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Review

Recent trends and scenario of antibiotic use in veterinary practices for livestock production in Bangladesh: a review

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Abstract: Antibiotics are used for the treatment and control of diseases as well as a growth promoter in livestock production in Bangladesh. The frequent use of these antibiotics in veterinary practices may lead to residue and creates some potential problems not only in livestock but also in public health issues. The presence of residues of antibiotics in animal-derived foodstuffs may induce carcinogenic and mutagenic effects and leads to the condition of an allergic reaction, and the development of antibiotic resistance in human gut bacteria. Although misuse of antibiotics in human medicine is the principal cause of the problems, some antibiotic-resistant bacteria originating in animals may also be the contributory factors to the resistance. However, some of the antibiotic resistance problems can be attributed to the transfer of resistant bacteria from animals to humans and resistance genes from animal pathogens and commensal bacteria to human pathogens. Even though the antibiotics and their residues in feed and food products of animal origin cause serious public health problems but little is known by society due to the lack of proper information. So, this is important to review the uses of antibiotics in food animals and insight their public health significance in Bangladesh. However, the safety levels of animal feeds and food of animal origin must be strictly observed and the antibiotics should be used in accordance with the labeled directions public awareness should be developed about the indiscriminate use of antibiotics in animals and their hazardous residual impacts on the human body. Therefore, the present review focuses on the aspects of antibiotic use in the livestock production of Bangladesh.

Keywords: antibiotic uses; livestock production; residue; human health

1. Introduction

Antibiotics are substances produced naturally from living organisms or synthetically in the laboratory that can be administered orally, parenterally, or topically to kill or inhibit the growth of microorganisms (Sattar *et al*., 2014). Antibiotics can be categorized according to their effects as bactericidal or bacteriostatic and on the basis of their efficacy as narrow or broad in the spectrum (Manyi-Loh *et al*., 2018). Antibiotics are generally used to treat, control, and prevent diseases and for other purposes including enhancing animal growth and feed efficiency in different counties of the world including Bangladesh (Bacanlı and Başaran, 2019; Islam *et al*., 2016). Now a day, about 80% of all food-producing animals receive medication for part or most of their lives. In

Bangladesh, there are about 402.56 million livestock (Hamid, 2020) and 0.15 million poultry farms of which about 94.16% of farmers use antibiotics in their farms (Ferdous *et al*., 2019). The most common antibiotic classes use for livestock production in Bangladesh are β-lactams, tetracyclines, aminoglycosides, lincosamides, quinolones, polypeptides, amphenicols, macrolides, and sulfonamides (Chowdhury *et al*., 2009).

The use of antibiotics in food-producing animals may deposit as residues in food products such as milk, meat, eggs, and other products. Globally including in Bangladesh, these residues usually occur due to some reasons such as indiscriminate and irrational use of antibiotics in livestock without following a withdrawal period, extra-label dosages for animals, contamination of animal feed with the excreta of treated animals, or the use of unlicensed antibiotics (Chowdhury *et al*., 2015).

Antibiotic residue in food products of animal origin may be the cause of numerous potential problems to public health such as the transfer of antibiotic-resistant bacteria and genes to humans, mutagenicity, carcinogenicity, allergy or hypersensitivity reaction, and low-level may cause alteration of microflora and the possible development of resistance (Ahaduzzaman *et al*., 2014; Hassan *et al*., 2014; Islam *et al*., 2016). In recent years, the residual effect of antibiotics is one of the major threats to public health that is faced by the human population worldwide but the antibiotic residue in foods of animal origin has rarely been considered as a serious concern in developing countries like Bangladesh. Recently, the sanitary authority is concerned to protect public health against possible harmful effects of veterinary drugs in foods of animal origin like milk, sweets, meats (Khatun *et al*., 2019). With the advance of veterinary medical practices, the use of antibiotics in modern animal production are increased in Bangladesh which is potentially increasing the selection pressure on bacteria to become resistant (Ferdous *et al*., 2019). Globally, the average estimated annual consumption of antimicrobials in poultry is around 148 mg/kg (Van Boeckel *et al*., 2015).

In Bangladesh, agricultural sectors consume a large portion of antibiotics in parallel to the incautious use of antibiotics in human medicine as well as from animal farming that is used to treat and minimize the potential outbreaks of diseases to promote animal health. But there is a debate in veterinary medical practices regarding the use of antibiotics in animal production for human consumption. Inappropriate antimicrobial drug use for humans is diffusive in developing countries and is thought to be a significant contributor to antibiotic-resistant bacteria (Roess *et al*., 2013). Poor-quality veterinary medicine is an important factor in antimicrobial resistance in livestock (Clifford *et al*., 2018). However, the potential threats to human health may result from the improper use of antibiotics in food-producing animals resulting from antimicrobial resistance transmission in the food supply chain (Masud *et al*., 2020). Some commensal bacteria found in food-producing animals are frequently propagated in fresh meat, and milk products and may serve as reservoirs for resistant genes that could be transferred to pathogenic organisms in humans (Diarrassouba *et al*., 2007; Islam *et al*., 2016; Mena *et al*., 2008; Neogi *et al*., 2020).

