk, eggs, and honey are analyzed. Methods for LCMS/MS determination of chloramphenicol, nitrofurans, nitroimidazole in food stuffs of animal origin are also developed.

The methods of analysis used to identify antibiotic residues have advantages and disadvantages, as shown in Table 3.

| Analytical Method | Advantages | Disadvantages |
|-------------------|------------|---------------|
| Screening analysis methods | easy to operate | mainly qualitative methods |
| | low price | any result obtained by a screening method must be confirmed by a confirmation method |
| (a) Microbial inhibition test (microtest) | specificity–if the test sample has an antibiotic, it will not allow the development of specific colonies, thus opening a halo area around the sample to be analyzed | expensive test that involves specific endowments specific to a food microbiology laboratory as well as specialized personnel |
| | | obtaining of results only after an average of 18 h of incubation |
Table 3. Cont.

| Analytical Method | Advantages | Disadvantages |
|-------------------|------------|--------------|
| (b) Delvotest     | classic test for determining antibiotics in milk | more expensive than conventional tests |
|                   | very sensitive to β-lactam antibiotics | detects only substances that react immunologically with the receptor |
| (c) Enzyme-linked immunosorbent assay (ELISA) | sensitivity of this method is sometimes superior to confirmatory methods | fairly high percentage of false positive results due to cross-reactions |
|                   | used for the multi-residue determination of antibiotics in different foods | low reproducibility |
|                   | fast, sensitive and easy to implement test | |
| (d) Radioimmunotest (RIA) | high selectivity | high concentrations of other molecules with antibody affinity could inactivate it |
|                   | high sensitivity | |
| (e) Chemiluminescence immunooassay (CLIA) | easy, fast, sensitive and selective test | measurement problems due to the compounds used, such as acridinium derivatives and the immediate emission of light |
| (f) Colloidal gold immunochromatographic assay (CGIA) | rapid determination of chloramphenicol simultaneous determination of quinolones, tetracycline and sulfonamide in milk; 36 different antibiotics in less than 10 min | high price |
|                   | requires a sample preparation step to extract the antibiotic from the sample | |
|                   | a filtering step to obtain a colorless sample that does not affect the reading of the sample relative to the fluorescence points | |
| (g) Fluorescence polarization assay (FPIA) | easy-to-implement screening method that allows the simultaneous detection of various antibiotics in a short period of time | |
|                   | increased shelf life—up to 2 years at room temperature | many false positive or false negative results, |
| (h) Lateral flow immunoassay (LFIA) | ease of use | |
|                   | increased shelf life—up to 2 years at room temperature | |
|                     | low reproducibility | |
| Confirmatory analysis methods | higher specificity than screening methods | use of expensive equipment |
|                   | allows the simultaneous determination of many classes of antibiotics | super qualified personnel |
| (a) Liquid chromatography coupled with mass spectrometry (LC/MS/MS) | Determination of 7 classes of antibiotics, 30 antibiotics in less than 8 min | high price |
|                   | method of analysis must meet the performance criteria of European Commission Decision No. 2002/657 | |
| (b) Gas chromatography coupled with mass spectrometry (GC/MS/MS) | standardized methods or provided by European reference laboratories | applications are much lower because the derivatization stage is cumbersome and affects the long-term life of the equipment, so the applications are restricted to 1–2 classes of antibiotics that can be determined simultaneously |

4. Impact of Food Consumption with Antibiotic Residues on Consumers’ Health

The concept of “One Health”, promoted by the World Health Organization and the World Organization for Animal Health, emphasize the idea of an intimate relationship between humans, animals, and the environment, all leading to a unique concept of health.
Thus, the entire chain must be considered in order to maintain equilibrium, carefully using medicinal products at all three levels [20]. Today, there is major public awareness about the consequences of prolonged and increased use of antibiotics in animal livestock production [118]. Microorganisms have the ability to develop antibiotic-resistant genes, resulting in increased survival, thus minimizing treatment options for microbial infections and leading to increased mortality among humans [119–122]. Foods from animal origins are considered key reservoirs of antibiotic residues, which occur as a result of the use of antibiotics industrially, thus contributing to the induction of globally antibiotic resistance. Antibiotic-resistant bacteria have been identified in animal-origin food products, in feeds, as well as in humans. Globally, very large differences have been reported between geographical areas in terms of prevalence of animal-origin antibiotic-resistant bacteria and antibiotic-resistance genes [123]. According to recent studies, antibiotics remain in animal-origin food products, such as milk, meat, and eggs, even after heat treatment, and lead to the development of gastrointestinal disorders and allergies in humans, or even the appearance of antibiotics-resistant superbugs. Furthermore, along with antibiotic resistance, the ineffectiveness of antibiotic therapy for human treatments is increasing [22]. There are a number of studies that mention that the continuous and abusive use of antibiotics frequently causes the development of antibiotic-resistant bacteria. Moreover, multidrug-resistant bacterial infections can progressively increase mortality, thus posing a threat to public health [124]. The major problem frequently mentioned by researchers is that, over time, bacteria may adapt and acquire resistance to active phenolic components similar to antibiotics; therefore, their use must also be taken into account [8]. Kumar et al. (2020) reviewed this topic in order to better understand the mechanisms of development and dissemination of antibiotic resistance genes in nutritional, clinical, agricultural and environmental contexts [125–127]. In the same study, other dietary strategies were considered to replace medicated feed with probiotics, essential oils, or antibodies, with a preventive role against bacterial infections. A solution to antibiotic resistance needs efforts from several fields of activity, including agriculture, but also veterinary medicine (microbiology, biochemistry, medical clinic, and genetics), by replacing medicated feed with alternative therapies [124,128,129]. Animal husbandry is a key component of the global economy, and is a major contributor to food provision. In order for animals to gain weight, they receive medicated feed containing antibiotics or antibiotics are introduced into drinking water. Antibiotics are introduced into farm animal feed, even for preventive purposes. Allen mentioned (2014) that this activity leads to massive accumulation of antibiotics in the environment, and subsequently leads to the acquisition of antibiotic resistance by microorganisms [130]. Several studies have indicated that the spread of antibiotic-resistant microorganisms in humans is mainly due to the consumption of animal-origin foods and beverages contaminated with antibiotic residues, or through the consumption of water contaminated by environmental pollution [25,124,131].

Therefore, in order to reduce antibiotic-resistant bacterial infections worldwide, measures regarding the use of antibiotics for non-therapeutic purposes, such as the use of antibiotics in animals feed, have been taken, when the products are intended for human consumption. Banning the use of avoparcin in animal feed in the European Union has reduced the incidence of antibiotic resistance in animals, and thus its occurrence in humans [124,132]. Antibiotic resistance is a global problem that affects public health, with socio-economic repercussions and it significantly influences the use of antibiotics in animal feed of economic interest. The development of the WHO Global Action Plan and the FAO Global Action Plan, in line with the One Health concept, is a requirement to prevent the transmission of antibiotic resistance, from farm to fork [125].

Every year, 33,000 people die as a direct consequence of infections caused by antibiotic-resistant bacteria, a number comparable to the passengers of more than 100 medium-sized aircraft [133].

Many classes of antibiotics have been recognized, and their use should be limited. In December 2019, the EMA classified antimicrobials into four categories, A to D (Figure 1).
The irrational use of antibiotics in animal husbandry and subsequent pollution of the environment (wastewater, animal- and non-animal-origin food products, soil in places where manure was applied), inevitably leads to the formation of antibiotic resistance. Erofeeva et al. (2021) mentioned that the problem is that scientists have not discovered any new group of antibiotics since 2004 [25] (Figure 2).

