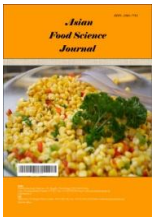

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The Outbreak of Foodborne Disease by Pathogenic Enterobacteriaceae Antimicrobial Resistance - A Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author FMBAl-S designed the review, wrote the protocol and supervised the work. Author MSAl-S carried out all the literature searches and wrote the first and final draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Chemicals, bacteria, viruses, and parasites can cause contamination of food. The general signs and symptoms of food poisoning include vomiting, diarrhea, headache, abdominal cramps, and fever. Paralysis and death could occur in severe infection. Most cases of food poisoning in Saudi Arabia are caused by the Enterobacteriaceae family of bacteria which is comprised of Shigella, Salmonella, and *Escherichia coli*. Most medications that are used to treat infections that are caused by these bacteria have become ineffective due to resistance. *Escherichia coli* reaches intestines due to fecal-oral contamination, consuming contaminated food, animal products, and water. Affected individuals present with fever, bloody diarrhea, vomiting, kidney failure, and hemolytic uremic syndrome. Some strains do not cause fever. Food hygiene is the best way of breaking the transmission cycle of *Escherichia coli*. *Salmonella typhi* is the causative agent of typhoid fever. The clinical picture of the affected individuals includes typhoid and non-typhoid symptoms. Typhoid symptoms include high fever, stomach pain, weakness, cough, diarrhea, and loss of appetite. On the other hand, non-typhoid signs are comprised of fever, septicemia, and prostration. Food contamination by Shigella spp. culminates in fever, cramps, diarrhea, and bloody

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stool. The microbe gets into healthy humans through contaminated food, tools, and water or via direct contact (like in sexual intercourse). Effective management of food poisoning entails rehydration, use of antibiotics, and encouraging adequate rest for the affected patients. One challenge that is likely to hamper the current treatment modality is the microbial resistance that the microbes have gained. Thus, new drugs have to be developed. The objectives and aims are to investigate the current biohazard of these types of microbes on foods and human safety in the Kingdom of Saudi Arabia and across the world, as well as to identify mutated and antibiotic-resistant types.

Keywords: Foodborne; enterobacteriaceae; antimicrobial; resistance; gastroenteritis.

1. INTRODUCTION

Food is an essential necessity every day for healthy people, sick people and animals, but sometimes can be a harmful for human due to the contamination by microbial or chemicals during any stage of the food chain, as a result of contamination in food, it leads to foodborne diseases as a worldwide issue. Food toxicity must be assumed when two or more people who share a meal within the previous 72 hours have an acute disease with gastrointestinal manifestation [1]. The term was being frequently used to refer to both food-borne infection and food-borne intoxication. According to some microbiologists, microbial food poisoning is separate from food-borne infections. In microbial food poisoning, the microbes multiply quickly in the food before consumption, while in food born infection, food contains the microorganisms then the food is consumed with microbes[2,3]. Furthermore, bacteria (66%), chemicals (26%), viruses (4%) and parasites (4%) are the main causes of food-borne illness. Intoxication and infection are the two most common types of foodborne diseases [4]. The symptoms usually include one or more of the following: diarrhea, vomiting, abdominal cramps, headaches, nausea and fever. In addition, the symptoms could more complicated that leads to paralyzing, bacteremia and other symptoms or death in some cases. The high-risk groups affected by food poisoning are adults Aged 65 or older, children younger than 5 years, people with weakened immune systems, and pregnant women [5].

According to world health organization (WHO), every year 1 out of 10 people ill that equals 33 million ill people from a foodborne disease that results in 420 thousand deaths and it is about one-third are children less than 5 years old. Therefore, Saudi Arabia is one of the countries affected by the burden of foodborne diseases, and concerted efforts must be considered to evaluate the risks of this issue by conducting some studies [6,7].

