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Review paper

ANTI-MICROBIAL RESISTANCE (AMR) IN BHUTANESE LIVESTOCK: A REVIEW

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ABSTRACT: The inappropriate use of antimicrobials in humans and livestock have led to development of resistance by bacterial pathogens. The studies on imported chicken carcass in 2007 revealed prevalence of Salmonella (13%) with *Salmonella enteritidis* serotype (84.62%) and *Salmonella typhimurium* (15.38%). The pathogens were found to be resistant to nalidixic acid, amoxicillin and cephalexin. Similarly, a study conducted in the domestically produced broiler chicken carcass during 2016 also detected *Salmonella typhimurium* and *Salmonella paratyphimurium* type B with prevalence of 73.9% and 26.1%, respectively. They were resistant to Tetracycline (95.6%), Trimethoprim (86.9%) and Amoxycillin (65.2%). The investigation of *Escherichia coli* in three government pig-breeding farms revealed (2.4%, 2/83) ESBL producers harbouring beta lactamase genes for CTX-M-15 and TEM-1, of which two isolates were multidrug resistant (MDR) and belonged to sequence type (ST) ST156 and ST4173, respectively. This indicates the emergence of MDR ESBL producing *Escherichia coli* among breeding pigs in Bhutan. Likewise, common pathogens like *Escherichia coli* (33%), *Staph. Aureus* (19%), *Enterobacter* (15%), *Corynbacterium* (11%), *Streptococcous* (8%), *Pseudomonas* (5%), *Klebsiella pneumoniae* (4%) were isolated from milk samples collected from dairy farms from various parts of the country. The pathogens were found resistant to antibiotics like Penicillin G (23%), Ampicillin (20%), Amoxicillin (20%), Erythromycin (17%), Tetracycline (7%), Gentamicin (7%) and Streptomycin (6%). Rational use of antibiotics must be promoted for controlling AMR.

Keywords: Antibiotic; antimicrobial; pathogen; public health; risk.

1. INTRODUCTION

Antimicrobials are a special class of medicines that have been long and widely used as medicine in both humans and animals. They also contribute to food security by meeting the increasing demand for food of animal origin. In animals, they are used either for therapeutic and prophylactic purposes or as growth promoters. However, its inappropriate use over the past had led to emergence of bacterial resistance known as "Antimicrobial Resistance (AMR)". Globally, this has resulted in high morbidity and mortality with serious social and economic implications in both humans and animals. Resistant pathogenic bacteria from humans, animals and environment can spread from one source to another and could pose a serious risk to public health. The spread of these resistant organisms is through trade, travel and migration, which has led to a global concern.

The World Organization for Animal Health (OIE), World Health Organization (WHO), Food and Agriculture Organization (FAO) are working hand in hand to address the concern through the tri-partite approach at a global and regional level. The OIE member states were recommended to pursue the same issue at the national level. In Bhutan, studies (Dahal 2007; Gurung 2016) have revealed the existence of pathogens resistant to various antibiotics. These pathogens detected were even zoonotic in nature.

1. ANNUAL ANTIMICROBIAL CONSUMPTION

The annual consumption of antimicrobials was calculated based on the reporting option 3 of the OIE template-over all amount sold or used in animals by antimicrobial class. This option was selected as the government of Bhutan provides medicines free of cost. The data from the annual procurement record were compiled by the Drugs Vaccines and Equipment Unit (DVEU) of National Centre for Animal Health (NCAH).

Annually, about 631 kg and 441 kg of antimicrobials were procured during 2014-15 and 2015-16, respectively. The antimicrobials are supplied to the animal health facilities and central farms throughout the country. Huge number of oral antimicrobials are procured and distributed compared to the injectable (Table 1). Table 2 shows various antimicrobials under each classification used in the country.

3. Status of AMR in animals

Few studies revealed the presence of various bacterial pathogens, including the zoonotic ones (Dahal 2007; Gurung 2016). The details of the pathogens are summarized in Table 3. A study conducted by Dahal (2007) on the prevalence of *Salmonella spp.* and drug resistance in imported chicken carcasses in Bhutan showed 13% prevalence of Salmonella with *Salmonella enteritidis* as the most frequently isolated serotype (84.62%), followed by *Salmonella typhimurium* (15.38%). Among the seven antimicrobials tested, resistance to nalidixic acid was the highest, followed by amoxicillin and cephalexin. Another study conducted on domestically produced broiler chicken carcass showed that the prevalence of *Salmonella typhimurium* and *Salmonella paratyphimurium* type B were 73.9% and 26.1%, respectively. The antibiotic susceptibility test for 23 isolates of *Salmonella* species showed highest sensitivity to Gentamicin with 73.9%, followed by Streptomycin (56.5%) and Ampicillin (47.8%).

Similarly, the result showed the highest resistance to Tetracycline with 95.6%, followed by Trimethoprim 86.9% and Amoxycillin 65.2% (Gurung 2016). The antibiotic susceptibility test

Table 1: Quantities of antimicrobials consumed in the country (2013-2016) as per annual submission to OIE.

