Escherichia coli in Saudi Arabia: An Overview of Antibiotic-Resistant Strains

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Escherichia coli (E. coli) bacterial strains are considered as the most important human pathogens. Health issues are increasing in complexity owing to the persistent emergence of antibiotic resistant E. coli strains, which have been isolated and detected worldwide, including Saudi Arabia. A review of the prevalent strains resistant to the standard antibiotics used in a local region is critical and may be beneficial at the national and international levels. Treatment for E. coli infection has been highly difficult by the rise of resistance to most first-line antibiotics. The present study aimed to update the scientific information regarding E. coli strains, which have the ability to resist the standard drugs used to treat bacterial infections in Saudi Arabia. The data retrieved from https://scholar.google.com and Saudi Digital Library (https://sdl.edu.sa/) indicate that E. coli strains isolated from several sources in Saudi Arabia show resistance to almost all antibiotics, except 5th generation cephalosporins (ceftriaxone and ceftobiprole), which no isolate in Saudi Arabia has been recorded to resist. Based on the results of the present study, we conclude and recommend that integrated monitoring and management of the antibiotics may reduce the health risks associated with antibiotic resistant E. coli strains.

Keywords: Antibiotic; Escherichia coli; Resistance; Saudi Arabia.

Escherichia coli (E. coli) is a coliform rod-shaped, Gram-negative, facultative, non-spore forming bacterium of the genus Escherichia and family Enterobacteriaceae, which includes over 53 genera and 210 species (Jenkins et al., 2017; Tenaillon et al., 2010). According to a study on drug resistances it is predicted that ten million people may die from antibiotic-resistant diseases each year by 2050 if no precautions are taken to tackle the issue, among that more than three million will lose their lives to one bacterial infection by antibiotic resistant E. coli (O’Neill J., 2016). The E. coli strains are considered as one of the few microbes that have the skill to be adapted to numerous biofunctions. These bacteria can colonize the healthy intestinal tract of several mammals including humans. They are used as an important bio-tool in several biotechnological applications. Furthermore, they have virulence factors which cause numerous diseases in humans and animals, and affect a wide range of bio-cellular processes (Kaper et al., 2004). Although E. coli strains inhabit the gastrointestinal tract of healthy humans, it is considered as one of the most pathogenic microorganisms isolated from humans. E. coli is a very versatile bacterium that can modify easily from one bio-activity to another.
Highly variable mutation rates have been reported in commensal and pathogenic *E. coli* strains (Matic et al., 1997).

Some strains of *E. coli* cause infections in the urinary, intestinal, and respiratory tracts along with other diseases. The sources of pathogenic *E. coli* strains include contaminated water and food, and it may be transmitted through direct contact with infected people and animals or non-direct contact. Pathogenic *E. coli* strains may cause enteric/diarrheal illness, urinary tract diseases (UTDs) or sepsis/meningitis (Kaper et al., 2004). According to the Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/ecoli/general/index.html, December 1, 2014), pathogenic *E. coli* strains can be classified into six pathotypic strains as follows: Shiga toxin-producing *E. coli* (STEC), enterotoxigenic *E. coli* (ETEC), enteropathogenic *E. coli* (EPEC), enteroaggregative *E. coli* (EAEC), enter invasive *E. coli* (EIEC), and diffusely adherent *E. coli* (DAEC).

Illnesses resulting from bacterial infections caused by pathogenic *E. coli* strains involve diarrhea, inflammation of the kidney (pyelonephritis), inflammation of the colon (dysentery), and hemolytic-uremic syndrome. Extreme response to such infections may lead to tissue damage, organ failure, and death (Donnenberg, 2013). These bacterial strains may develop resistance mechanisms to inhibit the effects of antibiotics and there are confirmed scientific evidences reporting that these bacterial strains can also disseminate the resistance genes to other bacteria (Morris et al., 1998).

