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Review Article

Mastitis vaccine the need of hour

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Abstract: Mastitis caused by *Staphylococcus aureus* is a major health and economic concern in dairy animals, including Camelus dromedarius. Its ability to cause chronic, recurrent, and subclinical infections, combined with increasing antimicrobial resistance, makes it one of the most difficult pathogens to eliminate. Traditional treatments are often ineffective due to *S. aureus's* biofilm formation, intracellular survival, and immune evasion mechanisms. These challenges have shifted attention toward preventive strategies, particularly vaccination. This review summarizes key findings on the prevalence, immune dynamics, and vaccine development against *S. aureus* induced mastitis, with a focus on adjuvanted killed vaccines. Various adjuvants, notably Montanide (oil-based) and alum (aluminum hydroxide), have shown effectiveness in enhancing immune responses. Killed vaccines, due to their safety and stability, are frequently used and have demonstrated significant reductions in somatic cell counts, infection rates, and milk production losses in multiple studies. Improved vaccines were found to sustain high antibody levels for up to 60 days post-vaccination, while oil-based adjuvants improved immunity by slowly releasing antigens and stimulating stronger responses against key toxins. Though many studies focus on bovines and rabbits, research specific to camels is lacking. Vaccination during dry or periparturient periods appears to offer the most protection due to increased immune responsiveness and higher susceptibility during early lactation. While vaccines alone may not eliminate mastitis, they are a valuable part of integrated disease control when combined with good hygiene and management. Development of camel-specific vaccines remains a critical need to effectively control mastitis in camelid populations.

Keywords: Mastitis, *Staphylococcus aureus*, Camelus dromedarius, Killed vaccine

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Introduction

Mastitis in all of its forms is a health- and production-compromising malaise. Camel milk, which is nutritious and effective in various ailments, is deteriorating due to mastitis. Camel is third in number after cattle and buffaloes in contributing to milk production despite a comparatively low population [1]. Camel milk is highly nutritious and can be used for infant feeding because it is similar to human milk, with the additional benefit of lower lactose content [2]. This lower lactose content remains almost unchanged throughout lactation, substantiating camel milk as a blessing for lactose-intolerant individuals [3]. Camel milk has three times higher vitamin C content than cow milk, is ten times richer in iron, has fat equivalent to cattle milk, and has higher contents of unsaturated fatty acids. Antimicrobial proteins, including lactoferrin, lysozyme, and lactoperoxidase, help combat pathogens such as *Lactococcus spp*., *Escherichia coli*, *S. aureus*, *Salmonella typhimurium*, and rotavirus [4]. These proteins increase milk's shelf life, making it marketable even at higher-than-room temperatures [5,6]. Patients with diabetes may benefit from camel milk due to its 150 IU/mL insulin content [7]. Camel milk is a proven nutraceutical commodity at risk of deterioration due to bacterial contaminants. Milk-producing animals may experience mammary gland inflammation and mastitis, which deteriorate milk quality and quantity and cause pathological changes in the udder parenchyma [8]. The disease may spread through reservoir infection (e.g., infected animals, farmyards, or milking facilities), transfer from teat to teat, microbial penetration through the teat canal, or pathogenic colonization within the mammary gland [9]. Studies report a high prevalence of *S. aureus* (>60%) in Pakistan, with increasing antibiotic resistance [9].

Prevalence of mastitis in *Camelus dromidarius*

Prevalence of mastitis was seen 46.5% in the world's camel community, as per 16 papers, with different values starting from lowest 22% in Sudan, and highest 90% in Pakistan examined camel milk for estimation of mastitis using California mastitis test 76.0% in Ethiopia. Similar findings were noted by [10] in Sudanese camels, giving figures of 66.8%. This much higher prevalence was attributed to poor hygienic conditions of milking area and milking system. The techniques that had been used so for the estimation of mastitis in camel are not sure to indicate the presence of bacteria, for example, higher values of CMT, SCC, and ATP some-where were seen with no bacteria from quarters[9]. In camel milk there are a nucleated cell fragments which give the size range of somatic cells giving overestimation of SCC when counted by particle counters or methylene blue staining. Basal levels of cells and their physiological variations and no well-set threshold level of SCC in camelidae creates difficulty in enumeration of SCC and problem with mastitis diagnosis, respectively. Many a quality parameters like laboratory pasteurization count, preliminary incubation count, psychotropic bacterial count, and differentiated bacterial count are yet to be established [11].

