Volume-8
Issue- I
June - 2023

Rajarata University Journal

ISSN: 2362-0080
www.ruj.ac.lk/journals/

Category: Review Article

Recent Developments of Vaccines to Control Mastitis in Dairy Cows - A Review

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ARTICLE DETAILS

Article History
Received: 04th November 2022
Accepted: 09th September 2023
Published Online: 15th May 2025

Keywords
Dairy industry, Dairy cattle, Immunization, Mastitis, Pathogens, Inflammation, Therapeutics, Vaccination

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ABSTRACT

Recently the dairy industry has become one of the economically important fields in the livestock sector worldwide. Transmission of infectious diseases among animals is a major problem that significantly affects the quality and quantity of dairy products. Bovine mastitis is an economically significant disease in the dairy industry caused by several contagious and environmental pathogens. The disease is considered a most costly and complex disease which causes a struggle to achieve the quality goal of milk producers. Control and prevention of bovine mastitis are needed to reduce the effect on the quality and quantity of dairy producers and maximize the dairymen's profit. Although some conventional controlling programs, including lactation and dry cow therapy, dietary supplements, antibiotic therapy, and hygiene cleaning procedures, have been developed with time, veterinary researchers have recommended vaccination as the most effective way of controlling bovine mastitis. Due to the efficacy of vaccination-induced immunization and the reduction of incidence of bovine mastitis, veterinary researchers have further evaluated different vaccination clinical field trials against mastitis. This review article is an attempt to analyze recently developed vaccination strategies against different causative infectious pathogens, their challenges, and future trends towards vaccine development against mastitis.

1. Introduction

As a traditional raw material for the production of a range of dairy products, it is important to produce quality bovine milk with proper nutritional conditions. However, maintaining a dairy cow in good health is a major challenge for the dairy industry.[i]Mastitis, an inflammation of the mammary gland has been an economically significant disease in the dairy industry [1]. As a multifactorial disease, mastitis has been one of the most frequent and costly contagious diseases for all involved in primary milk production including small-scale and large-scale farmers worldwide. Bovine mastitis affects both the quality and quantity of milk by influencing negatively the animal welfare and dairy industry. Most veterinarians have concluded that mastitis is a powerful risk factor in dairy farms due to the vertical transmission of infection. Because of the struggle to achieve the quality goal of many producers, it causes significant loss in the dairy industry imposing a serious economic burden [2].

Mastitis is caused by a very wide variety of infectious pathogens which are classified as contagious pathogens and environmental pathogens. Environmental pathogens which are present in the feces, soil, and bedding include *Enterococcus spp, Escherichia coli, streptococcus uberis,* and *staphylococcus epidermis.* The most common contagious pathogens associated with mastitis are *streptococcus agalactiae, Staphylococcus aureus, streptococcus deglaciate, Klebsiella pneumonia, Mycoplasma Bovis,* and *Corynebacterium spp* [3].

During the infection of the mammary gland, those pathogenic bacteria release some substances which lead to an increase in the permeability of vessels. So, bacteria can penetrate easily into the udder through the teat channel of milk-producing tissues. As a result of the invasion of pathogenic microorganisms, they start to multiply and produce some virulence factors inside the udder. They attach leukocytes which can engulf and destroy the bacteria. The damaged milk-secreting tissues lead to lower the quality of milk yield by elevating the somatic cell count in milk, reducing curd firmness on fat and casein composition of milk [4].

As a deadly prevalent disease which rapidly spreading among dairy cattle, diagnosis of bovine mastitis is a major challenge for veterinarians.

Although the diagnosis of the disease is depended on the type of infectious pathogen, the most common signs of the infected cattle are redness, swelling of the udder with high temperature and pain, anorexia, depression, and disease in milk production in affected quarters and watery milk. Also, the infected milk may contain clots or flakes. According to their clinical features, mastitis can be classified into two groups subclinical mastitis and clinical mastitis. Based on the stage of disease, clinical mastitis is also three types such as acute mastitis, subacute mastitis, and chronic mastitis [2].

As one of the most frequent and contagious diseases, mastitis infection can't be fully eradicated. So, control and prevention have been recommended as the most suitable treatment process for mastitis. As it is not caused by a single pathogen, the development of a single controlling method is not effective to eradicate mastitis. Effective control can be achieved through applying hygienic measures during milk collection, using proper milking machines, lactation and dry cow therapy, sanitary programs, disinfection, and maintaining a dry and clean environment. Antiseptic and disinfectant agents can be used to prevent the occurrence and transmission of infectious pathogens [5]. Although several strategies have been developed to control mastitis, they are not always practical and successful. So improved control and prevention are needed to maximize the dairymen's profit and to improve the quality of milk for consumers. Furthermore, some advanced therapeutic regimens such as antibiotics, immunotherapy, bacteriocins, bacteriophages, antimicrobial peptides, genetic selection, and probiotics have been developed to treat mastitis. However, antibiotic therapy remains some problems such as the development of antibiotic-resistant strains, and resistant strains entering into the food chain. So veterinary researchers have recommended that vaccination can be used as a prevention method against mastitis thereby eliminating the use of antibiotics in food animals. As other methods are often apparently insufficient to control the disease, vaccination has been recommended as an effective method with a reduced overall incidence of disease [6], [7].

