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Article Review

Bovine Mastitis: Pathogen factors and antibiotic resistant genes "Article Review"

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ABSTRACT

Bovine mastitis is one of the most harmful diseases in the dairy herds worldwide. The prevalence rate of antimicrobial resistance (AMR) pathogens causing bovine mastitis increased rabidly all over the world causing high economic losses and public health hazard. Therefore, this review summarized the phenotypic and genotypic characterization of AMR in the main pathogens causing mastitis in Egypt and different countries in the world. Also some plans or recommendation programs to decrease and overcome AMR.

INTRODUCTION

Bovine mastitis, from the most harmful diseases in the dairy herds worldwide. The contributing pathogens for bovine mastitis include a variety of Gram-positive besides Gram-negative bacteria which can be contagious or environmental. Treatment of active mastitis infection depends primarily on antibiotics. However, the widespread use of antibiotics has a raised concerns about the emergence of antibiotic-resistant pathogens and the prevalence rate of antimicrobial resistance (AMR). Pathogens causing bovine mastitis increased rabidly all over the world causing high economic losses and public health hazard.

Bovine mastitis is an inflammatory response of the tissues in the mammary gland initiated by physical trauma or microbial infection. It considered the greatest common disease causing economic loss in the dairy industry due to low yields and poor milk quality **(Gomes Henriques, 2016)**. According to the degree of inflammation, bovine mastitis can be divided into three categories: clinical type, subclinical type and chronic mastitis.

Clinical mastitis in cattle is obvious and easily recognized by visible abnormalities such as redness and fever in the cow's udder and the milk looked watery with flakes and lumps **(Khan and Khan, 2006)**. While, subclinical mastitis has no obvious abnormalities in the udder or milk, but decreases milk production with an increase in somatic cell count (SCC) **(Abebe et al. 2016)**. Chronic mastitis is an inflammatory process that lasts for several months with irregular clinical onset **(Cheng Han, 2020).**

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Bovine mastitis cause high losses, in milk as it has to be discarded, together with the cost of treatment and other expenses **(Kumar et al. 2010)**. Antimicrobials are one of the main medications for management and treatment of mastitis, however, due to extensive use of antimicrobials, antimicrobial residues can be still in milk, causing the risk of bacteria to emerge and developed AMR in the consumers of milk or milk products **(Oliver Murinda, 2012)**. The largeness and improvement of the AMR problem caused it being highly significant for health policy producers worldwide, with many relatives that will affect the human health, animal health, and environmental county in the future. **(Juhász-Kaszanyitzky et al. 2007)**.

The incidence of resistant bacteria causing mastitis is higher, which might be due to uncritical use of antibiotics and intra mammary preparations containing combinations and broad spectrum antibiotics **2007)**. The continuous unsuccessful antibiotic treatment of the potential biofilm in mastitis infections increased the risk of antibiotic resistance **(Schönborn Krömker, 2016)**. More ever, other mechanisms for bacterial resistance include the presence of antimicrobial resistance genes which can spread from bacteria to another through horizontal transfer by the mean of mobile genetic elements such as plasmids, phages, and pathogenicity islands, or as a result of random mutations when the bacteria exposed to stress **(Pantosti et al. 2007)**.
The aim of this review is to summarize the most prevalent bacterial pathogens causing bovine mastitis and associated antimicrobial resistance (AMR). Furthermore, some references to overcoming AMR.

Bacterial causes of bovine mastitis:

Bacterial intra-mammary infection (IMI) is considered the leading cause of bovine mastitis. Depending on the bacterial source, bacterial infections can be divided into two categories: infectious or contagious and environmental. Contagious pathogens that own to live on the cow's udder and teat skin and can be transmitted between cows, especially during milking, such as *Staphylococcus aureus, Streptococcus agalactiae* and less common species such as *Mycoplasma bovis* and *Corynebacterium* that live in the udder, teats of cows or on the skin, colonizes and grows in the teat canal. Meanwhile, environmental pathogens are not usually present on the udder and teat skin of cows; instead, they are present in the bedding and housing of the flock. They are best described as opportunistic pathogens looking for a way to cause infection. They can enter the teat and cause clinical mastitis during milking or when the cow's natural immunity is weakened **(Bradley, 2002)**. A variety of bacteria have been reported to cause environmental mastitis, namely *Streptococcus* species. (eg *Strep. uberis),* coliforms (as eg *E. coli*, *Klebsiella spp.*, *Enterobacter spp.*), *Pseudomonas spp* and other bacteria **(Bogni et al. 2011)**.