Etiology

S. aureus and *S. agalactiae* were noted the commonest causes of camel mastitis in Sudan and Kenya [10,11]. *S. aureus* was found in almost all of the studies with the mean prevalence of 20.35% (1.8% in Saudi Arabia to 52.3% in Pakistan) among different studies. Although *S. aureus* resides intra-mammary but if found in the environment of mammary gland should be taken into ac-count for the intramammary infection. It was noticed that somewhere during lactation phase *S. aureus* is not much prevalent while in some other phases found in abundant. The high prevalence of *S. aureus* cannot be thought for eradication, so culling is solution. However low prevalence with *S. aureus* can be controlled. *S. agalactiae* was found 19.5% (2.3% in UAE to 64% in Kenya) on an average top second causative agent for camel mastitis. *S. agalactia* was found highest bacterial agent in camel mastitis. In some of the studies it was the top most mastitis causing bacteria in camel. Some of bacteria like *S. dysgalactiae* and *E. coli* were found with 20% among the bacterial count but were very fewer.

***S. aureus* camel mastitis**

S. aureus gets entry into teat orifice, breaks streak canal, and goes into mammary gland. The breakage progresses to streak canal keratin creating chances of intramammary infections because of injured or chapped teats. The first line defense by mammary gland, the washing out of bacteria by milk flushing, is no more effective once *S. aureus* adheres to epithelial cells. Moreover, the primary defense mechanism, the phagocytosis by neutrophil, is hampered by certain antiphagocytic factors depicted by *S. aureus* including capsule, protein A, and pseudocapsule. In addition to these lower contents of complement and opsonizing antibodies in milk are facilitating the survival of bacteria in mammary gland and establishment of intramammary infection [12]. *S. aureus* is such a potential pathogen that single colony identification on culture media reflects quarter infection. Moreover, the animal identified with Staphylococcus aureus is suggested to cull from production system. *S. aureus* was found in almost all of the studies with the mean prevalence of 20.35% (1.8% in Saudi Arabia to 52.3% in Pakistan) among different studies. Although *S. aureus* resides intramammary but if found in the environment of mammary gland should be taken into account for the intramammary infection. It was noticed that somewhere during lactation phase *S. aureus* is not much prevalent while in some other phases found in abundant. The potential issue with variable *S. aureus* is its false positive results because of irregular shedding of bacteria [13]. There is however a solution exists that is based on use of higher inoculum up to 0.1mL that will result in lowering risk of false negative estimation of results [14,15]. To overcome issue of false results of *S. aureus*, freeze-thaw and centrifugation is worthwhile. Freezing breaks clusters and hence increase sensitivity of test. Centrifugation of milk samples gives sedimentation that is reported to give positive results when there are low-shedding phase of Staphylococcus aureus is going on.The high prevalence of S. aureus cannot be thought for eradication, so culling is solution. However low prevalence with S. aureus can be controlled. However keratin is reported as bacterial growth inhibiter. *S. aureus* is known to associate with decreased milk production for longer period starting from initial signals of mastitis. The largest cow milk decrease was noticed to be 5.5 liter per day exactly week after its diagnosis as *S. aureus* mastitis. It is important to be noted that cure is limited with this kind of pathogen. Heifers harboring *S. aureus* in their gland are nearly four times more susceptible to give birth to calf with *S. aureus* intra-mammary infection. This was noted the largest disease risk factor. In addition to heifer as risk factor for *S. aureus* IMI, the milking machine is another salient risk factor. Some researchers also reported other factors like udder skin, teat skin, clothing, bedding, and flies.

Predisposing factors

Age of animal

Early age is less susceptible than to late age. It was found 80% of mastitis in camels of age 14-16 while camels of age of 5-7 years was 33.3% susceptible for camel mastitis in Pakistan [16]. Whereas same situation but with quite high percentage was reported that 75% of camels with age 4-7 years were affected with mastitis while 7-10 years were 91.43%, and 94.44% of 10 years of age were found infected sub clinically with mastitis [17]. High prevalence with later age was justified by reduced physiological immune system in later ages which allows the opportunity to minor bacteria to develop mastitis in the gland. Age of camel was significantly correlated with lactoferrin concentration where higher content were noted in younger animals (3-4 years). Lactoferrin was associated with subclinical mastitis which could be regarded as sign of severity of inflammation. The older animals are more prone to mastitis because of comparatively more dilation of teat. The teats of older animals, due to years of repeated lactations, is left partially opened on permanent basis which invites environmental and skin microorganism to get chance into teat canal. It was reported that older age animal is at double risk of contracting mastitis compared to younger lactating animal.