Vaccination is capable of protecting against predominant, environmental and contagious pathogens. The main focus of vaccination against mastitis is to obtain reduced inflammation at the site of infection with high efficiency and cost-effectiveness. Veterinary researchers have focused their attention on vaccine development to prevent or mitigate inflammatory infections. Several vaccination strategies have been developed with the use of advanced technology associated with molecular biotechnology, molecular biology, and immunology. Normally vaccine development can be achieved through several experimental technologies like DNA, RNA (nucleic acid vaccines), whole pathogen vaccines, protein vaccines as well as subunit vaccines. Recently developed vaccine strategies against mastitis include surface polysaccharides, inactivated bacteria, and toxoids, DNA expression vector plasmids, live attenuated vaccines, autogenous vaccines, crude extracts of encapsulated bacteria. With several clinical experimental trials, veterinary researchers have achieved the spontaneous cure rate of infections and lessened the severity of numerous infectious diseases. Several vaccination strategies against mastitis have been involved in elevating the level of specific antibodies in the blood, inducing both humoral and cellular immune responses, as well as reducing the incidence of mastitis. So vaccination has been recommended as a highly considerable and applicable prevention option generating memory T cells to maintain an adequate level of immune responses in the mammary gland [8].

2. Vaccine development strategies against Mastitis

Mastitis, one of the economically devastating costly diseases is the inflammation of the mammary gland in dairy cows due to several bacterial, mycoplasma infections. As it affects both the quality and quantity of milk, prevention of mastitis using effective immunological tools like vaccines is needed. Most veterinary researchers have focused their attention on several vaccination strategies against different causative microorganisms for mastitis. The recently developed mastitis vaccines have been classified into several groups such as whole organisms (cellular lysates, inactive and attenuated vaccines), subunit vaccines (toxins, surface proteins, polysaccharides, and also mutant core antigens. Also, they can be categorized as monovalent and polyvalent vaccines according to the number of targeted pathogens [9].

2.1 Vaccine development strategies against *Staphylococcus aureus*

Staphylococcus aureus is one of the predominant mastitis pathogenic bacteria which mostly present in the surrounding environment of dairy farms. So, researchers have developed different vaccination strategies against *Staphylococcus aureus*. (R, 10, 21) A group of veterinary researchers has studied a mastitis vaccination strategy using bacterins, crude bacterial extracts, or a purified exopolysaccharide from biofilm bacteria [10]. Also, several field trials have been conducted with the pseudo capsule or slime, capsular polysaccharide, types CP5, CP 8, and

CP336 linked to protein carrier CP5 co entrapped in liposomes with the alpha-toxin, a mixture of slime in liposomes, toxoid, and different inactivated bacteria to protect against mastitis. The main target of this type of vaccination strategy was to obtain reduced inflammation at the site of injection, and high efficiency against disease [11]. DNA Expression vector plasmids have been used as vaccines to activate the humoral and cellular immune responses. The ability to express and secretes a large number of proteins that are essential for the virulence of bacteria lead to the use of the *Staphylococcus aureus* plasmid as a vaccine to treat mastitis. Here they have tested the recombinant protein alone as genes in a plasmid expression vector. Two plasmid expression vectors against *staphylococcus aureus* have been tested to express the Fnbp or CIFA proteins. The main target of their experimental trials is to test the induced expression of appropriate antigens after transfection into cells [11].

More researchers have performed their studies aiming at the prevention of mastitis caused by *Staphylococcus aureus*. Whole pathogen vaccines devaccinet is one of the developed strategies which induce robust immunity against natural exposure. The inactivation of whole bacteria has done by heat or formalin [11]. Some vaccinations have also been tested with some commercially available vaccines against mastitis caused by *Staphylococcus aureus* such as the Lysigin vaccine which contains a lysed culture of five strains of bacteria [12]

To reduce the somatic cell count and the fat content of the milk composition, a vaccine was employed in the basis (Denis et al.) of a crude extract of *Staphylococcus aureus exopolysaccharides*, inactivated highly encapsulated *Staphylococcus aureus* cells. The results of their experimented trials have revealed a protective effect against *Staphylococcus aureus* mastitis with high efficacy [13].

