

## A brief review on prevalence of antimicrobial residues and antimicrobial resistant bacteria isolated from food in Saudi Arabia

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**Abstract:** Antibiotics are used in livestock production (food animals) not only for treatment and control of diseases but also as growth promoters. Antibiotics residues in meat/food have serious consequences for public health, it contributes to the development and/or transmission of resistant bacterial pathogens. Further, transfer of such pathogens threatens the effective prevention and treatment of bacterial infections. Ultimately, this can result in human infections caused by nearly pan-drug resistant bacteria, making it highly difficult to cure. WHO, the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE) have recognized the importance of antibiotic resistance, including in relation to food safety. This brief article tries to review the health impact of antibiotic residues and the prevalence of antimicrobial resistance in food in Saudi Arabia.

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**Key words:** Antimicrobial residues; Antimicrobial resistant; ESBL; MDR

**Abbreviations:** ESBL, extended-spectrum beta-lactam; MDR, multidrug resistant; HPLC, High performance liquid chromatography; MRSA, Methicillin-resistant *Staphylococcus aureus*.

### 1. Introduction:

Antibiotics are used to control the growth of microorganisms and they are produced naturally or synthetically in the laboratory. Indiscriminate use of antibiotics in food-animals leads to the presence of antibiotic residues in meat and tissues of slaughtered animals. Antibiotics are used for disease prevention and treatment in animals and humans (Gustafson, 1992). Antimicrobials are also used to improve animal growth and disease control (Tollefson and Miller, 2000). Antimicrobials that widely used in poultry and animal farms include, the  $\beta$ -lactams, tetracyclines, aminoglycosides, lincosamides, macrolides, pleuromutilins, and sulfonamides (Lee *et al.*, 2001).

The use of antibiotics in food animals may lead to presence of some residues in its meat, milk, and eggs which may be attributed to the failure to observe the withdrawal periods, using high doses for animals, or the use of unlicensed antibiotics (Paige, 1994).

In poultry or animal farming, antibiotics can kill the susceptible bacterial strains, at a therapeutic dose, but can also leave behind strains with unusual traits that can resist antibiotics and multiply, increasing their numbers a million fold (Apata, 2012). Some of the antimicrobial resistance genes identified in food bacteria have also been identified in humans who are

exposed to resistant bacteria via contact with or consumption of food and this emphasize the indirect transfer by food handling and/or consumption (Marshall and Levy, 2011). Antimicrobial resistance is a global public health concern and the prevalence of antimicrobial resistance among food-borne pathogens increased during recent decades (Van *et al.*, 2007; Akbar and Anal, 2014) (Akbar and Anal, 2014). Antibiotic residues in meat and its association with drug resistant bacteria have gained a lot of attention. Many countries have no system for surveillance of antibiotic uses in food animals and they also lack the data that link between the uses of antibiotics in animals and development of multi-drug resistant (MDR) bacteria. Hence, the scientific community is forced to follow and research the reservoir of resistant microorganisms. Further, improved surveillance of antibiotic use and its judicial use is urgent and vital.

### 2. Occurrence of antibiotic residues in food

The use of antibiotic drugs in food-producing animals may result in the presence of residues in meat and offal, hence protection of public health against possible harmful effects of veterinary drug residues is a very important problem (Pavlov *et al.*, 2008). WHO and FAO established tolerances for drugs in the

relevant tissues of food producing animals. The edible animal tissue is considered safe for human consumption when the antibiotic tissue concentration is below the maximum residue level (MRL) (Nisha, 2008). Antibiotic withdrawal period and residue control should be conducted in slaughter houses to prevent harmful drug residues in food of animal origin that consumed by human being (McEwen and Fedorka-Cray, 2002). Microbial inhibitions assays have been used to detect antibiotic residues in poultry, meat and meat products and they are still widely used (Mitchell *et al.*, 1998). High performance liquid chromatography (HPLC) procedures are used to estimate the quantities of antibiotic residues in food products with good sensitivity and specificity (Muriuki *et al.*, 2001).