Lactation stage of camels

Lactating animals were found predominant with mastitis particularly associated with *Staphylococcus [18]*. Early and late lactation stages were more prone to mastitis compared to the middle period of lactation [19]. This factor was reported high in Pakistan, 54.5% early stage, 54.17% late, and 28.57% mid stage. However percent-age was less in some other countries having 39.8%, 32.6%, and 27.61% early, late, and mid lactation in Saudi Arabia. Highest mastitis was found near calving in studies conducted by [20]. The reason justification was lower resistance during these periods that make animals susceptible to mastitis. A positive correlation of mastitis with lactation stage was also stated in a sense that early lactation was associated with higher mastitis occurrence. The reason behind could be newer infections during early portion of dry period and two months of post lactation. This factor is significant in case of environmental mastitogens.

Tick infestation

The higher prevalence of mastitis was associated with tick infestation in study conducted previously [21]. They found udders to be infected nearly 98.3% as one or more CMT (California mastitis test), screening test for mastitis used in this study. Hence the tick infestation are predispose factor for udder bacterial pathogenicity. Tick infestation produces suitable environment for microbial invasion to udder.

Disinfection and Teat dipping

Studies have revealed that teat dipping is effective practice to beware of mastitis. Disinfection of teats and subsequent drying before start of milking was found lowering the teat end microbial pressure [22]. It was reported 54% reduction in *S. aureus* intra-mammary infections by application of pre-milking teat disinfection. Various teat dips are under practice most common of which carries chlorhexidine and iodine as an active agent. There has been debate of genotypic and phenotypic variation in Staphylococcus aureus due to stress induced by sub lethal levels of iodine[23]. This can alter antibiotic resistance of food born bacteria. In a study there was significant decrease of 5 mm of zone of inhibition of tetracycline antibiotic sensitivity due to use of 0.01% iodine against *S. aureus*. However variation in antibiotic sensitivity against use of iodine against *S. aureus* is variable. It must be worth mentioning that increased and frequent doses of iodine as teat dip may cause resistance in *S. aureus* [24]. Hand washing and teat/udder cleaning is very important to avoid contamination. There are few organisms that reside in human hands, and if proper disinfection is done leads to transmission of pathogens from hand to quarters wile milking.

Hygiene milking protocol

Subclinical form of mastitis caused by contagious pathogens especially *S. aureus* spreads among animal during milking. The foremilk stripping is associated with higher risk of contagious disease spread. However mentioning of foremilk as risk factor for intramammary infection is questionable. On the other hand herds with higher prevalence of intramammary infection with *S. aureus* are strictly advised to avoid foremilk stripping in order to limit the spread of contagious pathogen. It is mention-worthy that foremilk stripping had no effect on spread of environmental pathogen like *E. coli.*

Udder

The lower prevalence in some of studies revealed the setting posture of udder that presents decreased udder infections. Udder inflammation was associated with lower levels of somatic cell count that can be taken as sign of udder inflammation risk factors. Almaw and Molla (2000), 72% of the udder were infested by ticks and the incidence of mastitis was higher in heavily infested (30%) than non-infested (9%) udder [25]. Similarly, Bekele and Molla (2001) have also observed an association of mastitis prevalence with tick infestations and udder lesions [26]. Udder was reported a predilection site for tick infestation which caused udder skin and teat lesions that facilitated bacterial entry and left behind

permanent tissue damage [8]. Teat canal, teat orifices, and teat skin are supposed to be key sites of Staphylococcus aureus introduction and invasion that later on go thorough adherence in large numbers to teat epithelial cells of ducts of bovines compared to other bacterial isolates [27].

Antibiotic Resistance

The *S. aureus* has been studied extensively for antimicrobial resistivity as an eminent mastitis pathogen by various researchers and was reported to show 38-80% resistance. However *S. agalactiae* was found sensitive to antibiotics. However later in a study (Berghash et al. 1983) beta lactam group of antibiotics were found effective against *S. agalactiae*. In a survey of US Department of Health it was found that antimicrobial resistant due to selective pressure in *S. aureus* and *E.coli* facilitate antimicrobial resistance.

Improper Selection of Drug

One of important aspect of microbial resistance is improper administration of antibiotics. It is very important to take in account effective choice of drug and its fair enough concentration at injection site. For example, aminoglycosides are said to be showing lower lipid solubility hence decreased distribution of drug. Moreover to this, the particular nature of *S. aureus* staying intracellular and extracellular invasive organism results in tissue necrosis and hence reduced blood supply to the injured supply. In such conditions, no drug can work on necrotic area. The signs of inflammation like edema and swelling block the diffusion of antibiotics to milk duct system due to compression. The impaired drug distribution throughout gland makes it very difficult for drugs to come into direct contact with bacteria of mastitis.