Staphylococcus aureus

Staphylococcus aureus is the most common gram-positive pathogen known to be associated with various forms of clinical and subclinical mastitis **(Vasudevan et al. 2003)**. *Staphylococcus aureus* is considered as the main cause of clinical as well as subclinical bovine mastitis. It is usually exist as commensals on nares and skin, which may change to opportunistic pathogen causing superficial or invasive infections both in humans and animals **(Lowy, 1998; Foster Geoghegan, 2015)** . *Staphylococcus aureus* is a Gram-positive bacterium that is spherical in shape and tends to be arranged in "grape-like" clusters. These organisms can grow in the environments with up to 10 % salt, and their colonies are often golden or yellow in colour. These organisms can be grown aerobically or anaerobically (optionally) at temperatures between 18°C and 40°C. Typical biochemical identification tests include catalase positive, coagulase positive, and mannitol fermentation positive **(Rasigade Vandenesch, 2014)**.

Coagulase-negative *Staphylococci*

Coagulase-negative *Staphylococcus* (CNS), for example *Staph. epidermis, Staph. simulans*, *Staph. hyicus* , and *Staph. chromogens,* signifies an emerging mastitis pathogen that have been isolated from dairy cattle, they can behave as both contagious and environmental pathogens. Mastitis caused by CNS are comparatively mild, commonly remain sub-clinical and are associated with an elevated SCC and decreased milk quality **(Taponen Pyörälä, 2009)**.

Streptococcus **species**

Streptococcus is a genus of gram-positive cocci that tend to form pairs or chains. Most streptococci are oxidase-negative and catalase-negative, and many are facultative anaerobes **(Ray Ryan, 2004)**. *Streptococcus spp.* are of the major pathogenic bacteria present in dairy farms **(Forsman et al. 1997)**. *Streptococcal species*, mainly, *S. agalactiae*, *S. uberis* and *S. dysgalactiae*, are identified in clinical in addition to subclinical bovine mastitis **(Richards et al. 2014)**. *S. agalactiae* has been predictable as a very contagious obligate parasite of the bovine mammary gland, which generally does not survive for long times outside the mammary gland **(Keefe, 1997)**. It causes intra-mammary infections in cattle which usually are chronic and subclinical, with intermittent episodes of clinical mastitis **(Zadoks et al. 2004)**.

Escherichia coli

E. coli from the gram-negative bacteria which appeared as rod-shaped, non-spore former, facultative anaerobes, and coliform bacterium, that normally inhabits the environment, foods, and warm-blooded animals' lower gut **(Campbell Reece, 2002)** . It grow at 37°C, and takes as little as 20 min to reproduce in favourable environments, motile. Some strain possesses polysaccharide capsule **(Köhler Dobrindt, 2011)**. it can be easily cultured on a common medium, such as Nutrient agar, Mac Conkey agar, and EMB agar **(Fotadar et al. 2005)**.. *Escherichia coli* is a prominent cause of environmental, acute clinical mastitis in dairy cattle worldwide, *E. coli* constitute a highly heterogeneous group of commensal inhabitants of the gut; conversely, because of the flexibility of its genome **(Blum et al. 2017)**. This organism has developed into pathogenic strains which are capable of causing diseases, including bovine mastitis when it entered to the mammary gland through fecal contamination of the teat skin **(Richards et al. 2015)**.

Therapeutic *treatment* of bacterial mastitis

The main strategy for the treatment of mastitis is the use of antibiotics, such as penicillin, ampicillin, tetracycline, gentamicin, etc., which can be administered through intra-mammary infusion, intramuscular or intravenous injection **(Hossain et al. 2017)**. Antimicrobial susceptibility determined in vitro is taken into account as a qualification for treatment. Antimicrobial resistance of mastitis pathogens has not yet become a clinically relevant problem. However, geographic regions may vary in this regard **(Kibebew, 2017)**. At the present days, antimicrobial susceptibility tests revealed that gentamicin, enrofloxacin and ciprofloxacin showed the highest susceptibility to different bacterial isolates from milk of cows and buffaloes with mastitis **(Ali et al. 2021)**. Several studies have also reported the highest susceptibility of bacterial isolates from bovine mastitis to aminoglycosides, including gentamicin, kanamycin, gentamicin, neomycin, and tobramycin **(Han et al. 2022)**, fluoroquinolones such as enrofloxacin, and ciprofloxacin **(Alekish et al. 2013)**. In particular, the antibiotics gentamicin and enrofloxacin are included in the list of antibacterial drugs approved for veterinary use by the World Health Organization and the World Organization for Animal Health **(WHO, 2016)**.