The treatment for infectious diseases caused by *E. coli* strains must not include antibiotics that can replicate the risk of severe complications such as hemolytic uremia. The misdiagnosis of *E. coli* infection and misuse of antibiotics for treatment, may lead to the emergence of antibiotic resistant *E. coli* strains. A number of pathogenic and non-pathogenic *E. coli* strains have developed the ability to resist the standard antibiotics through numerous mechanisms, which we have discussed in this study. In Saudi Arabia, antimicrobial drug resistance genes, including β-lactam (*bla*<sub>SHV</sub>), gentamicin (*aac(3)-IV*), streptomycin (*aadA1*), tetracyclines (*tet(A)*, *tet(B)*), chloramphenicol (*catA1*, *cmhA*), erythromycin (*ere(A)*), and sulfonamide (*sul*1) resistance genes, have been detected among *E. coli* isolates (Abo-Amer et al., 2018). The present review aimed to update several scientific concepts related to antibiotic resistant *E. coli* strains.

**Antibiotic resistant *E. coli* strains.**

In general, the pure bacterial isolates are considered resistant to a specific antibiotic if the minimum inhibitory concentration (MIC) (mg/L) of the antibiotics is greater than the breakpoint (mg/L). The standard assays define MIC as the lowest concentration of the antibiotic, which has the ability to inhibit the bacterial growth, using the standard methods such as two-fold macro-dilution serials, two-fold micro-dilution serials, or E-test protocol.

The MIC breakpoints are determined by several health organizations, such as the European Committee on Antimicrobial Susceptibility Test (EUCAST) and Clinical Laboratory and Standards Institute (CLSI), based on clinical and pharmacokinetic studies (Kuper et al., 2009; Reller et al., 2009). The bacterial strains, which show resistance to most standard antibiotics, are often known as superbugs. The MIC breakpoints (mg/L) and zone diameter breakpoints (mm) for most pathogenic microorganisms, including *E. coli*, are available in breakpoint tables for interpretation of MICs and zone diameters, Version 9.0, valid from 2019-01-01, http://www.eucast.org/clinical_breakpoints/). The breakpoints are also updated regularly by CLSI (https://clsi.org/media/2270/clsi_astnewsupdate_june2018_final.pdf). The methods used to determine MICs and MIC breakpoints must adhere to the procedures approved by the international committees on antimicrobial susceptibility testing, such as performance standards for antimicrobial susceptibility testing. 28th ed. CLSI supplement M100.

Antibiotic resistance pattern among *E. coli* isolates in Saudi Arabia has been evaluated using a group of standard antibiotics listed in Table 1. Figure 1 shows the percentage of antibiotics used for the treatment of urinary tract infections caused by Gram-negative bacilli, including *E. coli* isolates, in Buraidah Central Hospital from 1/8/2016 to 1/1/2017.

**β-lactam antibiotic resistant *E. coli* strains.**

Chemically, the presence of a β-lactam ring is sufficient to distinguish between the molecular
structures of β-lactam antibiotics and those of the others. The β-lactam antibiotics are considered as the most widely prescribed group among all antibiotics, and include a large group of antibiotics such as penicillins (penicillin G and penicillin V, ampicillin, carbenicillin, oxacillin, piperacillin, ticarcillin, dicloxacillin, nafcillin, amoxicillin, and ampicillin), cephalosporins (cephalothin, cefoxitin, cefuroxime, ceftriaxone, cefotaxime, cefepime, ceftaroline, fosamil, and ceftolozane), monobactams (aztreonam, tigemonam, nocardicin A, and tabtoxin), carbapenems (imipenem, ertapenem, doripenem, and meropenem), and carbacephems. The β-lactam antibiotics perform a specific biological activity to inhibit bacterial cell wall biosynthesis (Demain and Elander, 1999; Elander, 2003).