Table 4. Maximum residues limits of antibiotic in products of animal origin marketed in the European Community [135].

| Active Substance | Animal Species         | Target Tissue | MRL       |
|------------------|------------------------|---------------|-----------|
| Amoxicillin      | All food-producing      | Muscle        | 50 µg/kg  |
|                  |                        | Fat           | 50 µg/kg  |
|                  |                        | Liver         | 50 µg/kg  |
|                  |                        | Kidney        | 50 µg/kg  |
|                  |                        | Milk          | 4 µg/kg   |
| Ampicillin       | All food-producing      | Muscle        | 50 µg/kg  |
|                  |                        | Fat           | 50 µg/kg  |
|                  |                        | Liver         | 50 µg/kg  |
|                  |                        | Kidney        | 50 µg/kg  |
|                  |                        | Milk          | 4 µg/kg   |
| Avilamycin       | Porcine, poultry, rabbit | Muscle        | 50 µg/kg  |
|                  |                        | Fat           | 100 µg/kg |
|                  |                        | Liver         | 300 µg/kg |
|                  |                        | Kidney        | 200 µg/kg |
| Bacitracin       | Bovine                  | Milk          | 100µg/kg  |
| Benzylpenicillin | All food-producing      | Muscle        | 50 µg/kg  |
|                  |                        | Fat           | 50 µg/kg  |
|                  |                        | Liver         | 50 µg/kg  |
|                  |                        | Kidney        | 50 µg/kg  |
|                  |                        | Milk          | 4 µg/kg   |
| Cefacetrile      | Bovine                  | Milk          | 125 µg/kg |
| Cefapirin        | Bovine                 | Muscle        | 50 µg/kg  |
|                  |                        | Fat           | 50 µg/kg  |
|                  |                        | Kidney        | 100 µg/kg |
|                  |                        | Milk          | 60 µg/kg  |
| Cefazolin        | Bovine, ovine, caprine  | Milk          | 50 µg/kg  |
| Chlortetracycline| All food-producing      | Muscle        | 100 µg/kg |
|                  |                        | Liver         | 300 µg/kg |
|                  |                        | Kidney        | 600 µg/kg |
|                  |                        | Milk          | 100 µg/kg |
|                  |                        | Eggs          | 200 µg/kg |
| Clavulanic acid  | Bovine, porcine         | Muscle        | 100 µg/kg |
|                  |                        | Fat           | 100 µg/kg |
|                  |                        | Liver         | 200 µg/kg |
|                  |                        | Kidney        | 200 µg/kg |

Figure 1. Comparison listing of CIAs by WHO (2019), OIE (2018), and AMEG—EMA (2019) for the major classes of antibiotics adapted from [134].

Figure 2. Discovery of antibiotics adapted from [25].
In the European Union, the provisions of European Regulation 37/2010 concerning maximum permitted limits by product categories and by food producing species are applicable (Table 4).

**Table 4. Maximum residues limits of antibiotic in products of animal origin marketed in the European Community [135].**

| Active Substance | Animal Species                  | Target Tissue | MRL       |
|------------------|---------------------------------|---------------|-----------|
| Amoxicillin      | All food-producing species      | Muscle        | 50 µg/kg  |
|                  |                                 | Fat           | 50 µg/kg  |
|                  |                                 | Liver         | 50 µg/kg  |
|                  |                                 | Kidney        | 50 µg/kg  |
|                  |                                 | Milk          | 4 µg/kg   |
| Ampicillin       | All food-producing species      | Muscle        | 50 µg/kg  |
|                  |                                 | Fat           | 50 µg/kg  |
|                  |                                 | Liver         | 50 µg/kg  |
|                  |                                 | Kidney        | 50 µg/kg  |
|                  |                                 | Milk          | 4 µg/kg   |
| Avilamycin       | Porcine, poultry, rabbit        | Muscle        | 50 µg/kg  |
|                  |                                 | Fat           | 100 µg/kg |
|                  |                                 | Liver         | 300 µg/kg |
|                  |                                 | Kidney        | 200 µg/kg |
| Bacitracin       | Bovine                          | Milk          | 100 µg/kg |
| Benzylpenicillin | All food-producing species      | Muscle        | 50 µg/kg  |
|                  |                                 | Fat           | 50 µg/kg  |
|                  |                                 | Liver         | 50 µg/kg  |
|                  |                                 | Kidney        | 50 µg/kg  |
|                  |                                 | Milk          | 4 µg/kg   |
| Cefacetride      | Bovine                          | Milk          | 125 µg/kg |
| Cefapirin        | Bovine                          | Muscle        | 50 µg/kg  |
|                  |                                 | Fat           | 50 µg/kg  |
|                  |                                 | Kidney        | 100 µg/kg |
|                  |                                 | Milk          | 60 µg/kg  |
| Cefazolin        | Bovine, ovine, caprine          | Milk          | 50 µg/kg  |
| Chlortetracycline| All food-producing species      | Muscle        | 100 µg/kg |
|                  |                                 | Liver         | 300 µg/kg |
|                  |                                 | Kidney        | 600 µg/kg |
|                  |                                 | Milk          | 100 µg/kg |
|                  |                                 | Eggs          | 200 µg/kg |
| Clavulanic acid  | Bovine, porcine                 | Muscle        | 100 µg/kg |
|                  |                                 | Fat           | 100 µg/kg |
|                  |                                 | Liver         | 200 µg/kg |
|                  |                                 | Kidney        | 400 µg/kg |
| Cloxacillin      | All food-producing species      | Muscle        | 300 µg/kg |
|                  |                                 | Fat           | 300 µg/kg |
|                  |                                 | Liver         | 300 µg/kg |
|                  |                                 | Kidney        | 300 µg/kg |
|                  |                                 | Milk          | 30 µg/kg  |
| Colistin         | All food-producing species      | Muscle        | 150 µg/kg |
|                  |                                 | Fat           | 150 µg/kg |
|                  |                                 | Liver         | 150 µg/kg |
|                  |                                 | Kidney        | 200 µg/kg |
|                  |                                 | Milk          | 50 µg/kg  |
|                  |                                 | Eggs          | 300 µg/kg |
| Active Substance | Animal Species                        | Target Tissue | MRL         |
|------------------|---------------------------------------|---------------|-------------|
| Cloxacillin      | All food-producing species             | Muscle        | 300 µg/kg   |
|                  |                                       | Fat           | 300 µg/kg   |
|                  |                                       | Liver         | 300 µg/kg   |
|                  |                                       | Kidney        | 300 µg/kg   |
|                  |                                       | Milk          | 30 µg/kg    |
| Dicloxacillin    | All food-producing species             | Muscle        | 300 µg/kg   |
|                  |                                       | Fat           | 300 µg/kg   |
|                  |                                       | Liver         | 300 µg/kg   |
|                  |                                       | Kidney        | 300 µg/kg   |
|                  |                                       | Milk          | 30 µg/kg    |
| Doxycycline      | Bovine                                | Muscle        | 300 µg/kg   |
|                  | Porcine, poultry                       | Liver         | 100 µg/kg   |
|                  |                                       | Kidney        | 300 µg/kg   |
|                  | Not for use in animals from which milk is produced for human consumption | | 600 µg/kg |
|                  |                                       | 100 µg/kg     | 100 µg/kg   |
|                  |                                       | 300 µg/kg     | 300 µg/kg   |
|                  |                                       | 100 µg/kg     | 100 µg/kg   |
|                  |                                       | 300 µg/kg     | 300 µg/kg   |
|                  |                                       | 600 µg/kg     | 600 µg/kg   |
| Enrofloxacin     | Bovine, ovine                          | Muscle        | 100 µg/kg   |
|                  | Porcine, rabbit                        | Fat           | 100 µg/kg   |
|                  |                                        | Liver         | 300 µg/kg   |
|                  |                                        | Kidney        | 200 µg/kg   |
|                  |                                        | Milk          | 100 µg/kg   |
| Enrofloxacin     | Poultry                               | Muscle        | 100 µg/kg   |
|                  |                                        | Fat           | 100 µg/kg   |
|                  |                                        | Liver         | 200 µg/kg   |
|                  |                                        | Kidney        | 300 µg/kg   |
|                  |                                        | 100 µg/kg     | 100 µg/kg   |
|                  |                                        | 100 µg/kg     | 100 µg/kg   |
|                  |                                        | 200 µg/kg     | 200 µg/kg   |
|                  |                                        | 300 µg/kg     | 300 µg/kg   |
| Erythromycin A   | All other food-producing species       | Muscle        | 200 µg/kg   |
|                  |                                        | Fat           | 200 µg/kg   |
|                  |                                        | Liver         | 200 µg/kg   |
|                  |                                        | Kidney        | 200 µg/kg   |
|                  |                                        | Milk          | 150 µg/kg   |
|                  |                                        | 200 µg/kg     | 200 µg/kg   |
|                  |                                        | 200 µg/kg     | 200 µg/kg   |
|                  |                                        | 200 µg/kg     | 200 µg/kg   |
|                  |                                        | 200 µg/kg     | 200 µg/kg   |
|                  |                                        | 150 µg/kg     | 150 µg/kg   |
| Gentamicin       | Bovine, porcine                        | Muscle        | 50 µg/kg    |
|                  |                                        | Fat           | 50 µg/kg    |
|                  |                                        | Liver         | 200 µg/kg   |
|                  |                                        | Kidney        | 750 µg/kg   |
|                  |                                        | Milk          | 100 µg/kg   |
| Kanamycin A      | All food-producing species except fin fish | Muscle        | 100 µg/kg   |
|                  |                                        | Fat           | 100 µg/kg   |
|                  |                                        | Liver         | 600 µg/kg   |
|                  |                                        | Kidney        | 2500 µg/kg  |
|                  |                                        | Milk          | 150 µg/kg   |

