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Antimicrobial Resistance in Veterinary Practices: A Review

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Abstract

Antimicrobial Resistance (AMR) is the ability of a microbe to resist the effects of medication which was previously used to treat them. Veterinary pharmaceuticals include a wide range of anti-infectives and additives in the use for animal health, nutrition, reproduction, and productivity. The introduction of penicillin in 1943 and other antibiotics thereafter provided remedies for many infections in humans and animals, reducing mortality and productivity losses. Since then, a repertoire of antibiotics and antimicrobials has been introduced as chemotherapeutics and prophylaxis. This success notwithstanding, many pathogens of consequences are no longer susceptible owing to emergence of antimicrobial resistant (AMR) microorganisms. This has made treatment of infectious diseases less effective. Beside spontaneous emergence of mutant microorganisms, scientists are wary of AMR caused by intensive use of antimicrobials in humans and animals, sometimes in subtherapeutic doses as preventive medicine. In developing countries, environmental exposure and persistent use of antibiotics in food animals may leave residues in the food chain. In addition to that, the consequences include development of antibiotic resistance are occurred. Alternatives to growth-promoting and prophylactic uses of antimicrobials in agriculture include improved management practices, wider use of vaccines, and introduction of probiotics. Monitoring programs, prudent use guidelines, and educational campaigns provide approaches to minimize the further development of antimicrobial resistance. In this manuscript, antimicrobial resistance in veterinary practices and sequel in the emergence, the current status and possible mitigation strategies to tackle antimicrobial resistance have reviewed.

Keywords: Antimicrobials; Antimicrobial resistance; Mitigation strategies

Introduction

Since the discovery of penicillin in the late 1920s, hundreds of antimicrobial agents have been developed for anti-infective therapy. Antimicrobials have become indispensable in decreasing morbidity and mortality associated with a host of infectious diseases and, since their introduction into veterinary medicine, animal health and productivity have improved significantly. The emergence of antimicrobial resistance(AMR) was not an unexpected phenomenon and was predicted by Alexander Fleming, who warned in his Nobel Prize lecture in 1945 against the misuse of penicillin. However, loss of efficacy through the emergence, dissemination, and persistence of bacterial antimicrobial resistance in many bacterial pathogens (defined as the ability of a microorganism to withstand the effect of a normally active concentration of an antimicrobial agent) has become a general problem and a serious threat to the treatment of infectious diseases in both human and veterinary medicine. However, the invaluable benefits of antimicrobials over the past few decades, in both humans and animals are being increasingly threatened by the selection and spread of antimicrobial resistance (AMR), with some infections now effectively becoming untreatable. Estimated a median of 1.27 million deaths in 2019 directly attributable to AMR, a value that is roughly the same as HIV deaths (680,000) and malaria deaths (627,000) combined on a global scale. This number is expected to increase to 10 million in 2050 if no action is undertaken. New class of antimicrobial has not been discovered since daptomycin and linezolidinthe1980s [1-9] which can alleviate the burden of AMR, and only the optimization of the chemical structure or combination of already known compounds have recently been commercialized. Hope remains for antimicrobial peptides (AMPs), which have attracted great interest in recent years due to their promising potential; it is understood that they could be used as alternative or complement approaches for the treatment of bacterial infections. Antimicrobials have been used, since the 1950s, therapeutically, prophylactically, and even for growth promotion in farm animals to maintain animal health and increase overall productivity. The misuse of antimicrobials in human health care and in livestock is believed to be the major driver of AMR. It is noteworthy that despite the current critical worldwide situation related to the COVID-19 pandemic, and the unprecedented efforts and budgets dedicated to managing this crisis, AMR was a priority of the health agenda of both the June 2021 G7 and the September 2021 G20 meetings. Antimicrobial resistance is the worldwide topic of discussion in the recent decades similar to climatic change as it affects the human and animal well being despite the geography and the developmental status of the countries. Antibiotic resistance has been described as the ability of bacterial to survive and spread despite treatment with specific and combination therapy that are normally used against them. The World Health Organization also emphasized that resistance happens when microorganisms change when they are exposed to antibiotics drugs. Some microorganisms that develop antibiotics resistance are sometimes referred to as “superbugs”. Antimicrobial resistance may be spontaneous and occur as a natural process, and resistance to antimicrobials dates back as far as when the first generations of antibiotics including penicillin were introduced in 1943 by Alexander Fleming. The current study indicated that resistant pathogens in food-producing animals included both gram-positive and negative ones. The most common drug-resistant foodborne bacteria of relevance to human health were *Salmonella*, *Campylobacter*, and *E. coli*. *Salmonella* bacteria are prevalent in food animals such as poultry, pigs, and

