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LIVESTOCK AS AN UNDERESTIMATED SOURCE OF ANTIBIOTIC RESISTANCE

S u m m a r y

Background. Antibiotic resistance (AR) has emerged as one of the most critical threats to global public health. This issue primarily results from the inappropriate and/or excessive use of antibiotics, not only in clinical medicine but also within food production systems, particularly those involving livestock. Farm animals are frequently exposed to feeds enriched with antibiotics for prophylaxis, metaphylaxis and growth promotion, exerting constant selective pressure on bacterial populations and facilitating the spread of resistant strains through the food chain, environment and human contact. This review critically examines the contribution of livestock systems to the development and dissemination of AR, integrating genetic, environmental and socio-economic perspectives. It summarizes current scientific data on patterns of antibiotic use in animal production, highlights international regulations and control strategies, and evaluates the associated health and economic impacts. Moreover, we discuss promising alternatives to antibiotics, including vaccination, probiotics, plant-derived compounds and improved biosecurity measures.

Results and conclusions. A substantial proportion of global antibiotic consumption is intended for livestock production, especially β-lactams, tetracyclines and fluoroquinolones. The continued and excessive use of these drugs in developing countries still drives resistance, which leads to serious health and economic consequences. Strengthening coordinated "One Health" policies harmonization and sustainable farming practices is therefore essential to mitigate this growing global threat.

Key words: Foodborne pathogens, horizontal transmission, resistance genes, selection pressure, zoonotic diseases

Introduction

The era of antibiotics (ATBs) is almost over due to growing antibiotic resistance (AR) and public health concerns [55]. Farm animals are a critical component of this system, as they are frequently exposed to a wide range and of ATBs [197]. Livestock farms are even referred to as hotspots in antimicrobial resistance (AMR) prevalence, development and transmission [69] for therapeutic, growth promotion, prophylactic

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and metaphylactic purposes [108]. The misuse and overuse of antimicrobials in food-producing animals are now recognized as major drivers of antimicrobial resistance (AMR) at the human–animal–environment interface [188] leading to a worldwide rapid increase in this issue [154]. Without targeted interventions, the global livestock antibiotic use could rise to 143,481 tons, with an increase of nearly 30 % by 2040 [63]. Although regulatory bans – such as the EU prohibition of antibiotic growth promoters in 2006 – have shown partial success, resistance persists due to residual ARG pools in microbial communities and environmental reservoir [66]. Well before that, Sweden had prohibited the use of AGPs since 1986 [64, 65] and Denmark in 1998 [132]. This was followed by a decrease in AMR in animals [43]. The prohibition on the sub-therapeutic use of ATBs in animal feed resulted in decreased animal production [153]. This has been due to the higher rates of infections in livestock and has also increased the risk of food-borne infections in consumers [132]. The WHO thus recently recommended avoiding the use of medically important ATBs for growth promotion or for prevention of infectious disease that have not yet been clinically diagnosed in food-producing animals [188]. If an effective action plan is not implemented, the annual death rate is expected to reach 10 million deaths per year by 2050 [173]. Understanding the link between human, animal, plant health and the environment is crucial to inform the implementation of new regulations and practice regarding the use of ATBs in agriculture application [197]. Understanding the genesis of AR associated with livestock and its ability to transmit to humans is essential to managing this public health risk.

ATB use in livestock

Since the 1940s, livestock feed has been supplemented with non-therapeutic doses of ATBs, as they were found to improve meat production [92]. They are used for a number of reasons: as therapeutics, metaphylactics, prophylactics and growth promoters [219], thus maintaining financial [102], food security and safety, as well as animal health and welfare [56]. Nowadays, the use of ATBs has become a central component of modern practices, since the world population is increasing at an unprecedented rate, leading to increased pressure on the agricultural industry to increase production [197] associated with modern animal practices and for covering the high demand for animal protein for human consumption [198]. ATBs improve feed conversion, animal growth and reduce morbidity and mortality due to clinical and subclinical diseases [1]. The most commonly used veterinary ATBs are β-lactams, tetracyclines, fluoroquinolones, sulfonamides and macrolides [189]. In the survey of [207], tetracyclines, particularly oxytetracycline, and penicillins were the most commonly prescribed ATBs in animals due to their availability and familiarity among the animal health workers. In turn, this use is contributing to AR due to the presence of ATB residues in animal-derived products (e.g. muscles, kidneys, livers, fat, milk and eggs) [171]. Some banned drugs in

human medicine used in veterinary medicine with no allowable extra-label uses in any food-producing animal species are chloramphenicol, clenbuterol, diethylstilbestrol, fluoroquinolone - class antibiotics, glycopeptides - all agents, including vancomycin, medicatedfeeds, nitroimidazoles, including dimetridazole, ipronidazole, metronidazole and others, nitrofurans–all agents, including fura-zolidone, and nitrofurazone [130]. Table 1 reports the most often used ATBs in breeding and veterinary according to the literature. It is clear that tetracyclines and β-lactams are the most commonly used ATBs in breeding, as well as in veterinary medicine, despite the fact that chlortetracycline was proven to increase the abundance of ARGs in pig feces and defined the incidence of ARGs in broiler chickens feces [155]. Some countries have banned the use of certain ATBs in animals; Sweden (1985), the use of avoparcin (1995) and virginiamycin (1998) in Denmark, the avoparcin (1997) banned by the European Union (EU) and Spiramycin, Tylosin phosphate, virginiamycin and Zinc bacitracin (2005), the FDA enrofloxacin and Australia banned the Quinolones (2004) [18].

Table 1. Most ATBs used and prescribed in livestock farming and clinical veterinary

ATB	Class	Purpose of use	Field	Region	Reference
Amoxicillin Penicillin	β-lactams	Treatment, prophylaxis	Veterinary clinics	Pakistan	[172]
Amoxicillin trihydrate Chlortetracycline, Oxytetracycline, Doxycycline Colistin Tylosin, Erythromycin Ciprofloxacin, Enrofloxacin Penicillin Bacitracin Trimethoprim Sulfamethoxypyridazine, Sulfamethazine Neomycin, Streptomycin, Gentamycin Furaltadone Amoxicillin trihydrate + colistin sulfate	Aminopenicillins Tetracyclines Polymyxins Macrolides Fluoroquinolones Penicillin Polypeptides Trimethoprim Sulfonamides Aminoglycosides Nitrofurans derivatives Aminopenicillins / polymyxins	Growth promoters, treatment,	Poultry	Pakistan	[79]
Chlortetracycline and oxytetracycline Tulathromycin Ceftiofur	Tetracyclines Macrolides cephalosporins	Treatment	Cattle	Australia	[9]
Oxytetracycline Gentamicin Enrofloxacin Tylosin Ceftriaxone Tetracyclines Aminoglycosides Cephalexin	Tétracyclines Aminosides Fluoroquinolones Macrolides Cephalosporines Tetracyclines Aminoglycosides Cephalosporins	Growth promoters, prophylaxistreatment	Poultry	India	[181]

Levocin, Enrofloxacin Oxytetracycline Penicillin Gentamicin Trimethoprim Sulfamethazine	Fluoroquinolones Tetracyclines β-lactams Aminoglycosides Diaminopyrimidine Sulfonamides	Treatment	Cows, goats, sheep, equines	Peru	[21]
Oxytetracycline	Tetracyclines	Treatment	Pigs	Denmark	[75]
Oxytetracycline, Penicillin Streptomycin Enrofloxacin	Tetracyclines β-lactams Aminogly-cosides Fluoroquinolones	Prophylaxis	Cattle	Kenya	[108]
Monensin	Ionophores	Growth promoter	Cattle	Australia	[1]
Ceftiofur	Cephalosporin	Treatment	Calves, rabbits, poultry	China	[131]
Tilmicosin	Macrolide	Treatment	Pigs	China	[123]
Penicillin Amoxicillin Oxytetracycline Lincomycin Spectinomycine	β-lactams Tetracyclines Lincosamides Aminocyclitols	Cattle	during or after surgery	Belgium	[50]
Oxytetracycline Sulfadrugs	Tetracyclines Sulfonamides	Treatment	Veterinary clinics	Ethiopia	[60]
	β-lactams Tetracyclines	Treatment	Cattle, sheep	UK	[54]
Amoxicillin, Penicillin, Ampicillin Amikacin, Gentamicin, Metronidazole Erythromycin Enrofloxacin Rifampin	β-lactams Aminogly-cosides Nitroimidazoles Macrolides Fluoroquinolones Rifamycines	Treatment	Equine		[98]
Acetylkitasamycin	Macrolides	Treatment	Pigs	China	[88]
	Tetracyclines Sulfonamides β-lactams Lncosamides Macrolides	Treatment	Poultry	Taiwan	[36]
Nitroimidazole Sulfonamides Oxytetracycline Trimethoprim Nitrofurazone Penicillins	Nitroimidazole Sulfonamides Tetracy-clines Diaminopyrimidine Nitrofurans β-lactams	Treatment	Bovine, avian, equine	Bhutan	[201]
Oxytetracycline Penstrep Sulfonamides	Tetracyclines β-lactams +aminoside Sulfonamides	Treatment	veterinary clinics	Ethiopia	[196]
Streptomycin, Gentamicin Penicillin , Amoxicillin Sulfadimidine, Sulfadiazin Trimethoprim	Aminosides β-lactams Sulfonamides Diaminopyrimidines	Treatment	Poultry	Bangladesh	[39]