Saudi Arabia is one of the largest countries in the Middle East with an area equal to around 2,000,000 square kilometers with a population of more than 33 million. Moreover, due to the scarcity of water sources in Saudi Arabia, it depends highly on imported food, which about 80% of food products are imported. Furthermore, a recently high percentage of the population consumes prepared food at a restaurant that leads to an increase in the probability of infection with one or more microbial foodborne diseases [8,9]. Each year in Saudi Arabia, several outbreaks include many people (cases) are reported to the ministry of health (MOH) due to gastroenteritis symptoms because of contaminated food consumption. Based on the annual report issued by the ministry of health in 2018, the outbreaks are divided into general sources and home sources. From 2014 to 2018, the total number of outbreaks are 1632 outbreak, and the total number of cases is 11458 cases related to those outbreaks as illustrated in Fig. 2 and Fig. 3. Furthermore, in the same period, the death rate of foodborne disease cases per 10000 was 41 cases [10]. Moreover, most outbreaks and cases increased during summertime between April and September due to the temperature increase, which is an optimum temperature as an important factor for bacterial growth rapidly. Additionally, most causes of outbreaks were Salmonella because the most requested tests for samples were Salmonella and Shigella. Furthermore, *E.coli* and Shigella are food causes of foodborne diseases too in Saudi Arabia [11]. Thus, in Saudi Arabia, based on most cases of food-borne diseases from bacteria especially some pathogenic Enterobacteriaceae family, which are Salmonella. *Escherichia coli* and Shigella, this paper will focus on these bacteria and clarify some differences between them. Moreover, these particular bacteria need treatment, and the

most common type of treatment is antibiotics which recently became less effective toward them due to a highly resistant mechanism. Therefore, this paper will demonstrate some information about antibiotic treatment mechanisms, resistance mechanisms and some statistics about antibiotics resistance [12,13].

2. PATHOGENIC ENTEROBACTERIACEAE

2.1 Escherichia coli

Escherichia coli (E. coli) belongs to a family of Enterobacteriaceae and are gram-negative rod shape, non-spore-forming, 1-3 x 0.4-0.7 µm in diameter, and facultatively anaerobic. It is found in people's intestines, animal's intestine, environment and food. Though this bacterium is a normal flora in the human intestine and keep the digestive tract, healthy but can be harmful for human and cause some diseases [4].

2.1.1. Types and symptoms

There are two common types of diseases associated with *E.coli* extraintestinal diseases and intra-international disease. Extraintestinal diseases like Urine Tract Infection (UTI) and gastrointestinal disease like gastroenteritis symptoms or called food poisoning and the *E.coli* food poisoning is the interesting topic in this article.

There are many types of *E. coli* linked with food poisoning, which are *Enterohaemorrhagic E. coli (EHEC), Enteroinvasive E. coli (EIEC)*, *Enteropathogenic E. coli (EPEC)*, *Enteroaggregative E. coli (EAEC),* and *Enterotoxigenic E. coli (ETEC).*

All these types reach the human intestine causing intestinal symptoms for humans, but there are differences in some pathological symptoms such as modes of transmission, type of target intestine and etcetera [14].

The most common type of *E. coli* food poisoning is Enterohaemorrhagic *E. coli* (EHEC), especially the serotype *E. coli* O157:H7 [14]. Most food associated with foodborne diseases by *E. coli* is Undercooked meat like hamburgers, unpasteurized milk and juice, raw fruits and vegetables and contaminated. As known, this bacterium is fecal contamination from humans or animals and it can reach foods at any stage of the food chain. Thus, good hygiene practice during the food chain is important to prevent the risk of infection by *E. coli* [15].

2.1.2 Pathogenesis

The pathogenesis of *E. coli* generally starts with the consumption of contaminated food then bacteria attach to an intestinal cell and colonize in the intestine then affect on epithelium cell by virulence factors and toxins releasing that cause diarrhea. Furthermore, each type of food poisoning *E.coli* varies from each other in pathogenesis based on the type of virulence factors and toxins as clarified in Fig. 1 [16].

2.2 *Salmonella* spp.

