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Antibiotic resistance: Current global issue and future challenges

Rahim AA, Ahmadissa SM, Muhamad LR, Hama Soor TA*

Technical College of Health, Sulaimani Polytechnic University, Kurdistan Region of Iraq, Sulaimani City, Iraq.

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ABSTRACT

Understanding antibiotic resistance and control measure is a challenge because it causes dissemination of multidrug resistance bacteria, and it causes high morbidity and mortality. Bacteria expressing extended spectrum beta lactamases (ESBL) have been recently reported globally at an alarming level and these issues exist in Middle East and Iraq. Bacteria bearing beta lactam resistance genes shows multi-drug resistance and it cause delay in treatment. The huge number of studies has been carried out to indicate the causes of drug resistances and the outcome of this problem in clinical fields. Therefore, this study is about to reviewing different causes and aspects of drug resistances such as: causes of drug resistance, antibiotic resistance mechanisms, antibiotic resistance reversibility, and different types of beta lactamase resistance genes, Resistance Genes (ESBL) in Middle East, and Resistance Genes (ESBL) in Iraq. The review highlighted all research showing the existence of different types of ESBL in humans, animals and environments in different places of Middle East and Iraq. Bacteria bearing β-lactamases resistance genes have been spread in all parts of Middle East which is public health threating; therefore, it's important to limit Antibiotic use by people. Further research is required in the studied area to understand the reason of antibiotic resistance and an attempt to find new antibiotic is very necessary to save future humans life.

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Introduction

Antibiotic resistance is a typical phenomenon that the bacteria uses to survive by using both natural and engineering response strategies in bacterial communities (Canto, Ramo 2009; Cruz et al. 2002). In the last decade, antibiotic resistance emerged rapidly and spread worldwide, which lead to identify as a threat to the public health by numerous public health organization and Center for Disease and Prevention (CDC) (Rice et al. 2020; Frieden 2013). CDC has classified germs as urgent, serious, concerning threat and watch list that includes three uncommon threats (Roca et al. 2015). According to a CDC report in 2019, numerical data reveals more than 2.8 million antibiotic resistance infection occur in US each year and more than 35 thousand people die consequently (Frieden 2013). Many recommendations and decisions have been proposed, with various reports written, in order to diminish the rate of antibiotic resistance propagation. Unfortunately, distribution of antibiotic resistance have not been extremely reduced, and is still a continuous issue (Roca et al. 2015; Wang et al. 2018), that causes many potential problems in health care system (CDC 2013; Golkar et al. 2014; Lushniak 2014; Rossolini et al. 2014), such as the treatment of pathogenic bacteria becoming harder, developing large numbers of bacterial disease, and increasing the cost of

*** Corresponding author**
E-mail address: taib.ahmed@spu.edu.iq (Taib Ahmed Hama Soor)

treatment (Frieden 2013). Mobile genetic element (insertion sequence, transposon, conjugative plasmid) and spreading of antibiotic resistance genes (ARGs) between bacterial species via horizontal gene transfer (HGT), make large trouble in the battle against antibiotic resistance (Musovic et al. 2006; Johnsen et al. 2012; Partridge et al. 2018). HGT, the non-vertical transportation of genetic material occur through different mechanisms: conjugation, transduction, transformation, and gene transfer agent (Wintersdorff et al. 2016). Some bacterial species naturally resist some types of antibiotic due to mutation in DNA or acquired extra DNA harboring resistance genes such as plasmid (Canto, Ramo 2009; Cruz et al. 2002).

Improper use of antibiotic is a global health problem which is the main cause of antibiotic resistance (Al-tawfiq et al. 2010). Antibiotic resistance happens innately, but wrong use of antibiotics in humans and animals increase the speed of the work (WHO, 2020), leading to an important worldwide risk of growing affect in the human, animal and the public health. This is owing to the rapid disseminate and continuity of multidrug-resistant bacteria or "superbugs" (Wang et al. 2018). In developing countries, it is believed that antibiotic resistance of bacterial pathogens is considered to be high and elevating (Okeke et al. 2005). The worldwide antibiotic resistance is due to increase utilization of antibiotics in foods and water of animals and pets, excess consumption of antibiotics by humans, use of antibiotics without prescription, bad infection control practices in hospitals, increase multinational journeys, bad sanitization/cleanliness, and the releasing of non-metabolized antibiotics or their remaining part into the surrounding environment throughout dungs and stools (Wang et al. 2018). All of these are reasons leading to the genetic selection pressure for the emergence of a multi-drug resistance bacterial disease in society (Al-tawfiq et al. 2010; Wang et al. 2018). The growing of numeral infections – for example pneumonia, tuberculosis, gonorrhea, and salmonellosis – these are becoming difficult to deal with as the antibiotics used to treat them become less efficient (WHO, 2020).

Antibiotic consuming has intensive impact on human health and even animals positively. However, the intensive use of antibiotics (which was estimated in 2002 to be 100,000–200,000 tonnes per annum worldwide (Wise 2002; Andersson, Hughes 2010) and which is, in total, well over 1 million tonnes since the 1940s has dramatically increased the frequency of resistance among human pathogens and threatens a loss of therapeutic options and a post-antibiotic era in which the medical advances to date are negated (Guay, 2008; Woodford, Livermore 2009; Review et al. 2017). Resistance becomes a clinical problem that affects the effectiveness of the drug therapy (Andersson and Hughes 2010). The level of exposure of the pathogen population to the drug influences the selection of resistant variants (Bergman et al. 2004, 2009). Resistance reduces the drug action on pathogens and infection treating and increasing the risk of complications and fatal outcomes (Andersson and Hughes 2010). Resistance is often associated with reduced bacterial fitness, and it has been proposed that a reduction in antibiotic use and, therefore, in the selective pressure to acquire resistance would benefit the fitter susceptible bacteria, enabling them to outcompete resistant strains over time (Levin et al. 1997; Andersson and Levin 1999).

This study aimed to review different causes and aspects of drug resistances. Bacteria bearing β-lactamases resistance genes have been studies well in all parts of Middle East and Iraq which is health concerning. All species of bacteria harboring β-lactamases resistance genes has been shown; therefore it's important to limit Antibiotic use by people in the area of the study. Further researches are required in the studied area to understand the reason of antibiotic resistance and an attempt to find new antibiotic is very necessary to save future humans life.

Causes of antibiotic resistance

Societal causes

The overuse and misuse of antibiotics are main cause for the development of antibiotic resistance (Bonten et al. 2001; Bertrand and Hocquet 2017). Epidemiological studies have indicated a direct association of antibiotic consumption with the emergence and spread of resistant strains of bacteria (Nature 2013; Mobarki et al. 2019). Inappropriate antibiotic prescriptions contribute to upgrade of resistant bacteria. Studies have demonstrated that in 30% to 50% of cases, treatment indication, choice of agent, or duration of antibiotic consumption is incorrect (CDC 2013; Luyt et al. 2014; Mobarki et al. 2019). Sub-inhibitory antibiotic concentrations can encourage the progress of antibiotic resistance through facilitating of genetic alterations, such as changes in gene expression modification, mutagenesis, and horizontal gene transfer (HGT) (Viswanathan 2014). Alteration in gene expression, which induced by antibiotics, can increase virulence and pathogenicity, while increased mutation rate and HGT contribute to antibiotic resistance and dissemination. For example, strain diversification in Pseudomonas aeruginosa was detected, resulting from using subinhibitory concentrations of antibiotics (Viswanathan 2014; Mobarki et al. 2019).

Another cause is a wide range of using antibiotics in agriculture (Bartlett et al. 2013; Perović et al. 2018), effecting the animals and become a source of distribution for the antibiotic resistance genes (ARG) (Fitzpatrick and Walsh 2016). Then, spreads of ARG in soil, water polluted by fecal of animals and environment cause to transmit to

humans through the food supply. These bacteria which carry ARB can cause infections in humans and may lead to adverse health consequences (CDC 2013). Availability of few new antibiotics, antibiotic research team has been reduced in pharmaceutical companies due to funding cuts and the economic crisis (Piddock 2012). But reduction in clinical trials for antibiotic development is no longer thought about due to economical reason, but because antibiotics are used for relatively short periods, and because antibiotics are not profit-making as drugs that are used for the treatment of chronic conditions, such as diabetes mellitus, psychiatric disorders, asthma, or gastroesophageal reflux (Piddock 2012; Bartlett et al. 2013; Gould, Bal 2013; Golkar et al. 2014).

The other factors that have led to this problem include the obtainability, general affordability and ease of use of antibiotics (Piddock 2012; Bartlett et al. 2013; Gould and Bal 2013; Wright 2014) and also, using antibacterial products for cleaning purposes may contribute to antibiotic resistance and limit the development of immunities to environmental antigens in humans (Golkar et al. 2014; Michael et al. 2014). Application in pharmaceutical industry still overlooked until now (Oran 2016).

Biological causes

Selective pressure is a general concept that refers to many factors, which form an environmental condition and enable organism with novel mutations or newly acquired characteristics, so that they survive and proliferate (Mcgowan 1996; Baquero and Negri 1998). The most often proposed hypothesis about the beginning of antibiotic resistance, is that originated from resistance genes in antibiotic producing organisms, they used these genes to prevent self-inhibition (DAvies 1992). Then, these genes may have transmitted to the bacterial organism in the vicinity. These bacteria may have modified DNA sequence of the acquired genes, which may have used to eliminate of antibiotics. Spread of naturally produced antibiotic in environment and presence in soil and water in a highly diluted concentration. All these hypotheses point to advancement of antibiotic resistance due to a selective force of natural antibiotics, but it is unbelievable that many of the very efficient mechanisms of resistance derived from natural antibiotics selective pressures. Surely, most data support that the highly resistance bacteria may have originated from strong selective force due to massive use of manufacturing antibiotics in medicine and agriculture (Mcgowan 1996).