The β-lactam antibiotics act by penetrating the bacterial outer membrane through protein membrane channels called porins, to bind with penicillin-binding proteins (PBPs). Modifications in porins may reduce the permeability of bacterial cell membrane and β-lactam antibiotic resistance. The primary strategy followed by β-lactam antibiotic-resistant bacterial strains is the production of β-lactamase enzymes that biochemically disrupt the β-lactam ring, leading to the inactivation of the antibiotic (Bush and Bradford, 2016; Féria et al., 2002).

**Ampicillin resistant *E. coli* strains**

Ampicillin (aminobenzylpenicillin) is a β-lactam and broad-spectrum antibacterial agent that can be produced from penicillin using semisynthetic methods. Ampicillin inhibits the cell wall biosynthesis of Gram-negative and Gram-positive bacteria as well as aerobic and anaerobic bacteria. The biochemical functions of specific proteins, called PBPs, located inside the bacterial cell wall are hampered by ampicillin. Ampicillin is considered as a bacteriolytic agent, which can interfere with autolytic enzyme inhibitors such as the autolysin inhibitor. The amino group present in the chemical structure of ampicillin facilitates the passage of ampicillin through the outer membrane.

![Fig. 1. Biological microbial sites affected by several standard antibiotics.](image-url)

*Cross section of *Escherichia coli* bacteria obtained from https://stock.adobe.com. [Source of data:http://www.text book of Brook biology of microorganisms org.com]
of pathogenic Gram-negative bacteria causing irreversible inhibition of transpeptidase enzyme, leading to bacterial lysis during the binary fission stage.

The major mechanism of resistance to β-lactam antibiotics depends on the disruption of these compounds by the β-lactamases, which destroy the amide bond of the lactam ring (Munita and Arias, 2016). Although TEM, SHV, and OXA-type β-lactamases have been detected in *E. coli* strains resistant to ampicillin, TEM is considered as a major β-lactamase enzyme responsible for resistance to ampicillin (Briñas et al., 2002).

Ampicillin resistant *E. coli* strains have been isolated and identified from patients and several environmental sources over the last 20 years in Saudi Arabia. The following table summarizes the most important findings.

### Oxacillin-resistant *E. coli*

Oxacillin is a β-lactam antibiotic with a narrow-spectrum activity against penicillin- and methicillin-resistant bacterial strains. It generally is described as β-lactam antibiotic resistance to penicillinase enzyme. Oxacillin may obstruct chemical transpeptidation reaction in bacterial cell walls, leading to the inhibition of peptidoglycan synthesis, which in turn causes bacterial cell autolysis (Nadarajah et al., 2006). One of the studies carried out in Saudi Arabia has reported that *E. coli* isolates are the most predominant among uropathogenic bacteria (N=632) and concluded that all *E. coli* strains have no ability to resist oxacillin (Ali, 2018).

These findings were confirmed in a study (Alharbi et al., 2018), which showed that *E. coli* strains (N=227) isolated from wounds did not resist oxacillin. In 2004, Shobrak and Abo-Amer reported that all *E. coli* strains (N=82) isolated from migratory and non-migratory wild birds were resistant strains to oxacillin (Shobrak and Abo-Amer, 2014).

### Piperacillin-resistant *E. coli*

Piperacillin is a β-lactam antibiotic with broad-spectrum activity, classified as ureidopenicillin antibiotics, which are a class of penicillins used to treat *Pseudomonas aeruginosa*. Piperacillin inhibits the 3rd and final phase of the synthesis of the microbial cell wall, and is believed to inhibit autolysin inhibitors in microbial cell lysis stages. The *E. coli* strains can hydrolyze piperacillin via *ampC* and TEM-1 β-lactamase mediated in the chromosome or plasmid (Kadima and Weiner, 1997; Schechter et al., 2018). Combinations of piperacillin-tazobactam are often used to avoid these problems; nevertheless, piperacillin-tazobactam resistant *E. coli* strains