A study identified twenty-nine antimicrobial agents used in poultry industry in Saudi Arabia, among twenty nine, 22 (75.9%) happen to be most frequently used antibiotics, including enrofloxacin, tetracycline, ampicillin, neomycin, sulphamethoxazole, colistin, doxycycline and erythromycin used also for treating human infections. Food-borne hypersensitivity reactions and the emergence of microbial resistance, as well as cross-resistance to the various groups of antibiotics in animals and its transfer to human pathogens, are well documented (Al-Mustafa and Al-Ghamdi, 2002).

Administration of sulphadimidine to lactating camels resulted in residues in milk and its consumption during the 5 days from injection harbored public health hazards, including the carcinogenic effect (Littlefield *et al.*, 1990). A 9.2% of cow milk collected from supermarkets of Al-Hassa region in Saudi Arabia contained antibiotic residues. Overall, 17.1% milk from clinical mastitis infected cows grew *S. aureus*. These staphylococci were resistant to different antibiotics such as Penicillin G, ampicillin, cephalexin, erythromycin, streptomycin, neomycin and tetracycline (Al-Nazawi, 2006). Tetracycline residues have been reported exceeding permissible limits in chickens and eggs used for human consumption (Al-Ghamdi *et al.*, 2000).

Antibiotics can cause strong allergic reactions in sensitive people during treatment of bacterial infection which may be triggered by antibiotic residues (Sundlof *et al.*, 1993; Ishizuka, 2013).  $\beta$ -lactam antimicrobials appear to be responsible for most of the reported human allergic reactions (Fein *et al.*, 1995). Aminoglycosides, sulphonamides, and tetracyclines may also cause allergic reactions (Paige *et al.*, 1997). Certain macrolides may cause liver injury due to a specific allergic response to macrolide metabolite-modified hepatic cells (Dewdney *et al.*, 1991). Penicillin residues in meat may cause chest tightness and angioneurotic edema (Schwartz and Sher, 1984).

Meat consumption containing antibiotic residues may cause disruption of normal human flora in the intestine; these benign bacteria act as a barrier to prevent growth of pathogenic bacteria from causing disease (Myllyniemi *et al.*, 2000). The development and dissemination of antibiotic resistance should be studied and understood through the surveillance of MDR bacteria in meat and meat products which can provide risk assessment data and assist in implementation of targeted interventions. The MDR bacteria surveillance necessitates continuous data collection, analysis and reporting the occurrence and distribution of resistance to antibiotics. For framing effective public health policies and strategies, this has to be evaluated and performed in parallel to the obtaining data of developing and spreading antibiotic resistance in the food-chain and the association between usage and the occurrence of antibiotic resistance in meat, animals and humans. There are many knowledge gaps related to association of antibiotic resistance with food safety to be filled by research findings. The data generated can support the risk assessment and management to curb the evolution of antibiotic resistance (WHO, 2011).

### **3. Occurrence of AMR in bacteria isolated from food**

The classes of antibiotics used in food-producing animals and in humans are mostly the same, thereby increasing the risk of emergence and spread of resistant bacteria, including those capable of causing infections in both animals and humans (WHO, 2007). Food-producing animals are reservoirs of some pathogens which can carry resistant genes to infect humans. The spread of resistance genes from animal bacteria to human pathogens is another potential danger (White *et al.*, 2002; Mølbak, 2004).

The emergence of antibiotic resistance in bacteria that may be encouraged by extra use of antibiotics in poultry and animal farm can make treatment of human infections more difficult, so it has been recommended that antibiotics used for animal diseases treatment and control should not be used for human treatment (Ishizuka, 2013). Bacterial resistance in food producing animals can be developed during control and treatment and can spread among animal groups including fish, or to the local environment (i.e., local soil, air, and water). Spread of resistance can happen through manure or through contaminated food to humans. The contamination of food/ meat can occur through improper handling before cooking. There are studies revealing the presence of many antimicrobial-resistant *E. coli* strains which originated from contaminated retail meat and led to infections of the urinary tract and bloodstream in humans (Carlet *et al.*, 2012). Antimicrobial resistance has become a

worldwide problem for both human and animal health, particularly transmission of resistance to humans from animals and food (WHO, 2014).