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cattle. Salmonellosis affects 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. The 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. The diarrheal and invasive infections caused by non-typhoidal *Salmonella enterica* infections caused the largest burden of disease. The 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. The 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. The current study listed B-lactams, aminoglycosides, and Quinolones/fluoroquinolones as themost commonly encountered antibiotics drug classes in the retrieved literature. These drug classes are important therapeutic choices in human health. These drugs were listed as critically important drugs in human medicine. The misuse/overuse of these drug classes threatens the efficacy and safety of antibiotics in clinical use and governmental action is needed. The 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. The 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. This 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 specified.

The withdrawal time for antimicrobials is intended to prevent harmful drug residues in meat, milk, and eggs. These waiting periods need to be observed from the time of treatment to when the animals are slaughtered for food. This 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 different strategies aimed at reducing the use of antimicrobials in veterinary medicine(for example, the use of colistin in farm animals) have positively contributed to a decrease in the prevalence of colistin-resistant *E. coli* and the mobile colistin resistance (mcr)-1-positive *E. coli* in animals, humans and the environment [7-9]. In the Netherlands, an overall decrease of the use of antimicrobials by approximately 70% in 2015 compared to the index year 2009 has been attained, while investigating how to reduce this number further in the next few years [3, 5]. This reduction had no impact on the health and welfare of farm animals [3]. However, a decrease in the prevalence of AMR bacteria and/or genes in human medicine, as a consequence of the reduction in antimicrobials use on farms, has not been evident by now, and no environmental impact as a result of this reduction has been measured. Nevertheless, the management of AMR at the human–animal–environment interface requires the urgent implementation of the One Health approach for effective control and prevention. Veterinary pharmaceuticals, therefore, contribute in many ways to the emergence of antimicrobial resistance either directly in suboptimal usage in animals or indirectly in human who consume sub therapeutic doses in animal products. When resistant organism emerges, it has also been argued that human sources also seed these resistant bacteria to animals and the environment through sewage.

Therefore, objectives of this seminar are:

- To highlight driving factors for occurrence of antimicrobial resistance in veterinary medicine
- To review current status of antimicrobial resistance at veterinary clinical settings
- To summarize possible mitigation strategies to combat antimicrobial resistance

Antimicrobial resistance in veterinary practices

History of antimicrobial use and antimicrobial resistance

The introduction of antimicrobial drugs into agriculture and veterinary medicine shortly after the Second World War caused a revolution in the treatment of many diseases of animals. In the "wonder drug era" of the late 1940s and early 1950s, the effective treatment of many infections that were previously considered incurable astonished veterinarians, such that some even feared for their livelihoods. Not all use of antimicrobial drugs in food animals is yet under veterinary prescription globally, despite repeated recommendations by the World Health [5-7] Organization and other responsible organizations, so that the term "veterinary medicine" is used here rather generically to suggest use in animals rather than just use by veterinarians. A broad overview of key features of the history of antimicrobial drug in animals is given in Table 1, which traces developments from the pre-antibiotic era to the present day, where there are arguable fears that we are moving into the "post-antibiotic" era but which may better be described as the antimicrobial stewardship era. Much of this overview will focus on antimicrobial use in food animals, the subject of an earlier review that partly focused on the public health aspects of the use of antimicrobials in food animals.

Table 1: Historical time line of important events and trends in the use of antimicrobial drugs in animals.