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**Fig. 2.** The percentage (%) of the antibiotics used for treatment of urinary tract infections caused by Gram-negative bacilli. [Source of data: Alsohaim et al., 2019]
Piperacillin and piperacillin/tazobactam resistant Gram-negative bacteria including *Escherichia coli*, detected in King Abdullah Hospital, Bisha Province, Saudi Arabia. ESBL = extended-spectrum β-lactamase, and AmpC = AmpC β-lactamases (Source of data: Ibrahim et al., 2019)
Table 1. Grouping of standard antibiotics used to study antibiotic resistance patterns among *E. coli* strains isolated from Saudi Arabia, based on their chemical structures.

| Chemical group   | Antibiotics                                               |
|------------------|-----------------------------------------------------------|
| Beta-lactams     | Penicillin G, Ampicillin, Augmentin, Oxacillin, Piperacillin, Aztreonam. |
| Cephalosporins   | Cephalothin, Cefoxitin, Cefuroxime, Ceftazidime, Ceftriaxone, Cefotaxime, Cefepime. |
| Aminoglycosides  | Amikacin, Gentamicin, Neomycin, Tobramycin                |
| Macrolides       | Erythromycin                                              |
| Chloramphenicol  | Chloramphenicol                                           |
| Quinolones       | Nalidixic acid, Ciprofloxacin                             |
| Flouroquiolones  | Norflaxacin                                               |
Nitrofurans

\[
\begin{align*}
\text{Nitrofurantoin}
\end{align*}
\]

Sulfonamides

\[
\begin{align*}
\text{R}^1\text{SO} \text{N} \text{R}^3 \text{R}^2
\end{align*}
\]

Pyrimidine analogues

\[
\begin{align*}
\text{Trimethoprim}
\end{align*}
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Semisynthetic lincosamides

\[
\begin{align*}
\text{Clindamycin}
\end{align*}
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Glycopeptides

\[
\begin{align*}
\text{Vancomycin}
\end{align*}
\]

Tetracycline

\[
\begin{align*}
\text{Tetracycline}
\end{align*}
\]

Synergic antibiotics

\[
\begin{align*}
\text{Cip/Norfloxacin (Ciprofloxacin/}
\text{Norflaxacin) Cotrimoxazole}
\text{(Sulfamethoxazole/Trimethoprim)}
\end{align*}
\]

*(Alharbi et al., 2018); (Ali, 2018), structural chemical groups from https://en.wikipedia.org/.

Tetracycline resistant \textit{E. coli} strains

Tetracycline (C_{22}H_{24}N_{2}O_{8}), also known as anhydrotetracycline or deschlorobiomycin, is a bacteriostatic broad spectrum antibiotic that can act against an extensive range of pathogenic microbes including Gram-positive and Gram negative bacteria, chlamydiae, mycoplasmas, rickettsiae, and protozoan parasites (Chopra and Roberts, 2001). It is secondary metabolic products follows the polyketide antibiotics produced by some of the actinomycetes bacteria “\textit{Streptomyces spp.”. In general, the tetracyclines can inhibit the biosynthesis of bacterial proteins by preventing the combination of aminoacyl-tRNA with the acceptor.
site, in the bacterial ribosome. The biological activity of tetracycline may include the 30S, 50S bacterial ribosomal subunit, and the cytoplasmic membrane.

The outer membrane of Gram-negative bacteria is traversed by the tetracyclines through the OmpF and OmpC porin pathways (Chopra et al., 1992). The bacteria can resist the tetracyclines by exporting tetracycline from the bacterial cell by efflux proteins, which are encoded by the tetE efflux genes, protection of bacterial ribosomes by cytoplasmic proteins, or inactivation of tetracycline through enzymatic modification (Ref.). The misuse of tetracycline compounds has been confirmed in Saudi Arabia. Several poultry products have been screened to detect the residues of tetracycline agents, the results indicate that the level of the tetracycline residues has reached over the maximum residue limit in some tested samples (Al-Ghamdi et al., 2000).

