Chapter

Antimicrobial Resistance and Rational Use of Antimicrobials in Livestock: Developing Countries' Perspective

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Abstract

India is one of the top consumers of antibiotics in agriculture worldwide, which accounts for 3% of global consumption, which is estimated to double in 2030. The use of antibiotics, particularly in chickens, is expected to triple in India by 2030. The overuse, injudicious use, and misuse of these antimicrobial drugs have spawned the evolution of life-threatening bacteria that is making the current antimicrobials' reserve useless. Suitable extension outreach and continuing programmes should be devised to promote the judicious use of antimicrobials. Innovative approaches, such as One Health, Antimicrobial Stewardship, and antimicrobial conservation are the need of present alarming situation. There is need to reduce the antimicrobial use in animals, particularly domesticated animals; provision of infection surveillance in hospitals; improving hospital surveillance for monitoring antibiotic resistance; promoting rational and judicious use of drug through education, monitoring, and supervision; researching new drugs; and developing and implementing a more restrictive and participatory antibiotic policy by including various stakeholders. Thus, tracking the rate of veterinary antimicrobial use, resistance, and residues, through a nationwide surveillance and monitoring system, and educating farmers, veterinarians, and consumers could pave the way to fight against this catastrophic situation of antimicrobial resistance.

Keywords: antimicrobial resistance, antimicrobial stewardship, One Health, stakeholders, surveillance

1. Introduction

Antimicrobial agents are widely used in food-animal production for disease prevention and treatment in animals, to control disease spread, to prevent contamination of the food chain via horizontal and vertical transfer of antimicrobial resistance, and to increase productivity [1]. However, their overuse in humans and animals leads to the emergence of antimicrobial resistance, a general term that encompasses decreased and poor efficacy of antimicrobials to treat disease [2]. Recent projections revealed that by 2050 global livestock production would fall by 3–8% each year, as result of which annual global gross domestic product will decline by 1.1–3.8%. Due to rise in disease incidence, low income countries will be affected more severely, with a predicted rise of extremely poor people from 6.2 to 18.7 million by 2030 [3]. Rise in frequency of treatment failures have been reported in treatments with infections caused by multi-, extensive-, and pan-drug resistant bacteria. Once antimicrobials (antibiotics) normally used against bacteria lose their efficacy to treat disease, it becomes necessary to use others, so-called “reserve” or “last resort” options that are often more expensive and/or toxic preparations [4]. In several developing countries, antimicrobial consumption is expected to rise considerably due to increase in meat consumption, from Indonesia (202%) and Nigeria (163%) to Vietnam (157%) and Peru (160%), by 2030 [5]. Organization for Economic Cooperation and Development (OECD) estimated that antimicrobials used in food-animal production will increase by 67% globally, i.e., from 63,000 in 2010 to 106,000 tonnes by 2030—an increase of 67% [6]. Thus, overuse of antimicrobials in the food-animal production sector gives rise to antimicrobial resistance in animal pathogens, leading to increase in therapy failure with a negative effect on animal health and welfare [7]. The immediate cost of withdrawal of non-therapeutic antimicrobials at animal level, without adjustments in production processes, may decrease the feed efficiency, growth, survival, and number of animals born [8].

2. Genesis of antibiotic resistance and its spread across geographical boundaries

The World Health Organization (WHO) has emphasized the need for an integrated and coordinated global effort to control antibiotic resistance. In 2001, the World Health Organization Global Strategy for Containment of Antimicrobial Resistance has provided a framework of interventions to slow the emergence and reduce the spread of antimicrobial-resistant microorganisms across geographical boundaries and species [9]. For understanding the genesis and spread of antimicrobial resistance across species and increase in resistosome burden, the following sub-heads points the focus.

