

Antimicrobial Resistance in Bovine Mastitis Pathogens with Special Reference to Egyptian Situation: A Review

Kareem A. Elhossary¹, Ahmed Elsify², Mohamed Nayel², Akram Salama², Walid Mousa², Mai A. Dawoud³, Eman M. Sharaf¹ and Ahmed Zaghawa^{2*}

(1) Bacteriology, Immunology and Mycology Department, Animal Health Research Institute, Shebin EL-Kom, Menoufia (ARC), Egypt.

(2) Department of Animal Medicine and Infectious Diseases. Faculty of Veterinary Medicine. University of Sadat City. Sadat City. Menoufia, Egypt.

*Corresponding author: ahmed.zaghawa@vet.usc.edu.eg Received: 12/1/2025
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ABSTRACT

The most problem affecting dairy cows, causing considerable financial losses, is udder inflammation. It is regarded as the most crucial and costly disease impacting the dairy industry, lowering the quality and quantity of milk. The rise of bacterial strains resistant to antibiotics makes it difficult to treat cow mastitis. An emerging problem is the rise in antibiotic resistance in various bacterial pathogens. Antimicrobial resistance is an escalating danger as new and emerging resistance mechanisms are surfacing and disseminating worldwide. Antibiotic susceptibility is a crucial instrument in managing bovine mastitis. Bovine mastitis was commonly managed with various commercial antibiotics; the regular application of antibiotics has occasionally been unsuitable for an extended period. This review outlines the antimicrobial resistance responsible for bovine mastitis, with particular emphasis on Egypt. Genetic factors identified globally in *Staphylococcus* spp., *E. coli*, and *Klebsiella*.

Keywords: Mastitis, Dairy cows, AMR, Antibiotic resistance.

1. INTRODUCTION

Various microorganisms, such as fungi and bacteria, have been associated with cow mastitis as contributing factors (Krukowski & Saba, 2003). A common issue impacting high-producing dairy cows, leading to considerable financial losses and diminishing milk's technological quality, is the udder's inflammation (Kalińska et al., 2017). Inflammation of the mammary glands parenchyma affects milk chemical and physical composition (Redistils et al., 2000). Changes in the udder's color

and texture and physical, chemical, and microbiological changes in the milk are indicators of clinical mastitis. Subclinical mastitis is characterized by an elevated somatic cell count in milk; it is diagnosed in the lab setting with specialized assays such as California mastitis test (Brennecke et al., 2021; Constable et al., 2017; Hoque et al., 2015 and Mungube et al., 2005).

S. aureus, *Streptococcus agalactiae*, and *Mycoplasma* spp., causing contagious mastitis, as well as *E. coli*, *Enterococcus faecalis*, *Streptococcus*

dysagalactiae, and coagulase-negative *Staphylococci* causing environmental mastitis (Keane et al., 2013). In recent years, much of the research in the dairy field has concentrated on managing mastitis, with numerous attempts underway to develop alternative and effective treatments (Gomes & Henriques, 2016). Antibiotic susceptibility is a crucial method in managing bovine mastitis. Bovine mastitis was often managed with various commercial antibiotics; the frequent application of antibiotics has occasionally been unsuitable over an extended period. The rise of antibiotic resistance has been observed in numerous bacterial pathogens (Robert et al., 2006). This review seeks to encapsulate the existing state of antimicrobial resistance found in the primary pathogens responsible for bovine mastitis, with particular emphasis on Egypt. Genetic factors are identified in *Staphylococcus* spp., *E. coli*, and *Klebsiella pneumoniae* worldwide.

Genetic Factors Influencing Resistance in Mastitis Pathogens:

Gram-Positive Microbes The primary gram-positive microorganisms that cause mastitis infections belong to the *Staphylococcus* genus. It has been reported that *Staphylococcus* spp. become resistant to several antimicrobial classes, including trimethoprim, tetracyclines, aminoglycosides, macrolides, and β -lactams (Wendlandt et al., 2013a; Nobrega et al., 2018b).

Resistance to β -Lactams.