While antibiotic use in food animals may represent a risk to human health but the degree and relative impact on public health still have not been well characterized due to a lack of proper information about the antibiotic residues in animal-originated foods of Bangladesh. Moreover, food safety issue has become extremely important, and ensuring safe foods is an international public health concern as well as in Bangladesh (Murshed *et al*., 2016).

Therefore, based on the above facts the objectives of this paper are to reveal the supply chain and uses of antibiotics in livestock production of Bangladesh; to review the problems associated with the improper use of antibiotics in veterinary practices; to review the antibiotic residues in animal-originated food products; to describe the current situation of antibiotic resistance and its impact on public health; strategies to reduce the uses of antibiotics in livestock production, and finally, provide some recommendations to minimize the hazardous public health impact resulting from the indiscriminate use of antibiotics in livestock production in Bangladesh.

2. Definitions of use of antibiotic

2.1. Therapy, control, prevention, and growth promoter

The National Committee for Clinical Laboratory Standards of the USA has defined the terms to describe the uses of antibiotics (Watts *et al*., 2008) in the animal herd. Therapy is the administration of an antimicrobial agent to a clinically ill animal or group of animals. Control is the administration of an antibiotic to the infected animals which exceeded the baseline of morbidity and/or mortality. Prevention is the administration of antibiotics to healthy animals considered at risk. Growth promotion is the administration of antibacterial agents, usually as feed additives, over a period of time to promote animal growth by enhancing physiological performance.

2.2. Maximum residue limit (MRL)

Maximum residue level (MRL) is the maximum concentration of a veterinary antibiotic or drug residue resulting from the use of that product that is legally permitted or accepted by the controlling authority in feed or foods intended to be used for animal or human consumption at a certain period of time. The MRL is fixed on the basis of relevant toxicological data. The unit used for MRL is milligrams per kilogram of solid products and milligrams per liter for liquids (Kebede *et al*., 2014).

2.3. Withdrawal period

The withdrawal period is the time between the last doses of antibiotic administered to the animal and the time when the level of residues in the tissues or products is lowers than or equal to the MRL. The withdrawal time may vary due to the chemical and physical properties of the antibiotic and the route of administration (Beyene, 2015). Until the withdrawal period is over, the animal or its products cannot be used for human consumption.

3. Pharmacodynamics of antibiotic use

The main purpose of the use of antibiotics is to treat infections and to eradicate the pathogen as quickly as possible with minimal adverse effects on the recipient. To achieve this goal, three basic conditions must be considered (Capitano and Nightingale, 2001). First, the antibiotic should bind to a specific target-binding site on the microorganism. Although the active sites are different for different classes of antibiotics but their principle is the same. Secondly, the concentration of the antibiotic is sufficient to occupy the specific active sites on the microorganism. And finally, the antibiotic should be occupied a sufficient number of active sites for an adequate period of time. The relationship between the concentration of antibiotics and the retention time of that concentration at the active sites is termed the area under the concentration-time curve ($Cp \times time = AUC$) which is crucial to the life and death of the bacteria (Mouton *et al.*, 2007). Simply, pharmacodynamics can be defined as the indexing of the total drug exposure in the serum or other body sites to measure the microbiological activity of the agent against the organism (Capitano and Nightingale, 2001). The measure of microbiological activity commonly known as minimum inhibitory concentration (MIC) is an important parameter in pharmacodynamics and the AUC/MIC ratio is thought to be a crucial point to explore the antimicrobial activity of an antibiotic (Mouton *et al*., 2007). Generally, the higher the AUC/MIC ratio, the more likely the organism will be maximally eradicated. Resistance can occur as a result of using low doses of antibiotics on an organism that has higher MIC values (Tenover, 2001). Therefore, using a higher AUC/MIC ratio is critical to eradicating organisms and minimizing the risk of selecting resistant organisms. These basic principles of pharmacodynamics are thought to be important for using antibiotics in food-producing animals (Lees and Aliabadi, 2002).

4. Supply chain, distribution, and common antibiotics used for the livestock sector in Bangladesh

In Bangladesh, most life-saving antibiotics are manufactured by local pharmaceutical companies (Anesary *et al*., 2014). It is assumed that about 70 % of the total quantity of antibiotics used in the food-producing animal is produced locally and the rest of them are imported by different trading companies. The supply chain and distribution of antibiotics both from domestic and importers are distributed to wholesalers, chemists, retail pharmacies, and feed sellers, and even to poultry farmers to some extent (Masud *et al*., 2020). Most farmers in commercial poultry use antibiotics themselves directly from feed dealers or even directly from companies or suppliers. A major portion of antibiotics is sold to customers or animal farm owners through over-the-counter and also by the veterinary quacks. A study showed that most of the farmers (>60%) in Bangladesh use antibiotics without the prescription of veterinarians (Masud *et al*., 2020). Only a very negligible amount of the total sale of antibiotics is done through registered veterinarians or prescriptions. The most common antibiotics used for livestock production in Bangladesh are summarized in Table 1 (Chowdhury *et al*., 2009).

Table 1. Common antibiotics used in livestock production of Bangladesh.