Tissue Invading Character of Pathogens

The bacteria that are not in scar may be killed, but any time later on scar is broken down and multiplication starts resulting further damage to udder tissue and more scar formation. Host defense survival is another ability of *S. aureus* in udder tissue. The milk leukocytes, neutrophils in particular, are interacted by bacteria to produce intramammary infection. There is reduced opsonization, unavailability of source of energy, and milk casein and butter fat hindrance is important factors that make phagocytosis insufficient[28]. Even inside neutrophils some of *S. aureus* survive and most of drugs are unable to reach bacteria because of their inability to break the neutrophil wall. This particular ability of *S. aureus* i.e. surviving phagocytosis, make it resistant to host immunity if activated.

Improper treatment protocol toward *Staphylococcal* infection

The in vitro susceptibility of drugs used to be no assurance of treatment success in vivo. The usual methods of in vitro like MIC (minimum inhibitory concentration) and Kirby-Bauer disc diffusion method also show poor correlation with mastitis treatment outcome. In addition to this delicate tissue of teat duct and irresponsible manipulation of cannula creates risk for activity of antibiotic efficacy. Moreover to this trauma to quarter predisposes to re-infection. Pharmacokinetic behavior of mastitis drugs at trauma site is not known. Contaminated cannula may also source of infection. Hence, in in vitro testing that is not surety of in vivo efficacy, delayed drug therapy, non-specific drug selection, and too soon mastitis treatment stoppage causes anti-microbial resistance in *S. aureus*.

Immune dynamics

S. aureus is major cause of intramammary infections in dairy animals resulting in both clinical and subclinical ailment. Many of enzymes and several toxins and some of virulent elements like fibronectin binding protein, capsular polysaccharides are yielded by *S. aureus[29]*. All of the toxins seem to act on cell membrane. Alpha toxin specifically kills neutrophils and macro-phages, and resultantly infection is prolonged. However specific antibody (anti-alpha) deactivates toxins and blocks cytolytic activity of toxin on phagocyte. Other toxins e.g. beta and delta are problematic only when they come together. The most animal origin produced toxin is beta toxin which is secreted by *S. aureus*.

***S. aureus* vaccine production**

Need for vaccine production against *S. aureus*

Mastitis was worldwide economic loss tethering disease. Mastitis associated organisms were enumerated nearly 137 in numbers where *S. aureus* remained major and constant mastitogen. *S. aureus* was normally associated with subclinical, clinical, and even in chronic cases where antibiotics failure is not uncommon. This factor depicted its history of poor elimination rate from herd. Biofilm production, survival within macrophages and epithelial cells, and antibiotic resistivity were considered responsible factor for lesser elimination of this disease from herd. These limitations compelled towards vaccine development to avoid new *staphylococcal* infections that were considerable threat to dairy industry economics in terms of decreased milk production.

***S. aureus* vaccine effect on clinical and subclinical mastitis**

Calzolari et al., (1997) in their study vaccinated lactating and 7month pregnant cattle [30]. The findings of their results indicated significant ($P < 0.056$) decreased prevalence of clinical mastitis to 0.6% that were previously 2.3% from one of