Time line	Feature of period	Antimicrobial drug development	Important events
1925–1940	Antiseptic era	Discovery of sulfonamides	Discovery of penicillin, first beta-lactam, by Alexander Fleming
1941–1965	"wonder drug" era	Streptomycin, first aminoglycoside, is covered	Second World War is impetus for antimicrobial drug discovery for treatment of war wounds
1966–1990	New drug analog period	first-generation cephalosporin first used	New drug analogs successfully address resistance problem
1991–1995	Increasing resistance problems	Azithromycin and and other drugs improved	First fluoroquinolone, enrofloxacin, introduced into food animal (poultry) use in USA
1996–2010	Resistance crisis in medicine	Oral, third-generation cephalosporins in human medicine	Global emergence of multidrug multi drug resistance
2011–2016	Resistance crisis	Avilamycin introduced as first-in-class, animal-use-only	Transatlantic task force on Antimicrobial Resistance to cooperate between USA
2017	Stewardship era	Intense activity to find alternatives to antibiotics	stewardship and "One Health" approach as global response The story continues

Drivers of antimicrobial resistance in veterinary medicine

Antimicrobial use

Excessive use and misuse of antimicrobials are widely recognized as two of the major drivers for acquired AMR, both directly and indirectly, due to the selection pressure imposed on human and animal microbiota. Usage of third-generation cephalosporins (e.g., ceftiofur), deemed as critically important antimicrobials in humans, has been associated with the selection of co-resistance to disparate antimicrobials such as tetracycline and chloramphenicol in enteric Escherichia coli bacteria. This has been observed in hospitals, farms, waste water and sewage environments and in the gut of treated animals and humans. The persistence of antimicrobial residues in feed and animal waste contaminating soil and water also affects the aquatic and environmental microbiomes. The emergence of AMR strains is dependent on several factors relating to the antimicrobial itself (e.g. amount, dosage, frequency and duration of selection pressure) and the organism (e.g. presence of genes conferring resistance to that particular substance, and advantage provided by the expression of these to the survival of the bacteria). Use of antimicrobials may unblock gene expression, resulting in the development of resistance genes in bacteria.

Antimicrobial growth promoters (AGPs)

Exposure of bacteria to sub-therapeutic concentrations of antimicrobials is likely to have an important role in AMR evolution. The use of AGPs as feed additives in intensively produced animals has been found to alter the gut microbiota of treated animals and promote resistance transfer within the animal and the environmental microbiome. AGPs are administered at sub-therapeutic dosages to groups of animals via drinking water or feed for prolonged periods to improve growth rates. AGPs are sold and used in many countries without veterinary prescription or supervision.

Prophylaxis

Administration of antimicrobial to susceptible but healthy animals to prevent the occurrence of infectious disease is a common. Infiltration of mammary glands of dairy cattle with antimicrobials such as penicillins, cephalosporins or other lactams after cessation of lactation. Nevertheless, this may not be the case when the administration occurs in animal groups through water and feed (e.g. pigs, poultry) due to the variations in consumption by individual animals and the number of animals exposed. It must also be noted that particularly in countries where antimicrobial production and storage chains are inadequate (due to environmental or infrastructure-related issues) antimicrobials may be susceptible to degradation through oxidation-reduction reactions, hydrolysis, biodegradation or photo degradation .

Therapeutic use

This describes treatment of active bacterial infection in a single animal, or a group, via antimicrobial administration. Whereas even a single dose of antimicrobial administered to a single animal has the propensity to generate AMR within bacterial populations resident in that animal, the repeated and continued usage of antimicrobials, for example to treat recurrent infections, compounds this risk. Often, broad-spectrum antimicrobials are used in livestock before, or in place of, a confirmed diagnosis (for example before undertaking any antimicrobial susceptibility testing) due to economic considerations. The administration of macrolide antimicrobials such as erythromycin to pigs, regardless of the route of administration, has been shown to select for resistance in Campylobacter spp. strains. The duration of systemic treatment should only be long enough to ensure elimination of infection in the affected animal or animal populations as this could result in further selective pressure on the gut microbiota. Correct dosing is very important for the reasons stated above. In addition, for antimicrobial substances that have been licensed for veterinary use for many years, recommended dosages by manufacturers in the Summaries of Products Characteristics (SPCs) may not always be adequate as these may have not been calculated in accordance with updated pharmacokinetics and pharmacodynamics principles, or may not have taken account of the evolution of antimicrobial susceptibility in bacterial populations.