Antimicrobial resistance in *Staphylococcus aureus*

β- lactams resistance: β-Lactams considered from the most successful drugs for the treatment of microbial infections caused by numerous species for the previous 60 years **(Coleman, 2011)**. The first β-lactam antibiotic drug introduced in the treatment was penicillin G in the first of 1940s, but by 1944 penicillin-resistant *Staphylococcus aureus* initiated to appear , mainly as a result of the production of β-lactamases enzymes **(Jovetic et al. 2010)**. Numerous strains isolated from mastitis infections have been described to show resistance against multiple antimicrobials such as penicillin-G (**Ahmed et al. 2020; Talaat et al. 2023)**.

MRSA : β-lactamase resistant penicillins such as methicillin and oxacillin are used for dairy cows in the products for intra mammary administration **(Turutoglu et al. 2006)**. Methicillin resistance *staphylococcus aureus;* MRSA has grown significance in veterinary medicine in the last 2 decades, as MRSA which show resistance not only for β-lactams but for additional classes of antimicrobials **(Baptiste et al. 2005)**. Several MRSA strains showed multi-drug resistance against different antimicrobial classes, this clarify the significance of the following efforts for controlling the antimicrobial resistance (AMR) and determination of the proper antimicrobial agent used in both the veterinary and public operations **(Saei, 2012).** MRSA had been isolated mastitis in dairy herds samples and retain the ability to complicate the treatment **(Javed et al. 2022) .**

Cephalosporins resistance : *S. aureus* isolated from mastitis cases have been stated to show a greater resistance rate for cephalosporins, cefotaxime and ceftiofur was reported by **Elias et al. (2020)**.

Tetracyclin resistance *:* *S. aureus* isolated from cases of bovine mastitis have been recorded to show resistance against oxytetracycline **(Rajagopal et al. 2016).** Recent studies also shown increased resistance against tetracycline among *S. aureus* **(Abdi et al. 2018);** and **Qu et al. (2019)** who reported that tetracycline resistance were higher in CNS than *S .aureus* isolates . In Nepal, **Shrestha et al. (2021)** stated that *S. aureus* isolates showed resistance with 48.3% to tetracycline and in Egypt **Talaat et al. (2023)** recorded higher resistance to tetracycline (73.3%).

Aminoglycosides resistance*:* The percentages of *S. aureus* resistant to aminoglycosides such as kanamycin, neomycin increased since 2015 **(Rossi et al. 2021)** and for gentamicin and vancomycin **(Majumder et al. 2023)**. Gentamycin resistance in *S. aureus* isolates from bovine mastitis was 43.5% in Egypt **(M.A. et al. 2018)**, and only (10.5%) by **Munive Nuñez et al. (2023)**.

Quinolone Resistance: Quinolones have been a widely used type of synthetic antimicrobials **(Kim and Hooper, 2014)**. With a concern to inherent or natural resistance, *Staph. aureus* showed reduced susceptibility to ciprofloxacin **(Rajagopal et al. 2016)**. In China**, Wang et al. (2022)** reported that quinolone resistance in *S. aureus* isolated from bovine mastitis with a prevalence rate of (36.23%) and it was the second resistant antibiotics detected after beta-lactams . Also quinolone resistance in *S. aureus* isolated from bovine clinical mastitis was reported by **Majumder et al. (2023)**.

Macrolides and Lincosamide resistance : High resistance to erythromycin was detected in *Staphylococcus aureus* associated with subclinical and clinical mastitis in Uruguay **(Santos et al. 2017)**. In German, Brazil and Argentina by **Monistero et al. (2020)**. *Staph aureus* isolates from cattle mastitis were resistant to macrolides with a percent of (34.08%) , and lincosamides (23.39%) **(Wang et al. 2022)**. High resistance to erythromycin recorded by **Rossi and Del Matto, (2023)**.

Genetic contributing factors for antibiotic resistance in *Staphylococci*

β- Lactam- resistance genes : Beta-lactams have been widely used in the treatment of *Staphylococcus* mastitis for several decades, but their efficacy is decreased as a result of β-lactamase synthesis by bacteria, which is encoded by *blaZ* **(Olsen et al. 2006)**. The *bla*Z gene encodes the PC1 β-lactamase coded for penicillin resistance both in *staph. aureus* and CNS species, and included isolates from mastitis **(Bolte et al. 2020)**. Lastly, a β-lactamase encoding gene, *bla*ARL, has been characterized in (CNS) isolated from bovine mastitis in Switzerland and Canada, they investigate it located on the chromosomal DNA with the regulatory genes *blaI*ARL and *blaR1*ARL **(Andreis Perreten, 2017)**.

MRSA Genes : Different β-lactam resistance mechanism, called methicillin/oxacillin resistance, is mediated by low-affinity penicillin-binding protein (PBP2a) encoded by *mecA* was investigated **(Sawant et al. 2009)**. Resistance to oxacillin and methicillin is mediated by the *mec*A gene, which encodes PBP2a, and its expression is controlled by the inducer-repressor genes *mec*R1 and *mec*I **(Blázquez et al. 2014)**. The *mec*A gene and its regulators are located on a cassette chromosome recombinase responsible for the movement of the system, in a mobile genetic element known as staphylococcal cassette chromosome *mec* (SCCmec) **(Elements, 2009)**.