Bacterial species can share genetic material with related and unrelated species (Ochman et al. 2000; Koonin et al. 2001), by horizontal gene transfer. HGT is the acquisition of foreign genes by organisms (Senka et al. 2008), which is associated with acquired resistome (Hu 2017). Antibiotic resistance genes may be transferred by one of the mechanisms of HGT, including conjugation, transformation, and transduction (Sitaraman 2018). Conjugation is the process of transformation of the DNA molecule (plasmid or conjugative transposon) via the conjugation apparatus (physical attachment between donor and recipient cell) (Zechne 2000; Senka et al. 2008). Conjugation is the major identified mechanism responsible for emergence of multi-drug resistance in hospital environments (Guglielmetti et al. 2009; Lerminiaux and Cameron 2019). Also, responsible for the spreading of different antibiotic resistance genes in the Enterobacteriaceae family (Bello-López et al. 2019). Transformation is another HGT mechanism, which is absorption, incorporation, and expression of exogenous DNA from closely related bacteria (Lorenz and Wackernagel 1994). Transduction is DNA acquisition, which is arbitrated by independently replicating bacteriophages, bacterial viruses that mistakenly collect segments of host DNA in their capsid, and then inject it into a new host cell (Arber 2014; Bello-López et al. 2019). Both biological and societal causes coordinate together and lead to emerge antibiotic resistance.

Antibiotic Resistance Mechanisms

Bacteria have great genetic flexibility which permits them to make a response against wide range of ecological menaces, such as antibiotic molecules that may pose a threat to their presence. Bacteria defend themselves against antibiotics through many mechanisms, in general realization the mechanisms in which bacteria use to fight antibiotics will be helpful for resolving the difficulties. Inappropriate use of antibiotics involves in the evaluation of resistant bacteria. Uncompleted course of antibiotics run the possibility of not completely eliminating the colony, thus contribute to growing of resistant bacteria. There are several type of drug resistance mechanisms including efflux pumps, drug deactivation or alteration, modification of drug binding sites or targets, alteration in cell permeability leading to decrease accumulation of drugs within cells, formation of biofilms and others (Wilson 2014; Ali et al. 2018).

In bacteria one of the main factors contributing to drug resistance is efflux pumps; it transmits a wide range of antibiotics to the outside the organism (Giedraitienė et al. 2011). Thus, it can be difficult to treat infections caused by these pathogens (Mckeegan et al. 2003). Efflux pumps are transport proteins that contribute in removing toxic substances from inside to the outside of the cell. Some efflux pumps are intended for one drug while others are able to transport various substrates, and the genes of the efflux pumps can be self or acquired (Yalew 2020).

Bacteria use different mechanisms to develop antibiotic resistance including antibiotic inactivation, enzyme hydrolysis of antibiotics, group transfer and process of redox. A typical example of antibiotic inactivation is β- lactamases production that hydrolyses the β-lactam ring of penicillin. The first mechanism is secretion of enzymes that lead to antibiotic inactivation before reaching its target inside the bacteria. The second mechanism is drug structural alteration by functional group transferring such an acyl, phosphoryl or ribosyl (Yalew 2020). The antibiotic incapable to bind the target due to the structural change (Varela and Kumar 2014).

Target modification is another antibiotic resistance mechanism. Alteration of antibiotic binding site inhibits antibiotic to bind to the target site properly. Bacteria modify the target of antimicrobial agent (Yalew 2020). Typical drug target modification example is staphylococcal mechanism, that modifies the penicillin binding protein (PBP), which is a target for β-lactam antibiotics (Davies and Davies 2010).

Antimicrobials mostly need to enter the cell of microbe in order to take action on its target site. So, reducing entry of antimicrobial agents by the microbes is one of the mechanisms of antimicrobial resistance. Antibiotics pass through prion channels to enter the bacterial cell (Yalew 2020). Some bacteria inhibit antimicrobial accessing into them thus they can protect themselves (Poole 2002). Mutation is sudden alteration in the genetic material generally causes to a change in the end-product of the mutant gene or in a phenotype (Ali, Rafiq, Ratcliffe, 2018; Yalew 2020). Substitution (replacement of a nitrogenic base by another type), deletion (the removal of bases causes to alter in the codons), addition (insertion), inversion and duplication deficiency are the five mechanisms of genetic mutation (Coculescu 2005, 2009). Spontaneous mutation in bacterial chromosomes occur rarely (one mutation in 106-108 individuals in a population), due to deficiencies in DNA replication processes and incorrect DNA repair mechanism (Rice and Sahm 2003; Giedraitienė et al. 2011). Despite, certain resistance genes have derived through accidental mutations (Todar 2008; Coculescu 2009).

Antibiotic resistance can be attained by adaptive mutations in bacterial genome. Under the stress of antibiotics, the rate of mutation increased in pathogenic bacteria and they become hypermutant (Mihăescu and Chifiriuc 2007). For example, some bacteria during the stress of antibiotics start to exchange their genes that are necessary for the production of proteinic substances. These proteinic substances play a role inside the cell, to augment the rate of mutation that is 10,000 times faster than the rate of mutation in normal condition of binary cell division (Kaiser 2007; Coculescu 2009). Also, low antibiotic concentrations, short time of exposure, slow rate of killing by antibiotic, starvation, pathogenic stress, bacteria with hypermutable phenotype, unstable sequences surrounding the nucleotides responsible for the resistance phenotype, and long distance between resistance gene and origin of replication, are all factors that rise the rate of antibiotic resistance mutation (Baquero 2000).

Mutations in a single gene (independent mutation) can reveal resistance phenotype. For example, resistance to some quinolones result from alteration in the gene codes either GyrA or GyrB subunit of topoisomerase II (Nakamura et al. 1989). Whereas, in some cases, mutations in several different genes (cooperative mutation) are required to develop resistance. For instance, mutations in gyrA and grlA genes and also in efflux pump regulatory sequence, together result in high level fluroquinolone resistance (Munoz 1999; Baquero 2000).

Mutation cooperates and effects the other mechanisms, such as mutations in rpoB in S. aureus and M. tuberculosis, lead to alter the target of Rifampin and lessen affinity to β-lactam antibiotics results of the mutation in penicillin binding proteins (PBPs) (Rice and Sahm 2003; Wright 2005; Chen et al. 2011; Giedraitienė 2011). Microbial biofilm is the complicated network of assembled microbial communities, which embedded in an extracellular polymeric substance such as proteins, exopolysaccharides (EPS), extracellular DNA (e-DNA), and amyloidogenic proteins (Whitchurch et al. 2002; Donlan 2001; Jost 2001; Sharma et al. 2019). Together form a matrix in multistep process, beginning from adsorption of molecules to surfaces, then, bacterial adhesion and release of extracellular substances, finally, microbial colony formation and biofilm growth and maturation (Flemming et al. 2016; Sharma et al. 2019). Microbial biofilms have great role in antibiotic resistance, because biofilm-associated microorganisms present reduced rate of the susceptibility to antibiotics (Williams et al. 1997; Ceri et al. 1999; Todar 2008).

Biofilm community increases resistance rate through many strategies, including slow or insufficient penetration of the antibiotics into the biofilm due to presence EPSs, which is able to hold up the diffusion rate of antibiotics in the biofilm (Hoyle et al. 1992; Donlan 2001). The alterations of chemical environment (pH, osmolarity…) that enclose the cells within a biofilm, may provide further protection of microorganism (Gordon et al. 1988; Hausner and Wuertz 1999; Maya-hoyos et al. 2015; Sharma et al. 2019). And increased rates of horizontal plasmid transportation by conjugation have been observed in a biofilm, that higher than its rate in a liquid culture of the same organism. Such as, an investigation indicated that transference of plasmid between gram negative bacteria by conjugation raised in biofilms (Christensen et al. 1998; Ehlers 1999; Hausner and Wuertz 1999; Roberts et al. 1999; Donlan 2001). All these strategies in biofilms result

in the increased rates of antibiotic resistance correspondingly.

Antibiotic resistance reversibility

A reduction in antibiotic prescribing is one strategy to decreasing the development and spreading of antibiotic resistance, and it promotes reversing of resistance, through decreasing the selective pressure (Runehagen et al. 2010; Holmes et al. 2015). Reversibility of resistance is theoretically attractive, while its investigation difficult in practice (Sundqvist 2014). Despite whole eradication of antimicrobial resistance, only by reducing selective pressure is not straightforward (Johnsen et al. 2009; Holmes et al. 2015).

Microbes can acquire resistance easily, and persistence of antimicrobial resistance microbes can occur on human and animal skin and as fecal flora, for many years without any exposure to antimicrobial substance or under selection pressure (Sjölund et al. 2003). There is an obvious relation between heavy antibiotic consumption within a population and the recovery of resistant bacteria, but the process of reversing antibiotic resistance by reductions in antibiotic use is less clear (Enne et al. 2001).

Many studies were done in order to find more information about resistance reversibility. Such as, a prospective study was performed in Kronoberg County, Sweden in 2004. An antibiotic intervention was performed for 24 months, 464 physicians were requested to substitute trimethoprim-containing antibiotics (85% reductions in use during the intervention) with other antibiotics (pivmecillinam, nitrofurantoin and ciprofloxacin), for the treatment of urinary tract infection, that caused by E. coli. The result was marginal effects on the resistance frequency, but statistically significant effect on the increase in trimethoprim resistance was registered, due to a low fitness cost and co-selection due to high levels of associated resistance.

