Infection and Drug Resistance

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REVIEW

Is AMR in Dairy Products a Threat to Human Health? An Updated Review on the Origin, Prevention, Treatment, and Economic Impacts of Subclinical Mastitis

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Background: Bovine mastitis is the most frequent and costly illness impacting dairy herds worldwide. The presence of subclinical mastitis in dairy cows has an impact on the decreased output of milk and milk quality, culling of affected cows, mortality rate, as well as mastitis-related treatment expenses, generating significant financial loss to the dairy industry. The pathogenic bacteria invade through the mammary gland, which then multiply in the milk-producing tissues causing infection, and the presence of pathogenic bacteria in milk is concerning, jeopardizes human health, and also has public health consequences. Intervention to promote herd health is essential to protect public health and the economy.

Results: This review attempts to provide an overview of subclinical mastitis, including mastitis in different species, the effect of mastitis on human health and its pathogenic mechanism, the prevalence and incidence of subclinical mastitis, and current preventive, diagnostic, and treatment methods for subclinical mastitis. It also elaborates on the management practices that should be followed by the farms to improve herd immunity and health.

Conclusion: This review brings the importance of the threat of antimicrobial resistance organisms to the dairy industry. Furthermore, this review gives a glimpse of the economic consequences faced by the farmers and a futuristic mastitis market analysis in the dairy industry.

Keywords: subclinical mastitis, human health, economy, pathogenic mechanism, management

Background

Milk is basic sustenance for humans all over the world, but it also constitutes a public health concern when taking unpasteurized milk since milk has high microbial populations and it is an ideal environment for bacterial development. Mastitis is the most common disease in dairy cows, with well-known negative consequences for animal welfare and dairy farm revenue. Clinical, sub-clinical, and chronic mastitis are the three types of bovine mastitis based on the degree of inflammation. The visible abnormalities such as red and swollen udders, as well as fever in dairy cows, indicate clinical bovine mastitis. The cow's milk seems watery, with flakes and clots present.[1] Farmers have been looking for effective ways to reduce the incidence of mastitis in their cattle ever since the dawn of modern dairy farming. Manual milking has enabled rapid diagnosis of abnormalities in milk and the mammary gland for centuries, but very little was understood about the causes or treatment of mastitis. It required the invention of microscopes that permitted the discovery of bacteria that are the key etiological agents to have a greater understanding of mastitis. Mastitis is usually a prevalent disease in

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dairy herds worldwide with a high economic impact. Mastitis is the inflammation of the mammary gland regardless of its causative agent. It is classified as clinical or subclinical mastitis based on the inflammatory effects of the mammary gland. Bovine mastitis can be caused by allergies, physical trauma, or pathogens such as *Staphylococcus aureus, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus uberis*, coliforms, and *coagulase-negative Staphylococcus species*.[2–5] Subclinical mastitis has an important effect on milk composition, mainly increasing somatic cell count (SCC) in the milk,[6] which many producers undervalue because of lack of visibility and also requires a specific kit or device to detect.[6,7] Mastitis loss causes decreased milk production and control of mastitis includes its treatment, preventive measures with separate manpower, and in worst cases leads to culling.[8] Dairy cows with a high yield are more likely to be harmed than those with a low yield. Mastitis is more common in exotic and cross-bred cows than in Indian zebu cows. Early detection of udder health conditions is significant for dairy farmers and veterinarians to maintain not only the animal's well-being but also the quality of milk and dairying profitability.[9] In 2001, studies show the incidence of sub-clinical mastitis from 19.20 to 83% in a cow. The milk protection was decreased by about 70% of the total cost of mastitis due to bovine mammary epithelial cell death and injury to the milk production tissue.[3] However, economic estimations differ across countries and even between the region in the countries. Hence, there is a need for precise detail about the economic loss in-order to provide a financial incentive to prevent and treat mastitis. It can aid in understanding the feasibility of the preventive steps concerning a single dairy cow, flock, as well as a whole dairy industry.[10] The cost of bovine mastitis can be illustrated by production losses and control-related expenditures.[11] Although it is difficult to estimate the financial loss caused by sub-clinical mastitis, experts believe that it causes more financial losses in the herd than in clinical instances.[3,12] Major consequences do not always refer to financial indicators, and it has an important effect on human health. Food quality (foodborne diseases) and the reliability of dairy products (such as cheese) are also significant factors, as milk from infected individuals might very well consist of harmful bacteria and have changed the constituents that the dairy industry would not prefer. From the global perspective, cattle seem to be the most essential dairy species, accounting for above 80% of global dairy production, preceded by buffaloes (15%), goats (2%), and sheep (1%), with camel accounting for 0.5% as well as other dairy species accounting for 1.5%.[13] The direct cost of veterinary services, diagnostics, mastitis treatments, labor requirements, and the milk discarded during the treatment period. Indirect cost losses include hidden costs for milk producers that are not well recognized by many farmers reduced milk yield caused due to the inflammation in the udder, culling of animals and reduced quality of milk have made it a global problem for cattle businesses.[14] Mastitis control and management techniques need the detection of subclinical mastitis.[15]

Milk is not just the nourishment for each newborn mammalian species but also a wonderful source of nutrients for children's growth and has been suggested by a large number of dietary standards throughout the world.[16] Numerous studies have looked into the relationship between milk consumption and a number of health effects. Yet, there were disagreements between the findings of several human studies.[17] Considering the significance of milk in our diets, it is imperative to routinely evaluate the vast amounts of data pertaining to the impact of milk consumption on health-related factors. Some people have symptoms of bloating, abdominal pain, gas, and diarrhoea after consuming the milk, these symptoms might be so severe and make them avoid all dairy products. Undigested lactose raises osmolarity in the small intestine and reaches the colon where it becomes fermented by the microbiota, causing digestive symptoms.[18]

Many literatures were available on this topic, hence it drags attention because of its economic issues. This review aims to provide an overview of subclinical mastitis infection in cows and their economic importance. It also provides information about the managemental practices that should be followed on the farm to avoid infections. Further, we have exclusively discussed the current and prospective mastitis market throughout the globe.

Causative Agents-Microorganisms

Mastitis is caused by a variety of bacterial strains, but occurrences of viral, algal, and fungal mastitis have also been documented in the literatures. The most important bacterial organisms causing mastitis are *Staphylococcus aureus, S. agalactiae, S. zooepidemicus, S. faecalis, S. pyogenes, Klebsiella spp, Mycobacterium bovis, E. coli, Brucella abortus, Pseudomonas pyocyaneus, Leptospira pomona, Pasteurella multocida*. Among these, *S. aureus* is the most commonly isolated infectious pathogen in both subclinical and chronic bovine mastitis around the world.[19] The fungal organisms responsible for mastitis are *Trichosporon spp, Aspergillus fumigatus, A. modulus, Candida spp.*

Figure 1 Various sources of micro-organisms causing bovine mastitis.

The most common pathogens found in mastitis could be identified in the mammary gland or the environment, including excrement, surface of the soil (Figure 1) Infectious and environmental infections are the most common causes of mastitis. *S. aureus* and *S. agalactiae* are the most prevalent infectious pathogens. During the milking process, they transmit from infected to clean udders via contaminated milker's hands and cloth towels used to wash or dry udders from many animals, as well as flies. *Streptococcus* is the most frequent bacterium found in environmental infections (*S. uberis, S. dysgalactiae*) and coliforms like *E. coli* and *Klebsiella*. In between the milking, environmental infections are considered to be transmitted. Coliform infections are often linked to an unclean environment, whereas *Klebsiella* can be found in sawdust containing bark or dirt. Symptoms of coliform infections include abnormal milk, swelling udders, watery milk, and a loss of appetite. Minor pathogens or commensals are microorganisms that colonize the mammary gland, such as *Corynebacterium bovis* or *coagulase-negative Staphylococci* (CNS). Bacteria that are common residents of the teat canal and can be identified from milk samples, but have limited clinical importance and seldom induce inflammation, are classified as minor pathogens. Minor infections produce a lower rise in the mean SCC of milk. Clinical cases are frequently caused by microorganisms found in the environment.[20]