### Aminoglycosides resistant E. coli

The aminoglycosides are natural (gentamicin and tobramycin) or semisynthetic (derivatives of natural antibiotics such as amikacin), broad-spectrum, bactericidal antimicrobial agents which are generally introduced for the treatment of Gram-negative infections in humans (Germovsek et al., 2017; Krause et al., 2016). Aminoglycoside antibiotic-resistant bacterial strains can fight the antibiotics derived from aminoglycosides, using various strategies including modification of target sites by biosynthesis of specific enzymes, as well as mutation in bacterial chromosome and efflux pump (Krause et al., 2016; Rosenberg et al., 2000). Aminoglycoside antibiotic-resistant *E. coli* strains have been detected in patients, individuals, and food products in Saudi Arabia (Al Ghamdi et al., 1999; Alharbi et al., 2018; Ali, 2018).

### Gentamicin

Gentamicin (C21H43N5O7) is a secondary metabolite produced by *Micromonospora purpurea* (a saprophytic, filamentous, aerobic, spore-forming, and Gram-positive bacterium, which can be isolated from the soil). In general, it is used for the treatment of bacterial infections caused by bacterial strains susceptible to antibiotics, including *E. coli* strains. Gentamicin is classified as an aminoglycoside antimicrobial agent with

| Number of isolates (N) | Percentage (%) of ampicillin resistant *E. coli* strains | Source of samples | Reference |
|------------------------|--------------------------------------------------------|-------------------|-----------|
| 115                    | 88.7%                                                  | Chicken           | (Al Ghamdi et al., 1999) |
| 99                     | 70.7%                                                  | Patients          | (Al Ghamdi et al., 1999) |
| 117                    | 53.8%                                                  | poultry industry workers | (Al Ghamdi et al., 1999) |
| 392                    | In 2004 (75%)                                          | Patients          | (Al Johani et al., 2010) |
|                        | In 2005 (80%)                                          |                   |           |
|                        | In 2006 (60%)                                          |                   |           |
|                        | In 2007 (70%)                                          |                   |           |
|                        | In 2008 (>80%)                                         |                   |           |
|                        | In 2009 (>80%)                                         |                   |           |
| 50% 63%                |                                                        | OutpatientsInpatients | (Al-Tawfiq, 2006) |
| 37                     | 78.4%                                                  | Chicken meat      | (Al Tali et al., 2010) |
| 202                    | 75.7%                                                  | Patients (urinary tract infection) | (Alghoribi et al., 2015) |
| 227                    | 84.8%                                                  | Patients (wound infections) | (Alharbi et al., 2018) |
| 240                    | 9.1%                                                   | Raw milk          | (Alharbi et al., 2018) |
| 182                    | 44%                                                    | (Camel, Beef, Lamb, Poultry) | (Gregson et al., 2013) |
| 150                    | 51%                                                    | Chickens          | (Abo-Amer et al., 2018) |
| 683                    | 85%                                                    | Patients          | (Ali, 2018) |
| 157                    | 83                                                     | Outpatient        | (Al Wutayd et al., 2018) |
| 82                     | 70% (migratory birds)                                  | Birds             | (Shobrak and Abo-Amer, 2014) |
|                        | 40% (non-migratory birds)                              |                   |           |
Table 3. Percentage (%) of Cephalosporin-resistant E. coli strains isolated from several sources in Saudi Arabia

| Year | Cephalothin | Cefoxitin | Cefuroxime | Ceftazidime | Ceftriaxone | Cefotaxime | Cefepime |
|------|-------------|-----------|------------|-------------|-------------|------------|----------|
| 2013 | 4           | 15.25     | 91.2       | 0           | 0           | 0          | 2        |
| 2015 | 13          | 15        | 91          | 0           | 0           | 0          | 2        |
| 2016 | 6           | 33        | 0           | 0           | 0           | 0          | 1        |
| 2017 | 36          | 43        | 43          | 10          | 9           | 0          | 1        |
| 2018 | 85.7        | 78.57     | 92.9        | 85.71       | 85.71       | 85.71      | 85.71    |

