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Chapter

Veterinary Pharmaceuticals and Antimicrobial Resistance in Developing Countries

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Abstract

Veterinary pharmaceuticals include a wide range of anti-infectives and additives in the use for animal health, nutrition, reproduction, and productivity. Antimicrobials are among the most extensively used drugs in developing countries largely due to large population of livestock and the burden of infectious diseases. 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/or 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 antibiotics 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. The consequences include development of AMR. In this chapter, we reviewed antimicrobial use in veterinary medicine and sequela in the emergence of AMR and described the imperative of antimicrobial stewardship in veterinary practice to combat AMR in developing countries.

Keywords: veterinary drugs, antimicrobial resistance, stewardship, developing countries

1. Introduction: veterinary pharmaceuticals and antimicrobials

Veterinary pharmaceuticals include drugs, medications, and other substances in use to treat or prevent animal diseases for health, growth promotion, and productivity [1]. These drugs can be broadly divided into categories according to the different pathogens or targeted infections. They include antiparasitic drugs, antiinflammatory, reproductive medication, surgical medications, anesthetics, nutritional drugs, and feed additives sometimes used as growth promoters (**Table 1**). Among commonly used drug in veterinary medicine are antibiotics. These drugs and medicaments can be administered in form of injectable, tablet, bolus, drench, and bath/wash or added to feed and drinking water. There are documented evidence of earlier norms and practices of animal husbandry regarding how shepherd and nomads provide

Antibiotics	Antiparasitic	Antiinflammatory	Anesthetics	Growth promoters
Terramycin	Banminth	Ibuprofen	Phenobarbital	Feed grade antibiotics
Penicillin	Ivermectin	Meloxicam	Thiamylal	Probiotics
Streptomycin	Diminazene aceturate	Dexamethasone	Xylazine hydrochloride	Dihydropyridine
Colistin	Amprolium	Prednisone	Chlorpromazine	Organic acids
Erythromycin	Piperazine	Prednisolone	Diazepam	Amino acids
Doxycycline	Albendazole	Aspirin	Thiopental sodium	Racto-amine
Enrofloxacin	Closantel	Phenylbutazone	Pentobarbital	Sodium-bicarbonate
Tylosin	Dermatocide	Dimethylsulfoxide	Chloral hydrate	Potassium chloride
Oxytetracycline	Diazinon	Flunixin	Methohexital	Fatty acids
Amoxicillin	Nitroxynil	Meglumine	Methoxyflurane	Zytomil
Gentamycin	Cypermethrin	Cortisone	Halothane	Renature-Z oral powder
Chloramphenicol	Pyrantel pamoate	Methimazole	Diethyl ether	Vita-Sel-E oral solution
Ciprofloxacin	Praziquantel	Celecoxib	Isoflurane	Eucament plus oral solution
Griseofulvin	Mectizan	Colchicine	Enflurane	Chicktonic
Norfloxacin	Nitroxyl	Cyclooxygenase	Nitrous oxide	Aminogrow WS
Rifampin	Diclazuril	Pylorus	Glyceryl quiacolate	Electromix WS
	Novidium chloride	Mavacoxib	Succinyl choline	Introvit A+ WS
	Isomethadone	Tepoxalin	Curare	Introvit-ES-200 WS
Furazolidone	Homidium chloride	Piroxicam	Lidocaine	Introvit-K-200 WS

Source: survey of commonly use veterinary antimicrobials in Nigeria, courtesy of Dr. Jolly Amoche of National Veterinary Research Institute, Vom.

Table 1.
Some veterinary pharmaceuticals distributed in Nigeria.

medication for livestock. Some were written document by priests in monasteries, such as the use of garlic (*Allium sativum L.*) and ointment made from honey and grease [2]. This is similar to what has now been recognized in modern veterinary medicine as ethno-veterinary or alternative medicine in human and according to the World Health Organization (WHO); 75% of the world's population are using herbs for basic health-care [3]. Such practices predate modern day pharmacopeia, which has, however, refined and synthesized the delivery of veterinary and human medicines. Some global industrial leaders in modern veterinary pharmaceuticals include Zoetis (formerly Pfizer Animal Health), Merck, Bayer, Elanco Animal Health, Boehringer Ingelheim Animal Health (Merial), Norvatis Animal Health, and many others. These companies and their subsidiaries are engaged in the multibillion dollars profitable business of drug distribution in developing countries (and also from Asia to Africa) in millions of doses some of which may be overused and contributing to drug resistance [4, 5].