The *bla* regulatory system can also regulate *mec*A, particularly when *mec*R1 and *mec*I are not present **(Liu et al. 2016)**. The incidence rate of *mec*C isolates in English and Welsh dairy farms was 2.15% **(Paterson et al. 2014)**. It has been shown that Africa, Latin America, and Asia recorded higher levels of oxacillin or cefoxitin resistance than Europe or North America **(Molineri et al. 2021)**. More ever, it have been identified that, CNS can express *mec*A genes in SCC*mec* elements and display resistance to oxacillin **(Xu et al. 2018)**.

Methicillin resistance caused by *mec*A is frequently detected in *Staphylococcus* spp. causing bovine mastitis **(Khazandi et al. 2018)**. Furthermore, 100% of *S. aureus* tested strains harbored *mecA* genes in Egypt **(Algammal et al. 2020)**.

Tetracycline resistance genes: Tetracycline resistance has been recorded in staphylococcus isolated from mastitis and it is principally related to the *tet*(K) and tet(L)genes, which code for membrane-associated efflux proteins and these are transmitted through plasmids **(Enany Alexander, 2017; Schwarz et al. 2018)**. Resistance gene tet(38) is encoded by a chromosomal efflux pump which can be overexpressed by plasmid **(Truong-Bolduc et al. 2014; Chen Hooper, 2018)**. Furthermore, the *tet*(M) gene is frequently detected and codes for a ribosome-protective protein, it is usually found on the conjugative transposons Tn916-Tn1545 **(Schwarz et al. 2018)**. *Staph. aureus* isolates from bovine mastitis were contained the *tet*M, *tet*K, and *tet*L genes, respectively, with each gene found alone or in combination **(Jamali et al. 2014)**. Tetracycline resistance genes were identified in *S. aureus* and CNS from dairy farms in Switzerland **(Frey et al. 2013)** , China **(Qu et al. 2019)** and Australia **(Lima et al., 2020)**. In Egypt *tet*K gene was detected in *Staphylococcus aureus* isolates **(Ahmed et al. 2020)** , Moreover **Abo-Shama et al. (2022)** and **Talaat et al. (2023)** reported that *tet*K gene was detected with a percent of 50% in *S. aureus* isolated from clinical and subclinical mastitis in dairy cows

Aminoglycoside resistance genes: Resistance to aminoglycosides can be mediated through several genes that code for inactivating enzymes in staphylococci. The gene *aph*A3 is codes for phospho transferases and it is referees resistance to kanamycin, amikacin and neomycin. While, *aac*A*aph*D which codes for acetyl trans-ferase and phospho-transferase which conversing resistance to gentamicin, kanamycin and topramycin **(Schwarz et al. 2018)**.

Aminoglycoside resistance genes can be localized on a plasmid, transposon, or on the bacterial chromosome. *The gene aph*A3 was detected in CNS from bovine mastitis with higher rate than *Staph. aureus* isolates, while *aac*A-*aph*D gene was found in *Staph. aureus* **(Qu et al. 2019)**. Furthermore, the *aad*E, *ant* (6)-Ia, and *str genes* code for streptomycin resistance, and they have been detected in *Staph. aureus* and CNS isolates from mastitis **(Antók et al. 2019)**.

Quinolones resistance genes : Quinolone resistance occur due to mutation or acquisition of resistance-conferring genes. Resistance mutations occur in one or both of the two drug target enzymes , DNA gyrase (GyrA , and GyrB) and DNA topoisomerase IV (composed of 2 ParC and 2 ParE), that decrease the drug binding to the enzyme-DNA complex. Another resistance mutations happen in the regulatory genes which control the expression of efflux pumps . Also , plasmid-mediated resistance is due to the *Qnr* proteins which protect the target enzymes from the quinolone action **(Hooper Jacoby, 2015)**. Quinolone resistance in *S. aureus* from mastitis was reported to be essentially due to the expression of a *Gyr*B protein **(Nobrega et al. 2018).** Fluoroquinolone resistance in bovine mastitis isolated *S. aureus* recorded by **Neelam et al. (2022)**. The gene *mepA* coding for fluoroquinolone resistance was identified for the first time in *Staphylococcus. aureus* from bovine mastitis by **Pérez et al. (2020)**.

