1

Antimicrobial Residues and Food of Animal Origin

AUTHORS DETAIL

Noor Fatima[1], Muhammad Shahid Mahmood[1], Muhammad Naveed Anwar[1], Rizwan Aslam[1], Muhammad Imran Arshad[1], Zeeshan Nawaz[2], Muhammad Umar Zafar Khan[1], Mudassir Ali[3], Mavra Chouhdary[1] and Sultan Ali[1]*

[1]Institute of Microbiology, Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
[2]Department of Microbiology, GC University, Faisalabad, Pakistan
[3]Teesside University, Middlesbourgh, United Kingdom
*Corresponding author: sultanali@uaf.edu.pk

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INTRODUCTION

Antimicrobial compounds produced naturally by microorganisms, plants, or modified chemical substances, and are used extensively for the treatment or cure of various infections in humans and animals (Asredie and Engdaw 2015). Many antimicrobial products are used in food-producing animals for different purposes i.e. to treat disease, as feed additives, and to enhance animal growth. The widespread consumption of these products results in antimicrobial residues in the tissues of these animals and the foods derived from them. On the other hand, these residues have numerous consequences on health and on a broad perceptive, on the environs (Treiber and Beranek-Knauer 2021). Fig. 1 illustrate the antibiotics given to animals through feed, water, injections as a feed additive, as growth promoter, and for treatment of disease, lead to antibiotic residues in food animals.

Metabolites called antimicrobial residues are formed after antimicrobial chemicals are administered to an animal and can be found in both non-edible and edible tissues. These antimicrobial residues in animal food that exceed the maximum acceptable limit may cause antibiotic resistance and other complications in humans and animals (Ngangom et al. 2019).

Antimicrobial Products used for Growth Promotion

Antimicrobial compounds are used to boost animal growth, primarily in fattening animals or broilers. The reason for the better growth is due to the gut's mucosal membrane becomes thinner, enabling improved absorbance, changing gut mobility to improve more suitable absorption and making optimal conditions for valuable microorganisms in the animal's gut by killing pathogenic bacteria. Furthermore, antimicrobials promote growth by reducing the immune system's scope of action, reducing toxin generation, and reducing nutrient waste. Antimicrobials used for growth promotion are particularly effective in poultry and small growing animals since they are more receptive to them. According to research, chicks fed the fermenting waste of manufactured tetracycline as a source of vitamin B_{12} matured quicker than hens fed as the controls. It was soon determined that the tetracycline residue (not the vitamin level in the feed) was the reason of this influence (Edqvist and Pedersen 2001).

Antimicrobial Products used for Therapeutics

The use of antimicrobials in all cases of inflammation, fever, viral infections and injuries has a significant residual effect on edible tissues. Antimicrobials are effective in usual conditions since their job is to eliminate frequently diverging cells through cell invasion (Mahmoudi et al. 2018).

Antimicrobial Products used for Prophylactics

Poultry or animals have been administered suboptimal groups of antimicrobials to stop potential illness. However, the antimicrobial agents are explicit in the range of their action merely in the vigorous reproducing phase of microorganisms; nevertheless, they will not deliver complete defense. In specific cases, i.e., surgical methods and dry cow therapy need antibiotic treatment (Callens et al. 2012).

Other use of Antimicrobial Products

These antimicrobial products are also utilized in many practices throughout the processing, manufacturing, and storing of dairy products. The contaminants in dairy products may arise from water, soil, or air through manufacturing, transportation, or storage. Moreover, the indirect contamination through feed provided to animals leads to antimicrobial residues in man. Various other major issues include the deficiency of extension activities, shortage of safe drugs, insufficient information given by manufacturers, utilization of animals for additional profit or production and unawareness. The United States Food and Drug Administration bans the additional usage of furazolidone,

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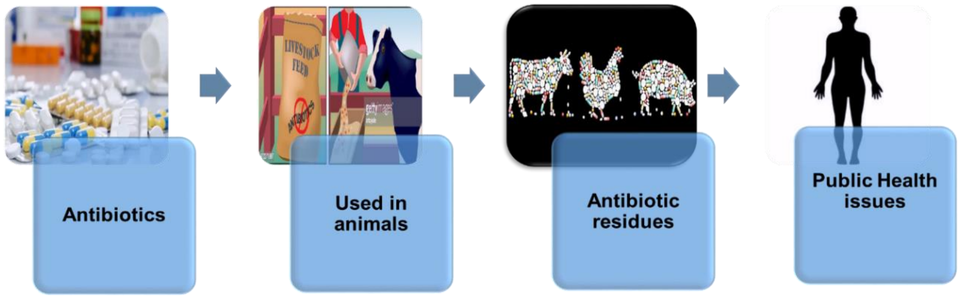

Fig. 1: Development of antibiotic residues.