2.1 Development and spread of antimicrobial resistance

The development of resistance in microbes arises in two ways: (i) intrinsic resistance, which occurs when the microbial species is able to innately resist the activity of an antimicrobial agent (by preventing either the entry or binding of the antimicrobial agent); and (ii) acquired resistance, in which once-susceptible microbial species mutate or obtain genes from other microbe, to acquire resistance. Antimicrobial resistance cannot be prevented because every time antimicrobials are used, the effective lifespan of that antimicrobial drug is shortened [10]. In general, few categories of pathogen are responsible for a large portion of resistant infections in humans. One of them is New Delhi metallo-β-lactamase-1 (NDM-1) gene which confers broad resistance to most antibiotics, including carbapenems, and can be transferred to a wide variety of bacterial species [11]. Another is resistant Gram-negative bacteria which carry extended-spectrum beta-lactamase enzymes (ESBLs), responsible for high levels of resistance to some of the most commonly prescribed antibiotics [12].

2.2 Antibiotic use in livestock and resistance

Livestock contributes for over a fourth of India’s total agricultural output, and 4% of the gross domestic product (GDP). India is one of the top consumers of antibiotics in agriculture worldwide, which accounts for 3% of global consumption, which is estimated to double in 2030 [13]. Resistant microbes and residues have been detected in living bovines, chickens, honey, pigs, horses, donkeys and mules, and fish and shellfish. In cattle, resistant strains of coagulase-negative staphylococci, *Escherichia coli*, and *Staphylococcus aureus*, extended-spectrum beta-lactamase (ESBL) and New Delhi metallo-beta-lactamase (NDM-1) genes, have been reported. *E. coli*, *S. aureus*, enterococci, *Pasteurella multocida*, *Campylobacter jejuni*, and *Salmonella*, including ESBL-producing strains have been found in poultry. The chances for antimicrobial resistant microbes in the race for survival are in direct proportion to the volume of antibiotics used, this makes it more critical to examine current habits and encourage rational and conservative use of antimicrobials. Due to antimicrobial resistance, easy-to-treat infections are becoming difficult or impossible to cure, with an unambiguous global increase in both livestock mortality and treatment costs [12].

2.3 Use of antimicrobials for different purposes

Therapeutic use of antimicrobials is meant for treatment of diseases. However, if a few animals are found to be sick, often the whole flock or herd will be treated (known as meta-phylaxis or sub-therapeutic) to prevent the disease spreading. Thus, there is not always a clear distinction between treatment and prevention [14]. In this condition, treatment usually occurs at high doses for a relatively short period of time. Prophylactic treatment is done for prevention of disease. The treatment of animals is done with low, sub-therapeutic doses of antibiotics via feed or drinking water, even in the absence of any signs of disease but when there is risk of infection. Treatment can be given over a period of several weeks, and sometimes longer. Antibiotics are also used for growth promotion. Here, very low sub-therapeutic doses of antibiotics are given to animals (particularly intensively kept pigs and poultry) in their feed, in order to increase their growth-rate and productivity. Treatment is continuous and it lasts for a long time [15].

2.4 Use of antimicrobials in food animals

A study revealed that annually, 45, 148, and 172 mg/kg antimicrobials are consumed by cattle, chicken, and pigs, respectively, to produce each kilogram of their meat. The global consumption of antimicrobials estimated to increase by 67% from 2010 to 2030, i.e., from 63,151 ± 1560 to 105,596 ± 3605 tons [16]. At present time, more antibiotics are used worldwide in poultry, swine, and cattle production than in the entire human population [12]. In aquaculture, antibiotics are used for therapeutic and prophylactic purposes often in high concentrations because bacteria travel in water easily, here antibiotics are not used for growth promotion. In the BRICS countries (Brazil, Russia, India, China and South Africa), antibiotic use in animals is expected to double by 2030. Use of antibiotics, particularly in chickens, is expected to triple in India by 2030 [16].