Table 4. Cont.
Improper use of antibiotics in food-producing animals contributes to the appearance of antibiotic resistance. WHO recommends that farmers and the food industry stop using antibiotics routinely to promote growth and prevent disease in healthy animals. Recommendations aim to help preserve the effectiveness of antibiotics that are important for human medicine by reducing their unnecessary use in animals. WHO declares that, in different countries, approximately 80% of total antibiotic consumption appears in the animal sector, largely to promote the growth of healthy animals. Overuse and misuse of antibiotics in animals and humans is contributing to the rising threat of antibiotic resistance. Some types of bacteria that cause serious infections in humans have already developed resistance. WHO strongly recommends a reduction in use of all classes of antibiotics for food-producing animals, including a complete restriction of these antibiotics for growth promotion and disease prevention without a diagnosis. “Scientific evidence demonstrates that

| Active Substance | Animal Species | Target Tissue | MRL      |
|------------------|----------------|--------------|----------|
| Lincomycin       | All food-producing species | Muscle     | 100 µg/kg |
|                  |                 | Fat         | 50 µg/kg  |
|                  |                 | Liver       | 500 µg/kg |
|                  |                 | Kidney      | 1500 µg/kg|
|                  |                 | Milk        | 150 µg/kg |
|                  |                 | Eggs        | 50 µg/kg  |
| Marbofloxacin    | Bovine, porcine | Muscle      | 150 µg/kg |
|                  |                 | Fat         | 150 µg/kg |
|                  |                 | Liver       | 50 µg/kg  |
|                  |                 | Kidney      | 150 µg/kg |
| Neomycin B       | All food-producing species | Muscle     | 500 µg/kg |
|                  |                 | Fat         | 500 µg/kg |
|                  |                 | Liver       | 500 µg/kg |
|                  |                 | Kidney      | 1500 µg/kg|
|                  |                 | Milk        | 500 µg/kg |
| Oxacillin        | All food-producing species | Muscle     | 300 µg/kg |
|                  |                 | Fat         | 300 µg/kg |
|                  |                 | Liver       | 300 µg/kg |
|                  |                 | Kidney      | 30 µg/kg  |
| Oxytetracycline  | All food-producing species | Muscle     | 100 µg/kg |
|                  |                 | Liver       | 300 µg/kg |
|                  |                 | Kidney      | 600 µg/kg |
|                  |                 | Milk        | 100 µg/kg |
|                  |                 | Eggs        | 200 µg/kg |
| Streptomycin     | All ruminants, porcine, rabbit | Muscle     | 500 µg/kg |
|                  |                 | Fat         | 500 µg/kg |
|                  |                 | Liver       | 500 µg/kg |
|                  |                 | Kidney      | 1000 µg/kg|
| Sulfonamides     | All food-producing species | Muscle     | 100 µg/kg |
|                  |                 | Fat         | 100 µg/kg |
|                  |                 | Liver       | 100 µg/kg |
|                  |                 | Kidney      | 100 µg/kg |
| Tylosin A        | All food-producing species | Muscle     | 100 µg/kg |
|                  |                 | Fat         | 100 µg/kg |
|                  |                 | Liver       | 100 µg/kg |
|                  |                 | Kidney      | 100 µg/kg |
|                  |                 | Milk        | 50 µg/kg  |
|                  |                 | Egg         | 200 µg/kg |
overuse of antibiotics in animals can contribute to the emergence of antibiotic resistance” says Dr. Kazuaki Miyagishima, Director of the Department of Food Safety and Zoonoses at WHO. Many countries have already taken actions to reduce the use of antibiotics in food-producing animals. For example, since 2006, the European Union has banned the use of antibiotics for growth promotion. In addition, consumers promote the marketing of meat raised without the routine use of antibiotics, with some major food chains adopting “antibiotic-free” policies for meat supplies. The general objective is to encourage the prudent use of antibiotics in order to slow down antimicrobial resistance and maintain the effectiveness of antibiotics for medicine [136]. About two-thirds of U.S. antibiotics that are important to people are sold for use in food animal production. Yet, experts have long warned of the public health threat from regularly exposing herds of thousands, even tens of thousands, of animals to human-class antibiotics in their feed for prolonged periods of time. The U.S. Food and Drug Administration (FDA) lists 89 medically important antibiotics currently added to animal feeds. According to the www.nrdc.org website (accessed on 6 May 2022), since 2016, the FDA has flagged the lack of clear antibiotics use limits as a significant problem needing a remedy, thus, at this moment in the USA, there are no clear limits for the use of antibiotics. The same site mentions the deadline for establishing and publishing these data as 2023 [137].

Numerous studies from different parts of the world mention that antibiotic residues in feed stuffs are, at present, a large problem, and can lead to major associated health problems, including antibiotic resistance, toxicity, hypersensitivity reactions, teratogenicity, and carcinogenicity (Figure 3) [1].

![Diagram of effects of antibiotics use on human health](image_url)

**Figure 3.** Effects of antibiotics use on human health.

Most antibiotics cause side effects in humans (Table 5) [134].