Antimicrobial Resistance

Staphylococcus aureus, is one of the most common infectious mastitis pathogens recognised globally. It is known for generating severe intramammary infectious diseases that do not respond well to antimicrobial treatments and spread throughout the herd, resulting in significant economic losses.[21] Antimicrobial resistance (AMR) turnout when the organism is no longer responding to the antimicrobial drug to which it was initially sensitised. AMR screening in bacteria has clinical and public health implications. Furthermore, antibiotic use is thought to be a potential source of AMR. The most often used antibiotic classes for curing intramammary infections globally include lactam group of antibiotics (penicillin, and cephalosporin), aminoglycoside, lincosamide, and macrolide.[22]

A study conducted by Yang et al 2016 proposed that the *Staphylococcus aureus* was resistant to penicillin (84.09%), erythromycin (20.45%), tetracycline (15.91%), gentamicin (9.09%), tobramycin (6.82%), kanamycin (6.82%), and methicillin (2.27%). The genotype showed resistant to rifampicin (100%, *rpoB*), penicillin (95.45%, *blaZ*), tetracycline (22.73%, *tetK, tetM*), erythromycin (22.73%, *ermB*, or *ermC*), gentamicin (2.27%, *aacA-aphD*), methicillin (2.27%, *mecA*).[23] Several antimicrobial resistant bacteria have been isolated from the milk in India. The study conducted by Kar et al discovered the presence of extended spectrum beta-lactamases (ESBL) producing *Escherichia coli* in milk samples.[24] Recently, ESBL producing *Klebsiella pneumonia* was identified from the buffalo milk. Furthermore, majority of the ESBL producers from bovine milk even had AmpC type beta-lactamase and plasmid mediated fluoroquinolone resistance genes.[25] Sharma et al discovered that the *E. coli* isolated from the milk samples was resistant to ampicillin, penicillin, nitrofurantoin and *S. aureus* was resistant to tetracycline, penicillin, cefotaxime, ampicillin, chloramphenicol.[26] Verma et al discovered that isolated organism from the milk was resistant to oxytetracycline, streptomycin, ampicillin, and cloxacillin.[27] Milk samples from mastitis affected cow were identified as having methicillin-resistant *S. aureus*, methicillin-resistant *S. epididymis*, and ESBL *E. coli*.[28] Additionally, vancomycin-resistant *S. aureus* was identified in bovine and goat milk and it turns into main concern because vancomycin plays a very important role in the human medication to treat a wide range of infections.[29] The appropriate use of antibacterial drugs by physicians and the quest for treatment alternatives to reduce the antimicrobial usage (AMU) and AMR occurrence in dairy products remain important concerns in veterinary medicine and human health.[30] The intramammary pathway is the most frequently applied route for administrating these antibiotics, but the parenteral route is indeed routinely employed for treating clinical mastitis. The widespread use or mismanagement of antibiotic therapy in bovine mastitis may pose a threat to human health due to the potential growth-resistant bacteria and their entry into the food chain.

Antibiotic Surpluses in Milk

Antibiotic residues have been found in animal foods fairly soon after the therapies, and the best step to prevent them is to put them on hold for a predefined timeframe, to transmit prior slaughtering an animal or drinking milk. This timeframe varies depending on the therapeutic agent. Farmers really are not strictly adhering to these criteria for few reasons, they are lack of knowledge to the farmers about the usage of antibiotics and its link to the public health. The most important reason is the financial status, where the farmers are aware that they should not use the milk while the animal in treatment but they cannot afford to do it. They are much concerned about losing milk, where it affects their daily income. Milk from the antibiotic treated cows is either consumed by the calves, sold for human consumption, or discarded. Dairy farmers have been frequently advised to remove treated animals from the milk distribution network for a particular duration which enable the antibiotic residues to decline to the necessary standard. If animal does not respond well to the therapies, farmers may decide to sell it for slaughtering to reduce their losses. AMR could have greatly impact the animal health and milk production.

Mechanism of Mastitis Infection and Host Response

Mastitis in dairy cows is almost invariably caused by microorganisms, most commonly bacteria, that enter the udder, proliferate in the milk-producing tissues, and release toxins that cause acute damage. The body's first line of defense against infection is the teat end. A smoothly muscled membrane surrounds the teat channel, keeping it tight, preventing milk leakage, and inhibiting pathogens from accessing the teat. Keratin is a protein with bacteriostatic sterols, being generated by the cells lining the teat canal. This Keratin acts as a shield against micro-organisms. Due to unsanitary and wet conditions at the teat tip bacteria could enter the canal while milking. Teat sinuses with damaged keratin or mucous membrane are more susceptible to invasion, proliferation, and illness (Figure 2). A teat channel that has been injured can partially open. Injury can be caused by improper udder wipes or cleaning with chemicals, moist teats, inadequate mixture or chilling of teat dips, frostbite, failure to prepare cows for milk evacuation, overmilking, and other issues.[31]

An inflamed response is initiated when bacteria invade the mammary gland, but this is the body's best defense mechanism. Toxins, enzymes, and cellular constituents produced by these microorganisms trigger inflammatory cells to secrete a multitude of proinflammatory cytokines. The pathogenic infection, lactation stage, age, immunological condition of the cow, genetics, and nutritional status can all impact the severity of the inflammatory response.[32] Chemical messengers or chemotactic chemicals from injured tissues attract huge numbers of polymorphonuclear neutrophil (PMN) leukocytes and phagocytes from the bone marrow to the invading microorganisms. PMN can migrate between milk-producing cells and into the alveolus lumen, causing an increase in somatic cell count (SCC) and damage to secretory cells. PMN, or white blood cells, constitutes the majority of somatic cells. PMN surrounds the bacteria at the infection

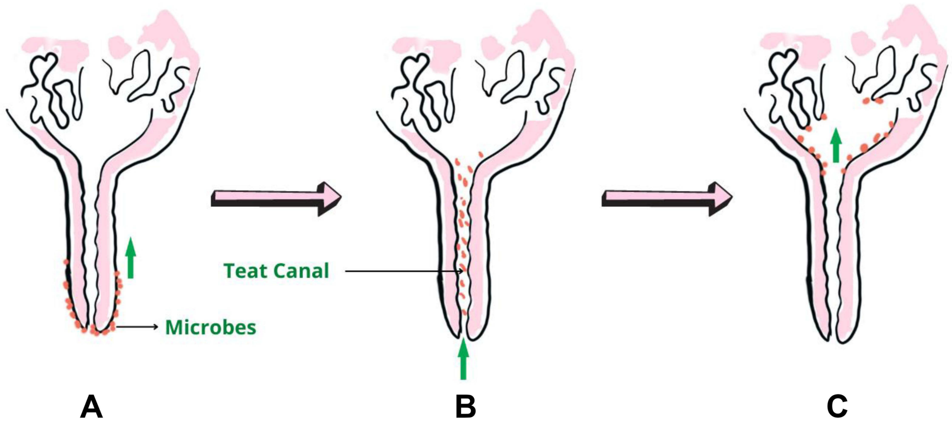

Figure 2 Process of infection. (**A**) Microbes stick to the teat. (**B**) Migrate into the teat canal. (**C**) Microbes colonized in secretory cells and produce toxins in milk-producing cells.

site and releases enzymes that can kill the microorganisms. Milk leukocytes may also produce particular chemicals that recruit more leukocytes to the infection site to combat it. After the bacteria have been removed, huge numbers of somatic cells remain in the gland until it heals. Clots will be formed when leukocytes and blood coagulation components clump together would block small channels, rendering milk discharge difficult. Scar tissue could occur as a consequence of damage to epithelial cells and blockage of tiny ducts, giving rise to fixed functional impairment of that portion of the gland. In some cases, inflammation may subside, tissue regeneration will take place, and performance will be recovered during lactation or even after the next lactation.[32]

Effects of Mastitis on Human Health

Acute and severe SCM not only injure mammary cells and milk supply but also create financial loss by harming animal health. They also present a serious hazard to human health by diminishing the nutritious quality of milk.[33–35] Mastitis influences milk's physicochemical and sensory quality. Mastitis-related high somatic cell counts are linked to a decrease in lactose and non-fat solids in milk; however, the magnitude of change varies depending on the causative pathogen.[36] When antibiotic residues in milk are consumed, they can induce allergic responses, but this can be prevented by eliminating milk during antibiotic therapy. Bacterial resistant strains are constantly evolving as a result of antibiotic usage, and their transmission to humans cannot be overlooked.[37] Antibiotic-treated dairy animals' mastitis milk might be a cause of antimicrobial resistance in humans. Antibiotics must be used to promote the safety and quality of milk.[38] Mastitis milk has reduced protein and calcium levels, and injured epithelial cells in milk increase the release of specific enzymes, suggesting that it might be used as a diagnostic for mastitis diagnosis.[39,40]