Occurrence of infectious diseases and pathogens

The endogenous risk factors of infectious disease relate directly to the decisions of farmers who can control them. They include how the farmer adapts to the exogenous risk factors of a given system as well as how he reacts to the occurrence of disease. These two topics represent the preventive and curative aspects of the disease management. Both aspects are the quintessence of a farmer's role in antimicrobial use. For instance, animal nutritional status, housing and raising conditions, feed quality and quantity, and choice of breed are examples of endogenous factors. Poor decision making in regards to endogenous risk factors such as the absence of quarantine, having a shared air space for several groups of calves, and the lack of clinical examination upon arrival at the farm may lead to development of respiratory diseases which have also been associated with increased incidence of antimicrobial treatments.

Animal feed preservatives and biocide use

These are substances, which through chemical or biological action hinder the activity of a broad spectrum of microorganisms. Not only are they commonly used in agricultural settings their use is also frequent in human health-care systems and at community level. They may lead to emergence of AMR through cross-resistance, co-resistance and clonal drift 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 induce a selection pressure on gut bacteria.

Other potential sources of resistance

Stressors identified as associated with emergence and transfer of resistance include extreme temperatures and variations on osmotic pressure and pH that could have an impact on the integrity of the DNA and affect bacterial survival (2). Heavy metals may be used in agriculture as part of livestock feed supplements, and in a Chinese study were detected in manure from pig farms. Heavy metals have been associated with the emergence and spread of AMR in environmental bacteria due to co-selection. The presence of heavy metals has also been associated with the reduction of susceptibility of bacterial populations in soil.

Principal forms of antibiotic resistance

Natural resistance (Intrinsic, Structural)

In this type of resistance, the usage of antibiotics is notassociated with the resistance but it caused by the bacteria's structural properties. This occurs as a result of intrinsicresistance, or microorganism which doesn't follow the targetantibiotic structure, or antibiotics which due to its characteristics do not encounter its target. Intrinsic resistance is the natural ability of bacteria to resist the effects of an antibiotic due to inherent structural or biochemical features of the bacteria e.g., if an antibiotic is too large to cross the cell wall of a bacteria and get access to its target within the cell. Knowing which bacteria were never susceptible or have a natural resistance to particular antibiotics helps vets and clinicians to prescribe appropriate and effective treatments. Gram-negativebacteria and vancomycin, for example, vancomycin antibiotics do not move through the outer membrane sothat these Gram-negative bacteria are naturally insusceptibleto vancomycin. Likewise, L-form bacteria that are cell wall-less types of thebacteria, such a Ureaplasma and *Mycoplasma. maycoplasma* that are naturally owning beta-lactam antibiotics resistance.