Macrolides and Lincosamides resistance genes : Concurrent resistance to macrolides and lincosamides is mainly due to the acquisition of the erythromycin ribosome methylase (*erm*) genes **(Roberts, 2008)**. About 35 *Erm* methylases genes were identified indifferent bacterial species **(Schwendener Perreten, 2012)**. Only 10 genes from which [*Erm*(A), *Erm*(B), *Erm*(C), *Erm*(F), *Erm*(G), *Erm*(Q), *Erm*(T), *Erm*(Y), *Erm*(33), and *Erm*(43)] have been identified on plasmids, transposons, or the integrated elements on the different species of *Staphylococcus* **(Roberts, 2008; Schwarz et al. 2011)**.

The genes *erm*(B) and *erm*(C) have been founded in *Staph. aureus* and CNS isolated from mastitis **(Li et al., 2015)**. While *erm*T gene has been reported to be more common in *Staph. aureus* than CNS from bovine mastitis **(Qu et al. 2019)**. Different mechanisms for macrolide resistance caused by an efflux pump from ABCF sub family protein and coded by *msr*, *mph*, *ere*, *Inu*, vga, *lsa*, or *sal* genes. *msr* (A) and *msr*(B), and other gene B. *mph*(C) phospho-transferase which inactivates some macrolides antibiotics, and *ere*(A) that codes for an esterase and hydrolyzes the macrocyclid nucleus **(Schwarz et al. 2018)**. Most of these resistance gene to macrolide were detected in *Staph. aureus* and CNS isolated from mastitis **(Antók et al. 2019)**. The gene *erm*C/T , *erm*C/ T and *erm*B were recorded in *Staphylococcus aureus* from clinical mastitis **(Rossi Del Matto, 2023)**.

Antibiotic resistance in *Streptocccu*s *species*

Macrolides and lincosamides resistance : Resistance of *streptococci* for erythromycin (ERY) firstly appeared in the USA and Europe, with an incidence rate between 20% and 50% **(Sadowy et al. 2010)** , whereas in Brazil, it did not exceed 10%**(Palmeiro et al. 2010)**. It is also detected in *Strep. agalactiae and Strep. dysgalactiae* isolated from bovine mastitis by **Rato et al. (2013)** and **Haenni et al. (2018)** .

Tetracycline resistance: The wide spread use of tetracycline lead to its addition in the resistance list of many bacteria, including *streptococci* . Primarily, tetracycline resistance of *Streptococcus* species was recorded in *Strep. uberis* in French dairy farms science 2006 to 2016 **(Boireau et al. 2018)**. After that, the resistance spread between *streptococcal* species, with a higher resistance frequency rate in *Strep. dysgalactiae* **.**

Aminoglycoside resistance: Aminoglycoside resistance have been detected in *Strep. uberis* and *Strep. dysgalactiae* with low incidence rate (**Kaczorek et al. 2017)** and in Egypt by **Ahmed et al. (2020)**. In Emilia Romagna region (Northern Italy) all *S. agalactiae* isolates from dairy farms were resistant to aminoglycosides **(Carra et al. 2021)**. In China *Streptococcus agalactiae* isolated from mastitis milk samples showed gentamycin resistance **(Zhao et al. 2022)**.

β- lactams Resistance: Penicillin was the first drug of choice used for prevention and control of group B *streptococcal* (GBS); however, improved resistance of GBS to penicillin has been occasionally reported since 1994 **(Seki et al. 2015)**. and in North China by Tian et al., who isolated streptococci from mastitis with 100% resistance rate to penicillin **(Tian et al. 2019)** . **Guo et al. 2018;** mentioned that *Streptococci* have been presented to be highly resistant to penicillin **(**as cited in **Han et al. 2022)**. Also, **Han et al. (2022)** reported that *agalactiae* isolated from Chinese dairy cows with clinical mastitis show high resistance rate to β-lactams (penicillin, amoxicillin, ceftazidime, and piperacillin) with a percentage up to 98.1%.

Genetic contributing factors of antibiotic resistance in *Streptococcus* Species

Macrolides and Lincosamides resistance grenes : Macrolides and lincosamides phenotypic resistance in Gram-positive bacteria, including streptococci occurred due to the ribosomal modification, antibiotic efflux, and drug inactivation . Erythromycin and Lincosamide resistance phenotypes incorporated to macrolide lincosamide streptogramin$_B$ (cMLS$_B$) resistance MLS$_B$ resistant phenotypes of either constitutive or inducible rather than M phenotype and/or L phenotype alone as previously recorded **(Brzychczy-Włoch 2010).** The ermB gene was the most commonly characterized genes that result in a macrolide and lincosamide resistant phenotype, however other genes such as mef, msr, or mre families, code for efflux pumps, are also characterized **(Haenni et al. 2018; Saed Ibrahim, 2020)**.

