

Pharmacological Interventions for Antimicrobial Resistance in Animals and its Implications for Human Health

AUTHORS DETAIL

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Abstract

This book chapter explores the growing concern of antimicrobial resistance (AMR), focusing on its impact on animal and human health. The sources emphasize that the overuse of antimicrobials in livestock, particularly in dairy farming, is a major contributing factor to the development of resistant strains. This practice poses a significant risk as these resilient microorganisms can be transferred to humans through numerous trails, together with direct interaction with animals, feeding of tainted food yields (meat, milk, etc.), and environmental exposure. The chapter highlights the complexities of tackling AMR. It calls for a multi-pronged approach involving stringent regulations on antimicrobial use, enhanced surveillance and monitoring programs, and the development of new antibiotics and alternative treatments. A key takeaway is the emphasis on a One Health perspective, recognizing the interconnectedness of human, animal, and environmental health in addressing this global challenge. In conclusion, the chapter paints a stark picture of the growing threat of AMR and its potential consequences. It underscores the urgent need for collaborative efforts across sectors to mitigate the spread of resistant organisms and safeguard the effectiveness of antimicrobial therapies for both human and animal populations.

Keywords: Antimicrobial Resistance, Livestock, Dairy Animals, Antimicrobial Use, Public Health, Surveillance

Introduction

Tick-borne encephalitis (TBE) is a serious infectious disease that affects the central nervous system (CNS) of animals and one of man's greatest allies and worst adversaries are microorganisms. Since Leeuwenhoek and other distinguished scientists discovered them and recognized them as infectious agents, our understanding about these has rapidly expanded. Establishing their function in food and fermentation, as well as their subsequent beneficial effects on human health required time (Thakur et al., 2016). Since ancient times, people have used microorganisms and their metabolites for food, feed, dairy, fermentation, pharmaceuticals, and other purposes (Adrio et al., 2017). Despite their positive functions, they continue to pose a hazard to

people, animals, and vegetation through food spoiling and numerous human and animal illnesses, which places a significant burden on both the local and global economies. Globally, a number of strategies are used to combat these living danger agents, most notably the administration of antibiotics. The discovery of penicillin, the first antibiotic, prevented the spread of transferrable infections and protected masses of lives, predominantly during World War II. However, Sir Alexander Fleming claimed in his 1945 Nobel Prize speech that bacteria could become resilient to antibiotic actions, and reports of the wonder drug's ineffectiveness did not surface until much later (Kumar et al., 2016).

The effectiveness of contemporary treatment regimens was called into question when reports of other medicinal medications' failure to combat pathogenic pathogens began to surface. These reports were ultimately identified as drug confrontation, antimicrobial resistance (AMR), or antibiotic resistance. Microbes that are resistant to conventional dosages of clinically relevant antimicrobial medications are said to exhibit antimicrobial resistance (AMR) (Abraham et al., 2016). In general, it is the ability of microorganisms to overwhelm the antagonistic belongings of antibiotics to which they were previously vulnerable, allowing them to survive exposure to predictable antibiotic dosages. The selective pressure caused by the use—more precisely, abuse—of antibiotics speeds up this natural tendency even quicker.

AMR has become a danger to the successful treatment of a growing number of microbial infections. It causes antibiotics to be less effective, which makes therapy more difficult, expensive, time-consuming, and occasionally even impossible. Reports of novel antibiotic resistance have surfaced after each new antibiotic is introduced (Ganguly et al., 2019). A worldwide public health emergency that jeopardizes our capacity to effectively treat bacterial illnesses is antimicrobial resistance (Chiu CH et al., 2002). The issue has long been acknowledged by microbiologists and infectious disease experts; Sir Alexander Fleming, the inventor of penicillin, himself brought attention to the danger of resistance from under-dosing, but broader audiences are just now becoming aware of the extent of the resistant threat.

