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r t q r j { n c e v k e " w u g u " q h " c p v k o k e t q d k c n u " k p " c i t k e w
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cattle. Salmonellosis a ects humans through the consumption of contaminated food of animal origin (mainly eggs, meat, poultry, and milk). A recent study in Brazil investigated the occurrence of resistance in *Salmonella* spp., isolated from products and raw material of animal origin (swine and poultry) to antimicrobials found that 51 (38%) out of 134 isolates were resistant to at least one of the eight antibiotics used, and 28 (55%) of resistant isolates were multi-resistant. A recently published systematic review on the prevalence of antibiotic resistance in *E. coli* strains simultaneously isolated from humans, animals, food, and the environment indicated that colistin had the lowest prevalence and amoxicillin the highest in isolated human *E. coli* strains. e systematic review also indicated that the prevalence of Extended-Spectrum Beta-Lactamase (ESBL)-producing *E. coli* was highest in animals compared to human or environmental/food isolates. A study of the global and regional burden of 22 foodborne diseases indicated that the leading cause of the foodborne illness was norovirus followed by campylobacter. e diarrheal and invasive infections caused by non-typhoidal *Salmonella enterica* infections caused the largest burden of disease. e authors found that the burden of food borne illness was highest in WHO's African region. Enterococci such as *Enterococcus faecalis* and *Enterococcus faecium* were reported in the current study and had been reported to have intrinsic and acquired resistance to a wide range of antibiotics including vancomycin. Currently, vancomycin-resistant enterococcus (VRE) is a challenge in clinical settings. e emergence of VREs in food-producing animals was attributed to the widespread use of avoparcin in the 1990s in Europe for growth-promotion in animals [1]. In North America, the emergence of VRE in animals was not seen until 2008 and was attributed to the extensive use of vancomycin in clinical settings. *Staphylococcus aureus* is another gram-positive opportunistic pathogen in animals and harbors several AMR genes. e current study listed B-lactams, aminoglycosides, and Quinolones/ uoroquinolones as themost commonly encountered antibiotics drug classes in the retrieved literature. ese drug classes are important therapeutic choices in human health. ese drugs were listed as critically important drugs in human medicine. e misuse/overuse of these drug classes threatens the e cacy and safety of antibiotics in clinical use and governmental action is needed. e fast development of chloramphenicol resistance upon use in animals led the FDA to ban the use of chloramphenicol in food-producing animals. In the last two decades, the growing problem of multidrug-resistant bacteria (MDRB) has made the routine therapy of some infections resulting from treatment in a hospital or healthcare unit, i.e., nosocomial infections, complicated and in few cases, impossible. e widespread nature of the problem has led some experts to speculate about a post antibiotic era. In evolution, selection pressure is bound to cause subpopulation of microorganism with resistance genes to emerge. is selective pressure has been ascribed to appropriate and inappropriate use of antibiotics but aggravated by intensity of usage, persistence of usage, under usage and sub therapeutic doses that animals are exposed to in prophylactic treatment and unintended animals' exposure through antimicrobials in food residues and the environment [1-6]. Veterinary practices use drugs for mitigating these diseases in animals, including food animals that have to be maintained in health and productivity (meat, egg, and milk). To prevent these drugs from getting into the food chain and being consumed by humans, "withdrawal time," which is the last time any drug may be administered before egg/milk and meat from such animals are collected and consumed is speci ed.

e withdrawal time for antimicrobials is intended to prevent harmful drug residues in meat, milk, and eggs. ese waiting periods need to be observed from the time of treatment to when the animals are slaughtered for food. is is important because food products that contain antimicrobial residues not metabolized leaves residues beyond permissible limits at the end of the withdrawal period may be considered unwholesome for consumption and may contribute to antimicrobial resistance in humans [6]. Several studies have reported that the application of d

they commonly used in agricultural settings their use is also frequent in human health-care systems and at community level. ey may lead to emergence of AMR through cross-resistance, co-resistance and clonal dri mechanisms, and by activating an SOS response in bacteria leading to the repair and integration of DNA, some of which may include resistance genes. Preservatives such as citric acid or sodium benzoate protect animal feed against decay caused by microorganisms. Such organic acids when ingested by food-producing animals may