Tetracyclines resistant genes : Genes involved for tetracycline resistancein *Streptococcus* comprise, membrane efflux systems [*tet* (K) , *tet*(L)], and ribosomal protection enzymes *tet*(M), *tet*(O), *tet*(S) **(Haenni et al. 2018).** The gene *tet*(M) is the most commonly found in *Strep. uberis*, *Strep. agalactiae*, or *Strep. Dysgalactiae* isolated from France , Brazil **(Duarte et al. 2005),** in Canada **(Reyes et al. 2019),** Poland **(Kaczorek et al. 2017),** Argentina , and in China **(Tian et al. 2019) .** In Egypt by **Ahmed et al. (2020)**

Aminoglycoside resistance genes : Resistant genes to aminoglycosides such as *aph*A-3 and *aad*-6 have been recorded in *Strep. uberis* and *Strep. dysgalactiae* but with low frequencies **(Kaczorek et al. 2017; Ahmed et al. 2020).** Yang et al. detected that the rates of aminoglycoside resistance genes in *S. agalactiae* (*ant* (3')-I and *aac* (6')-Ib were 75.0%, and 31.3%, respectively **(Yang et al. 2018)**.

β - lactams resistance genes *:* Guérin-Faublée et al.,(2002) said that β-lactam resistance in *streptococcus* species isolated from bovine mastitis is commonly low as they cannot effectually attain exogenous β-lactam resistance genes. Even though, reduced sensitivity, or resistance, has been recorded in certain studies but with low frequency**.** Latest investigation in Canada revealed a higher incidence of penicillin and ampicillin resistance in *Streptococcus* which species is indicated by the presence of bl2b gene in *Strep. uberis* and *Strep. dysgalactiae* **(Kaczorek et al. 2017)**, in addition to TEM genes including (TEM-1, TEM-127, TEM-136, TEM-157, TEM-163, TEM-47, TEM-89, and TEM-95 in *Strep. uberis* and TEM-71, TEM-1, TEM-136, TEM-157, and TEM-47 in *Strep. dysgalactiae* were charactrized by **Vélez et al. (2017).** Resistance of β-lactam in *Streptococcus* species can be acquired due to mutation (substitutions) at the penicillin binding proteins **(McDougall et al. 2020)**

Antimicrobial resistance in *E. coli* and *Kellepsiella* :

β- lactam resistance: The incidence rate of ESBLs increases in different parts all over the world. This could be explained and clarified the fact that resistance genes are commonly carried on plasmids that can be transmitted from strain to another and between bacterial species, increasing their prevalence. The percentage of ESBL-*E. coli* grow and raised from 33.2% in 2008 to 48.83% in 2013 **(Tekiner and Özpınar, 2016)**. In Egypt and Germany, the incidence of ESBL-producing *E. coli* associated with cattle mastitis was 17% **(Ibrahim et al. 2018)** and 39.3% **(El-Mohandes et al. 2022)** respectively .

Cephalosporin resistance : It was stated that , all of ESBL-producing *E. coli* were multidrug-resistant and displayed resistance to cephalosporins **(Ombarak et al. 2019)**. High proportion of ceftiofur- and cefotaxime-resistant *E. coli* isolates from bovine mastitis **(Yakovlieva Bahlai, 2019)**. In Egypt cephalosporin resistance also detected by **Ali et al.(2017)** and **Ahmed et al. (2021)**, resistant of *E. coli* to aztreonam, cefotaxime, ceftazidime and ceftriaxone was recorded by **Campos et al. (2022)**.

Colistin resistance : Colistin is presently known as the last-alternative antimicrobial agent for the treatment of infections caused by MDR Gram-negative bacteria **(Poirel et al. 2017)**. Colistin has been significantly utilized in the agricultural and veterinary medicine for decades, also as a growth promoter and in the treatment of enteric -bacterial infections **(Catry et al. 2015)**. So, the extensive colistin using in livestock lead to the rapid spread of the mcr resistance genes **(Chen et al. 2019)** .

Colistin-resistant *E. coli* have been appeared in dairy farms **(Brennan et al. 2016)**. High level of correlation was detected between ESBL- and colistin-resistance in *E. coli* from bovine mastitis **(Shafiq et al. 2021; Dhaouadi et al. 2023)**.