A large number of studies refer to the management of antibiotic residues, antibiotic-resistant bacteria (ARB), and antibiotic resistance genes (ARG) can be found in dairy manure and may contribute to the spread of antibiotic resistance (AR). More than 60 ARGs can be found in milk manure (including β-lactam and tetracycline resistance genes), although correlations with antibiotic use, residues, and ARBs have been inconsistent, possibly due to sampling and analytical limitations. Antibiotic resistance genes often persist through these systems, although optimal management and a higher operating temperature may facilitate their attenuation [138–140]. Elements related to the mechanism of action and resistance in humans are presented in Table 6 [141] (after Iwu et al., 2020).
Table 5. Possible effects due to antibiotics in human.

| Group of Antimicrobials | Main Effects                                         | Clinical Signs                                                                 |
|------------------------|------------------------------------------------------|-------------------------------------------------------------------------------|
| Sulphonamides          | Skin reactions                                       | Mild rash to severe toxidermia are some of the skin reactions following human exposure to sulphonamide |
|                        | Hypersensitivity mentioned adverse reactions         | Contact sensitization confirmed for topical medicinal products               |
|                        | Blood dyscrasias                                     | Hemolytic anemia, neutropenia, thrombocytopenia and pancytopenia             |
|                        | Carcinogenicity (thyroid)                            | Sulfamethazine dose-dependent increase in follicular cells adenomas of thyroid gland |
| Penicillins            | Hypersensitivity reactions                            | Association with IgE-mediated allergic anaphylaxis 10% of the human population is believed to be allergic |
|                        | Anaphylaxis                                          | Human reaction based on penicilloylated (amoxicilloylated) residues in milk and meat. Amoxicillin (AX), with or without clavulanic acid, is the most common elicitor of allergy. Very low levels (6 µg/L) can cause this reaction; therefore, especially for milk low MRLs (4 µg/kg) were established for the group of penicillins by EMA and JECFA (Codex). USA—zero tolerance for residues in milk |
|                        | Influence of starter cultures in food processing     | Sufficient evidence that consumption of beef or pork containing residues of penicillins exceeding MRLs causing anaphylactic reactions |
| Tetracyclines          | Possible influence of human intestine microbiome     | MRLs set based on the microbiological ADI. In the period of EMA assessment, it was concluded that there is no induction of resistant enterobacteria at the dose 2 mg per person per day—on the other hand, in an in vitro study to assess the impact of tetracycline on the human intestinal microbiome, there was screened the variability of the presence of tet genes after exposure of low concentrations 0.15, 1.5, 15 and 150 µg/mL of tetracycline, after 24 h and 40 days and variable to slight increase of the tetracycline gene copies occurred. |

Table 6. Mechanism of action and resistance mechanism of antibiotics in human. Adapted from [141].

| Antibiotics Class    | Example (s)                                      | The Mechanism(s) of Action                        | Resistance Mechanism(s)                                                                 |
|----------------------|--------------------------------------------------|--------------------------------------------------|----------------------------------------------------------------------------------------|
| β-lactams            | Cephalosporins, Penicillins, Cefotaxime, Monobactams, Carbapenems | Cell wall biosynthesis inhibition                | Cleavage by β-lactamases, ESBLs, Carbapenemases, Cefotaximases, and altered Penicillin-binding proteins |
| Aminoglycosides      | Gentamicin, streptomycin                         | Protein synthesis inhibition                      | Ribosomal mutations, enzymatic modification, 16S rRNA methylation, and efflux pumps    |
| Phenics              | Chloramphenicol                                   | Inhibition of protein synthesis                   | Mutation of the 50S ribosomal subunit, reduced membrane permeability, and elaboration of chloramphenicol acetyltransferase |
Table 6. Cont.

| Antibiotics Class | Example (s) | The Mechanism(s) of Action | Resistance Mechanism(s) |
|-------------------|-------------|---------------------------|------------------------|
| Macrolides        | Erythromycin, azithromycin | Alteration of protein synthesis | Ribosomal methylation |
| Tetracyclines     | Minocycline, tigecycline | Alteration of translation | Mainly efflux |
| Rifamycins        | Rifampin    | Alteration of transcription | Altered β-subunit of RNA polymerase |
| Glycopeptides     | Vancomycin, teicoplanin | Alteration of cell wall biosynthesis | Altered cell walls, efflux |
| Quinolones        | Ciprofloxacin | Alteration of DNA synthesis | Efflux, modification, target mutations |
| Streptogramins    | Synercid, streptogramin B | Alteration of cell wall biosynthesis | Enzymatic cleavage, modification, efflux |
| Oxazolidinones    | Linezolid   | Alteration of formation of 70S ribosomal complex | Mutations in 23S rRNA genes followed by gene conversion |
| Lipopeptides      | Daptomycin  | Depolarization of cell membrane | Modification of cell wall and cell membrane |

Worldwide, and under the auspices of the World Health Organization (WHO), lectures and interactive broadcasts are organized to emphasize the importance of judicious administration of antibiotics in both human and veterinary use, or in agriculture. People should be aware of the need for antibiotics to be used correctly and to reduce the abuse of antibiotics. In addition, national programs aimed at the screening of antibiotic residues in various types of food are being continuously updated.

5. Conclusions

The issue of the presence of antibiotic residues in food is intensely debated. Numerous research studies have highlighted the irrational use of antibiotics and the risk of problems with consumer antibiotic resistance, spread by foods with antibiotic residues.

The concentration and type of antibiotic found in the form of residues varies depending on the geographical area and the type of food analyzed. Available studies present antibiotic residues in all food groups: meat and meat products, milk and dairy products, eggs, honey, and non-animal-origin products.

Although alarm signals are drawn regarding irrational antibiotic use, exceeding applicable legal requirements are identified. While the European Union has clearly established limits for antibiotic residues, in the United States, legislation does not include such values, with a deadline set for 2023 to draw up these legislative requirements. Additionally, in recent years, awareness of the irrational use of antibiotics programs have been launched, but still it is necessary to develop these in order to increase the understanding of producers and consumers regarding the use of antibiotics. These measures should be implemented worldwide.

Author Contributions: O.M.G., C.D.P., O.D.M. and D.C.P.: Conceptualization, writing—original draft; E.N.P., N.D. and T.D.—writing, review and editing; E.N.P.: funding acquisition. All authors have read and agreed to the published version of the manuscript.

Funding: This paper was funded by USAMV Bucharest Internal Research Projects Competition, 2021, Contract No.2021-003/30.07.2021—Assessment of consumer exposure to antibiotics coming from animal products in Romania.

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.
Foods 2022, 11, 1430

20 of 25

References

1. Darwish, W.S.; Eldaly, E.A.; El-Abbasy, M.T.; Ikenaka, Y.; Nakayama, S.; Ishizuka, M. Antibiotic Residues in Food: The African Scenario. Jpn. J. Vet. Res. 2013, 61 (Suppl. S13), S13–S22. [PubMed]

2. Page, S.W.; Gautier, P. Use of Antimicrobial Agents in Livestock. Rev. Sci. Technol. 2012, 31, 145–188. [CrossRef] [PubMed]

3. Simonite, C.; Burow, E.; Tenhagen, B.-A.; Käsböhrer, A. Oral Administration of Antimicrobials Increase Antimicrobial Resistance in E. Coli from Chicken—A Systematic Review. Prev. Vet. Med. 2015, 118, 1–7. [CrossRef] [PubMed]

4. Chantziras, I.; Boyen, F.; Callens, B.; Dewulf, J. Correlation between Veterinary Antimicrobial Use and Antimicrobial Resistance in Food-Producing Animals: A Report on Seven Countries. J. Antimicrob. Chemother. 2014, 69, 827–834. [CrossRef]

5. 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]

6. Muaz, K.; Riaz, M.; Akhtar, S.; Park, S.; Ismail, A. Antibiotic Residues in Chicken Meat: Global Prevalence, Threats, and Decontamination Strategies: A Review. J. Food Prot. 2018, 81, 619–627. [CrossRef]

7. Hammerum, A.M.; Heuer, O.E.; Emborg, H.-D.; Bagger-Skjøt, L.; Jensen, V.F.; Rogues, A.-M.; Skov, R.L.; Agersø, Y.; Brandt, C.T.; Seyfarth, A.M.; et al. Danish Integrated Antimicrobial Resistance Monitoring and Research Program. Emerg. Infect. Dis. 2007, 13, 1633–1639. [CrossRef]

8. Disseminating Innovative Solutions for Antibiotic Resistance Management. Available online: https://disarmproject.eu/ (accessed on 27 March 2022).

