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CURBING THE CHALLENGES AND LOSES FROM ANTIMICROBIAL RESISTANCE CAUSED BY ANTIMICROBIAL USAGE IN LIVESTOCK PRODUCTION FOR ECONOMIC RECOVERY IN NIGERIA

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Abstract

Antimicrobial drugs are fed to animals at low levels to treat diseases, promote growth, and increase feed efficiency. Incorporating low levels of antimicrobial drugs in livestock feeds has been shown to be a factor stimulating the development of antimicrobial drug resistant bacteria in livestock. Since many of the drugs used to treat livestock are related to drugs used in human health care, there is concern that resistant organisms may pass from animals to humans through the handling of animals or food derived from animals. Human health, animal health and ecosystems are interconnected; consequently, it is necessary to curb antimicrobial usage as antimicrobial use in one environment will drive selection and impact microbial diversity in another. Infectious disease is encouraged by the crowded and stressful conditions in which animals are reared in farms, antimicrobials are fed to livestock to promote growth and treat diseases caused by crowded, stressful and unsanitary conditions. Farmers ignore the services of veterinarians in the diagnosis and control of animal diseases but resorts to drug marketers for help who prescribe antimicrobials without physically examining sick animals but based their prescriptions on verbal reports of clinical signs by farmers and on their personal experience. This paper provides an updated overview on the use of antimicrobials in livestock production with making individual treatment the norm and herd treatment the exception, reducing the need for antimicrobials by improving animal health through antimicrobial stewardship on the farm among others for repositioning production practices and economic recovery at large.

Keywords: *Antimicrobial Usage (AMU), Feed Efficiency, Innovation and Antimicrobial Resistance (AMR).*

Introduction

Livestock are those animals that are reared or raised for producing food to humans; they include cattle, pigs, goat, sheep and poultry which
 are often consumed after heating by boiling, frying and so on [1]. When raised, they provide meat, milk and egg which serves as food; invariably they are also referred to as meat animals. Livestock are raised in various production/management systems such as the intensive, semi-intensive and extensive systems. The frequently used of these three is the intensive production system which allows for close monitoring of animals and efficient commercial production [2].

Antimicrobials are a broad class of natural, synthetic or semi-synthetic product that kills or inhibits the growth of bacteria or other micro-organisms. Antimicrobials include antibiotics and these terms are often used simultaneously [3]. Antibiotics are antimicrobial compounds, including antibacterial, antiviral, antifungal, anti-parasite and anti-protozoa compounds. The biggest medical advance of the 20thcentury was the discovery of antibiotics. Penicillin was the first antibiotic to be discovered in 1929 by Alexander Fleming [4]. Antibiotics and other antimicrobial agents are used in a wide range of livestock production for disease prevention (prophylaxis) and treatment (metaphylaxis), to curtail disease spread, prevent food chain contamination and to increase productivity [5]. Thomas Juke in 1949 discovered that feeding livestock with small portion of antibiotics in feed or water additive increased the animal growth rate; since then for over 60 years, the animal industry has been feeding different kinds of antibiotics, particularly livestock such as goats, pigs, cattle and poultry referring to these drugs as "growth promoters" [6].

The feed industry calculated that the use these drugs increases the daily growth and food conversion ratios of animals by 3% to 11%, thus feed industries make more profit by using antibiotics in the animal feeds [4]. In modern times, more antibiotics are used on animals than on humans. The World Health Organization (WHO) says more than half of the global antibiotic production is used on farm animals. Over the last 30 years, the use of penicillin-type drugs in livestock has increased by 600% and tetracycline by 1500% [7]. In the United States, more than 70% of its antibiotics are fed to livestock; not to treat their diseases, but to promote growth and repair the illnesses caused by crowded, stressful, and unsanitary conditions. Farmers use antimicrobial drugs to cover for lapses such as poor management, inadequate resources and substandard facilities that could predispose animals' health to risk such as infections [8].