their farms while 1.2% clinical mastitis was decreased to 0.5% in cattle that were vaccinated on other farm. Overall 40% reduction in *S. aureus* intramamary infection was noted whereas higher reduction was noted in clinical cases (65%) whereas in case of subclinical mastitis 44% reduction was noted collectively at both farms. The data of 582 cows from five different farms of Australia was collected vaccination with *S. aureus* and found 50% reduction of clinical while 25% of subclinical cases were noted. The research findings of Nordhaug et al (2010) from 114 heifers' revealed positive results of *S. aureus* vaccination, however results were not significant. Overall studies found positive effects on milk fat and also decreased somatic cell count. Some researchers suggested continued use of vaccines for better efficacy of *S. aureus* vaccines [31]. Heifers vaccinated with in-activated un-capsulated *S. aureus*, highly encapsulated *S. aureus*, *S. aureus toxoid*, and *streptococcus spp* cells gave finding of 54% reduction in clinical mastitis in prepartum while 75% reduction of clinical mastitis in postpartum vaccinated heifers compared to un-vaccinated [32]. The latent phase mastitis in vaccinated was found 69 and 58% reduced in prepartum and postpartum heifers, respectively, compared to non-vaccinated. The vaccine was shown as effective for six months. Similar results were also noted previously [33] regarding efficacy of *S. aureus* vaccine. The higher efficacy of vaccine used by formers is justified by higher bacterial antigen concentration and presence of polysaccharide capsule. Moreover the calving period appeared to be free of intramammary infection contrary to the later study was one of the beneficial points in the favor of higher efficacy of vaccine. Vaccination at drying off period was found advantageous by various research [34] stating that first week of lactation after calving is highly susceptible to infection. Higher positive results in later study were attributed to greater frequency of *S. aureus* intra-mammary infection and poor sanitation standards that were found existing in herds. Yousaf et al., (2009) in their trial evaluated montonoid adjuvant *S. aureus* vaccine in buffaloes. Efficacy of vaccines was determined in term of cumulative and point prevalence of mastitis at day 1, 30, 60, 120, and 180 post-vaccination. The vaccine efficacy was found more than 50% better in vaccinated than to control group. In addition to this minimum prevalence was noted in group of animal given levamisole HCl orally. The Holstein Friesian cattle did not develop new intramammary infection *with S. aureus*. However at herd level it was noticed that vaccine was not effective for staphylococcal intramammary infection rate. The opsonizing antibody level was not up to the mark which might be because of insufficient vaccine. Hence clearing of staphylococcal infection was by process of phagocytosis was no more optimum.

S. aureus mastitis vaccine and immunogenicity

Previous study used staphylococcal antigens in cows has been used in dry period and systemic antibody was noticed in serum, colostrum and milk against plain vaccine two weeks prior to calving [35]. Antibodies were increased in colostrum but fall back to background level just by two weeks which was indication of local antibody production due to plain vaccine inoculation. Commercial bacterin (Somatostaph®) and protein A against *S. aureus* was evaluated in cows to estimated response against intramammary infections. The cytological analysis of milk samples revealed 73% spontaneous response against bacterin while 83% was response noted against protein. However no differences were found in case of production lactation. Anticapsular antibodies against *S. aureus* in the process of phagocytosis by neutrophil was studied in cows. Injections of three smith *S. aureus* strains i.e. nonencapsulated, ridged capsule, and large clearing encapsulated were given to intramuscularly and supramammary lymph nodes with booster doses at 14, 42, and 70th day of primary inoculation. ELISA and serum agglutination titers were higher in diffuse and larger diffused variants till the end of experiment. Phagocytosis was also enhanced after immunization. Compact variants did not show any enhanced phagocytosis or higher antibody response while larger clearing diffused variants showed anti-compact antibodies along with noticed opsonic. There were found significantly lower clinical and subclinical mastitis in vaccinated animals with unexpected results in those given vaccine prepared from *S. aureus* isolated from them own. [36] injected heifers five weeks and two weeks before calving to check the efficacy of *S. aureus* hard-specific vaccine against intramammary infection. The results could not be significant regarding control of intramammary infections, however somatic cell count was found lower. There was antibody detection 35 days after primary immunization. In addition to this non-specific health betterment was noted in udder. A novel Trivalent mastitis vaccine equipped with encapsulated polysaccharide (type5, typ3 8, and type 336) was checked to see phagocytosis by neutrophils and antibody production in pregnant heifers. IgG1 and IgG2 found significantly higher in pregnant stage and sustained response were noted three weeks after parturition. The antibodies titers presented phagocytic effect against three killed *S. areus* serotypes. Healthy pregnant buffaloes were vaccinated with four different types of *S. aureus* vaccines to investigate their effect on milk production, fat yield, protein percentage, and somatic cell count. Simple bacterin, dextran sulphate adjuvant, live attenuated *S. aureus* vaccines were tested with twice administration of dose at 4 and 8 weeks prior to parturition. Somatic cell count was reduced significantly in vaccinate. Similarly, vaccines proved to be helpful in provision of quality and quantity milk production. In another trial avirulent strain of *S. aureus* was used as vaccine against challenge of virulent *S. aureus*.