9. Van Boeckel, T.P.; Brower, C.; Gilbert, M.; 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]

10. Albero, B.; Tadeo, J.L.; Miguel, E.; Pérez, R.A. Rapid Determination of Antibiotic Residues in Cereals by Liquid Chromatography Triple Mass Spectrometry. Anal. Bioanal. Chem. 2019, 411, 6129–6139. [CrossRef]

11. EU Approves Limits on Antibiotics Use in Farm Animals. Available online: https://www.meatpoultry.com/articles/20383-eu-approves-limits-on-antibiotics-use-in-farm-animals (accessed on 30 March 2022).

12. Regulation (EU). 2019/6 of the European Parliament and of the Council of 11 December 2018 on Veterinary Medicinal Products and Repealing Directive 2001/82/EC (Text with EEA Relevance); European Commission: Brussels, Belgium, 2018; Volume 4.

13. Hiraku, Y.; Sekine, A.; Nabeshi, H.; Midorikawa, K.; Murata, M.; Kumagai, Y.; Kawanishi, S. Mechanism of Carcinogenesis Induced by a Veterinary Antimicrobial Drug, Nitrofurazone, via Oxidative DNA Damage and Cell Proliferation. Cancer Lett. 2004, 215, 141–150. [CrossRef]

14. Yang, X.; Chen, Z.; Zhao, W.; Liu, C.; Qian, X.; Zhang, M.; Wei, G.; Khan, E.; Hau Ng, Y.; Sik Ok, Y. Recent Advances in Photodegradation of Antibiotic Residues in Water. Chem. Eng. J. 2021, 405, 126806. [CrossRef]

15. Huang, F.; An, Z.; Moran, M.J.; Liu, F. Recognition of Typical Antibiotic Residues in Environmental Media Related to Groundwater in China (2009–2019). J. Hazard. Mater. 2020, 399, 122813. [CrossRef] [PubMed]

16. Ahmed, S.; Ning, J.; Peng, D.; Chen, T.; Ahmad, I.; Ali, A.; Lei, Z.; Hau Ng, Y.; Shabbir, M.; Cheng, G.; Yuan, Z. Current Advances in Immunoasays for the Detection of Antibiotics Residues: A Review. Food Agric. Immunol. 2020, 31, 268–290. [CrossRef]

17. Regulation (EC). No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on Additives for Use in Animal Nutrition (Text with EEA Relevance); European Commission: Brussels, Belgium, 2003; Volume 268.

18. Kirchhelle, C. Pharming Animals: A Global History of Antibiotics in Food Production (1935–2017). Palgrave Commun. 2018, 4, 96. [CrossRef]

19. Hassali, M.A.A.; Yann, H.R.; Verma, A.K.; Hussain, R.; Sivaraman, S. Antibiotic Use in Food Animals: Malaysia Overview; School of Pharmaceutical Sciences, Universiti Sains Malaysia: Penang, Malaysia, 2018.

20. Regulation (EU). 2019/4 of the European Parliament and of the Council of 11 December 2018 on the Manufacture, Placing on the Market and Use of Medicated Feed, Amending Regulation (EC) No 183/2005 of the European Parliament and of the Council of Repealing Council Directive 90/167/EEC (Text with EEA Relevance); European Commission: Brussels, Belgium, 2018; Volume 4.

21. Regulation (EC). No 767/2009 of the European Parliament and of the Council of 13 July 2009 on the Community Protection against the Introduction of Parasites and Their Products Collected in Stores and Markets Worldwide. J. Antimicrob. Chemother. 2015, 71, 118. [CrossRef] [PubMed]

22. Landers, T.F.; Cohen, B.; Wittum, T.E.; Larson, E.L. A Review of Antibiotic Use in Food Animals: Perspective, Policy, and Potential. Public Health Rep. 2012, 127, 4–22. [PubMed]

23. Mayororova, Y.; Glebov, V.; Erofeeva, V.; Yablochkovnikov, S.; Laver, B. Physiological Evaluation of the Cardiology System of Nonresident Students at Different Training Periods. E3S Web Conf. 2020, 169, 04004. [CrossRef]

24. Maslennikova, O.; Erofeeva, V. Biological Contamination of Soils in Urbanized Ecosystems by Toxocara sp. Eggs. E3S Web Conf. 2020, 169, 04002. [CrossRef]

25. Erofeeva, V.; Zakirova, Y.; Yablochkovnikov, S.; Prys, E.; Prys, I. The Use of Antibiotics in Food Technology: The Case Study of Products from Moscow Stores. E3S Web Conf. 2021, 311, 10005. [CrossRef]

26. Regulation (EC). No 726/2004 of the European Parliament and of the Council of 31 March 2004 Laying down Community Procedures for the Authorisation and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Medicines Agency (Text with EEA Relevance); European Commission: Brussels, Belgium, 2004; Volume 136.
27. Sarmah, A.K.; Meyer, M.T.; Boxall, A.B.A. A Global Perspective on the Use of Sales, Exposure Pathways, Occurrence, Fate and Effects of Veterinary Antibiotics (VAs) in the Environment. *Chemosphere* 2006, 65, 725–759. [CrossRef]

28. Callaway, T.R.; Edrington, T.S.; Rychlik, J.L.; Genovese, K.J.; Poole, T.L.; Jung, Y.S.; Bischoff, K.M.; Anderson, R.C.; Nisbet, D.J. Ionophores: Their Use as Ruminant Growth Promotants and Impact on Food Safety. *Curr. Issues Intest. Microbiol.* 2003, 4, 43–51.

29. Asante, A.D.; Boyle, L.A.; Leonard, F.C.; Carroll, C.; Sheelhan, E.; Murphy, D.; Manzanilla, E.G. Prodigy Antibiotics from Pig Feed: How Do They Affect Their Performance and Health? *BMJ Vet. Res.* 2019, 15, 67. [CrossRef]

30. Daros, R.R.; Eriksson, H.K.; Weary, D.M.; von Keyserlingk, M.A.G. The Relationship between Transition Period Diseases and Lameness, Feeding Time, and Body Condition during the Dry Period. *J. Dairy Sci.* 2020, 103, 649–665. [CrossRef]

31. Buchal, M. The Use of Insulin in Poultry Feeding: A Review. *J. Anim. Physiol. Anim. Nutr.* 2016, 100, 1015–1022. [CrossRef]

32. Adewole, D.I.; Kim, I.H.; Nyachoti, C.M. Gut Health of Pigs: Challenge Models and Response Criteria with a Critical Analysis of the Effectiveness of Selected Feed Additives—A Review. *Asia-Pacif. J. Anim. Sci.* 2016, 29, 909–924. [CrossRef]

33. Regulation (EU). 2018/848 of the European Parliament and of the Council of 30 May 2018 on Organic Production and Labelling of Organic Products and Repealing Council Regulation (EC) No 834/2007, European Commission: Brussels, Belgium, 2018; Volume 150.