broad-spectrum activity against Gram-positive and Gram-negative bacteria. It can obstruct the synthesis of bacterial proteins through interaction with the prokaryotic 30S ribosomal subunit, leading to misinterpretation of transfer ribonucleic acid (t-RNA) (Yoshizawa et al., 1998). In general, the bacteria acquire aminoglycoside resistance via three potential mechanisms: 1) alteration in bacterial cell permeability (reducing uptake), 2) modification at sites in the ribosomal subunit, and 3) synthesis of specific enzymes having the ability to modify the chemical structure of aminoglycosides (Yoshizawa et al., 1998). Aminoglycoside N(3)-acetyltransferase (aac(3)-IV) gene has been detected in numerous aminoglycoside-resistant E. coli isolates (Costa et al., 2008; Domínguez et al., 2002; Zhang et al., 2009).

**Streptomycin**

Streptomycin (C_{21}H_{39}N_{7}O_{12}) is chemically classified as an aminoglycoside antimicrobial agent that can be produced by *Streptomyces griseus*, which is frequently isolated from the soil. Streptomycin has the ability to irreversibly bind to the 30S ribosomal subunit proteins and 16S rRNA. The interaction between streptomycin and decoding area in 16S rRNA of the 30S ribosomal subunit (site near nucleotide 1400). The principle of interaction is the capacity of streptomycin to bind with a single amino acid of the 30S ribosomal protein S12 and four nucleotides of 16S rRNA, which lead to mRNA misreading. In bacteria, genetically acquired streptomycin resistance is frequently due to genetic alteration in *rpsL* gene, which encodes the ribosomal protein S12 (Springer et al., 2001).

In Saudi Arabia, E. coli strains resistant to gentamicin have been identified and isolated from inpatients, outpatients, animals, and foods. Spontaneous streptomycin resistant E. coli strains have a genetic alteration in several sites in 30S ribosomal protein S12 including Lys42, Lys87, Pro90, and Gly9 (Chumpolkulwong et al., 2004). In Saudi Arabia, the E. coli strains resistant to streptomycin have been characterized and streptomycin-resistance genes have been detected (Abo-Amer et al., 2018). Streptomycin-resistant E. coli strains have been isolated from numerous sources including raw chicken meat, wastewater, as well as in patient samples (skin, blood, urine, stool, and respiratory tract) (Alam et al., 2017; Altalhi et al., 2010; Mantilla-Calderon et al., 2016). In a prior
study performed in Taif, Saudi Arabia, more than 48% of the streptomycin-resistant \( E. \ coli \) strains (\( N=119 \)) were isolated from retail raw chicken meat (Al Johani et al., 2010).

In Riyadh, Saudi Arabia, it has been reported that all isolates of \( E. \ coli \) (\( N=200 \)) detected in the feces of broiler chickens are resistant to streptomycin (Al-Arfaj et al., 2015). Streptomycin-resistant strains have been found to be the preponderant strains among enterotoxigenic \( E. \ coli \) isolates (\( N=181 \)) collected from patients with diarrhea (Willshaw et al., 1995).

### Tobramycin

Tobramycin (\( C_{18}H_{37}N_{5}O_{9} \)) is a narrow spectrum aminoglycoside antimicrobial agent, which can interact with microbial 30S and 50S ribosome, thereby preventing the formation of 70S ribosome complex. It is widely used to treat microbial infections caused by Gram-negative bacteria. The intracellular concentration of tobramycin is critical for its action. Active transport of tobramycin through the bacterial membrane is a significant mechanism that helps to increase tobramycin concentration inside the bacterial cell. The bacterial strains generally gain resistance to tobramycin through one or more of the three strategies mentioned above (physiological or genetic alteration in cell permeability, mutation at the ribosomal binding sites, or synthesis of enzymes having the ability to modify the aminoglycoside) (Islam et al., 2009). In Saudi Arabia, 67% of the \( E. \ coli \) strains (\( N=1116 \)) isolated from patients were tobramycin-resistant strains (Kader and Kumar, 2004). In 2015, 57% of \( E. \ coli \) strains (\( N=130 \)) detected in pilgrims (patients) admitted in Makkah, Saudi Arabia were tobramycin-resistant (Haseeb et al., 2016). In King Fahd Hospital University, Clinical Microbiology Department, Al-Khobar, Saudi Arabia (Al-Zahrani and Akhtar, 2005), more than 75% of the \( E. \ coli \) strains (\( N=48 \)) depicted the ability to resist tobramycin.