2.5 Use of antibiotics in dairying

The antibiotic residues are at alarming rate in dairying in India. A study by Ramakrishna and Singh [17] in 1985 revealed that streptomycin was found in 6% milk samples in Haryana. One decade later, in Hyderabad, Secunderabad, and surrounding villages dairy farmers were surveyed on antibiotic use practices. Among 38 dairy farmers, about 50% of them used oxytetracycline to treat diseases such as mastitis and fever; the survey revealed that oxytetracycline residues were found in 9% samples from markets and 73% individual animals, while no residues were found in government dairy samples [18]. A survey conducted by the National Dairy

Research Institute near Bangalore in 2000 revealed that tetracyclines, gentamycin, ampicillin, amoxicillin, cloxacillin, and penicillin were commonly used to treat dairy animals and mastitis was treated with beta-lactam class of antibiotics. The prevalence of antibiotic residues in milk samples has been found to be higher in silo and tanker samples as compared to market and commercial pasteurized milk samples [19]. These findings prove that that antibiotic are used in dairy animals in these regions, though details of the frequency, duration, and reasons for use and overuse are not well recognized.

2.6 Use of antibiotics in poultry

The level of resistance in Indian poultry is reported to be high for many antibiotics. A recent study conducted by members of the Global Antibiotic Resistance Partnership [20] reported significant differences in the resistance pattern of broiler farms of Punjab with level of antibiotics used in normal poultry production. Results revealed that antibiotic use in broiler farms were likely to be more than 20 times to harbor-resistant *E. coli*, and prevalence of multi-drug resistance was much higher which was found 94% in broiler farms. In meat shops of Bikaner (Rajasthan), 96% of chicken samples contained *S. aureus* (n = 48), which were sensitive to ciprofloxacin, doxycycline, and gentamycin, and all were resistant to ampicillin, cloxacillin, and tetracycline [21].

2.7 Transfer of antimicrobial resistance from livestock to humans

Farm workers and slaughterers are at high risk of exposure to resistant antimicrobials due to direct contact with infected animals. Handling pigs and poultry while working in a farm environment puts farm workers at risk of picking up resistant bacteria from the animals' bodies or their feces. A study in the Netherlands in 2001–2002 revealed the same genetic patterns of resistance in *E. coli* samples from turkeys and broiler chickens, their farmers and slaughterers [22]. Consumption of food contaminated with resistant bacteria such as *Salmonella*, *Campylobacter*, and *E. coli* can increase the resistant bacteria in the human beings. Contamination of meat from fecal material getting onto the carcase during the slaughter and evisceration process, during the removal of animal gut, can contaminate other foods in domestic or restaurant/catering kitchens. The European Food Safety Authority (EFSA) revealed in 2010 that live chickens colonized with *Campylobacter* are 30 times more likely to contaminate meat as compared to uninfected birds [23]. Resistant bacteria can be transferred in water, soil, and air because animals excrete a significant amount of antibiotics they are administered, which make manure a potential source of both antibiotics and antibiotic-resistant bacteria that can enter soil and groundwater [15].

3. Rationale and approaches to limit the spread of antimicrobial resistance

Synchronization of international, national, and local approaches is advised for control and prevention of antimicrobial resistance. Promoting the rational use of antimicrobials, control on over-the-counter availability of antimicrobials, improvement of hygiene, prevention of infection, and control are the major recommended approaches. Thus, proper understanding of mechanism of resistance and accordingly innovation in development of new drugs is the need of the hour. A multidisciplinary, collaborative, regulatory approach is demanded for combating antimicrobial resistance [24].

