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What Nepalese can Learn about Antimicrobial Resistance?

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ABSTRACT

Antimicrobial Resistance (AMR) is a worldwide public health problem. The sub-therapeutic use of antimicrobials diminishes the significant threat where and how poultry are raised caused by AMR. AMR in critically important drugs may reduce options on antimicrobial use and bring us back to the post-antimicrobial era. Antimicrobial stewardship should be perceived uniformly by every stakeholder for targeted and appropriate antimicrobial use. Out of six criteria prepared by WHO to combat AMR, Nepal has implemented only three of them. Hence, this study aimed to analyze the AMR situation and the scope of antimicrobial use in poultry in Nepal to improve understanding on how to develop actions that address AMR in poultry.

Keywords: *Antimicrobial resistance; Nepal; Poultry.*

INTRODUCTION

Antimicrobials are the crucial means to fight against infectious diseases to save human and animal lives. They also contribute to food safety and security, protection of livelihood, animal resources and poverty alleviation by improving animal health and productivity.[1] On the contrary, there is an alarming threat in the effectiveness of antimicrobial use in humans and livestock. Besides, some human, food, animal and environmental samples showed high resistance rates and treatment failure due to resistance in bacteria.[2]

Antimicrobial Resistance (AMR) is a worldwide public health problem and concerns all stakeholders in every country.[3] Without any difficulties, a new form of antimicrobials can cross international boundaries and can spread throughout the world in remarkable speed in many forms of resistance.[4] The Food and Agriculture Organization (FAO) estimated that there will be about ten million human fatalities per annum and a decrease in global GDP by 2 to 3.5% by 2050.[5] Hence, the global health leaders have described antimicrobials as "nightmare bacteria that pose a catastrophic threat to people in every country in the world".[4] As a consequence, instead of successful treatment intervention, there will be failure to treatment leading to soaring mortality rate. Food security and livelihood will be shrunken leading to loss of production as well as emerging more severe and chronic diseases among human and animal lives.[5]

THE USE OF ANTIMICROBIAL AGENTS IN FOOD-PRODUCING ANIMALS

In food-producing animals, antimicrobials have three roles: firstly, to treat bacterial infection in individual animals, secondly to control and prevent infections among animals and lastly, to increase the efficacy of animal growth. The first two parts are not different from its uses in humans whereas antimicrobials can be given to entire herds to control and inhibit infections from animal populations at vulnerable stages in their lives. The third role is growth promotion, which is not used in the human population and accounts for the majority of antimicrobials used in animals. Globally more antimicrobials are used to treat healthy animals than unhealthy humans as estimated by WHO.[6] Antimicrobial use in food producing animals will be increased globally with increasing human population, from 7 to 10 billion

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by 2050 and increasing global economic development.[7,8] Increase in use of antimicrobials is due to increase in caloric intake and improvement in the quality of food of the global population. Change in farming practice with a large proportion of animals will be raised in intensive farming and contribute to rise in antimicrobial use in animals. A study done by Bockel et al showed that there was a wider array of antimicrobials used globally among intensive chicken production than pork production.[8]

There is no definite data that can give a global picture of the situation of AMR on a global level. In the European Union, data on AMR in pathogenic bacteria isolates from food-producing animals have been reported including Campylobacter, Salmonella, Escherichia coli and Methicillin-resistant Staphylococcus aureus (MRSA). In the USA, AMR bacteria isolates (non-Typhi Salmonella, Campylobacter, E.coli and Enterococcus) from swine, cattle, chickens, and turkeys at slaughter was reported.[7] A High percentage of resistance among poultry was reported at significant levels in different developed countries. Isolates were reported to resist antimicrobials like penicillin, sulphonamides, tetracycline, and ampicillin.[9,10] In low and middle-income countries small numbers of studies were conducted but those studies have shown high AMR among poultry. It was reported that there was extensive resistance to erythromycin, carbenicillin, amikacin and penicillin.[7] There is linkage between antimicrobial uses as growth promoter or preventive use in food-producing animals and effects in human health but there is gap of enough strong evidence generated in the concern. Several studies have shown evidence to connect antimicrobial use in livestock with effects in humans. There are direct and indirect transmission routes of resistance from animals to humans e.g. consumption of animal products, infection of foodborne bacteria and contact to animals and their surroundings.[7]