SL	Class	Antibiotics
A	**Drug used in Food animals (other than poultry)**	
	Tetracycline	Oxytetracycline
	Penicillin	Procaine penicillin, Benzyl penicillin, Ampicillin, Amoxicillin
	Sulphonamide	Cotrimoxazole, Sulfadimidine,
	Fluorquinolone	Ciprofloxacin
	Cephalosporin	Ceftriaxone
B	**Drugs used in poultry**	
	Tetracycline	Oxytetracycline, Chlortetracycline, Doxycycline
	Penicillin	Amoxicillin
	Sulphonamide	Cotrimoxazole, Sulfadimidine, Sulphadiazine
	Fluorquinolone	Ciprofloxacin, Enrofloxacin, Norfloxacin
	Macrolides	Erythromycin, Gentamycin
	Ionophores	Salinomycin, Maduramycin
	Nitrofurans	Furazolidone

The frequency distributions of common antibiotic groups prescribed for livestock production in Bangladesh are demonstrated in the Figure 1 (Ferdous *et al*., 2019; Islam *et al*., 2016; Sarker *et al*., 2016).

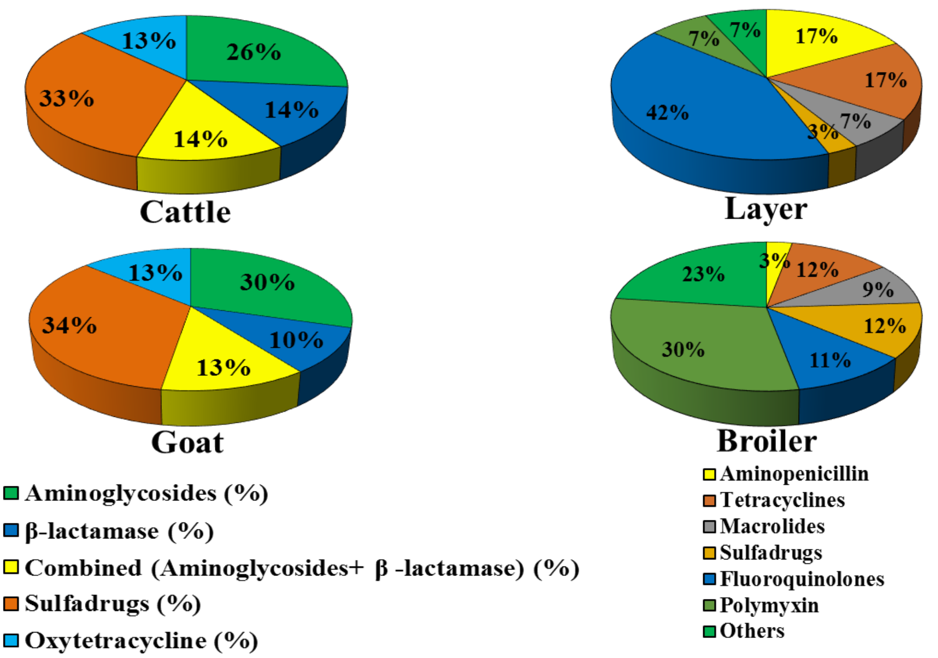

Figure 1. Frequency distributions of different antibiotics prescribed for livestock in Bangladesh.

5. Uses of antibiotics for livestock production in Bangladesh

Antibiotics are lifesaving drugs that are typically used for three purposes in the livestock sector of Bangladesh such as (i) treatment, (ii) prevention and control, and (iii) as growth promoters to enhance animal growth and feed efficiency (Islam *et al*., 2016; Sattar *et al*., 2014).

- **Therapeutic purposes for the treatment of diseases**

Antibiotics are extensively used for therapeutic purposes to treat sick animals in Bangladesh. Therapeutic use generally involves the treatment of sick animals on an individual basis, but occasionally can require the use of medicated feed or water to treat a group or flock of animals. Although it uses for therapeutic purposes of livestock is only recommended by registered veterinary doctors but some indiscriminate and irrational uses of antibiotics are performed by non-veterinarians (Chowdhury *et al*., 2015).

- **Prophylactic purposes for prevention and control of diseases**

Most prophylactic uses of antibiotics involve mass medication of a group or flock of animals via feed or water. The antibiotics registered for prophylactic use are categorized country-wise and according to their value in human medicine. In Bangladesh, nearly all dairy cows receive intra-mammary infusions of prophylactic doses of antibiotics following each lactation to prevent and control future mastitis (Anika *et al*., 2019).

- **Growth promotion**

Sub-therapeutic doses of antibiotics increase animal growth rates and improve feed efficiency. Although all antibiotics are not recommended for food animals a large proportion of antibiotics are used as a growth promoter in livestock production in Bangladesh and very little published information is available about their effects on animals. About 90% of all antibiotics used for livestock production in farms are reported to be administered at the sub-therapeutic concentration (Sarker *et al*., 2016) and are mostly used as growth promoters in the livestock sector of Bangladesh to facilitate feed conversion ratio and disease control purposes (Anika *et al*., 2019). Although widespread uses of antibiotics in food animals are noticed in Bangladesh, reliable data about the quantity and pattern of uses such as dose, frequency, and duration are not available. Quantifying antibiotic use in food animals is a big problem in Bangladesh due to the variation of studies conducted by the investigators and the lack of clarity and proper definitions of therapeutic versus nontherapeutic uses. According to the Fish Feed and Animal Feed Act 2010, the use of certain antibiotics as growth promoters in animal feed is banned. But some studies revealed that antibiotic residues are still present in poultry meat and eggs (Hoque *et al*., 2020). However, this may happen due to a lack of proper veterinary regulation and low enforcement of the act. As a result, antibiotic-resistant bacteria are being increased and which is a big threat to animals and humans in Bangladesh.