3.1 Reasons to focus on antibiotics' use in livestock vis-à-vis antibiotic overuse and resistance

For decades, meat industry has fed antibiotics to chickens, pigs, and cattle for their weight gain and disease prevention in the stressful and unhygienic conditions that is prevalent in industrialized animal agriculture production facilities. A strong scientific consensus asserts that this practice fosters antibiotic resistance in bacteria, which is detrimental to human health (HSUS Report). Food animals are quite susceptible to benign or commensal opportunistic microbes, so they are often exposed to antimicrobials, such as the antibiotic, for disease treatment and prevention, sub-therapeutic purpose and prophylactic purpose to promote growth and improve feed efficiency. Many of these antimicrobials used to treat diseases common to both livestock species and humans closely resemble drugs used in this species [25]. On the one hand, these miraculous antimicrobial drugs are pillars of modern medicine to prevent and diagnose dangerous bacterial infections and save lives. On the other hand, the overuse, injudicious use, and misuse of these antimicrobial drugs have spawned the evolution of life-threatening bacteria that is making the current antibiotics reserve useless [26]. Thus, antimicrobial resistance can be defined as the ability of microbes, such as bacteria and fungi, to grow and continue to multiply even in the presence of administered antimicrobial with purpose to kill or limit their growth (NIAID).

3.2 Philosophy of judicious use of antimicrobials in line with animal welfare

Animal agriculture by human needs to be predicated on ethical judgments where sub- or non-therapeutic use of antibiotics on food producing animals on ethical judgement scale seems to be objectionable. The problem is that food-animal producers do not realize the ethics in their business because they claim that the conditions and processes in the factory farm are not a matter of ethics but of a societal necessity to fulfil the feed demand of the population. These producers seem to fail to realize the ethical dimensions of their practices, not only for food safety issues for consumers, but also welfare issues for their animals [27]. Any policy judgment including the danger of tolerable resistance or the level of animal abuse tolerable for the sake of the benefits from antibiotics overuse in animal feed is the subject of ethical judgment [28]. Lack of treatment protocols and solidarity of animal from herd and stopping the course of treatment after apparently realizing the disappearance also comes under the purview of animal welfare.

3.3 Current scenario in India and developing countries

Antibiotic use has been increasing steadily (e.g., between 2005 and 2009, 40% increase has been found in units of antibiotics sold). Cephalosporin sales increased by 60% over that 5-year period (in units sold) [20]. Antibiotics are used to treat human illness, livestock, and poultry diseases. In livestock sector, it accounts for more than 50% in order to control and treat diseases, and in low doses in animal feed, to promote growth and improve production of animal products [29]. There is no regulation in India to regulate the use of antibiotics in food animals, such as poultry and dairy animals raised for domestic consumption. As per, Prevention of Food Adulteration Rules (1995), Part XVIII: use of antibiotic and other pharmacologically active substances are applied only to certain types of seafood and poultry intended for export only [30]. Very few studies on antibiotic residues in animal products have been conducted in India, where one on honey was widely recognized [31]. Centre for Science and Environment, New Delhi, in a study revealed that 11 of 12 samples of honey taken from the domestic market were not in compliance with standards for its export. The level of antibiotic residues found was not high enough to cause an adverse effect in consumers, but it appealed for regulation and monitoring of antibiotic residues in honey because continuous long-term exposure to low levels of antibiotics could increase antibiotic resistance in pathogenic bacteria making their treatment difficult [32]. The National Policy for Containment of Antimicrobial Resistance—India was documented in years 2007, 2011, and 2017, which covers a range of topics, including reduction of antibiotic use in animals, particularly domesticated animals; provision of infection surveillance in hospitals; improving hospital surveillance for monitoring antibiotic resistance; promoting rational and judicious use of drug through education, monitoring, and supervision; researching new drugs; and developing and implementing a more restrictive and participatory antibiotic policy by including various stakeholders 65. Under the new Schedule H1, selling of antibiotics over-the-counter will be banned [20].

4. Delineating the use of antibiotics by farmers from farm-to-fork

Low income countries should follow the approaches of World Health Organization, World Organization for Animal Health, and the Food and Agriculture Organization of the United Nations, which recommends to implement national action plans encircling human, food animal, dairy animals, and environmental sectors to formulate appropriate policies, interventions, and activities that could address the prevention and containment of antimicrobial resistance from farm-to-fork. Suitable interventions should be designed, which include the following fields and coverage.