The antibiotics frequently used in livestock feeds include penicillin, tetracyclines, erythromycins, bacitracin, flavophospholipol, olaquindox, carbodox, avilamycin, avoparcin, efrotomycin, virginiamycin, spiramycin, tylosin and oleandamycin among others [9]. For humans, these antibiotics are available only on a prescription basis but for livestock producers they are available without prescription in the name of "growth promoters", even in advanced countries like USA and Europe [4]. With the increasing demands and need for antimicrobials in Nigeria, its marketing has become a very lucrative business. The use of antimicrobial drugs especially in animals has been implicated as a major contributor to the increasing emergence and dissemination of antimicrobial resistance among bacteria [10].

In Nigeria, the proliferation of veterinary drug marketing and ready availability of antimicrobial agents promote the excessive/indiscriminate use of antimicrobials in livestock production. More so, the activities of antimicrobial marketers may have impact on antimicrobial usage level, choice of antimicrobial agents, mode of administration and consequently the outcome of antimicrobial treatment [11]. Often a time, these marketing strategies focus on profit making with little or no consideration for the preservation of antimicrobial efficacy and animal health/welfare. At such, antimicrobials are readily accessible to the general public without restrictions resulting to indiscriminate use which have grave consequences [12].

Low-level antimicrobial usage in livestock production introduces additional complexities into the general pest-management/pest-resistance framework as feeding antimicrobial drugs at low levels is not only output enhancing but also is an input that interacts with other inputs, especially feeds [13]. The growing demand for animal proteins has resulted in intensive production of pigs, poultry, and fish, with the frequent use of antibiotics as growth promoters [5]. In poultry production, antimicrobial drugs are used as growth promoters in the place of growth hormones for at least two reasons; first, no growth hormones are approved for use in poultry production. Second, hormones are ineffective in young birds because natural levels of hormones remain high for most of their relatively short production cycle [13].To mitigate against economic losses linked with disease outbreaks, farmers rely heavily on antimicrobial agents for the prevention and treatment of infections on the farm [12].

The emergence of antimicrobial resistance is primarily due to excessive and indiscriminate use of antibiotics in animals and humans [14]. Despite the benefits derived from the use of antimicrobials in poultry and other livestock production, the increased use has been shown to contribute to the increasing prevalence of bacterial antibiotic resistance in humans. Reports revealed widespread presence of antibiotic-resistant pathogens in poultry farms and products in Nigeria and many other areas around the world [15]. Isolated pathogens include *Staphylococcus aureus*, *Campylobacter, Salmonella, Escherichia coli*, *Proteus mirabilis,* and some other *enterobacterias*. Antibiotic resistant organisms can get to the general population from the farm through food chain or animal handlers and through the application of animal manure on crop lands [16]. It has been shown that farm-raised superbugs can exchange genetic materials and give their resistance to other bacteria, even of other genera and species that have never been exposed to antibiotics prior to their contact. Therefore, an attempt to control the emergence of antimicrobial resistance in humans will entail taking care of its occurrence in livestock production [17].

Development of Antimicrobial Resistance

Resistance to antimicrobials have been identified as one of the greatest threats to future human health with an increasing number of resistant microbial strains documented each year across both human and animal populations in developed and developing countries respectively including Nigeria [18].

The emergence of resistance is a natural process though it accelerates and spreads by antibiotic misuse and overuse. While some bacteria are naturally resistant, antibiotic use exerts greater selection pressure on bacteria, causing susceptible populations to die and resistant ones to survive. At a cellular level, resistance is acquired through mutations in bacteria or transfer of genetic material (such as resistance genes) from other bacteria through horizontal gene transfer (HGT). This means that resistance in one bacterium can be passed on to other kinds of bacteria, even for multiple antibiotics [19].

Subsequently, the bacteria undergo structural and chemical alterations that render the antibiotic ineffective. These changes may include one or more of the following: reduced membrane permeability to the drug, alteration of the drug-binding site at the cell wall, enzymatic degradation of the drug and normal function of bacteria bypassing the drug-affected enzyme or pathway [20].