Current regulations on the use of ATBs in livestock

The use of ATBs in food animals is primarily associated with sub-therapeutic doses as growth promoters or substituting more expensive hygiene measures [192]. Nevertheless, the antimicrobial stewardship for the selection, dosage and duration of antimicrobial treatment is critical to reduce AR occurrence in the livestock industry [115]. According to [44], institutions related to food production from animal sources are responsible for establishing rules on the use of medicine in animals and plant production, from marketing authorization to pharmaco-vigilance. However, on a global scale, various organizations, namely the World Health Organization (WHO), the Food and Agriculture Organization (FAO), World Organization for Animal Health (OIE), the European Union (EU), the European Centre for Disease Prevention and Control (ECDC), the European Medicines Agency (EMA) and governments across the globe, commit to develop guidelines and policies to limit the ATB use based on scientific evidence [203]. For instance, the OIE International Committee unanimously adopted the list of antimicrobials of veterinary importance at its 75th General Session in May 2007 [141]. Likewise, the EU requires that ATBs should not be used for prophylaxis other than in exceptional cases only for an individual animal and for metaphylaxis only when the risk of spread of an infection or of an infectious disease in a group of animals is high and where no appropriate alternatives are available [61]. For its part, the FAO recommends the use of non-antimicrobial drug feed additives, for replacing the antimicrobial growth promoters' use without long-term adverse effects on livestock health, welfare and productivity [65]. Nevertheless, legislative policies can be improved and combined with other strategies to promote behavior change in the use of ATBs in livestock production and influence stakeholders [144]. Complying with regulations governing the use of ATBs in livestock farming could reduce the number of resistant strains, which is very important for all stakeholders, especially consumers.

Routes of administration and dosage regimens

Whatever the route, careful administration of drugs is very important in all species [198]. ATBs used for veterinary therapy are often administered orally through feed and drinking water, or by injection, in order to relieve animals' suffering and reduce production losses [90, 152], via intramuscular, intravenous, parenteral [90], intramammary or intrauterine forms [56]. Moreover, they are injected intra-articularly by equine veterinarians, either prophylactically or therapeutically when other drugs are administered for osteoarthritis or septic arthritis [156]. Not all ATBs can be administered in the same dose to all animals [90]. Appropriate dosing of ATBs is the key to control or clear bacteria on the site of infection [7], which could alleviate the resistance and ensure the antibacterial effect [131]. Thus, pharmacokinetic and pharmacodynamic properties are very important in the determination of dosing regimens of drugs [89].

However, if certain animals in livestock are sick, the whole animals need to be treated to prevent the spread of disease and ATB treatment is usually given in high doses, intermittently within a relatively short period of time [90]. Nevertheless, veterinarians could modify a dose to improve treatment effectiveness without significantly altering the level of the selection of resistant bacteria [75].

Figure 1. Global Timeline of Antibiotic Regulations in Livestock

Diseases commonly treated with ATBs

More than two-thirds of emerging infectious diseases in humans today are known to be of animal origin [72]. The most prevalent infectious diseases in livestock are respiratory disease, mastitis and enteric disease involving E. coli and Salmonella [90], in addition to arthritis, and other bacterial infections [18]. Some animal diseases, such as contagious bovine pleuropneumonia, are notifiable diseases because they have a high potential for dissemination and are particularly serious, capable of spreading beyond national borders, have serious socio-economic or health consequences and have a very significant impact on international trade in animals and animal products [213].

Well documented zoonotic diseases are anthrax caused by *Bacillus anthracis*, bovine tuberculosis by *M. tuberculosis*, brucellosis by *Brucella abortus*, and hemorrhagic colitis by *E. coli* [45], in addition to mastitis often reported in the literature since it is one of the most common and prevalent diseases affecting the dairy sector [15]. Table 2 summarizes the diseases commonly encountered in livestock.

Table 2. Diseases commonly treated with ATBs

Disease	Bacterial species	Livestock	ATBs	Reference
Mastitis	*S. aureus, Mycoplasma spp., S. uberis, S. dysgalactiae, E. coli, K. pneumonia, A. pyogenes,* different *Streptococci, C. bovis* and *M. bovis*	Cattle	Tilmicosin	[55]
Mastitis	*S. aureus* and *S. uberis*	Cattle	Benzylpenicillin	[163]
Anthrax, pneumonia, brucellosis	*Bacillus anthracis, Actinobacillus pleuropneumoniae Pasteurella multocida, Streptococcus pneumoniae,*	Cattle, poultry, sheep and goats	Worldwide	[148]
Bovine tuberculosis, Brucellosis, Leptospirosis, bovine pleuropneumonia, pneumonia, diarrhea, Digital dermatitis	*Mycobacterium bovis Brucella abortus, B. melitensis, B. suis Leptospira sp Mycoplasma mycoides Salmonella spp.* and *Campylobacter spp., Treponema sp.*	Cattle, buffalo and poultry	Worldwide	[5]
Mastitis and diarrhoea	*S. aureus, Streptococcus agalactiae, E. coli, Streptococcus uberis, Mycoplasma spp., Salmonella spp., C. perfringens*	Cattle	Tetracycline, streptomycin, penicillin, enrofloxacin and cephalexin	[108]
Keratoconjunctivitis	*Mycoplasma conjunctivae*	Sheep and goats	Gentamycin	[180]
Diarrhea	*E. coli, Shigella spp., S. enterica, V. cholerae,* and *Yersinia spp.*	bovine and porcine	Madagascar	[29]
Mastitis, Tuberculosis,	*Staphylococcus aureus, Mycobacterium bovis*	dairy cows	Worldwide	[69]
Contagious bovine pleuropneumonia	*Mycoplasma mycoides,*	Cattle, sheep and goats	Ghana	[138]
Ehrlichiosis and anaplasmosis, bartonellosis	*Anaplasma ovis, Ehrlichia Dermacentor nuttalli Ixodes persulcatus Bartonella spp. Francisella, Leptospira, Rickettsia*	Sheep and goats, cattle, camels	Mongolia	[35]
Paratuberculosis	*Mycobacterium avium subsp. paratuberculosis*	Cows	United Kingdom	[199]
bovine respiratory meningoencephalitis	*Histophilus somni*	Cattle	Australia	[9]

Acquisition of antibiotic resistance

AR is the situation where pathogens/microorganisms develop resistance to an initially effective drug that no longer works against the same pathogen [47]. Whenever antimicrobials are used, bacteria inevitably develop resistance mechanisms [43] as a result of spontaneous mutations in chromosomal genes [28] or more commonly via mobile genetic elements, such as plasmids and transposons, often carrying genes associated with AR. Nordhoff et al. [137] reported that plasmids may be transmitted between strains isolates from animals and humans. Understanding their acquisition and maintenance is central to predict the emergence and evolution of resistant pathogens [127]. The genetic resistance determinants located on those mobile elements can be transferred horizontally not only between the same species but also to other species [46] by conjugation, transformation and transduction [235]; a novel plasmid carrying the erythromycin resistance gene demonstrated capacity to confer resistance to erythromycin in other microbes from different genera [1]. Therefore, in a microbiologically rich environment, it may be possible to exchange genetic material between pathogenic, potentially pathogenic and non-pathogenic bacteria [46] because under high bioaerosol density this promotes close interactions within microbial communities, facilitating the transfer of ARGs between pathogenic and non-pathogenic bacteria [70]. The acquisition of acquired resistance mechanisms through horizontal transfer has been shown to occur in different stress conditions, such as alterations of ion concentrations, extreme temperature changes, starvation conditions or exposure to ATBs [80]. Some bacteria, including lactobacilli, become resistant not only via the acquisition of resistance genes from other organisms through horizontal transfer but also by de novo mutation [46], since AR can cause the appearance of new mutations in animals, plants and humans [106]. In general, this gene transfer alters the ATB action via one of these mechanisms, i) modifications of the antimicrobial target, ii) a decrease in the drug uptake, iii) activation of efflux mechanisms to extrude ATBs, or iv) changes in important metabolic pathways [133].