The genetic foundations for resistance to the β -lactam antibiotics penicillin and methicillin vary in their genetic components and cellular locations, yet their regulatory mechanisms exhibit certain similarities. The *blaZ* gene

encodes the PC1 β -lactamase that is accountable for penicillin resistance in *Staphylococci*, including mastitis isolates like *Staph. epidermidis*, *Staph. haemolyticus*, or *Staph. Chromogenes* (Nobrega et al., 2018a; Bolte et al., 2020b). The *blaZ* gene is located within the transposon Tn552, a mobile genetic element that presents in the bacterial chromosome or a plasmid, and is controlled by two genes, *blaR1* and *blaI*, organized within the *blaZ*-*blaR1*-*blaI* operon (Olsen et al., 2006; Llarrull & Mobashery, 2012) and (Blázquez et al., 2014).

Resistance against Tetracyclines.

The tetracycline resistance in staphylococcal spp. obtained from mastitis samples is mainly associated with the *tet(K)* and *tet(L)* genes, which are carried by plasmids (Enany & Alexander, 2017). These genes were identified in *Staphylococci* obtained from dairy farms in Switzerland (Ali & Shrief, 2016; Qu et al., 2019; Lima et al., 2020).

Resistance to Aminoglycosides.

It may be facilitated by various genes that encode for inactivating enzymes in staphylococcal spp.. The gene *aphA3* encodes phosphotransferase and contributes to resistance against kanamycin, neomycin, and amikacin. In comparison, *aacA-aphD* encodes an acetyltransferase and phosphotransferase, providing resistance to gentamicin (Schwarz et al., 2018).

Resistance genes to antibiotics in *S. aureus* found in Egypt.

Multiple studies were carried out on mastitis in Holstein cows to assess the susceptibility of *S. aureus* isolates to various antibiotics for identifying antibiotic-resistance genes. A total of

415 Holstein dairy cows were randomly chosen from three governorates in Egypt (Damietta, Sharkia, Dakahlia). Chosen cows were assessed for mastitis between October 2014 and June 2018. The occurrence of *S. aureus* derived from milk samples was 15.4%, with 14.3% in clinical

instances and 15.7% in subclinical instances. The molecular PCR test showed that all 16 *S. aureus* isolates (100%), whereas 15 (93.7%) had the *blaZ* gene; conversely, 8 (50%) possessed the *tetK* gene (Talaat et al., 2023).

Table 1. Incidence of *S. aureus* antibiotic resistance genes in the governorates of Damietta, Sharkia, and Dakahlia.

	Locality	Target Genes	%	Oligonucleotide primers References
<i>S. aureus</i>	Damietta, Sharkia, and Dakahlia	<i>blaZ</i>	93.7	(Bagcigil et al., 2012).
		<i>mecA</i>	100	(McClure et al., 2006).
		<i>tetK</i>	50	(Duran et al., 2012)
		<i>fexA</i>	0.06	(Kehrenberg & Schwarz, 2006)

mecA: Methicillin resistance gene.

blaZ: lactams resistance gene.

Research carried out to investigate the incidence and pathogens responsible for subclinical mastitis (SCM) in North Upper Egypt (Beni-Suef, El-Fayoum, and Giza), indicating that the isolation rate in subclinical mastitis was 90.4%. The bacterial isolates most frequently

identified were *E. coli* (49.8%), *S. aureus* (44.9%) and *Streptococci* (44.1%). *mecA* and *blaZ* genes were detected in 60% and 46.7% of *S. aureus* isolates, respectively (Abed et al., 2021), employing primers listed in (table 2).

Table 2. Incidence of *S. aureus* antibiotic resistance genes in the governorates of Beni-Suef, El-Fayoum, and Giza.

	Locality	Target Genes	%	Oligonucleotide primers References
<i>S. aureus</i>	Beni-Suef, El-Fayoum and Giza	<i>mecA</i>	60	(McClure et al., 2006)
		<i>blaZ</i>	46.7	(Duran et al., 2012)

mecA: Methicillin resistance gene and *blaZ*: lactams resistance gene.