Acquired resistance

Resistance to antibiotics can also be acquired either from the result of mutation of bacterial genes involved in normal physiological processes and cellular structures. These genetic mutations are changes in the DNA sequence of bacteria that occur continuously, to varying degrees. Bacteria can also become resistant through the acquisition of foreign DNA originally from other bacteria, e.g. via plasmids (small circular DNA strands), in a process called Horizontal Gene Transfer (HGT). Sometimes these genetic mutations or the acquisition of foreign resistance genes can lead to the emergence of bacteria with an improved ability to survive treatment with particular antibiotics. If those bacteria are then exposed to these antibiotics, they increase in numbers, while the more susceptible bacteria are killed off. Bacterial population changes are inevitable without the careful management of antibiotics used against them and, as explained above, will occur more quicklyif antibiotics are not taken in accordance with their prescribing instructions. Regardless of resistance development due to alteration in the genetic features of bacteria, an acquired because it is not affected by the antibiotics it was previously susceptible to it. This form of resistance comes from the main chromosome or extra chromosome structures (plasmids, transposons, etc.). Chromosomal resistance results from mutations that change randomly bacterial chromosome, these mutations can occur by certain physical and chemical factors. This may be due to changes in the composition of bacterial cells, so that may be decreased bacterial drug permeability, or may be changes to the drug's target in the cell. Streptomycin, aminoglycosides, erythromycin, and lincomycin can develop resistance to these forms. Extrachromosomal resistance relies on extrachromosomal genetic materials that can be transmitted via plasmids, transposons, and integrons. Plasmids are segments of DNA that areplication dependently of chromosomal DNA. A plasmid is typically responsible for the development of antibiotic inactive enzymes. There are main forms of holding genetic material (resistance genes and plasmids) from bacterial cells, this form are transduction, transformation, conjugation, and mechanism of transposition. The genes with antibiotic resistance on the chromosome or plasmid are inter twined and are situated at the beginning with different integration groups, or integrons. Recombination is very normal in integrons.

Cross-resistance

It is mean the resistance to a specific antibiotic by specific microorganisms, that work with the identical or related mechanisms and that are also resistant to other antibiotics. This is generally seen when antibiotics have common structures: such as resistance to erythromycin, neomycin kanamycin, or resistance to cephalosporins and penicillins.

However, cross-resistance can be sometimes seen in acompletely distinct group of drugs as well, like a cross-resistance that exists amongst erythromycin-lincomycin, this resistance might be the chromosomal origin or not.

Multi-drug and other types of antimicrobial resistance

Multidrug-resistant species are typically pathogens that have been resistant to their antibiotics, this ensures that the bacteria will no longer be eliminated or regulated by a single drug. Inappropriate utilization of antibiotics for treatment culminated in the introduction of multidrug resistant pathogenic bacteria. Either of the two mechanisms can induce multidrug resistance in bacteria. Firstly, these bacteria will acquire several genes; each coding for specific drug resistance, this form of resistance usually exists on R-plasmids. Secondly, the form of multidrug resistance may also occur by enhanced gene expression encoding for efflux pumps, enzymatic inactivation for antibiotics, changes in target structure, and others. If the bacterial strains are not susceptible to three or more antimicrobial types, they are called multidrug-resistant (MDR) bacteria. If the species resistant to all but one or two classes of antibiotics are deemed highly resistant to medicines, whether the species resistant to all usable antibiotics are known as pan-drug resistant. For example, Acinetobacter species with multidrug resistance (MDR) can be identified as the bacteria that having the resistant ability to at least three groups of antibiotics classes, for example for all penicillin and cephalosporin, aminoglycosides and quinolones groups. Extensive Acinetobacter spp., drug resistant (XDR), isolate resistant to the three types of antibiotics classes mentioned above in (MDR), and even carbapenem-resistant, Acinetobacter spp. , Pan drug resistant, or pan-resistant (PDR), these bacteria can be going to be the XDR as well as polymyxin-resistant and tigecycline resistance.

Mechanisms of antibiotics resistance

Modifications that happen in the drug-related receptor and the location of the target regions of the relation with the antibiotics are distinct; these can be complex enzymes and ribosomes. The most frequently identified resistance consistent with variations in the ribosomal target is in macrolide antibiotics. The 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 ofthe most important antibiotics resistance mechanisms.In this group, beta-lactamases, aminoglycosidase, chloramphenicol, and erythromycin modifying enzymes arethe most popular examples. This mechanism results from changes in the permeability ofthe 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 specific 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. This mechanism of resistance is in plasmid and chromosomal control. Active pumping systems for example are effective 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.