Salmonella spp. are gram-negative rod-shaped, facultative anaerobic and non-spore-forming. The latter's principal habitat is the human and other animals' intestinal tract. Some species do not have symptoms of disease in animals; others may have a wide variety of mild to severe infections called human salmonellosis [17].

2.2.1 Types and symptoms

The most common types of illnesses associated with salmonellosis outbreaks are nontyphoidal salmonella and typhoidal salmonella. In addition, more than 2500 serotypes could involve in food poisoning outbreaks [18]. The spread of Salmonella by the fecal-oral route and can be transmitted by food and water, direct animal contact, and from person to person. About 94% of salmonella infection from food source which results in salmonellosis in humans from eating foods. There are many food groups are the appropriate environment for salmonella growth that include contaminated eggs, poultry, unpasteurized milk or juice, cheese, contaminated raw fruits and vegetables, and contaminated water [17].

2.2.2 Pathogenesis

After ingesting the contaminated food with salmonella, the bacteria ingested in food persist and pass through the gastric acid barrier and attach to the mucosa of the small and large intestine then produce toxins as a result of epithelial cells Invasion, the proinflammatory is released, cytokines encourage an inflammatory reaction. The acute inflammatory response causes diarrhea and may lead to ulceration and destruction of the mucosa. The bacteria can

spread from the intestines through the bloodstream then cause systemic disease [17].

2.3 Shigella spp.

Shigella spp. are gram-negative rod-shaped, non-motile, encapsulated, and facultative anaerobes that do not ferment lactose, or do so slowly. Shigella is a species of enteric bacteria that causes disease in humans and animals. The bacteria are primarily a human disease, that causes many cases around the world. Shigella, similar to symptoms of *E. coli*. The symptoms occur after consuming a contaminated food with Shigella and signs include abdominal cramps, fever, and diarrhea, stools that may contain blood and mucus [4].

2.3.1 Source and transmission

The fecal–oral route is the way of Shigella transmission by direct way like person-to-person or sexual contact or indirectly through contaminated food, water, or contaminated tools. The low infectious dose can cause the infection or Shigellosis [5].

In general, food or water contaminated with human fecal material is the main way of infection. Usually person-to-person spread and fecal-oral transmission. Furthermore, ready-to-eat foods touched by infected food workers, e.g. raw vegetables, salads, sandwiches [19].

2.3.2. Pathogenesis

Shigella spp. attaches to the intestinal cell walls of the small intestines and penetrates these by producing toxins, which can promote the disease's diarrhea. According to Fig. 2, the Shiga toxin enables the bacteria to penetrate the epithelial lining of the intestines, leading to a breakdown of the lining and hemorrhage. Shigella spp. also have adhesions that facilitate adherence to cell surfaces and invasive plasmid antigens, allowing the bacteria to invade cells to increase their virulence [20].