The United States of America has experimented with a polyvalent whole-cell vaccine comprising 5 phage types of lysed cultures. They have concluded that some staph / Lysigin vaccine gives a positive effect on *Staphylococcus aureus* cells by reducing the clinical severity of bovine code mastitis and lowering the somatic cell count on milk. Also, they have reported a trivalent vaccine composed of S aureus serotypes 5,8 and 336 lysates which stimulate the production of IgGI and IgG2 in serum [14]. Although several vaccines are developed against *Staphylococcus aureus* due to the lower efficacy of vaccines, a type of conjugative vaccine comprising an *S aureus* cellular polysaccharide type 5, 8, and 336 combined with poly (DL-lactide co glycolide) microsphere has developed to enhance the phagocytosis and trigger the production of antibodies. Furthermore, a DNA vaccine encoding CIFA has shown a high level of antibody response in dairy cattle. To reduce the multiplication of *S aureus* in the mammary gland, another trial has been conducted with a vaccine composing an S aureus extracellular compound—a conjugate vaccine [15]. A conjugate vaccine with CIFA and diacetylated play N β (1, 6) acetyl glucosamine (DPNAG) OF S aureus was shown to have high immunogenic effects and prevention of mastitis caused by *S aureus* [16].

In the case of controlling mastitis caused by *Staphylococcus aureus*, researchers have developed two vaccines using the extracted protein A for *Staphylococcus aureus* and commercially available *staphylococcal* bacteria. To evaluate the vaccine, they tested the somatic cell count of the milk collected from vaccinated cows with two vaccines. Vaccination with *Staphylococcus aureus* mastitis vaccine containing whole inactivated bacteria with pseudo capsule α, β toxoids, and mineral oil as an adjuvant has shown a potential protective effect for controlling mastitis by reducing the staphylococcus dissemination in the farms [17].

MASTIVACS 1 is a vaccine designed using a *Staphylococcus aureus* bacterial strain grown in Columbia broth and Freund's adjuvant. It has shown an adequate level of production of IgG-specific antibodies and highly significant protection against *Staphylococcus aureus* causing mastitis. Research work has been conducted to develop a mucosal vaccine to reduce the incidence of disease caused by *Staphylococcus aureus*. They have resulted in a high satisfactory level of T cell migration at the mammary mucosal site according to this vaccination approach [18].

Different vaccination strategies involving bacterin formulations from strong biofilm bacteria with different Slime Associated Antigenic Complex (SAAC) have been evaluated to check the efficacy of the SAAC-specific antibodies induced by the immunizations in the protection against an inflammatory effect with mastitis caused by *Staphylococcus aureus.* To reduce the *S aureus* infection, one commercially available intramuscular vaccine has been tested [18].

As the main udder pathogen causing mastitis, Researchers have found some commercially available vaccines like STAR VAC, and SP 140 against *Staphylococcus aureus.* Although these commercially available polyvalent vaccines were not beneficial in improving udder health, reporters have shown the transmission of the disease has been somewhat controlled among vaccinated dairy cows with these types of vaccines. MASTAVAC is also one of the recombinant enterotoxin type C mutant vaccines which have been developed to lower the somatic cell count.

Researchers have shown protection against *S aureus* intramammary infection during the lactation with MASTAVAC vaccinated cows [19], [20] .

A south Brazil group of researchers have focused their attention on a different opinion on the prevention and control of mastitis. Some plants have some antibacterial activities against *S aureus* due to the presence of several secondary metabolic phenolic compounds. Plant extracts from *Alternanthera brilliant, Foeniculum Vulgare, Alore arborescence, Saligago chilensis Meyer, and Metha spp-like* plants with antibacterial activity have been examined to develop a vaccine against *Staphylococcus aureus* effect on the occurrence of mastitis. Inactivation and inhibition activity of the antibacterial plant extracts has been used to prevent the activity of *S aureus*. Furthermore, they have examined the anti-inflammatory activity of these plants and also promote the efficacy of these types of vaccines against mastitis caused by *Staphylococcus aureus* [21].

2.2 Vaccine development strategies against *Coliform Bacterial spp*

2.2.1 *Escherichia coli*

As a major etiological agent of environmental mastitis, researchers have focused their attention on the prevention of coliform mastitis. Heterogeneous oligosaccharide antigens derived from *E Coli* have been tested as a vaccine against coliform mastitis. Also, there are some commercially available vaccines includes (MASTIGUARD, and J VAC) against coliform mastitis. The researchers have observed a significant reduction of clinical mastitis with these commercially available vaccines compared to non-vaccinated animals [22].

The potential mechanism of the J5 vaccine against *Escherichia coli* has been studied in a research process due their efficacy to protect the mammary gland from mastitis stimulating the cell-mediated arm of the immune response.

As most researchers have worked on J 5 vaccination strategy against coliform mastitis, the action of the J 5 vaccine has been reported in some events. Initially, the vaccine binds to the AC cells migrate into CD4 or CD 8+ cells which are related to the class of α, β T cells. This phenomenon leads to developing a memory response after 2nd or 3rd contact [23].

There are two commercially available vaccines recommended against mastitis including the Bacterin toxoid vaccine and Endovac Bovi R with re 17 mutant Salmonella Typhimurium bacteria toxoid. As the main focus of the coliform vaccines, they have concluded that the reduction of incidence, severity, and duration of infections [24].