Fig. 2: Global consumption of antibiotics in humans and animals.

chloramphenicol, sulphonamide, fluoroquinolones, and nitrofurazone in lactating animals (Nisha 2008).

Widespread Antimicrobial Gourmandization in Food of Animals Origin

In 2010, there were roughly 63,151 (or 1,560) tonnes of antimicrobials used in animals raised for food. By 2030, it is predicted that this quantity will rise by 67% to 105,596 (or 3,605) tonnes. According to estimates, the rise in the number of animals bred for food production accounts for two-thirds (66%) of the overall increase (67%) in the consumption of antibiotics (Tiseo et al. 2020). While the farming methods used to produce remaining of the third proportion (34%) have changed, with a bigger proportion of animals by 2030 anticipated to be grown in intense agricultural setups. Due to the shift in production systems, Asia alone is consuming around 46% of antimicrobial products by 2030. Asia is predicted to consume 51,851 tonnes per annum of antimicrobials in 2030, which is 82% of the present worldwide consumption in 2010 in food animals (Van Boeckel et al. 2015). Fig. 2 highlights the global consumption of antibiotics in humans and animals.

According to WHO, today almost eighty percent of food-producing animals have been given different drugs in most or part of their life. Frequently used antimicrobials include sulphonamides, aminoglycosides, tetracyclines, spectinomycin, trimethoprim, macrolides, nitrofurans, Nitroimidazoles, β-lactams, pleuromutilins, Lincosamides, polymyxins, and quinolones (Cháfer-Pericás et al. 2010; Tadesse and Tadesse 2017).

The topmost antibiotics used in cattle include macrolides and tetracycline through drinking water and feed while sulphonamides as a therapeutic and prophylactic drugs and growth promoters. Generally, tetracycline, florfenicol and tylosin are used orally for the treatment of diarrhea, respiratory diseases, foot rot, and liver abscesses at sub-therapeutic levels (Mor et al. 2012). Fig. 3 represent the percentage of antibiotics to be used in animals.

Maximum Residue Limit

The maximum residue limit (MRL) is a concentration of antimicrobial products below the hazardous level and permitted by various organizations in feed or food projected to be used for human and animal intake at a given duration called as maximum residue limit. The measuring unit of MRL for liquid is mg/L and for solid mg/kg (Sachi et al. 2019). The food product below the MRL is non-hazardous for the health of consumers and does not interrupt manufacturing procedures. The concept of MRL maintains the balance between producer and consumer to use antibiotics safely. The main points to be considered while calculating MRL include potential effects or the toxicological possibility of residues on the digestive flora of humans (Anonymous, 2009; Ma et al. 2021).

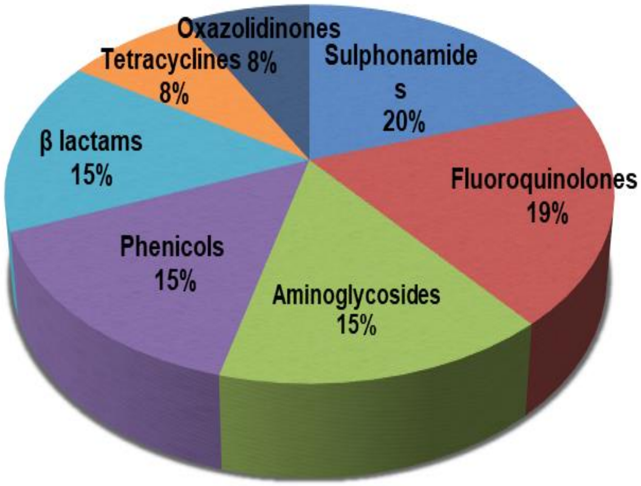

Fig. 3: Percentage of antibiotics used in animals.

