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Current Status of Antimicrobial Use in Animals

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Abstract

Antimicrobials are used for preventing and treating infectious diseases in animals and humans. In animals they are also commonly used to improve productivity and welfare. The overuse or misuse of antimicrobials can contribute to the development of antimicrobial resistance (AMR), which can have serious implications on both human and animal health. It is important to increase AMR awareness and coordinated surveillance at the global, continental, and national levels to quantify antimicrobial usage and monitor AMR spread. This will help to formulate better and effective strategies and policies for the judicious use of antimicrobials and combat AMR.

Keywords: *Antimicrobials, resistance, food animals, companion animals, surveillance, AMR*

Background

Antimicrobials are synthetic or naturally occurring compounds that can inhibit the growth or kill microorganisms, such as bacteria, viruses, fungi, or parasites. This review will focus on the use of antibiotics in animals. Antibiotics are a specific class of antimicrobials that are used to treat bacterial infections in both humans and animals. The misuse and overuse of antibiotics have led to the emergence of antimicrobial-resistant (AMR) bacteria causing major challenges to human and animal health (Byarugaba, 2004). AMR is a pressing global problem and is among the top-ten worldwide public health threats facing humanity (WHO, 2021). Few studies have attempted to estimate the impact of AMR in terms of mortality and financial burden. An analysis of the AMR burden in 2019 estimated that 4.95 million deaths worldwide were associated with bacterial antibiotic resistance which was on par with COVID-19 fatalities worldwide, and surpassed the overall global death toll from HIV/AIDS and Malaria combined (Eisinger et al., 2023). Human deaths as a consequence of AMR have been estimated to increase to 10 million globally by 2050 with a cumulative economic burden greater than $100 trillion (Dadgostar, 2019).

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AMR is known to be a natural and ancient phenomenon. This is evidenced by the detection of resistance genes in bacterial isolates from pristine environments such as caves, phytoliths (bacterial communities under rocks), freshwater lakes, permafrost, and mummies that maintain bacterial species from the pre-antibiotic era (Bhullar *et al*., 2012; D'Costa *et al.*, 2011; Perron *et al*., 2015; Santiago-Rodriguez *et al*., 2015). AMR has also been reported in animals raised under antimicrobial-free practices. Mir *et al.* (2018) reported the prevalence of AMR in third generation cephalosporins in multiple bacterial species isolated from unexposed cattle. However, over the past 70 years, the use of antibiotics in animals for therapeutic and non-therapeutic purposes has contributed to a proliferation of AMR in different bacterial species (Xu *et al*., 2022). An extensive study conducted on broiler farms in India revealed AMR in *Escherichia coli* and other pathogenic bacteria. The resistance pattern was correlated with particular-farming practices (Brower *et al*., 2017). Beta-lactam and multi-drug-resistant (MDR) bacteria have been reported in cattle, pigs, and poultry (Davis *et al*., 2018; Fischer *et al.,* 2013; Kock *et al*., 2018; Webb *et al*., 2016). Various studies have reported an increase in vancomycin-resistant enterococci (VRE) associated with the addition of avoparcin in animal feeds (Aarestrup, 1995; Aarestrup *et al.*, 1996; Bager *et al.*, 1997). Colistin-resistant bacteria were found in food samples including meat, mutton, fish, fruits, and vegetables collected from food outlets in India (Ghafur *et al*., 2019). 100% resistance to doxycycline has been reported in *Salmonella* isolates from poultry in India (Sohail *et al*., 2021). In addition to food producing animals, AMR has been reported in companion animals including cats, dogs, horses, and exotic pets (Sternberg, 1999; Li *et al*., 2020; Ferradas *et al*., 2022; Haulisah *et al*., 2022; Munoz-Ibarra *et al*., 2022).

In animals, antimicrobials are used for therapeutic, prophylactic, and growth promotion purposes. The need for food security and the demand for animal protein globally has led to the expansion of animal production where antimicrobials are utilized to maintain animal health and productivity (Van Boeckel *et al*., 2015). About 73% of antimicrobial sales worldwide are estimated to be for use in food animals (Van Boeckel *et al*., 2017). The use of antimicrobials in livestock is expected to rise by 67% globally between 2010 and 2030 (Van Boeckel *et al*., 2015). China, Brazil, India and USA, account for the majority of global antimicrobial use (Mulchandani *et al*., 2023).