In the case of controlling mastitis caused by *Escherichia coli*, a vaccine containing 0111:34 *E Coli* rough mutant bacteria has developed and the effect of vaccination on the incidence of clinical mastitis and milk production has been examined [25].

An autogenous vaccine has been developed using *E Coli* strains due to their high antigenicity and immunogenicity. In the vaccine preparation, the antigenicity of *E Coli* has increased by a well-defined lipopolysaccharide complex which can be used as a powerful stimulant of the immune system. Here *E coli* isolates are used as immunogens for the autogenous vaccines [26].

2.2.2 Klebsiella pneumoniae

Klebsiella pneumonia is another type of coliform bacteria that causes serious infectious diseases in the livestock sector. Although several antibiotic therapeutic techniques were used to eliminate infectious diseases caused by *Klebsiella pneumonia,* their efficacy has become very low due to their widespread antibiotic resistance. So many researchers have recommended vaccination as the most feasible and promising strategy to prevent mastitis caused by *Klebsiella pneumonia* infections. Different vaccination strategies against *Klebsiella pneumonia* have been proposed to develop protective immunity [27], [28].

The recently developed vaccination approaches include attenuated vaccines based on genetically modified bacteria, inactivated whole-cell vaccines, outer membrane vesicles containing numerous virulence factors, polysaccharide, and lipopolysaccharide-based vaccines, protein-based vaccines (recombinant or purified from bacterial extracts), conjugate vaccines including PS protein or LSP protein fusions and ribosomal vaccines. Furthermore, a novel vaccination approach has been tested using a siderophore receptor protein-based vaccine to prevent bovine mastitis caused by *Klebsiella pneumonia*.The ride subunit vaccine is another tested mastitis vaccine against *Klebsiella pneumonia*. To evaluate the protective efficacy of the novel recombinant subunit vaccines, veterinary researchers have developed this vaccine containing the protein YidR against bovine mastitis caused by *Klebsiella spp* [29].

2.3 Vaccine development strategies against *Streptococcus uberis*

Streptococcus uberis is one of the mastitis-causing minor pathogens. Due to their ubiquitous presence in the dairy environment, it has been a significant problem in the case of clinical and subclinical mastitis. So, researchers have targeted the vaccination against *Streptococcus uberis* to decrease the number of intramammary infections and to prevent the usage of antibiotics [30]. An

experiment has been conducted using a crude culture filtrate protein cocktail containing plasminogen activator against *Streptococcus uberis*. It has been suggested as an efficient vaccine against *streptococcus uberis* which reduces the incidence of infection and reduce the severity of infection in vaccinated animals [31].

Further veterinary researchers have experimented with several vaccine approaches like killed *S uberis*, and plasminogen activation factor to reduce the severity of infection. With the advancement of technology, a recombinant adhesion molecule of *S aureus* and sortase anchored proteins derived from *S uberis* have proven their efficacy against clinical mastitis. Most of the vaccine approaches have targeted the increasement of the level of interferon γ which is specific for the invitro killing of *S uberis* in milk. However, there were no commercial vaccines available.

A vaccine has been developed based on the several virulence factors of *Streptococcus uberis* such as CAMP Factor, PAU A, lives *Streptococcus uberis* 0140J, and bacterial surface extract. (Larriestra.) Due to the increment of frequency of mastitis caused by *Streptococcus uberis* bacteria, the researchers have conducted more attempts to produce a vaccine against *Streptococcus uberis*. As one of a target, a killed *S uberis* bacteria has been used to reduce the number of bacteria in milk. Although some studies have targeted the development of live vaccines against *Streptococcus uberis,* they have concluded their lower applicability of them. So, there were no commercially available vaccines found against *Streptococcus uberis* [32], [33].

UBAC is a one-subunit vaccine developed to reduce the clinical signs of mastitis and bacterial counts. Lipoteichoic acid from the biofilm adhesion components of *S uberis* has been used here. Using the whole killed *S uberis* multiple inflammatory vaccines have been developed to protect the bovine mammary gland from the infection of *Streptococcus uberis* [34].

2.4 Vaccine development strategies against *Streptococcus agalactiae* and *Streptococcus dysagalactiae*

Due to the disavailability of commercially available vaccines against mastitis caused by *Streptococcus agalactiae* and *Streptococcus dysagalactiae*, researchers have focused their attention on a recombinant vaccine containing surface immunogenic protein of *S agalactiae* and a conjugate vaccine using a capsule of predominant serotypes. According to their results, a recombinant vaccine containing surface immunogenic protein of *S agalactiae* has shown a positive effect in increasing serum IgGI antibodies against mastitis [35].