The author summarized that the antibiotic cycling strategy will not be useful, unless non-using period is much longer than 24 months, the fitness cost of resistance is distinctly higher than that seen for trimethoprim resistance in E. coli, and the replacement drugs must be devoid of associated resistance (Runehagen et al. 2010). In contrast, both studies, erythromycin-resistant S. pyogenes in Finland and penicillin-resistant S. pneumoniae in Iceland, showed greatly reduced resistance rates after decreasing the use of these antibiotics (Kristinsson 1997; Seppala et al. 1997; Runehagen et al. 2010). Another study in Korea revealed that the decrease in erythromycin resistance was caused by decreasing of a certain resistant emm-type of S. pyogenes rather than decreasing of erythromycin usage (Koh, Kim 2010).

Reversing resistance only by reducing antibiotics use alone is inadequate, because many several factors help to persist resistance without the presence of selective pressure (Lopatkin et al. 2017). Such as co-selection, which is a connection between resistance and other characteristics (Baker-austin et al. 2006). On the other side, several factors such as genetic factors and evolutionary processes have been identified, which may help reverse of resistance in the absence of selective pressure (Comas et al. 2012).

Depending on the genetic biological process, three types of resistance reversion were recognized (Bonhoeffer et al. 2017):

First, isogenetic reversion is recovery of the ancestral sensitive genotype, which was predominant in the population before become resistant. Isogenetic reversion mechanisms are regrowth, reinvasion and mutation for chromosomal resistance, and losing of resistance genes require for horizontally transferred resistance (Foucault et al. 2010; Baym et al. 2016). Coexistence of sensitive and resistance strains together is possible after reduction of antibiotic uses, especially using antibiotics that stop the growth and duplication of bacteria, instead of killing this reduction help revival of susceptible strains by regrowth and reinvasion (Pader et al. 2016). Possibility of backward mutation depend on several characteristic in the pathogens such as rate of mutability, and pathogen migration (Levin and Walker 2000). Resistance reversion via backward mutation is rare, but its likelihood is higher in the resistance that result from single mutation than multiple mutation such as fluoroquinolones resistance in pathogenic bacteria (Lindgren et al. 2005). Probability of losing resistance gene is higher than backward mutation on the chromosome. Especially resistance genes that are located on plasmid, because losing of plasmid by segregation can occur at high rate, in the absence of positive selection frequency of plasmid reduces consequently (Ponciano et al. 2007; Inca et al. 2011).

Second, paragenetic reversion is reducing of resistance without bringing back of the ancestral genotype through obtaining of additional alleles (Foucault et al. 2010; Baym, et al. 2016). Mutation is the mechanism of paragenetic for both chromosome and horizontally transferred resistance and its possibility is higher than in isogenetic (Bonhoeffer et al. 2017). Mutations in ileS gene in Salmonella enterica Typhimurium and S. aureus can reduce the mupirocin resistance, and completely recovering susceptibility in some cases is an example of paragenetic reversion (Hurdle et al. 2004; Paulander et al. 2007). Potentially the re-evolve of resistance in paragenetic reversion is significant, because the obtained genotype differs from the susceptible ancestor (Vilhelmsson and Tomasz 2000). Resistance deactivation by catting out of resistance genes has been identified on plasmid of E. coli. Removing or deactivation of resistance genes depend on the essentiality of those genes. If

resistance outcomes of mutations in vital enzymes, such as the ribosome and RNA polymerase, it's lethal to bacteria to delete or deactivate those genes (Gelder et al. 2004; Enne et al. 2006). Alteration in level of gene expression is another mechanism of paragentic reversion (Bonhoeffer et al. 2017). This type of reversion has been detected in vancomycin-variable strains of E. faecium as an insertion sequence in the upstream of the vanHAX operon results in silencing of the VanA resistance phenotype (Sivertsen et al. 2016). And, silencing mutations have been distinguished in plasmid-carrying E. coli, which bring back susceptibility but they able to re-gaining resistance (Enne et al. 2006).

Third, allogenetic reversion is substitution of resistant genotypes by less resistant or sensitive genotypes of the same species or strain, which are not originated from the ancestral genotype (Foucault et al. 2010; Baym et al. 2016). The interactions between different lineages of the same species or strains are important because related strains and species are able to have different characteristic in resistance phenotypes, such as penicillin susceptibility in *Streptococcus pyogenes* is deferent between species, and proportionately high antibiotic resistance of *E. coli* that differ with clonal complex 87 (Horn et al. 1996; Skurnik et al. 2015). Allogenetic reversion occurs by migration and competition between species, and also transmission and local adaptation effect within-host reversion (Bonhoeffer et al. 2017).

Beta lactamase resistance genes

There is no agreement on the exact definition of Extended-spectrum beta-lactamases (ESBLs). In general, ESBLs are known as a group of enzymes which can break down antibiotics, be affiliated to the penicillin and cephalosporin groups and make them ineffectual. ESBL has been illustrated as a transportable b lactamase which can be suppressed by tazobactam, clavulanic acid, or sulbactam, and which's coded by genes that can be substituted among bacteria. The presently most common genotype for ESBL is CTX-M (Actions et al. 2004; Paterson and Bonomo 2005a).

Beta-lactamase is generally categorized according to two common schemes: the molecular classification of Ambler and the functional classification of Bush-Jacobi-Medeiros (Ambler 1980; Bush et al. 1995). The Ambler b-lactamas- scheme is classified into four classes according to the protein homogeneity of enzymes. Beta-lactamases category A, C and D are b-lactamase enzymes and category B enzymes are metallo-b-lactamases. The Bush–Jacoby–Medeiros scheme depends on the functional properties of enzymes, that is, the substrate and inhibitory features (Shaikh et al. 2014).

1-SHV type

The SHV family of b-lactamases seems to be obtained from *Klebsiella* spp. The predecessor of the SHV class of enzymes, SHV-1, is widely arrive in pneumonia K. In many *K. pneumonia* strains, the encoded gene SHV-1, or its pronounced precursors, LEN-1, is also found inside the bacterial chromosome; The gene for SHV-1 b-lactamase may have evolved as a chromosome gene in *Klebsiella* and was subsequently attached to a plasmid that diffuse to other species of *Enterobacteria* (Shaikh et al. 2014). SHV-1 gives resistance to wide ranges of penicillins, such as piperacillin, ampicillin and tigecycline, but not to alternative cephalosporins that replace oxygen (Livermore 1995).

2-TEM type

TEM-1, for the first time reported in 1965 from E. coli isolation, has features of substrate and inhibition which is alike to those in SHV-1 (Datta and Kontomichalou 1965). TEM-1 is able for hydrolysis of penicillins and the first creation of cephalosporins but is not capable to work over cefalosporin oxymenoids. The first TEM variable with more activity against cephalosporins extended spectrum was TEM-3 (Sirot et al. 1987; Sougakoff et al. 1988). The fist by product of TEM-1 is TEM-2, a shift in the isoelectric point of pI from 5.4-5.6, cause one amino acid substitution from the original b-lactamase, but it did not alter a substrate feature (Barth et al. 1985). First TEM type B-lactamase to display ESBL phenotype was TEM-3, which is first reported in 1989 (Sougakoff et al. 1988). Later, TEM-3 may not be the first TEM-type ESBL. *Klebsiella oxytoca* contains a plasmid having the encoded gene for resistance of ceftazidime (Bois et al. 1995). TEM-12 was called responsible b-lactamase. The strain obtained from a neonatal unit that was infected with an outbreak of K. oxytoca producing TEM-1 (Bois et al. 1995).

3-CTX type

A family of β-lactamase has risen that inactivate cefotaxime action. It has been found in samples of E. coli, *Salmonella enterrica* serovar and some Enterobacteriaceae species. (Gazouli et al. 1998). CTX not related to TEM or SHV β-lactomases very closely (Tzouvelekis et al. 2000). CTX has two unique features, first cefotaxime rapid hydrolysis and another one better inhibited by β-lactamase inhibitor tazobactam than clavunate (Bradford et al. 1998). CTX M β-lactamase are from functional group 2 and considered that originate ESBL chromosomal gene of *Kluyvera* spp (Bush and Jacoby 2012). They can be divided to five groups according to sequences of the amino acids, groups are (CTX M group 1,2,8,9 and 25) (Bonnet 2004). CTX M enzyme differently originated from that of TEM and SHV

ESBL. TEM ESBL and SHV ESBL produced by amino acid substitution of parent ESBL while CTX M ESBL gained by horizontal gene transfer through transposon or conjugative plasmid using genetic materials. CTX M enzyme gene sequences are highly similar to *Kluyvera* species β-lactamase sequences. Enterobacteriaceae CTX M gene surrounding also similar to *Kluyvera* species chromosome gene surroundings (Olson et al. 2005). CTX M β-lactamase hydrolyse cephaloridine better than benzyl penicillin and advantageously hydrolyse cefotaxime over ceftazidime (Tzouvelekis et al. 2000). However, this enzyme recorded some hydrolysis of ceftazidime, but it is not enough to provide resistance to the organisms they reside. It has been thought that serine at 237 position that occurs in all CTX M enzymes, has important role in activity of spectrum of CTX M □-lactam (Tzouvelekis et al. 2000). It has been thought Arg 276 is on a position that equivalent to Arg 244 of TEM or SHV ESBLs, although it has been shown that is not essential (Gazouli et al. 1998). Toho 1enzyme crystallographic data showed that interacting flexibility increasing for b3 strand and X loop of this enzyme than to other class A β-lactamase. Hydrogen bond absence near X loop counted for extended spectrum phenotype (Ibuka et al. 1999).