6. Problems associated with antibiotic uses in livestock production of Bangladesh

6.1. Antibiotic residues

Antibiotics extensively used for food-producing animals in Bangladesh are- beta-lactams, tetracyclines, macrolides, sulfonamides, aminoglycosides, fluoroquinolones, lincosamides, cephalosporins groups (Chowdhury *et al*., 2009). About 90% of all antibiotics used for livestock production in farms are reported to be administered at sub-therapeutic concentrations. Recent reports have revealed that the use of large amounts of antimicrobial drugs could result in the deposition of antibiotics as residues in animal products (Sanz *et al*., 2015; Sarker *et al*., 2016). Milk, meat, and other dairy products containing drug residues beyond the MRL may produce serious health problems for the consumers (Chowdhury *et al*., 2015). Though good quality milk, meat, and other related products are a prime need for maintaining proper public health (Shamsuddin *et al*., 2007), the presence of antibiotic residues in these food items and their subsequent consumption may cause serious health problems to consumers including the development of antibiotic resistance, hypersensitivity reaction and cancer (Hassan *et al*., 2014). The consequences of such resistance are even more threatening when antibiotics become ineffective clinically for the treatment of illness. FAO/WHO reported that antibiotic residues in edible animal products have grown beyond the permissible levels in developing countries (Oloso *et al*., 2018). Developing countries are in greater risk compared to developed countries due to poor detection facilities as well as a lack of proper monitoring system of residues in foods considering the MRLs (Kebede *et al*., 2014). Indiscriminate and irrational use of antibiotics in livestock without following the withdrawal period are the main causes of residues in animal-originated food products in Bangladesh (Chowdhury *et al*., 2015). Some studies have shown that antibiotics administered to poultry and livestock deposited in liver, kidney, muscle, and bones exceeding the MRL (Sarker *et al*., 2016). A high percentage of poultry meat and eggs for human consumption were found to have antimicrobial residues such as amoxicillin, tetracycline, ciprofloxacin, and enrofloxacin (Hoque *et al*., 2020). A study performed in Chittagong region of Bangladesh on dairy and poultry farms demonstrated that the tetracycline, amoxicillin, and ciprofloxacin residues were significantly higher in commercial farms compared to local and the concentration of amoxicillin residue in milk and eggs were 56.16 μg/ml and 48.82 μg/g respectively (Chowdhury *et al*., 2015). In another study tetracycline, ciprofloxacin, enrofloxacin, and amoxicillin residues were found in poultry liver as 48%, 44%, 40% and 42% cases respectively and the concentration of amoxicillin particularly in the liver was 16.92 μg/kg to152.62 μg/kg and in breast muscle was 45.38 μg/kg to 60.55 μg/kg (Sattar *et al*., 2014).

6.2. Development of antimicrobial resistance (AMR)

Resistance to antimicrobial drug is one of the most serious medical problems in the world including Bangladesh (Ahmed *et al*., 2019) in which antimicrobial agent such as antibiotic is not effective for the treatment of infections by bacterial acquired resistance to all available antibiotics. The improper antimicrobial drug used for humans is diffusive in developing countries and is a significant contributor to growing the public health threat of AMR-resistant bacteria (Roess *et al*., 2013). In recent years, the indiscriminate use of antibiotics in animals and poultry is thought to be an important factor to develop of AMR (Kabir *et al*., 2015; Al-Salauddin *et al*., 2015; Sohidullah *et al*., 2016; Rahman *et al*., 2016; Talukder and Ahmed, 2016; Roy *et al*., 2017; Jahan *et al*., 2017; Kabir *et al*., 2018a; Kabir *et al*., 2018b; Kamal *et al*., 2018; Islam *et al*., 2018; Alam *et al*., 2019; Rumi *et al*., 2019; Saif *et al*., 2019; Masud *et al*., 2020; Alam *et al*., 2020; Sarker *et al*., 2020; Mridha *et al*., 2020; Matubber *et al*., 2021; Uddin *et al*., 2021; Tresha *et al*., 2021; Eashmen *et al*., 2021; Haque *et al*., 2021; Hosain *et al*., 2021; Arif *et al*., 2022; Hoque *et al*., 2022). In Bangladesh, the most common reason for choosing an antimicrobial is personal experience and perception (68%), rather than the cultural sensitivity test which may be due to a lack of vet diagnostic facilities and the unwillingness of the veterinary personnel (Pokharel *et al*., 2020). Farmers' wisdom about the use of antibiotics is another important determinant to provoke the problem of antibiotic resistance (Friedman *et al*., 2007). A study showed that 100 % of farmers in Bangladesh have no clear idea about antimicrobial resistance and the withdrawal period of antibiotics (Bhowmik *et al*., 2018). Resistance to antibiotics includes- firstly, the transfer of AMR pathogens through the food chain, and the transfer of AMR genes from animal enteric flora to human pathogens. Secondly, there is a reduced efficacy of antibiotic therapy in animals colonized with resistant bacteria (Pokharel *et al*., 2020). Only a few comprehensive studies were performed on antibiotic resistance in bacterial isolates from animals and poultry products in Bangladesh. There is evidence that resistance in some human enteric pathogens has emerged due to the transfer of resistant bacteria or resistance genes from animals to humans via the food chain or via the contaminated environment (Alam *et al*., 2019; Chowdhury *et al*., 2015; Neogi *et al*., 2020). The scientific reports that have been published on antibiotic resistance properties of bacteria isolated from livestock products in Bangladesh are summarized in Table 2.