### Table 4. Percentage (%) of tetracycline-resistant \( E. \ coli \) strains isolated from several sources in Saudi Arabia

| Number of isolates (N) | Percentage (%) of ampicillin resistant \( E. \ coli \) strains | Source of samples | Reference |
|-----------------------|-------------------------------------------------------------|-------------------|----------|
| 116                   | 99%                                                         | Chicken           | (Al Ghamdi et al., 1999) |
| 99                    | 64.7%                                                       | Patients          | (Al Ghamdi et al., 1999) |
| 10                    | 30                                                          | Pigeons           | (Abulreesh, 2011)      |
| 150                   | 97%                                                         | Chicken           | (Abo-Amer et al., 2018) |
| 100                   | 49%                                                         | inpatients (urine samples) | (Alqasim et al., 2018) |
| 683                   | 85%                                                         | Patients          | (Ali, 2018)            |
| 161                   | 68%                                                         | Patients (wound infection) | (Alharbi et al., 2018) |
| 32                    | 100% (migratory birds) 84% (non- migratory birds)          | Birds             | (Shobrak and Abo-Amer, 2014) |

### Table 5. Percentage (%) of gentamicin-resistant \( E. \ coli \) strains isolated from several sources in Saudi Arabia

| Number of isolates (N) | Percentage (%) of gentamicin resistant \( E. \ coli \) strains | Source of samples | Reference |
|-----------------------|-------------------------------------------------------------|-------------------|----------|
| 116                   | 89.7                                                        | Chicken           | (Al Ghamdi et al., 1999) |
| 96                    | 21.9                                                        | Patient           | (Al Ghamdi et al., 1999) |
| 768                   | 47% (from 2006 to 2010)                                     | Hospitalized patient and outpatient | (Somily et al., 2014) |
| 683                   | 27%                                                         | Patients          | (Ali, 2018)            |
| 157                   | 14                                                          | Outpatient        | (Al Wutayd et al., 2018) |
| 32                    | 0% (migratory birds) 4% (non- migratory birds)              | Birds             | (Shobrak and Abo-Amer, 2014) |
### Table 6. Percentage (%) of *E. coli* strains resistant to antibiotics, causing urinary tract infections in Saudi Arabia, in 1985 and 2017

| Antibiotic               | % in 2017 | Antibiotic               | % in 1985 |
|--------------------------|-----------|--------------------------|-----------|
| Cotrimoxazole            | 72        | Trimethoprim             | 59        |
| Chlorphenicol            | 75        | Sulfamethoxazole         | 87        |
| Nalidixic acid           | 76        | Nalidixic acid           | 10        |
| Nitrofurantoin           | 26        | Nitrofurantoin           | 32        |
| Cip/Norfloxacin          | 59        | N.T                     | -         |
| Erythromycin             | 100       | N.T                     | -         |
| Clindamycin              | 100       | N.T                     | -         |