Current status of antimicrobial resistance at veterinary clinical settings

In 2010, the global usage of antimicrobials in farm animals was estimated at 63,151 tonnes, while this quantity was estimated at 93,309 tonnes in 2017 and projected to increase by 11.5%, ultimately reaching 104,079 tonnes by 2030. However, the aquaculture sector, despite its rapid growth globally, was not included in this estimation due to the uncertainty regarding the level of antimicrobials used in this animal production. This aspect could lead to an underestimation of the real quantities of antimicrobials used in the veterinary sector on a global scale. Interestingly, pig production had the largest projected increase in AMU globally and contributed by 45% to the total increase between 2017 and 2030. Moreover, it has also been estimated that there will be an increase of 15% for AMU in humans between 2015 and 2030. The causal link between the use of antimicrobials in animal production and the selection of resistant bacteria and their genetic determinants is not universal. This indicates a complex causality involving the interaction of several other factors that determine the magnitude of selection pressure, the spread, and the persistence of AMR bacteria and genes within the animal intestinal microbiota and in the farms environment. Several factors can be implicated, including the way antimicrobials are used on the farm (therapeutically, prophylactically or as a growth promoter), routes of administration, duration of antimicrobial use, veterinary control, herd size, and the level of biosecurity and sanitation as well as the genetic linkages of genes in the bacteria. Generally, reducing the use of MIAs in livestock is associated with a reduced selective pressure of these antimicrobials on animal gut microbiota, leading to gradual reduction of the resistant bacterial population. However, the co-existence on a single plasmid within the same bacterial strain of several AMR genes causing co-resistance selection may always trouble the relationships. Nevertheless, through the use of neural networks and other statistical analysis, complex relationships could be demonstrated. This illustrates the importance of implementing a comprehensive strategy, at the farm level, that includes the reduction of all antimicrobials. From an animal health and welfare perspective, a complete ban on all antimicrobial use (AMU) is not advisable, and it has been shown that this is not required as long as the judicious use of these drugs is respected.

Possible mitigation strategies to combat Amr

One-health approach

AMR being ubiquitarians, microorganisms represent a pool of AMR traits in all ecological niches. The complex network of interactions occurring between microbial specimens from diverse "environments" facilitate the gene flow, expanding the AMR between humans, animals, and the environment, resulting in an overall issue. Thus, a coordinated multisectoral approach such as One-Health is desired to investigate and address this warning phenomenon. It is defined as One-Health, "the collaborative effort of multiple health science professions, together with their related disciplines and institutions -working locally, nationally, and globally to attain optimal health for people, domestic animals, wildlife, plants, and environment". Most of the classes employed in the treatment of human infections are shared with the veterinary sector, resulting in a cumulative selective pressure exerted to the microorganisms; thus, reduced efficacy of the antimicrobial-based treatments in both human, veterinary and environmental field. In the human sector, the main actions undertaken by the One-Health approach include a higher consciousness while prescribing antibiotic treatment, preventing over-prescription and improvement of the hygiene conditions and infection control plans. The One-Health actions in regard to the environment sector include the appropriate treatment of industrial, civil and farm waste, on the attempt to reduce the overall dissemination of the AMR traits between sectors.

Antimicrobial stewardship in veterinary medicine

The concept and practice of antimicrobial stewardship continues to evolve in human and veterinary medicine, but it is an approach that takes an active, dynamic process of continuous improvement encapsulated in the idea of good stewardship practice (GSP). Only a GSP mind-set will ensure the long-term sustainability of antimicrobial drugs. Antimicrobial stewardship and GSP involve coordinated approaches and interventions designed to promote, improve, monitor, and evaluate the judicious use of antimicrobials to preserve their future effectiveness and promote and protect human and animal health. This involves a "5R" approach of responsibility, reduction, refinement, replacement, and review.

Awareness and education

Regarding the importance of a farmer's knowledge in the decision making process, one can assume that all the measures implemented to raise awareness and responsible AMR should be encouraged, although little evidence of the benefit of such measures in veterinary medicine exists. Improvement of education and awareness can be attained by proximity technical transfer or as part of coordinated actions. These two methods are based on the constant interactions between farmers and organizations public or private playing a role in health care. The major influence of veterinarians on farmers' AMU has been reported in several papers. In some cases, institutions can coordinate collective action to face a collective problem. In human medicine, for example, 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 significant reduction of drug consumption. Conversely, wide diffusion 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. Therefore, governments have implemented specific 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 effect on the externality AMR of commensal bacteria, due to the existence of cross-resistance between the different classes.