During the investigation of mastitis in Menoufia Governorate, Egypt, the study concentrated on its phenotypic and genotypic traits. Out of 500 lactating cows, 140 (28%) milk samples were positive for the California Mastitis Test (CMT). A sensitivity assessment of 9 antibiotics revealed resistance for penicillin

(90.69%), oxacillin (81.39%), chloramphenicol (58.14%), and tetracycline (53.48%). Furthermore, fifteen isolates were selected to identify antibiotic-resistance genes in *S. aureus* strains. The *mecA* gene was the most prevalent (100%), followed by *blaZ* gene (80%), *tetK* gene (66.7%), and *ermB* gene (40%),

whereas the *vanA* gene was absent (Abdeen et al., 2021) .

Table 3. Incidence of *S. aureus* antibiotic resistance genes in El-Menoufia Governorate.

	Locality	Target Genes	%	Oligonucleotide primers References
<i>S. aureus</i>	Menoufiya	<i>mecA</i>	100	(McClure et al., 2006)
		<i>blaZ</i>	80	(Duran et al., 2012)
		<i>tetK</i>	66.7	(Duran et al., 2012)
		<i>ermB</i>	40	(Schlegelova et al., 2003)
		<i>vanA</i>	0 No detection	(Patel et al., 1997)

mecA: Methicillin resistance gene, *blaZ*: lactams resistance gene, *tetK*: tetracycline resistance genes, *ermB*: macrolides resistance genes and *vanA*: vancomycin resistance genes.

Out of the 444 cow milk samples, *S. aureus*: 296 (66.6%), *Enterococcus* spp.: 230 (51.80%), *E. coli*: 210 (47.29%), and *Streptococcus agalactiae*: 106 (23.87%) were

isolated. Resistance to antimicrobials. Through PCR, pertinent resistance genes were discovered (Youssif et al., 2021).

Table 4. Incidence of *S. aureus* antibiotic resistance genes in Fayoum Governorate

	locality	Target Genes	%	Oligonucleotide primers References
<i>S. aureus</i>	Fayoum	<i>tetK</i>	100	(Duran et al., 2012)
		<i>blaZ</i>	100	(Duran et al., 2012)
		<i>mecA</i>	100	(McClure et al., 2006)

mecA: Methicillin resistance gene, *blaZ*: lactams resistance gene, *tetK*: tetracycline resistance genes

A total of 285 milk samples were gathered from (150 cows and 135 buffalo) maintained by small-scale farmers throughout various governorates of Egypt, such as Giza, Fayoum, and Beni-Seuf. Examination revealed that 34 (22.7%) milk samples from cows and 36 (26.7%) from

buffalo exhibited clinical mastitis. *S. aureus* were obtained 14 (41.2%) from cattle and 17 (47.2%) from buffalo. The resistance genes detected were 64.5% (*ermB*), 70.9% (*ermC*), and 9.6% (*msrA*) (Abd El-Razik et al., 2023) .

Table 5. Incidence of *S. aureus* antibiotic resistance genes in the governorates of Cairo, Giza, Kalyobia, Fayoum, and Kafr El-Sheikh.

	Locality	Gene Target	%	Oligonucleotide primers References
<i>S. aureus</i>	Cairo, Giza, Kalyobia, Fayoum, and Kafr El-Sheikh	<i>ermA</i>	9.6	(Martineau et al., 2000)
		<i>ermB</i>	64.5	(Martineau et al., 2000)
		<i>ermC</i>	70.9	(Martineau et al., 2000)
		<i>ermT</i>	19.3	(Feßler et al., 2010)
		<i>msrA</i>	9.6	(Aktas et al., 2007)

Genetic factors contributing to resistance in mastitis-causing pathogens: *E. coli* and *Klebsiella* spp.

E. coli, which causes mastitis in cows, can lead to mastitis in cattle, especially during calving or early lactation because of the immunosuppression occurring at these times. Infections may lead to serious clinical mastitis and can occasionally recur, but they are generally of shorter duration compared to those caused by different pathogens, and many do not require treatment (Blowey & Edmondson, 2010). *Klebsiella*, though not often isolated, can still lead to severe clinical mastitis that results in significant inflammation and necrosis of the mammary gland (Schukken et al., 2012).