Globally, there are more livestock in the world than human, with livestock systems occupying about 30% of the planet's ice-free terrestrial surface area [6]. Most of these animals are kept in free range husbandry systems in under-developed countries where the enterprise supports the livelihood of about 600 million small holders [7]. The livestock sector in developing countries is also evolving in response to rapidly increasing demand for livestock products with changes in the demand for livestock products being driven among other factors by human population growth, urbanization, and increasing income [8, 9].

A major limiting factor in profitable livestock production in developing country is the burden of infectious diseases. These livestock diseases cause great socioeconomic impact, and the burdens are most of the time exasperated by poor biosecurity in both intensive and open production systems. This has made the use of antimicrobials for treatment of diseases indispensable [10]. It is important to emphasize that the reduction in the burden of infectious livestock diseases has been possible due in part to the use of a wide range effective drugs and vaccines and improvements in diagnostic techniques and services [11].

Therapeutic treatments are targeted at animals that are diseased. In food animals, it is usually often more convenient to treat entire groups by administering medication through feed or water, though individual animals may also be treated. For animals like poultry and fish, mass medication is the most feasible means of treatment but with the possibility of drug dispersal into the environment via leaching and agricultural wastewater [12]. Furthermore, certain mass-medication procedures called metaphylaxis, aimed at treatment of sick animals while medicating others in the group that may not be sick but exposed, can also be counterproductive. Other prophylactic antimicrobial treatments are typically used during high-risk periods for infectious diseases even, while the animals may not be infected also described as nonspecific infection prevention [13]. These practices, however plausible, are currently considered as contributing to emergence of antimicrobial resistance due to subtherapeutic exposure to veterinary pharmaceuticals by both infected and noninfected animals, as well as the environment [14].

Antimicrobial resistance has been described as the ability of bacterial, parasites, viruses, and fungi to survive and spread despite treatment with specific and combination therapy that are normally used against them [15]. The World Health Organization also emphasized that resistance happens when microorganisms change when they are exposed to antimicrobial drugs (such as antibiotics, antifungals, antivirals, antimalarials, and antihelmintics). These microorganisms that develop antimicrobial 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 1943/44 by Alexander Fleming [13]. In evolution, selection pressure is bound to cause subpopulation of microorganism with resistance genes to emerge [16]. This selective pressure has been ascribed to appropriate and inappropriate use of antimicrobials but aggravated by (1) intensity of usage, (2) persistence of usage, (3) under usage and subtherapeutic doses that animals are exposed to in prophylactic treatment, and (4) unintended human exposure through antimicrobials in food residues and the environment [10].

The burden of infectious diseases in developing countries and intensive use of antimicrobials to combat this has also been stressed in a study that suggested that up to a third of the global increase (67%) in antibiotic consumption will be in food animals, over the period 2010–2030 and attributable to low-middle income countries [17]. This challenge is in view of the high burden of foodborne infectious and zoonotic diseases especially also in developing countries [18]. 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 [19]. 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 [20].

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 subtherapeutic doses in animal products [13]. When resistant organism emerges, it has also been argued that human sources also seed these resistant bacteria to animals and the environment through sewage [21]. A recent study by Marcelino et al. [22] described high levels of antibiotic resistance gene expression among birds living in a wastewater treatment plants. The study observed that birds feeding at a wastewater treatment plant carried greatest resistance gene burden, suggesting that human waste, even after treatment, contributes to the spread of antibiotic resistance genes to the wild. Domestic and wild animals, including rodents, and birds, can acquire these environmental contaminants and pass them on via their excreta to grazing land or feed of food animals, which may in turn end up in human through the food chain [23]. While it is imperative to canvass AMR stewardship through rational and circumspect usage of antimicrobial in animals, it is important to bear in mind that human also present risk to animals. The USFD described the phenomenon of antimicrobial resistance as a very complex and nonvictimless phenomenon, affecting both human and animal health [13].