Numerous infectious pathogens that were previously effectively treated with any one of several drug classes have developed resistance to the majority of these medications, and in certain situations, almost all of them (Littmann et al., 2019). This research focuses on antibiotics and synthetic antimicrobial drugs, which pose the greatest threat, but antifungals, antiparasitics, and antivirals are also at risk. How did we go from antimicrobials being genuinely "wonder drugs" that could be used to treat a variety of potentially fatal illnesses to the current situation, where resistance to the majority of antimicrobials is pervasive and the supply of new drug classes has decreased to a trickle? Unfortunately, neither the remedy nor the full response is straightforward. There is little doubt that the primary issue, which needs to be addressed, is the over use of these valuable medications in a variety of fields, including agriculture, human, and animal (O'Neill et al., 2016).

Antimicrobial Resistance in Animals: A Global Concern

Every age group in the world consumes milk, the most popular natural health food. This is the foundation upon which dairy farming and business are built. Dairy animals are raised for meat in 'addition to milk. Compared to dairy cows kept on small holdings and engaged in organic farming, those kept in large crowds and on conservative dairy farms are more expected to be exposed to antimicrobials. Additionally, the demand for food derived from animals is rising quickly (Krehbiel et al., 2013). The value of veterinary medications on the global market increased from 8.65 billion dollars in 1992 to 20 billion dollars in 2010 due to this growing demand, and it is expected to reach 42.9 billion dollars by 2018 (Hao et al., 2014). Animal farming around the world mostly depends on the overuse of antibiotics to enhance animal health and increase productivity. AMU in edible animals was expected to be answerable for 80% of the United States' yearly antimicrobial consumption, according to the Food and Drug Administration (FDA) (Food Drug Administration, Silver Spring, 2010). The ordinary use of antimicrobials in 26 EU nations in 2012 was 144 mg/kg of estimated biomass in animals and 116.4 mg/kg in humans (Lhermie et al., 2015). Fig. 1 illustrates the factors contributing to antimicrobial resistance (AMR) in animals, including unrestricted drug availability, improper diagnosis, and unmonitored antimicrobial use. Poor infection prevention, lack of monitoring, and selective pressure from antibiotics encourage the emergence of resistant bacterial strains, posing a significant threat to animal health.