Therapeutically, antimicrobials aid in the treatment of infectious diseases in both livestock and companion animals (Lloyd, 2007; Bandyopadhyay and Samanta, 2020). The prophylactic use of antimicrobials in animals is mainly implemented when there is a high risk of exposure and infection to pathogens, such as during periods of stress, transportation, or intensive production settings (Cabello, 2006). Metaphylactic antimicrobial interventions are used to prevent the spread of disease within a group by treating animals that are at risk of developing an infection due to exposure or proximity to known infected animals (Ives and Richeson, 2015; Word, 2020). Antimicrobials are also used to prevent and control diseases in animals with the aim to protect the health and welfare of animals and maintain productivity in agricultural systems (Kimera *et al.*, 2020). Certain classes of antibiotics have been used as growth promoters in livestock production (Grave *et al*., 2006; Martin *et al.*, 2015)and have been recognised as a contributor to AMR development (Castanon, 2007; Grave *et al.*, 2006).

Public health impact of AMR

Antibiotic resistance is a major problem affecting food and companion animals. Resistance to several antibiotic classes has been observed in a wide variety of bacterial species derived from different animal hosts. Many of these pathogens have zoonotic significance and are of public health relevance.

Methicillin-Resistant *Staphylo-coccus aureus* (MRSA) : *S. aureus* are commensal bacteria and have been commonly associated with skin and soft tissue infections in both humans and animals (Witte *et al*., 2007). Methicillin resistance is conferred by the *mecA* gene which is located on a mobile genetic element (MGE) named the Staphylococcal Chromosomal Cassette mec (SCCmec) that gets integrated into *S. aureus* genome (Katayama *et al*., 2000). MRSA has been reported in companion animals and livestock including cattle and swine (Weese *et al*., 2005; Cui *et al*., 2009; Faires *et al*., 2009; Fessler *et al*., 2010; Walther *et al*., 2012; Papadopoulos *et al*., 2019). Reports of MRSA transfer from human to animal and vice versa (Voss *et al*., 2005; Papadopoulos *et al*., 2019;) have raised concerns about potential transmission to humans through direct contact or foodborne routes (Cui *et al*., 2009; da Silva *et al*., 2020). Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) has been reported in companion animals such as dogs and cats (van Duijkeren *et al*., 2011) with potential zoonotic implications (Moses *et al*., 2023).

***Escherichia coli*:** Antibiotic-resistant strains of *E. coli* have been identified in companion animals, poultry, and livestock (Nielsen *et al*., 2021; Nielsen, 2021a, 2021b). Resistance has also been noticed against common antibiotics such as carbapenems, gentamycin, streptomycin, fluoroquinolones, ciprofloxacin, and colistin, raising concerns about the potential to impact human health (Poirel *et al*., 2018). Resistance to common antibiotics also raises unique treatment challenges especially in food-producing animals (Ramos *et al*., 2020).

***Salmonella enterica* and *Campylobacter* spp.** *S. enterica* and *Campylobacter* spp. are common food-borne pathogens in which AMR has been detected. *Campylobacter* spp. are mainly associated with poultry and resistance against aminoglycosides, β-lactams, chloramphenicol, cotrimoxazole, lincosamides, macrolides, quinolones, tetracycline, and tylosin have been reported (Padungton and Kaneene, 2003; Alfredson and Korolik, 2007; Koluman and Dikici, 2013) . *Salmonella* is one of the leading causes of food-borne disease and many domestic and wild animals carry *Salmonella spp.* in their gastrointestinal tracts (Bakkeren *et al*., 2019). *Salmonella* Infantis is common in cattle, swine, and poultry with many strains exhibiting MDR (Cosby, 2015; McMillan *et al*., 2019). The risks that AMR strains of these pathogens pose to human health are significant (Bell, 2002).