Table 2. Percent of antibiotic resistance of different bacteria isolated from different samples in Bangladesh.

Bacteria	Samples	Antibiotic resistance (%)	References
E. coli	Poultry	penicillin, ampicillin, tetracycline, erythromycin, ciprofloxacin, kanamycin, streptomycin, cefixime and rifampicin-52-58%, neomycin and chloramphenicol-20%	Akond *et al*., 2009
		cotrimoxazole-100%, penicillin and gentamycin-75%	Hashem *et al*., 2012
		oxytetracycline-92%, sulphonamide-trimethoprim-84%, amoxicillin-76%, erythromycin-60%, doxycycline-48%, ciprofloxacin-44%, azithromycin-32%, gentamicin-16%, neomycin-08%	Rahman *et al*., 2017
	Beef	ciprofloxacin and gentamicin-100%, erythromycin-86%, oxytetracycline-71%, amoxycillin-43%, sulphonamide-trimethoprim, doxycycline and azithromycin-29%	
	Milk	amoxicillin-50%, sulphonamide-trimethoprime-47%, doxycycline-44%, erythromycin-41%, oxytetracycline-33%, azithromycin-28%, ciprofloxacin-16%, neomycin-6%	
	Cloacal swabs	Tetracycline-95.25%, ampicillin-91.25%, streptomycin-88.25%, erythromycin-84.75%, trimethoprim- 65.5%	Al Azad *et al*., 2019
Salmonella spp.	Poultry	erythromycin-100%, doxycycline-79%, sulphonamide-trimethoprim-76%, azithromycin-72%, oxytetracycline 67%, amoxicillin-45%, amikacin-34%, ciprofloxacin and neomycin-17%, gentamicin-14%	Rahman *et al*., 2018
	Beef	erythromycin and azithromycin-83%, oxytetracycline and doxycycline-67%, sulphonamide-trimethoprim and amoxicillin- 33%, amikacin and ciprofloxacin-17%	
	Milk	amoxycilin, doxycycline and erythromycin-100%, sulphonamide-trimethoprim and azithromycin-50%, ciprofloxacin, gentamicin and neomycin-0%	
Campylobacter spp.	Poultry	ampicillin-100%, erythromycin-78%, tetracycline-67%, norfloxacin-67%, nalidixic acid-44% gentamicin-22%, ciprofloxacin-22%, azithromycin-11%, streptomycin-0%, chloramphenicol-0%	Kabir *et al*., 2014

Table 2. Contd.

Bacteria	Samples	Antibiotic resistance (%)	References
	Milk	erythromycin-100%, amoxicillin, tetracycline and azithromycin-86%, streptomycin-57%, norfloxacin-50%, ciprofloxacin-29%, gentamicin-14%	Kabir *et al*., 2019
Staphylococcus aureus (Non-enteric bacteria)	Poultry	oxytetracycline-72%, azithromycin-64%, erythromycin-59%, sulphonamide-trimethoprim-49%, doxycycline-41%, ciprofloxacin-28%, gentamicin-18%,amoxicillin-5%, neomycin-0 %, amikacin-0 %	Rahman *et al*., 2014
	Beef	oxytetracycline-29%, sulphonamide-trimethoprim, amoxicillin, neomycin and amikacin-14%, doxycycline, erythromycin, gentamicin ciprofloxacin and azithromycin-0%	
	Milk	amikacin-56%, erythromycin-44%, oxytetracycline-20%, azithromycin-16%, amoxicillin and doxycycline-12%, sulphonamide-trimethoprim, gentamicin and ciprofloxacin-8%, neomycin-0%	
	Egg	erythromycin-82%, amoxicillin-73%, sulphonamide-trimethoprim-73%, ciprofloxacin-72%, oxytetracycline-63%, doxycycline-36%, amikacin-36%, gentamicin, azithromycin and neomycin-9%	
	Meat and food handler sample	penicillin-G-57.14% and tetracycline-53.57%.	Parveen *et al*., 2002
E. coli, *Salmonella*, *Pasturella multocida*, *Staphylococcus aureus* and *Proteus*	Poultry	erythromycin-100%, doxycycline-98%, bacitracin-96%, sulphamethoxazole and trimethoprim-94%, oxytetracycline-91%, ampicilln, and cloxacillin-89%, co-trimoxazole-87%, streptomycin-85%, flumequine-84%, pefloxacin-83%, amoxicillin-81%, norfloxacin-75%, enrofloxacin-65%, spiramycin-52%, cephalexin-37%, ciprofloxacin-28%, gentamicin-27%, neomycin-23%, colistin-20%, fosfomycin-17%, florfenicol-2%	Chowdhury *et al*., 2009

6.3. Allergy or hypersensitivity reactions

Allergy or hypersensitivity reactions to an antibiotic can be developed in a sensitized patient which is a common problem in Bangladesh along with other countries of the world. This effect is acquired after human beings consume food of animal origin, which contains drug residue that has allergic effects. About 50% of the human population is considered to be hypersensitive to a number of antibiotics including penicillin (Bayou and Haile, 2017). Humans who consume meat products having penicillin residues are at risk of developing allergies in the skin or even severe anaphylaxis (Baynes *et al*., 2016). Mild rash to severe toxidermia is also reported in humans following exposure to sulfonamide (Choquet-Kastylevsky *et al*., 2002).