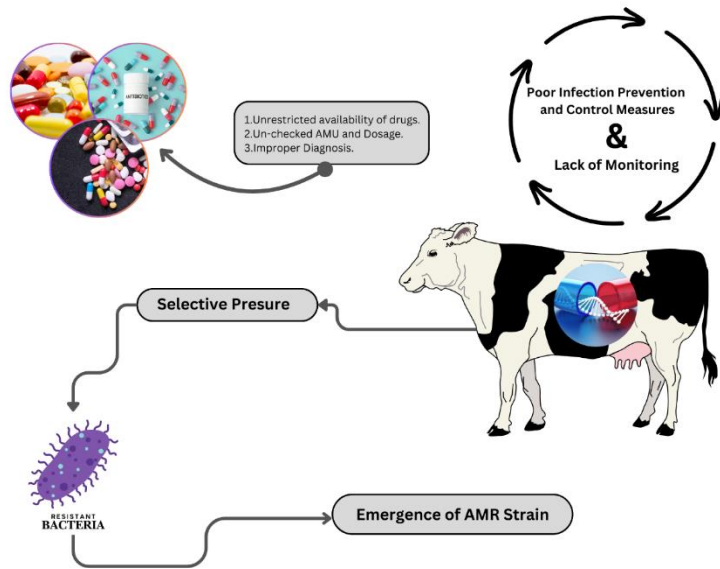


Fig. 1: Possible factors leading to antimicrobial resistance (AMR) in animals

The need for premium cattle products will only grow as the population grows. By 2030, AMU in food animal production will increase by more than 67% to meet the world's need for animal proteins (Van Boeckel et al., 2016). Widespread resistance episodes might have a greater impact on developing nations like India, where the pervasiveness of communicable diseases is high and antimicrobial use is enlarged to reduce morbidity and mortality. Anti-microbial usage in edible animal production is extensive in India, as evidenced by reports of antibiotics remains in food animal yields (broiler meat and milk) from numerous areas of the country (Maron et al., 2013). Numerous factors, including limited dependence on veterinarian guidance, management by the owner, and privation of keeping of antibiotic usage registers and printed strategies for treating repulsive animals, make it difficult to calculate real values of AMU in dairy farms. Furthermore, there is a great transaction of modification in antibiotic use management actions, which differ from farm to farm globally. Statistics about AMU in dairy animals is therefore more hypothetical. According to a survey by the World Association for Animal Health (OIE) in 2012, just 27% of OIE associate nations implemented an official system for tracking AMU in livestock (Diaz et al., 2015). The main factor contributing to the development of AMR in animal husbandry is the use of antibiotics. Antibiotics target both pathogenic and commensal microorganisms, and AMR arises as a result. Suboptimal antibiotic concentrations in humans and the addition of subtherapeutic antibiotic doses to aid in food animal growth have been identified as the primary causes of drug resistance development (McManus et al., 2024). A little one of the four contrivances—antibiotic inactivation or amendment; variation of the antibiotic marked site; adjustment of metabolic passageways to counteract the antibiotic effect; and lessening of antibiotic entry and/or elevation of active efflux—has been found to be the machine by which bacteria develop resistance (Anderson et al., 2020).

Pharmacological Interferences for AMR in Animals

A number of factors, including the target pathogen's inherent and native arrangements of antimicrobial vulnerability, the contagion site, drug pharmacokinetics (PK) and pharmacodynamics (PD), host aspects that disturb drug efficiency or poisonousness (specifically, class, era, magnitude, gravidity, comorbidities, insusceptible competence, and drug communications), as well as concerns about the commercial and noneconomic value of the individual visceral, treatment costs, drawing periods, and flock production, must be taken into account when choosing the best antimicrobial treatment. A strategy to antimicrobial stewardship that is universally applicable is challenging due to the notable variations among animal species. Nonetheless, there is a fundamental line of reasoning that can facilitate antibiotic stewardship for all animal species and treatment difficulties. This rational procedure calls for (i) veterinary advice when creating case definitions and confirming them through caregiver education and diagnostics; (ii) evaluation of potential substitutes to avoid, manage, or cure the bacteriological infection; (iii) choice of a first-line proxy for pragmatic treatment in the absenteeism of alternatives for antimicrobials; and (iv) safe and efficient submission of the chosen cause (Rhouma et al., 2020).

Furthermore, if a medical treatment is attained before the inference of the suggested course of management, or if the patient's or herd's health conditions do not improve following first treatment, the results of the treatment should be sufficiently monitored to enable any necessary modifications. Avoiding the ultimate antimicrobial transgression—antimicrobial exposure that has no

positive impact on the course of the disease—is the aim of this procedure. There is proof that the total amount of antimicrobials used, the way they are administered (Chantziaras et al., 2015), the dosing schedule, and the length of treatment all contribute to AMR (Dorado-García et al., 2019). In light of this, we have dogged four most important goals for smearing the idea of optimal antimicrobial cure in veterinary treatment and livestock production: (i) lowering the total amount of antibiotics used, (ii) enhancing diagnostic testing, (iii) using second-line, vitally important antibiotics wisely, and (iv) optimizing dosage schedules.

Novel Antimicrobial Agents for Animal and Human Health

Certain kinds of antibiotics are more or less solely used to treat human diseases, such as tuberculosis (e.g., isoniazid) or other contagions that animals usually do not receive treatment for (e.g., livestock with bovine TB are usually slaughtered rather than treated). Some, like flavor phosphor lipols and ionophores, are only used in veterinary medicine due to their toxicity to humans. Weese et al. (2015) stated that the vast widely held of antimicrobial classes are consumed by both people and animals, such as native animals, fowl, cultivated fish and lobsters, honey bees, and others. Horticulture occasionally uses tetracycline's, streptomycin, and other antimicrobials to use and inhibit bacterial infections of fruit, such as apples and pears.