Financial alternatives to prices' control: taxes and insurances

A first 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. The 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 differentiated taxes on antimicrobials have been applied since 2013 in order to promote the use of vaccines instead of antimicrobials with a specific focus on CIA. The 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 financing activities on AMR, they did not greatly affect antimicrobial consumption.

Surveillance of antimicrobial resistance

Surveillance represents a key component of the control of AMR. The World Health Organization developed standards to detect emergence of resistance. In parallel, several countries implemented monitoring of resistance among commensal and zoonotic bacteria. These 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 first step to limit the impact of antimicrobials on commensal floras. For example, recently in veterinary medicine, the marbofloxacin dosage regimen was re-evaluated for treatment of Gram negative infections and the current labeled dose of 10 mg/kg given in a single injection was added to the first label approved dosage of 2 mg/kg over 3–5 days, leading to a decrease in the time of residence of the drug in the body while maintaining clinical efficacy. Dosage regimens of existing drugs previously determined according to results of clinical trials can also be evaluated based on standard Pharmacokinetics/ Pharmacokinetics concepts, as performed with tulathromycin in calves. Innovations in veterinary AMR should also aim to limit the impact of antimicrobials on the commensal flora (especially the digestive flora) of the treated animals, without reducing their curative efficacy on the targeted bacterial infection. A recent review depicted the Pharmacokinetics/ Pharmacodynamics characteristics of the ideal antimicrobial for food-producing animals.

Veterinary precision medicine

In human medicine, Personalized Medicine is defined as a form of medicine built on information about patients' genes and their environment, aiming to refine diagnosis, to select the most appropriate treatment and increase the patient's chances of recovery. In parallel, Precision Agriculture emerged in the late 20th century, fulfilling an objective of optimization of agricultural practices while considering their environmental impacts. In crop science, digital technologies (satellite mapping, climate and epidemic alarm systems) provide farmers tools for supporting decision making. These tools allow for example, limitation of consumption of fertilizers or pesticides. In animal production, precision farming is defined as "the use of technology for monitoring physiological indicators, behavioral or production on animals to improve herd management strategies and breeding performance". In field conditions, the lack of cheap and practical diagnostic tools constitutes a major barrier to rationalization of antimicrobial treatment, and innovation in this domain should be firmly encouraged. Optimization of the antimicrobial regimen can also be achieved by combining early detection of disease with a low antibiotic usage regimen. New techniques of bovine respiratory diseases diagnostics, such as cough captors or ruminal temperature boluses, can be used to monitor early signs of illness before appearance of clinical signs. Recent studies conducted with mice and calves suggested that a decrease in the administered dose of fluoroquinolone allowed achievement of similar bacterial cure, when low bacterial inocula are targeted and the disease is detected early.

Alternatives to antimicrobial for disease prevention

Vaccines

Vaccines have been widely used in veterinary medicine to prevent diseases caused by viruses or certain bacteria, and they are promising substitutes for some antibiotic uses. Notably, reducing viral infections may lead to decreased antibiotic use because of the risk of misdiagnosis and because antibiotics may be used to prevent or treat secondary bacterial infections. Therefore, vaccines for both viral and bacterial infections are relevant to the discussion around alternatives to antibiotics. Evidence suggests that at least some vaccines may also have positive effects on growth rates and animal performance, even

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

Immune modulators

Immune modulators, which as defined 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 effective against a broad range of pathogens. A very broad variety of immune stimulatory substances has been investigated as potential alternatives to antibiotics. These 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. The efficacy 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. There are also safety concerns about using immune-stimulants before the immune system is fully formed because of the potential risk for adverse developmental effects.