In Nepal, there is no proper data available on AMR among both humans and animals. With increasing poultry production antimicrobial use among poultry is also increasing but there is no record on use of antibiotics. Antimicrobials are used for growth promotion and as disease prevention but there were no proper guidelines to regulate their usage among poultry or any other food producing animals. Low doses mixed with animal feed are used for disease prevention and growth promotion. From 2008 to 2012 the volume of veterinary antimicrobial sales rose more than fifty percent. Approximately, seventy one percent of veterinary drug sales were not prescribed by veterinary professionals but by retailers.[11] Currently, Nepal lacks veterinary drug use regulations and guidelines but the government has imposed a ban on import of chicken from India due to outbreak of bird flu.

In order to meet the demand of poultry meat, use of antimicrobials among poultry is significantly high at a global level. Sweden was the first country to ban antimicrobial use among food producing animals as growth promoter and they successfully developed a management system for reduction of AMR in their country.

Rocketing demand of animal protein is accelerating worldwide which is fueled by population growth and increasing incomes in LMICs. To meet the demand of meat, antimicrobials are used to accelerate animal growth.[7] For growth promotion and treatment of land and aquatic animals, antimicrobials play a critical role. Below 200 gram antimicrobials per ton of feed are used as growth promoters for animals.[12] Those antimicrobials which are used in threatening the human population are similar to those which are used for animal production.

Only nine out of twenty-seven antimicrobial agents are exclusively used in animals. In 2009 antimicrobials which are classified as critically important for human medicine like macrolides, penicillin and tetracyclines were the top three classes by global sales for animal use.[7] These lifesaving drugs should be easily available and accessible to the agriculture sector and for livestock use. Due to poor surveillance and data collection systems, global annual total consumption of antimicrobials in the agriculture sector contrasts significantly. According to the Organisation for Economic Co-operation and Development (OECD) there are only 42 countries that have systematic data collection mechanisms on the use of antimicrobial in livestock.[1] In 2010, it was estimated that about 63,151 tons of antimicrobial was consumed in food producing animals and in 2030 the projected consumption of antimicrobials in food producing animals will rise by sixty seven percent, to 1,05,596 tons. By 2030, antimicrobial use in Asia is projected to be 51,851 tons which represent eighty-two percent of the current global antimicrobial consumption in food animals in 2010. In future, growth of antimicrobial uses is expected to increase within the animal production sector. In the pig and poultry production sector, it is predicted that use of antimicrobial will be double.[8]

Numerous antimicrobials which are used in production of food animals were originally developed to treat infections in humans. The largest nonhuman use of antimicrobial agents is for food producing animals. Most of the antimicrobials are used in healthy animals in order to increase growth or prevent infection. Non-therapeutic uses of antimicrobials are used to promote increase in weight, incline the meat production per pound of feed used, and to avoid the spread of infections in feedlots. Sub-therapeutic uses of antimicrobials diminish significant threat in the congested conditions in which livestock and poultry are typically raised.[13]

GLOBAL EPIDEMIOLOGY OF ANTIMICROBIAL RESISTANCE IN POULTRY

The weight of the AMR problem is not quantified properly at the global level. There are no death register records "deaths caused by antimicrobial-resistant infection".[14] According to a report in 2014 published by WHO, there are three agents of great concern: Klebsiella pneumoniae, Escherichia coli and Staphylococcus aureus. High proportion of resistance to third generation cephalosporins is associated with nosocomial and community acquired infections. In many settings treatment of severe infection caused by these bacteria must rely on the last resort of Antimicrobial which is carbapenems. As reported by countries from five WHO regions, E. coli resistance was found often more than fifty percent to third generation cephalosporins and fluoroquinolones. Resistance rate to third generation cephalosporins in K. pneumoniae was above thirty percent and in all WHO regions the rate of MRSA resistance exceeded twenty percent and in some regions in six out of six WHO regions resistance rate was above eighty percent.[15] As reported from Centers for Disease Control and Prevention (CDC) in the US more than 2 million infections as well as 23,000 deaths each year is due to AMR with a direct cost of 20 billion dollars and another 35 million dollars as additional productivity losses.[4] In the EU, AMR was increased among some gram-negative bacteria such as E. coli. In Europe, each year about 25,000 patients die from infection by multidrug resistant bacteria that directly and indirectly cost €1.5 billion pounds annually.[16]