Vaccines nullified the effect of virulent strains and no damage to tissues was seen. There was higher concentration of IgG antibodies seen both in blood and milk. In addition to this milk yield was increased in vaccinated animals. *S. aureus* bacterin, commercially available vaccine was tested against *S. aureus* and coagulase negative *S. aureus* intramammary infections and their subsequent effects on milk yield and milk somatic cell count in Holstein Friesian cattle in lactation. The trial revealed no significant (P>0.005) difference among vaccinated and control groups. The reason that justified this non-significant response was insufficient opsonization to help phagocytosis and elimination of staphylococci from mammary gland. A trial with 25 rabbits injected with four different vaccines of *S. aureus* i.e. Oil adjuvant killed vaccine, dextran sulphate adjuvant killed vaccine, live attenuated, and alum bacterin vaccines. Vaccines were injected subcutaneously at the rate of 0.2 mL per animal. In addition to this, separately, vaccine with booster dose at 15 days post primary injection in rabbit. Highest antibody titer was noted in live attenuated and dextran sulphate killed vaccine with geometric mean titer of 32-128 both, following which were oil adjuvants and alum adjuvanted killed *S. aureus* with 16-64 and 16-32 geometric mean titers, respectively, using indirect haemaglutination test. The control group of rabbits did not show such increased response. This could be justified the dextran sulphat's immune provoking ability. The least immune response produced by plain bacterin compared to oil adjuvanted and dextran sulphate was also noted by [37]. The oil adjuvant vaccine obtained slow higher level of antibodies which is correlated with slow release of vaccine from depots that are made by oil droplets (Watson (1987) and Nordhaug et al. (2010). Addition of dextran sulphate has also been reported to provoke the immune re-sponse significantly with sustained effects [37]. The information about vaccination of mastitis in camels has not been seen yet. The review presented here about vaccine trials will be from other ruminants especially bovines. Mastitis in no doubt complex disease but optimism towards some of efficient vaccines is the need of the hour. The advancement of bacterial pathogenesis knowledge and positive immunological signs against pathogens prompted workers to develop vaccines for control and eradication of mastitis. Pellegrino et al (2008) experimented S. aureus a virulent vaccine in heifers challenged with virulent strain of same pathogen before parturition. Specific immunoglobulin (IgG) to this pathogen in the blood, and in-creased slight increased milk yield was observed. Observing no clinical signs they conferred increased specific im-munity and improved post challenged state in inoculated heifers. Vaccine containing oil as adjuvant prompted higher production of immune response against alpha and beta production than to cabopol [38]. Concentration of IgG1 in the milk was high in case of oil adjuvant S. aureus vaccine local swelling was observable at injection site, however immune response was not reduced rather protective char-acteristics were noted. Decreased milk yield loss, milk fat and protein, and lower somatic cell count with increased immunity level was seen significant compared to control group. Isolated *S. aureus* and *S. agalactiae* from n=95 bovine milk samples to check pathogenicity and immunogenicity. They found Al (OH) 3 adjuvant bivalent mastitis vaccine quite safe, stable, and sterile to use. The cumulative mean titer of antibody was found many folds higher in vaccinated (44.9) than to non-vaccinated (2.12) experimental animals [39] evaluated challenged vaccine against *S. aureus* organism cultured from cows' milk. Total of 9 cows were vaccinated and com-pared against 10 non-vaccinated cows. Results were reporting 70% protection in vaccinated whereas non-vaccinated cows were 90% vulnerable to udder infection by Staph aureus. Mata, (2013) evaluated the worth of the current mastitis vaccines using fifteen research program comprised of 7941 cows. Compared to control there was slight improvement but economics were important to consider. Hence vaccine against mastitis was used as complement of all preventive measures.

Vaccine evaluation

Rabbits as mastitis experimental animal

S. aureus induces suppuration, abscessation at infection, pododermatitis, and mastitis in rabbits in genera. Rabbits can be induced experimentally with high and low virulent form of *S. aureus*, and colonization can be found everywhere in rabbit body. Among other infections, mastitis is one of the leading causes of culling in rabbitries, followed by abscesses and pyometra. *Staphylococcus's* infection caused by *S. aureus* may produce fatal form of septicaemia and supporative inflammation in any site or organ of rabbits. According to one of recent report 78% of *S. aureus* prevalence was noted in rabbits on animal basis. It is described that mastitis may occur at any stage during lac-tation. It was also noted that re-infection may occur during subsequent infections even after recovery. Reports have declared that there used to 4-19% of mastitis prevalence in rabbits in lactation at any time [35]. Rabbits do suffer two types of *staphylococci infection*; acute/gangrenous and chronic/purulent mastitis. The former type is also called blue-breast, characterized by swollen, reddened, and, warm, and later becoming cyanotic mammary gland [40]. The lesion changes to oedamatous and haemorhagic type and puts doe to death due to starvation within hours or changes to chronic on survival. The later form is characterized by abscess formation measuring 2-10 cm diameter and developing into caseous material in mammary gland during period of 14-21 days. Rabbits look lethargic and suckling to their kits seems difficult. Studies on immunizations have been also carried out. *Staphylococcal* bacterins have been tested in rabbits. There are reports to

partial protection against *S. aureus* in various experiments. Autogenous vaccines in field trials have been found effective against sever virulent organisms. However, infections by *S. aureus* are complex and results due to autogenous vaccines are not consistent. Extensive research to combat staphylococcal issues is suggested [41].