location of the target regions of the relation with the antibiotics are distinct; these can be complex enzymes and ribosomes. e most frequently identi ed resistance consistent with variations in the ribosomal target is in macrolide antibiotics. e most popular examples hereare the evolvement of penicillin resistance due to the mutations of penicillin-binding proteins beta-lactamase enzymes in Staphylococcus aureus, Streptococcus pneumoniae, Neisseria meningitides, and Enterococcus faecium strains. Most of the bacteria synthesize antibiotic degrading enzymes; the enzymatic inactivation mechanism is one o he most important antibiotics resistance mechanisms.In this group, beta-lactamases, aminoglycosidase, chloramphenicol, and erythromycin modifying enzymes arethe most popular examples. is mechanism results from changes in the permeability o he internal and external membrane so that decreased drug uptake into the cell or rapidly ejected from the pump systems. Due to a decrease in membrane, permeability because of porin mutations that may occur in proteins of resistant strains for example; a mutation in speci c porins called OprD can cause resistance to carbapenem in Pseudomonas aeruginosa strain. Reduction in outer membrane permeability can play an important role in quinolone resistance and aminoglycoside resistance. Resistance develops most commonly in the tetracycline group of antibiotics via the active pump systems. With an energy-dependent active pumping system, tetracyclines are thrown out and cannot concentrate within the cell. is mechanism of resistance is in plasmid and chromosomal control. Active pumping systems for example are e ective in resisting quinolones, 14-membered macrolides, chloramphenicol and beta-lactams. Unlike some of the target alterations in bacteria, the latest drug-susceptible pathway eliminates the need for objective development. Bacteria can prepare folic acid from the environment, rather than synthesizing folic acid so that it becomes resistant among sulfonamide and trimethoprim.

consumer awareness through communication campaigns coordinated by the French government (campaign “Antibiotics are not automatic”) led to a decrease in volumes of antibiotics consumed. Educating practitioners in small groups led by an expert also results in a signi cant reduction of drug consumption. Conversely, wide di usion of treatment guidelines appears to produce less tangible results. In the animal health sector, research documenting the impacts of the implemented measures is lacking and should be encouraged, in addition to the national monitoring programs of antimicrobial consumption which depict the global trends in antimicrobial consumption. Furthermore, recent research suggests that a deep understanding of the decision making process is needed, as it can explain success or failure of policy interventions.

Regulations

Across countries, organization of the veterinary drug delivery system varies. erefore, governments have implemented speci c measures in accordance with their local scheme. Denmark, the Netherlands and France have implemented restrictive measures on usage of CIA, leading to a massive decrease in consumption of these targeted antimicrobial classes. However, the impact of such restrictions on misuse or overconsumption is questionable. Indeed, for a given condition, it is likely that a CIA will be substituted by a non-CIA, which ultimately (i) will not decrease exposure of animals to antimicrobials, and (ii) will have only little e ect on the externality AMR of commensal bacteria, due to the existence of cross-resistance between the di erent classes.

Financial alternatives to prices’ control: taxes and insurances

A rst alternative to prices’ control consists of setting a tax on antimicrobial sales, on the basis of costs developments supported by pharmaceutical industries. A Pigovian tax system could also be implemented. Its implementation nevertheless requires a quantitative evaluation of the costs of AMR associated with AMU. e complex evaluation of these costs might be a factor explaining that the countries introducing taxes in their set of measures chose to tax consumers. In Denmark, a range of di erentiated taxes on antimicrobials have been applied since 2013 in order to promote the use of vaccines instead of antimicrobials with a speci c focus on CIA. e tax rates vary between drugs: 0% for vaccines, 0.8% for narrow-spectrum penicillins and other veterinary medicines, 5.5% for other veterinary antimicrobials and 10.8% for CIA. However, a recent report mentioned that even if the taxes generated fund nancing activities on AMR, they did not greatly a ect antimicrobial consumption.

Surveillance of antimicrobial resistance

Surveillance represents a key component of the control of AMR. e World Health Organization developed standards to detect emergence of resistance. In parallel, several countries implemented monitoring of resistance among commensal and zoonotic bacteria. ese measures should be associated with the monitoring of antimicrobial consumption. Harmonization of the methods of collecting data is in progress in Europe, as comparison between countries could be a major driver for change. In low-income countries, monitoring of antimicrobial consumption and resistance is rare and international organizations have a major role to play to address these issues.