Extended-Spectrum Beta-Lactamase (ESBL)-Producing Entero-bacteriaceae: Common ESBL-producing bacteria include *E. coli* and *Klebsiella pneumonia* and are commonly seen in cattle and poultry (Munoz *et al*., 2006; Eibach *et al*., 2018; Tello *et al*., 2022; Tseng *et al*., 2023). ESBL enzymes confer resistance to extended-spectrum beta-lactam antibiotics, such as third generation cephalosporins. ESBL-producing bacterial strains pose challenges for treatment as they are often resistant to critical antibiotics used in human medicine (Oli *et al*., 2017).

***Enterococcus* spp.**: *Enterococcus faecium* and *Enterococcus faecalis*, can acquire resistance genes and display innate resistance to multiple antibiotics (Hollenbeck and Rice, 2012; Golob *et al*., 2019). These bacteria are commonly found in companion animals and swine posing potential risks for transmission to humans (Bortolaia *et al*., 2016).

Carbapenem-Resistant Enterobacteriaceae (CRE): Carbapenem-resistant bacteria, including CRE, have been increasingly reported in animals, especially swine and companion animals (Anderson and Boerlin, 2020; Bonardi *et al*., 2022). The emergence of CRE in animals and the potential spread to humans is alarming especially since carbapenems are broad-spectrum antibiotics that are mainly reserved for the treatment of MDR infections (Kock *et al*., 2018; Feng *et al*., 2021).

Mechanisms of antimicrobial resistance development

Although antimicrobial resistance can occur spontaneously in nature, indiscriminate use of antimicrobials can impose selective pressures leading to the emergence and rise of resistant microbial communities (Tripathi and Cytryn, 2017; Nadeem *et al*., 2020). Some bacteria are intrinsically resistant to antibiotics independent of previous antibiotic exposure or any history of the acquisition of resistance genes (Cox and Wright, 2013). Intrinsic resistance in bacteria can be conferred*via* outer membrane impermeability or by efflux pump activity (Fajardo *et al.*, 2008; Sharma *et al*., 2015). The majority of bacteria develop AMR through mutations in chromosomal DNA.

The common chromosomal mutations include mutations in the *gyrA* gene (Devasia *et al*., 2012; Woolums *et al*., 2018) and mutations in *mgrB*, *pmrAB,* and *phoPQ* genes (Olaitan *et al.,* 2014) conferring resistance to fluoroquinolones and colistin, respectively.

Another method of AMR development is the acquisition of MGE through horizontal gene transfer (HGT). Common MGEs include plasmids, integrons, transposons, and integrated conjugative elements (ICE) (Yelin and Kishony, 2018). HGT can occur through conjugation (transfer of genetic elements between bacterial cells), transformation (direct uptake and incorporation of genetic elements from the environment), or transduction (genetic elements transferred by bacteriophages). Some examples for the acquisition for AMR through HGT include: the transfer of the *tet*(O) gene to *Campylobacter coli* in turkey (Guernier-Cambert *et al*., 2021), the transfer of *mcr-8* gene on IncFII-type plasmid through conjugation in pigs and chickens (Wang *et al*., 2018), and acquisition of IncK2 plasmid carrying $bla_{\text{CMY-2}}$ via conjugation in *Salmonella* Heidelberg (Oladeinde *et al*., 2019). Integrons are an efficient means for the dissemination of resistance genes and the emergence of multiresistant strains that can capture, integrate, and express gene cassettes (Sabbagh *et al*., 2021). Class 1 integrons are highly prevalent with MDR microbes within Enterobacteriaceae and are characterized by the presence of the conserved integrase (*intl*) gene (Kaushik *et al.,* 2018). Integrons have been reported in bacteria isolated from livestock including poultry, cattle, and swine (Colello *et al*., 2018;McMillan *et al.,* 2019; Fernandez Rivas *et al*., 2021). The ability of integrons to rapidly spread resistance phenotypes can adversely impact human health (Sabbagh *et al.,* 2021). Transposons play a major role in the dissemination of resistance between a wide-range of bacterial species due to their efficient recombination activity and are considered to be natural vectors for HGT (Lipszyc *et al.,* 2022). Transposons encode transposase enzymes that catalyze MGE transposition and induce the transfer of genes that confer AMR in bacteria (Partridge *et al*., 2018). Transposons have been detected in sequenced bacterial genomes and microbial metagenomes and they can significantly affect the structure and function of bacterial genomes (Mahillon, 1998; Aziz *et al*., 2010). A wide range of transoposons have been reported in bacteria isolated from different animals (Chaudhuri *et al*., 2013; Chen *et al*., 2019; Chen *et al*., 2018; He *et al*., 2020).Integrative and conjugative elements (ICEs) are genetic elements that can integrate into host chromosomes or circularize and transfer (through conjugation) between bacterial species (Wozniak and Waldor, 2010). They play a major role in the transfer of an array of resistance genes (Woolums *et al*., 2018) and have been described to carry multiple resistance genes in livestock bacteria (Dordet Frisoni *et al*., 2013; Klima *et al*., 2016; Sun *et al*., 2022). ICEs have been commonly reported in livestock such as cattle, swine, and goats. Active surveillance is needed to monitor their spread in cattle (Andres-Lasheras *et al*., 2022).