Tetracycline resistance : Tetracycline resistance were observed in *E. coli* from Holstein dairy cattles in New York State throughout 1999–2000 **(Srinivasan et al. 2007)**, and from mastitis (**Supré et al. 2014)**, and reached to (15.93 %) by **Majumder et al. (2021)**, (23.1%) in *E. coli* isolated from mastitis in dairy cattle in France in the period from 2006-2016 by **(Boireau et al. 2018)** and 48% by

Das et al. (2017) . Meanwhile, high prevalence rate of resistance for tetracycline was observed in *Klebsiella spp.* and *E. coli* isolates from subclinical mastitis showed resistance to Tetracycline (91.2%) **(Ahmed Shimamoto, 2011**)

Aminoglycosides resistance: Aminoglycosides are a significant class of antimicrobials that are commonly used, alone or in combination with the β-lactams, in treatment of severe infections occurred by Gram-negative bacteria **(Ramirez Tolmasky, 2010)**. Aminoglycosides resistance has been progressively reported by **Fernández-Martínez et al. (2015)** and **Fernández-Martínez et al. (2018)**. In Egypt *E. coli* isolates showed resistance for kanamycin and streptomycin **(Ombarak et al. 2019)** , and reach to 71.4% for amikacin, by **Ahmed et al. (2021)** and (72%) for gentamycin by **Abed Menshawy, (2021)**.

Quinolone resistance: Quinolones from the effective antimicrobial agents used in treatment of several infections caused by *E. coli* in veterinary medicine. Quinolone resistance in gram-negative bacteria has been increased all over the world, predominantly *E. coli* **(Robicsek et al. 2006; Xiao et al. 2011)**. Quinolone-resistant have been increased in *E. coli* in food-producing animals because of extensive usage of quinolones **(Zhao et al. 2014**)

Genetic contributing factors for antibiotic resistance in *E. coli* and *Kellepsiella*

β-lactam resistance genes : Resistance to β-lactams is certainly the most found in *E. coli and K. pneumonia* isolates from bovine mastitis. In *E. coli*, TEM, SHV, and CTX-M types are the most common ESBLs genes were detected in dairy farms isolates **(Liebana et al. 2013)**. TEM-1 , SHV-1 and SHV-2 β-lactamases inactivate penicillins and narrow-spectrum cephalosporins **(Hazards, 2011)**.

Their achievement is probably due to their easy spreading through plasmids and other mobile genetic elements **(Tooke et al. 2019)**. *bla*TEM-1 has been revealed to be detected in *E. coli* isolates from mastitis in China **(Yu et al. 2015)** , Greece **(Filioussis et al. 2020)**, and Canada **(Majumder et al. 2021)**, and in *K. pneumonia* from Egypt **(Ahmed Shimamoto, 2011)**. SHV-1 and 2 enzymes carried by plasmids and they are less common, although *bla*SHV-1 was detected in *K. pneumonia* mastitis strains from the United States **(Zhang et al. 2022)** or *E. coli* from China **(Ali et al. 2016)**, and *bla*SHV-1 and *bla*SHV-2a in *K. pneumoniae* from Indonesia **(Sudarwanto et al. 2015)**. Multidrug resistance was observed in *E. coli* isolates, these isolates carried one or more blaCTX-M and AmpC ESBL genes **(Tark et al. 2017)**. *blaTEM*, *blaCTX-M*, and *blaSHV* were detected also by **Tekiner and Özpınar, (2016)** and **Kamaruzzaman et al. (2020)**. Many sub-groups of *blaCTX-M* were detected in *E. coli* such as (blaCTX-M-1, blaCTX-M-2, blaCTX-M-8, blaCTX-M-9, blaCTX-M-15 , blaCTX-M-25) by **Ali et al. 2017; Różańska et al. 2019**. Since the year 2000, *blaCTX-M8* gene described firstly in *Enterobacteriaceae* resistant to cefotaxime in Brazil **(Bonnet et al. 2000)**. Then, it has been frequently identified in *E. coli* isolates from South America , North America , Africa, Asia (Japan) and in Europe **(Aizawa et al. 2014)**.

In China by **Ali et al. (2016)**, and in Egypt by **Ahmed et al. (2021)** and **El-Mohandes et al. (2022).** In *K. pneumoniae* SHV and CTX-M β-lactamases are widely detected in more than one country such as France, Jaban, Italy, Indonesia, Brazil **(Sudarwanto et al. 2015; Nobrega et al. 2021)**.

AmpC genes hydrolyze cephalosporinases and cephamycins and not sensitive to β-lactam inhibitors. In *E. coli* AmpC genes are mediated by chromosome , while in Klebsiella spp. or these genes are mediated only by plasmid transfer . AmpC genes were detected in *E. coli* from bovine milk **(Tark et al. 2017; Abboud et al. 2021)**

Tetracyclines resistant genes : Tetracyclines resistant genes in *E. coli* are often carried by plasmid **(Poirel et al. 2018)** . The most predominant genes of tetracycline resistance are *tet*(A) , *tet*(B), or combination of both can be detected in *E. coli* isolates **(Lan et al. 2020; Majumder et al. 2023)**. Tetracycline resistance gene mainly (*tet*A) was detected in 100% of the tetracycline resistant *E. coli* Isolated from mastitis in dairy farms of Bangladesh **(Bag et al., 2021)**. More ever *tet(E), tet (G)* genes, and *tet(D)* were determined from bovine mastitis in Jordan by **Ismail Abutarbush, (2020)**. In *K. pneumoniae*, *tet*(B) and *tet* (D) genes were determined **(Zheng et al. 2022)**.