4-OXA type

The OXA – beta lactamases enzyme was classified as class D beta lactamases, they act against oxacillin and methicillin in a significant degree, by their enzymatic inactivation, through opening the β-lactam ring of antibiotics irreversibly (Fisher et al. 2005; Walther-rasmussen and Høiby 2006; Pratt and Mcleish 2010; Antunes and Fisher 2014; Evans and Amyes 2014). The name 'OXA' derived from their abilities to hydrolyze oxacillin (Bush et al. 1995; Shaikh et al. 2014). The OXA-type ESBLs had been identified originally from *Pseudomonas aeruginosa* isolates (Weldhagen et al. 2003), then, they have been observed in the many gram-negative bacteria, for example, the most common OXA type is OXA-1 which found in 1% to 10% of E. coli isolates (Livermore 1995; Paterson and Bonomo 2005b). Their gene are located on both the chromosomes and the plasmids of various bacterial species such as *Acinetobacter*, *Shewanella*, *Pseudomonas*, and *Burkholderia* (Sanschagrin et al. 1995; Poirel et al. 2010; Antunes and Fisher 2014). This class contains large numbers of heterogeneous enzymes, more than 400 variants recognized (Evans and Amyes 2014). For the classification of this diversiform class, using a value of ≥80% amino acid identity to separate into groups, and within each group 95% amino acid identity to divide into subgroups (Antunes and Fisher 2014).

5-PER type

PER is an enzyme among class A beta lactamases. It is not related to other ESBLs strongly, but its catalytic machinery and three-dimensional structure have similarity with the class A superfamily. PER-1 beta-lactamase hydrolyzes penicillins and cephalosporins (cefotaxime, ceftazidime) and aztreonam effectively (Ronco et al. 1993; Nordmannl et al. 1994; Naas et al. 2008). The blaPER-1 gene is predominant in Acinetobacter spp. and P. aeruginosa, also can be found in Salmonella enterica serovar Typhimurium and Providencia rettgeri (Aktas and Poirel 2005; Kolayli et al. 2005). PER-2 shares 86% amino acid homology with PER-1. BlaPER-2 gene was detected in S. enterica serovar Typhimurium in Argentina in 1996 (Giakkoupi et al. 2000; Naas et al. 2008). It has been found in *E. coli*, *K. pneumoniae*, *Proteus mirabilis*, and *Vibrio cholerae* subsequently (Petroni et al. 2002). The PER-types take part in around 25–27% homology with TEM- and SHV-type ESBLs (Bauernfeind et al. 1996; Shaikh et al. 2014).

6-GES type

GES type, also named IBC, is commonly detected in gram-negative bacilli, such as *P. aeruginosa*, *E. coli* and *K. pneumoniae*. blaGES-1 gene located on plasmid (Giakkoupi et al. 2000; Poirel et al. 2000). At first, GES-1 was observed in a *Klebsiella pneumoniae* isolate from a newborn patient in France (Poirel et al. 2000). GES-1 is able to hydrolyze penicillins and expanded-spectrum cephalosporins, but it has no hydrolytic activity against Cephamycins and Carbapenems (Shaikh et al. 2014). Also, GES-1 cannot hydrolyze Aztreonam, while most ESBLs do (Naas et al. 2008). GES-2 also hydrolyses carbapenems, but is not so much susceptible to beta lactamase inhibitor because of a 2-bp substitution, resulting in a single Gly170Asn alteration within the catalytic site (Poirel et al. 2001). The first described example of an ESBL that extended its spectrum of activity against carbapenems was GES-2 and then four other forms (GES-4, GES5, GES-6 and GES-8) have been described, all with carbapenemase activity (Yigit et al. 2001).

Other ESBL types

SOF-1 was found in *Enterobacter cloacae* isolate from Japan in 1988. It hydrolyses cefotaxime effectively and ceftazidime poorly (Bonnet et al. 2000).

BES-1 was isolated from a Serratia marcescens strain in Brazil in 1996. It resists to aztreonam at a high level. The blaBES-1 gene is plasmid-encoded and it shares 48% amino-acid similarity with the CTX-M group 1 b-lactamase (Poirel et al. 2005).

BEL-1 was detected in a *P. aeruginosa* strain isolated in Belgium in 2004. It has the ability to hydrolyze most

expanded-spectrum cephalosporins and aztreonam (Silva et al. 2000; Bogaerts et al. 2007).

TLA-1 was observed in an *E. coli* isolate from a patient in Mexico in 1993. It is able to hydrolyze expanded-spectrum cephalosporins but cannot hydrolyze imipenem and cefoxitin (Silva et al. 2000; Alcantar-curiel et al. 2004).

TLA-2 was isolated from an unknown bacterial strain in Germany in 2002. TLA-2 has good catalytic activity against most cephalosporins but doesn't against penicillins (Girlich et al. 2005; Naas et al. 2008).

SOF-1, BES-2, BEL-1, TLA-1 and TLA-2 are rare ESBLs that have been described, and also many others infrequent type of ESBLs identified such as CME-1 and VE-B-1 (Naas et al. 2008; Shaikh et al. 2014).

Resistance Genes (ESBL) in Middle East

Antibiotics lead to saving millions of lives, but drug resistance have been observed due to its overuse in clinical fields since its discovered in early 1940s (van Hoek et al. 2011; Frieri et al. 2017). Drug resistance phenomenon impedes the treatment of infectious diseases and claiming a large number of morbidity and mortality (Kon and Kateryna 2016). The emerging of resistance bacteria is increasing dramatically in recent decades and poor sanitation measure control accelerates the dissemination of these bacteria in environments and among patients (Frieri et al. 2017).

Enterobacteriacaea (Gram negative Bacilli) that are found in gastrointestinal tract of animals and humans are common causes of infectious diseases (Tian et al. 2012; Verraes et al. 2013). Gram negative Bacilli are distinct in developing resistance against extended spectrum beta lactam antibiotics because of their ability to produce extended spectrum beta lactamases (ESBL) (Schill et al. 2017).

Poor sanitation, control measure and misuse of antibiotic in both humans and animals in Middles East cause dissemination of drug resistance genes in bacteria in large scales. Furthermore, due to economical and war crises in the area, a large population movement has been observed between countries that causes difficulties in infectious disease and sanitation controls (Dandachi et al. 2019). This review study is to discuss and investigate the existence of different types of resistance genes in Middle East and in Iraq. The epidemiology of beta lactamase resistance genes in different countries of Middle East is well studied in recent years and is illustrated in tables 1-5.

Resistance genes in Iraq

Iraq is one of the countries of Middle East which is counted as a developing country. Using antibiotics in clinical fields and animal industry is enormous. Selling of antibiotics is not restricted in pharmacy shops and people are free to buy them on shelves. Like middles east, dissemination of drug resistance genes in bacteria is in high and alarming levels in Iraq because of poor sanitation, control measure and wrong use of antibiotics in both humans and animals. In addition, Iraq also faced economical and war crises in the last two decades that caused a large population movement between Iraq cities and neighbor countries. These problems in the country became additional reasons of losing ability to cease the spread of infectious diseases and sanitation controls (Dandachi et al. 2019). The common beta-lactamase resistance genes in different bacteria that exist in Iraq have been shown in this section.

Different types of ESBL gene were reported in Iraq in different clinical fields. In one study which was carried out on patients who have repeated urinary tract infection caused by *E. coli*, TEM, SHV, and CTX-M1 was recovered in a high level in comparison to non-ESBL genes (Al-mayahie et al. 2016). ESBL producing bacteria, *Klebsiella* spp. and *E. coli* harboring six different ESBL genes CTX-15 and SHV, TEM1, OXA1, AMPC were discovered from samples collected in patients and hospital environment. SHV gene was identified only in *K. pneumoniae* (Huang et al. 2012). The rate of TEM, SHV, CTX-M was found at high rates in *E. coli*, and *K. pneumonia* caused urinary tract infections in Thalassemia Patients. The rate of ESBL in E. coli was blaTEM (81%), blaSHV (16.2%), and blaCTX-M (32.4%). In K. pneumonia, the rates were as follow: blaTEM (64.7%), blaSHV (35.2%), and blaCTX-M (41.1%) (Ahmad, Khalil 2019).

The ESBL was reported in bacteria that isolated from clinical infections, *Morganella morganii* including OXA, SHV, TEM, and CTX-M (Al-muhanna et al. 2016). OXA-23/OXA-24 carbapenemase were discovered in *A. baumannii* in a different study in the same bacteria (Kusradze et al. 2011; Ganjo et al. 2016). Another study recorded OXA-23 and OXA-24 producing *A. baumannii* isolated from hospital environments and respiratory tract of patients (Obeidat et al. 2014). OXA-10 also found infectious strain of P. aeruginosa (Burgh et al. 2018). *Acinetobacter baumannii* isolated from clinical samples (Wounds, Sputum, UTI, Burns, and blood) was tested to detect ESBL, TEM gene. Out of 39 bacteria, 25 (64.1%) isolates were positive to TEM genes (Taif et al. 2020).

In another study in north part of Iraq, TEM resistance gene was observed in *Proteus* bacteria by the rate of 10.3%. All of the isolates harboring TEM were discovered in Proteus mirabilis that recovered from meat of different animals and poultry species (Sabiha et al., 2019). Another study was conducted in the same area to find the rate of TEM and CTX in E. coli isolated from feces of humans and animal species. It was concluded that the rate of CTX-M was significantly high in *E. coli* isolated from human, while TEM was significantly high in *E. coli* isolated from farm chickens. Furthermore, it was detected that the rate of ESBL was obviously higher in those hosts using large

amount of antibiotic (human and farm chickens) in comparison to wild animals (non-antibiotic users) (Alaa et al. 2020). In another study in Kirkuk, the high rate of CTX-M-G2 gene was discovered in S. aureus, E. faecalis and *Klebsiella* spp. isolated from blood of patients in hemodialysis unit of the hospital (Shaker et al. 2020).

In a new study in southern part of Iraq, CTX-M1 resistance gene was detected in *E. coli* and *K. pneumonia*. Bacteria were isolated from urinary tract infection with high rates of CTX-M1, 29.8% (E.coli) and 23.8 % (*K. pneumonia*) (Nasser et al. 2018). In the same area, CTX.M was recovered at the rate of 30% in environmental P. aeruginosa isolated from tap and sewage water in Baghdad (Khdair et al. 2017).