Although they are occasionally used in groups (e.g., to prevent meningo-coccal sickness) or as a preventative measure in people (e.g., after surgery), antimicrobials are primarily used to treat clinical infections in individuals. In veterinary medication, there are notable alterations in the use of antimicrobials in mate animals (such canines, felines, pet fowls, and equines) and animals produced for food. Antibiotic use in pet animals is essentially the same as in humans; that is, the drugs are mostly administered to each animal separately to treat clinical infections, with a small amount also being used to prevent infections in particular animals, such as after surgery (Vidaver, 2002).

On the other hand, in the situation of foodstuff faunas, when a subsection of animals is clinically diseased and require antibiotic treatment, the medicines are often given to the entire group (e.g., pig coops, chicken flocks) through feed or water for practical and efficient reasons, even if the majority of the animals are not presenting signs of infection (in effect, prophylaxis). However, many practitioners in the animal health industry today incorrectly describe this as "therapeutic" use. Additionally, antimicrobials can be utilized to treat specific clinically ill animals, such as dairy cows with mastitis, in a manner similar to that which occurs in humans (Giguère et al., 2000). The term "metaphylaxis" can refer to a variety of therapeutic and/or preventive group-level treatments, typically when therapeutic doses of an antimicrobial are administered in large quantities to a group of animals at high risk of infection. For example, when calves arrive at a feedlot due to a high risk of bovine respiratory disease, an injectable antibiotic is administered to groups of calves (Vidaver AK et al., 2002). Antimicrobial prophylaxis in large populations is rare and typically only used to treat severe, highly contagious infections like meningococcal disease. Antimicrobials should only be administered to people who have had close, extended contact, usually inside the same family, and not to all students in the same school or classroom, even in circumstances like meningococcal disease in a child attending school (Bartlett et al., 2019).

Implications of AMR in Animals for Human Health

Even at a reasonable dosage, AMU in veterinary treatment may select the genes encoding resistance, as has been seen in human medicine. These strains, which now encode resistance characteristics, pose a risk to public health since they are highly transmissible to humans. A host of these types in dairy animals suggests that people may be at danger of contracting them. Humans can contract drug-resistant types of animal origin by straight animal communication, the food restraint (i.e., essence and dairy foods), or the environment (Carattoli et al., 2018). Numerous researchers have shown a fitting together between AMU and the prevalence of antibiotic-resistant strains in general public and animals that come into close contact (Sun et al., 2019). Any human-animal contact, whether direct or indirect, has the potential to spread antibiotic-resistant genes and strains from food faunas to general public. Agriculturalists, food supervisors, and veterinarians are among the occupationally unprotected persons who are more possible to become occupied or diseased with impervious strains (Marshall et al., 2015). Consuming tainted food merchandises, including as kernel, profit, and milk stuff, might expose consumers to resistant strains and genes. Numerous research have recently shown that a wide range of animal food products contain a significant number of resistant bacteria and the genes that go along with them (Chang et al., 2019).

Methicillin-resistant *Staphylococcus aureus* (MRSA) in animals has changed from methicillin-susceptible *S. aureus* strains of human source, according to whole-genome sequencing and phylogenetic investigation. Numerous studies have also linked the handling and/or consumption of food to the presence of identical or clonally linked bacteriological strains of animal source in human populaces deprived of any direct animal disclosure (Horigana et al., 2012). Examined the risk assessment method for ESBL-producing *E. coli*'s food chain transfer from food animals to people. The fact that farm animals commonly spread livestock-associated MRSA to exposed humans is also mentioned. Human diseases that are caused by resistant (Kock et al.,

2018) is particularly prevalent in poor nations, where there are either no recognized rules or strategies that are not followed, as well as a high prevalence of infectious diseases and relatively little health care spending. In poor nations with unregulated AMU, MDR bacteria have been secluded from food animals. Bacteria that come from animal sources are quite concerning (Aslam et al., 2019). Fig. 2 shows the conceptual representation of movement of antibiotic-resistant bacterial strains in ecosystem.