Human Health and Environmental Toxicity

Many food borne bacteria that can cause disease in humans, such as *Salmonella*, *Campylobacter*, and strains of *E. coli*, are found in the intestinal tracts of healthy livestock. According to Food and Drug Administration (FDA), When an animal is treated with an antimicrobial drug, a selective pressure is applied to all bacteria exposed to the drug, the ones that are sensitive to the antimicrobial are killed or put at a competitive disadvantage; while those that have the ability to resist the antimicrobial have an advantage and are able to grow more rapidly than the more susceptible ones [21]. Resistant bacteria can then be transferred to the human population through either direct contact with the animals or through consumption of improperly handled food [22]. Human exposure through the ingestion of antimicrobial resistant bacteria from animal derived foods represents the most significant pathway for human exposure to bacteria that have emerged as a consequence of antimicrobial usage in animals. Scientific and medical authorities have warned that if measures are not urgently taken the general population might return to the pre-antibiotic era, where people had no medicines and simple infections could kill, as a result of antimicrobial misuse/overuse which causes accumulation/residual effect and eventual resistance in animals and humans respectively [23]. In 2014, Centre for Science and Environment (CSE) found residues of multiple antibiotics such as fluoroquinolones (enrofloxacin and ciprofloxacin) and tetracyclines (oxytetracycline, chlortetracycline, doxycycline) in chicken meat samples.Antibiotics were used throughout lifecycle of the animals and in parent stock, with no withdrawal periods observed [24].

Another channel of resistance is the release of antibiotics into the environment for example, through runoff from farm waste. Studies that show some pharmaceuticals, including antibiotics, not being completely used in human or animal bodies and can be passed into the sewage system, where treatment does not break them down completely. Significant concentrations of certain drugs have been reported in drinking water and antimicrobial-resistant bacteria found in groundwater sampled near hog farms [25]. The transmission of resistant bacteria from animal farms into the surrounding and larger environment has also been studied. Poultry litter or manure has also been indicated as a source of resistant bacteria bearing linkages to the transmission of antimicrobial resistance into external environment. Studies have reported isolation of some of the common drug-resistant *Staphylococcus, E. coli* and *Salmonella* from samples of poultry litter, nearby surface water and groundwater samples, boot swabs and exhaust air samples from poultry farms [24].

The Challenges and Loses

Despite studies that link antibiotic use in livestock to residues in consumer food products and evidence that antimicrobial usage in animal husbandry and aquaculture far outweighs human usage [26]; in prescribing and dispensing antibiotics for livestock, the importance but difficult to observe withdrawal periods (the time from when an animal was last given a drug to when it is considered safe for human consumption, marketing of the animal product or as part of food chain), the potential impact of financial losses incurred by farmers and the necessary but often lacking provision of sanitary waste disposal for animal products deemed unfit for sale and consumption are challenges which lead to economic loses. Veterinarians felt pressured to protect the efficacy of antimicrobials and to reduce the potential for antimicrobial residues in human consumables while simultaneously ensuring the economic survival of farmers and their families; these commitments were often contradictory and led to hard decisions in which behaviour often diverged from knowledge of best practice [18].

For instance, you tell a farmer, destroy all the eggs because it is not fit for human consumption due to the trace of antibiotic residues, are you going to compensate the farmer? This is a serious challenge. Can the farmer totally do without the use of antimicrobial drugs in livestock production on the farm without compromising the health and welfare of the animals or resulting to loss of the animals which is of great financial/economic loss?

The farmer cannot afford to lose money, some of these drugs you cannot use without the farmer losing money, because if he administer a drug and it says that withdrawal period is one week, what will the farmer do with one week supply of eggs? Is he supposed to destroy them? Or give them away? Is there a way that he can use them without having to do any of these? If he decides to sell them, he is endangering public health/safety, but he has to find a way of disposing them, unfortunately we are not at that level of industrialization, the level of disposing contaminated products safely without the poor fraction of the masses laying hands on them or the effectual impact of these contaminated products on the environment causing environmental toxicity [18].