6.4. Disruption of the normal intestinal flora

The bacteria that live in the gut act as a barrier and prevent the incoming microorganisms from causing diseases. Antibiotic residues may reduce the total number of bacteria or kill some important species and adversely affect the intestinal flora and consequently may cause a gastrointestinal disturbance. Residues of antibiotics consumed through food of animal origin might reduce the total number of these beneficial bacteria or selectively kill them (Myllyniemi *et al*., 2000).

6.5. Carcinogenic, teratogenicity, and mutagenic effects

The presence of antibiotic residues in food of animal origin produces a potential threat to direct toxicity in humans such as cancers, teratogenicity, and mutagenicity (Chowdhury *et al*., 2015). The carcinogenic impact is produced by interfering with the normal phenomenon of cellular elements such as DNA and RNA. The mutagenic effect is another danger¬ous effect of antibiotics resulting from mutation of DNA molecules or damage of chromosomes and it may result in infertility of human beings (Beyene, 2015; Sachi *et al*., 2019).

Various congenital anomalies might be happened in a newborn child due to long-term exposure of antibiotic resistance during the gestation period (Sachi *et al*., 2019).

7. Strategies to reduce the uses of antibiotics in livestock production

The livestock production system is one of the largest consumers of antibiotics in Bangladesh where the antibiotics are mainly used as growth promoters, prophylactic and therapeutic agents. However, the possibility for the transfer of antibiotic resistance genes from livestock to humans via the food chain and the environment is probably a direct threat to public health. The following strategies can be adopted to reduce antibiotic use in livestock production.

7.1. Highlighting the importance of the One Health approach in combating AMR

AMR is a complex, multifaceted problem that threatens human and animal health as well as the world economy resulting from improper use of antibiotics. Globally, AMR is increasing (Klein *et al*. 2018) and it is thought that if the current trends continue, AMR will result in 10 million deaths per year from a wide range of infections by 2050 (O'Neill, 2016). Numerous cases of antimicrobial resistance in humans have been traced to resistant microbes suspected of originating in livestock (Mamun *et al*., 2017; Paphitou, 2013), which is particularly from asymptomatic infected livestock (Mamun *et al*., 2017). Transmission of resistant bacteria from livestock to humans can occur through the consumption of meat, direct contact with colonized animals, or manure spread in the environment (Paphitou, 2013). Thus, AMR is a multi-sectoral problem, and a coordinated response of the human, animal, and the environmental sectors adopting a comprehensive approach such as that of One Health is needed to combat the effect of AMR. Based on this concept, controlling the transmission of infection from animals and environment to human the government of Bangladesh came up with the National One Health Strategy in 2012 (Hoque *et al*., 2020). In 2016, a One Health Secretariat was established at the IEDCR of Bangladesh with staff from three ministries (human health, animal health, and environment) and support from the development partners (Dahal *et al*., 2017). Although, improving awareness among professionals and practitioners across the sectors for consensus actions, and coordination among different sectors and ministries will be a big challenge but we need a more comprehensive approach (Thakur and Gray, 2019) to move forward to response the health emergencies such as outbreaks of epidemics and pandemics including AMR. Therefore, One Health approach may be an effective way to reduce the use of antibiotics and subsequently the hazardous impact of antibiotic on livestock as well as humans.

7.2. Development of organic livestock production

Organic livestock production may be defined as a process that enhances the use of organic and biodegradable inputs from the ecosystem for animal nutrition, health, housing, and breeding (Chancier *et al*., 2011). Organic livestock production can be a simple model for the successful elimination of the non-therapeutic use of antibiotics in livestock production. Certified organic production is also the best way to combat antibiotic resistance and protect the health of farmworkers, communities, and consumers. Besides, organic farming may be an essential part of the future of the food systems, together with a dramatic change in the food culture and reduction of antibiotics in food (Muller *et al*., 2017). Some studies have demonstrated that organic farms harbor fewer antibiotic-resistant organisms compared to conventional methods (Sapkota *et al*., 2014, 2011; Schwaiger *et al*., 2010) and also reduce the usage of antibiotics (Kumar *et al*., 2018). Organic livestock production systems require producers to adhere to a number of standards. The standard will be strictly verified by the certification agencies authorized by respective governments (Chancier *et al*., 2011; Misiewicz and Shade, 2016). A farm may be classified as organic if it meets the criteria provided in a set of guidelines known as 'organic standards'. Organic farming can be practiced by any farmer who is willing to follow its principles and guidelines and if the food is to be marketed or traded, it must be certified by an accredited agency. In Bangladesh, the organic agricultural movement has been active since the 1980s but its expansion has remained limited due to some core problems such as poor farmers, poor farmer knowledge of organic farming and its benefits, insufficiency of organic inputs, and poor marketing of organic foods (Sarker and Itohara, 2008). However, some key points that need to be considered for organic farming by producers and stakeholders are given below:

the origins of livestock- all livestock and their products that are sold or labeled as organic must be raised under continuous organic management from the last third of gestation or at hatching.