Several studies worldwide have reported the bacterial contamination of milk and meat supposed to be for human consumption. Foodborne outbreaks can occur from ingestion of food contaminated with pathogens such as *Salmonella* spp., *Staphylococcus aureus* and *Escherichia coli* which lead to serious disease and may be to death. Intestinal tracts of humans and other mammals contain *Enterococcus* spp. which is responsible for nosocomial infections and outbreaks. *Enterococcus* spp. are also known to transfer resistance traits to and from other bacteria (Valdivia *et al.*, 1996; Simjee and Gill, 1997).

Antibiotic resistance could be conferred from commensals to pathogenic bacteria when both types are present on food animals (Geeson *et al.*, 2013).

Antibiotic resistant *Salmonella* was identified in acute *salmonella* food poisoning in patients in Saudi Arabia, and all the identified isolates were resistant to 2-5 antibiotics. The molecular characterization of the resistance determinants of these salmonellae suggests inappropriate use of antibiotics (Halawani and Shohayeb, 2008). In another study, 9.5% of nontyphoidal *Salmonella* (NTS) isolated from pediatric patients with acute gastroenteritis in Najran, Saudi Arabia, were resistant to a single antimicrobial agent each and 14.3% were MDR (Al Ayed, 2014). Most of the isolated bacteria from raw retail frozen imported freshwater fish in Eastern Province of Saudi Arabia showed resistance to tetracycline (90.71%, n=127) followed by ampicillin (70%, n=98) and amoxicillin-clavulanic acid (45%, n=63) (Elhadi, 2014).

Multidrug resistant bacteria were found in different types of meat (beef, lamb and camel) collected from local outlets in Riyadh region where *S. aureus* and *Enterococcus* spp. showed either resistance or moderate resistance to Erythromycin (79 and 86%, respectively) while *E. coli* and *Salmonella* spp. showed resistance to ampicillin (44%) and ceftiofur (67%), respectively (Geeson *et al.*, 2013).

The antimicrobial resistant *E. coli* isolated from retail raw chicken meat were studied in Taif, Saudi Arabia. *E. coli* cultured showed resistant to one or more of the antibiotics and resistance was most frequently observed against sulphurazole (89.2%), ampicillin (78.4%), nalidixic acid (70.3%), streptomycin (48.6%), chloramphenicol (32.4%), and gentamicin (24.3%). In addition, fifteen *E. coli* strains had MDR phenotypes and harbored at least three antibiotic resistance genes (Altalhi *et al.*, 2010).

Maximum resistance to extended-spectrum beta-lactam antibiotics were studied in bacteria isolated from Fresh Vegetables sold in Saudi markets (Hassan *et al.*, 2011) which reported that 2.3% of the bacteria isolated could produce extended-spectrum beta-lactamase (ESBL) and multiple resistances to four or more antimicrobial agents emphasizing the occurrence of antibiotic resistance and plasmid carriage among bacterial isolates populating raw vegetables.

There was a wide spread of MDR *S. aureus* and coagulase negative *staphylococci* (CoNS) in food and the environment in Makkah, western Saudi Arabia (Abulreesh and Organji, 2011), who found that all *S. aureus* strains which were isolated from raw milk, romy cheese and biofilm were resistant to penicillin G and oxacillin.