2.5 Vaccine development strategies against *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a mastitis-causing pathogen that poses a significant hazard in the livestock sector by causing 51,000 infections per year. Due to the presence of a large genome compared to the other sequenced bacterial spp, *Pseudomonas aeruginosa* has a higher degree of capability to develop vaccines against different infectious diseases. Many researchers have focused their attention on controlling mastitis against *Pseudomonas aeruginosa* based on their ability to produce a huge number of regulatory enzymes involved in the transportation, metabolism, and expulsion of organic compounds. A vaccination attempt has been made to develop a novel multiepitope vaccine for *pseudomonas aeruginosa* by mainly targeting the major membrane proteins on their membrane. Immune informatics, bioinformatics, and molecular modeling studies have been involved in the development of these advanced therapeutic elements as more efficient prevention methods against mastitis [36], [37].

Additionally, to the multiepitope vaccines, an autogenous vaccine has been developed to control and prevent *Pseudomonas aeruginosa* mastitis outbreaks. The efficacy of the *Pseudomonas aeruginosa* autogenous vaccine has been confirmed due to the lower respective incidence rate among vaccinated dairy cows [38].

2.6 Leptospirosis Vaccine development against *Leptospira serovars*

Leptospira serovars have been recognized as a mastitis causative agent which infects different infection patterns. It does not introduce an important cause of mastitis. However, Leptospirosis vaccine has shown a protective effect on mastitis reducing the transmission risk [39].

2.7 Development of polyvalent vaccines

Instead of using several vaccines for several pathogenic mastitis causative agents, some research works have been conducted on a single vaccine against several pathogenic microorganisms. As they are targeting different microorganisms for a single purpose, these vaccines are called a polyvalent vaccine. A polyvalent vaccine against bovine mastitis has developed by targeting the most mastitis causative pathogen such as *Staphylococcus*

aureus, Streptococcus agalactiae, Escherichia coli, Streptococcus pneumonia, and Klebsiella pneumonia. Here prepared culture mediums of seed material have been inactivated using Ethylenimine dimer (EID) and the adjuvant gel. The effectiveness of the prepared polyvalent vaccine has been examined by different levels of antibodies in the blood serum of cows using an agglutination reaction [40], [41].

To achieve a high level of specific antibodies in the blood of dairy cows, the polyvalent vaccine has been used against both *Staphylococcus aureus* and *Streptococcus uberis* in mastitis control programs. The researchers also reported a reduction in somatic cell count in the milk as well as a reduction in the incidence of mastitis in contrast to untreated dairy cows [42].

Furthermore, another multivalent bacterial vaccine has also been developed containing heat-killed versions of *Streptococcus pyogenes, Klebsiella pneumonia, Staphylococcus aureus, and Streptococcus pneumoniae strains*. The efficacy of this mixed bacterial vaccine has been confirmed due to the reduction of frequency and severity of infection among vaccinated dairy cows [33].

2.8 Challenges of vaccine development Strategies

The livestock sector makes a significant effect on the economy of a country. Infectious diseases among animals are one of the major threats to livestock farm animals which reduce the quality and quantity of animal products. Though several control and prevention strategies have been developed, veterinary researchers have recommended vaccination as the most efficient and cost-effective way to prevent the transmission of infectious diseases. Vaccination against mastitis is one of their targets which focused on several mastitis-causing pathogens [32].

However, as they have tested different mastitis vaccines, with the advancement of technology, they have recognized some challenges regarding these vaccination strategies. Funding needed for testing vaccines in large animals like cattle is a major challenge in research fields related to veterinary science [43]. Also, the failure of vaccination to induce a rapid and long-lasting protective immunity against mastitis has become a major challenge with the vaccination. Timing of vaccination is also has been one of the major challenges due to the life stages of different dairy cattle. Researchers have noticed that there are some safety issues related to living or modified live vaccines including exposure for non-targeted microbial species, reversion to wild-type agents also some possibilities for environmental contaminations during production [41].

The economic effect is the other major factor that affects for development of different therapeutic regimens against mastitis. As all of the animal products have been commercialized with time all around the world, vaccine production against one of the major diseases related to animal production and health has been completely associated with the economy of the veterinary vaccine market. So, the scale-up of vaccine production has been challenging with the economic issues [41].

03. Future Trends in Vaccine development strategies

As vaccination provides an adequate level of immune responsiveness in the mammary gland against mastitis pathogens, veterinary researchers will further focus on the development of effective biotechnology-based vaccines ignoring some difficulties related to the conventional vaccine development strategies against mastitis [30].

3.1 New Bioinformatics algorithms-based vaccine development strategies

As a high-throughput sequencing technology, bioinformatic algorithms can give a significant contribution to research in vaccine development against diverse pathogens. In vaccine development, targeting a causative pathogen, determining of dynamics of the pathogen, its host genome, as well as their interactions, is such an important phenomenon. However, the conventional vaccination strategies have failed to determine those things due to the lack of opportunities for biotechnology-based research [31]. The identification of the dynamics of pathogens and their infections with the use of bioinformatics algorithms, will provide a better understanding of the dynamics of pathogens related to pathogenicity and also their interactions with host cell genomes. As currently there are several genome sequencing projects are conducted with the advancement of biotechnology, in the future, many bioinformatics algorithms for novel pathogenic genomes are available. It will help to produce an effective and safer vaccine against the economically significant disease, mastitis [19].