Factors influencing the development of AR

Poor management, inadequate prescription and use of ATBs for whatever purpose play a major role in the dissemination and selection pressure of resistant strains and their proliferation;

- The misuse of ATBs: Generates unnatural selective pressure, which is detrimental to human and animal health [173]. The widespread and expanding use of antimicrobials can lead to the development of drug-resistant bacteria in animal guts, and these resistant bacteria can spread to humans [155] limiting the availability of treatments [161]. The ATB misuse and overuse in animals were identified as the main driving forces behind the development of antimicrobial resistance (AR) in

bacteria [94], this more often involves low- and middle-income countries, where farmers self-diagnose and administer ATBs without proper guidance from a veterinarian and the use of falsified or sub-standard antimicrobials has been reported due to poor regulatory systems [108]. Even repeated exposure to low doses of antimicrobial agents (the context in which growth-promoting antimicrobials and prophylactics are administered) creates ideal conditions for the emergence and spread of AR in animals [198]. Administering ATBs without a clear indication is a good example of common misuse [171], some people who lack clarity in distinguishing between ATBs and antimicrobials, believe that ATBs can hasten recovery of cold, cough and other diseases caused by common flu virus [175]. Inappropriate prescribing of ATBs by prescribing them when they are not needed or selecting inappropriate ATBs or using the wrong dose and duration contribute significantly to promoting AR [171].

- Farm management practices and biosecurity measures: Farm management practices play a significant role in the development and spread of AR. One of the wrong practices in breeding is that farmers who stockpile antimicrobials on their farms may have better access to them and may therefore self-prescribe antimicrobials without reservation, which is a common problem in developing countries [104]. In a survey conducted by [207], it was noted that a quarter of animal health workers mentioned that ATBs could be used in all types of infection, even if ATBs were not necessary. On the other hand, livestock farms discharge ARG-containing bacteria effluents via drainage, treated wastewater and solid waste into the environment [235]. Unsanitary conditions that increase the risk of infections and the lack of isolation of sick animals that can transmit pathogens to healthy animals encourage the frequent use and dependence on ATBs. In addition, the use of water or feed contaminated with ATBs or resistant bacteria contributes to the spread of resistance. Finally, the limited use of vaccines leads to greater reliance on ATBs.

Transmission of ATB-resistant bacteria from livestock to humans

AR bacteria have the potential to enter human bodies through various means, including ingestion of contaminated food [235]. Nevertheless, the transfer of ARGs is a multifactorial issue involving complex interactions between the environment, humans, animals and plants [197]. This transfer can occur through several pathways; by the consumption of contaminated animal products, which starts during slaughter, and spreads throughout the food supply chain [187], or by direct contact by handling animals, especially their bodily fluids (urine, feces, saliva), and cleaning animal enclosures or managing manure. Dust and aerosols on farms and in abattoirs which may also play a role as vehicles that transport resistant bacteria and are inhaled by animals and humans [178].

Transmission via food products

AR strains propagated livestock pose a threat to animals and could be widely disseminated via the food chain. The commensal bacteria present in livestock can acquire ARGs and may accelerate the cross-sectorial AR problem by the transmission of resistant microorganisms to humans through livestock products [203]. Globally, 73 % of all ATBs sold are used in food animals and their extensive use is considered a key driver of antimicrobial resistance development in animals and spread to humans [192]. Many of the bacteria (such as *Campylobacter* and *E. coli*) carried by animals are frequently antimicrobial-resistant and can contaminate our food supply, such as through slaughtering and processing [210]. Reports of recent outbreaks in the US found *Salmonella sp*. associated foodborne pathogens in various food products, including chicken, ground beef, pork and turkey [142]. The spread of *Salmonella* resistant to ciprofloxacin has led to serious human infections. This resistance is due, for instance, to the excessive use of fluoroquinolones, particularly enrofloxacin, in food-producing animals oriented to human consumption [106]. Poultry is considered to be a major source of these foodborne pathogens [126]; commensal microflora of the gastrointestinal tract of poultry are frequently present in fresh poultry meat products and may serve as reservoirs of resistant genes that could be transferred to bacterial pathogens of people [46]. Generally, food-producing animals may act as potential reservoirs of ARGs that are transferred to and survive in their gut microbiota and then are transferred to human or animal pathogens that enter the gut via the food chain [87]; another transmission route that occurs when ATB residues are present in foods such as milk, eggs and meat [18] which will favor the selection pressure procedure of resistant strains within these products.

Public health implications of AR

Risks associated with zoonotic transmission of ATB-resistant bacteria

Zoonoses is a great public health concern and a direct human health hazard that may even lead to death [162]. As pathogens sometimes jump between species, this can affect the health of humans as well as livestock [134]. Zoonoses are caused by pathogens that can infect animals and humans, causing outbreaks in humans, they account for 70 % of emerging infectious diseases [220], otherwise said, more than half of the microbial diseases affecting humans (61 %) are attributed to zoonotic transmission [174]. Workers in constant contact with animals (veterinarians, veterinary students, farmers, slaughterhouse employees and farm workers) are often exposed to zoonoses, which was confirmed by [85], who found that infections with the multidrug-resistant *Salmonella* Newport strain were significantly associated with dairy farm exposure. Animals are recognized as the routes of the transmission of many bacterial pathogens

including *Enterococcus spp.*, *E. coli*, *K. pneumoniae*, MRSA, vancomycin-resistant enterococci, *A. baumannii*, *P. aeruginosa* having significant multidrug-resistance profiles, thus limiting treatment options, increasing and prolonging morbidity [129] and increasing mortality rates; the zoonotic pathogen, *Streptococcus suis*, can cause human death [88]. Outbreaks of salmonellosis, campylobacteriosis and *E. coli* infections have been reported in association with direct contact of animals (calves, lambs, goat kids and live poultry, etc.) [78]. Bacteria from animal sources, mainly nontyphoid *Salmonella enterica* serovars, *E. coli*, *Campylobacter spp.* and vancomycin-resistant enterococci, might account for 3.88 % of the human AR problem [178]. Bacteria as ESBL-producing *E. coli* and AmpC β-lactamases, MRSA and *K. pneumonia* are shared between humans and animals [49]. The emergence of various strains of MRSA from farm animals in Denmark, Europe and the Netherlands was found to be transmitted within human's populations [45]. Likewise, a study from Ghana revealed that locally raised poultry and hospitalized patients share the same ESBL-producing *E. coli* lineages, suggesting the transmission or spread of global clones between animals and humans [146]. Moreover, livestock-associated (LA) MRSA has been associated with increasing numbers of human infections, even without direct contact with livestock [127], and clinical pictures, with hospitalized patients, correspond to those caused by *S. aureus* and hospital-associated MRSA [42], whereas infections with pathogens, which include *Enterococcus*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *E. coli*, known for their widespread β-lactamase-mediated resistance to ATBs, are often linked to a higher risk of death [19]. Infections with the multidrug-resistant *Salmonella* Newport strain were significantly associated with dairy farm exposure [85].

Transfer of resistant genes bacteria to humans

There is considerable evidence that zoonotic pathogens carrying antimicrobial resistance genes are shared between animals and humans [85]. The presence of these genes in livestock products can provide information on their two-way transfer between humans and animals. Some ARGs were reported to be widely shared between humans, such as colistin-resistant gene (*mcr-1*) and tigecycline-resistant gene *tetX*, [49]. Young et al. [223] reported the co-occurrence, in both human and animal samples, of genes (*blaSHV*-1, *QnrS*, *TetA*, *tetB*, *aacC2* and *aadA1*) which encompass resistance to a broad range of drug classes, including aminoglycosides, β-lactams, tetracyclines, macrolides, and fluoroquinolones. Similarly, the analysis of the resistance genes present in LA-MRSA isolates has revealed novel and/or resistance genes that have been rarely detected in staphylococci so far; including the phenicol exporter gene *fexA*, the multiresistance gene *cfr*, the tetracycline resistance gene *tet(L)*, the trimethoprim resistance gene *dfrK*, the macrolide–lincosamide–streptogramin B-resistance gene *erm(T)*, the lincosamide–streptogramin A-pleuromutilin resistance genes *vga(C)* and *vga(E)*, and

the apramycin resistance gene *apmA* [99]. Tigecycline resistance genes (*tet(X4), tmexCD1-toprJ1*) were abundant in chicken, pig and cattle feces [68], although tigecycline is a last-resort ATB against severe infections caused by extensively drug-resistant bacteria [83]. Bovine mastitis is recognized as the root cause of antimicrobial compound use in dairy farms worldwide, leading to the potential selection and introduction of AMR-encoding genes in milk [170]. Thus, staphylococcal enterotoxin genes *sea, seb, sec, sed, seg* and *sei* in *S. aureus* [120] and an abundance of β-lactamases (*blaTEM*) resistance genes [160] were isolated from animal milk in China.