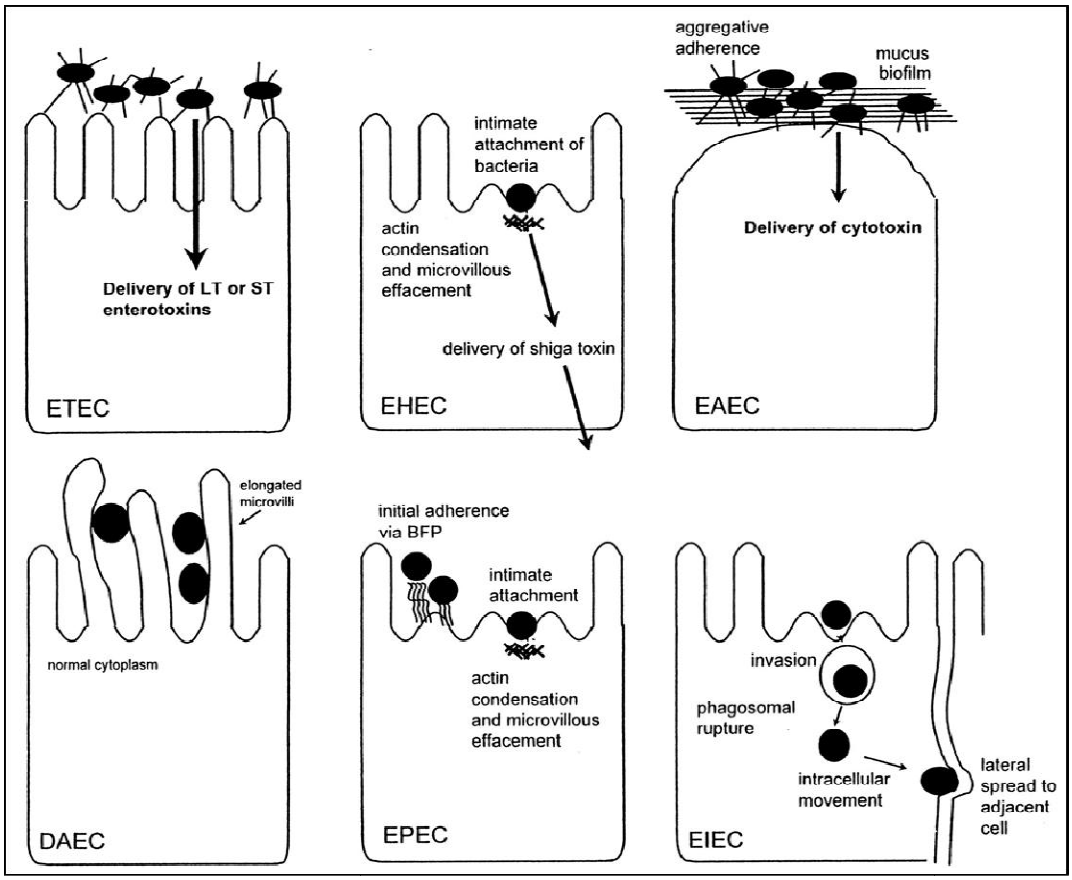

Fig. 1. Pathogenesis of *E. coli* [16]