- livestock feed- livestock feed must be 100% organic and cannot contain any plastic pellets, feces, or slaughter by-products.
- living conditions- an organic livestock producer must create and maintain living conditions that must accommodate the natural behavior of the livestock and provide access to outdoors, fresh air and sunlight,

and access to suitable pastures for ruminants. Animals must be supplied with adequate nutrition and when kept indoors, they must have dry, clean bedding and substantial ventilation.

- waste management- manure produced by organic livestock must be handled to ensure that it will not contaminate crops, soil, or water with heavy metals, or pathogenic organisms, and managed in a way that maximizes nutrient cycling back into the environment.
- health care- organic livestock producers require to establish preventive health care practices which include selecting the appropriate type and species of livestock and providing adequate feed and an appropriate environment that minimizes stress, disease, and parasites. The organic livestock producers cannot provide preventive antibiotics and they are encouraged to treat animals with appropriate protocols, including antibiotics and other conventional medicines when needed, but these treated animals cannot be sold or labeled as organic
- record keeping- organic livestock producers need to maintain records of the organic farm. These records are important to ascertain the ecological state of the animals and the production, harvesting and handling practices associated with the animals and their products. It is also important to demonstrate that records must comply with the relevant legislation, the Organic Food Production Act.
- If organic farming methods can follow in livestock production, this will drastically reduce the risk of infection and transmission within organic operations. Moreover, this organic livestock production will reduce the use of antibiotics in livestock.

7.3. Regular antibiotic residues test

Antibiotic residues test for animal-originated products such as milk, meat, and eggs should be done regularly by rapid screening and confirmatory methods.

7.4. Using alternative growth promoters instead of antibiotic

Alternatives to antibiotic growth promoters such as probiotics, prebiotic, symbiotic (Kabir *et al*., 2004; Kabir, 2009; Roy *et al*., 2015; Sarker *et al*., 2016; Kabir *et al*., 2016; Sarker *et al*., 2017; Sarker *et al*., 2017; Islam *et al*., 2018; Markowiak and Ślizewska, 2018; Rahman *et al*., 2019; Tuhin-Al-Ferdous *et al*., 2020; Rahman *et al*., 2020; Roy and Khatun, 2020; Arif *et al*., 2021), organic acid (citric acid, acetic acid) (Giger *et al*., 2003) and bioactive compound (tannin, saponin) (Ghosh *et al*., 2011) are safe and have no negative impact on the environments can be used for livestock production that improves the growth performance and immunity in livestock (Callaway *et al*., 2008; Markowiak and Ślizewska, 2018; Murugesan *et al*., 2015; Roodposhti and Dabiri, 2012) that will dramatically reduce the uses of antibiotic in livestock.

7.5. Vaccine

Regular vaccination may be one of the most effective ways of disease prevention as it directly prevents bacterial infections and may reduce the need for antibiotics. Besides, Indirect vaccination also provides herd immunity, which extends the protection to unvaccinated livestock (Adam, 2018) and may lead to a significant decline in total antimicrobial drug use (Raith *et al*., 2016).

7.6. Phage therapy

Phage therapy can be used to kill the pathogenic bacteria in which a physical breakdown of bacteria is occurred to escape the progeny virus. This process is more specific to the target bacteria than antibiotic therapy (Thakur *et al*., 2019). Besides, these have fewer side-effect on the eukaryotic cells. Thus, the phage cocktail containing a group of viruses can be used as an effective tool for reducing the use of antibiotics and combating bacterial resistance. A study demonstrated a successful reduction of bacteria in poultry disease following using phase therapy (Ahmadi *et al*., 2016).

7.7. Immune modulators

Immune modulators (e.g. Antimicrobial peptides, hybrid nanoparticles containing anti-inflammatory agents etc.) elicit a passive immune response by transfer of antibodies and changing the inflammatory responses of the host (Hosain *et al*., 2017; Kumar *et al*., 2015). The immune modulators stimulate the immune system in a process that is less dependent on the pathogen causing infection, which makes them effective for a broad range of pathogens (Hye *et al*., 2006). Antimicrobial peptides particularly bacteriocins have broad-spectrum activity against microorganisms which can provide a non-specific defense against infections by directly attacking microbes, maintenance of normal gut homeostasis, and changing the host inflammatory responses (Wang *et al*., 2016).

7.8. Vitamins and minerals supplementation

Vitamins and minerals play an important role in regulating immune function and inflammatory responses in animals (Thakur and Gray, 2019) and in improving performance in poultry (Salahuddin *et al*., 2017). Vitamin A and D are potent modulators of mucosal immune function and deficiencies of these vitamins may lead to marked changes in barrier function, gut microbiota, antigen-presenting cells, polarization, and activation of T cells and Macrophages (Smith *et al*., 2018). Some minerals such as Zinc (Zn), Iron(Fe), and Selenium(Se) has a significant impact on immunity (Smith *et al*., 2018). Studies demonstrated that Zn deficiency produces profound effects on T cell-mediated immunity, Fe levels affect the micro biota composition and resistance to bacterial infection and Se has an effect on inflammation, T cell, and Macrophage polarization via alterations in prostaglandin production (Smith *et al*., 2018). A study revealed that dietary supplementation of Copper (180 mg/day) + Zinc (Zn) (300 mg/day) +Vitamin E (500 IU/day) + Selenium (6 mg/day) + Vitamin A (53000 IU/day) + beta carotene (300 mg/day) during the last 2 month of gestation is beneficial for control of sub-clinical mastitis in dairy cattle (Sahu and Maiti, 2014).