2. Livestock diseases and the application of veterinary pharmaceuticals

In the management of infectious and noninfectious diseases of livestock in developing countries, a number of veterinary pharmaceuticals are administered. The choice of drugs is often determined by efficacy, availability, and cost. These factors are explored by manufacturers mostly based in developed countries from where the drugs are exported to developing countries. This distribution chain is also largely driven by business interest such that drug companies sell volumes that are targeted at frequent, intensive usage that may have deleterious effect such as emergence of AMR.

Intensive use of veterinary chemotherapy on the other hand may be justifiable considering that many bacterial, viral, and parasitic diseases like mycoplasmosis, Newcastle disease, avian influenza, anthrax, coccidiosis, brucellosis, foot and mouth disease (FMD), rift valley fever, etc. threatens socioeconomics, instills fear that shock systems, either by suddenly and rapidly killing large number of animals or causes large-scale drop in demand through fear of zoonotic diseases [24, 25]. On the other hand, the growing concern that animals are major sources of human diseases and that around 60% of all animal diseases are zoonotic [26] make treatment of such diseases in animals an essential control measure before it is transmitted to human, and to reduce their capacity to cause epidemics and pandemics.

The livability and economic impacts of animal disease disaster is well documented, for instance, highly pathogenic avian influenza recently killed millions of poultry birds in Nigeria (including other countries in West Africa) and wiped out entire farms [27]. The costs of epidemic African swine fever in Cote d'Ivoire was estimated at

$9.2 million; Nipah virus in Malaysia $114 million, while contagious bovine pleuro-pneumonia in Botswana costs about $300 million [25]. In the absence of preventive measures such as biosecurity and vaccination, the use of antimicrobial especially for nonviral infections is essential for profitable livestock production and to prevent infections that may be transmitted from animals to human as attested to by WHO [28].

3. Development of AMR in veterinary practice

The global antimicrobial resistance (AMR) crisis is predicted to kill roughly 10 million people annually by 2050 due to antibiotic-resistant infections, with Africa alone accounting for about 4.15 million [29]. This is estimated to cost the global economy about $100 trillion [30] with about 28.3 million people pushed into extreme poverty [31]. The alarming rate of AMR in developing countries can be attributed to gross misuse of antimicrobials in human and animals [32]. Although resistance can still develop even at an appropriate antimicrobial use, however the situation can be made worse whenever there is excessive and unnecessary usage [33]. The global revolution in livestock and aquaculture is an underlying factor for frequent antimicrobial use and subsequent development of AMR. This is also driven by population increase, urbanization, improving economic conditions, and globalization. Countries like Brazil, China, and India are currently the hotspots for livestock intensification, while Nigeria, Myanmar, Peru, and Vietnam are future spots (Van [17]). In developing countries, most nonhuman-medical use of antimicrobials is almost certainly in livestock and farmed fish production and it is likely that most veterinary use is in intensive production rather than pastoralist or small-holder systems [34]. In Nigeria and other developing countries in sub-Saharan Africa, Asia and Middle East, there is paucity of information on antimicrobial drug resistance in farm animals, although little information exists on residue level [35–38]. However, there is information on antimicrobial drug resistant microbes isolated from human patients from different parts of Nigeria [39, 40]. Previous report by Adesokan et al. [41] on pattern of antimicrobial usage in livestock production in three states of South-Western Nigeria between the period of 2010 and 2012 showed an increased use of tetracyclines (33.6%) followed by fluoroquinolones (26.5%) and beta-lactams/aminoglycosides (20.4%). Similar trend was also reported in Africa for tetracycline & beta-lactams [42]. However, studies by Idowu et al. [35] showed level of tetracycline residues between the ranges of 0.1–1.0% in chicken eggs.