Monitoring of AMR

To combat AMR, global cooperation is necessary at the individual, community, municipal, regional, national, and international levels. To put it simply, every strategy should aim to maximize the use of antibiotics, reduce the unintended interactions between antibiotics and pathogenic microorganisms, stop the emergence of resistance strains, and treat illnesses with antibiotics sparingly in order to cure them (Laxminarayan et al., 2020). To achieve this, the WHO, FAO, and OIE established a Tripartite Alliance using the One Health approach. The Global Action Plan on AMR was released by the tripartite partnership in 2015. Similarly, in order to support the appropriate implementation of the WHO Global Action Plan in the food and agriculture sectors, FAO likewise introduced its AMR Strategy in 2016 (DiMasi et al., 2014). The WHO Global Action Plan places a strong emphasis on rising sentience and thoughtful of AMU and related AMR, increasing knowledge about AMR through appropriate surveillance and research, using antibiotics optimally and sensibly, reducing the incidence of infectious diseases, and allocating resources for research and development in order to properly prevent and contain antibiotic resistance (Elder et al., 2016). Researchers, legislators, veterinarians, businesspeople, and end employers must all work organized to manage AMR in both humanoid and veterinary contagions.

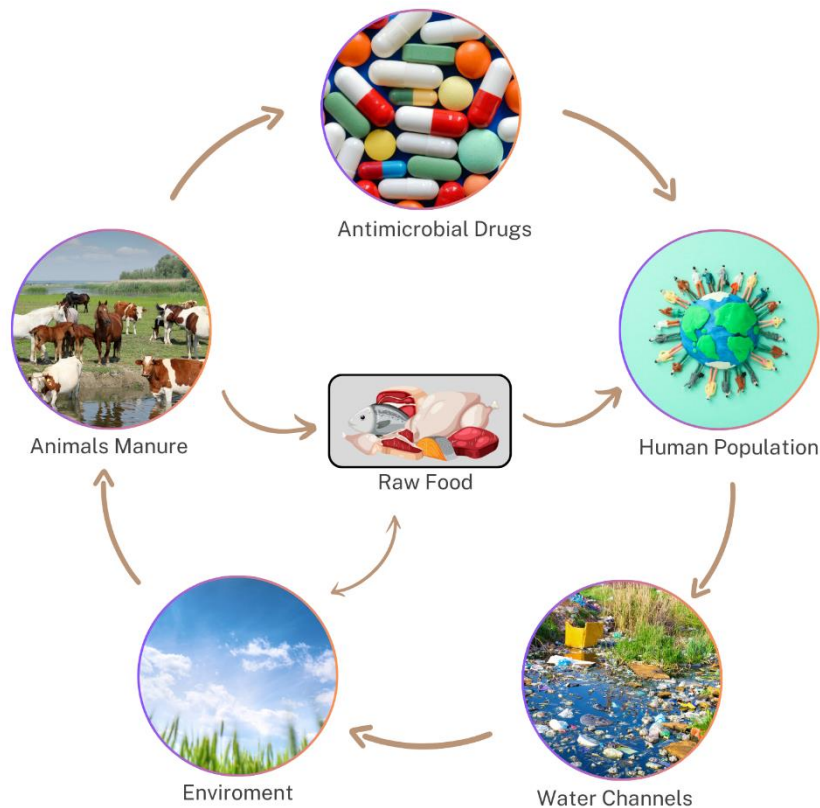


Fig. 2: This diagram illustrates the cycle of antimicrobial resistance. It begins with the use of antimicrobial drugs, which impacts human populations and contributes to the contamination of raw food. These drugs and resistant microbes can then enter water channels and the environment, eventually affecting animal manure. This manure can further spread resistance back to the environment, perpetuating the cycle.