4.1 Use of antimicrobials by farmers

In strong sense, there is dependence among piggery farmers on antimicrobials to sustain production, improve farm performance, and maintain health status. Lack of concern about the harmful effects of antimicrobial use on their own and public health was identified among pig producers as a result of a reduction in the curative ability of antimicrobials and the selection of antimicrobial resistance bacteria [33]. A study conducted in Danish system revealed that 82% of antimicrobials sold by pharmacies were direct to individuals on prescription with specifications for use, 78% of antimicrobials sold by pharmacies used for pigs, and 20% for cattle [34]. The overuse of antibiotic has exploited this miracle drug to such an extent that a study in the Netherlands revealed that 79% of farmers used antibiotics routinely and 18% occasionally extended antibiotic treatment. The choice of progressive farmers for adopting prudent use of antibiotics by avoiding routine use of antibiotics was perceived as good practice by fellow farmers. This was followed by repeating the initial label treatments [35]. There are certain specific antibiotics which are used by farmers to treat animals without veterinary consultation (e.g., gentamicin in Ohio). Thus, improving information flow from Veterinarians to farmers may be the most effective means of promoting prudent use of antibiotics on dairy farms [36]. Subjective norms and moral obligations together, in which perceived moral obligations to peers, clients, and the regulatory norm setting sector associated with the feedlot industry increase social pressures to use antibiotics in acutely sick, chronically sick, and high-risk feedlot cattle [37].

4.2 Understanding the antimicrobials overuse in small dairy farms

The incidence of death of farm workers due to treatment failure attributed by antimicrobial resistance is likely much higher in developing countries where more people live in close contact with livestock, where food hygiene is not well practiced [38]. A report by WHO revealed that in developing countries throughout the world, even less than 50% of human are treated according to standard treatment protocol, and prescribing patterns were found substandard regardless of the type of prescriber [39]. Antibiotic-resistant food-borne infections, emergence of new multi-resistant strains of bacteria, and spread of resistant genes are some main areas of risk due to indiscriminate and overuse of antibiotics [15].

4.3 Antimicrobial resistance and intensive animal farming

The basic reason for increase in antimicrobial resistance in food animals is factory farming. In intensive pig and poultry production, animals are reared in confined and overcrowded conditions, usually with no outdoor access, and they are bred and managed for maximum production yield, i.e., to grow faster in size and number or to produce more meat, milk, and eggs. This forces them to compromise their health and their immune responses and encourage infectious disease to develop and spread easily among these livestock [40, 41]. Without the aid of drugs for disease prevention, it would not be possible to keep the animals productive in the intensive conditions, in which they are often kept and managed without proper care by the livestock keeper. Earlier, the policy-makers of 50 years ago permitted antibiotics to be used for non-therapeutic reasons in animal production, often in spite of scientific misgivings, which can be perceived as a serious mistake now. Fifty years later, while the evidence continues to be disputed by some sections of the industry, the actual and potential damage to public health is acknowledged by scientists and policy-makers due to the spread of antibiotic resistance among livestock species and human being (vertical and horizontal transfer of resistance) [15].

5. Synchronized efforts by stakeholders to reduce the pace of spread of antimicrobial resistance

All the stakeholders including veterinarians, paravets, farmers, and pharmaceutical companies should be made aware about their interacting roles from antimicrobial prescription to use, in which decision made by one stakeholders affects the worth and value of choices and decision for other stakeholder [42]. These aspects can be highlighted under following sub-heads.

5.1 One Health approach to combat antimicrobial resistance

One Health approach recognizes that human, animals, and ecosystem health are inextricably linked to each other. It came in to light because many factors have changed the interaction between humans, animals, and environment. Thus, for achieving the mutual optimal health outcomes, it needs the cooperation of human health, livestock, and environment health. Resistance to infectious diseases increase the cost of treatment as well as serious biosecurity concerns due to spread of antibiotic resistance. Thus, the animal production is hampered due to rise in incidence of infections.