Mastitis in Different Species

Human Mastitis

Breastfeeding is recommended by international and national health organizations throughout the initial six months after the birth of infants.[41,42] But continuous breastfeeding would not be a possibility for females in some circumstances for a variety of reasons, including mastitis being the most common source of unwanted weaning. Mastitis, or irritation of the breasts, is a painful and even fatal disorder that could progress to mammary rupture and a sepsis infection. Milk blockage and inflammation are the two most common explanations of mastitis.[43] Milk blockage happens if milk is not evacuated effectively from the gland due to inadequate feeding to the baby.[44,45] It is commonly known that most mastitis infections are associated with alterations in the gland's microbiome, but most mastitis-causing micro-organisms have the potential to build biofilms in the milk-producing glands resulting in impaired milk circulation and milk accumulation. Mothers below 21 and above 35 years tend to have a lower incidence,[46] mastitis occurred in previous child birth, dry or sore nipples, usage of lotion/ointments, inappropriate breastfeeding methods are all considered to be significant risk factors.[47,48] Mastitis might appear with the presence or absence of infection. Mastitis is a prevalent breast ailment that could impact women are breastfeeding.[49] Mastitis can be lactational or non-lactational. Lactational mastitis is indeed a type of severe mammary infection that occurs during pregnancy. Bacteria from a child's mouth are prone to acquire entry through cracks or fissures in the breast area causing lactational mastitis.[50] Idiopathic granulomatous irritation and other inflammatory diseases are among the reason for non-infectious mastitis. Breast infection is an accumulation of pus material within the breast that could also result in the development of mastitis. This infection is more prevalent in women among 18–50 age.[51,52] Lactational lesions are more common in women of menstrual age. However, non-lactational lesions could also be observed in premenopausal elderly women and overweight individuals and chain smokers are much more prone to the infection than the regular population. Non-lactational breast infections are frequently sub-areolar and had been originally identified for glandular tissue channel fistulas.[53]

In newborn babies, breast infections are rarely observed.[54] Breast cancer risk in females having non-lactational mastitis would be poorly understood. A connection involving inflammatory processes and carcinogenesis has been discovered as a result of numerous research.[55] Similarly, inflammation in the mammary gland is a risk for breast cancer.[56] Infectious mastitis is a frequent illness affecting approximately 33% of lactating women. SCM is a frequent, nonspecific inflammatory process of the udder that nutritious content of milk. SCM is found in 2–66% of breastfeeding mothers. The majority of existing knowledge about human SCM ecology originates from cattle investigations, where it is understood that cytokines are produced spontaneously in milk by the mammary gland and immunological cells in response to pathogenic illness. Bacteria that colonise the skin are indeed the primary route of infection for mastitis and breast ulcers. The most prevalent causal organism is *Staphylococcus aureus*, preceded by coagulase-negative *Staphylococci*. The predominant species found in the mastitis includes *Staphylococcus aureus, S. epidermidis* and *Corynebacterium sp*. It is possible that certain mammary infections are polymicrobial. Once the granulomatous mastitis was thought to be a mild infection, but there is an increasing existence of the relationship to Corynebacterium infection. Antibiotic treatment for mastitis should be started immediately to prevent difficulties.

Canine Mastitis

Inflammation of the mammary gland affects bitches of all breeds at different ages. Despite this, mastitis is commonly misdiagnosed or underestimated. Although bacteria are the most common pathogens, certain cases of fungal mastitis have been reported in endemic areas or dogs with immunodeficiency.[57,58] Acute mastitis, gangrenous mastitis, chronic mastitis, and subclinical mastitis are the four clinical manifestations of mastitis. Poor sanitary circumstances, trauma, and systemic infections are all risk factors. The ascending route from the nipple is the most prevalent route of infection, while trauma and hematogenous routes are less common. During breastfeeding, sucking pups can cause trauma. Injuries involving foreign substances or insect bites might result in identical lesions in some circumstances. In the most extreme situations, the bitch may show no indications of the illness or be in a serious state. The mammary gland is generally altered, although it can also be normal in the event of a subclinical presentation. It is more common in non-spayed bitches, since it occurs frequently throughout the postnatal period, lactation peak, or false pregnancy. It might, however, be linked to a variety of mammary gland pathologies, such as galactostasis, mammary hyperplasia, or breast neoplasia. Mastitis can sometimes be mistaken for a breast tumor with active inflammation.[59]

Mastitis in Camel

Camel is one of the most significant animals in countries in the Middle East, and it has been strongly entrenched in their way of life. There are approximately 11.24 million camels throughout the globe, with 61% living in the Arab countries and the rest dispersed throughout the world. Camel has a benefit over other livestock in that they can produce milk consistently throughout the year.[60] Dromedaries' significance as a source of milk and meat will be preserved and increased with the continued care and consideration of health. Mastitis in the camel has indeed been linked to a variety of infectious agents, the most widely known bacterial agents in camel are *Streptococcus, Staphylococcus, Micrococcus*, and *Aerobacter*, and *E. coli. Streptococcus agalactiae* and *Staphylococcus aureus* have been identified as important mastitis-causing organisms in camel.[61] The clinical manifestation can range from acute inflammatory with toxemia to necrosis that advances to chronic mastitis till the mammary gland is destroyed. Furthermore, milk from the infected camels will make it unfit for human intake, disrupt production processes, or, in exceptional situations, serve as a vehicle for disease transmission to humans. Acute necrotizing mastitis has indeed been observed in an Arabian camel breed, with an estimated rate of death of around 80% among the milk-producing camels. They displayed rapid onset, painful difficult swelling of the damaged teat, quarter, or entire mammary glands. Due to complete or partial invasive removal of mammary gland apartments, approximately 41.7% of diseased animals were engraved for slaughtering. *Streptococcus agalactiae* was found to be a major causative agent of gangrenous mastitis in the Arabian camel.[62] Overall mastitis prevalence in camels was estimated to be 29% at the animal level and 17.9% at the quarter level.[62] In California mastitis test, direct microscopic somatic cell count has been widely used to identify subclinical mastitis in camel. MALDI-TOF MS analysis and molecular techniques are also involved in the detection of species-specific diagnosis of mastitis pathogens.

Caprine Mastitis

Goats and sheep have been frequently managed to be maintained through environments with limited grazing and unfavorable weather. Because of the low capital investment and minimized production cost in the dairy industry, they are considered poor in some countries. Appropriate response revenue, short pregnancy complications, and milk production in portions appropriate for instant consumption are also characteristics for the dairy industry. Small ruminants, on the other hand, have become widely attractive in advanced economies, as they are kept as pets, especially in suburban areas.[63] Sheep have been considered to have one of the first species, as well as mammary gland infection has indeed likely been an issue. Individual milk losses of 2.6–43.1% have been reported in the literature for mastitis in sheep, and these damages are influenced by many aspects such as disease intensity, levels of production, and causal agents. Mastitis has a detrimental effect on milk yield and milk production.[13,64] The negative impact of rising somatic cell count on the clotting properties of milk, curd yield, and the efficiency of cheese is attributed to the damage of physicochemical characteristics caused by insufficient udder general health, which prevents manufacturers from meeting the quality guidelines demanded by consumers.[65] Although most of the sheep have been managed to keep to produce meat in several nations, most of the researchers focussed on mastitis symptoms in ewes. Only serious clinical mastitis is prevalent and identified in these flocks. The said absence of importance placed on milk-producing ewes has resulted in the incidence of clinical mastitis and a complete lack of study for subclinical mastitis. Subclinical mastitis affects up to 30% of the animals.[66] Mastitis in goats/sheep is indeed an extreme inflammatory condition affecting one or both sides of the glands in the udder. Fever, lack of appetite, breathing difficulties, signs of sepsis are typical diagnostic indications that arise in the first week of milk production. The udder becomes discolored, cold, and has a sharp distinction of the damaged tissues, as well as a lesion that discharges pus as the development progress continues. The clinical manifestation of a potentially lethal condition is marked by deterioration of the physical condition, bronchitis, sepsis, and toxemia. Goat mastitis is caused by bacteria such as *S. aureus, Mycobacterium haemolytica, C*. perfringens, and E. *coli*. Antimicrobial and anti-inflammatory drugs, as well as intravenous fluids, minimally invasive drainage, surgical excision, and reduction of necrotic lesion tissue have been used to treat this condition.[67,68]