In addition to the creation of more effective and modern antimicrobials, there are potential intervention strategies that could aid in preventing AMR. First and foremost, AMU is subject to stringent laws and oversight regarding over-the-counter sales

that do not require a prescription. Strict regulation is required to prevent irrational use caused by financial incentives for both the physician and the dispenser. Standard treatment guidelines must be updated on a regular basis to become more straightforward, locally relevant, evidence-based, and easily accessible publications. Government authorities should introduce some incentive measures, such as a pay for performance program, in addition to an impartial review response appliance on the drug recommending rates of separable consultants and healthcare services. Interventions for infection control must be reevaluated and enhanced. It is desirable to have national task groups that involve all pertinent stakeholders and have a broad, cross-sectoral coordinating role. Annual action strategies and marks in several areas, including investigation, guideline, treatment course of action, contagion control, learning, and mindfulness, should be outlined by such task groups (Cheng et al., 2014). A lack of efficient treatments for microbial diseases has resulted from the spread of AMR and the sluggish development of new antibiotics. According to estimates, the cost of a newer drug's mobility from the discovery, clinical efficacy, and safety evaluation phases to approval is currently more than double (Merino et al., 2019).

Because of this, it is now more difficult to find and release new antibiotics, and investors seeking rapid, large returns are no longer interested in antimicrobial research. To lower antibiotic resistance and hasten the discovery and distribution of safe, reasonably priced, and resistance-free antibiotic alternatives, more innovative and audacious strategies are required. The best antibiotic substitutes should be non-poisonous, easy to eliminate from the body, stable during gastrointestinal transit, easily broken down, environmentally friendly, selectively vigorous against pathogens with little to no effect on the inhabitant gut flora, increase feed efficiency and promote animal growth, and above all free of resistance, (Prachi et al., 2019).

History of AMR in Health Sector

A study of how different nations use the available scientific information to antimicrobial policy may be found in the history of struggles to speech the One Health aspects of antimicrobial usage in edibles animals (Cheng et al., 2019). Since the 1950s, both microbiological and toxicological impacts of antimicrobial usage in animals have been the focus of public health concerns (Mishra et al., 2015).

When combined by toxicological dose-response statistics from animal trainings, it is comparatively stress-free to use pharmacokinetics and pharmacodynamics to forecast rates of lessening of antimicrobial remains in eatable foodstuffs (flash, dairy products, and eggs) from treated animals. This allows one to regulate the meditations of antimicrobial residue in foods (also known as maximum residue levels, or MRLs) that are compatible with acceptable levels of risk in humans who are exposed to them (Codex Alimentarius et al., 2019). This allows for the creation of a "withdrawal time," or the interval between drug administration and the point at which drug residues in animal products are consistently below the maximum recommended level (MRL). Many years ago, regulations were established that mandated the avoidance of amounts of antimicrobial residues that were above MRL (i.e., hazardous) and potentially chemically harmful. These regulations are enforced by testing programs and penalties (Wang et al., 2019). Veterinarians and farmers who give beneficial antibiotics to animals have recognized for periods that following withdrawal periods is essential to preserving product quality. As long as the taking out periods and other label necessities were pragmatic, this forthright idea did not significantly hamper the veterinarian's contact to antimicrobials. It was also easy to interconnect and apply. However, antimicrobial confrontation is not taken into contemplation (Tang Q et al., 2000).