The process of AMR development is very complex, and all of the factors that contributed to the events are not fully understood. It is clear that genetic change or mutation in microbial DNA may often cause resistance to antimicrobial agents, and this change might also be passed to the offspring or transferred to other related or even unrelated microorganisms [43]. This is known as "selection pressure" where the use of antimicrobial drugs in health care, agriculture, or industrial settings favor the survival of resistant strains (or genes) over susceptible ones, thus leading to a relative increase in resistant bacteria within microbial communities [44]. This is because no matter how effective an antimicrobial is, it rarely kills 100% of the organisms, meaning some may still survive due to genetic change, which can be passed forward. Currently, science has not fully proved the causes of different types of AMR that are causing great public health risks. The widespread use of antimicrobials in food production system especially in food-producing animals is another cause of AMR [45]. The extensive use of antimicrobials in animal production as growth promoters widely exposes the microbes to the drugs, thus enhancing the development of microbial resistance causing health consequences in both animals and humans. However, the scientific evidence of how and to what extent such drug

exposure affects human health still remains unclear. It is interesting to note that antimicrobial resistance would not develop in animals if antimicrobial drugs were never used in them [12].

There is danger to public health if resistant organism from animals can also cause disease in human exposed by a way of food consumption or direct contact with food-producing animals, companion animals, or through environmental spread [46]. The threat to public health also exists even if the organisms do not cause disease in human, because they may still be able to transfer the resistant genes from food-producing animals to unrelated human pathogenic bacteria as well as normal commensals [47]. It is then clear that the increase use of antimicrobials in animal production for variety of purposes such as for therapeutic and nontherapeutic use has contributed to increasing AMR in bacteria affecting man and animals [48]. In Africa and other developing countries, studies have suggested a strong correlation between the use of antimicrobials in veterinary practice and the development of AMR [49], because it is shown that a larger proportion of antimicrobial medications have been used in animals than humans mainly for food production purposes [50]. There is presence of high antimicrobial residue in meat and milk meant for human consumption correlating with the detection of multidrug resistance (MDR) bacteria in animals and their products [51] as well as in humans in contact with the animals [52–54]. This is also because a large proportion of the population in developing countries lives in close proximity with livestock, which enhance the chances of transfer of resistant microorganisms from animals to humans [55, 56]. Similarly, the increasing use of antimicrobials as prophylaxis in aquaculture in developing countries further contributed to the emergence of AMR causing problems in human, animal, and environmental health [57]. The risk to humans further exists especially when similar antimicrobial is used in both animals and humans, or there is presence of cross resistance between antimicrobial used in human and veterinary practice. Using antimicrobials that are also used in human medicine for growth promotion is especially conducive to AMR because exposure of many animals to low dosages makes resistance more likely to emerge [34].

For some antimicrobials, there is development of resistance by bacteria through plasmid-mediated transferable resistance [58]. The minimum inhibitory concentrations (MIC) for a target pathogen might be considerably different from those of commensals, and thus, the resistance gene in commensals may be selected and transferred to humans and then to human pathogens leading to development of AMR [59]. Despite the fact that the exchange of genetic materials and the short generation time of organism contributed to the development of AMR by many bacteria [60], some drugs such as penicillin still retains excellent activity on certain organism (e.g., *Streptococcus agalactiae*) after about 6 decades of usage [61].

AMR development can often be caused by inhibition of specific antimicrobial pathways such as cell wall synthesis, nucleic acid synthesis, ribosome function, protein synthesis, foliate metabolism, and cell membrane function by the organism [62–64]. The various steps involved in the production, distribution, prescription, dispensing, and finally consumption of the drug by human patient or its use in animal production often contributed to the emergence of AMR especially when there is imprudent or irresponsible practice along the supply chain [65]. Part of veterinary medical education is to understand how antimicrobials affect microorganisms, and how they can be used responsibly to protect human and animal health [66]. In food production systems, veterinarians are on the frontline when it comes to keeping nation's food supply safe. Advances in animal health care and management have greatly improved food safety over the years and have reduced the need for antimicrobials in food production systems [67]. Nevertheless,

antimicrobials are an important part of the veterinarian's toolkit, and so veterinarians are aware that they should be used judiciously and in the best interest of animal and public health [66]. More importantly in the development of AMR is the quality of antimicrobials. Though difficult to implement, it has been suggested that incidence of microbial resistance can be reduced if the antimicrobials that are used in human health are not used in veterinary practice [68]. Moreover, the practices of mass treatment of all animals in a group when only one animal is sick (metaphylaxis) as well as the treatment of all animals when they are exposed to conditions that can make them likely to be ill (prophylaxis) will result in an increased antimicrobial use and as such would encourage the development of resistance [69].