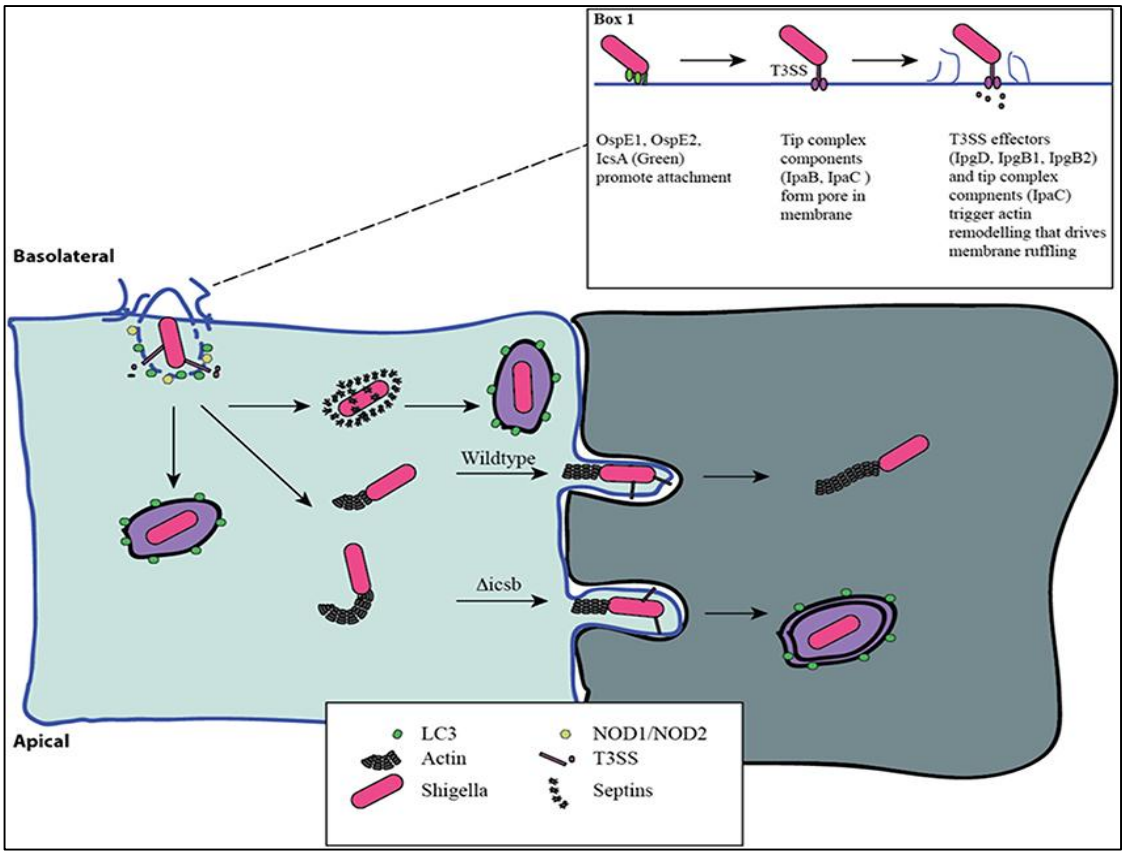

Fig. 2. Pathogenesis of Shigella [20]

3. TREATMENTS

The treatment of food-borne diseases depends on drugs, anti-dehydration and rest. As known, every year health agencies report a million cases of foodborne disease, and most of them from a bacterial infection that leads to use of antibiotics as a treatment to cure the cases that are infected with bacteria such as *E.coli*, Salmonella and Shigella [21]. The major mechanisms of antibiotics against bacteria various based on the targeted part of a bacterial cell that includes Inhibition of cell wall synthesis, Disturbance of cell-membrane function, Inhibition of protein synthesis, inhibition of nucleic acid synthesis both the DNA synthesis and RNA synthesis, and Effects on metabolisms.

As shown in Fig. 3, the group of each antibiotic has specific mechanisms on the bacterial cell. The antibiotics treatment for food poisoning *E.coli* is varies based on the type of *E.coli.* For example, azithromycin, cefixime, ceftriaxone, ciprofloxacin, and levofloxacin are used to treat the Enteroinvasive *E.coli* (EIEC) that affects cell wall synthesis and DNA synthesis. While, the antibiotics treatment for salmonella are fluoroquinolones, azithromycin, and ceftriaxone that inhibit DNA synthesis. Moreover, in shigellosis cases ciprofloxacin and azithromycin are two recommended oral antibiotics that impede nucleic acid synthesis [21].

In contrast, even though the antibiotics innovation was important for curing many cases infected by bacteria, unfortunately, the bacteria became resistant to them recently under the name antimicrobial-resistant (AMR) which is a big concern topic on public health. There are many types of bacteria resistant against one or more antibiotics whether in the clinical, food and environmental field by gaining the resistant genes. In general, there are three ways to exchange the genes between bacteria that are conjugation, transformation, and transduction as described in Fig. 4. Conjugation is the DNA transfer directly from one cell to another via cell-cell contact. The conjugation method is often done by plasmids. Plasmids are circular pieces of DNA that can replicate in the bacterial cell,

separately from the chromosome. Transformation is obtaining the DNA directly from the environment and integrating it into their genomes. Transduction is the transfer of DNA from one cell to another by a virus known as bacteriophage [22,23].