Conclusion

Currently, antibiotic resistance is a worldwide issue, and it causes high morbidity and mortality. Existence of EXBL (OXA, TEM, CTX, CMY) in gram negative bacteria are mostly responsible of the emergence of multidrug resistant bacteria. Dissemination of multidrug resistant bacteria is common in the world which causes difficulty in treatment and result in a high mortality. Many studies recorded the existence of multidrug resistant gram-negative bacteria in Middle East and Iraq and most of them bearing ESBL. EXBL in Iraq is common and all types of ESBL are reported in high rates. Drug resistant genes are discovered in humans, animals, and even environments. The spread of multidrug resistant bacteria expressing EXBLs is related to many reasons such as: selling of antibiotics without physician prescriptions, using of antibiotics in poultry industry in large scales, lack of proper health education to people regarding using antibiotics, lack of proper sanitation, economic crisis of the country in different times because of different issues, movement of people between cities for different reasons, fleeing of people from war places to safer cities in different times.

Declaration of competing interest

The authors declare that they have no competing interests.

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Table 1 Epidemiology of beta lactamases resistance gene, CTX in Middle East.

	CTX			
Acinetobacter baumannii				
Egypt	CTX-M-15	Human	Wound, burns infection, patients attended in ICU (from buccal cavity, skin swab and eye swab)	(El-baky et al. 2020)
Iran	CTX-M-2, CTX-M-1, CTX-M-8 CTX-M-9	Human	Endotracheal tube, urine, blood, wound, body fluids	(Ali et al. 2020)
Lebanon	CTX-M	Chicken and soil	Feed sample and soil sample	(Dandachi et al. 2019)
***Proteus* species**				
Sudan	CTX-M	Human	Urine and wound swabs	(Musa et al. 2019)
Enterobacteriaceae				
Lebanon	CTX-M-15, CTX-M-9, CTX-M-2	Human	Rectal swabs	(Hijazi et al. 1989)
***Klebsiella* spp.**				
Egypt	CTX-M-15, CTX-M-27, CTX-M-14	Human	Lower respiratory tract specimens, urine and pus or abdominal fluid of hospitalized patients with lower respiratory tract infections (LRTI), complicated urinary tract infections (cUTI), and complicated intra-abdominal infections (cIAI).	(El-kholy et al. 2020)
Turkey	CTX-M	Human	Blood culture	(Midilli 2020)
Iran	CTX	Human	Urine and sputum	(Malekjamshidi 2020)
Palestine	CTX-M-15, and CTX-M-14	Human	Urine, wound swabs, blood and ear discharge	(Tayh et al. 2020)
Iran	CTX-M-1	Human	Diarrheal samples	(Hajikarim et al. 2020)
Iran	CTM-X	Human	(Unknown) clinical samples nine cities in Iran	(Armin et al. 2020)
Yemen	CTX-M-15	Human	Aspiration, pus, blood, sputum, urine, ear swab	(Alsharapy et al. 2019)
Turkey	CTX-M	Human	Catheter urine, Diabetic wound swab, sputum, decubitus wound aspirate and abscess aspirate	(Evren et al. 2019)
Egypt	CTX-M-15, CTX-M-14, and CTX-M-9	Human	Ryle tube swab, blood, sputum, endotracheal tube swab, ear swab, diabetic foot pus, eye swab, urine, Cerebrospinal fluid, Ovarian cyst abscess, left ureter, intraperitoneal fluid	(Nations et al. 2019)
Egypt	CTX-M-9, and CTX-M-15	Broiler farms	Cloacal swabs	(Moawad et al. 2018)
KSA	CTX-M-15	Human	Rectal swab	(Aljindan et al. 2015; Abdalhamid et al. 2016)
Turkey	(CTX-M-15 and CTXM-1) and CTX-M-group2	Human	Elderly male patient, urine, blood and wound	(Elaldi et al. 2013; Görgeç et al. 2015; Iraz et al. 2015)
Kuwait	CTX-M-15, CTX-M-14	Human	Urine, sputum and wound swab	(Jamal et al. 2015)

Table 1 (continued).

CTX				
Yemen	CTX-M-15	human	Urine, pus, blood, sputum, vaginal and ascites fluid	(Gharout-Sait 2014)
Egypt	CTX-M-15	Cattle	Milk samples, rectal swabs and stalls	(Hammad and Shimamoto 2011; Braun et al. 2016)
United Arab Emirates	CTX-M-15	Human	Urine, blood, tracheal/bronchial aspirates, wound swabs, sputum and ear discharges	(Alfaresi et al. 2011)
Iran	CTXM-1, CTXM-2, CTXM-3, CTXM-8 and CTXM-15	Human	Urine, trachea, wounds, blood, sputum, hospitals in Tehran, respiratory and vaginal secretions, ascites, biopsies, and body fluids, Chronic obstructive pulmonary disease (COPD) patients.	(Feizabadi 2010; Peerayeh et al. 2014; Bialvaei et al. 2016; Akya et al. 2018; Dehshiri et al. 2018)
***Salmonella* spp**				
Saudi Arabia	CTX−M−1, CTX−M−9	Human	Stool	(Desin 2019)
Iran	CTX-M 1 /CTX-M-15	Human	Stool culture, blood culture, urine, sputum, wound, respiratory and vaginal secretion, ascites, biopsies, body fluids, diarrhea	(Rizi et al. 2015; Bialvaei et al. 2016; Aminshahidi et al. 2017)
Turkey	CTX-M-3	Human	Neonate gastroenteritis	(Ağın et al. 2014)
***Shigella* spp.**				
Iran	CTX-M	Human	Stool sample	(Ghannadi and Ghane 2019)
Iran	CTX-M-15 /CMY-2	Human	Stool culture, blood culture, urine, sputum, wound, respiratory and vaginal secretion, ascites, biopsies, body fluids, diarrhea	(Rizi et al. 2015; Bialvaei et al. 2016; Aminshahidi et al. 2017)
Enterobacter cloacae				
Turkey	CTX-M	Human	Blood culture	(Midilli 2020)
Lebanon	CTX-M	Soil	Soil sample	(Dandachi et al. 2019)
Iran	CTX-M-15	Human	Urine, wound, sputum, broncho alveolar lavage, trachea, blood and cerebrospinal fluid	(Peymani et al. 2014)
E. coli				
Lebanon	CTX-M-15, CTX-M-103 and CTX-M-189	Human	Rectal swabs from hospitalized patients	(Nawfal et al. 2020)
Turkey	CTX-M	Human	Blood culture	(Midilli 2020)
Palestine	CTX-M-15, and CTX-M-14	Human	Urine, wound swabs, blood and ear discharge	(Tayh et al. 2020)
Iran	CTM-X	Human	Unknown) clinical samples nine cities in Iran	(Armin et al. 2020)

Table 1 (continued).

		CTX		
Egypt	CTX-M-28	Raw beef	Burgers, kofta (balls of minced meat mixed with spices and onion), and sausage sandwiches.	(Sabala et al. 2020)
Egypt	CTX	Chicken, animal and human	Retail chicken carcasses, ground beef, human diarrheic patient	(Ramadan et al.)
Tukey	CTX-M	Human	Urine	(Demirci-duarte et al. 2020)
Egypt	CTX-M	Human	Urine	(Elshamy et al. 2020)
Iran	CTX-M	Human	Kidney transplant patients	(Resistance et al. 2020b)
Iran	CTX-M	Human	Urine	(Lesani et al. 2020)
Egypt	CTX-M-15	Human	Urine, stool, blood and wound swab samples	(Resistance et al. 2020a)
Egypt.	CTX-M-55, CTX-M-15, CTX-M-27, CTX-M-14	Human	lower respiratory tract specimens, urine and pus or abdominal fluid of hospitalized patients with lower respiratory tract infections (LRTI), complicated urinary tract infections (cUTI),andcomplicatedintra-abdominalinfections(cIAI)	(El-kholy et al. 2020)
Egypt	CTX-M	Human	Urine	(Hassuna et al. 2020)
Turkey	CTX-M-1, CTX-M-2, CTX-M-8/25 and CTX-M-9	Raw chicken	Meat	(Baran and Adiguzel 2020)
Lebanon	CTX-M	Human	Vaginal samples of pregnant women between 35–37 weeks of gestation	(Ghaddar et al. 2020)
Saudi Arabia	CTX-M	Camel	Meat sample	(El-ghareeb et al. 2020)
Saudi Arabia	CTX-M-15 and CTX-M-14	Human	Blood	(Alqasim et al. 2019)
Egypt.	CTX-M-15, CTX-M-14, and CTX-M-9	Human	Ryle tube swab, blood, sputum, endotracheal tube swab, ear swab, diabetic foot pus, eye swab, urine, Cerebrospinal fluid, Ovarian cyst abscess, left ureter, intraperitoneal fluid	(Nations et al. 2019)
Yemen	CTX-M-15, CTX-M-216	Human	Aspiration, pus and blood	(Alsharapy et al. 2019)
Lebanon	CTX-M	Chicken, human and soil	Chicken sample, farmer sample litter sample, soil sample	(Dandachi et al. 2019)
Iran	CTX-M-3, CTX-M-8, CTX-M-2, and CTX-M-25	Human	urine	(City et al. 2019)
Egypt	CTX-M-9, and CTX-M-15	Broiler farms	Cloacal swabs	(Moawad et al. 2018)
Lebanon	CTX-M	Swine farms	Fecal samples	(Dandachi et al. 2018a)

Table 1 (continued).