Although the development of animal-related AMR is associated with the quality and quantity of antimicrobial usage in veterinary practice, there are other underlining factors that can influence AMR development:

- Lack of awareness: in developing countries, there is little or no awareness or concern in the use of antimicrobials as compared to developed nations who recognize AMR as a global challenge. Omulo et al. [70] showed that only 24% of studies in Africa are related to AMR in animals or their products. In East Africa for example, despite the relevance of antibiotic procurement in health budgets, there was still a slow progress in research focusing on AMR of enteric pathogens. There is still lack of awareness among many veterinarians and other food producing personnel on the negative impact to human health as a result of extensive use of antimicrobials in animals [71].

- Lack of information: the information is lacking in developing countries concerning the existence and prevalence of AMR in animals and animal products and the negative health consequence as well as the cost of AMR illness in people and animals.

- Fake and substandard drugs: there is much concern over counterfeits and substandard drugs in animal health care, but there is insufficient data to understand its importance. Counterfeits and substandard products, which contain active ingredient at a lower level, will increase the chance of developing resistance. There is no comprehensive information on fake/substandard veterinary drugs.

- Lack of adequate 'One Health' integration between animal and human healthcare: in developing countries, there is poor collaboration in healthcare sectors between human and veterinary practice especially on collection and sharing of data on antimicrobial usage. However, at international level, good collaboration exists in the area of AMR between human and animal world health bodies like WHO, OIE, and FAO.

- Lack of substitution to the use of antimicrobials: alternative to the use of antimicrobials is lacking in developing countries unlike the developed nations that had successfully banned the use of antimicrobials as growth promoters and replaced with alternative growth promoters and good practice without having negative impact on the performance of their livestock industries. This could hardly be achieved in developing nations that have propensity to source antimicrobials from the black markets, which may be of poor quality, thus exacerbating the problem and creating a considerable increase in disease, with consequent mortality and morbidity losses [34].

4. Prevention of AMR in veterinary practice

In a bid to ensure measurable containment of AMR, there is a global formal declaration on AMR calling for the development of action plans on AMR by both international and national bodies. The Global Action Plan on Antimicrobial Resistance was approved in May 2015 by the World Health Assembly with the key strategies to increase global AMR awareness as well as developing policies that will attract more investment in the area of new medical interventions [72]. There is also a call to all Member States for establishing National Action Plans for AMR by 2017 of which about 57 countries have formalized such plans so far. The 2016 meeting of the UN General Assembly was another milestone focusing on multidisciplinary solution to the problems of AMR [73]. Moreover, the G20 called for the creation of a Global Research and Development (R&D) Collaboration Hub on AMR in July 2017 that could coordinate international funding efforts [74], and the search for the appropriate individuals to lead that hub began early this year. In line with the global agreement to develop National Action Plan on AMR, Nigeria (with some other developing nations) keyed into this agreement in 2017 through a 'One Health' approach [75] and then enrolled into a Global Antimicrobial Resistance Surveillance System (GLASS). The Action Plan addresses five strategic objectives:

1. improving awareness and understanding of AMR through effective communication, education, and training

2. strengthening the knowledge and evidence base through surveillance and research

3. reducing the incidence of infection through effective sanitation, hygiene, and preventive measures

4. optimizing the use of antibiotics in human and animal health

5. preparing the economic case for sustainable investment and increasing investment in new medicine, diagnostic tools, vaccines, and other interventions

Several challenges exist regarding AMR containment in developing country like Nigeria; however, the development of this action plan is an important positive step in the right direction as it aims to address the problem at all level of governance and society [75].