Aminoglycosides resistance genes: The most common mechanism for aminoglycoside resistance in family Enterobacteriaceae is the enzymatic modification **(Ramirez Tolmasky, 2010)**. The genes aaC(3)-II/IV and aaC(6)-Ib code for aminoglycoside N-acetyltransferases are the most common in *E. coli* **(Messele et al. 2019)**. *E. coli* isolates carried at least one aminoglycoside resistance determinant gene such as *aad*A1*, aad*A4*, aac*6*-aph*2*, aph*A*, str*A and *str*B genes **(Ahmed et al. 2021)**. It was reported that *aad*A gene had a high frequency in *E. coli* isolates from mastitis in Egypt **(Fazel et al. 2019)**. Aminoglycosides resistance gene *aad*A2 was detected by the first time in Canadian cattle from mastitis **(Majumder et al. 2021)**. More ever *arm*A gene detected by **Xu et al. (2023)** in China.

Quinolone resistance genes : Plasmid-mediated quinolone resistance (PMQR) genes can be transferred between bacterial species **(Correia et al. 2017)**. In Algeria multidrug-resistant *Escherichia coli* from dairy cows milk with clinical mastitis harbored *qnr*B and only one isolate harbored *qnr*A **(Tahar et al. 2020)**.

In Egypt quinolone resistance-associated genes *qnr*A1 and *qnr*S were found in lower frequency **(Ahmed et al. 2021)**. For quinolone resistance in *E. coli* derived from bovine clinical mastitis, the incidence rates of *oqx*A and *qnr*S genes were 37.2% and 29.5%, respectively **(Xu et al. 2023)**.

Colistin resistance genes : Colistin resistance genes coded by *mcr-1* gene has been detected in raw milk *Escherichia* coli isolates by **Hassen et al. (2019)** and from bovine mastitic milk in China and Greece **(Liu et al. 2020)**. Colistin-resistant genes *mcr‑(1–9)* were charactrized in *E. coli* of bovine mastitis **(Shafiq et al. 2021)**. Furthermore colistin resistance, mcr-1 detected by **Dhaouadi et al. (2023)**.

Overcoming and control of AMR in bovine mastitis

Earlier application of the antibiotic sensitivity test is recommended to select the appropriate antibiotic drug, avoiding time leftover and high costs, also to reduce the multidrug resistance incidence. Also, monitoring antimicrobial resistance patterns of bacterial isolates from mastitis infections is important for the treatment decisions and selection. The sensible use of antimicrobials in dairy farms reduces the occurrence, persistence, and spread of antimicrobial-resistant bacterial strains from farms animals to, humans, and the environment **(Talaat et al. 2023)**.

Dry cow therapy, planned culling and distinct biosecurity protocols are effective and actual measures to control and prevent the restoration of other virulent strains causing bovine mastitis such as *S. aureus and S. agalactiae* . Also, correct combination of antibiotic treatment and culling of unresponsive cows may showed decline in the transmission and reduction of the rate of infection **(Halasa, 2012)**. Several approaches of conventional and advanced therapeutic measures are presented for management and control of mastitis, which include antibiotics, vaccination, herbal therapy, nanoparticle-based therapy, and bacteriocins **(Gomes Henriques, 2016)**.

The National Action Plan to Combat Animal Origin Antimicrobial Resistance (2017–2020) (Beijing: China Ministry of Agriculture and Rural Affairs, 2017) is a national protocols to regulate and standardize veterinary medications in combination with strict biosecurity measures and careful use of antimicrobials to aggravate the risk of resistant pathogen transmission **(Wang et al. 2022)**.

Particular research studies on the antimicrobial sensitivity of mastitis pathogens are essential for controlling the induced resistance and to obtaining useful information for effective therapeutic decisions **(Denamiel et al. 2005)**. Characterization of pathogenic strains causing bovine mastitis and investigation are important to obtain data and information that permits evaluation of the level and advancement of antimicrobial resistance **(Góchez et al. 2019)**.

Decreasing the use of antimicrobials to stop the development of different resistant strains, regulation of veterinary medicine products and regulation of medicated feed. Reduce the antimicrobials using in animal health sector , presenting a new restrictions, and the potentials to reserve confident antimicrobials for human use only **(Simjee Ippolito, 2022)**.

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