Resistance against β -Lactams.

Resistance to β -lactams is likely the most commonly observed in mastitis. β -Lactamases are enzymes that can break down chemical substances containing a β -lactam ring. Numerous enzymes utilize various hydrolyzing methods and possess unique functional abilities (Bush, 2018) (EFSA, 2011). The present study has recognised

CTXM, SHV, or TEM (ur Rahman et al., 2018).

The blaCTX gene has been discovered in many *E. coli* and *Klebsiella* spp. isolates associated with mastitis from various locations worldwide. Additional instances of ESBL identified in *E. coli* comprise CTX-M-1, CTX-M-2, CTX-M-3, CTX-M-14, CTX-M-55, CTX-M-96, and SHV-12 from countries such as Germany, Switzerland, Japan, France, or Colombia (Geser et al., 2012; Dahmen et al., 2013; Ohnishi et al., 2013; Ali et al., 2016).

In opposition, AmpC cephalosporinases break down cephalosporins and cephamycins and can withstand inhibition by β -lactam inhibitors. Ultimately, Enterobacteriaceae that produce carbapenemase are capable of hydrolyzing penicillins, every cephalosporin, and β -lactamase inhibitors (Papp-Wallace et al., 2010; Locatelli et al., 2010; Ahmed & Shimamoto, 2011; Dahmen et al., 2013). *K. pneumoniae* was the initial bacterium recognized for producing carbapenemase enzymes (Munoz-Price et al., 2013). The designation for this enzyme family stemmed from the initial *K. pneumoniae* carbapenemase

(KPC) outbreak, occurring in *E. coli* taken from the milk of cattle affected by clinical or subclinical mastitis in India, while *K. pneumoniae* in milk samples from Pakistan's cows were found to harbour blaNDM-1 and bla_{oxa}-48 (Ghatak et al., 2013; Chaudhry et al., 2020). The blaNDM-5 gene has been discovered in isolates from milk specimens from Algeria (Yaici et al., 2016; He et al., 2017).

Resistance to Tetracycline antibiotics.

Resistance to tetracyclines in *E. coli* from animals is prevalent because tetracyclines are commonly used in veterinary care. This is probably the same in *Klebsiella* spp.. The most common genes are tet(A) and tet(B), which can occur together in the same isolate (Metzger & Hogan, 2013). A recent study conducted in Jordan found that all *E. coli* isolates harboured tet (A) 39% and tet (D) 71 % (Ismail & Abutarbush, 2020). In China, only tet (C) was found, whereas a separate study identified only tet (A) when searching for tet (A) and tet (B) (Yu et al., 2020). In the United States, tet (C) exhibited a greater prevalence (Metzger & Hogan, 2013).

Aminoglycoside Resistance.

Resistance to aminoglycosides like neomycin, streptomycin, gentamicin, or kanamycin is common and can be developed through two primary mechanisms: target modification and enzymatic deactivation. The initial 16S RNA methylase, armA, was detected (Yu et al., 2015; He et al., 2017; Ramírez & Tolmasky, 2010).

AAC (3)-II/IV and AAC (6)-Ib, which are aminoglycoside N-acetyltransferases, are the primary acetyltransferases found in *E. coli* and typically exist as components of gene

cassettes within integrons (Poirel et al., 2018) and (Freitag et al., 2017; Saidani et al., 2018).

Quinolone resistance can result from mutation in the gyrA, gyrB, par C and parE chromosomal genes that encode gyrases and topoisomerases, respectively (Kim et al., 2011; Yang et al., 2018). Out of 92 *E. coli* isolates collected in China, 97.8% had gyrA mutations, while 95.6% exhibited gyrB mutations (Lan et al., 2020).

Resistance against Sulfonamides.

The genes associated with sulfonamide resistance are sul1, sul2, and sul3. These are carried on plasmids that can contain other antimicrobial resistance genes and are extensively spread. The genes sul1 or sul2 are frequently detected and were identified in *Klebsiella* spp. such as *K. pneumoniae* from Brazil and Canada, as well as *E. coli* from Germany, Ireland, Switzerland, or Australia (Lanz et al., 2003; Keane, 2016; Freitag et al., 2017).