Porcine Mastitis

Postparturient abnormalities are indeed a financially significant disorder challenging in sows around the globe, resulting in production efficiency and higher death rates. The term mastitis metritis agalactia (MMA) complex and postpartum dysgalactia syndrome was widely used to identify these conditions. Mastitis is one of the most common clinical manifestations among the various conditions associated with sow disorder. Coliform bacteria, such as *E. coli, Citrobacter, Enterobacter*, and *Klebsiella*, seem to be the most frequently detected pathogens from infected sows' Approximately 13% of sows have been culled due to mammary gland problems, however the major downside effect on the economy of coliform mastitis for piglet death.[69–72] The fever and lack of appetite are common systemic symptoms of this illness, and they are often accompanied by digestive problems and anxiety. The diseased glands exhibit serious swelling and skin congestion. Even though edema without evidence of acute mastitis could be encountered, particularly in primiparous sows, there might be some severe induration of a lobular area. The decreased feed consumption in piglets induces a range of therapeutic indicators. Crushing is more widespread as a result of the sow's predisposition to remain lateral prone position and susceptibility of starved piglets. The overall piglet death rate in coliform mastitis affected sows ranges from 5 to 38.6% for one year age group.[73,74] Sows do not have the access to the same rapid mastitis diagnostics that cows have. Cell count assessment is uncommon, and the threshold information might be even rarer. The most common occurrence of coliform mastitis occurs within the first 24 hours following delivery, demonstrating a significant link to postpartum. Moreover, cortisone and estrogen impact infection susceptibility through altering the immunological reaction, and these hormones have a broad range of amounts at the period of parturition.[75] After the diagnosis of coliform mastitis, antibiotic therapy should be initiated early as feasible to minimize the detrimental impacts on the sow and piglets but the antimicrobial susceptibility has been not assessed.[72]

Mare Mastitis

The compact size and hidden placement of the mare's udder, combined with a shorter storage capacity than cows and goats, might be the reason to have a lower occurrence of mastitis. Equine udders and teats have become less susceptible to damage and infection than animals with bigger udder and nearer to the floor. Although mastitis is less common in mares, significant mastitis-related complications may arise in horses and ruminants. Infectious agents have been transmitted to the breastfeeding calf, and the calf may develop scarlet fever, polyarthritis, and pneumonia.[76] Mastitis could indeed cause long-term functional impairment in the damaged udder due to glandular tissue damage or blockage if the mare is pregnant and systemically damaged. Less widely, serious disease can cause permanent functional impairment in the diseased mammary gland. Mastitis can spread to the mare's circulatory system, resulting in life-threatening abscesses. Mastitis commonly affects breastfeeding wares within the first 2–3 days after delivery or subsequently in lactation.[77] Inflammation, edema, or heat in the affected area, gland hardness, lower limb swelling, blocked mammary circulation, calf abortion, and severely aberrant pus have seemed to be the clinical symptoms of mastitis. Due to a noxious stimulus, many mares could have become hesitant to move, irritable, or angry. Mastitis can develop into udder inflammation, including *Corynebacterium sp. Streptococcus sp*. and *Staphylococcus sp*. are the most common bacterial causes of udder lesions in mares. Mastitis with breast infection is more probable in horses arriving from pigeon fever endemic areas. Mare mastitis has a complex etiology that is unknown. Infectious agents can enter the duct through the nipple hole or may propagate by hematogenous diseases, skin damage. Mares keep producing milk beyond the weaning stage, the duct gets thickened, milk leakage from the duct, and bugs could graze on the leaking discharges of the mares. This condition renders mares at greater risk for developing mastitis. Neutrophils with degenerative alterations are abnormally large.[78] Topical antibiotics, intramammary infusion of antimicrobial agents or disinfectant solution, anti-inflammatories, regular milking, cold washing, or heating pads were used to treat mastitis. Observing mares after weaning can minimize the malnutrition for foals and reduce bug counts on the farm.[79]

Mastitis in Donkey

In European smallholding farms select a variety of output, donkey milk is utilized as a replacement for breast milk. This foodstuff has been considered a special enterprise with significant economic potential.[80] The consumption of donkey milk has been recognized as a valuable remedy for the cure of babies with various food intolerance and babies with cow milk allergies. However, it should be supplemented with medium-chain triglyceride to fulfill the complete calorie consumption as suggested to dystrophic patients in the developmental delivery period.[81] Donkey milk has a significant concentration of omega 3 fatty acids that encourage its usage as a multifunctional diet for the prevention of chronic inflammatory and cardiovascular diseases.[82] The robust protective barrier (large level of lysozyme) of udder gland in donkey attributed to the limited quantity or absence of pathogens. Low mean SCC in the donkey milk validated the distinction among other milk animal species with the excluded case of mastitis and also confirmed that mastitis is rare in donkeys and not considered a concern for milk quality. However, the presence of *S. aureus* and *E. coli* pathogens in the milk should be identified before the infants consume raw milk.[83]

Feline Mastitis

Mastitis is a somewhat rare reproductive condition and poorly understood disease among dogs and cats.[84] It happens when the mammary gland gets affected by the bacteria as a consequence of increasing infection, injury, or unhygienic conditions.[85] *Escherichia coli, Staphylococci*, and *Streptococci* have been the most regularly identified pathogenic organism.[86] Mastitis can be severe, hemorrhagic, and a persistent low-grade illness. The common clinical symptoms include stiffness, painful, enlarged, discolored glandular tissue with aberrant discharges.[87] While parenting sick newborn cats, affected animals might become anorexic, pyrexia, sad, and lazy.[88] Infected glands could develop oozing pus or gangrene in serious circumstances. The condition is diagnosed primarily on the individual medical history, clinical indicators, and cytological examination of the milk. Antibiotics that are sensitive to the pathogenic bacterium can enter and accumulate in the milk and mammary tissue and make sure that it is non-toxic to the feeding newborn cats.[89] Susceptibility assay for the isolated pathogen is essential. Amoxicillin has been recommended as a secure initial choice for cats because it enters and accumulates in the milk and therefore is suitable for breastfeeding puppies and kittens. If systemic damages occur, fluid treatment is required. If the mammary gland is severely damaged, necrotic the newborn babies should be stopped from breastfeeding by the mother cat. Additionally, artificial milk must be given until the infection to cure. Neonatal should be weighed often to evaluate the growth.[84,85]

Management of Mastitis

On the farm, a better portfolio of practices for dairy cattle can reduce the issues like mastitis. It is possible to eliminate the development of mastitis rather than curing the disease. As a consequence, appropriate management techniques are indeed an important element of preventing mastitis.