Due to lack of reliable information, there is no such global picture which can show antimicrobial resistance in food animals. Only a few developed countries have mechanisms to collect and record data regarding antimicrobial drug resistance.[7] Reports from different agencies of the US stated antimicrobial resistance among isolated bacteria: Campylobacter, E. coli, and Enterococci including non-typhi Salmonella from pig, chickens, cattle and turkeys at slaughter. Resistance was reported for most types of animal and antimicrobial at significant level. High rates of Salmonella resistance have been seen in the US. Around 7 to 27 % of poultry are resistant to penicillin, 8 to 22 % were resistant to sulfonamides and 41 to 46 % of poultry were resistant to tetracycline.[9] In European countries, the resistance rate of Salmonella isolated from chicken to tetracyclines (4-85 %), sulphonamides (5-85 %) and ampicillin (5-98 %) was reported.[10]

In LMICs a relatively small number of studies were done and there is no proper systems for information collection and management regarding resistance so there is a huge gaps in knowledge in resistance level. In India, Pasteurella multocida isolate in chickens were hundred percent resistant to sulfadiazine and there was extensive resistance to erythromycin, carbenicillin, amikacin and penicillin.[7] In another study, Staphylococcus and other bacteria have developed AMR which has also been reported in poultry litter in India. A study conducted by Dharani in 2009 showed that seventy-five percent of isolates were resistant to streptomycin and among those bacteria more than fifty percent were resistant to ampicillin, tobramycin and erythromycin.[17]

KEY NATIONAL POLICIES ON USE OF ANTIMICROBIALS IN POULTRY IN NEPAL AND WHO

After understanding the growing problem of AMR around the world and moving towards the post antibiotic era WHO alerted the World Health Assembly (WHA) about the problem and adopted a global action plan on AMR in May 2015 during Sixty-eighth WHA as resolution. This action plan emphasizes on "One Health approach" with multi-sectoral coordination with partners in national and international sectors of veterinary, human medicine, agriculture, environment, finance to solve the complex problem of AMR.[18] For the benefit of all and with a common objective to control AMR: World Organization for animal health (OIE), World Health Organization (WHO) and Food and Agriculture Organization (FAO) work closely in triplet initiatives with other partners as well.[19] The objective of WHO action plan was to assist Member States of WHO to develop and implement multi sector National Action Plans to combat AMR by May 2017.[18] Also parallel to the global action plan prepared by WHO; FAO and OIE also prepared their action plan.

WHO global action plan on AMR have adopted following five objectives to combat AMR[18]

- Improve awareness and understanding of antimicrobial resistance through effective communication, education and training
- Strengthen the knowledge and evidence base through surveillance and research
- Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures
- Optimize the use of antimicrobial medicines in human and animal health
- Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions

To support WHO global action plan on AMR OIE adopted the essence of WHO action plan and prepared their own action plan. There are four main objectives in OIE Strategy on AMR and the prudent use of antimicrobials.[19]

- Improve awareness and understanding

- Strengthen knowledge through surveillance and research
- Support good governance and capacity building
- Encourage implementation of international standards

Through OIE strategy on AMR, they mainly focus on reducing antimicrobial resistance addressing animals, zoonoses diseases and public health risks associated with zoonoses. Through objective one OIE strategy improves and increases awareness and understanding of AMR among its member state, veterinarian, farmers, different stakeholders and general population. It emphasizes mainly on responsible and ethical use of antibiotics in animals by organizing and conducting conferences and workshops that promote rational use of antimicrobial animals and addresses the issue at the local, national and international level. While second objective mainly focuses on monitoring, data collection, research and establishment of the World Animal Health Information System. Third objective highlights on development of national plan on AMR, policy to regulate antimicrobial production and use, capacity development of veterinary services. Whereas last objective emphasizes on implementation of OIE standards and Collaboration with WHO and FAO.[19]