3.2 Proteomics and Genomic applications

Functional genomes and proteomics are some of the more focusing powerful tools in the vaccinology field. So, most of the researchers have been forwarded towards the genomics and proteomics-based studies with the time. The necessity for a fast, cost-effective, and safer vaccine

leads to developing a vaccine by determining the different proteins related to the pathogenicity of microbial pathogens and their interactions. Proteomics and genomics-related studies will contribute to analyzing the genome of the mastitis-causing pathogens and their different proteins which affect pathogenicity. It will be important to link the genome characteristics of the pathogens and the immune system-related pathways of the host cell genome [20].

3.3 Structural Biology

To, enhance the vaccine efficacy, designing particular antigens for certain diseases focusing on research studies based on structural biology is possible. In the understanding of the molecular nature of host-pathogen interactions, naturally occurring epitopes of the different antigens and their interaction pathways with the host cells is very important. So researchers will be focused their attention on this emerging strategy for next-generation vaccine development projects. Production of a mastitis vaccine, designing specific engineered antigens using structural biology will lead to developing an effective vaccine to avoid exposure to non-targeted pathogens [22].

04. Conclusion

Although the demand for safe and qualitative animal products on the market has considerably increased, infectious diseases cause a significant impact on animal production and health. So veterinary researchers have focused their research studies on the elimination of infectious diseases among livestock animals. As one of the most abundant, economically devastating diseases of dairy cattle, mastitis prevention has been a major challenge for the dairy industry. Several vaccine approaches against mastitis have been developed with time and the advancement of technology. Though veterinary researchers faced some challenges with the development of different vaccines in several ways for mastitis, vaccination against mastitis is highly warranted for the reduction of the incidence of bovine mastitis. Also, the capability of vaccines to provide effective broad-spectrum protection against predominant environmental and contagious pathogens, confirm the efficacy of the vaccination over other control and prevention strategies. As most veterinary researchers have noticed a reduction in inflammation at the site of infection, vaccination can be recommended as a logical approach to the control of bovine mastitis of dairy cows. The vaccines which have been developed based on molecular biological approaches including DNA vaccines, recombinant viral vector plasmids, and polyvalent vaccines against multiple infectious pathogens, can be recognized as the most effective vaccine to prevent mastitis among dairy cows.

Conflict of interest

"The authors declare no conflict of interest".

References

1. M. Denis, D. N. Wedlock, S. J. Lacy-Hulbert, J. E. Hillerton, and B. M. Buddle, "Vaccines against bovine mastitis in the New Zealand context: What is the best way forward?," N Z Vet J, vol. 57, no. 3, pp. 132–140, 2009, doi: 10.1080/00480169.2009.36892.
2. D. B. Goulart and M. Mellata, "Escherichia coli Mastitis in Dairy Cattle: Etiology, Diagnosis, and Treatment Challenges," Jul. 07, 2022, Frontiers Media S.A. doi: 10.3389/fmicb.2022.928346.
3. M. Zouharova, K. Nedbalcova, P. Slama, J. Bzdil, M. Masarikova, and J. Matiasovic, "Occurrence of virulence-associated genes in Streptococcus uberis and Streptococcus parauberis isolated from bovine mastitis," Vet Med (Praha), vol. 67, no. 3, pp. 123–130, 2022, doi: 10.17221/95/2021-VETMED.
4. F. Zigo, M. Vasil', S. Ondrašovičová, J. Výrostková, J. Bujok, and E. Pecka-Kielb, "Maintaining Optimal Mammary Gland Health and Prevention of Mastitis," Feb. 17, 2021, Frontiers Media S.A. doi: 10.3389/fvets.2021.607311.
5. B. M. Bröker, D. Mrochen, and V. Péton, "The T cell response to Staphylococcus aureus," Pathogens, vol. 5, no. 1, Mar. 2016, doi: 10.3390/pathogens5010031.
6. Y. E. Shahein et al., "Identification of four novel rhipicephalus annulatus upregulated salivary gland proteins as candidate vaccines," Protein Journal, vol. 32, no. 5, pp. 392–398, 2013, doi: 10.1007/s10930-013-9498-x.
7. M. K. Obaid et al., "Acaricides Resistance in Ticks: Selection, Diagnosis, Mechanisms, and Mitigation," Jul. 06, 2022, Frontiers Media S.A. doi: 10.3389/fcimb.2022.941831.
8. Z. Kovačević, M. Radinović, I. Čabarkapa, N. Kladar, and B. Božin, "Natural agents against bovine mastitis pathogens," Antibiotics, vol. 10, no. 2, pp. 1–16, Feb. 2021, doi: 10.3390/antibiotics10020205.