Regulation of antibiotic usage

The use of antibiotics in animal feeds for growth promotion without a veterinarian's prescription was approved in 1951 by the United States Food and Drug Administration (FDA) (Lees *et al*., 2021). Later studies showed that antimicrobial use for the growth promotion of farm animals can result in the emergence of antibiotic resistance and contribute to the transfer of resistant bacteria between animals and humans (Smith, 1968, 1969, 1970, 1971). Recognizing these risks, it was recommended (Randall, 1969) to revoke the use of penicillin, chlortetracycline, and oxytetracycline as growth promoters without a prescription. A subsequent FDA study estimated that > 70% of food animals receive antimicrobials in animal feeds leading to considerable human health concerns in the US (Lehmann, 1972). With the growing concern about the use of antimicrobials as growth promoters in animals, several European Union (EU) countries - Sweden in 1986, Norway in 1995, and Denmark in late 1995–98, stopped antimicrobial incorporation in animal feed and this was later followed by all other EU countries since 2006 (Castanon, 2007; Van-Den Bogaard and Stobberingh, 1996).

In the United States, there are various laws, guidelines, and government agencies that regulate the use of antibiotics in animals. Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994 regulates the prescription of approved animal or human drugs for extra-label use in animals including food animals. It outlines the conditions and limitations for the extra-label use of drugs in animals, including antibiotics, and provides guidelines for ensuring the safety and efficacy of such use. Animal Drug Availability Act (ADAA) of 1996 provides provisions for the approval process of new animal drugs, ensuring their safety and efficacy for animal use. It allowed for the creation of a new category of drugs called veterinary feed directive drugs. The Veterinary Feed Directive (VFD) rule implemented by the U.S. Food and Drug Administration (FDA), regulates the use of medically important antimicrobials (antimicrobials important for human health) in or on animal feed and provides veterinarians with a framework to authorize their use for specific health applications. The VFD aims to ensure that antimicrobials are used judiciously in food-producing animals. Guidance for Industry #152 and #120, implemented by the FDA, detail veterinary oversight for the use of antimicrobials in animal agriculture. These guidelines emphasize the importance of veterinary involvement in diagnosis, prescription, and oversight to ensure the safety of human health and promote the judicious use of antibiotics.

In India, antibiotic use in animals is regulated by various laws, guidelines, and regulatory bodies. The Drugs and Cosmetics Act, of 1940 provides the legal framework for the regulation of the import, manufacture, distribution, and sale of drugs and cosmetics, including veterinary drugs. It establishes standards for the quality, safety, and efficacy of drugs, including antibiotics. The Central Drugs Standard Control Organization (CDSCO) is the authority responsible for drug regulation in India under the provisions of The Drugs and Cosmetics Act. The Drugs and Cosmetics Rules, 1945, classify drugs under specified schedules and regulate the storage and sale of drugs. Antibiotics requiring prescription-only sale are listed under Schedule H1 with the aim to ensure the supervision of a registered veterinary practitioner and responsible antibiotic use. Food Safety and Standards Act, 2006, establishes the Food Safety and Standards Authority of India (FSSAI) as the regulatory authority responsible for food safety in India. The FSSAI sets rules for antibiotic use in food-producing animals and sets standards for acceptable drug residue levels in food with the goal of ensuring consumer safety.