Withdrawal Time

The time interval required after the administration of the drug in food-producing animals to ensure that the toxicological impact of antibiotic residue reaches a safe concentration or below MRL in milk or edible portion of the animal. This time reduces or prevents the detrimental effects of drug residues in foodstuffs for consumption (Ngangom et al. 2019). This largely depends on the route of administration, and the physical and chemical properties of drugs (Sachi et al. 2019). For checking antibiotic residues, throughout withdrawal procedures after drug administration is being stopped, the targeted tissue is selected and animal samples are collected and tested at different time intervals. Furthermore, the kidney and liver are the most important organs as residues required a longer time to pass through these organs (Ngangom et al. 2019).

Causes of Antibiotic Residues

The main causes of antibiotic residues in edible portions or tissue comprise overdose of injection, negligence to follow proper withdrawal time, use of contaminated equipment with antibiotics while administrating or mixing the drug, error in mixing and accidental feeding with medicated feed or spilled chemicals (Chen et al. 2019). Among the different routes of administration i.e. topical, oral and parenteral, it has been described that antimicrobial residues surpassing the criteria are mainly faced when directed through injection. This causes persistence in animal tissue, limiting their elimination (Arsène et al. 2022). Animal factors include pregnancy, allergies, age, infections, congenital illness, etc. Temperature variation of water for aquatic species, contaminated environment, and improper use of antibiotics. The presence of antimicrobial residues in seafood might result in the development of toxicity and bacterial resistance to customers, which can result in various diseases and even can cause disease in severe case. (Okocha et al. 2018).

The global requirement for products of animal is increasing as it is rich in protein for human consumption, commonly leading to the excessive utilization of antimicrobials in agriculture. Antimicrobials are used in 73 percent of meat production around the world. Assessments on the use of antimicrobials concerning the manufacturing of products of animal are expected to increase in 2030 by 11.5%. The spontaneous emergence of antimicrobial resistance in farm animals and indirectly in humans through animal food consumption is mainly due to the addition of antimicrobial compounds in animal feed. Apart from this issue the use of wastewater contaminated with antibiotics and dung disposal of animals in the environment are additional challenges that are repeatedly revealed in many scientific studies as a source of the spread of antibiotic residue and antimicrobial resistance (Treiber and Beranek-Knauer 2021). Fig. 4 highlights the major sources of antibiotic residues.

Public Health Risk

Public health risks arise by ingesting food containing antimicrobial residue above the acceptable daily intake or residual limit higher than MRLs. The sudden consequence of antimicrobial residue induces various illnesses throughout the food chain in humans. The adverse effects involve exposure to antimicrobial residues for a relatively long time (Agmas and Adugna 2018). Dairy and other food products from animals that contain antibiotic residues have major health issues as listed in Fig. 5. The harmful impact of the drugs comprises immunological diseases, cancer, toxic effects, (e.g. oxytetracycline, sulphamethazine, and furazolidone), nephropathy, mutagenicity, (e.g., gentamicin), and bone marrow toxicities, reproductive disorders, hepatotoxicity (e.g., chloramphenicol) (Tadesse and Tadesse 2017).

The possible effects of antimicrobial residues on public health are as follows:

- **Antibiotic Resistance:** The development of antibiotic resistance due to these residues is a major concern as these promote resistant bacteria and induce severe pathologies. Even the existence of low antibiotic residues renders microbes resistant to antibiotics. The antibiotic-resistant microorganisms can be transferred between people through contact directly or indirectly via exchanging resistant genes in the surroundings, further details of antimicrobial resistance are discussed below in the chapter.
- **Allergic Reactions:** Numerous allergic responses, such as anaphylaxis and serum sicknesses, are linked to various antibiotic residues, primarily in penicillin's case.
- **Carcinogenicity:** Antibiotic residues may cause cancer by interacting with biological components including RNA or DNA.