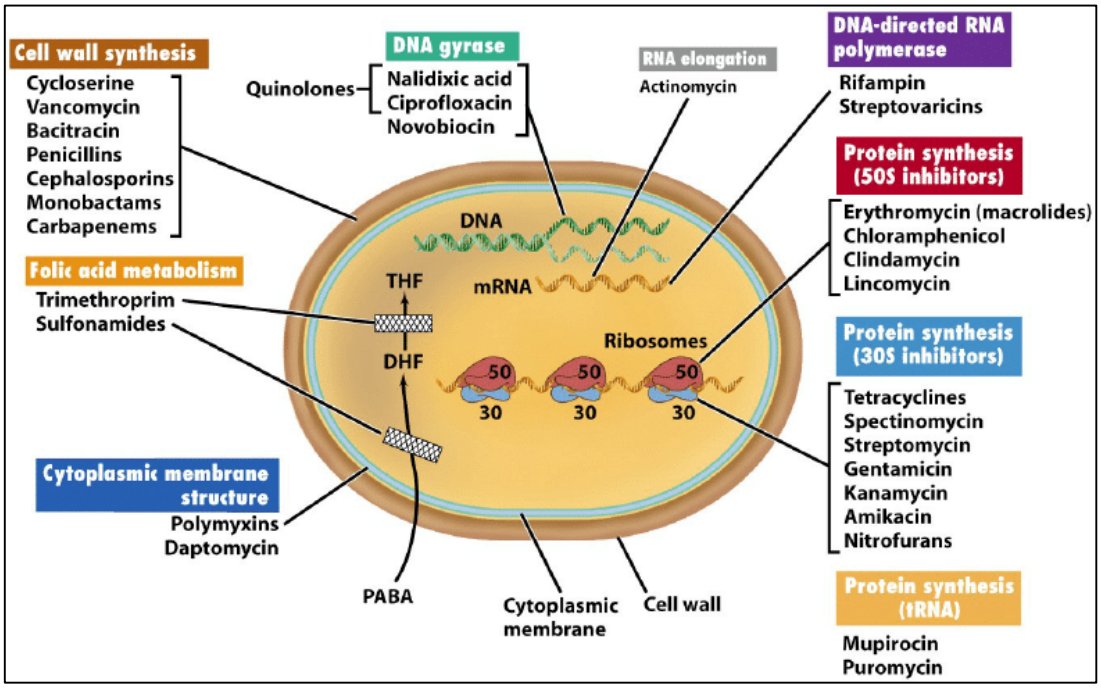

Fig. 3. Different mechanisms of antibiotics against bacteria [21]

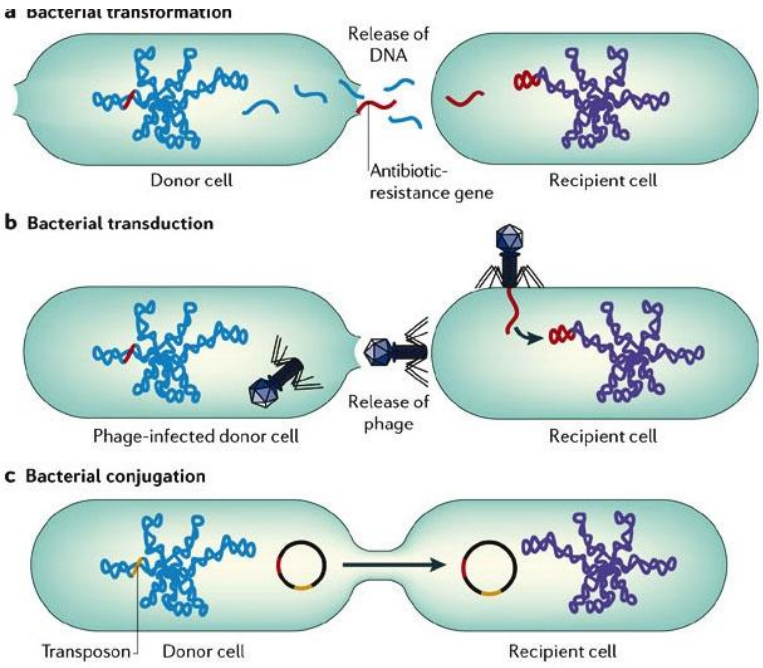

Fig. 4. Mechanisms of gene exchange between bacteria [23]

E. coli resist antibiotics by producing Extended Spectrum β-lactamase (ESBL) and this mechanism is common in *E.coli* by disrupting the functionality of Beta-lactam antibiotics. In Salmonella and Shigella become resistant to antibiotics by producing some enzymes that gaining by genes from other bacteria. In addition, these pathogens can be multidrug-resistant by some mechanisms like efflux pump to prevent the DNA synthesis destruction. Another method of resistance such as Beta-lactamase enzyme production to avoid the effects of beta-lactam antibiotics [24-26].