Transgenic Cows

Genetic engineering is a potential method for improving cattle production qualities that has yet to be achieved.[90] The notion of disease resistance is a complicated and dynamic process including the link between the host-parasite and host-pathogen. Host defence mechanisms against diseases or parasites could be split into two categories: resistance and tolerance. Resistance mechanisms effectively decrease infection burdens, while tolerance reduces the severity of disease induced by the pathogen. It is commonly recognized that only disease-resistant animals withstand a disease epidemic.[91] Transgenic cattle studies rapidly shifted their focus to the development of compounds principally for human therapeutic use. Following that, xenograft transplantation possibilities were investigated.[92] Over the last two decades, very few but dedicated teams of researchers have collaborated towards agricultural targets with the major aim of improving animal growth and nutritional enhancement.[93,94] The very first transgenic cattle were developed using recombinant DNA technology, pronuclear microinjection methods, and sophisticated reproductive strategies such as superovulation and embryo transfer.[95] The genome-editing approach includes a nuclease enzyme that cuts DNA sequence and a targeting technique that directs the enzyme to a specific location on the genome.[96] The clustered regulatory interspaced short palindromic repeats (CRISPR)/ CRISPR-associated protein 9 (Cas9) system is one of the most recent genome-editing techniques to gain popularity in animals and has become a commercial practice[97] (i) increasing the frequency of favorable traits linked alleles, (ii) phenotypic variation of beneficial alleles from other breeds, advanced usage of CRISPR/Cas 9 could help to increase the drug resistance in cattle and a game-changing tool for enhancing disease resistance in cattle.[98] The greatest difficulty will be identifying genome-editing targets for a disease-resistant phenotype, which will necessitate a mix of strong annotated livestock genomes and extensive understanding of pathogen-host immune system relations molecular genetics. Breeding approaches that safeguard the environment, animal protection, public welfare, and also suitable monetary gains for farmers are required for effective long-term management of cattle illnesses. Various conventional breeding efforts have been undertaken to generate a disease-resistant strain. A common initial phase of marker-assisted breeding selection, genome editing is to assess the level of genetic variation on the individual trait by deconstructing the genetic profile. Immunogenomics enables for further precise detection of possible biomarkers for resistance to disease. For *S. aureus* infections, lysostaphin has been recommended as a systemic treatment. Lysostaphin was generated spontaneously by *Staphylococcus* inert ingredients, effectively inactivates glycyl-glycine linkages present in the *Staphylococcus* cell membrane. This glycyl-glycine endopeptidase appears extremely toxic to *S. aureus*.[99] In many countries, *S. aureus* is an important causal agent of bovine mastitis and it has been identified frequently from subclinical mastitis rather than clinical mastitis. Prolonged use of antibiotic use, on the other hand, causes multidrug resistance in bacteria, especially *S. aureus*. As a result, 70%–90% of mastitis caused by *S. aureus* in cattle is resistant to antimicrobial therapy, forcing 25% of cows to quit sucking their calves. Therefore, extensive research is needed to identify the regulatory mechanism of *S. aureus* infected mastitis to develop effective treatment.[100] It is critical to raise immunocompetent, healthy cattle for the long-term production of healthy food. Identifying the genetics of host immunocompetence against infectious diseases is essential to develop disease resistance in animals. Advanced immunology and molecular genetics approaches might reveal a direct correlation between disease resistance and phenotype.[101] The fast development of fully accessible in-silico omics techniques is identified as a target for genome engineering in livestock to improve disease resistance. Restoring the animal protection standard and increasing consumer acceptability of food items from genome-edited cattle is considered to be an important aspect.

Nutrients

There is indeed a strong correlation between an animal's diet and infection resistance in mammary tissue. The very primary approach towards becoming a good breeder is to have a healthy herd with proper nourishment. Because dietary components impact various mammary resistance mechanisms, a well-balanced diet plays a vital role in udder infection resistance. This is due to the nutrient's capacity to provide antioxidant activity, which boosts immunological resistance to infections. Increased resilience of dairy cows to mastitis-causing micro-organisms may be achieved by cattle breeders using a properly prepared and blended feed diet that fulfils all of the requirements imposed during the various stages of lactation. It is important to use the right feeds that are free of mycotoxin when preparing and blending the feed ration. Contaminated feeds weaken the immune system, rendering it less capable to defend itself against infections invading the udder. An overall deficiency of calories, nitrogen-containing chemicals, and other vital nutrients required for the functional integrity of the system have a clear impact on immunity. Dietary nutrients could have a powerful effect on immunological function and mastitis susceptibility in cows, and they can also enhance mastitis risk influencing by affecting peripartum metabolic disorders.

Non-infectious variables such as genotyping, environmental factors, feed with the nutritional deficiencies on supplements could influence the development and degree of mastitis. It is strongly known that the immune response could manage against microbial infection and avoid inflammation. Any nutritional deficit could cause a weaker immune reaction, which would increase the risk of udder inflammation. Minerals are a category of nutrients that have been shown to get an influence on udder health. They are involved in making structural components of the body and are essential for proper immune function. Mineral deficiencies in veterinary cattle medicine are mostly linked to metabolic diseases notably hypocalcemia, hypophosphatemia, and hypomagnesemia. It is important to note that mineral insufficiency causes immunosuppression, which is a well-known causative factor for infectious illness including mastitis.[102] Therefore, mastitis is a recurring issue even on well-managed farms, and mineral supplementation may be a strategy to boost the mammary glands' innate immune system and reduce the chances of udder inflammation.[103] The injection of the multimineral mixture (including selenium, copper, zinc, and manganese) has improved the udder function by lowering somatic cell count (SCC) scores and the rate of clinical and subclinical mastitis. Furthermore, it enhances serum superoxide dismutase (SOD) activity without affecting leukocyte performance.[104] The supplementation of vitamin E with selenium lowered the probability of slaughtering and mastitis by 10%. The study conducted by Smulski et al has confirmed that the antibiotic treatment with selenium increases the efficacy of clinical mastitis treatment.[105,106]

Dry Cow Therapy

Lactating cows are frequently treated at dry periods with antibiotic infusions to prevent and treat intramammary infections. Dry cow therapy is used to eliminate the existing intramammary inflammations (IMIs) and suppress future infections.[107] This period is crucial for herd-level mastitis control. Since IMIs have a greater therapeutic response when administrated antibiotics during this period.[108] Antimicrobials were selected based on the culture, and susceptibility data are referred to as selective dry cow therapy, which also minimizes the usage of antimicrobial drugs in dairy production, which is not essential.[108] The somatic cell count (SCC) acquired from a milk sample could be used in identifying the animals for selective dry cow therapy in a simple and precise manner. The SCC value of 100,000 cells/mL for primiparous cows and 200,000 cells/mL for pluriparous cows have been used as the study's prescribed criterion for selecting cows for dry cow therapy (SDCT).[109] In comparison to typical dry therapy, the use of ciprofloxacin with interior teat sealant was demonstrated to be effective, revealing a 24–31% reduce the risk of total IMIs related to the most common infections.[110] To reduce the usage of antibiotic usage, a study assessed an approach to antibiotic-based dry cow therapy and was unaffected by cultures and aids in the selection of antimicrobial agents. Through this approach, sixty percent usage of antibiotics was reduced. But even so, new infection risk quarters enduring infection rates, dairy production, slaughter activities, or clinical mastitis did not vary for both the algorithm and antibiotic utilized group.[111]

Teat Sealants

Internal teat sealant (ITS) is indeed a non-antimicrobial product that is as effective as dry cow treatment (DCT) in preventing IMI during the dry phase. ITS may function as a protective border and act as a bacterial growth inhibitor.[112] The implementation of an ITS in the SDCT program assures that all the quarters were guarded against dry-period. SDCT has shown more effective results than blanket dry cow therapy (BDCT) in the management and therapy during the dry phase, also decreasing the need for antimicrobials by 21%.[113] The adoption of teat sealant will be a promising strategy for the replacement of BDCT in healthy cows. Benzathine cloxacillin and bismuth subnitrate (ITS) were used as effective teat sealants for SDCT and aided in the reduction of several clinical and SCM cases, as well as the rate of previously reported SCM.[114] External teat sealant reduces the prevalence of IMIs and better mastitis control in dairy heifers.[115]

Acoustic Pulse Therapy

Cows are more susceptible to bacterial infection after drying off and before calving. The handheld gadget that creates pulsing pressure waves has been used in acoustic pulse therapy (APT). This pulse can reach deeper tissue and eliminate damaged tissue. In treating subclinical mastitis, APT significantly decreased subclinical mastitis in cows more than antibiotics and other treatments. APT is an easy-to-apply therapy of cow's udder unlike existing therapeutic interventions for subclinical mastitis, which involve early diagnosis. APT does not involve bacterial detection or disposal of milk before and after therapy. So it is highly recommended that every cow suspected of carrying mastitis be cured with APT equipment to recover the decreased milk supply.[116]

Consequences of Subclinical Mastitis (SCM)

The consequences of SCM include treatment, production losses, culling, and variation in the quality of milk. The associated costs include drugs, discarded milk, services, labour, quality of the dairy products, investments and materials required, diagnostic instruments, other diseases associated with SCM, and culling of the animal. These factors and costs differ between countries and between regions.[117] SCM does not produce any visible effects on milk/udder quality but has a notable effect on the milk compositions results in the loss of milk production and other related expenses for treatment of the infection.