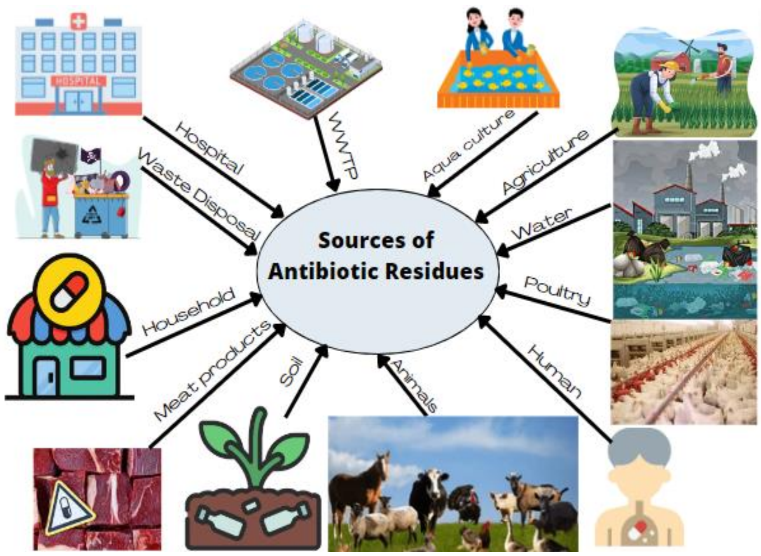

Fig. 4: Major sources of antibiotic residues

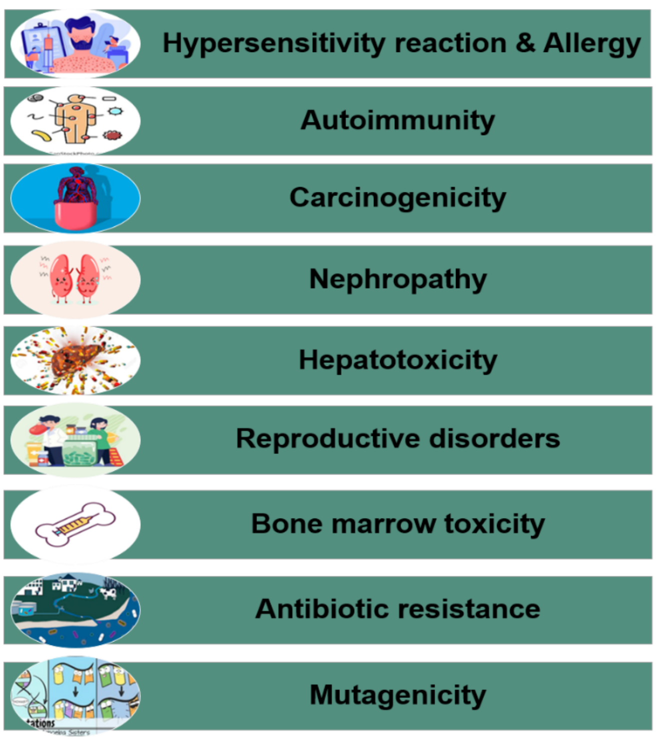

Fig. 5: Public health risk due to antibiotic residues

- **Mutagenicity:** Another negative effect of antibiotic residues is their mutagenic effect, which can provoke DNA mutation or chromosome dysfunction. Human infertility may result from these alterations.
- **Teratogenicity:** Due to the presence of antimicrobial residues for an extended time during gestation, several inborn defects may be seen in the newborn child.
- **Disruption of the usual Condition of the Intestinal:** The intestine's normal flora coexists with diverse microorganisms and fills its space to prevent illnesses caused by pathogenic microorganisms. A large number of normal intestinal flora that has non-pathogenic microorganisms may be destroyed by antimicrobial residues, by using a broad range of antibiotics. This can highlight disease-causing microbes and disturb the normal intestinal flora (Kyuchukova 2020).

Antimicrobial Residues: A Leading Cause of Antimicrobial Resistance

The antibiotic residues may cause the mutation in susceptible bacteria prolonging the survival of bacteria and promoting their multiplication as drug-resistant bacteria which carry the resistant genes.

The transferable genetic elements, involving integrons, prophages, and plasmids, will promote the spreading and raise of genomic recombination of antibiotic-resistant genes by conjugation, transduction, and transformation, together known as horizontal gene transfer (Ben et al. 2019).

The main cause impelling the rise of antimicrobial resistance include duration of exposure to antimicrobials, drug concentration, host immune status, organism type, and antimicrobial type (Ngangom et al. 2019).

The transmission of antimicrobial resistance among the environment, animals, and humans occurred through many routes. Among them environment act as a bridge between several components of human and animals to water, sewage, soil and air. The ecosystem serves as a reservoir to blend mobile genetic components that spread and interact with other parts of the environment or animal and human hosts. The spread of antimicrobials arises through numerous ways such as the manufacturing industry, hospital, and municipal waste, landfill leachates of antibiotic discharge, and surface runoff from agricultural fields comprising livestock manure and animal husbandry. The antimicrobial compounds have a half-life ranging from minutes, and hours to several days but antimicrobial residues are determined as the permanent part of the environment (Ahmad et al. 2021).