4. STATISTICS PROBLEMS

Antimicrobial resistance is a major issue worldwide and needs more consideration by doing more studies and researches. Always the statics data from health studies give a vision about the particular issue to control or develop methods to solve the problem. Thus, some data from few studies in Saudi Arabia will be stated as examples in this section. Every year, hundreds to thousands of human cases of intestinal diseases are reported as a result of pathogenic *E. coli* and most cases need antibiotics as treatment and some cases become resistant to antibiotics. As mentioned above about mechanisms of exchange resistance genes which play a role directly or non-directly for bacteria to prevent the action of the antibiotics [11].

There are some local studies in Saudi Arabia on the prevalence of antibiotic-resistant *E.coli*. In 2013, a study was conducted on pilgrims traveling for Hajj, where 129 samples of swabs were collected 10 days before they travel to Mecca and one day before returning to the same Pilgrims (persons). The test of *E. coli* producing ESBLs genotypes (CTX-M, TEM and SHV) has been done on the samples then the microbial isolates are tested on six types of antibiotics are colistin (CST), ticarcillin (TIM), clavulanic acid, ceftriaxone (CRO), gentamicin (GEN), piperacillin-tazobactam (TZP), imipenem (IPM). The results of samples before arriving in Makkah were 18 samples out of 129 samples (14%) were positive for *E.coli* resistant to one or more of the six antibiotics, while the results on return increased to 36 samples out of 129 (28%) positive for *E.coli* resistant to one or more of the six antibiotics. The study demonstrated that the risk of acquired antimicrobial resistance like ESBLs can be spread among people in many ways like food [12,27].

Another study in Saudi Arabia published in 2016, the study was done on clinical and environmental isolates *(n=33)* to detect the antimicrobial-resistant mechanisms in *Salmonella enterica.* The study found about 33 strains of *S. enterica* were resistant to one or more antibiotics. The results have shown that all strains were resistant to antibiotics with different percentage of resistance as follows: Erythromycin (100%), Cefalotin, cefuroxime, cefuroxime axetil (90.9%), Cefoxitin (87.9%), Aminoglycosides antibiotics including gentamicin (90.9%), amikacin and tobramycin (87.9%), 57.6% *(n=19)* of the isolates were resistant to nitrofurantoin, 27.3% *(n=9)* to streptomycin, 24.2% *(n=8)* to tetracycline, 18.2% *(n=6)* to trimethoprim-sulfamethoxazole, 15.2% *(n=5)* of the isolates were resistant to neomycin and about 3.1 % of isolates *(n=33)* were resistance to piperacillin/ tazobactam, cefpodoxime, cefotaxime, and norfloxacin.

Bacteria can be found everywhere, in humans, animals, and the environment and all these circumstances are a good chance for bacteria to exchange the resistant genes. Therefore, the acquired gene of antimicrobial resistance by bacteria not from the clinical environment only as known in the past [28].

5. CONCLUSION

Foodborne disease outbreaks are a global matter and have effects on health and the economy. Saudi Arabia still suffers from this issue and continues. One of the most important indicators of food safety is cases number from foodborne diseases. Thus, the investigation process which includes the procedure, tracing, tools, and data are essential to finding the gap in the food chain and the source of contamination then find the solution then control and prevent from the problem happening again in the future. Due to the result of cases of bacterial foodborne diseases in Saudi Arabia, the high consumption of antibiotics is required for treatment, and the risk of resistance increase more and more [29]. Consequently, government entities must collaborate and put more effort to reduce the prevalence of antibiotics resistance by bacteria. Finally, as antimicrobial resistance (AMR) one of the top ten threats to health, the one health approach is one of the solutions that assist in the reduction of this issue [30].

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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