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 affecting 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. Therefore, 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 effective. 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 efficacy when administered more than 16 hours after 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 significantly 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 effective 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 different bacteriophage strains can help address these limitations, but to date, efficacy 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. The hydrolases can be derived from a number of different sources, including bacteriophages, as well as animals, plants, bacteria, and insects, with varying specificity for target bacteria. Endolysins, also commonly referred to as virolysins, are generated by bacteriophages. Bacteriophages generate endolysins at specific stages of their life cycle, shortly before the virus destroys the bacterial cell. In that process, endolysins aid in the release of the newly generated bacteriophages. Endolysins tend to have a relatively narrow spectrum of bacteria against which they are effective and are highly thermo stable. In experiments at 100 degrees Celsius, some retained over 70 percent of their activity against *Staphylococcus aureus*. Such heat stability can be important to assure product integrity, as some feed is processed at high temperatures. The mechanism by which endolysins target and eliminate pathogenic bacteria has been fully described and depends on two distinct functions: binding to specific sites in the bacteria cell wall and cleaving the bonds between the peptidoglycans in the cell wall. Endolysins are tentatively promising enzymes for the prevention and treatment of certain bacterial infections. In part, this is because it is believed to be more difficult for bacteria to develop resistance against them, and in part, because it may be possible to specifically engineer endolysins with the desired host spectrum. However, concerns about potential adverse immune responses and the downsides of a relatively narrow host spectrum have to be considered. Yet, although efficacy data specific for the use of endolysins in food-producing animals have so far remained scarce, endolysins have shown promising results against a relatively broad range of bacteria. It should be noted that endolysins are not effective against all bacteria. Because of differences in the bacterial cell wall, endolysins tend to have limited efficacy against Gram-negative bacteria. Lysozymes and autolysins are hydrolases generated by eukaryotic organisms (i.e., animals and plants) and bacteria, respectively. In humans, lysozymes are an important component of the innate immune system and naturally present in the skin and secreted into saliva, urine, milk, and other bodily fluids. Lysozymes in particular tend to have activity against a broad spectrum of bacteria and are known to effectively break down the carbohydrate component of peptidoglycan layer of bacteria. They are also known to be effective against viruses and other pathogens. Lysozymes and autolysins are promising alternatives to antibiotics, although they share many of the limitations discussed under endolysins.

Other disease prevention alternatives

A variety of other approaches for disease prevention has been proposed, including biofilm inhibitors and quorum-sensing inhibitors (i.e., substances that disrupt biofilm formation, a bacterial communication system that plays an important part in the infection process). While these approaches may offer innovative alternatives to antibiotics, data on safety and efficacy are to date largely lacking. In addition, their impact on production performance for growth promotion purposes replacing antibiotics remains largely unknown. One class of specific and particularly promising products is virulence inhibitors: molecules that directly affect the harmful microbes and block key functions they need in order to survive and infect. For example, they may prevent bacteria from forming pili, structures that allow them to adhere to animal cells. Experimental data for inhibitors remain limited, so the safety and efficacy of these approaches are unclear; however, such novel approaches represent a new path, one that does not attempt to directly kill bacteria but rather tries to restrain some of their pathogenic activities. This approach may for instance be less likely to disrupt the healthy balance in the gut. Biosecurity and management practices are an important part of disease prevention that can improve overall animal health and significantly reduce the risk of pathogen introduction into the herd or flock. Notably, a comprehensive approach that includes alternative products and improved management practices is likely to be more effective 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 effective means of preventing the introduction of diseases into herds or flocks. This concept applies widely across species, production systems, and pathogens.

Conclusion and Recommendations

The current antimicrobial resistance crisis is likely to be a permanent feature of animals and human society, causing increased animals suffering and social-economical costs. Managing this crisis to limit its effect upon animals will require a fundamental shift in the global perception of anti usage. A variety of products and management practices may eventually be able to replace a substantive proportion of current antibiotic use for prevention and growth promotion purposes, but this effort will require a comprehensive approach that considers alternatives as one part of a herd health management program.

Therefore, the following points are recommended for the antimicrobial resistance in veterinary medicine:

- Continuous awareness creation should be done for antimicrobial resistance among animal health professionals, animal producers and the general community.
- Implementable and inclusive antimicrobial usage policy formulation and enforcement should be done.
- Developing new antimicrobials is important, but strategies to prevent infectious diseases by immunization or other public health measures should also be done.

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