7.9. Selective dry cow therapy

Usually, dairy cows are susceptible to mammary infection during the dry period, and a study revealed that cows receiving antimicrobial dry cow therapy (DCT) had a significantly higher cure rate (86.6%) than cows that did not receive antimicrobial treatment (59.2%) at this time (Kiesner *et al*., 2019). In DCT, antibiotics prevent both new and existing infections. ‘Blanket’ or conventional DCT is the treatment of all quarters of all cows with an antibiotic at drying-off is a common practice in most dairy farms. Whereas in selective DCT infected cows are treated with antibiotics along with teat sealant and uninfected cows are treated with teat sealant only (Firth *et al*., 2019). Given the concerns about antibiotic resistance, this is a challenge for the farmers to consider if it is necessary to treat all cows in their herds. A study demonstrated that selective DCT in a group of cows had a reduction in usage of antibiotics compared to blanket antibiotic DCT in other groups of cows with no significant difference regarding new intra-mammary infections (Tho Seeth *et al*., 2017). Therefore, selective dry cow therapy may lead to a decrease in the overall use of antimicrobials in dairy farms compared to conventional dry cow therapy.

7.10. Herbal medicine

The use of herbal medicine in veterinary practices is old but it can be adapted to animal/poultry health care (Biswas *et al*., 2017; Begum et al., 2018; Sarkar *et al*., 2018; Amin *et al*., 2019; Rahaman *et al*., 2020; Sarkar *et al*., 2021) and this practice may reduce the use of antibiotics and minimize the antibiotic residues in the animal-originated products (Ranganathan, 2017).

7.11. Strengthening the regulatory control for antibiotic usage in livestock

The Bangladesh government already had taken some steps to reduce the indiscriminate use of antibiotic in livestock sectors and to promote sustainable improvements in livestock production. The ministry of fisheries and livestock (MoFL), Government of the People’s Republic of Bangladesh produced a comprehensive “National Livestock Extension Policy-2013 ” for the sustainable development of the livestock sector (Mia, 2013). To ensure the quality and standard of livestock feeds used by the livestock stakeholder “Fish Feed and Animal Feed act 2010 as well as Animal Feed Rule 2013 were circulated (Masud *et al*., 2020) by the MoFL, Government of the People’s Republic of Bangladesh. The major objective of these Acts and Rules is to monitor the quality of poultry and animal feed of both local and import origin and to check the adulteration and standard of feeds. Uses of some antibiotics as growth promoters has been banned according to the Fish Feed and Animal Feed Act 2010 (Masud *et al*., 2020) although some antibiotics are still present in poultry meat and eggs (Alam *et al*., 2019). Strict regulation around the limited use of antibiotics as a growth promoters is needed. Recently a quality control laboratory for livestock inputs and its food product (QC Lab) has been established in the department of livestock services under MoFL, Government of the People’s Republic of Bangladesh to ensure the standard and quality of food products of animal origin.

8. Conclusions

The use of antibiotics in food-producing animals has a potential role to generate antibiotic residues in animal-derived products and exerts a health hazard to humans. After the administration of antibiotics to animal bodies, some portions become residue at high or low concentrations in their food products though it depends on the duration of administration and rational use of antibiotics. So failure to maintain the withdrawal period and improper use of antibiotics results in exposure to antibiotic residues in food products and subsequently leads to mutagenicity, carcinogenicity, allergic reaction, antibiotic resistance, and even death. Food safety has become extremely important and ensuring product safety is an international public health concern as well as in Bangladesh. Therefore, based on the above conclusion the following recommendation could follow to reduce the antibiotic residues in animal-originated products and minimizes the health-related problems of the consumers:

- Before purchasing of antibiotics, labeled instructions and consequences of its usage should be read carefully.
- Maintaining the proper withdrawal time for using antibiotics in food-producing animals.
- Indiscriminate use of antibiotics especially at sub-therapeutic doses for prophylaxis in animals should be ceased.
- Strictly follow the scientific guidelines and precautions to minimize the antibiotic residue in foods of animal origin.
- Data regarding the uses of antibiotics in food-producing animals should be preserved properly with the date and cause of treatment, name, and dosage of antibiotic used, withdrawal time, etc.
- The use of antibiotics in animals by Non Veterinarian should be discouraged.
- Proper biosecurity should be maintained to prevent infectious diseases in animals following good production and good management practices to reduce antibiotic use in animal production.
- Effective surveillance and monitoring of antibiotic residues in milk and milk products, meat and meat products, eggs, etc. should be continued by the regulatory authority.
- Overall, public awareness about the indiscriminate use of antibiotics in animals and their potential residual impacts on the human body should be developed.

Data availability

Not applicable.

Conflict of interest

None to declare.

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