Economic Consequences: A Framework

The total cost of disease has production loss and control expenditures.[11] Economic losses due to subclinical mastitis were calculated in terms of milk reduction, medicine, and other obtained veterinary expenses in addition to the resources used. Economical loss of clinical mastitis was estimated to be from €61 to €97 per cow on a farm with differences between farms.[118] Here, of the literature available for mastitis in India, the annual economic loss in India due to mastitis was reported to be 60,532.1 million, where the majority of the loss was due to subclinical mastitis accounted around 43,653.2 million as of studies in 2001.[119] According to Varshney and Naresh 2004, the annual loss in the dairy industry due to mastitis was almost 2.37 thousand crore rupees in India.[120] Banal and Gupta reported that the annual economic loss is estimated to be 7165.51 crores, which combine both clinical and subclinical mastitis of 4151.16 crores and 3014.35 crores, respectively.[121] In 2014, the SCM loss was estimated at Rs. 1390 per lactation in which 49% contributes to milk reduction and 37% contributes for other veterinary expenses related to infection. Mastitis is estimated to cost the global dairy industry USD 19.7 to USD 32 billion annually as published by the University of Glasgow.[122] In which subclinical mastitis contributes a loss of about USD 110 per cow annually. The annual losses in the dairy industry due to mastitis in 2016 were estimated to be 2.37 thousand crore rupees in India. As a study proposed in China where the monthly economic loss due to mastitis was high among the farm and it is about 12,000–76,000 USD per farm per month. This cost shows approximately 29–135 USD per cow per year.[123] A similar study has been conducted in Ethiopia where the average cost of 119 USD per cow per year (0–406 USD per cow per year).[124] A similar study in India shows the total economic loss of Rs. 7824 in one month per cow. The total production loss due to clinical mastitis was 9.9 litres/day and cost of Rs.297/day and total economic loss in subclinical mastitis was Rs.7824/- in one month per cow, whereas in subclinical mastitis the average milk loss was 2.58 litres/day and cost of Rs.77.4/- day and total economic loss of Rs.2322/- per cow/month.[125] In 2017, Prakashkumar et al estimated costs for loss of SCM in India were about Rs. 21,677- Rs. 88,340 per animal for a lactation period.[126] In Colombia, the studies reported that the milk production losses ranged from 1.3% to 13.5%, which costs around USD 800.[12] McInerney et al were estimated the cost of SCM to be EUR 102 per case per year.[11] Beyene and Tolosa estimated that the financial loss due to SCM in Ethiopian dairy farms gives a total cost of 2949.8 USD with an average milk loss of 22.3%.[127] The annual SCM economic loss in Ethiopia estimated in 2019 was about 21,933,258.6 LE, which was due to the results of decreased milk production, which costs about 1,369,602.1 LE and decrease in quality of the milk cost was estimated to be 20,563,656.5 LE.[10] Annual loss due to Mastitis in the Dairy industry is about 2.2 billion USD in India and about 2 Billion USD in the US. Mastitis reduces the milk production in a cow by about 21% in India and 11% in the US.[128] In the Indian dairy sector approx. loss of Rs.4,4000 million due to subclinical mastitis and approx. about Rs.17000 million per annum.[129] The economic loss due to mastitis in India is about Rs.575 million per annum and it reduces milk by 21%.[130] In India, the economic losses due to mastitis have increased about 135 folds in the last five decades from Rs.529 million per annum in 1963[131] to Rs.71,655.1 million per annum in 2012. Mastitis causes 70% of all avoidable losses during milk production. It ranked second after infertility as the main reason for culling (slaughtering) cows. The total cost of treatment contributes to the major proportion of the economic loss.[125]

Prevalence and Incidence of Subclinical Mastitis

The majority of research on SCM prevalence outnumbers clinical mastitis all across the globe, emphasizing the significance of SCM in the dairy industry. This might be because the SCM is not readily identifiable in milk and involves a diagnostic test, hence, dragging the attention of researchers on early identification in dairy animals. Throughout the world, prevalence estimates for SCM and CM were 42% and 15%, respectively, while SCM holds the greatest prevalence when compared to CM. The study demonstrated the global importance of SCM over CM in dairy cattle and buffaloes. Continent wise analysis for SCM prevalence shows that high prevalence in North America (46%), following that Africa shows 44%, Asia (42%), Europe (37%), Oceania (36%), and Latin America (34%).[132] The prevalence study and estimate were higher in the African continent, and this is because of lack of preventive and control practices education to the farmers in dairy farms.[133] The species-wise prevalence shows a higher prevalence in buffaloes (46%) than cattle (42%). The SCM prevalence of diagnosis method was analyzed, and the highest prevalence was observed in SCC (46%), when compared to other methods California mastitis test (CMT) (43%), surf field mastitis test (SFMT) (41%), Whiteside test (WST) (37%). Uganda had a high prevalence of SCM (85%), and Uruguay had a low prevalence (1%).[132] The increased prevalence in Uganda could have been linked to the risk variables for SCM, which included grazing restrictions, poor mammary cleanliness practices, and a larger percentage of cows in late parity and late lactation.[134] Indonesia shows 82% prevalence rate for SCM, Malaysia shows 82% prevalence for SCM.[135] In Bangladesh, the reported prevalence varied from 15.8% to 53.1%.[136] In India, the overall prevalence of SCM was estimated to be 45%–46.35%.[137] State-wise prevalence of SCM shows the highest prevalence rate in West Bengal, which was estimated to be 75%. Mizoram state has a prevalence of 65% for SCM, and Karnataka shows about a 58% prevalence rate for SCM.[132]

The SCM prevalence has increased recently, indicating the need for prevention and management in dairy cows, and this could be correlated with increased farmer knowledge of mastitis. Low udder immunity in old cows and buffaloes, raising animals with drooping udders, and a lack of genetic selection of dairy cows with sufficient udder confirmation for infection control may also elevate the prevalence of SCM. The prevalence estimate was greater in the African continent, which could be due to the herd owner's failure to follow the mastitis prevention and control procedures on dairy farms.[133] The cattle showed a lesser prevalence than the buffaloes.[138] The prevalence of mastitis varies between studies, which could be due to the screening test, sampling, as well as risk factors associated such as lactation stage, parity, cattle, and buffalo breeds.[139] To minimize the occurrence of mastitis all over the world, there should be skilled field vets to evaluate and start medical treatment. The farmers should be adopted with the scientific dairy management practices by incorporating the dairy outreach approaches with the importance on mastitis knowledge and understanding, hygienic milk production practices, routine mastitis testing, dry cow therapy, and slaughtering of animals with chronic mastitis infection.[139] Furthermore, mastitis has been present in dairy animals for over a millennium, and appropriate immunization or modern methodologies might well be constructed focusing on the causative organism widespread in specific geographical regions around the world.

Current Preventive Methods

Mastitis Control Popularisation Programme (MCPP) is a mastitis Disease Control Project launched in Sabarkantha Milk Union at Gujarat in October 2014 to raise awareness about the importance of subclinical mastitis. Rapid detection of diseases by understanding the pathogenesis, developing new sensitive tests for early screening, and implementing good management practices to reduce the risk of transmission and prevent uninfected animals from being infected.[140] Mastitis, unlike other contagious diseases such as brucellosis, is a management disease, which indicates that a person can take action were it to be controlled on his dairy. Preventing lactation in the infected quarter is one method of the best methods to control SCC, healthy nutrition, housing management, dipping teats after milking, and early treatment of clinical cases to improve the health and wellbeing of the cows are all currently available methods for preventing mastitis.[141] IAccording to Smith et al 1985,[142] by limiting teat ends exposure to the environmental pathogen. The risk of developing subclinical and clinical mastitis in heifers can be lowered by employing an internal teat canal sealant during the pre-calving stage as the teat canal opened before calving.[143] Numerous researches prove that the internal teat sealant (ITS) dramatically decreased SCC and improved subclinical mastitis prevention when used in combination with antibiotic dry-cow treatment.[144,145] Tracking samples for SCC provides a regular reminder to the owner and veterinarian of the herd's overall mastitis control effectiveness.[146] The pre-and post-milking practices, as well as the cleanliness of the equipment used to milk the cows, are all part of milking hygiene, which includes pre-dipping, dry wiping, fore stripping, and cleaning the teats or teat ends. Good nutrition and feeding management are additional factors affecting udder health to be considered to have successful preventive methods.