The suitable expansion and application of One Health tactics to discourse antimicrobial fighting in animals has been hampered by the fact that the undercurrents of antimicrobial confrontation are not nearly as expectable and that bacteriological risks cannot be assessed, achieved, and communicated in the same straightforward, easy-to-understand means as drug poisonousness (Wang et al., 2020). Antimicrobials in instinctive feedstuffs, particularly those given without a veterinarian recommendation for growth promotion, were the initial focus of concerns over the hazards of antimicrobial resistance to human health resulting from the use of antibiotics in animals. The Swann Committee suggested in 1968 that "feed antibiotics" and "therapeutic antibiotics" be regulated separately, with the latter only being used on veterinarian prescriptions (Prescott, 2017). Penicillin, tetracycline, sulfonamides, and other antibiotics with clinical uses in humans and animals were no longer accessible over-the-counter in Europe as growth promoters as a result of the United Kingdom and other European countries quickly adopting these recommendations. The European example of clearly dividing antibiotics for edible animals into those for veterinary use and those for feed flavors was not followed by the US, Canada, or many other nations (Robertson et al., 2020).

Risk to Public and Animal Health

Since it decreases the effectiveness of antibiotic therapy and to be likely to raise the harshness, occurrence, and expense of illness, antibiotic resistance is detrimental to health (Barza, 2002). There is now plenty indication that the use of antibiotics in animals contributes meaningfully to the improvement of antibiotic confrontation in human implementation microbes, particularly common enteric pathogens like *Salmonella* spp., *Campylobacter* spp., *Enterococcus* spp., and *E. coli*, as well as in

certain instances other microbes that can also be zoonotic, such as *S. aureus* (Frost et al., 2009). Antibiotic use in humans has been linked to resistance in a number of significant human pathogens that affect different body systems (Wales and Davies, 2015). Additionally, there is growing concern that bacteria exposed to biocides (such as disinfectants and antiseptics) and heavy metals in animals and environmental niches may co-select for antimicrobial resistance (Helms et al., 2020). One of the most prevalent bacteria found in human foodborne illnesses is nontyphoidal *Salmonella*. Nontyphoidal *Salmonella* gastroenteritis is thought to cause about 94 million cases worldwide each year, including 155,000 fatalities (Mollenkopf et al., 2002). In addition to other management issues including transit and mixing animals from diverse sources, antimicrobial usage in animals has been linked to resistance in nontyphoidal *Salmonella*, which is the most significant reservoir for humans (Helms et al., 2002).

In addition to being a major foundation of antimicrobial-resistant *Salmonella* infection of meat and poultry foodstuffs, carrier animals' fecal shedding may also be the cause of environmental fecal contamination of fruits and vegetables (Mølbak et al., 2005). *Salmonella* resistance to any medically significant antibiotic is a public health worry, but it is especially a concern for those that are vital to human health, including fluoroquinolones and cephalosporins (Kennedy et al., 2010) for which there may be few available treatments. Due to concerns about antibiotic toxicity, therapy may be severely limited for certain populations (such as youngsters and expectant mothers). For severe infections, beta-lactam antibiotics, such third-generation cephalosporins, are frequently the sole treatment option (Laxminarayan et al., 2013).

Conclusion

The sources conclude that antimicrobial resistance (AMR) is a serious worldwide risk to both human and animal health that requires a multifaceted approach to mitigate its impact. The sources stress the importance of responsible antimicrobial use, particularly in animal agriculture, as the overuse of these drugs in livestock has been a significant driver in the development and spread of resistant bacteria. These resistant strains can then be transmitted to humans through various routes, including direct contact with animals, consumption of contaminated food products, and through the environment. To address this challenge, the sources advocate for a One Health perspective, recognizing the interconnectedness of human, animal, and environmental health. They call for a combination of strategies, including stricter regulations on antimicrobial use, enhanced surveillance and monitoring programs, and the development of new antibiotics and alternative treatments. Ultimately, the sources argue that collaborative efforts across sectors are crucial to effectively control the spread of AMR and preserve the efficacy of antimicrobial therapies for both human and animal populations.

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