Veterinarians play an important role in limiting and minimizing the spread of antimicrobial resistance (AMR). Because vets are often the first point of contact for livestock owners seeking animal medical attention, they can therefore play a part in addressing the problem of AMR [45]. One of the ways to reduce the risk of transfer of AMR from animals to humans is by minimizing the zoonotic transfer of bacteria [76]. This could be achieved by practicing stringent hygiene in the farms and any meat processing plants including the abattoirs and the markets. Thorough and effective cooking of meat product can also reduce the risk of AMR [77]. There is need to strengthen the information resources in developing countries to support health workers, patients, animal owners, and attendants as well as the general public to help in reducing the risk of AMR arising from the use of antimicrobials in animals. This will enable the society to better understand the importance and value of antimicrobials. The excessive and inappropriate use of antimicrobials in veterinary practice should be discouraged. Because antimicrobials are an extremely valuable resource in livestock production, their prudent use in animals will continue to provide benefits to society and will help ensure high

standards of welfare for those animals in the care of veterinarians [78]. Since exposure of bacteria to subtherapeutic concentrations of antimicrobials is thought to increase the speed of the selection of resistance, this should always be avoided [14, 15, 79]. Appropriate pharmacokinetic and pharmacodynamic relations for antimicrobials used in animals should be developed [12]. Optimal dosage strategies for eliminating zoonotic organisms in animals will reduce the risk of transferring resistance to humans [80].

According to Delia [34], broad consensus on the management of AMR in human and animal healthcare will require to:

- reduce antibiotic use in humans and animals through public health improvement such as hygiene and sanitation, immunization, infection control, as well as good housing and environment.

- regulate the sale and use of antibiotics through prescription.

- encourage research and development of new antimicrobials.

- minimize the level of environmental contamination of antimicrobials emanating from manufacturing process as well as agricultural, hospital, and community use.

- develop integrated global policies on the use of antibiotics.

- ban the nontherapeutic use of antimicrobials as growth promoters in agriculture.

Currently, there is no adequate information on animal production losses due to disease burden and the extent at which it could be prevented through proper use of antibiotics or their alternatives.

Although in Europe and other developed nations, the use of alternatives to antimicrobials as growth promoters is a success; their applicability in developing countries is not fully understood.

Despite the huge investments in the control of diseases in developing countries through vaccination, vector control, and the use of resistant breeds, evaluation from the angle of reduction in the usage of veterinary drug is lacking. In developing countries, the incidence and composition of substandard and fake drugs as well as their effects on treatment failure and resistance development is not well known. Similarly, the level of resilience of livestock farmers in developing countries to ban or restrict access to antimicrobials is equally not well known. It should be noted that policy and regulation alone is unlikely to improve use of vet drugs and the options for improving the use of vet drugs in agriculture and their effectiveness, feasibility, and affordability are not well understood.

4.1 Rational drug use

There have been success factors in the improvement of drug use in human health through wide range of intervention studies. Similarly, the World Animal Health Organization (OIE) and other world veterinary bodies also developed frameworks on rational use of vet drugs to which there is a limit veterinarians can make profit from antimicrobial sale for food animal production [71]. This is not the case in developing countries where the sale and use of veterinary antimicrobials is facing challenges for improvement. It was found from series of intervention studies that training remains the most common strategy for improving drug use, but this gave little success unless when combined with other strategies like changing the market condition [1].

4.2 Governance of antimicrobial use

Antimicrobial use in human and veterinary practice requires holistic approach in order to improve drug governance. There is need to list the critical or essential drugs in human and veterinary practice with requirement for prescription and guidelines such as banning the use of medically important antibiotics in agricultural practice and off-label use of antimicrobials as well as monitoring antimicrobial use and resistance. Not much success has been recorded in this regard in developing countries especially in livestock production and aquaculture due to little investments. According to OIE, better governance of veterinary antimicrobials comes from empowering veterinarians and limiting prescription to them. Most of the private veterinary service providers in developing countries are not operating at a significant scale and as such are often employed directly by agriculture and agro-allied companies making them to be less independent. The few that are successful are not operating with the guidelines of current OIE policy [81]. The community animal health workers (CAHWs), that have proven to be effective, are very expensive to train and may not be politically acceptable [82]. This is because there is lack of resources to support them by public veterinary services, and the private veterinarians often see them as potential competitors. A study investigated rational drug use by farmers and found that farmers in West Africa were mainly responsible for buying and using antimicrobials, and providing simple information on correct drug use could lead to improved drug usage as well as reduced amount of underdosages, which is an important factor for the development of AMR [83].