Impact of the presence of ATBs in animal products

Due to intensification combined with high levels of ATBs used in farming, particular concerns about livestock as reservoirs of ATB-resistant human infections are imposed [127]. ATBs are among the most frequently detected group of potentially toxic pharmaceuticals [38]. Many ATBs used as therapeutics and growth promotion agents in animals can lead to ATB residues in animal-derived food [37] such as milk, egg and meat [18]. These residues may lead to various toxic effects in humans and present a threat to health [102] resulting in the production of a large number of drug-resistant strains, loss of resistance to certain diseases or toxic effects on the human body due to large accumulation [194]. Additionally, antimicrobials above the regulatory concentration in food items could result in either allergic reactions, disruption of normal intestinal human flora in the intestine, blood dyscrasias and cancer [20]. They negatively influence the immune system, with cinogenic effects (sulfamethazine, oxytetracycline and furazolidone), damage kidneys (gentamicin), increase the frequency of mutations, damage the liver, damage the bone marrow (chloramphenicol) and affect the human reproductive organs [18, 195]. Tetracyclines have been associated with allergies, rashes, phototoxicity, gastrointestinal problems, tooth discoloration in young children, delayed fetal development and proinflammatory, cytotoxic, and immunopathological effects [130]. In the study of [229], tetracycline, doxycycline (133.3 μg/kg: higher than the maximum residue limit of 100 μg/kg) and ettilmicosin were detected in pork products, enrofloxacin, ciprofloxacin, ofloxacin in chicken and enrofloxacin, ciprofloxacin, florfenicol (113.6 μg/kg) and sulfamethazine in eggs despite the fact that their detection is prohibited in egg samples. On their part, Soares et al. [189] detected monensin, doxycycline, oxytetracycline, chlortetracycline, chloramphenicol, florfenicol and thiamphenicol in many animal products.

Environmental spread

Novel AR factors could potentially emerge anywhere, at any time [22]. Livestock breeding has become a fixed and unavoidable source of ARGs in the environment [118]. ATB-resistant bacteria and genes have been widely found in animal feces, farm

wastewater and farm air (Table 3). The content of resistance genes in industries associated with animal husbandry is much higher than that in hospitals, soil, groundwater and surface water [95]. Animal husbandry practices such as high stocking density or poor ventilation promote the spread of infectious diseases and additionally weaken the immune system [94]. AR genes could spread among various farming environmental media through adsorption, desorption and migration [206]. After reaching the environment, AR bacteria can colonize humans via several routes by direct contact, e.g. by handling manure, by contact with contaminated water or by aerosol formation during manure spreading [84], knowing that air/dust can act as an important transmission vector of AR bacteria and ARGs in animal farming environments [170]. Fertilizers from fecal origin (such as manure) have already been identified as a route of entry of veterinary important ATB-resistant bacteria and resistance genes into the environment [84, 153]. Therefore, the application of manure to agricultural land is a potential route for the transmission of ATB-resistant bacteria from livestock to crops, animals and humans [197], it also poses potential human health risk when it is routinely applied to the land as a fertilizer [134]. The presence of ATBs in such environmental media at specific concentrations leads to an increase in bacterial resistance [232]; isolated bacteria of a soil fertilized with cattle manure showed 70 % resistance to ampicillin, penicillin, tetracycline, vancomycin and streptomycin [27]. The use of ATBs in animal husbandry is considered the most important factor for the selection of ATB-resistant bacteria in manure [84], creating a selective pressure for ARGs in the gut microbiome of animals, which is then excreted in the feces. It was reported that after ATB administration, between 30 % and 90 % of the initial dose administered is excreted in urine or feces as active metabolites or in unmetabolized form [152]. Then, these residues will be released in sediments or in aquatic systems, thus the emergence of a resistant pathogen could occur distantly from the original place where such drugs were prescribed and a long time after the original selection pressure [43]. ATB residues can be taken up by plants [134], even vegetables which were grown on manured fields contained increased abundances of resistance genes not only at harvest, but also on retail-level [84]. Since most ATBs are used in both human and animal interfaces [175], there was a development of resistance against most critical and remarkably important ATBs (streptomycin, gentamicin, ampicillin, sulfamethoxazole, sulfisoxazole, trimethoprim, chloramphenicol, spectinomycin, tetracyclines) in animals, as well as in humans [146].

Table 3. Some resistant bacteria found in livestock products and livestock environment

Bacteria	Antibiotic	Sample	Livestock	Reference
Bacillus Pseudomonas	Monensin, cefotaxime and ampicillin,	Fresh and composted manure	Cattle	[1]
E. coli S. enterica C. jejuni, Campylobacter coli	Colistin, Ampicillin, oxytetracycline tetracycline, sulfamethoxazole-trimethoprim, nalidixic acid chloramphenicol, ampicillin, streptomycin amoxicillin, erythromycin, ciprofloxacin, norfloxacin and azithromycin	Fecal samples	Poultry	[39]
Methicillin-resistant *S. aureus* (MRSA)	Tetracycline, fusidic Acid, Erythromycin, Clindamycin, Cefoxitin Penicillin	Nasal prelevement Animal products: meat (chicken, pork, beef) and eggs	Cattle, buffalo, pigs, goats, poultry	[114]
S. typhimurium	Ampicillin	livestock and food products thereof	broilers	[34]
E. coli	Tetracycline, trimethoprim/sulfamethoxazole, ampicillin	Fecal samples	pigs and poultry, goats, bovine, sheep	[145]
E. coli	Tetracycline	Cow feces, water samples from a drainage pit, wastewater processing tank	Cow	[191]
E. coli	Tetracycline, ampicillin and enrofloxacin, amoxycillin-clavulanic acid	Faecal sample, boot sock	Poultry	[128]
Enterococcus faecalis, E. faecium, E. casseliflavus and E. hirae.	Oxacillin, vancomycin, linezolid	Milk	Sheep	[57]
S. aureus	Erythromycin, clindamycin/norfloxacin, tetracycline, gentamicin	Milk	Cow	[120]
Enterococcus faecalis	Nisin	Milk	Buffalo	[113]
S. aureus, S schleiferi, S. intermedius, S. xylosus, S. haemolyticus, S. epidermidis	ampicillin, cefoxitin, amoxicillin–clavulanic acid, cefuroxime, clindamycin, chloramphenicol, vancomycin	Milk	Cow	[3]
E. coli	Colistin	Meat	Poultry	[186]
Enterococcus faecalis, E. faecium	Erythromycin, tetracycline, ciprofloxacin, chloramphenicol, linezolid, ampicillin and vancomycin	Meat	Beef, chevon and mutton	[10]

Economic impact

AR causes significant challenges increasing morbidity and mortality, with serious implications at individual, social and economic levels [43]. It is suggested that 3.5 % of global admissions include a resistant infection [2017]. Estimates state that AMR might result in a 1 % yearly economic decline, with this number reaching as high as 5 ÷ 7 % in underdeveloped nations. This would result in a loss of between 100 and 200 trillion euros globally [81]. The World Bank estimates that AR could result in USD 1 trillion additional healthcare costs by 2050, and USD 1 trillion to 3.4 trillion gross domestic product losses per year by 2030 [212], while the spread of resistant pathogens from

livestock to humans, could cost up to USD 5.2 trillion by 2050. On the other hand, the AR could result in production losses in the livestock sector equivalent to the consumption needs of 746 million people, or more than two billion people in a more severe scenario by the same year [218]. Increased resistance leads to higher healthcare costs [47] associated with more expensive antibiotics, specialized equipment, longer hospital stay and isolation procedures for patients; in the European Union, Iceland and Norway, the burden of additional hospital care costs due to antibiotic-resistant infections was estimated to be approximately s1.6 billion Euro in the year 2012 [8]. The economic impacts are not only in monetary terms but also include the social and labor-loss effects including death, loss of productivity [159], therapeutic failures and treatment substitutions, apart from a broader economic perspective where other societal impacts regarding equity and death, development and food security were described [126].