Impact of Consuming Antibiotic Residues Containing Food and Antibiotic Resistance

The World Health Organization promotes the idea of "one health," which encompasses both animal and human health. It highlights the broad relationship between the environment, animals and humans, all of these direct the distinctive approach to health. Thus at all of these three levels, the entire chain should consider maintaining equilibrium by using medicinal products carefully. Nowadays there is much public awareness about the effects of increased and prolonged use of antibiotics in the production of animal livestock. Antibiotic resistance genes can be developed in microorganisms, which is helpful in their survival, minimizing treatment of microbial infections, selection pressure, and increasing mortality in humans. A fundamental source of antibiotic residues is animal food which is a result of the indiscriminate use of antibiotics at the industrial level. Worldwide differences in antibiotic-resistance genes and the prevalence of animal-based antibiotic-resistant bacteria have been reported between different geographical areas. Even after the heat treatment antibiotic residues remain in animal-based food such as eggs, meat, and milk and cause antipathy and gastrointestinal diseases in consumers or lead to the appearance of superbugs because of antimicrobial resistance. Antibiotic resistance as well as the ineffectiveness of antibiotic therapy is increasing in humans. It is mentioned in the literature that the abusive and constant use of antibiotics can induce the production of antibiotic-resistant bacteria. Infections of multidrug-resistant bacteria can pose a threat to public health by increasing mortality. The researchers have mentioned that after a while, bacteria will develop resistance to compounds similar to antibiotics such as phenolic compounds (Ghimpețeanu et al. 2022).

Kumar et al. (2020) investigated the topic to comprehend more promising mechanisms for developing or spreading antibiotic-resistant genes in clinical, nutritive, agricultural, and environmental settings. Alternate dietary plans were also assessed to replace medicated feed and antibiotics with prebiotics, probiotics, antibodies, and essential oils having a prophylactic role against infections caused by microorganisms. Animal husbandry is a curtail contributor to food requirements and a significant component of the global economy. Antibiotics are not only given to animals through feed but also in drinking water for treatment purposes or to gain weight. Various preventive measures should be taken globally to eliminate the resistant bacteria such as avoiding the use of antibiotics for non-therapeutic purposes. Antibiotics should be strictly avoided when animal food is intended for the consumption of humans (Singh et al. 2014).

Avoparcin has been banned in European Union to reduce the occurrence of antibiotic resistance in humans and animals (Ghimpețeanu et al. 2022). To control antibiotic resistance transmission from farm to fork, the expansion of the World Health Organization or Food and Agriculture Organization of the United Nations, Global action plan is necessary along with one health concept. Infections caused by antibiotic-resistant bacteria kill 33,000 people every year. WHO prohibited the use of antibiotics for animals that produce food and fully restricted the prevention of disease using antibiotics without the diagnosis. Several countries are already taking measures to decrease antibiotic usage in food-producing animals. European Union has banned the use of antibiotics for growth promotion since 2006. Additionally, consumers also promote the marketing of meat from animals that are raised without using antibiotics, some food chains also supply meat with "antibiotic-free" policies. The main objective is to use antibiotics when it is necessary so that the effectiveness of antibiotics is maintained for treatment purposes (WHO 2022). FDA listed 89 antibiotics that are medically important and added to the feeds of animals. Furthermore, national programs for the inspection of antibiotic residues in different types of food products are being updated constantly (Mensah et al. 2014).

Environmental Risk

The environmental occurrence of antibiotic residue is a result of countless configurations of antibiotics normally subjected to combat microbial infections and increase the production of livestock. The antibiotics use in the treatment of animals and humans are reaching the environment settings through waste matter discharged from the body, especially feces and urine. About 40 to 90% depends upon the type of antibiotic excreted in active form, returning to the atmosphere and contaminating the water, soils, fields, plants, air, etc. (Oloso et al. 2018). The routine usage of huge volumes of antibiotics in animal farming can result in the contamination of farmed lands through the use of adulterated manure on fields as fertilizer and the wastewater used for the irrigation of crops. Further concern rises from the inappropriate disposal of antimicrobial products into sewage systems. Many wastewater treatment plants are working to treat antibiotic-contaminated water but 100% removal of antimicrobials is not possible, therefore the final effluent or sludge contains antibiotics in excess amounts. This sludge is then used in plants as a fertilizer and discharged in water and this water might end up in drinking water sources like lakes and rivers (Polianciuc et al. 2020).