4.3 Antimicrobial alternatives in veterinary practice

As previously mentioned, developed countries banned the use of medically important antibiotics as well as growth promoters in animal production, which has led to better farming practices as well as reduction in AMR of medically important microbes found in farm animals. With this natural experiment, it demonstrated that routine antimicrobial usage is not a precondition for healthy animals as long as there is better hygiene and sanitation with good housing condition, and the use of antibiotics is only limited to clinical condition. The benefit of antimicrobials as growth promoters may sound reasonable only under poor management and hygiene situations [71]. Although the type of intensive livestock production in developing countries makes them rely more on nontherapeutic use of antimicrobials, there are many other promising innovations that could support profitable and productive agriculture with less reliance on antimicrobials use such as:

- The use of nonantibiotic growth promoters like enzymes in feed, competitive exclusion products as well as probiotics and prebiotics

- The use of other animal health technologies such as vaccines, vector control, disinfectants, phyto-therapy, as well as phage-therapy, which are underutilized in developing countries. The phage products can readily be designed to thwart development of resistance. They have been used as antibacterial agents for nearly 100 years in the former Soviet Union, and they are now undergoing a renaissance in other countries due to the growing AMR problem [33, 84–87].

- The use of robust diagnostic techniques for improved drug selection and identification of AMR pathogens

- The management and bio-security innovations like all-in-all-out systems, pathogen-free systems, stocking density reduction, and improved waste management systems.

- The use of genetically disease resistant animals as well as avoidance of monocultures of genetically similar animals.

All these intervention strategies will improve animal welfare as well as reducing environmental externalities of animal agriculture. A more radical suggestion is to decrease the amount of consumption of animal source food or shift from intensive to organic animal production.

5. Veterinary antimicrobial stewardship in developing countries

The safeguarding of antimicrobial agents for future generations is of utmost priority as AMR threatens the very core of modern medicines and the sustainability of an effective, global public health response to the enduring threats from infectious diseases [72]. In many developing countries of the world, gaps exist among health care professionals on the current status of antibiotic resistance in their area due to lack of a systematic surveillance at country, provincial, and district level [88]. There is a paucity of clinical data on antibiotic resistance, and this is particularly the case in resource-poor settings. Tons of antibiotics are used annually in clinical and agricultural settings worldwide. The estimates of the total annual global consumption of antimicrobials in animal production vary considerably due to poor surveillance and data collection in many countries [89]. In 2013, food animals alone consumed over 130,000 tons of antibiotics [90]. It cannot be ignored that two-thirds of the estimated future growth of usage of antimicrobials is estimated to be within the animal production sector, with use in pig and poultry production predicted to double [89]. Nigeria, Pakistan, India, Bangladesh, China, and Egypt are the developing countries with massive consumption of antibiotics [88].

The implementation of rational and restricted use of antibiotics is lacking in most developing countries where you have the largest market of antimicrobial drugs and reports of the highest rate of antibiotic resistance [86, 87]. Due to these developments, antimicrobial stewardship programs have emerged as an essential means to attenuate the threat of a real possibility of the specter of a "postantibiotic era" [91, 92].

Antimicrobial stewardship is a harmonized program (the optimal selection, dosage, and drug regimen) that fosters the proper use of antimicrobials (including antibiotics) with the goal of optimizing clinical outcomes, reducing microbial resistance, and lessening the spread of infections produced by multidrug-resistant organisms. The main objectives of antimicrobial stewardship are to attain excellent patient outcomes associated with antimicrobial use while reducing toxicity and other unfavorable events, thereby curbing the discriminatory pressure on bacterial population that propels the emergence of multidrug-resistant strains [93, 94].