According to Ismail (2017),[147] *S. aureus, S. agalactiae*, and *E. coli* were the most commonly targeted udder pathogens. The complete organism (cellular lysates, inactive, and attenuated vaccines) or subunits (toxins, surface proteins, and polysaccharides) were utilized in vaccinations against *S. aureus* and *S. agalactiae*, while the mutant core antigen J5 was most widely used in vaccines against *E. coli*. In new research from[148] Rainard et al, 2021, the past and current mastitis vaccine research reveal the differences, as well as the similarities, among mammary gland infections caused by the major mastitis pathogens *Escherichia coli, Staphylococcus aureus, Streptococcus uberis, Streptococcus agalactiae*, or *Streptococcus dysgalactiae*, and vaccine development has changed to the generation of antibodies shortly. Chimertech Private Limited has developed a Teat dip "Fine Kine" that plays an important part in the milking process. After milking, bacteria can easily enter the teat orifice and cause mastitis. Dipping each teat with a disinfectant solution sanitizes the area while also sealing the orifices to prevent bacteria from entering the udder. To maximize cow health and production on your farm, you'll need a reliable and consistent milking teat dipping routine, both before and after milking. Pre-milking teat disinfection has been shown to reduce bacterial numbers on the udder and is most effective against environmental mastitis-causing bacteria like *Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Enterobacter aerogenes, Streptococcus uberis, Streptococcus bovis, Streptococcus dysgalactiae, Enterococcus faecium*, and *Enterococcus faecalis*, whereas post-milking teat dipping is required to control the spread of contagious mastitis-causing pathogens like *Streptococcus agalactiae, Staphylococcus aureus*, and *Streptococcus dysgalactia.*[149]

The Tamilnadu Veterinary Animal Sciences University's Translational Research Platform for Veterinary Biologicals (TRVPB) has developed mastitis prevention products called Masti-Guard, which includes Tanuchek SCC Kit (reflect udder health status) and Teat Protect (Antiseptic teat protective spray), which are significantly effective in the prevention of sub-clinical mastitis in dairy animals as well as the control of pathogens that pose serious health hazards in dairy animals.[150] The study conducted by Baipaywadi et al, 2022, suggested that Gallic acid loaded PLGA hydrogel can be used as a teat sealant for preventing mastitis in dry cows.[151]

Diagnosis

Mastitis affects all species; it is critical to detect the condition at an initial stage. In comparison to the clinical form, there is no visible detection of abnormalities in milk or the mammary gland in the subclinical form. It is necessary to have routine diagnostic screening procedures for early diagnosis of mastitis to treat the disease and minimize the associated financial losses.[152] Physical examination of the udder, Strip cup test, California mastitis test, Wisconsin mastitis test, modified white side test, pH determination test, chloride test, electrical conductivity test, and other common diagnostic tests are currently used in the diagnosis of mastitis (Table 1). The research from[153] Rees et al, 2017, demonstrated to

Table 1 Different Diagnostic Tools Used to Detect Subclinical Mastitis

Diagnostic Tool	Description	Reference
Physiochemical diagnostics • Electrical conductivity • pH • Biochemicals	Milk conductivity, pH, and Biochemicals including lactose, amyloid A, peptides, and enzymes [such as N-acetyl-β-d-glucosaminidase, LDH, ALP] have the potential to be used as a marker for subclinical mastitis.	[155,185–189]
Somatic cell count (SCC)	SCC has larger accuracy with sensitivity, specificity of 94.9%- 99.5%, and 48.1%-87.1%. It is expensive and done in laboratories with DeLaval cell counter, Fossomatic cell counter, Portacheck	[190,191]
California mastitis test	CMT is a simple, quick, and cost-effective approach with lower accuracy (87.4–90.8%), sensitivity, and specificity than other tests.	[192]
Automatic digital diagnostics	Automated milk leucocyte differential test (MLD) (Qscout)	[193]
Immunochromatographic strips	The development of a nanoparticle-based–coated immunochromatographic strip (ICS) that accurately identifies mastitis-causing bacteria helps in successful management by both dairy farmers and veterinarians and can be utilized to implement the selective use of antimicrobials for therapy.	[194,195]
Infra-red thermography	IRT is a simple, convenient, and portable diagnostic technique for diagnosing subclinical mastitis.	[196,197]
Sensor-based mastitis detection systems	The proteolytic activity of plasmin as a biomarker was used to develop a magnetic nanoparticles-based colorimetric biosensor assay that was sensitive enough to detect modest levels (1ng/mL) of plasmin present in vitro in milk samples.	[163,198]
Proteomic approach	Many proteins are being investigated for their diagnostic potential in proteomics-based disease diagnosis.	[199,200]
Specific culture	Accumast, Minnesota Easy system, *Staphylococcus, Streptococcus*, Gram-negative (SSGN), *Staphylococcus, Streptococcus*, Gram-negative chromogenic quad plate (SSGNC), Petrifilm system	[201,202]
PCR and its versions	PCR techniques for pathogen detection in mastitic milk samples with sensitivity of 76.9–100% and specificity of 63.3–98.7%.	[203,204]
MALDI-TOF	Modern phenotypic testing is based on proteomics and can be applied directly to milk samples using MALDI-TOF spectrometric analysis.	[205,206]
ELISA	ELISA could make the diagnosis of mastitis through new biomarkers.	[188,207]

determine the firmness of an udder by a dynamometer and could able to distinguish between healthy and inflammatory quarters. Mastitis was also diagnosed by the milk anti-trypsin assay, N-acetyl-D-glucosaminidase test (NAGase), Methylene blue reduction test (MBRT), and somatic cell count (MAUM TEST).[154] Haptoglobin (acute-phase protein) is a diagnostic biomarker commonly used for evaluating cow mastitis and for detecting haptoglobin at clinically relevant levels in milk using a label-free chemiluminescence bioassay based on magnetite nanoparticles (MNPs).[155,156] According to the research, vitronectin and serum paraoxonase-1 activity is a potential biomarker for diagnosing subclinical mastitis.[157,158] An immunoassay such as enzyme-linked immunosorbent assay (ELISA) was developed that targets the biomarker. The *S. aureus* antibody testing kit (SAATK) was developed to identify mastitis caused by *S. aureus*.[159,160] In the research from Coşkun and Aytekin, 2021,[161] IRT technology can be a beneficial diagnostic tool in the early diagnosis of mastitis. With nano-bio sensors, using nanotechnology in diagnosis is a possibility for rapid detection of mastitis. According to new research, mastitis-associated S. aureus strains from India reveal diversity, with the most variation occurring within the two CCs (CC97 and CC9), which may contribute to the development of better mastitis control and preventive measures.[162] Martins et al 2019[163] provided a list of commercially accessible and in-development technologies for mastitis diagnosis. However, different diagnosis tools of mastitis have their advantages and disadvantages. Major disadvantages include false-positive results, laborious work, less sensitivity and specificity.

Microfluidic E-tongue tool for the detection of bovine mastitis using crude milk and *S. aureus* detection in various types of milk samples. Layer by layer films were adsorbed on interdigitated gold electrodes in four sensing units that made up the e-tongue. E-tongue based electrochemical techniques and electrical impedance spectroscopy have been applied in a number of contexts, including milk analysis for mastitis detection. In this method, biomolecules are not necessary and the cost of test is lower and the sensor might be more durable.[164]

Chimertech Private Limited, a biotech start-up company developed "QuadMastest" that is a handheld device for early subclinical mastitis detection in the teat-to-teat milk of dairy animals – technology involved in the development of the mastitis solution is sensor-based to detect somatic cell count – a reliable method to detect mastitis compare to existing methods. First Point of Care to detect mastitis in real time and farmer-friendly. The results will be displayed withhin 10 seconds. It detects mastitis within 48hr of infection. Reusable low sample volume (5mL per teat-quarter) – ZERO Milk wastage for testing. The detection is noninvasive and does not need any reagent. Completely water-proof; easily washable by farmers before and after every test. No recurring, no consumables, chemicals, or reagents. Positive and negative results are indicated in colors, and hence farmers can know the results without depending on any experts. Battery operated with 8 hours backup.[149]