Research and innovation

It is very likely that new antimicrobial drugs will be restricted to human medicine. Hence research in veterinary antimicrobial therapy should be performed to optimize dosage regimen of existing drugs, as functions of the targeted bacteria, host species, and according to PK/PD considerations. Re-evaluation of antimicrobial dosage regimens, considering updated PK/PD requirements, constitutes a rst step to limit the impact of antimicrobials on commensal oras. For example, recently in veterinary medicine, the marbo oxacin dosage regimen was re-evaluated for treatment of Gram negative infections and the

though external factors such as the need to handle animals for vaccine application can impede them.

Immune modulators

Immune modulators, which as de ned here include the transfer of antibodies to elicit passive immune responses, are promising alternatives for disease prevention and potentially for treatment as well. In contrast with vaccines, immune modulators stimulate the immune system in a way that is less dependent on the pathogen causing infection, which makes them e ective against a broad range of pathogens. A very broad variety of immune stimulatory substances has been investigated as potential alternatives to antibiotics. ese include cytokines (i.e., substances that are secreted by certain immune cells to regulate other parts of the immune system), lipopolysaccharides (i.e., large molecules that are present in the wall of certain bacterial cells and trigger innate immune responses), short segments of bacterial DNA that also stimulate innate immune responses, antibodies derived from egg yolk that provide short-term immunity, and certain plant materials. e e cacy of immune-stimulants relies on a functioning immune system and therefore may not always be a feasible option; for instance, in very young animals, the immune system is not yet fully functional, and severe stress and disease can limit the functionality of the immune system. ere are also safety concerns about using immune-stimulants before the immune system is fully formed because of the potential risk for adverse developmental e ects.

Bacteriophages, endolysins, and hydrolases

A number of viruses and the enzymes they generate show promise as alternatives for antibiotics that may be used for disease prevention and potentially for treatment, thereby also potentially indirectly a ecting production performance. Bacteriophages are viruses that infect and kill bacteria. Most bacteriophages have a narrow range of bacterial strains they can infect, which in extreme cases can be restricted to a single strain of a bacterium. erefore, Bacteriophages can be used in a highly targeted way with minimal unintended impacts on other bacteria and the host. In addition, antibiotic resistance typically does not interfere with the bacteriophage's ability to infect and kill the bacterium, which may make them one of few treatment options for infections with multidrug-resistant bacteria. In addition, because the bacteriophages multiply in the bacteria they infect, a reasonably broad dosage range can be e ective. However, bacteria can become resistant to bacteriophages; bacteriophages may rapidly degrade in the environment; and there is some risk that certain bacteriophages may have the ability to spread antibiotic resistance genes. Overall, bacteriophage therapy tends to be extremely time-sensitive. For example, phage therapy had limited e cacy when administered more than 16 hours a er experimental infection. Notably, bacteriophages are actually naturally occurring and common in the environment. Phage therapy has also shown promising results in piglets and calves, where bacteriophages signi cantly reduced the prevalence of diarrhea caused by *E. coli* and successfully treated them in piglets. However, the major obstacles to using bacteriophages for disease treatment in animals include the lack of rapid and accurate diagnostics which are necessary because the phages typically are e ective only against a very narrow range of bacterial strains the risk of phage inactivation via the host immune response, and rapid emergence of resistant bacterial strains. Phage cocktails that contain several di erent bacteriophage strains can help address these limitations, but to date, e cacy for treatment of pathogenic organisms has remained limited.

Endolysins and lysozymes are hydrolases. Hydrolases are enzymes that degrade peptidoglycans, the main building block of the bacterial cell wall, and thereby kill bacteria. e hydrolases can be derived from a number of di erent sources, including bacteriophages, as well targenzymate show

that can improve overall animal health and signi cantly reduce the risk of pathogen introduction into the herd or ock. Notably, a comprehensive approach that includes alternative products and improved management practices is likely to be more e ective than relying on a single alternative product or approach to manage health and prevent disease. In fact, improvements in biosecurity have been widely accepted as an e ective means of preventing the introduction of diseases into herds or ocks. is concept applies widely across species, production systems, and pathogens.

Conclusion and Recommendations