Antimicrobial stewardship programs (ASPs) are a cornerstone of the response to the AMR crisis in human medicine but are still largely underdeveloped in veterinary medicine [95]. Antimicrobial stewardship is important to both animal health and food safety. Just like humans, animals get infections that require treatment with antibiotics. The rise of antimicrobial resistance is a serious threat to public health [30]. It is imperative that antibiotic stewardship programs seeking to preserve the effectiveness of existing antibiotics in human health also consider strategies that reduce overuse of antibiotics in the agricultural sector as antimicrobials are used in terrestrial animal production practices to preserve animal and public health, but also as growth

promoters at a subtherapeutic level [89]. Other aspects to be considered with regard to antimicrobial use include the distinction between therapeutic and nontherapeutic use, between the diverse existing production systems and between specifics related to the different animal species and their eco-geographical location [72, 89].

According to the WHO, FAO, and OIE global tripartite database for antimicrobial resistance country self-assessment in 2016–2017, 42% of the countries on question regarding antimicrobial stewardship and regulation in animals and crop production responded that no national policy or legislation regarding the quality and efficacy of antimicrobials and their use in animals, and crops was available [101]. Responses to other veterinary-related questions showed a huge gap in the preparedness for combating AMR and also the lack of policy making and implementation of a successful antimicrobial stewardship program.

Various strategies have been shown to improve appropriateness of antimicrobial use and cure rates, decrease failure rates, and reduce healthcare-related costs in human hospitals [96–98]. According to Guardabassi & Prescott [95], the following successful strategies used in human hospitals can be adopted with focus on their implementation in veterinary practice.

- educational approaches

- development and implementation of guidelines

- preprescription approval

- postprescription review

- computer-based decision support

It should be noted that one strategy does not exclude the other and that multiple strategies can be successfully used in combination.

A good antimicrobial stewardship program (ASP) needs remarkable input in research and training by all stakeholders including national and international veterinary organizations, funding concerns, and animal health industries [95]. At governmental levels, the growth and execution of ASPs need coordination of the task of national public health and veterinary authorities, veterinary clinics, organizations, and private practitioners. The concept of antimicrobial stewardship and of its continuous improvement is in its relative infancy in various sectors of veterinary practice in developing countries, but every veterinary component of the agricultural sector has the responsibility and access to a wide range of resources to develop an ASP.

Stewardship of antimicrobial drugs in human healthcare and veterinary settings is essential to slow the emergence of resistance and extending the useful life of effective antimicrobials according to FDA Center for Veterinary Medicine [99]. All developing countries should be committed to advancing efforts to implement good antimicrobial stewardship practices in veterinary settings as part of their role to protect human and animal health. Each program must be region-specific and constantly under review given that resistance patterns change, requiring changes to local policy of, for example, empirical antibiotic choice [100].

Therefore, the goals in all countries should be to align antimicrobial drug product use with the principles of antimicrobial stewardship, foster antimicrobial stewardship in veterinary settings, and enhance monitoring of antimicrobial resistance and use in animals to further preserve antimicrobial drugs to ensure human and animal health [99].

6. Conclusion and recommendation

Resistance to antimicrobial agents arises in some instance through excessive use in animals as chemotherapeutics, and as subtherapeutic additives in feeds. Prolong exposure of microorganisms to sublethal doses of antimicrobials can result in spontaneous emergence of resistance gene and its subsequent transfer among animals, environment and animal products in food chain, and transfer of resistance to human. A pragmatic approach to slow down the development of antimicrobial resistance is to control abuse of antimicrobials through a number of measures. First, it is important to recognize that veterinary pharmaceuticals are important beyond animals and include human health and the environment, hence the need for "One Health" guidance and regulation. Secondly, it is necessary to reduce drugs that are used as prophylaxis and should rather improve research and innovation for vaccine development, application and explore other alternatives to chemotherapies. The use of feed grade antibiotics and additives in feed as growth promoters also need to be discouraged in developing countries and instead promote organic, home grown livestock husbandry to complement intensive and factory farming. Alternatives to growth-promoting and prophylactic uses of antimicrobials in agriculture include improved management practices, wider use of vaccines, probiotics, and phage virus. Monitoring programs, prudent usage that are controlled, and educational campaigns are some of the approaches that can minimize further development of antimicrobial resistance in developing countries especially. These can be achieved through mutual and 'One Health' understanding of the challenges and informed solution through antibiotic stewardship by promoting collective action of all parties with interest including producers, consumers, and mediators.

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