Global Measures to combat AMR

The issue of antimicrobial resistance (AMR) has garnered an exceptional level of worldwide focus. This increased global attention has corresponded with a rise in the deliberation of AMR across multiple multilateral organizations and international forums. The World Health Organization (WHO), European Union (EU), United Nations (UN), and G20 nations have initiated several measures to combat AMR.

Declaration on Antimicrobial Resistance: In 2016, the G20 leaders embraced the “Declaration on Antimicrobial Resistance,” which recognizes the critical necessity of tackling antibiotic resistance promptly. It emphasizes the significance of fostering responsible utilization of antibiotics in both human and animal health domains. Furthermore, the G20 acknowledged the importance of research and development endeavors aimed at addressing antibiotic resistance. Various initiatives have been implemented to stimulate innovation in the creation of novel antibiotics, alternative treatments, and diagnostic tools. The G20 countries have actively encouraged collaboration between public and private sectors to bolster research efforts in this sphere (G20, 2017).

National Action Plans: Many nations including India and the USA have developed and implementedNational Action Plans to combat AMR as per WHO initiatives (Ranjalkar and Chandy, 2019; Nunes *et al.*, 2022). These plans serve as a comprehensive framework for synchronized endeavors spanning multiple sectors, aiming to combat AMR effectively. They prioritize key areas such as surveillance, responsible utilization of antibiotics, infection prevention and control, research and development of new antimicrobials, as well as improving public awareness.

Improved Surveillance: The presence of surveillance and monitoring systems for antimicrobial usage and AMR in humans and animals play a vital role in evaluating and managing globaltrends in antimicrobial use, and susceptibility patterns of bacteria among diverse populations *(Pandey et al.*, 2022). Strong surveillance systems that can closely monitor patterns of antibiotic resistance areof utmost importance. The veterinary pharmaceutical industry also plays an active role in surveillance activities in Europe. An antibiotic susceptibility monitoring program called VetPath is currently underway throughout Europe that collects aerobic bacteria from diseased non-treated food-producing animals (cattle, swine, and poultry) across Europe to monitor AMR *(El Garch et al.*, 2016).This entails monitoring resistance in both humans and animals populations, detecting the emergence of resistant strains, and assessing the efficacy of antibiotic usage policies. The data collected through surveillance enables informed decision-making and guides interventions.

Antibiotic Stewardship Programs: The promotion of responsible antibiotic use through stewardship programs holds great importance. These programs have the objective of enhancing antibiotic prescribing practices, fostering appropriate utilization, and minimizing unnecessary or inappropriate antibiotic use across human healthcare, veterinary, and agricultural domains. This encompasses the development of guidelines, provision for education, and implementation of training initiatives targeted at healthcare professionals and veterinarians (Scott *et al.*, 2019).

Regulation and Restriction: Countries have enacted regulations to limit the use of antibiotics for the purpose of promoting growth in livestock production. The European Union has implemented regulations to limit the usage of antimicrobials in the production of food animals, which has led to a significant 35% decrease in antimicrobial use from 2011 to 2018 (Wallinga *et al.*, 2022).Recent data by the FDA reported the use of medically important antimicrobials for food-producing animals has decreased by a substantial 38% between 2015 and 2021(USFDA, 2021). In 2017, the Chinese government introduced a national action plan that has resulted in a notable 22% reduction in antimicrobial usage over the past five years (Ministry of Agriculture and Rural Affairs, 2022). In certain countries specific antibiotics have been banned for use in animal agriculture have been banned or are subject to restrictions. The Indian government has banned the use of colistin as a growth promoter in animal feed and implemented regulations that mandate veterinary prescriptions for the use of antimicrobials in food animals (Ranjalkar and Chandy, 2019). These measures are implemented with the goal of diminishing the selective pressure that fuels antibiotic resistance.