Epidemiological evidence linking ATB use in livestock to human infections

Antimicrobial use on farms clearly contributes to the emergence of resistance and poses a human public health risk [85]. There is a correlation between the quantity of antimicrobials used in animals and the development of resistance in bacteria present in these animals for a range of combinations of specific pathogens, commensals, antimicrobial substances and livestock species [23]. Ardakani et al. [14] reported that there was a positive correlation between antimicrobial use in farmed animals and AR in humans; for a 1 % increase of antimicrobial use, AR in humans increases by 0.04 %. [58] found that that ATB use in cattle and poultry was positively associated with human AR. For example, *E. coli* resistance to Aminopenicillins was found at 73.3 % (extremely high), while *E. coli* resistance to Glycylcyclines, banned in animal farming, was found at 0.78 % (very low). For *S. aureus*, resistance to Macrolides represents 56.0 %, considered very high, while resistance to Vancomycin, a more recent ATB banned in animal farming, is very low (0.22 %) [14]. For their part, [97], showed that high farm level use of tetracycline and sulphonamides correlated with a high level of resistant isolates to these ATBs, moderate usage of gentamicin and ciprofloxacin correlated with moderate percentage of *Salmonella* resistant isolates to the same ATBs, and low usage of trimethoprim correlated with a low number of resistant isolates to this drug.

The fate ATB residues in the environment

Residual ATBs, released by humans and animals, could have adverse effects on the environment [106]; ATBs from a wide range of classes, including macrolides, lincosamides, sulfonamides, thiamphenicol analogs and fluoroquinolones have been detected in agroecosystems [187]. Generally 60 – 90 % of veterinary ATBs do not undergo metabolism after administration to livestock [209]. Consequently, a considerable amount of ATBs is excreted in the feces as either metabolites or in their original form

still-active [235], which could interfere with the recycling of nutrients in the soil [27], knowing the persistence period of ATBs ranges from < 1 to 3,466 days in the environment [45]. Furthermore, applying manure to agricultural fields further increases ATB waste in the soil, which can invade the food chain and contaminate the groundwater in addition to direct drug leaks from pharmaceutical factories and the disposal of unused ATBs [107]. Moreover, in dairy manure, tetracycline residues are common and perhaps persistent, and over 60 ARG can be found (including β-lactam and tetracycline resistance genes) [147]. All these residues end up in environmental sinks such as soil and water to cause contamination and induce resistance in the microflora [164]. However, ATBs are persistent and can survive in the natural environment for extended periods, existing in a variety of environmental media, such as farms, aquaculture and agricultural soil [232]. For example, Colistin has been demonstrated to remain chemically intact for at least 60 days solved in water [137]. The other issue is that conventional wastewater treatment plants are inadequate to remove these trace contaminants which are often detected in wastewater effluents, surface water, groundwater and drinking water [107]. Luckily, that ATBs can degrade to varying degrees by non-biological processes, including photolysis, hydrolysis, oxidative degradation and ionizing radiation degradation or by biodegradation, including degradation by microbes, algae and plants [231], but this is determined by their structural, physical and chemical properties [26] (molecular structure, size, shape, solubility, hydrophobicity) and of the soil (pH, texture field organic), in addition to climatic conditions (temperature, precipitation) and biological factors (microbial degradation) [27, 157]. It was found that in an aquatic ecosystem, ciprofloxacin is rapidly photodegraded at slightly basic pH, the half-life of sulfamethoxazole is decreased in the presence of dissolved organic matter. Heat, light and extreme pH sensitize β-lactams to degradation, whereas water and methanol rapidly hydrolyze them [26]. Various treatment technologies, including physical, chemical and biological processes, have been studied for the removal of ATBs, such as adsorption, coagulation, membrane separation, advanced oxidation processes, compost and aerobic and anaerobic degradation [204]. Although most ATBs are stable during manure storage, anaerobic digestion can break down and remove them to variable degrees depending on the ATB concentration and class [235], more specifically, thermophilic anaerobic digestion appears to be effective and provides more complete removal of ARB and ARGs [224].

Strategies for mitigating AR transmission

While the total eradication of antimicrobial resistance is unrealistic, comprehensive mitigation strategies can substantially reduce its emergence and spread of new types of AR [115]. Strategies that are enough to be a manageable issue and to protect the efficacy of antimicrobials needed to treat infections in animals, humans and plants

[47, 216]. On the other hand, existing technologies for controlling ARGs, such as composting, disinfection and sewage treatment, are not efficient in removing ARB and ARGs from waste. Furthermore, the remaining ARGs still possess a strong capacity for dissemination [119]. The biological treatment of manure through aerobic and anaerobic digestion has been shown to reduce the abundance and diversity of ARG. As a result, these two processes are thought to be potential manure pre-treatment strategies to mitigate ARG dispersal into the surrounding environment [197]. Hence, a ban on the use of growth promoters has not led to any consistent decrease in ATBs consumption [219]. Therefore, ATBs used in animal husbandry are difficult to replace in a short period of time [118]. In addition, this replacement may remain an economic challenge for countries with limited feed availability and inadequate local feed supplies [65]. Restricted use of antimicrobials has become a priority worldwide, with producers adopting best practices in biosecurity, health care, animal welfare, food handling and animal nutrition wherever possible from a practical, economic and animal welfare perspective [188]. In this context, increased efforts have been made in order to develop alternatives to conventional ATBs.

Contribution of antimicrobial stewardship programs

Antimicrobial stewardship plays a critical role in combating AR by promoting the responsible use of antibiotics, it is a coordinated program to educate and persuade prescribers to follow the appropriate selection, dosage and duration of antimicrobial agents in order to reduce microbial resistance and its spread [171], but achieving better antimicrobial stewardship on the farm is challenging: ATBs are an integral part of industrial agriculture and there are very few alternatives [219]. The study of [201] suggests that further improvements of ATB stewardship can be achieved through the standardization of ATB prescription to some species, a revision of the guidelines toward reducing the prescription of ATBs of high relevance for human medicine, and by including the details of clinical investigation, use of tests, and treatment outcomes in veterinary consultation records. To this end, programs at different levels of the system nationally address the emergence of AR, the WHO initiated a global action plan on AR; one of which is to enhance knowledge and surveillance skills on AMR through the global antimicrobial resistance surveillance system [207]. Successful national programs, such as those in the Netherlands (-56 % antimicrobial use) and China (-49.8 %) decreased the consumption of 49.8 % in only four years [92]. Moreover, surveillance data can help in identifying the areas for strategic interventions to maximize outcomes. Member States in the African region, raise stakeholder awareness and optimize antimicrobial stewardship, sharing and reporting of AMR data [211]. However, in order to launch successful intervention approaches through cooperative efforts from different stakeholders, the existing knowledge gap needs to be addressed first [171].

Phage therapy

Interest in the therapeutic applications of phages has waxed and waned over the past 100 years, but the idea is enjoying renewed interest today because of the alarming increase in AR bacterial infections [82]. Thus, they are suitable as alternatives to ATBs, being natural invaders of bacteria [96] by parasitizing and killing their host [182], including both gram-positive and gram-negative strains [124]. Bacteriophages can also act as alternative growth promoters, as they are active against specific strains, which allows them to be used against targeted pathogens in a mixed population without disturbing the composition of normal gut microflora [193]. Phages are typically added to a pre-existing ATB regimen, hence phage-ATB interactions are likely, including synergism, additive effects or antagonism, which is rare [82].

A rational approach to phage therapy has many potential advantages over a traditional ATB approach;

- The non-lethal nature of some bacteriostatic ATBs may allow AR to evolve more easily, while lytic phages are bactericidal [111].
- Due to phage's host specificity, distantly related bacteria (non-host) are unlikely to have ever been exposed to the phage of interest and thus are unlikely to contribute resistance genes to non-host via horizontal gene transfer [105].
- Phages show auto-dosing during infection (i.e. replication *in vivo*), in which the number of phages is relative to the number of bacterial hosts, this means that when there are no bacteria, there are also no viable phages [226], hence suggesting lower doses required.
- Although bacteria can become resistant to phages, phages mutate and therefore can evolve to counter phage-resistant bacteria like bacteria [74].
- While novel ATB discovery has stagnated in recent years, the discovery of new phage has proven expeditious due to the vast biodiversity of phages in nature that have useful properties in biotechnology [111].
- Bacteriophages cannot multiply in eukaryotic cells and therefore generate no direct pharmacological effects in animals, leaving no mechanism-based concerns about toxicity in animals [96].
- Unlike most ATBs, phages are able to target bacteria encased in biofilms [124] which are forms of AR.