		CTX		
Lebanon	CTX-M	Chicken farm	Rectal swab	(Dandachi et al. 2018)
Lebanon	CTX-M	Human	Solid tumor and blood disorder	(Christophy et al. 2017)
Egypt	blaCTX-M-14	Chicken	Liver and heart	(El-Shazly et al. 2017)
Turkey	CTX-M-15, CTX-M-3, CTX-M-1	Dog	Rectal swabs from companion dogs	(Aslantas and Yilmaz 2017)
Iran	CTX-M-15	Human	Urine, wound swab, blood, and sputum	(Namaei 2017)
Turkey	CTX-M-15	Bovine mastitis	Milk samples	(Pehlivanoglu et al. 2016)
Lebanon	CTX-M-15	Cattle farm	Fecal samples	(Diab et al. 2016)
KSA	CTX-M-15	Human	Throat swabs, rectal swab	(Leangapichart, T. 2016)
Jordan	CTX-M-15, CTX-M-2, and CTXM-1	Human	Rectal samples	(Badran et al. 2016)
Egypt	CTX-M-variants (CTX-M-15, CTX-M-104, CTX-M-3), TEM-52, SHV-12, and CMY-2	Chicken, beef and dairy products	Meat, milk, cheese and yoghurt, Karish and Ras cheeses	(Ahmed and Shimamoto 2015; Ombarak 2018)
UAE	CTX-M-15, CTX-M-3, and CTX-M-14	Human	Urine, blood, intra-abdominal specimens, wound swabs respiratory specimens and rectal swabs	(Peirano et al., 2014).
Kuwait	CTX-M-15, CTX-M-14, CTX-M-56, and CTX-M-2	Human	(Unknown) patients in 3 hospitals, CSF, Wound swab	(Dashti et al. 2014; Jamal et al. 2015)
Palestine	CTX-M (including CTX-M-1, CTX-M-9) and SHV-12	Chicken	Liver samples, carcasses	(Qabajah et al. 2014)
Israel	CTX-M-27, CTX-M-15, CTX-M-14, CTX-M-39, CTX-M-55	Human	Rectal swab specimen	(Izdebski et al. 2013)
Egypt	CTX-M-15, blaCMY-2	Poultry, human	Heart blood samples, carcasses, urine, Sputum, pus samples	(Ahmed et al. 2013; Abdallah et al. 2015; Ramadan et al. 2018)
Egypt	CTX-M	pet dogs	Feces	(Aly et al. 2012)
Egypt	CTX-M-15	Cattle	Milk samples, rectal swabs and stalls	(Hammad and Shimamoto 2011; Braun et al. 2016)
Turkey	CTX-M-group1 (CTX-M-15 and CTXM-1) and CTX-M-group2	Human		(Elaldi et al. 2013; Görgeç et al. 2015; Iraz et al. 2015)
***Pseudomonas* spp**				
Yemen	CTX-M	Human	Burn wound swab.	(Nasser et al. 2020)
Sudan	CTX-M-2	Human	Wound swab, urine, and pleural fluid samples	(Babour et al. 2020)
Iran	CTM-X	Human	Unknown) clinical samples nine cities in Iran	(Armin et al. 2020)
Iran	CTX-M-1	Human	Urine	(Hospitals et al. 2020)
Lebanon	CTX-M	Chicken, soil	Feed sample, soil sample	(Dandachi et al. 2019)

Table 1 (continued).

		CTX		
Egypt	CTX-M-15, CTX-M-14, and CTX-M-9	Human	Ryle tube swab, blood, sputum, endotracheal tube swab, ear swab, diabetic foot pus, eye swab, urine, Cerebrospinal fluid, Ovarian cyst abscess, left ureter, intraperitoneal fluid	(Nations et al. 2019)
Iran	CTX-M	Human	Burn wound swabs	(Piri et al. 2018)
Iran	CTX-M	Human	Urine, blood, tracheal tube, wound, ear discharge, wound infections, respiratory infections, urinary tract infections, bed ulcer, and burn	(Fazeli and Momtaz 2014; Rafiee et al. 2014; Bokaeian et al. 2015)
Serratia rubideae				
Lebanon	CTX-M	chicken	Feed sample	(Dandachi et al., 2019)
Serratia marcescens				
Egypt	CTX-M-15, CTX-M-14, and CTX-M-9	Human	Ryle tube swab, blood, sputum, endotracheal tube swab, ear swab, diabetic foot pus, eye swab, urine, Cerebrospinal fluid, Ovarian cyst abscess, left ureter, intraperitoneal fluid	(Nations et al. 2019)
Morganella morgana				
Turkey	CTX-M	Human	Blood culture	(Midilli 2020)
Enterobacter				
Turkey	CTX-M	Human	Unknown clinical specimen, wound infection, Urine cultures	(Nazik et al. 2011; Nazipk et al. 2016; Erdem, I. 2018)
Fecal carriage				
Egypt	CTX-M (CTXM-15, CTX-M-14, CTX-M-2, and CTX-M-grp9)	Human	Chest wound swab, central venous line, Rectal swabs	(Khalaf et al. 2009; Fam et al. 2014)

Table 2 Epidemiology of beta lactamases resistance gene, TEM in Middle East

			TEM	
***Klebsiella* spp.**				
Lebanon	TEM-1, TEM-163	Human	Rectal swab	(Nawfal et al. 2020)
Egypt	TEM-OSBL, TEM-ESBL	Human	Lower respiratory tract specimens, urine and pus or abdominal fluid of hospitalized patients with lower respiratory tract infections (LRTI), complicated urinary tract infections (cUTI),and complicated intra-abdominal infections	(El-kholy et al. 2020)
Iran	TEM	Human	Diarrheal samples	(Hajikarim et al. 2020)
Palestine	TEM-1	Human	Urine, wound swabs, blood and ear discharge	(Tayh et al. 2020)
Iran	TEM	Human	Unknown) clinical samples nine cities in Iran	(Armin et al. 2020)
Iran	TEM	Human	Urine and sputum	(Malekjamshidi 2020)
Yemen	TEM-1	Human	Aspiration, pus, sputum, urine	(Alsharapy et al. 2019)
Iran	TEM genes	Human	Isolated from different sample, urine specimens	(Gholipour et al. 2014; Maleki 2018)
E. coli				
Lebanon	TEM-1, TEM-163	Human	Rectal swab	(Nawfal et al. 2020)
Egypt	TEM-OSBL, TEM-ESBL	Human	Lower respiratory tract specimens, urine and pus or abdominal fluid of hospitalized patients with lower respiratory tract infections (LRTI), complicated urinary tract infections (cUTI), and complicated intra-abdominal infections	(El-kholy et al. 2020)
Lebanon	TEM	Human	Vaginal samples of pregnant women between 35–37 weeks	(Ghaddar et al. 2020)
Iran	TEM	Human	Unknown) clinical samples nine cities in Iran	(Armin et al. 2020)
Iran	TEM	Human	Urine	(Lesani et al. 2020)
Iran	TEM	Human	Kidney transplant patients	(Resistance et al. 2020b)
Egypt	TEM-OSBL, TEM-ESBL	Human	Lower respiratory tract specimens, urine and pus or abdominal fluid of hospitalized patients with lower respiratory tract infections (LRTI), complicated urinary tract infections (cUTI),and complicated intra-abdominal infections (cIAI)	(El-kholy et al. 2020)

Table 2 (continued).

			TEM	
Egypt	TEM-116	raw beef	Burgers, kofta (balls of minced meat mixed with spices and onion), and sausage sandwiches.	(Sabala et al. 2020)
Egypt	TEM	Human	Urine	(Elshamy et al. 2020)
Egypt	TEM	Chicken, animal and human	Retail chicken carcasses, ground beef, human diarrheic patient	(Ramadan et al.)
Saudi Arabia	TEM	camel	Meat sample	(El-ghareeb et al. 2020)
Egypt	TEM	Human	Urine	(Hassuna et al. 2020)
Saudi Arabia	TEM	Human	Blood	(Alqasim et al. 2019)
Egypt	TEM-1	Human	Sputum, vaginal secretion, stool, urine, burn swab, wound swab	(Soliman et al. 2019)
Yemen	TEM-1	Human	Pus	(Alsharapy et al. 2019)
Lebanon	TEM	Chicken, human and soil	Chicken sample , farmer sample litter sample, soil sample	(Dandachi et al. 2019)
Egypt	TEM	broiler farms	Cloacal swabs	(Moawad et al. 2018)
Lebanon	TEM	chicken farm	Rectal swab	(Dandachi et al. 2018)
Egypt	TEM	poultry hatcheries	Hatchling samples	(Osman et al. 2018)
Egypt	TEM-57	chicken	Liver and heart	(El-Shazly et al. 2017)
Iran	TEM	Human	Isolated from different sample, urine, blood, tracheal tube,ear discharge sputum, wound, respiratory and vaginal secretion, ascites, biopsies, body fluids	(Gholipour et al. 2014; Rezai et al. 2015; Shayan, Bokaeian 2015; Bialvaei et al. 2016)
Iran	TEM	Human	Diarrheic pediatric patients, Diarrhea	(Heidary and Madani 2014; Aminshahidi et al. 2017)
Egypt	TEM-104	Poultry	Heart blood samples, carcasses, urine, Sputum, pus samples	(Ahmed et al. 2013; Abdallah et al. 2015; Ramadan et al. 2018)

Table 2 (continued).