	2014-15				2015-16			
Class of antimicrobials	Oral (kg)	Inject. (kg)	Others (kg)	Total (kg)	Oral (kg)	Inject. (kg)	Others (kg)	Total (kg)
Aminoglycosides	0	4	0	4	0	12	0	12
Penicillins	16	16	4	36	60	9	0	69
Cephalosporins	12	0	2	14	32	3	0	35
Fluoroquinolones	0	1.5	0	1.5	1	1	0	2
Sulfonamides	449	14	2	465	236	22	4	262
Tetracyclines	30	42	0	72	43	18	0	61
Others	0	40	0	40	0	0	0	0
Total	507	117	8	631	372	65	4	441

for 23 isolates of *Salmonella* species showed the highest sensitivity to Gentamicin (73.9%), followed by Streptomycin (56.5%), and Ampicillin (47.8%).

The investigation of *Escherichia coli* in three government pig-breeding farms revealed (2.4%, 2/83) ESBL producers harbouring beta lactamase genes for CTX-M-15 and TEM-1 (Gurung 2016). The two isolates were multidrug resistant (MDR) and belonged to sequence type (ST) ST156 and ST4173, respectively. This indicates the emergence of MDR ESBL producing *E. coli* among breeding pigs in Bhutan and hence monitoring for ESBL producing bacteria should be continued in humans and animals in order to protect public health (Sharma et al. 2017).

In a study conducted on microbiological quality of raw milk in Bhutan (Chamling 2016), the common pathogens isolated were *Escherichia coli* (33%), *Staph. Aureus* (19%), *Enterobacter* (15%), *Corynbacterium* (11%), *Streptococcous* (8%), *Pseudomonas* (5%), *Klebsiella pneumoniae* (4%). The organisms were found resistant to antibiotics like Penicillin G (23%), Ampicillin (20%), Amoxycillin (20%), Erythromycin (17%), Tetracycline (7%), Gentamicin (7%) and Streptomycin (6%). The susceptibility profile indicated Tetracycline (27%), Streptomycin (17%), Amoxycillin (17%), Erythromycin (16%), Ampicillin (14%), Penicillin G (6%) and Gentamicin (3%). Several treatment failures of antimicrobials have been reported in veterinary clinical practices, especially against mastitis (Chamling 2016).

Table 2: Antimicrobials used in the country as per the classification.

Class	Antimicrobials
Aminoglycosides	Amikacin Gentamicin Cephalexin Erythromycin
Cephalosporins	Amoxycillin Streptomycin
Macrolides	Cefotaxine Ceftriaxone
Penicillins	Ampicillin Cloxacillin Penicillin G
Quinolones Sulfonamides	Tazobactum Sulfadimidine Trimethoprim Sulfadiazine Sulfamethoxazole
Tetracyclines	Tetracycline Oxytetracycline
Others	Metronidazole

4. SURVEILLANCE OF AMR IN BHUTAN

Currently, the laboratory facility for Antibiotic Sensitivity Testing (ABST) is available only at the National Centre for Animal Health (NCAH) and the tests are conducted on case-by-case basis. Although, some of the laboratories of Regional Livestock Development Centers (RLDCs) have facilities for ABST, they do not conduct the test.

5. LEGISLATION

Antimicrobials for veterinary use is classified under schedule E.2 prescription medicines (Medicine Act of Kingdom of Bhutan 2003 and Bhutan Medicine Rules and Regulations 2012). As per this classification, the antimicrobials are allowed to be sold or dispensed only with prescription. The Drug Regulatory Authority (DRA) regulates the sale and distribution of these medicines. In addition, DRA also regulates the therapeutic use of antimicrobials in animals, however, the use of antimicrobials as feed additives/growth promoters are monitored by the Department of Livestock (DoL) with technical advice of the National Veterinary Drug Committee (NVDC).

6. PREVENTION/CONTAINMENT ACTIVITIES

The antibiotic guidelines for animals in Bhutan were developed under the funding support of WHO. DoL also developed the Standard Treatment Guidelines for field staff, which helps in promoting rational use of antimicrobials in the field. All implementing agencies are expected to adhere strictly to these guidelines and support to reduce development of antimicrobial resistance.

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Table 3: Pathogens with antibiotic resistance (antimicrobial resistance) profile. NA-Nalidixic acid, AMP-Ampicillin, TET- Tetracycline, AMOX-Amoxicillin, CIP-Ciprofloxacin, S- Streptomycin, TMP-Trimethoprim, GENT-Gentamycin, CF-Cephalothin, CTX-Cefotaxime, C-Chloramphenicol, SMZ-Sulphamethoxazole, K-Kanamycin, CE Cephalexin.

Source of Pathogens	Pathogens	Prevalence (%)	AMR profiles	Investigator
Chicken carcass (imported)	Salmonella (N=52 isolates)	Over all (13)		
	S. entiridis (n=44)	84.6	NAL (95.5%) AMO (13.6%) CE (4.5%) CIP (2.3%) TMP (2.3%)	Dahal 2007
	S. typhymurium (n=8)	15.4	NAL (100%) CE (12.5%)	
Chicken carcass (Local)	Salmonella (n=23 isolates)	Over all (12.8)		
	S. typhymurium (n=17)	73.9	TET (95.6%), TMP (86.9%), AMO (65.2%), AMP (47.8%), AMP (47.8%), GENT (13%), S (8.7%)	Gurung 2016
	S. paratyphi type B (n=6)	26.1		
Faecal samples (Pig breeding farms)	*Escherichia coli* (n=83 isolates) Extended-Spectrum ß-Lactamase (ESBL) Producers	2.4	AMP, CF, CTX, CIP, S, C, NA, SMZ, TMP, TET, K	Sharma et al. 2017