Resistance against Trimethoprim

The most detected genes include dfrA1, dfrA5, dfrA7, dfrA12, dfrA15, dfrA16, and dfrA17 (Ahmed and Shimamoto, 2011; Keane, 2016; Koovapra et al., 2016).

Antibiotic resistance genes in *E. coli* and *Klebsiella* spp. in Egypt.

It was found that 30.4% of Gram-negative bacteria harboured at least one antimicrobial resistance gene. The most frequently detected isolates were *Enterobacter cloacae* 8 (7.1%), *Klebsiella pneumoniae* 7 (6.3%), *Klebsiella oxytoca* 7 (6.3%), *E. coli* 5 (4.5%), and *Citrobacter freundii* 3 (2.7%). The gene found in the isolates

resistant to trimethoprim (dfrA1, dfrA5, dfrA7, dfrA12, dfrA15, dfrA17, and dfrA25), aminoglycosides (aadA1, aadA2, aadA5, aadA7, aadA12, aadA22, and aac(3)-Id), chloramphenicol (cmlA), erythromycin (ereA2), and rifampicin (arr-3).

Furthermore, the genes responsible for encoding β -lactamases, namely blaTEM, blaSHV, blaCTX-M, and blaOXA, in addition to the plasmid-mediated quinolone resistance genes qnr and aac(6)-Ib-cr were also detected (Ashraf and Tadashi 2011).

Table 6. Antibiotic resistance genes in *E. coli* and *Klebsiella* spp. in Egypt.

	locality	Target Genes	Oligonucleotide primers References
<i>E. coli</i> and <i>Klebsiella</i> <i>spp.</i>	Different dairy farms in Egypt	<i>bla</i> TEM	(Ahmed et al., 2007)
		<i>bla</i> SHV	
		<i>flo</i> R	(Hussein et al., 2007)
		qnrA	(Park et al., 2006)

The bacteriological evaluation of different subclinical mastitis cases revealed that the most frequently identified bacteria were *E. coli* (49.8%), *S. aureus* (44.9%),

streptococci (44.1%), and *non-aureus staphylococci* (NAS) (37.1%). *E. coli* isolate possessed the *tetA* gene (Abed et al., 2021).

Table 7. Incidence of *E. coli* antibiotic resistance genes in the governorates of Beni-Suef, El-Fayoum and Giza.

	Locality	Target Genes	%	Oligonucleotide primers References
<i>E. coli</i>	Beni-Suef, El-Fayoum and Giza	tetA	100	(Randall et al., 2004).
		sul1	100	(Ibekwe et al., 2011)

sul1: Sulphonamides resistance gene. tetA: Tetracyclines resistance gene

This study was conducted to detect and determine the resistance genes in *E. coli* strains isolated from Friesen-Holstein cattle from different regions of Cairo Governorate. The incidence of *E.coli* (4.6%) was represented by 8 isolates/175 milk samples. The PCR

detected the presence of 4 resistance genes, sul1, mphA, aadA1 and ereA, in all tested isolates, while trimethoprim-resistant dihydrofolate reductase (dfrA) resistance gene was detected in 5 isolates only (62.5%) (El-hofy et al., 2023).

Table 8. Incidence of *E. coli* antibiotic resistance genes Cairo governorates

	Locality	Target Genes	%	Oligonucleotide primers References
<i>E. coli</i>	Cairo Governorate	sul1	100	(Ibekwe et al., 2011)
		mphA	100	(Randall et al., 2004)
		aadA1	100	(Nguyen et al., 2009)
		ereA	100	(Nguyen et al., 2009)
		dfrA	62.5	(Grape et al., 2007)

sul1: sulphonamide resistance gene, mphA: macrolide 2 phosphotransferase gene, aadA1: aminoglycoside nucleotidyltransferase gene, ereA: Erythromycin Esterase gene and dfrA: trimethoprim resistant dihydrofolate reductase gene.

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