Alpha-beta toxin

Rabbit as animal model for mastitis studies has been used since last few decades. It was studied to estimate effect of immunization in rabbits against alpha/beta toxins of *staphylococcal* species when are given intra-mammary challenge. Research showed higher antibodies due to alpha toxin immunization that shortened the presentation of blue-breast, a lethal hemorrhagic edematous. However anti-beta toxin antibodies were not effective against clinical picture of disease.

Panton-Valentine leucocidin or delta-toxin

In another experiment conducted on delta toxin (Panton-Valentine leucocidin) in combination with alpha toxoid and alone were used to investigate the effect of immunization on blue-breast disease. To astonished results, it was found that beyond presence of antibodies against all three toxins there was no protection seen in case of blue-breast that is produced due to challenge by *S. aureus* strain CN 6708. There could be some other antigen that could have produced protection against blue-breast.

Ovine mastitis pathogens

The ovine mastitis pathogens with 19 strains were also experimented to investigate their effects on mammary gland. Infections were produced against due to strains of ovine mastitis. The results also provided graded response against bacterial species in rabbits with *S. aureus* to be most dangerous following which were *Escherichia coli, Staphylococcus hyicus* and *Staphylococcus chromogens*.

Bovine mastitis pathogens

S. aureus avirulent mutant strain RC122 was studied in rabbit and bovine. The strain was found less pathogenic compared to RC108 for experimental skin model in rabbis. The RC122 strain was found potential strain to be used as vaccinal agent in experimental trials because of its ability to produce skin lesions on rabbits but reduced udder pathogenicity.

Mastitis vaccines

Vaccination used to be necessary effective measure when there is treatment is more costly than cost of vaccine, and prevalence to be in such number that can influence economy and health challenge to animal. Vaccines become fruitful in this scenario. Recent study carried out in United Kingdom evaluated its efficacy in nearly 3000 cattle from 17 randomly selected farms. The study plan comprised of three groups with vaccination of commercial vaccine as per manufacturer's prescription in first group, vaccination of cattle with each 90 days of duration, and third one left as un-vaccinated. The data of 120 days vaccine evaluation did not find significant difference in mastitis spread. Milk yield and milk solids were higher in group that was vaccinated as per commercial regime compared to control group. The additional vaccination reduced the odds of mastitis occurrence. No culling was found in the name of mastitis. However, in field trials vaccine failures was also noted that could be because of combined effects of direct and indirect effects. A recent study focused on staphylococcal infection reduction by vaccination with significant results. They found significant decrease in number of staphylococcal mastitis from two herds. Mastitis occurrence is affiliated with greater number of bacterial agent's along with specie variation. The proteomics could be effective tools to properly name the etiology of mastitis [42]. Despite of greater range of limitation in effective mastitis vaccine, culling has been significantly lowered with use of mastitis vaccine [43]. Vaccination has presented positive impact on economics.

Adjuvant killed *S. aureus* vaccines

An ideal mastitis vaccine is expected to lower current infection and to prevent new intramammary infections. Not only the antigen sufficient was obtaining optimum natural immunogencity but adjuvants played vital role as supportive agents. However, Freund's incomplete adjuvant and aluminum hydroxide were reported most common adjuvants in *S. aureus* mastitis vaccines [44]. Adjuvanted killed and live vaccines prepared against *S. aureus* were trailed in bovines by researchers in Pakistan during duration the year of 2006. The efficacy of vaccines was measured in terms of count of somatic cells, and effects on changes in fat, protein, and milk yield. The vaccines presented significant positive results. However, comparing the efficacies within vaccinated groups was found non-significant. This scenario reflects equally effective killed vaccines compared with live vaccines against *S. aureus*. Killed vaccines are safe to use, and there are no chances of reversion to virulence. Encapsulated killed *S. aureus* vaccine faced non-significant infections in study conducted on heifers from 16 dairies. Similar findings were concluded by (Nordhaug et al., 2010) and Compiling data on all parameters, the entire udder presented sound protection throughout lactation. Higher efficacy of vaccine was also correlated with higher concentration of antigen. In addition to this, higher frequency of *S. aureus* intramammary infections and poor sanitation were also helpful in vaccine's efficacy. However, first 3-4 week of calving and initial higher