34. Bacanlı, M.; Başaran, N. Importance of Antibiotic Residues in Animal Food. *Food Chem. Toxicol.* 2019, 125, 462–466. [CrossRef]

35. Donoghue, D.J. Antibiotic Residues in Edible Tissues of Cattle Slaughtered in Akure, Nigeria. *Poult. Sci.* 2003, 82, 618–621. [CrossRef]

36. Long, Y.; Li, B.; Liu, H. Analysis of Fluoroquinolones Antibiotic Residue in Feed Matrices Using Terahertz Spectroscopy. *Appl. Opt.* 2018, 57, 544–554. [CrossRef]

37. 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]

38. Kimera, Z.I.; Mdegela, R.H.; Mhaiki, C.J.N.; Karimuribo, E.D.; Mabiki, F.; Nonga, H.E.; Mwesongo, J. Determination of Oxytetracycline Residues in Cattle Meat Marketed in the Kilosa District, Tanzania. *Onderstepoort J. Vet. Res.* 2015, 82, 911. [CrossRef]

39. Nigerian, I.A.; Olufemi, O.I.; Agboula, E.A. Oxytetracycline Residues in Edible Tissues of Cattle Slaughtered. *Niger Vet. J.* 2011, 31, 2. [CrossRef]

40. Bedada, A.H.; Zewde, B.M. Tetracycline Residue Levels in Slaughtered Beef Cattle from Three Slaughterhouses in Central Ethiopia. *Glob. Vet.* 2012, 8, 546–554.

41. Tavakoli, H.R.; Firoozabadi, M.S.S.; Afsharfarnia, S.; Jafari, N.J.; Sa’adat, S. Detecting antibiotic residues by hplc method in chicken and calves meat in diet of a military center in tehran. *Acta Med. Medit.* 2015, 31, 1427–1433.

42. Er, B.; Onurdag, F.K.; Demirhan, B.; Ozgacar, S.O.; Oktem, A.B.; Abbasoglu, U. Screening of Quinolone Antibiotic Residues in Chicken Meat and Beef Sold in the Markets of Ankara, Turkey. *Poult. Sci.* 2013, 92, 2212–2215. [CrossRef] [PubMed]

43. Salama, N.A.; Abou-Raya, S.H.; Mabiki, F.; Nonga, H.E.; Mwesongo, J. Incidence of Tetracycline Residues in Chicken Meat and Liver Retailed to Consumers. *Food Addit. Contam. Part B Survell.* 2011, 8, 88–93. [CrossRef] [PubMed]

44. Guetiya Wadoun, R.E.; Zambou, N.F.; Anyangwe, F.F.; Njimou, J.R.; Coman, M.M.; Verdenelli, M.C.; Cecchini, C.; Silvi, S.; Orpianesi, C.; Cresci, A.; et al. Abusive Use of Antibiotics in Poultry Farming in Cameroon and the Public Health Implications. *Br. Poult. Sci.* 2016, 57, 483–493. [CrossRef]

45. Muriuki, F.K.; Ogara, W.O.; Njeru, F.M.; Mitema, E.S. Tetracycline Residue Levels in Slaughtered Cattle from Nairobi Slaughter House in Kenya. *J. Vet. Sci.* 2001, 2, 97–101. [CrossRef]

46. Chowdhury, S.; Hassan, M.M.; Alam, M.; Sattar, S.; Bari, M.S.; Saifuddin, A.K.M.; Hoque, M.A. Antibiotic Residues in Milk and Eggs of Commercial and Local Farms at Chittagong, Bangladesh. *Vet. World* 2015, 8, 467–471. [CrossRef]

47. Zheng, N.; Wang, J.; Han, R.; Xu, X.; Zhen, Y.; Qu, X.; Sun, P.; Li, S.; Yu, Z. Occurrence of Several Main Antibiotic Residues in Raw Milk in 10 Provinces of China. *Food Addit. Contam. Part B Survell* 2013, 6, 84–89. [CrossRef]

48. Nchima, G.; Choongo, K.; Flavien, B.; Muzandu, K.; Nalubamba, K.; Monga, G.; Kangwa, H.; Muma, J. Determination of Oxytetracycline and Sulphamethazine Residues in Marketed Beef from Selected Parts of Zambia to Assess Compliance with Maximum Residual Limits. *Am. J. Res. Commun.* 2017, 5, 42–64.

49. Oladayo, I.O.; Ehimowo, A.A. Oxytetracycline Residues in Edible Tissues of Cattle Slaughtered in Akure, Nigeria. *Niger Vet. J.* 2010, 31, 2. [CrossRef]

50. Cheong, C.K.; Hajeib, P.; Jinap, S.; Ismail-Elity, M. Sulfonamides Determination in Chicken Meat Products from Malaysia. *Int. Food Res. J.* 2010, 17, 885–892.

51. Kumari Anjana, R.K.N.; Jayachandran, K.G.M.C. Persistence of Antibiotic Residue in Milk under Region of Bihar, India. *Int. J. Curr. Microbiol. Appl. Sci.* 2017, 6, 2296–2299. [CrossRef]

52. Christou, A.; Agiera, A.; Bayona, J.M.; Cytres, E.; Fotopoulou, V.; Lambropoulou, D.; Manaia, C.M.; Michael, C.; Revitt, M.; Schröder, P.; et al. The Potential Implications of Reclaimed Wastewater Reuse for Irrigation on the Agricultural Environment: The Knowns and Unknowns of the Fate of Antibiotics and Antibiotic Resistant Bacteria and Resistance Genes—A Review. *Water Res.* 2017, 123, 448–467. [CrossRef]

53. Tasho, R.P.; Cho, J.Y. Veterinary Antibiotics in Animal Waste, Its Distribution in Soil and Uptake by Plants: A Review. *Sci. Total Environ.* 2016, 563, 564–569. [CrossRef]

54. Madikizela, L.M.; Ncube, S.; Chimuka, L. Uptake of Pharmaceuticals by Plants Grown under Hydroponic Conditions and Natural Occurring Plant Species: A Review. *Sci. Total Environ.* 2018, 636, 477–486. [CrossRef]
55. Chung, H.S.; Lee, Y.-J.; Rahman, M.M.; Abd El-Aty, A.M.; Lee, H.S.; Kabir, M.H.; Kim, S.W.; Park, B.-J.; Kim, J.-E.; Hacımüftüoğlu, E.; et al. Uptake of the Veterinary Antibiotics Chlorotetracycline, Enrofloxacin, and Sulphathiazole from Soil by Radish. *Sci. Total Environ.* **2017**, *605–606*, 322–331. [CrossRef]

56. Herklots, P.A.; Gürung, P.; Vanden Heuvel, B.; Kinney, C.A. Uptake of Human Pharmaceuticals by Plants Grown under Hydromorphic Conditions. *Chemosphere* **2010**, *78*, 1416–1421. [CrossRef]

57. Kurwadkar, S.; Struckhoff, G.; Pugh, K.; Singh, O. Uptake and Translocation of Sulfmethazine by Alfalfa Grown under Hydromorphic Conditions. *J. Environ. Sci.* **2017**, *53*, 217–223. [CrossRef]

58. Pan, M.; Chu, L.M. Transfer of Antibiotics from Wastewater or Animal Manure to Soil and Edible Crops. *Environ. Pollut.* **2017**, *231*, 829–836. [CrossRef]

59. Pan, M.; Wong, C.K.C.; Chu, L.M. Distribution of Antibiotics in Wastewater-Irrigated Soils and Their Accumulation in Vegetable Crops in the Pearl River Delta, Southern China. *J. Agric. Food Chem.* **2014**, *62*, 11062–11069. [CrossRef]

60. Albero, B.; Tadeo, J.L.; Escario, M.; Miguel, E.; Pérez, R.A. Persistence and Availability of Veterinary Antibiotics in Soil and Soil-Manure Systems. *Sci. Total Environ.* **2018**, *643*, 1562–1570. [CrossRef]