Implementation of prudent ATB use practices

There is no universal solution or strategy to improve ATB use in livestock, therefore, optimized approaches, including a varying mixture of strategies, need to be explored while considering their potential risks and benefits [77]. The challenge is to encourage a better ATB use through appropriate and accepted actions, while ensuring

animal health and welfare and the economic viability of actors' activities [77]. Prudent ATB use practices address all factors contributing to AR. Training programs for farmers, feed dealers and drug sellers may be helpful to raise awareness on good farm practices [39]. Nordic countries, a model for the prudent use of ATBs, allow the purchase of ATBs for use in animals only on a veterinarian prescription, not for prophylactic purposes or as growth promoters, the sale of ATBs is only through pharmacies or from veterinarians and veterinary use of critically important ATBs is strongly discouraged, otherwise veterinarians could lose their licenses, temporarily or permanently [163]. In addition, a prescription is considered non-prudent when ATBs are prescribed for non-bacterial cases (viral, parasitic) or when two antagonistic ATBs are prescribed, as well as the use of non-effective broad-spectrum ATBs for cases requiring a long duration of therapy or for inappropriate cases (1969). Thus, it is also necessary to work on the dosage regimen optimization (frequency, length of treatment) to reach the best clinical outcome and the lowest resistant bacteria selection [7]. On the other hand, it is imperative that antimicrobials should be prescribed or administered only when the presence of a pathogen that causes disease is confirmed or suspected on the basis of the animal's clinical signs and previous experiences with disease incidence in the area [196]. The non-prudent use of antimicrobials in livestock could also be associated with the absence of appropriate diagnostic tools and guidelines that assist veterinarians in selecting antimicrobials [196]. As a result, facilitating affordable antimicrobial susceptibility testing with easy accessibility is essential [175].

It has been proven that the outbreak and spread of AR are markedly reduced in farms that practice the prudent use and management of ATBs [191]. Practically, their prudent use in animals, resulted in a 43.2 % decrease of antimicrobial veterinary products sales in the EU between 2011 and 2020 [194]. Likewise, Suzuki et al. [191] confirm that the AR rate of *E. coli* in the animal feces and wastewater sampled from a farm, on which ATB use is strictly monitored and controlled, was maintained at extremely low levels compared with those reported on domestic farms in Japan. Private ATB access should be restricted through strict prescription audits to help curb poor ATB prescribing [47]. To date, AMR has been poorly documented in animals in low-income and middle-income countries, and this may be partly due to the absence of systematic surveillance systems and large epidemiological studies [154]. Therefore, it is important to promote proper herd management practices and reinforce veterinary services especially for marginalized farmers [108].

Improving livestock with disease resistance

Disease resistance is the ability of a host animal to limit its within-host pathogen load, either by preventing infection or by inhibiting within-host pathogen replication [109]. It was observed that appropriate cattle housing, such as using cattle sheds leads

to protection from harsh weather conditions or exposure to hazards in open fields which reduce risks of diseases [108]. Other approaches have been explored to enhance disease resistance in livestock, including selective breeding and cross breeding [69]. A simple understanding of host immunology and genetics better characterizes the disease-resistant phenotype [91]. On the other hand, since genetic variation in disease resistance invariably exists, it is possible to select resistant animals using DNA-based selection [24] leading to enhanced disease resistance, reduced disease transmission and improved animal welfare [70]. Advanced genetic approaches have been used to identify genes correlated with animal production and disease resistance phenotypic traits in animals [103]. Gene editing technologies, including Zinc finger nucleases, transcriptional activator-like effect nucleases and clustered regularly interspaced short palindromic repeats, enable precise modifications of the animal genome [69]. Expressing genes could disrupt or inhibit pathogenic microorganisms from the host's perspective or truncate their receptors and target microorganisms themselves by interfering with their life cycle process [70]. On its part, ommunogenomics deals with big data from immunology and genomics; it integrates molecular interactions among the host genome, the immune system and the pathogen through a series of integrated bioinformatics. Thus, it is considered an efficient tool for identifying disease resistance genes [91]. Liu et al. [121] reported that adding a copy of bovine macrophage protein gene, associated with innate resistance to intracellular pathogens such as *Mycobacterium*, *Salmonella* and *Brucella*, to the specific locus of bovine genome can provide cattle with increased resistance to tuberculosis.

Vaccination

Concerns about drug residue in food from animals have led to an increased interest in chemical-free food, highlighting the importance of innovative veterinary vaccines [166] that are considered an essential tool to decrease the demand for antimicrobial drugs [171]. Vaccination is the method of inhibiting pathogens by inducing the defense mechanisms of the host's immune system, in turn decreasing infections and improving animal health [193]. They are widely used to prevent bacterial infections in livestock and poultry and are currently the most promising alternative to ATBs [194]. Vaccines can help prevent AR by preventing disease and the proliferation of bacteria, by mechanisms of action less prone to inducing resistance, by reducing ATB use due to fewer infections, by preventing resistant strains from occurring and spreading, by preventing ATB misuse and by preventing viral diseases prone to bacterial co-infections or superinfections requiring ATBs [30]. Vaccines developed against *Salmonella* strains in pigs and dairy cows and against fecal Enterohemorrhagic *E. coli* in cattle can reduce foodborne pathogens prior to slaughter [153]. In addition, prophylactic vaccination will limit the inappropriate use of ATBs each year, for example, vaccination

against *Lawsonia intracellularis* in Danish pigs can reduce Oxytetracycline consumption for the condition by 80 % [47].

Antimicrobial peptides/enzymes

Antibacterial peptides (APs) are a structurally diverse group of cationic, amphiphilic peptides, expressed by most multicellular organisms [177] as the first line of defence against microbial infection in eukaryotes, or produced as a competitive strategy in prokaryotes, to inhibit the growth of other unrelated microbial species [73]. Their cationic characteristics can establish electrostatic interactions with the bacterial membrane [167], hence they provoke cell lysis through unspecific disruption of lipid bilayers [177]. Several peptides are also able to translocate into cytoplasm and to interfere with intracellular processes via binding to receptor molecules, including the induction of autolytic enzymes and the blocking of protein, DNA and cell wall synthesis [176]. They have the advantages of a broad antibacterial spectrum, immune function, promoting growth, not easily producing AR [194] high safety [228, 230], have several modes of action, are easily degraded in nature and present reduced accumulation [4]. Some of the APs of animal origin have shown promising results and have advanced to clinical trials [112]. Numerous studies have cited antimicrobial peptides; defensins, active against a broad range of infectious microbes, including bacteria and fungi [71], cathelicidin [112], esculentins, brevinins, ranacyclins, ranatuerins, nigrocin-2, magainins, dermaseptins, bombinins, temporins and japonicins, as well as palustrin extracted from amphibians [73], the insect-derived antimicrobial peptide Cecropin [67], histatin, a primates saliva-derived histidine-rich peptide [116], protegrin isolated from porcine neutrophils with a membrane-binding capacity [86], aurein secreted by an Australian frog [41] and melittin, extracted from bee venom which is characterized by a broad-spectrum activity, effectively suppressing and eliminating both $Gram^{+}$and $Gram^{-}$ bacteria, including specific drug-resistant strains [221]. Antimicrobial (proteolytic, oxidative, anti-quorum sensing or polysacccarides degrading) enzymes play a critical role in defending living organisms from bacterial attack, they possess abilities to directly attack the microorganism and/or catalyze reactions which result in the production of antimicrobial compounds [193]. In-feed enzymes as a substitute for ATB growth promoters improve nutrient absorption and digestibility, gaining body weight and animal performance [153]. Some enzymes are effective as independent antimicrobial agents [152]. Lysozyme, due to its high antibacterial activity against many pathogenic bacteria, is currently one of the most used ones [152]. Moreover, it is safe for human and animal consumption and environmentally friendly due to its biodegradability [13].

Nanotechnology

Nanotechnology is used to develop antimicrobial agents that exert their effect via physical mechanisms instead of the chemical mode of action [55] (table 4). They open up new possibilities for attacking bacteria with antibacterial methods that are not naturally present in their defense arsenal [234]. The size of nanoparticles allows for greater interaction with the bacterial cell and an easier penetration, it induces changes in the morphology and structure of bacterial cells, which is in relation to the large surface-to-volume ratio and their shape [143]. The usage of NPs can decrease the development of bacterial resistance via their high drug absorption, target delivery, intracellular entrance and controllable safety and manipulation [117]. ATBs conjugated with NPs in the recommendable size range have the potential to facilitate the drug binding more effectively at the desirable site [151]. Numerous techniques employing nanotechnology-based drug delivery systems, including liposomes, polymeric nano-vehicles and nanoparticles of silica mesoporous, have been validated and deemed to be effective in the fight against drug-resistant bacterial strains [136]. The use of some nanosized emulsions showed a potent antimicrobial effect even against multidrug-resistant pathogens [55]. In more advanced methods, biosensors based on nanomaterials have a rapid detection of high selectivity ARGs, as gold nanoparticles which have been created for the sensitive detection of mecA genes [173]. However, at least when using ATB is essential, nanoencapsulation systems can improve the efficiency of antibiotics, and thus, reduce the application dose [142].