9. Qudratullah, G. Muhammad, T. Jamil, I. Rashid, Q. Ullah, and M. Saqib, “Efficacy Evaluation of a Combined Hemorrhagic Septicemia–Mastitis Vaccine in Dairy Cows and Buffaloes,” Animals, vol. 12, no. 6, Mar. 2022, doi: 10.3390/ani12060706.
10. J. M. Finch, A. W. Hill, T. R. Field, and J. A. Leigh, “Local vaccination with killed Streptococcus uberis protects the bovine mammary gland against experimental intramammary challenge with the homologous strain,” Infect Immun, vol. 62, no. 9, pp. 3599–3603, 1994, doi: 10.1128/iai.62.9.3599-3603.1994.
11. A. E. Tabor et al., “Cattle Tick Rhipicephalus microplus-host interface: A review of resistant and susceptible host responses,” Dec. 11, 2017, Frontiers Media S.A. doi: 10.3389/fcimb.2017.00506.
12. R. N. Gonzailez, J. S. Cullor, D. E. Jasper, T. B. Farver, R. B. Bushnell, and M. N. Oliver, “Prevention of Clinical Coliform Mastitis in Dairy Cows by a Mutant Escherichia coli Vaccine.”
13. C. K. Michael et al., “Association of staphylococcal populations on teatcups of milking parlours with vaccination against staphylococcal mastitis in sheep and goat farms,” Pathogens, vol. 10, no. 4, Apr. 2021, doi: 10.3390/pathogens10040385.
14. “Animals and immunization protocol.”
15. M. L. Nordhaug, L. L. Nesse, N. L. Norcross, and R. Gudding, “A Field Trial with an Experimental Vaccine Against Staphylococcus aureus Mastitis in Cattle. 1. Clinical Parameters,” J Dairy Sci, vol. 77, no. 5, pp. 1267–1275, 1994, doi: 10.3168/jds.S0022-0302(94)77066-1.
16. M. L. Nordhaug, L. L. Nesse, N. L. Norcross, and R. Gudding, “A Field Trial with an Experimental Vaccine Against Staphylococcus aureus Mastitis in Cattle. 1. Clinical Parameters,” J Dairy Sci, vol. 77, no. 5, pp. 1267–1275, 1994, doi: 10.3168/jds.S0022-0302(94)77066-1.
17. N. Extension Service, “Mastitis Control Programs: Bovine Mastitis and Milking Management.” [Online]. Available: www.google.com/url?sa=t&rct=j&q=estimated%20annual%20losses%20due%20to%20mastitis&source=web&c
18. J. S. Hogan, K. L. Smith, D. A. Todhunter, and P. S. Schoenberger, “Field Trial to Determine Efficacy of an Escherichia coli J5 Mastitis Vaccine,” J Dairy Sci, vol. 75, no. 1, pp. 78–84, 1992, doi: 10.3168/jds.S0022-0302(92)77741-8.
19. M. I. Bellgard et al., “CattleTickBase: An integrated Internet-based bioinformatics resource for Rhipicephalus (Boophilus) microplus,” Int J Parasitol, vol. 42, no. 2, pp. 161–169, Feb. 2012, doi: 10.1016/j.ijpara.2011.11.006.
20. R. W. Mellenberger, “Vaccination Against Mastitis,” J Dairy Sci, vol. 60, no. 6, pp. 1016–1021, 1977, doi: 10.3168/jds.S0022-0302(77)83980-5.
21. A. Prenafeta, R. March, A. Foix, I. Casals, and L. Costa, “STUDY OF THE HUMORAL IMMUNOLOGICAL RESPONSE AFTER VACCINATION WITH A STAPHYLOCOCCUS AUREUS BIOFILM-EMBEDDED BACTERIN IN DAIRY COWS: POSSIBLE ROLE OF THE EXOPOLYSACCHARIDE SPECIFIC ANTIBODY PRODUCTION IN THE PROTECTION FROM STAPHYLOCOCCUS AUREUS INDUCED MASTITIS”, doi: 10.1016/j.
22. M. M. Pérez et al., “Protection from Staphylococcus aureus mastitis associated with poly-N-acetyl β-1,6 glucosamine specific antibody production using biofilm-embedded bacteria,” Vaccine, vol. 27, no. 17, pp. 2379–2386, Apr. 2009, doi: 10.1016/j.vaccine.2009.02.005.
23. L. Assoni, R. Girardello, T. R. Converso, and M. Darrieux, “Current Stage in the Development of Klebsiella pneumoniae Vaccines,” Dec. 01, 2021, Adis. doi: 10.1007/s40121-021-00533-4.
24. A. Helmy, N. Elgohary, and A. Mohamed, “EPIDEMIOLOGICAL STUDIES FOR PREVENTION AND CONTROL OF BOVINE MASTITIS,” 2012. [Online]. Available: https://www.researchgate.net/publication/282670467
25. M. Zemanova, L. Langova, I. Novotná, P. Dvorakova, I. Vrtkova, and Z. Havlicek, “Immune mechanisms, resistance genes, and their roles in the prevention of mastitis in dairy cows,” Oct. 25, 2022, Copernicus Publications. doi: 10.5194/aab-65-371-2022.
26. J. Gogoi-tiwari, D. Dorji, H. K. Tiwari, G. Shirolkar, J. W. Aleri, and T. Mukkur, “Phenotypic pia-dependent biofilm production by clinical non-typeable staphylococcus aureus is not associated with the intensity of inflammation in mammary gland: A pilot study using mouse mastitis model,” Animals, vol. 11, no. 11, Nov. 2021, doi: 10.3390/ani11113047.