The extra use of prophylactic and therapeutic doses from antimicrobials in poultry and animal farms is considered one of the contributing factors for the widespread dissemination of MDR bacteria (Angulo *et al.*, 2004). Multi-drug resistance is a major concern faced by clinicians around the world today and among both Gram-positive as well as Gram-negative microorganisms. Meat and poultry products are frequently contaminated with MDR *Campylobacter* spp., *Salmonella* spp., *Enterococcus* spp., and *E. coli* (Tamura, 2003). In intensive poultry production, a major source of most resistance is antibiotic usage as feed additive, for treatment, or prevention, which leads to the development of resistant bacteria strains (Apata, 2012). The problem concerns bacteria carrying different resistance mechanisms that can be transferred to humans, these bacteria can initially cause a silent carrier state and may later give rise to infections that are not recognized as being of foodborne origin; Examples are urinary tract or abdominal infections caused by *E. coli* that could have been transmitted via the food chain. There is also growing concern about transmission of MRSA between human populations (Casey *et al.*, 2013). We worry about the rapidly increasing number of ESBL producing and fluoroquinolones resistant *E. coli* in developed and developing countries, So we need to stop using fluoroquinolones and third or fourth generation cephalosporin's in food animals, including; poultry (Kennedy *et al.*, 2008).

Drug-resistant strains of *E. coli* isolated from humans are originated from meat and meat products; these strains are highly resistant to fluoroquinolones and can spread into the community from food chains. Nowadays, third- and fourth-generation cephalosporin's and fluoroquinolones are used in poultry and animals farms in some developing countries (Collignon, 2009).

**Table (1): Predominant Antimicrobial Resistant Bacteria Isolated from Food in Saudi Arabia.**

Microorganism	Sample	Reference
<i>Staphylococcus aureus</i>	Beef, lamb and camel	(Greeson <i>et al.</i> , 2013)
	Raw milk, Romy cheese	(Abulreesh and Organji, 2011)
<i>Escherichia coli</i>	Chicken meat	(Altalhi <i>et al.</i> , 2010)
	Beef, lamb and camel	(Greeson <i>et al.</i> , 2013)
<i>Salmonella</i> spp.	Food poisoning in patients	(Halawani and Shohayeb, 2008)
	Pediatric patients with acute gastroenteritis	(Al Ayed, 2014)
	Freshwater fish	(Elhadi, 2014)
	Beef, lamb and camel	(Greeson <i>et al.</i> , 2013)
ESBL producing bacteria	Vegetables	(Hassan <i>et al.</i> , 2011)
<i>Enterococcus</i> spp.	Beef, lamb and camel	(Greeson <i>et al.</i> , 2013)

**Table (2): Maximum residual limits (MRLs) of antimicrobial residues in food according to GCC Standardization Organization (GSO) prepared by Kingdom of Saudi Arabia.**

Antimicrobial drugs	Acceptable Daily Intake (ADI)	Tissue	MRL µg/kg
Amoxicillin	0 – 0.7 µg/kg	Muscle, liver & kidney	10
		milk	4
Ampicillin & Cloxacillin	200 µg/kg body weight	Muscle, liver, kidney & milk	10
Benzyl penicil in & Procaine Benzyl penicillin	30 µg penicillin/person/day	Muscle, liver & kidney	50
Tetracyclines	0-3 µg/kg body weight	Muscle, liver, & kidney	100 300 600
Cefalonium	0 - 20 µg /kg body weight	Muscle, liver & kidney	100
Cefapirin	0 - 0.02 mg /kg body weight	Muscle, liver & kidney	20
Ceftiofur	0-50 µg /kg body weigh	Muscle & milk liver, & kidney	100 2000 2000
Cefuroxime	0 - 30 µg /kg body weight	Muscle, liver, kidney & milk	100
Gentamicin	0.05 mg/k body weight	Muscle	500
		Liver	500
		kidney	10000
		milk	1500
Trimethoprim	20 ug/kg body weight	Muscle, li er, kidney & milk	50
Enrofloxacin	2 ug/kg body weight	Muscle Liver kidney	100 300 200
Sulfonamides	0-50 µg/kg body eight	Muscle, liver & kidney	100

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