Herbal extracts and phytochemicals

Herbal medicines are cost-effective, easily dosable and believed to be safe [47] by minimal side effects [119]. Traditionally in China, plants are used against mastitis such as *Taraxacum mongolicum*, *Lonicera japonica, Viola patrinu, Folium isatidis, Angelica dahurica, Coptis chinensis, Phellodendron amurense, Rheum officinale, Scutellaria baicalensis, Angelica dahurica* and *Rheum officinal* [55]. In the context of ATB reduction and replacement, the potential application of plant-based active ingredients as food additives has become increasingly prominent [149]. Therefore, ethnoveterinary practices, contribute to the health improvement of livestock animal production [25] in many poor rural areas and are frequently the only option for farmers to treat their sick animals [125]. Some bioenhancing phytomolecules increase the bioavailability, bioefficacy and biological activity of various drugs when administered at low concentrations, thereby reducing the dose, duration of treatment and increasing the treatment rate, as a consequence, decreasing drug resistance in livestock [225]. Phytobiotics, plant-derived natural bioactive components that can be used as feed additives, have been found to not only alter bacterial proliferation, but also influence the composition

Table 4. Some nanoparticles with antimicrobial effects

Nanoparticle	Target	Action	Reference
Nano gold	*S. aureus, S. epidermidis, E. coli and P. aeruginosa*	Interact with both outer and inner membrane, destabilize them, leading to leakage of bacterial contents and ultimately bacterial death.	[40]
Nano zinc oxide	*S. mutans*		[12]
Nano silver	*E. coli S. typhi S. aureus P. aeruginosa Candida krusei, C. albicans, Penicillium sp.*	Synergistic antimicrobial activity against several pathogens	[140]
Nano-Selenium	Inhibition of ARG genes	Inhibite ARGs by suppressing bacterial selenocompound metabolism pathways	[228]
Nano iron	ARGs	Inhibit the abundance of mobile genetic elements	[205, 222]
Nano iron	MRSA	Inhibit respiratory enzymes, interact with the peptidoglycan cell wall and plasma membrane, prevent bacterial DNA replication, increase cell permeability	[62]
Nano-cellulose	*S.epidermidis, P. aeruginosa*	Damage the membrane producing the cellular lysis	[51]
Graphene nano zinc oxide	ARGs	Reduces the expression and release of ARG, inhibiting chemotaxis	[227]
Chitosan	Fungal pathogens	Encapsulate drugs as well as active c ompound and delivers them to a specific place in the body penetrate cells, where it is suspected of binding to cell DNA	[93, 76, 158]
Nano silver	*E. coli, K. pneumoniae, S. Typhimurium, S. Enteritidis*	Penetrate into the cell, form of free radicals, inactivate proteins by silver ions.	[122]
Nano copper oxide	MRSA, *E. coli, P. aeruginosa, Acinetobacter spp., K. pneumoniae, Stenotrophomonas maltophilia.*	Fragment the cytoplasmic membrane, leading to leakage of cytoplasmic cellular components	[101]
Titanium Dioxide	*B. subtilis, E. coli, E. faecalis, K. pneumoniae, S. aureus, P. aeruginosa, A. flavus, A. niger, R. oryzae, Sclerotium rolfsii*	Inhibit the DNA replication and proteins	[11]
Magnesium oxide	*Ralstonia solanacearum*	Reactive oxygen species accumulation and DNA damage	[31]

and function of the livestock microbiota [150]. They offer various benefits in farming, such as improved growth performance, enhanced immune system, increased antioxidant capacity, stress alleviation from abiotic factors and enhanced disease resistance [208]. Some essential oils have been used as non ATB antimicrobials in animal feed additives for the purpose of both growth stimulation and bacterial inhibition [153].

Table 5. Plants traditionally used to treat microbial infection

Plant	Disease/Bacteria	Livestock	Purpose	Reference
Symphythum officinale, Sambucus nigra, Mentha sp., Ocimum basilicum, Parapiptadenia rigida, Cuphea carthagene nsis, Salmonella cholleraesuis, Alternanthera brasiliana, Achillea millefolium, Bac charis trimera, Solidago chilensis	Mastitis	Bovin	Prevention and control	[135]
Allium sativum, Camellia sinensis	Diarrhea	Calves, piglets	Treatment, prophylaxis	[16]
Allium sativum, Olinia rochetiana, Osyris quadripartite, Ricinus communis, Brucea antidysenterica, Chenopodium ambrosioides, *Aloe scundiflora, Solanum incanum, Withania somnifera* *Asparagus africanus, Momoridica boivinii, Olea eurepea* *Euphorbia schizacantha* *Momordica foetida*	Mastitis, diarrhea Cholera Blackleg, pneumonia Anthrax Babesiosis, Anaplasmosis	Cattle, sheep, goat Chicken Cattle Cattle, sheep, goat Cattle, sheep, goat	Treatment	[168]
Achyranthes aspera,. Ficus caria, Malvi parviflora, Vernonia species, Solanum hastifolium, Calpurinia aurea, Nicotiana tabacum, Ziziphus spinachristi, Croton macrostachys	Mastitis, wounds, gastrointestinal complications	Cows	Treatment	[100]
Croton gratissimus, Croton gratissimus *Dalbergia obovata* *Ziziphus mucronata*	Pneumonia Paratyphoid Mastitis	Cattle	Treatment	[179]
Cichorium intybus	Bodily ailments and disorders, prophylaxis		Treatment, prophylaxis	[139]
Citrus limon	*E. coli, Staphylococcus arlettae, Staphylococcus cohnii, Mammaliicoccus lentus, B. cereus*	Poultry	Treatment	[190]
Piper nigrum	Anthrax, pneumonia, diarrhoea, gastrointestinal disorder, respiratory disease	Cattle	Treatment	[192]
Hammada scoparia, Acacia tortilis, Zygophyllum gaetulum, Nucularia perrinii, Panicum turgidum	Dermatomycosis, respiratory infections and mastitis	Camel	Treatment	[202]
Boerhavia diffusa, Centella asiatica, Cleome gynandra, Croton gratissimus, Kleinia longiflora, Opuntia ficus-indica, Phyllanthus maderaspatensis, Portulaca oleracea, Ricinus communis, Schkuhria pinnata, Senna italica	Eye infection Anthrax	Cattle	Treatment	[32]
Ziziphus mucronate, Combretum collinum, Colophospermum mopane *Ziziphus mucronate* *Aloe esculenta and Salvadora persica. Ximenia Americana, Combretum. imberbe* *C. imberbe* *Fockea angustifolia*	Diarrhea, Mastitis Skin infections Eye infections Anthrax	Cattle, goats, sheep	Treatment	[53]
Cussonia spicata + Olea europaea	Endometritis/ vaginitis	Cattle	Treatment	[33]
Pentas lanceolata	Gonorrhea, syphilis and dysentery		Treatment	[48]

Probiotics

Probiotics are considered the ultimate alternatives to ATB growth promoters [193] that have enhancing effects on livestock health and productivity [110]. Various potential mechanisms of action have been proposed on probiotics, especially mediating the regulation mechanism of the intestinal flora on the host, mainly including competitive inhibition of pathogens [183] and immunostimulatory activities [89, 153]. On the other hand, and in contrast to traditional antibiotics, lactic acid bacteria bacteriocins target specific species and do not affect other populations within the same ecosystem with bacteriostatic or bactericidal activity toward sensitive organisms [200]. The most commonly used probiotics in livestock are the strains of lactic acid bacteria, including *Lactobacillus, Pediococcus, Lactococcus, Enterococcus, Streptococcus*, *Leuconostoc* species [200], in addition to *Bifidobacterium* [110], *Saccharomyces* and spore-forming *Bacillus* [4]. Practically, the use of probiotic strains such as *Lactobacillus plantarum* or *L. fermentum* was associated with a reduction in colonization with naturally resistant pathogens, such as *A. baumannii*, *P. aeruginosa* or *C. albicans* [214]. In broilers, probiotic species belonging to *Lactobacillus, Streptococcus, Bacillus, Bifidobacterium, Enterococcus, Aspergillus, Candida* and *Saccharomyces* have been shown to present a beneficial effect pathogen inhibition [4]. It was found that the direct addition of *Bacillus sphaericus* to feed increases the average daily weight gain of weaned piglets and broilers, and reduces the incidence of post-weaning diarrhea of piglets (by 30 %), which is comparable to that of antibiotic-treated groups, helping to minimize the abuse of antibiotics and promoting the healthy growth of livestock and poultry [96]. Similarly, when broilers were fed with *B. subtilis* C-3102, the number of *C. perfringens*, Enterobacteriaceae and *Campylobacter* in the excreta, *Salmonella* colonization was reduced [132]. Multi-species probiotics consisting of *L. acidophilus*, *L. casei*, *B. thermophilum* and *E. faecium* were successfully used to reduce diarrhea caused by enterotoxigenic *E. coli* in newly weaned pig [110].