inframammary infections by *S. aureus* were very important factors in determining vaccine efficacy. Studies had reported effective results of vaccination during dry period with speculation of better immune response during this period, and higher susceptibility of udder during first week post parturition [34]. However, contradiction existed regarding significant difference of prepartum and postpartum vaccine efficacy. In another study conducted in Canada revealed significant increased population of CD4 lymphocytes during 4th week of initial inoculation. There was also increased CD8 lymphocyte population during 2 weeks periparturition. An inactivated encapsulated and un-capsulated vaccine was developed against *S. aureus*. The data of 164 cows from two commercial dairy farms dis-closed fewer staphylococcal infections in vaccinated animals. The milk of vaccinated presented significant lower number of staphylococcal infections along with less than 500,000 cells/mL.

Oil adjuvant *S. aureus* vaccine

The oil adjuvant potentiate immune response, localize the antigen, and gives slow antigen release (Peters, 1993). Motanides are prepared by water in oil emulsions. Montanides were reported to elicit greater immunity against alpha and beta toxins [45]. They are also found inducing quicker and better immune response in recent trial. Montonoid adjuvanted plain bacterin *S. aureus* vaccine was used in buffaloes and studied for their effects on occurrence of mastitis. The study revealed significantly lower point prevalence in vaccinated group with 50% protection against mastitis. This study also used Levamisole HCl as immune modulator but concluded with non-significant results with this addition. An earlier study (Ishikawa et al., 1982) reported higher cure rate due to oral use of Levamisole HCl along with montonoid adjuvanted vaccine against *S. aureus* infection. The reduction of clinical cased has also reported by[38]. However, few newer cases was reported in groups that were vaccinated compared to unvaccinated animals (Norcross and Kenny, 1986). On the other hand studies done after presented reduction in prevalence of mastitis in vaccinated animals.

Alum adjuvant *S. aureus* killed vaccine

Alum adjuvants stimulate humoral respfpeteraonse. Alum (potassium aluminum sulphate) is mixed with bacteria that make it alum precipitated bacterin. In second method, Aluminum hydroxide gel is mixed with vaccinal agent that name it to be a luminum-adsorbed bacterin. Recently alum adsorbed by TLR7 has been used as adjuvant in staphylococcal vaccines. The adsorbed alum adjuvant enhanced effectiveness in protein-based vaccine. The researchers found this modified alum adjuvant tethering antibody response towards T-helper cells type 1[46]. Alum adjuvanted *S. aureus* vaccines was reported to elicit 4 month's consistent Ag-specific cellular and humoral response in mice against infection *S. aureus* vaccine adjuvanted with alum proved more efficacious compared to MF5 in some of parameters like FhuD2 and Csa1A. However, titers of antibodies remained consistently higher. *Staphyloccus aureus* adjuvanted with alum in phosphate buffered saline was investigated for its effects against skin and soft tissue issues [47]. *S. aureus* in association with aluminium hydroxide proved effective in saving mice while in other bacterial infections e.g. tetanus toxoid and Aluminum oxide alone. The data suggested higher eliciting of type 1 immunity because of aluminum hydroxide was an important aspect to explore its role in staphylococcal vaccine[48].

Conclusion

Mastitis caused by *S. aureus* is a complex and economically damaging disease affecting dairy animals, including Camelus dromedarius. The pathogen's ability to evade host defenses, resist antibiotics, and persist within mammary tissues has made treatment challenging and often ineffective. These limitations have driven interest in preventive approaches, particularly vaccination. Among the various options, adjuvanted killed vaccines have shown considerable promise in reducing infection rates, improving immune response, and minimizing milk production losses. Oil-based adjuvants like Montanide and aluminum-based adjuvants such as alum have been particularly effective in enhancing antigen presentation and sustaining antibody production. While positive results have been reported in bovine and rabbit studies, especially when vaccines are administered during the dry or periparturient periods, field outcomes remain inconsistent. These variations often stem from differences in farm management, vaccine formulations, and immune status of animals. Despite these challenges, killed vaccines stand out for their safety profile and ability to reduce somatic cell counts and the incidence of both clinical and subclinical mastitis. However, a major gap exists in camel-specific vaccine development. Current knowledge and data are largely derived from other ruminant species, and extrapolation to camels may not account for important physiological and immunological differences. Future efforts should prioritize targeted vaccine research and field trials in camels to establish effective immunization protocols. When integrated with sound management practices and hygiene protocols, vaccination holds strong potential as a cornerstone in long-term mastitis control strategies, reducing disease burden and improving overall productivity in camel dairy systems.

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