Apart from livestock and poultry, human dwellings, hospitals, and aquaculture farms antibiotic contaminated wastewater are occasionally released into the environment without undergoing any treatment. In many countries, the routine monitoring of the antimicrobials and their residues in drinking water is not possible due to the high cost (Lundborg and Tamhankar 2017).

Technological Risks

The antibiotic residues pose a major technological risk to food products processed by microbial fermentation for example in fish (shrimp paste, bagoong, surströmming, gravlax, fish sauce, garum and fesikh), meat (salami, corned beef, sausage, chorizo, soudjouk, and pepperoni) and milk (cheese and fermented milk product). The interference of antibiotic residues in these raw materials can hinder the fermentation process by obstructing the starter cultures, leading to poor quality of food and manufacturing faults (Arsène et al. 2022).

Current Detection Method of Antibiotic Residues

Traditionally the detection of antibiotic residues can be divided into three groups: chromatography/mass spectrometry detection techniques, immunoassay techniques, and microbial inhibition screening techniques (Wang and Zhao 2018). The widely and earliest-used method is microbial inhibitions assays. These assays are cost-effective and cover a broad spectrum of antibiotics in one go. There are two types of tests, one tube test, and the other agar plate or microtiter well plate test. The main principle of these tests includes spore suspension of the most highly sensitive bacteria in the growth medium, accompanied by an indicator (pH or redox). The bacterial growth begins at the optimum temperature and acid production by fermentation is indicated by color change. The absence of color change indicates the presence of antimicrobial residues that prevent the growth of bacteria (Pikkemaat 2009).

The confirmatory methods with high specificity are laborious, expensive, and need an adequate or personnel laboratory. These methods are essentially chromatographic techniques (mainly liquid chromatography) coupled with ultraviolet (UV) or mass spectrometry. Furthermore, enhanced surface Raman spectroscopy, high-performance liquid chromatography (HPLC) with a spectroscopic HPLC–photodiode array detector or with spectroscopic fluorometric detection (HPLC–RF) and capillary electrophoresis (CE), CE– laser-induced fluorescence, are also presented to be efficient in detecting antimicrobial residues. Now a day's fully automatic highly specific onsite application biosensors are becoming progressively significant in identifying antibiotic residues in various foodstuffs. These biosensors can be categorized based on biological element (microbiological, enzymatic, and immunosensory), transducer (calorimetric, piezoelectric, thermal, optical, electrochemical, and impedimetric) and immobilization of biological element procedure on solid support medium (encapsulation, adsorption, entrapment, cross-linking and covalent bonding) (Arsène et al. 2022).

Control of Antimicrobial Residues

The following steps may be taken to lower the risk of antimicrobial residues on animal and public health:

- The most important and initial step is educating people about the issue through various organizations, literature, government agencies, and veterinary personnel.
- Rapid analysis of all antibiotics spectrum in one test.
- Proper maintenance and monitoring of MRL and withdrawal time.
- Promote ethnoveterinary practices.
- Cost-effective and simple field test to determine the antimicrobial residues in food-producing animals.
- Ban food containing antimicrobial residues.
- Use of resins, UV irradiation, and activated charcoal help in the inactivation of antibiotics.
- Avoidance of irrational use of antibiotics in the field.
- Periodic surveillance and monitoring of the residues in food animals and their products (Nisha 2008).
- Antibiotics used as growth promoters should be banned.
- Only prescribed antibiotics should be given to animals by the veterinarian.
- For antibiotic therapy, a narrow-spectrum antibiotic should be chosen (Okocha et al. 2018).
- Alternative treatment strategies should be adapted for example probiotics and plant base elements (Bacanlı and Başaran 2019).

Conclusion

Allergies, cancer, altered intestinal flora, bacterial resistance, and the suppression of fermentation in the dairy sector are all possible outcomes of antimicrobial residues in foods of animal origin. The potential development of antimicrobial resistance by antimicrobial residues in meat, milk, egg, and fish poses a severe hazard to public health. There may be consequences for the food supply system, which is already under stress from the ongoing epidemic of COVID-19. The scientific data needed to advise political decision-makers to interact with veterinarians and livestock producers, and promote sustainable development plans. Health officials may take notice and begin formulating strategies to reduce or eliminate this risk.

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