			TEM	
Egypt	TEM	Dog	Feces	(Aly et al. 2012)
KSA	TEM	poultry	Meats, cloacal swabs	(Altalhi and Gherbawy 2010; Abo-amer et al. 2018)
Enterobacter				
Iran	TEM	Human	(Unknown) clinical samples nine cities in Iran	(Armin et al. 2020)
Iran	TEM-169	Human	Urine, wound, sputum, broncho alveolar lavage, trachea, blood and cerebrospinal fluid	(Peymani et al. 2014)
Turkey:	TEM	Human	(Unknown) clinical spicemen, wound infection, Urine cultures	(Nazik et al. 2011; Nazipk et al. 2016; Erdem, I. 2018)
Pseudomonas				
Yemen	TEM	Human	Burn wound swab	(Nasser et al. 2020)
Sudan	TEM-1	Human	Wound swab, urine, and pleural fluid	(Babour et al. 2020)
Iran	TEM	Human	Unknown) clinical samples nine cities in Iran	(Armin et al. 2020)
Lebanon	TEM	Chicken, soil	Feed sample, soil sample	(Dandachi et al. 2019)
Iran	TEM-116	Human	Urine, blood, tracheal tube, wound, ear discharge, wound infections, respiratory infections, urinary tract infections, bed ulcer, and burn	(Fazelim, Momtaz 2014; Rafiee et al. 2014; Bokaeian et al. 2015)
***Shigella* spp**				
Iran	TEM	Human	Stool sample	(Ghannadi and Ghane 2019)
Acinetobacter baumannii				
Iran	TEM	Human	Unknown) clinical samples nine cities in Iran	(Armin et al. 2020)
Lebanon	TEM	Chicken and soil	Feed sample and soil sample	(Dandachi et al. 2019)
Stenotrophomonas maltophilia				
Lebanon	TEM	Soil	Soil sample	(Dandachi et al. 2019)

Table 2 (continued).

		TEM		
***Proteus* spp**				
Sudan	TEM	Human	Urine and wound swabs	(Musa et al. 2019)
Enterobacter cloacae				
Lebanon	TEM	Soil	Soil sample	(Dandachi et al. 2019)
Fecal carriage				
Egypt	TEM	Human	Chest wound swab, central venous line, Rectal swabs	(Khalaf et al. 2009; Fam et al. 2014)
Salmonella				
Saudi Arabia	TEM−1	Human	Stool, urine, tissue, abdominal fluid, wound and blood	(Desin 2019)
Kuwait	TEM-1	Human	Blood	(Albert et al. 2019)
Egypt	TEM	chicken and pigeons	Chicken breast meat fillet without skin, cloacal swabs	(Ahmed et al. 2016; Abdeen et al. 2018)

Table 3 Epidemiology of beta lactamases resistance gene, SHV in Middle East

		SHV		
E. coli				
Egypt	SHV	Human	Urine	(Hassuna et al. 2020)
Saudi Arabia	SHV	camel	Meat sample	(El-ghareeb et al. 2020)
Lebanon	SHV	Human	Vaginal samples of pregnant women between 35–37 weeks	(Ghaddar et al. 2020)
Egypt	SHV-OSBL, SHV-12	Human	Lower respiratory tract specimens, urine and pus or abdominal fluid of hospitalized patients with lower respiratory tract infections (LRTI), complicated urinary tract infections (cUTI),and complicated intra-abdominal infections (cIAI)	(El-kholy et al. 2020)
Iran.	SHV	Human	Kidney transplant patients	(Resistance et al. 2020b)
Egypt	SHV	Human	Urine	(Elshamy et al. 2020)
Egypt	SHV	Chicken, animal and human	Retail chicken carcasses, ground beef, human diarrheic patient	(Ramadan et al.)
Iran	SHV	Human	Unknown) clinical samples nine cities in Iran	(Armin et al. 2020)
Iran	SHV	Human	Urine	(Lesani et al. 2020)
Egypt.	SHV-142, SHV-28, SHV-11, SHV-27, SHV-71, SHV-63, SHV-82, SHV-33, and SHV-2	Human	Blood, urine, sputum, eye swab, pus, diabetic foot pus, endotracheal tube swab, peritoneal swab, ear swab, cerebrospinal fluid	(Nations et al. 2019)
United Arab Emirate	SHV-12, SHV-11	Human	Urine, Wound, Blood	(Pál and Sonnevend 2019)
Lebanon	SHV	Chicken, human and soil	Chicken sample, farmer sample litter sample, soil sample	(Dandachi et al. 2019)

Table 3 (continued).

			SHV	
Iran	SHV	Milk and dairy products	Raw bovine, raw ovine, raw caprine, raw buffalo and raw camel milk samples and traditional cheese, yoghurt, kashk, dough, butter, cream and ice-cream	(Ranjbar et al. 2018)
Egypt	SHV	Broiler farms.	Cloacal swabs	(Moawad et al. 2018)
Egypt	SHV	poultry hatcheries	Hatchling samples	(Osman et al. 2018)
Egypt	SHV-12	Chicken	Liver and heart	(El-Shazly et al. 2017)
Turkey	SHV-12	Dog	Rectal swabs from companion dogs	(Aslantas and Yilmaz 2017)
Egypt	SHV-12	Chicken, beef and dairy products	Meat, milk, cheese and yoghurt, Karish and Ras cheeses	(Ahmed and Shimamoto 2015; Ombarak 2018)
Palestine	SHV-12	Chicken	Liver samples, carcasses	(Qabajah et al. 2014)
Iran	SHV	Human	Isolated from different sample, urine, blood, tracheal tube,ear discharge sputum, wound, respiratory and vaginal secretion, ascites, biopsies, body fluids	(Gholipour et al. 2014; Rezai et al. 2015; Shayan and Bokaeian 2015; Bialvaei et al. 2016)
Lebanon	SHV-5a	Human	Urine, respiratory tract, pus, digestive tract, blood, nasopharynx, sputum	(Charrouf et al. 2014; Daoud et al. 2017)
Kuwait	SHV-12	Human	(Unknown) patients in 3 hospitals, CSF, Wound swab	(Dashti et al. 2014; Jamal et al. 2015)
Israel	SHV-5, SHV-12	Human	Rectal swab specimen	(Izdebski et al. 2013)
Egypt	SHV	Dog	Feces	(Aly et al. 2012)
Egypt	SHV-12	Human	Urine, stool, sterile sites, blood, catheter tips, cerebrospinal fluid, ear discharge, endotracheal Tubing, midline subumbilical gaps, peritoneal discharge, pus, sputum, and wounds	(Hassan et al. 2012; Abdelaziz et al. 2013; Abdallah et al. 2015; Helmy, and Kashef 2017)
KSA	SHV-12, and SHV-5	Human	Hospitalized patient (different sites), urine, blood , wounds, sputum, and other body fluid, urine catheters	(Shibl et al. 2012; Sheikh et al. 2014; Alyamani et al. 2017; Yasir et al. 2018)
KSA	SHV	Poultry	Meats, cloacal swabs	(Altalhi et al. 2010; Abo-amer et al. 2018)

Table 3 (continued).

		SHV		
***Klebsiella* spp.**				
Lebanon	SHV-1	Human	Rectal swab	(Nawfal et al. 2020)
Lebanon	SHV-12, SHV-13, SHV-31, SHV-86, SHV-129, SHV-155, and SHV-172	Human	Urine sample	(Salloum et al. 2020)
Palestine	SHV-1 and SHV-12	Human	Urine, wound swabs, blood and ear discharge	(Tayh et al. 2020)
Iran	SHV	Human	Diarrheal samples	(Hajikarim et al. 2020)
Iran	SHV	Human	Unknown) clinical samples nine cities in Iran	(Armin et al. 2020)
Egypt	SHV-OSBL, SHV-12	Human	Lower respiratory tract Specimens, urine and pus or abdominal fluid of hospitalized patients with lower respiratory tract infections (LRTI), complicated urinary tract infections (cUTI),and complicated intra-abdominal infections(cIAI)	(El-kholy et al. 2020)
Iran	SHV	Human	Urine and sputum	(Malekjamshidi 2020)
Turkey	SHV	Human	Catheter urine, Diabetic wound swab, sputum, decubitus wound aspirate and abscess aspirate	(Evren et al. 2019)
Egypt	SHV-142, SHV-28, SHV-11, SHV-27, SHV-71, SHV-63, SHV-82, SHV-33, and SHV-2	Human	Blood, urine, sputum, eye swab, pus, diabetic foot pus, endotracheal tube swab, peritoneal swab, ear swab, cerebrospinal fluid	(Nations et al. 2019)
Egypt	SHV-33	Human	Sputum, vaginal secretion, stool, urine, burn swab, wound swab	(Soliman et al. 2019)
United Arab Emirate	SHV-12, SHV-11	Human	Sputum, Blood, Wound	(Pál and Sonnevend 2019)
Palestine	SHV-12, SHV-5, and SHV-33	Human	Wound, urine, and blood	(Tayh et al. 2016)

Table 3 (continued).

		SHV		
Kuwait	SHV-11	Human	Urine, sputum and wound swab	(Jamal et al. 2015)
Yemen	SHV-11, SHV-76, and SHV-184	Human	Urine, pus, blood, sputum, vaginal and ascites fluid	(Gharout-Sait 2014)
Lebanon	SHV-5a	Human	Urine, respiratory tract, pus, digestive tract, blood, nasopharynx, sputum	(Charrouf et al. 2014; Daoud et al. 2017)
Egypt	SHV-28	bovine	Milk samples	(Hammad, Shimamoto 2011)
United Arab Emirates	SHV-258	Human	Urine, blood, tracheal/bronchial aspirates, wound swabs, sputum and ear discharges	(Alfaresi et al. 2011)
Iran	SHV (SHV-12, SHV-11, SHV-5)	Human	Urine, trachea, wounds, blood, sputum	(Feizabadi, M. M. 2010; Shakib, P. 2018)
Enterobacter				
Lebanon	SHV	Soil	Soil sample	(Dandachi et al. 2019)
Iran	SHV	Human	Unknown) clinical samples nine cities in Iran	(Armin et al. 2020)
KSA	SHV-5	Human	Wound, blood, respiratory and urinary tract specimen	(Abdalhamid et al. 2017)
Iran	SHV-12	Human	Urine, wound, sputum, broncho alveolar lavage, trachea, blood and cerebrospinal fluid	(Peymani et al. 2014)
Kuwait	SHV-112	Human	blood and urine	(Dashti et al. 2013)
Turkey	SHV	Human	(Unknown) clinical spicemen, wound infection, Urine cultures	(Nazik et al. 2011; Nazipk et al. 2016; Erdem, I. 2018)
Stenotrophomonas maltophilia				
Lebanon	SHV	soil	Soil sample	(Dandachi et al. 2019)

Table 3 (continued).