Treatment

Mastitis when it is discovered, immediate treatment is required; therapy should be directed towards the causative bacteria or started based on herd information or personal experience. It is also important to determine if therapy is required or not, taking into account the cow's selection criteria. At every cause of mastitis, first aid is required, which includes applying ice cubes on the udder surface. Infected milk from infested teats should be drained three times a day and disposed of properly. To ensure sanitary disposal, a 5% phenol solution can be added to the contaminated milk. Suckling on diseased teats should be avoided by calves. When milking the herd, be sure to milk the healthy, non-infected cows first, then the infected cows. A familiar veterinarian should be consulted before therapy. The most common therapy for mild and moderate types of mastitis is intramammary antibiotic tubes, which are generally administered without knowing the type of bacteria that is causing the illness.[165,166] β-lactam antimicrobials, particularly penicillin G, are the first choice for treating mastitis caused by streptococci and penicillin-susceptible staphylococci. Systemic treatment, ideally in combination with IMM treatment, is advised in clinical mastitis caused by *S. aureus* and in severe cases of coliform mastitis.[167] Antimicrobial resistance is a major issue, and antibiotic selection should be based on the results of culture and sensitivity tests rather than on empirical therapy. It also produces antibiotic residues in milk, which may be very harmful to the health of consumers.[168] Bacteriophage therapy, probiotics, herbal therapy, immunotherapy, nanoparticle based therapy, stem cell therapy, native secretory factor, and other possible alternative therapies for mastitis must be used rather than antibiotics. Despite its many disadvantages, researchers argue that bacteriophage therapy could be a viable alternative tool against mastitis pathogens.[169,170] Animal feed containing microbial extracts and probiotics can be regarded as an efficient technique for treating cow mastitis.[171,172] Few research has stated that how probiotics taken orally affect the bovine mastitis. It was demonstrated that oral treatment of *L. casei* Zhang and *L. plantarum* P-8 drastically decreased SCC and increased milk production.[173] The self-assembly tilmicosin nanogel by a combination of SLN technology with in-situ hydrogel technology improves the treatment effect of tilmicosin against *S. aureus* cow mastitis.[174]

Herbal therapy can be used in the treatment of mastitis as it has no side effects.[175,176] Immunization and immunotherapy for the treatment of mastitis by sensitizing immune cells in the gland so that they are ready to respond quickly in the event of a new infection could be a viable alternative to the present dry cow therapy.[177,178] Advances in stem cell therapy and nanoparticle therapy are required to treat mastitis since they can be a novel approach to preventing mastitis in a safe, effective, and contamination-free manner, especially when dealing with multi-drug resistant bacteria. Leitner et al 2018[116] developed a new APT-based device that produces high-power, deep-penetration acoustic pulses that are distributed over a wide treatment area to cure clinical or subclinical mastitis in dairy cows. TRVPB has developed a mastitis treatment known as Bovine Mastitis Cure – PGF, which is a bovine platelet lysate (BPL), a freeze-dried preparation that speeds up the healing of mammary gland parenchyma and reduces tissue damage and its reoccurrence.

Perception and Creating Awareness About the Importance of the Disease

Researchers proposed three phases for mastitis (i) invasion of an organism (ii) infection (iii) inflammation. Cattle production contributes to economic development, rural income, poverty reduction, and satisfying the demand for animal-derived proteins in developing countries.[179] Around 1 billion people rely on livestock for their livelihood, moreover, livestock holders in developing countries are of small scale. The available literature on mastitis in developing countries makes to understand that the disease is a threat to small-scale farms due to its high occurrence in some herds. The detrimental effect is well established in developed countries, but it is extremely challenging in developing countries.[179] The key risk factor in identifying mastitis is due to lack of knowledge and awareness among the people. Creating knowledge and awareness among the farmers will improve the prevention by undertakings 18 preventive measures[118] and treatment for mastitis which includes teat disinfectant, sanitation in the farms, DCT, and udder health in the farms.[118,180–182] To address the problems, we should create the awareness of SCM in dairy cow owners on housing and management. Awareness should be made for the pathogens affecting the mammary tissue and for the transmission mode of mastitis to the dairy cow which is also in design and implementation of the control measures for SCM.[127] This review helps the farmers to raise awareness about the costs of mastitis and also motivates them to treat/take preventive measures. Many different control measures for mastitis include hygienic management principles, antibiotic treatments, teat dipping sealant, and intramammary devices. The use of cattle that are resistant to specific diseases can reduce the application of drugs of that disease which subsequently decreases the contaminated products and also improves the quality of the milk products.

Strategies to Reduce the Antimicrobial Usage in the Human and Animal Health

Lowering the need for antimicrobials and healthcare associated infections. Shifting the opportunities to encourage the antimicrobials being used to stimulate antibiotic control and management; limiting and ultimately phase out the antibiotic use in the agriculture; educating and informing health professionals, policymakers, and general public about the antibiotic susceptibility. Using a nationwide evaluation and control system that records rates of veterinary antibiotic use, resistance, and residues; attempting to change the incentives to prohibit the inappropriate usage of antibiotic in animals; Farmers, veterinarians, and pharmacist should be educated about the threats of antibiotic resistance, and the use of antibiotics in animals for non-therapeutic purpose should be phased out. Education on safe and effective medication use; regulation and the prohibition on the sale of over-the-counter drug accessibility; development of guidance at the community, state-wide and national level; enhanced sanitation and disease management. Routine statistical information and antimicrobial susceptibility testing observation to instruct the antibiotic selection. Increasing the number of accredited laboratories and these laboratories should issue antibiograms at a specified time frame to reduce inaccurate reporting and working to develop low-cost diagnostics.

Market Analysis

Bovine mastitis is becoming increasingly common each year as the number of dairy cows increases. With developments in the field of medical sciences, the overall mastitis market grows, and the global economy's GDP rises as well. Over the projected timeframe (2017–2023), the global mastitis market is expected to expand at a compound annual growth rate (CAGR) of 15.07%, with a market value of USD 7898.05 million. In 2021, the market was developing at a steady rate, and with major players increasingly adopting strategies, the market is likely to increase over the anticipate timeframe. According to the University of Glasgow's article "Potential Biomarkers of Mastitis in Dairy Cattle Milk Identified, 2016", mastitis costs the global dairy sector between US$19.7 and US$32 billion annually. Mastitis in dairy is estimated to cost the United States $2 billion annually and in the Canadian dairy sector CA$400 million (US$310 million) each year, or roughly CA$500 to $1000 (US$385 to 770) per cow, according to University of Montreal research. In research from Borchers and Bewley (2015), milk producers using technologies to measure mastitis parameters are about 25.5%. The average cost of mastitis is 50% for production loss, 35% for milk discarded due to disease, and 10% for medicine.[183] The cost of mastitis is divided between prevention, drug and diagnosis. In research from Aghamohammadi et al (2018), preventive measures cost roughly 105 CAD/cow-year.[184] According to a report published by a business research company, the global bovine mastitis medicine and diagnostics market has grown at a compound annual growth rate (CAGR) of 4.5% since 2015, reaching nearly $1,508.7 million in 2019. From 2021 to 2023, the market is expected to recover from the covid economics slowdown and grow at a CAGR of 4.6%, reaching $1,864.9 million. The market is expected to reach $2,046.0 million by 2025, and $2,705.0 million by 2030. The Bovine Mastitis Drugs segment is also predicted to grow by $293.5 million in global annual sales by 2023 that is veterinary centres segment will gain $202.2 million, the CTM kit segment will gain $25.7 million, the antibiotic segment will gain $110.7 million, and the sub-clinical mastitis area will gain $189.3 million in global annual sales.

Conclusion

In the present review, we have given an overview of subclinical mastitis infection. Milk quality should be taken into precedence above the quantity for farmers. Yet, in some cases, the volume of milk production draws greater concern. Subclinical mastitis as an economically significant illness in the dairy business requires further investigation. Mastitis is considered to be the second-largest cause of death in the dairy industry. To eliminate environmental infections and to minimize udder infection, comprehensive farm sanitation and strict milking control procedures are recommended. SCM has no obvious effects on the udder or milk quality, but it has a major impact on milk composition and human health. Subclinical mastitis is 30–40% more prevalent when compared to clinical mastitis. There is an immediate emergency to improve the milk quality and prevent unnecessary bacterial infection by implementing scientific management practices, hygienic milk production methods, and routine inspection of dairy cows for subclinical mastitis infection. Appropriate therapeutic approaches should be followed relying on antibiotic susceptibility testing. This approach will aid in the preservation of milk quality, hence reducing public health hazards and antibiotic resistance in humans.

Abbreviations

SCC, somatic cell count; AMR, Antimicrobial resistance; CNS, coagulase-negative Staphylococci; CARG, compound annual growth rate; IMIs, intramammary inflammations; ELISA, enzyme-linked immunosorbent assay; SAATK, *S. aureus* antibody testing kit; MBRT, Methylene blue reduction test; SOD, superoxide dismutase; MMA, mastitis metritis agalactia; AMU, antimicrobial usage; PMN, polymorphonuclear neutrophil; SDCT, selecting cows for dry cow therapy; DCT, dry cow treatment; BDCT, blanket dry cow therapy; APT, acoustic pulse therapy; ITS, internal teat sealant; MNPs, magnetite nanoparticles.

Data Sharing Statement

All the required data and materials are available within the manuscript.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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