It is estimated that by 2050, antimicrobial resistance (AMR; includes resistance to antibiotics as well as antifungal, antiviral, etc.) can lead to 10 million deaths per year and loss of outputs worth US $100 trillion globally. It can also impact food safety, nutrition security, livelihood and attainment of Sustainable Development Goals [24], antimicrobial resistance is known to cause greater spread of infectious diseases, difficulty in treating common infections, longer hospital stays, uncertainty in success of high-end procedures and more expensive treatments. It can put a huge burden on health and economics of individuals and nations [18].

Repositioning Cost

At the animal level, the immediate cost of withdrawing sub-therapeutic antimicrobial usage, without adjustments in management practices may include decreases in feed efficiency, growth, survival and higher variability of the end product [27]. At first, investment for these improvements may impose a considerable burden on smaller producers in low and middle income countries. These costs, however, might be incurred by the producer only in the short term. Over a long run, the improvement in production/management facilities will translate into better animal welfare and health, thereby reducing the need for misuse, overuse, sub-therapeutic use of antimicrobials and veterinarian costs. At the same time, better information and increased awareness of antimicrobial usage in livestock production can contribute to greater consumer demand for meat and fish products raised without antimicrobials [28]. Consumers not only might be willing to absorb the resulting price increases, but these shifts in consumer demand could also affect production practices as the demand for sourcing meat raised without the routine use of antimicrobials rises [28].

Implication on Agricultural Education

Antimicrobials are a valuable community resource. They should have been used judiciously instead; we overuse/misuse them, linked to over-eager prescribers. Those who should serve as gatekeepers recommend antibiotics and other life-saving antimicrobials when they ought to first make specific and confirmed diagnoses before prescribing [29]. Resistance and inappropriate antimicrobial usage outside of human medicine (especially in agriculture) fuels the fire. Antimicrobial resistance development is becoming an acknowledged problem worldwide. In Nigeria and other developing countries where sanitation needs improvement, resistant organisms spread between and within communities with ease and in hospitals; when infection control is lax, resistant epidemics thrive [30].

Implication of this knowledge will help farmers to reposition production practices, knowing vividly that inappropriate usage of antimicrobials in livestock production does not only have impact on animals' health/welfare, but also can be transferred to humans and the environment over time thereby posing a greater hazard. Farmers will become judicious in their use of antimicrobials as this knowledge can be passed down to farmers through extension workers and agricultural education programmes [31].

Conclusion

Antimicrobial residues in livestock highlighted rampant usage of antimicrobials in livestock. Curbing antimicrobial usage in livestock production is the most effective way to address resistance spread from farms to humans and environment. Animal husbandry departments, drug control departments and food safety departments should take a lead in this. Farm environment is a reservoir of multidrug resistant bacteria/pathogens and points towards the role of litter in spreading antimicrobial resistance in the environment.

Recommendations

1. Making alternatives available through vaccines at the early stage of animals' life cycle, probiotics, vitamins and herbal supplements.Human critical antimicrobials should not be used in animals.
2. Good farm management practices through bio-security measures like antimicrobial stewardship programme (high hygiene level on the farm), spacious/stress-free animal house, adoption/practice of appropriate drug withdrawal periods, therapeutic use should be metaphylaxisat, phase out prophylaxis and sub-therapeutic use of antimicrobial.
3. The need to conduct national-level surveillance database of antimicrobial resistance and residues in environment is paramount which should be developed and kept in the public domain for quick access.
4. Licensed antibiotics should reach registered users through registered distributors or stockers of veterinary medicines. Stringent control on import of antimicrobials and feed supplements should be implemented.
5. Introduction of a labeling system wherein livestock raised without antibiotics should be labeled through reliable certified schemes to facilitate consumer choice; livestock produced with antimicrobial drugsshould also be labeled accordingly. This would incentivize the farmer who can charge a premium and provide consumers with healthy choices.
6. Proper manure management approaches which pose lesser risk should be adopted. For example, bio-gas generation and compositing with litter/manure from farms.
7. Veterinarians and extension agents should train and educate farmers on judicious use of antimicrobials and infection prevention.