Improved Infection Prevention and Control: It is of utmost importance to enhance infection prevention and control measures in healthcare facilities, veterinary clinics, and animal production facilities (Taplitz, 2017). This encompasses the promotion of practices such as hand hygiene, appropriate sanitation, and robust biosecurity measures to effectively halt the transmission of resistant bacteria.

Research and Development: There is a growing necessity for new antibiotics to replace those that are progressively losing effectiveness. It is crucial to prioritize increased investments in research and development for the creation of new antibiotics and alternative treatments. Encouraging the advancement of innovative therapies, including phage therapy and plasma immunotherapies will help to effectively combat AMR (Bialik *et al.*, 1977; Kelly, 2000; McCulloch *et al*., 2022; Thanki *et al.*, 2023). Furthermore, providing support for research on diagnostics and rapid testing methods facilitates more precise targeting of antibiotic usage (Kaprou *et al.*, 2021).

International Collaborations: Global cooperation and collaborative research is vital for monitoring AMR spread and acquiring the necessary knowledge to check its dissemination. Organizations such as WHO, FAO, and World Organization for Animal Health (WOAH) collaborate to formulate policies, guidelines, and standards for addressing antibiotic resistance. The sharing of knowledge, resources, and best practices among countries will also play a pivotal role in this endeavor

(Sneddon *et al.*, 2022).

Public Awareness and Education: Surveys conducted among the general public regarding their awareness, knowledge, and behavior concerning AMR reveal a consistent trend of incomplete and incorrect understanding, as well as uneven usage of antibiotics and awareness of the issue of antibiotic resistance (McCullough *et al*., 2016; WHO, 2016). It is crucial to enhance public awareness regarding antibiotic resistance and encourage responsible antibiotic utilization. Public education campaigns are designed to educate individuals about the dangers associated with antibiotic misuse, the significance of completing prescribed courses, and the role of infection prevention measures in minimizing the reliance on antibiotics (WHO, 2019).

To mitigate the threat posed by antibiotic resistance and safeguard the efficacy of antibiotics for future generations, it is imperative to implement these measures while maintaining ongoing research, surveillance, and policy development efforts.

Conclusion

The future of antimicrobial use in animals will likely involve a transition towards more responsible and prudent practices. This shift will prioritize disease prevention by implementing improved animal management techniques, including vaccination, enhanced hygiene measures, genetic selection, and better nutrition. Establishing a global database for monitoring antibiotic use and resistance is crucial for estimating the emergence and dissemination of AMR. Genomics and metagenomics can be employed to swiftly profile resistance patterns, providing insights into the evolution and adaptation of organisms in diverse environments, including those containing antibiotics (McMillan *et al*., 2019; Osorio *et al*., 2023). There is a demand for targeted research in the development of broad-spectrum antibiotics with varied modes of action to effectively combat resistant strains (Ahmed *et al*., 2018). Furthermore, exploring alternative approaches like the implementation of phage-delivered CRISPR-Cas systems shows promise in combating AMR pathogens, as demonstrated by a recent study that exhibited reduced *Salmonella* colonization in chickens through the use of phages in feed (Thanki *et al*., 2023). Future research should also prioritize the investigation of alternative treatment options beyond antimicrobials, such as probiotics, prebiotics, and medicinal herbs, which can promote animal health and diminish the reliance on antimicrobials.

Global endeavors are underway to promote the responsible use of antimicrobials in animals to mitigate the risk of AMR. There exists a direct link between the use of antibiotics in humans, agri-food chains, and companion animals and the emergence of AMR. The use of antimicrobials in animals is necessary for animal welfare. Judicious use of antimicrobials and exploring alternative treatment options can contribute to controlling AMR. It is worth noting that efforts have been made to monitor and regulate antimicrobial use in animals, including the implementation of veterinary oversight and the establishment of guidelines for responsible use. To evaluate the regional and global risks associated with antimicrobial use, it is necessary to develop and strengthen monitoring systems at the global, continental, and national levels to quantify antimicrobial usage in various animals and agri-products. The ultimate objective is to strike a balance between the health and welfare of animals and the imperative to preserve the effectiveness of antimicrobials for both animal and human health.

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