		SHV		
Citrobacter freundii.				
United Arab Emirate	SHV-12, SHV-11	Human	Urine	(Pál, Sonnevend 2019)
Pseudomonas				
Yemen	SHV	Human	Burn wound swab	(Nasser et al. 2020)
Iran	SHV	Human	Unknown) clinical samples nine cities in Iran	(Armin et al. 2020)
Sudan.	SHV-1	Human	Wound swab, urine, and pleural fluid samples	(Babour et al. 2020)
Egypt	: SHV-142, SHV-28, SHV-11, SHV-27, SHV-71, SHV-63, SHV-82, SHV-33, and SHV-2	Human	Blood, urine, sputum, eye swab, pus, diabetic foot pus, endotracheal tube swab, peritoneal swab, ear swab, cerebrospinal fluid	(Nations et al. 2019)
Iran	SHV-12	Human	Urine, blood, tracheal tube, wound, ear discharge, wound infections, respiratory infections, urinary tract infections, bed ulcer, and burn	(Fazeli and Momtaz 2014; Rafiee et al. 2014; Bokaeian et al. 2015)
Fecal carriage				
Egypt	TEM	Human	Chest wound swab, central venous line, Rectal swabs	(Khalaf et al. 2009; Fam et al. 2014)
Salmonella				
Turkey	SHV-12	Human	Neonate gastroenteritis	(Ağın et al. 2014)

Table 4 Epidemiology of beta lactamases resistance gene, OXA in Middle East.

			OXA	
Pseudomonas				
Yemen	OXA-10	Human	From burn wound swab	(Nasser et al. 2020)
Saudi Arabia	OXA-48	Human	Blood, Pus, Stool, Urine, Sputum, Endotracheal tube, Vaginal swab, Peritoneal fluid	(Khan et al.)
Turkey	OXA-10, OXA-14	Human	Urine, blood, sputum, bronchoalveolar lavage, abscess, wound swabs, endotracheal aspirate, throat swabs, catheter tips, one of each pleural and peritoneal fluid	(Aktas 2012; Er et al. 2015)
KSA	OXA-10	Human	Burn, sputum, pus, urine, Eye discharge, Blood	(Al-agamy et al. 2012; Tawfik et al. 2012)
Iran	OXA-10/OXA-4	Human	Burn wounds , Trashes, Urine, Blood, Feces, Sputum, CSF, trachea, blood cultures, lesion and sputum, bronchoalveolar lavage, trachea	(Mirsalehian et al. 2010; Alikhani et al. 2014; Farshadzadeh, Dokht 2014; Emami et al. 2015; Davodian, et al. 2016; Amirkamali et al. 2017)
E. coli				
Egypt	OXA-48, OXA-181 ,OXA-244	Human	Lower respiratory tract specimens, urine and pus or abdominal fluid of hospitalized patients with lower respiratory tract infections (LRTI), complicated urinary tract infections (cUTI), and complicated intra-abdominal infections (cIAI)	(El-kholy et al. 2020)
Egypt	OXA-2, OXA-10	Human	Urine, blood and wound swab	(Resistance et al. 2020a)
Turkey	OXA-48	Human	Blood culture	(Midilli 2020)
Saudi Arabia	OXA	Human	Blood	(Alqasim et al. 2019)
Egypt	OXA	human	Diarrheic patient	(Ramadan et al.)
Yemen	OXA-48 ,OXA-181	Human	Urine ,aspiration	(Alsharapy et al. 2019)
Egypt	OXA-181, OXA-1	Human	Sputum, vaginal secretion, stool, urine, burn swab, wound swab	(Soliman et al. 2019)

Table 4 (continued).

		OXA		
United Arab Emirate	OXA-181	Human	Urine and rectal swab	(Pál, Sonnevend 2019)
Saudi Arabia	OXA-48		Blood, Pus, Stool, Urine, Sputum, Endotracheal tube, Vaginal swab, Peritoneal fluid	(Khan et al.)
Egypt	OXA-7	broiler farms	Cloacal swabs	(Moawad et al. 2018)
Egypt .	OXA-30	Poultry	Heart blood samples, carcasses, urine, Sputum, pus samples	(Ahmed et al. 2013; Abdallah et al. 2015; Ramadan et al. 2018)
Turkey:	OXA-10	Human	Elderly male patient, urine, blood and wound	(Elaldi et al. 2013; Görgeç et al. 2015; Iraz et al. 2015)
Klebsiella				
Egypt	OXA-48, OXA-181 OXA-232	Human	Lower respiratory tract specimens, urine and pus or abdominal fluid of hospitalized patients with lower respiratory tract infections (LRTI), complicated urinary tract infections (cUTI),and complicated intra-abdominal infections (cIAI)	(El-kholy et al. 2020)
Palestine	OXA-1	Human	From urine, wound swabs, blood and ear discharge	(Tayh et al. 2020)
Turkey	OXA-48	Human	Blood culture	(Midilli 2020)
Yemen	OXA-48, OXA-232	Human	Ear swab and pus, Sputum	(Alsharapy et al. 2019)
United Arab Emirates:	OXA-48	Human	Rectal swab	(Moubareck et al. 2019)
Saudi Arabia	OXA-48	Human	Blood, Pus, Stool, Urine, Sputum, Endotracheal tube, Vaginal swab, Peritoneal fluid	(Khan et al.)
United Arab Emirate	OXA-181	Human	Blood and rectal swab	(Pál, Sonnevend 2019)
Egypt	OXA-10	Bovine	Milk samples	(Hammad and Shimamoto 2011)
Acinetobacter baumannii				
Iran	OXA -23	Human	Blood, tracheal aspirate, bronchial washing, sputum, abscess, wound, catheter, ascitic fluid and urine	(Rahbarnia et al. 2019)

Table 4 (continued).

		OXA		
Egypt	OXA 51, OXA-23 and OXA-143	Human	Wound, Burns, buccal cavity, skin and eye swabs	(El-baky et al. 2020)
Enterobacter cloacae				
Saudi Arabia	OXA-48	Human	Blood, Pus, Stool, Urine, Sputum, Endotracheal tube, Vaginal swab, Peritoneal fluid	(Khan et al.)
Turkey	OXA-48	Human	Blood culture	. (Midilli 2020)
Yemen	OXA-181	Human	Urine	(Alsharapy et al. 2019)
Morganella morgani				
Turkey	OXA-48	Human	Blood culture	(Midilli 2020)
Salmonella spp				
Saudi Arabia	OXA−1 and OXA−48	Human	stool and wound	(Desin 2019)

Table 5 Epidemiology of beta lactamases resistance gene, CMY in Middle East

		CMY		
Shigella				
Iran	CMY-2	Human	Stool culture, blood culture, urine, sputum, wound, respiratory and vaginal secretion, ascites, biopsies, body fluids, diarrhea	(Rizi et al. 2015; Bialvaei et al. 2016; Aminshahidi et al. 2017)
Israel	CMY-4 and CMY-2	Human	Rectal swab specimen	(Izdebski et al. 2013)
E. coli				
Egypt	CMY-2, CMY, CMY-TYPE, CMY-4, CMY4-2 and CMY-59	Human	Lower respiratory tract specimens, urine and pus or abdominal fluid of hospitalized patients with lower respiratory tract infections (LRTI), complicated urinary tract infections (cUTI),and complicated intra-abdominal infections (cIAI)	(El-kholy et al. 2020)
Egypt	CMY-6, CMY-42, CMY-72 like, and CMY-2	Human	Eye swab, urine, intraperitoneal fluid, pus swab, and blood	(Nations et al. 2019)
Egypt	CMY 2	Human	Sputum, vaginal secretion, stool, urine, burn swab, wound swab	(Soliman et al. 2019)
Lebanon	CMY	Swine farms	Fecal samples	(Dandachi et al. 2018a)
Lebanon	CMY	Farm chicken	Rectal swab	(Dandachi et al. 2018)
Egypt	CMY-2	Broiler farms.	Cloacal swabs	(Moawad et al. 2018)

Table 5 (continued).

			CMY	
Turkey	CMY-2	Dog	Rectal swabs from companion dogs	(Aslantas and Yilmaz 2017)
Egypt	CMY-2	Chicken, beef and dairy products	Meat, milk, cheese and yoghurt, Karish and Ras cheeses	(Ahmed, Shimamoto 2015; Ombarak 2018)
Kuwait	CMY-2	Human	(Unknown) patients in 3 hospitals, CSF, Wound swab	(Dashti et al. 2014; Jamal et al. 2015)
Egypt	CMY-2	Poultry	Heart blood samples, carcasses, urine, Sputum, pus samples	(Ahmed et al. 2013; Abdallah et al. 2015; Ramadan, H. H., Jackson et al. 2018)
Israel	CMY-4 and CMY-2	Human	Rectal swab specimen	(Izdebski et al. 2013)
Turkey	CMY-2	Human	Urine, Blood	(Demirbakan, H. 2008; Sari et al. 2013; Yilmaz et al. 2013)
Enterobacter				
KSA	CMY-2	Human	Wound, blood, respiratory and urinary tract specimen	(Abdalhamid et al. 2017)
Klebsiella pneumoniae				
Egypt	CMY-6, CMY-42, CMY-72 like, and CMY-2	Human	Eye swab, urine, intraperitoneal fluid, pus swab, and blood	(Nations et al. 2019)
Salmonella				
Saudi Arabia	CMY−2	Human	Stool and wound	(Desin 2019)
Egypt	blaCMY-2	Dairy calves	Diarrheic neonatal calves	(Ahmed et al. 2009)

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