Organic acids

In food-producing animals, organic acids have been suggested as alternatives to other antimicrobials for use in nonclinical animal management practices [165]. The main targets of organic acids are the bacterial cell wall, cytoplasmic membrane and specific metabolic functions of pathogenic microorganisms leading to their disturbance and death [200]. Other organic acids (acetic, butyric and propionic acids) are able to strengthen the gut mucosal barrier by stimulating the expression of antimicrobial peptides in mucosa [2014]. Some pathogenic intestinal pathogens, such as *Salmonella spp*., *Campylobacter jejuni*, pathogenic *E. coli* and *C. perfringens* could be drastically affected by using organic acids [2, 233]. It has been proven that feed supplementation with formic, acetic and propionic acids, contributed to better growth performance and a

decrease in sulfamethoxazole, ciprofloxacin, ampicillin and tetracycline-resistant *E. coli* in the cecum of broilers compared to control supplemented with ATBs [196]. Butyric acid has been reported to reduce the virulent gene expression and invasiveness in *S. Enteritidis*, leading to its decreased colonization in the caeca of broiler chicken [6]. Butyric acid decreases the incidence of subclinical necrotic enteritis caused by *C. perfringens*, which is highly relevant for the poultry industry. Some acids, especially butyric acid, not only antibacterial, but also host effects, can play a role in the antimicrobial growth promoters replacement effect [190].

Education and awareness campaigns

Addressing AR in livestock requires a comprehensive approach [47]. The reduction of this resistance in the animal industries sector implies intervention from all stakeholders (veterinary students, para-vets, drug and feed sellers and farmers), and especially from veterinarians [175], since veterinarians and para-vets are crucial in spreading awareness about vaccination, ATB stewardship and AR [47], while safeguarding against any animal health risks associated with reducing nontherapeutic ATB use [59]. A community engagement approach towards behavioral change for antimicrobial use could potentially safeguard both existing and future treatment options and offer better strategies to combat AR [171]. Many farmers lack a good understanding of ATBs and antimicrobial resistance [47]. However, livestock farmers and managers must have an understanding and be able to differentiate between 'medicine', 'drugs', 'antimicrobials' and 'ATBs' [105]. Therefore, it is important to educate farmers on appropriate ATB usage [108] by effectively communicating with them and fostering trust. This should include targeted education and awareness programs for farmers, as well as improved access to veterinary services [47]. Regular awareness education on ATBs and AR in the form of refresher course/training must be provided to animal health workers to avoid inappropriate use of ATBs [207]. This would require a continuous awareness-raising of AM users and end-users of animal products so that these actors understand the impact of AM misuse on animal health and welfare and on public health, and their influence through their treatment choices, herd management and consumption [77]. For example, it is essential to comprehensively understand the occurrence of ARGs, ATBs in different livestock and poultry feces, so as to guide manure application and management of different animal feces [154]. Practically, it has been shown that introduction of ATB guideline led to significant reduction of ATB prescription and also led to use of lower generation drugs [207]. Private ATB access should be restricted through strict prescription audits to help curb poor ATB prescribing [47]. To date, AMR has been poorly documented in animals in low-income and middle-income countries, and this may be partly due to the absence of systematic surveillance systems and large epidemiological studies [155]. Therefore, it is important to promote proper

herd management practices and reinforce veterinary services especially for marginalized farmers [108].

Surveillance and monitoring programs for AR and future challenges

Surveillance and monitoring studies on AR in humans and animals are essential when studying changes in antimicrobial susceptibility patterns over time and to identify emerging resistance properties [184]. Data generated through such programs, whether publicly funded or private, can help to guide local treatment decisions, inform stewardship initiatives and reveal gaps in the antimicrobial armamentarium that new agent development should target [215]. Therefore, robust and actionable data are needed to drive changes and inform effective interventions to contain resistance [144]. However, to date, AMR has been poorly documented in animals in low-income and middle-income countries, and this may be partly due to the absence of systematic surveillance systems and large epidemiological studies [155]. Therefore, it is important to promote proper herd management practices and reinforce veterinary services especially for marginalized farmers [108]. The level of AR may be reduced by introducing an obligation to report to regulatory authorities the use of ATBs on a farm and by requiring AR tests before ATB use [46]. The mitigation of AR risks requires dialogue and coordinated engagement between stakeholders from public and private sectors along the animal and ATBs value chains, implicating veterinarians, public health scientists, microbiologists, environmental scientists (ecologists), agricultural/forestry scientists and epidemiologists [56]. Animal health authorities should also be actively involved in informing people about these topics and enhancing the availability of facilities, while promoting responsible ATB use [47]. The future of AMR surveillance is moving toward genotypic detection, and molecular analysis methods are expected to yield a wealth of information, nevertheless, phenotypic testing remains necessary in the detection of emerging resistant bacteria, new resistance mechanisms and trends of AMR [185].

Conclusion

Livestock production remains a significant, but often underestimated driver of antibiotic resistance worldwide. The inappropriate, use of ATBs in livestock accelerates the selection of resistant strains, with serious consequences for both humans, animals and the environment. The transmission of resistant bacteria and resistance genes to humans represents a real threat. Therefore, preserving the effectiveness of antibiotics, which are pillars of modern medicine, requires a global and concerted commitment, but the unevenness of surveillance systems and the poor accessibility of diagnostic tools in many countries aggravate the situation. Faced with this emergency, an integrated "One Health" approach is essential, combining strict regulation, increased harmonized sur-

veillance, awareness-raising among field stakeholders and the adoption of alternative strategies that must be supported by effective programs adapted to local contexts, particularly in low-resource countries. Priority actions include strict regulation of antibiotic use, expansion of genomic monitoring systems and implementation of economically feasible alternatives such as vaccination and stewardship programs. Quantitative targets such as reducing veterinary antibiotic consumption by 30 % globally – should be pursued to measure progress and ensure accountability. Ultimately, the sustainable control of antibiotic resistance depends on coordinated cross-sectoral policies, investment in innovation and responsible behaviors across all levels of the food chain.

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ZWIERZĘTA HODOWLANE JAKO NIEDOCENIANE ŹRÓDŁO OPORNOŚCI NA ANTYBIOTYKI

S t r e s z c z e n i e

Wprowadzenie. Oporność na antybiotyki (AR) stała się jednym z najpoważniejszych zagrożeń dla zdrowia publicznego na świecie. Problem ten wynika przede wszystkim z niewłaściwego i/lub nadmiernego stosowania antybiotyków, nie tylko w medycynie klinicznej, ale także w systemach produkcji żywności, zwłaszcza tych obejmujących zwierzęta gospodarskie. Zwierzęta hodowlane są często narażone na pasze wzbogacone antybiotykami w celach profilaktycznych, metafilaktycznych i wspomagających wzrost, wywierając stałą presję selekcyjną na populacje bakterii i ułatwiając rozprzestrzenianie się szczepów opornych w łańcuchu pokarmowym, środowisku i poprzez kontakt z ludźmi. Niniejszy przegląd krytycznie analizuje wkład systemów hodowli zwierząt w rozwój i rozprzestrzenianie się AR, integrując perspektywy genetyczne, środowiskowe i społeczno-ekonomiczne. Podsumowuje on aktualne dane naukowe dotyczące wzorców stosowania antybiotyków w produkcji zwierzęcej, podkreśla międzynarodowe przepisy i strategie kontroli oraz ocenia powiązane skutki zdrowotne i ekonomiczne. Ponadto omawia

obiecujące alternatywy dla antybiotyków, w tym szczepienia, probiotyki, związki pochodzenia roślinnego oraz ulepszone środki bezpieczeństwa biologicznego.

Wyniki i wnioski. Znaczna część globalnego zużycia antybiotyków jest przeznaczona na produkcję zwierzęcą, zwłaszcza β-laktamy, tetracykliny i fluorochinolony. Ciągłe nadużywanie tych leków w krajach rozwijających się nadal napędza oporność, co pociąga za sobą poważne konsekwencje zdrowotne i ekonomiczne. Wzmocnienie skoordynowanej harmonizacji polityki „Jedno Zdrowie" oraz zrównoważonych praktyk rolniczych jest zatem niezbędne do złagodzenia tego rosnącego globalnego zagrożenia.

Key words: patogeny przenoszone drogą pokarmową, transmisja pozioma, geny oporności, presja selekcyjna, choroby odzwierzęce