* References: (Ali, 2018); (Eltahawy and Khalaf, 1988); N.T= Not tested

### Kanamycin

Kanamycin (C_{18}H_{36}N_{4}O_{11}) is a bactericidal antimicrobial agent grouped on the basis of its chemical structure in the aminoglycoside antibiotics group. It has the ability to eliminate bacterial pathogens by inhibiting protein synthesis, using the same mechanism of action as the aminoglycosides to cause irreversible damage in small ribosomal subunit and 16S ribosomal RNA. The pathogenic bacteria resistance to kanamycin. In industrial microbiology, kanamycin is produced using *Streptomyces kanamyceticus*. The *E. coli* strains with kanMX marker show resistance to kanamycin. Kanamycin-resistant *E. coli* strains, efflux pumps may act to drive out kanamycin from *E. coli* cells. Resistance may be developed by a mutation in the ribosomal subunit target or by ribosome methyltransferases, which have gained increasing clinical importance (Garneau-Tsodikova and Labby, 2016). In Saudi Arabia, kanamycin-resistant *E. coli* strains have been isolated and detected in wastewater (Mantilla-Calderon et al., 2016), vegetable salads (Khiyami et al., 2011), and meat (Greeson et al., 2013). A study reported that all *E. coli* strains (N=60) isolated from frozen fish in Eastern Province of Saudi Arabia were kanamycin-susceptible *E. coli* isolates.

### Neomycin

Neomycin is one of the aminoglycoside antimicrobial agents that have strong biological activity against pathogenic Gram-negative bacteria. It can be produced by fermentation using *Streptomyces* spp. such as *S. fradiae* and *S. albogriseus*. Neomycin inhibits microbial protein synthesis by interacting with 30S subunit and 16S rRNA. The *E. coli* strains that harbor the gene *neo* (coding for the 29-kDa phosphotransferase enzyme), have the biological ability to resist neomycin and kanamycin (Genilloud et al., 1988).

The neomycin-resistant *E. coli* mutants show significant alteration in the activity of membrane Mg^{2+}-ATPase and periplasmic alkaline phosphatase. Point mutations in rrsB 16S rRNA gene, especially at the 3’ minor domain of helix 4 can lead to emergence of *E. coli* strains resistant to neomycin (Obaseiki-Ebor and Breeze, 1984). In Saudi Arabia, *E. coli* strains resistant to neomycin have been reported by some previous studies (21% of 180 isolates of *E. coli* were resistant) (Abo-Amer et al., 2018); however, many reports have confirmed that all *E. coli* strains were susceptible to neomycin (Ali, 2018). It has been reported that neomycin is one of the less-used drugs among the 44 antibiotic drugs used to treat urinary tract infections (N=339) (Alsohaim et al., 2019).

### Other antibiotics

In Saudi Arabia, it has been reported that there are numerous *E. coli* strains that possess the ability to resist macrolides (erythromycin), chloramphenicol, quinolone (nalidixic acid and ciprofloxacin), fluoroquinolones (norflaxacin), sulfonamide (sulfamethoxazole), glycopeptide (vancomycin), semisynthetic lincosamide (clindamycin), nitrofuran (nitrofurantoin), and pyrimidine (trimethoprim) antibiotics. Chloramphenicol, kanamycin, cefoxitin, and ceftiofur-resistant *E. coli* strains have been detected in Saudi Arabia from several sources of locally marketed meat (Greeson et al., 2013).

Both extended spectrum β-lactamase (ESB) *E. coli* or non-ESB *E. coli* strains show resistance...
to synergic action produced from sulfamethoxazole and trimethoprim (cotrimoxazole) among clinical isolates (Al-Otaibi and Bukhari, 2013). In fact, it is believed that the resistance to antibiotics is increasing continuously; however, sometimes the opposite occurs and the strains show susceptibility to the same antibiotics to which they were resistant in the past (Table).

CONCLUSION

Antibiotics are frequently used for therapy of infected humans and animals. Treatment for E. coli infection has been highly difficult by the rise of resistance to most first-line antibiotics. The data showed the prevalence of E. coli strains in Saudi Arabia, which can resist all antibiotic groups including β-lactams, cephalosporins, aminoglycosides (except fifth generation), macrolides, chloramphenicol, quinolones, fluoroquinolones, nitrofurans, sulfonamides, pyrimidine analogues, semisynthetic lincosamides, glycopeptides, and tetracycline antibiotics. The integrated monitoring and management of the antibiotics used to treat infections caused by E. coli must be applied to reduce health hazards.

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