61. Ahmed, M.B.M.; Rajapaksha, A.U.; Lim, J.E.; Vu, N.T.; Kim, I.S.; Kang, H.M.; Lee, S.S.; Ok, Y.S. Distribution and Accumulative Pattern of Tetracyclines and Sulphonamides in Edible Vegetables of Cucumber, Tomato, and Lettuce. *J. Agric. Food Chem.* **2015**, *63*, 398–405. [CrossRef]

62. Li, X.-W.; Xie, Y.-F.; Li, C.-L.; Zhao, H.-N.; Zhao, H.; Wang, N.; Wang, J.-F. Investigation of Residual Fluoroquinolones in a Common Vegetable under Field Conditions. *Environ. Sci. Technol.* **2014**, *48*, 570–574. [CrossRef]

63. Bassil, R.J.; Bashour, I.I.; Sleiman, F.T.; Abou-Jawdeh, Y.A. Antibiotic Uptake by Plants from Manure-Amended Soils. *Eur. J. Nutr. Food Saf.* **2009**, *19*, 925–933. [CrossRef]

64. Nisha, A. Antibiotic Residues—A Global Health Hazard. *Vet. World* **2008**, *2*, 375. [CrossRef]

65. Almashhadany, D.A. Monitoring of Antibiotic Residues among Sheep Meat in Erbil City and Thermal Processing Effect on Their Remnants. *Iraqi J. Vet. Sci.* **2020**, *34*, 217–222. [CrossRef]

66. Babapour, A.; Azami, L.; Fartashmehr, J. Overview of Antibiotic Residues in Beef and Mutton in Ardebil, North West of Iran. *World Appl. Sci. J.* **2012**, *19*, 1417–1422. [CrossRef]

67. Ibrahim, A.I.; Junaidu, A.U.; Garba, M.K. Multiple Antibiotic Residues in Meat from Slaughtered Cattle in Nigeria. *Internet J. Vet. Med.* **2009**, *8*, 354. [CrossRef]

68. Sanz, D.; Razquin, P.; Condón, S.; Juan Esteban, T.; Herráiz, B.; Mata, L. Incidence of Antimicrobial Residues in Meat Using a Broad Spectrum Screening Strategy. *Eur. J. Nutr. Food Saf.* **2015**, *5*, 156–165. [CrossRef]

69. 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]

70. Brown, K.; Mugoh, M.; Call, D.R.; Omulo, S. Antibiotic Residues and Antibiotic-Resistant Bacteria Detected in Milk Marketed for Human Consumption in Kibera, Nairobi. *PLoS ONE* **2020**, *15*, e0234313. [CrossRef]

71. McLaughlin, J.B.; Castrodale, L.J.; Gardner, M.J.; Ahmed, R.; Gessner, B.D. Outbreak of Multidrug-Resistant Salmonella Typhiurium Associated with Ground Beef Served at a School Potluck. *J. Food Prot.* **2006**, *69*, 666–670. [CrossRef]

72. Müller, P.M.; de Medeiros, E.S.; Mota, R.A.; de Rolim, M.B.Q.; Colombo, M.V.; Ribbensam, G.; Barreto, F.; de Silva, D.D.; de Silva, T.I.B. Avermectins Residues in Milk Produced in the State of Pernambuco. *Food Sci. Technol. Nutr.* **2020**, *40*, 979–984. [CrossRef]

73. Qibal, F. Milk Adulteration: A Growing Health Hazard in Pakistan. In *Nutrients in Dairy and Their Implications on Health and Disease*; Watson, R.R., Collier, R.J., Preedy, V.R., Eds.; Academic Press: Cambridge, MA, USA, 2017; pp. 215–222. [CrossRef]

74. Hajmohammadi, M.; Valizadeh, R.; Ebdalabadi, M.N.; Naserian, A.; Oliveira, C.A.F. de Seasonal Variations in Some Quality Parameters of Milk Produced in Khorasan Razavi Province, Iran. *Food Sci. Technol. Iran.* **2021**, *41*, 718–722. [CrossRef]

75. Moghadam, M.M.; Amir, M.; Riabi, H.R.A.; Riabi, H.R.A. Evaluation of Antibiotic Residues in Pasteurized and Raw Milk Distributed in the South of Khorasan-e Razavi Province, Iran. *J. Clin. Diagn Res.* **2016**, *10*, FC31–FC35. [CrossRef]

76. Ghanavi, Z.; Mollah, S.; Eslami, Z. Comparison Between the Amount of Penicillin G Residue in Raw and Pasteurized Milk in Iran. *Jundishapur J. Microbiol.* **2013**, *6*, 1A. [CrossRef]

77. David, V. Screening of cattle milk for the presence of antibiotic residues in selected districts of karnataka. *J. Indian Vet. Assoc.* **2021**, *19*, 98–104. [CrossRef]

78. Knappstein, K.; Suhren, G.; Walte, H.G.; Slaghuis, B.A.; Ferwerda, R.T.; Zonneveld, V. Prevention of Antibiotic Residues. Appropriate Management of Antibiotic Treatment of Cows in Automatic Milking Systems; Report D12, EU Project “Implications of the Introduction of Automatic Milking on Dairy Farms” QLK5-2000-31006. Available online: http://www.automaticmilking.nl (accessed on 6 May 2022).

79. Cornejo, J.; Pokrant, E.; Figueroa, F.; Riquelme, R.; Galdames, P.; Di Pillo, F.; Jimenez-Bluhm, P.; Hamilton-West, C. Assessing Antibiotic Residues in Poultry Eggs from Backyard Production Systems in Chile, First Approach to a Non-Addressed Issue in Farm Animals. *Animals* **2020**, *10*, 1056. [CrossRef]

80. Yang, Y.; Qiu, W.; Li, Y.; Liu, L. Antibiotic Residues in Poultry Food in Fujian Province of China. *Food Addit. Contam. Part B Survell* **2020**, *13*, 177–184. [CrossRef]
82. Petcu, C.D.; Ciobotaru-Pîrvu, E.; Goran, G.V.; Predescu, C.N.; Oprea, O.D. Study regarding the honey contamination degree assessed in a specialized production unit. Sci. Pap. Ser. D Anim. Sci. 2020, 63, 1.

83. Regulation (EC). No 396/2005 of the European Parliament and of the Council of 23 February 2005 on Maximum Residue Levels of Pesticides in or on Food and Feed of Plant and Animal Origin and Amending Council Directive 91/414/EEC Text with EEA Relevance; European Commission: Brussels, Belgium, 2005; Volume 70.

84. Regulation (EC). No 470/2009 of the European Parliament and of the Council of 8 May 2009 Laying down Community Procedures for the Establishment of Residue Limits of Pharmacologically Active Substances in Foodstuffs of Animal Origin, Repealing Council Regulation (EEC) No 2377/90 and Amending Directive 2001/82/EC of the European Parliament and the Council of Regulation (EC) No 726/2004 of the European Parliament and of the Council (Text with EEA Relevance); European Commission: Brussels, Belgium, 2009; Volume 152.

85. Johnson, D.S. Antibiotic Residues in Honey. Centre for Science and Environment: New Delhi, India, 2010; Volume 48.

86. Orso, D.; Floriano, L.; Ribeiro, L.C.; Bandeira, N.M.G.; Prestes, O.D.; Zanella, R. Simultaneous Determination of Multiclass Pesticides and Antibiotics in Honey Samples Based on Ultra-High Performance Liquid Chromatography-Tandem Mass Spectrometry. Food Anal. Methods 2016, 9, 1638–1653. [CrossRef]

87. Bargatska, Z.; NAMEJSNIK, J.; SLIEBIOIDA, M. Determination of antibiotic residues in honey. Trac-Trends Anal. Chem. 2011, 30, 1035–1041. [CrossRef]

88. Poetschke, G. Trarningsberichte Der Deutschen Gesellschaft Fur Hygiene. In Minutes of the Meeting of the German Society for Bigiene and Microbiology; German Society for Bigiene and Microbiology: Berlin, Germany, 1951.