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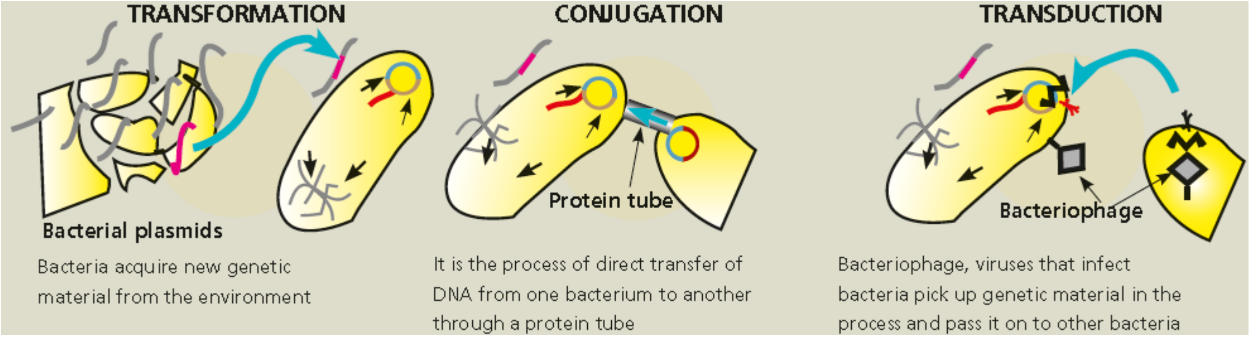
Fig. 1: Development of Antimicrobial Resistance (AMR)



Source: Chandra et al, 2017 (Adopted)

Table 1: Antibiotic Resistance Linkage with Human Health

ANTIBIOTIC CLASS	ANTIBIOTIC USED FOR LIVESTOCK (BRAND NAME) AND TYPE OF USE	RELATED ANTIBIOTIC USED FOR HUMANS (BRAND NAME) AND TYPE OF USE	HUMAN HEALTH CONCERNS
Fluoroquinolones	enrofloxacin (Baytril) Treatment of respiratory and alimentary tract infections in pigs and poultry (administered in poultry drinking water)	ciprofloxacin (Cipro) Important for treating severe Salmonella and Campylobacter infections. Drug of choice for immediate ('empiric') treatment of Salmonella in adults	Use of enrofloxacin as prophylactic for chickens implicated in increasing resistance to Cipro
Cephalosporins 3rd generation (belong to beta-lactam class of antibiotics)	Ceftiofur Treatment of bacterial infections by injection in cattle and pigs; control of infection and mortality in day-old chicks	cefotaxime, ceftriaxone Drugs of choice for treatment of severe Salmonella infections in young children	Use of ceftiofur implicated in development of resistance to 3rd generation cephalosporins
Streptogramins	virginiamycin "Growth promoter"	quinupristin-dalfopristin (Synercid) New antibiotic developed to treat resistant bacteria such as the 'superbug' vancomycin-resistant Enterococci (VRE) and hospital-acquired pneumonia	Use of virginiamycin for growth promotion threatens effectiveness of Synercid in treating VRE and other dangerous infections

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Glycopeptides	avoparcin "Growth promoter"	vancomycinis an antibiotic “of last resort” for resistant Staphylococcal infections, including the hospital “superbug” MRSA	The appearance of vancomycin-resistant Enterococci (VRE) has been linked to use of avoparcin growth promoter. Concern that a vancomycin-resistant MRSA could develop
Macrolides	spiramycin, tylosin “Growth promotion” in pigs and occasionally in chickens; tylosin also used for prevention, control and treatment of infections in pigs	erythromycin Treatment of respiratory infections and food-borne infections such as Campylobacter; treatment of people who are allergic to penicillins	Bacteria which develop resistance to tylosin are often cross-resistant to erythromycin

Source: Jacky, 2011 (Adapted)

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