5.2 Antimicrobial stewardship

The primary focus of an antimicrobial stewardship program is to optimize the use of antimicrobials to achieve the best treatment outcomes, reduce the risk of infections, reduce or stabilize levels of antibiotic resistance, and promote livestock safety. Creating an antimicrobial stewardship program needs baseline information, including institutional use of antimicrobial [43]. This would help to identify recurrent problems with antimicrobial use at the institution and frames the problems that need to be addressed [44]. The antimicrobial stewardship efforts should focus on improving adherence to documentation standards, optimizing the use of antimicrobials, appropriateness of drug dosing, halting treatment of asymptomatic bacteria and microbes, and minimizing the length of surgical prophylaxis [45].

5.3 Recommendations to control antibiotic overuse

Recognizing that antibiotic resistance is a reality crossing the geographical boundaries of the world, in developing countries, the prevalence of resistant microbes will rise over time, which demands urgent action. Vaccinations to prevent various disease falls into this category of recommendation, but their "antibiotic-sparing" effects are often overlooked because these are of secondary importance. Restricting the use of antimicrobials in livestock and poultry for non-therapeutic use, particularly growth promotion, could be beneficial. There is a need to eliminate irrational or inappropriate use, enforce prescription only laws, and eliminate over-the-counter antibiotic purchases, surveillance, distribution of Standard Treatment Guidelines (STGs), antibiotic sensitivity testing, checklists for surgical procedures, educating farmers and other stakeholders about appropriate use of antibiotics, and improving antibiotic supply chain and quality (Global Antibiotic Resistance Partnership (GARP)-India Working Group 2011). For gaining better understanding and subsequent action toward antimicrobial resistance, detailed social science research is needed to gather information on the processes of diagnosis, prescription, use of antimicrobials, the application of treatments besides antimicrobials, and the processes of data generation. Thus, sub-optimal use, potential users, and food chain pinch points could be identified. There is a general scantiness of data on on-farm application and use of antimicrobials. The tools for recording on-farm medicine use, such as paper spread sheets and computerized entries, may be of practical use to farmers in the health management of their animals/birds or to veterinarians in providing an accurate picture of how prescribed medicines are actually used [46].

5.4 Prescription of antimicrobials

Prescription of antibiotics are strongly influenced by the demand of farmers for antibiotics, fear of veterinarians blamed if antimicrobials later prove unnecessary, the expectation of farmers to be prescribed antimicrobials, confidence of veterinarians in diagnosis. Thus, prescription decisions are strongly influenced by multifactorial non-clinical influences such as farmer pressure and cost of drug, etc., to some extent [47]. Also, variations are present in beliefs of veterinarians regarding efficacy of systemic antibiotics for dry-cow therapy results in very different decisions being taken on farm and considerable discrepancies in treatment. Thus, it raises concern of the consistency and appropriateness of antibiotic prescription by them [48]. Antibiotic sensitivity testing should be preferred before prescribing the antibiotics [49].

6. Conclusion

The overuse of antimicrobials in livestock is leading to decline in antimicrobial effectiveness against infections in animals and eventually in humans. Use of antimicrobials purely as growth promoters and prophylactic purposes should be avoided and initiatives should be taken to phase out the sub-therapeutic use of antimicrobials. Injudicious use, overuse, and indiscriminate use of antimicrobials should be avoided. The obtaining of antibiotics from over—the counter sales should be checked and antimicrobial conservation practices should be encouraged to control the indiscriminate prescription and use of antimicrobials. Suitable strategies and policies should be formulated in line with the World Organisation for Animal Health and World Health Organization initiatives which call for harmonious efforts among stakeholders of different countries. Suitable extension outreach and continuing programmes should be devised to promote awareness among stakeholders about judicious use of antimicrobials and educate farmers, veterinarians, and consumers on the potential risk of antimicrobial resistance. There is need for surveillance and monitoring to track rates of antimicrobial use in veterinary sector, increase in resistance, and spread of antimicrobial residues in food chain.

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