89. Neaves, P. Monitoring Antibiotics in Milk—The Changing World of Test Methods. Available online: https://www.nugi-zentrum.de/fileadmin/webiste_uni_ulm/nugi/Experiminter/%C3%96kologie/Antibiotika-Nachweis/Neaves.pdf (accessed on 29 March 2022).

90. Barinova, K.V.; Khomyakova, E.V.; Kuravsky, M.L.; Schmalhausen, E.V.; Muronetz, V.I. Denaturing Action of Adjuvant Affects Specificity of Polyclonal Antibodies. Biochem. Biophys. Res. Commun. 2017, 482, 1265–1270. [CrossRef]

91. Franek, M.; Kolar, V.; Deng, A.; Crooks, S. Determination of Sulphadimidine (Sulfamethazine) Residues in Milk, Plasma, Urine and Edible Tissues by Sensitive ELISA. Food Agric. Immunol. 1999, 11, 339–349. [CrossRef]

92. Chafer-Pericás, C.; Maqueire, A.; Puchades, R.; Miralles, J.; Moreno, A. Multiresidue Determination of Antibiotics in Feed and Fish Samples for Food Safety Evaluation. Comparison of Immunoaasay vs. LC-MS-MS. Food Control 2011, 22, 993–999. [CrossRef]

93. Fan, G.; Yang, R.; Jiang, J.; Chang, X.; Chen, J.; Qi, Y.; Wu, S.; Yang, X. Development of a Class-Specific Polyclonal Antibody-Based Indirect Competitive ELISA for Detecting Fluoroquinolone Residues in Milk. J. Zhejiang Univ. Sci. B 2012, 13, 545–554. [CrossRef]

94. Gao, F.; Zhao, G.X.; Zhang, H.C.; Wang, P.; Wang, J.P. Production of Monoclonal Antibody against Doxycycline for Immunoassay Establishment of Residue Limits of Pharmacologically Active Substances in Foodstuffs of Animal Origin, Repealing Council Regulation (EEC) No 2377/90 and Amending Directive 2001/82/EC of the European Parliament and the Council of Regulation (EC) No 726/2004 of the European Parliament and of the Council (Text with EEA Relevance); European Commission: Brussels, Belgium, 2009; Volume 152.

95. Liu, N.; Song, S.; Lu, L.; Nie, D.; Han, Z.; Yang, X.; Zhao, Z.; Wu, A.; Zheng, X. A Rabbit Monoclonal Antibody-Based Sensitive Competitive Indirect Enzyme-Linked Immunobos assay for Rapid Detection of Chloramphenicol Residue. Food Agric. Immunol. 2014, 25, 523–534. [CrossRef]

96. Jiang, W.; Wang, Z.; Beier, R.C.; Jiang, H.; Wu, Y.; Shen, J. Simultaneous Determination of 13 Fluoroquinolone and 22 Sulfonamide Residues in Milk by a Dual-Colorimetric Enzyme-Linked Immunosorbent Assay. Anal. Chem. 2013, 85, 1995–1999. [CrossRef]

97. Wang, S.; Xu, B.; Zhang, Y.; He, J.X. Development of Enzyme-Linked Immunosorbent Assay (ELISA) for the Detection of Neomycin Residues in Pig Muscle, Chicken Muscle, Egg, Fish, Milk and Kidney. Meat Sci. 2009, 82, 53–58. [CrossRef] [PubMed]

98. Jeon, M.; Rhee Paeng, I. Quantitative Detection of Tetracycline Residues in Honey by a Simple Sensitive Immunoassay. Anal. Chim. Acta 2008, 626, 180–185. [CrossRef] [PubMed]

99. Wang, L.; Zhang, Y.; Gao, X.; Duan, Z.; Wang, S. Determination of Chloramphenicol Residues in Milk by Enzyme-Linked Immunosorbent Assay: Improvement by Biotin-Streptavidin-Amplified System. J. Agric. Food Chem. 2010, 58, 3265–3270. [CrossRef] [PubMed]

100. Jiang, W.; Beier, R.C.; Luo, P.; Zhai, P.; Wu, N.; Lin, G.; Wang, X.; Xu, G. Analysis of Pirlimycin Residues in Beef Muscle, Milk, and Honey by a Biotin-Streptavidin-Amplified Enzyme-Linked Immunosorbent Assay. J. Agric. Food Chem. 2016, 64, 364–370. [CrossRef] [PubMed]

101. Broto, M.; Matas, S.; Babington, R.; Marco, M.-P.; Galve, R. Immunochemical Detection of Penicillins by Using Biohybrid Magnetic Particles. Food Control 2015, 51, 381–389. [CrossRef]

102. Jiang, W.; Luo, P.; Wang, X.; Chen, X.; Zhao, Y.; Shi, W.; Shen, J. Development of an Enzyme-Linked Immunosorbent Assay for the Detection of Nitrofurantoin Metabolite, 1-Amino-Hydantoin, in Animal Tissues. Food Control 2012, 23, 20–25. [CrossRef]

103. Agarwal, V.K.; American Chemical Society (Eds.) Analysis of Antibiotic/Drug Residues in Food Products of Animal Origin; Plenum Press: New York, NY, USA, 1992; ISBN 978-0-306-44199-8.

104. Wang, C.; Wu, J.; Zong, C.; Xu, J.; Ju, H.-X. Chemiluminescent Immunoassay and Its Applications. Chin. J. Anal. Chem. 2012, 40, 3–10. [CrossRef]

105. Dodeigne, C.; Thunus, L.; Lejeune, R. Chemiluminescence as Diagnostic Tool. A Review. Talanta 2000, 51, 415–439. [CrossRef]

106. Puthuma-Tumprie, G.A.; Korf, J.; van Amerongen, A. Lateral Flow (Immuno)Assay: Its Strengths, Weaknesses, Opportunities and Threats. A Literature Survey. Anal. Bioanal. Chem. 2009, 393, 569–582. [CrossRef]

107. Zhou, C.; Zhang, X.; Huang, X.; Guo, X.; Cai, Q.; Zhu, S. Rapid Detection of Chloramphenicol Residues in Aquatic Products Using Colloidal Gold Immunochromatographic Assay. Sensors 2014, 14, 21872–21888. [CrossRef]
138. Oliver, J.P.; Gooch, C.A.; Lansing, S.; Schueler, J.; Hurst, J.J.; Sassoubre, L.; Crossette, E.M.; Aga, D.S. Invited Review: Fate of Antibiotic Residues, Antibiotic-Resistant Bacteria, and Antibiotic Resistance Genes in US Dairy Manure Management Systems. *J. Dairy Sci.* **2020**, *103*, 1051–1071. [CrossRef] [PubMed]

139. Wallace, J.S.; Garner, E.; Pruden, A.; Aga, D.S. Occurrence and Transformation of Veterinary Antibiotics and Antibiotic Resistance Genes in Dairy Manure Treated by Advanced Anaerobic Digestion and Conventional Treatment Methods. *Environ. Pollut.* **2018**, *236*, 764–772. [CrossRef] [PubMed]

140. Youngquist, C.P.; Mitchell, S.M.; Cogger, C.G. Fate of Antibiotics and Antibiotic Resistance during Digestion and Composting: A Review. *J. Environ. Qual.* **2016**, *45*, 537–545. [CrossRef] [PubMed]

141. Iwu, C.D.; Korsten, L.; Okoh, A.I. The Incidence of Antibiotic Resistance within and beyond the Agricultural Ecosystem: A Concern for Public Health. *Microbiologypopen* **2020**, *9*, e1035. [CrossRef]