Table 1. Comparing global action plan with Nepali strategy to combat AMR

Action Plan	WHO	Nepal
Awareness and understanding	√	√
Enhanced surveillance	√	√
Responsible use	√	√
Research and development	√	X
Supporting structure and system	√	X
Leadership	√	X

Though Nepal is a member state of WHO till now, it has not prepared a national plan to combat AMR. In Nepal, there are few policies and guidelines which indirectly influence to reduce AMR. Currently Drug Policy 1995[20] controls the use of antibiotics use in humans and animals whereas National Health Policy 2071.[21] Drug Category Rules 1986, Feed Act 1976, Feed Regulation Act 1984, Animal Health and Livestock Services Act 1999, Slaughterhouse and Meat Inspection Act 1999 indirectly support AMR. These acts set standards of feed ingredients and regulate healthy production, safe distribution and regulate safe import and export of animal products which also include poultry.[22] These acts also regulate the practice of sanitation and hygiene maintenance during production and slaughtering process .[23] Nepal Veterinary Council drafted the Veterinary Drug Act 2011 but it is not yet approved by cabinets of ministries.

LESSON LEARNED

Nepal has continuously been putting its efforts for prevention and control of major animal diseases. At central, regional and district level there is a network of national veterinary services. Under the Department of Livestock Services (DLS), Directorate of Animal Health is assisted by animal quarantine office, veterinary hospital, biological production laboratory, epidemiology center, veterinary standards and drug administration office, veterinary public health office, national Field Management Program (FMP) and Transboundary Animal Disease (TADs) laboratory and Veterinary laboratory at central level. Veterinary services at regional and district levels are being delivered through five Regional Veterinary Laboratories, five Regional Directorates of Livestock Services and one National Avian Diseases Investigation Laboratory, eight Animal Quarantine Offices with 24 Animal Quarantine Check posts, 5 Regional Livestock Training Centers and 75 District Livestock Services Offices. Furthermore, to provide veterinary services at the sub-district level there are 359 Livestock Service Centers and 640 Livestock Sub-Service Centers. They deliver animal health, breeding, nutrition, training and extension services to the livestock farmers.[24] In Nepal, veterinary service is being implemented with legal basis provided by Nepal Veterinary Council Act, Animal Health and Livestock Services Act, Bird Flu Disease Control Order, Slaughterhouse and Meat Inspection Act.

To preclude the abuse or misuse of drugs, the government of Nepal has enacted the Drug Act 1978. After that the Department of Drug Administration (DDA) was established in 1979 to implement and fulfill the aim of Drug Act 1978 and various regulations under it. DDA is the only authority responsible for regulating drug use in Nepal. DDA is responsible for regulating all types of medicines including veterinary drugs in the country. There is no separate organization for regulating veterinary medicines in Nepal. Veterinary Standards and Drug Administration Office has been established under the Directorate of Animal Health in Nepal to regulate the drug use but due to absence of Veterinary Drug Act, the office is not functioning as dreamed. Still the Veterinary standards and drug administration office has been involved in regulating veterinary vaccines imported in the country.[24]

Veterinary Inspectors are designated in each district by the Ministry of Agriculture Development. Designated veterinary inspectors regularly visit the drug stores and monitor their functioning but in the absence of the veterinary drug act they cannot act at the spot and have to report it to DDA for any legal actions.[24]

WAY FORWARD

There is a high prevalence of antimicrobial resistance among poultry in Nepal. As AMR is a multifaceted and multi-sectoral problem it is hard to control without a multi-sectoral approach. High prevalence of antimicrobial resistance in poultry, especially critically important drugs for humans, may reduce options on antimicrobial use and bring us back to the post-antimicrobial era. Antimicrobial stewardship should be perceived uniformly by every stakeholder for targeted and appropriate antimicrobial use. Political commitment and international support to developing countries should be increased as AMR is a geopolitical issue.

CONFLICT OF INTEREST

None

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