27. A. Zhylkaidar, K. Oryntaev, A. Altenov, E. Kylpybai, E. Chayxmet, and A. Zhylkaidar, “Prevention of Bovine Mastitis through Vaccination,” Arch Razi Inst, vol. 76, no. 5, pp. 1381–1387, Nov. 2021, doi: 10.22092/ari.2021.356008.1764.
28. P. Sankar, “Article History,” Vet Med Open J, vol. 1, no. 2, pp. 7–8, 2016, doi: 10.17140/VMOJ-1-e004.
29. C. Alexandre et al., “Cloning and partial characterization of a Boophilus microplus (Acari: Ixodidae) calreticulin q.” [Online]. Available: www.academicpress.com
30. M. J. Green, A. J. Bradley, G. F. Medley, and W. J. Browne, “Cow, farm, and management factors during the dry period that determine the rate of clinical mastitis after calving,” J Dairy Sci, vol. 90, no. 8, pp. 3764–3776, 2007, doi: 10.3168/jds.2007-0107.
31. E. J. Petridou, I. A. Fragkou, S. Q. Lafi, and N. D. Giadinis, “Outbreak of Pseudomonas aeruginosa mastitis in a dairy cow herd in northern Greece and its control with an autogenous vaccine,” Pol J Vet Sci, vol. 24, no. 2, pp. 303–305, 2021, doi: 10.24425/pjvs.2021.137666.
32. K. R. Petrovski, M. Trajcev, and G. Buneski, “A review of the factors affecting the costs of bovine mastitis.”
33. K. R. Petrovski, M. Trajcev, and G. Buneski, “A review of the factors affecting the costs of bovine mastitis.”
34. C. Augusto, M. Avancini, and R. Dall’agnol, “Antimicrobial Activity of Plants Used in the Prevention and Control of Bovine Mastitis in Southern Brazil,” 2008. [Online]. Available: https://www.researchgate.net/publication/282999413
35. B. Kurtyak et al., “Autogenous vaccines are an effective means of controlling the epizootic process of mastitis in cows,” U krainian Journal of Ecology Uk rainian Journal of Ecology, vol. 2021, no. 3, pp. 145–152, doi: 10.15421/2021_157.
36. H. Dosogne, F. Vangroenweghe, and C. Burvenich, “Potential mechanism of action of J5 vaccine in protection against severe bovine coliform mastitis,” 2002, EDP Sciences. doi: 10.1051/vetres:2001001.
37. K. R. Petrovski, M. Trajcev, and G. Buneski, “A review of the factors affecting the costs of bovine mastitis.”
38. J. S. Hogan, W. P. Weiss, D. A. Todhunter, K. L. Smith, and P. S. Schoenberger, “Efficacy of an Escherichia coli J5 Mastitis Vaccine in an Experimental Challenge Trial,” J Dairy Sci, vol. 75, no. 2, pp. 415–422, 1992, doi: 10.3168/jds.S0022-0302(92)77777-7.
39. A. S. . Bowman and P. A. . Nuttall, Ticks : biology, disease and control. Cambridge University Press, 2008.
40. A. J. Bradley, J. E. Breen, B. Payne, V. White, and M. J. Green, “An investigation of the efficacy of a polyvalent mastitis vaccine using different vaccination regimens under field conditions in the United Kingdom,” J Dairy Sci, vol. 98, no. 3, pp. 1706–1720, Mar. 2015, doi: 10.3168/jds.2014-8332.
41. J. A. Giraudo et al., “Field Trials of a Vaccine Against Bovine Mastitis. 1. Evaluation in Heifers,” J Dairy Sci, vol. 80, no. 5, pp. 845–853, 1997, doi: 10.3168/jds.S0022-0302(97)76006-5.
42. P. Ruegg, “Evaluating the Effectiveness of Mastitis Vaccines.”
43. F. Zigo et al., “PREVENTIVE METHODS IN REDUCTION OF MASTITIS PATHOGENS IN DAIRY COWS,” Journal of Microbiology, Biotechnology and Food Sciences, vol. 9, no. 1, pp. 121–126, 2019, doi: 10.15414/JMBFS.2019.9.1.121-126.

