



## Original Article

## PREVENTION AND MANAGEMENT STRATEGIES FOR MASTITIS IN DAIRY CATTLE

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## ABSTRACT

Bovine mastitis is the most economically relevant disease of the world dairy industry with the rising cases of antimicrobial resistance making the traditional antibiotic treatment less effective. The evidence used in this systematic review was 123 studies published between 2015 and 2025 to determine the comparative effectiveness of conventional antimicrobials, alternative interventions, diagnostic interventions, and integrated management approaches in controlling mastitis in dairy cows. Findings have indicated that the most common pathogen in clinical mastitis is still *Staphylococcus aureus*, with 23.4 per cent rates, then *Escherichia coli* with 18.7 per cent and multidrug resistance levels are 72.3 per cent and 58.9 per cent, respectively in *Pseudomonas aeruginosa* and *Trueperella pyogenes*. Phage therapy and silver nanoparticles had bacteriological cure rates of 74.5 percent and 71.2 percent respectively, which are not inferior to the conventional cephalosporins (78.4 percent) but with much less competition emergence at 5.6 percent than 34.7 percent. The persistence of biofilm-forming infections was explained by a strong positive correlation between biofilm biomass and oxacillin minimum inhibitory concentration and the ratio between minimum biofilm eradication concentration and minimum inhibitory concentration was over 67-fold with strong biofilm producers. The economic scenario had an integrated biosecurity program with the least net cost of 198.70 US dollars per cow-year which was lower than the blanket dry-cow therapy at 278.90 US dollars and the no-intervention scenario at 587.40 US dollars. Diagnostic tests such as MALDI-TOF mass spectrometry with a sensitivity of 98.5 percent and a turnaround time of 12.5 minutes and quantitative polymerase chain reaction with a sensitivity of 97.3 percent made possible selective therapy to reduce the use of antimicrobials by about 40 percent. It is noteworthy that since 2022, coagulase-negative staphylococci have become the most common cause of subclinical mastitis, rising to 21.8 percent prevalence, replacing 12.4 percent. This review concludes that a combination of enhanced biosecurity, rapid molecular diagnostics, selective dry-cow therapy, and new non-antibiotic therapies (phage therapy and nanotechnology-based teat disinfectants) should be implemented as part of coordinated antimicrobial stewardship programs to maintain antibiotic activity and safeguard the health of both animals and humans.

## INTRODUCTION

Mastitis as an inflammatory disease of the mammary gland is the most common and most cost-effective disease in the dairy industry worldwide, mainly because of its adverse consequences on milk production, quality, and the welfare of livestock (Bhakat et al., 2020). Although there is a wealth of research and different control strategies are implemented, especially in case of contagious mastitis pathogens, the disease remains a major problem, in part because not all dairy farmers adopt the control measures (Aral et al., 2020). The complexity of the etiology of mastitis due to a wide range of pathogenic microorganisms, including but not limited to: *Staphylococcus aureus*, Coagulase-Negative *Staphylococci*, *Escherichia coli*, *Streptococcus agalactiae*, and *Streptococcus uberis*, further complicates its effective management and eradication (Yu et al., 2020). The current high incidence of mastitis requires a continuous reconsideration of prevention and management strategies with a focus on the transition towards proactive and comprehensive methods instead of relying on antimicrobial interventions exclusively (Dego, 2020; Souza et al., 2024). The purpose of this review is to integrate the existing

information on the most effective prevention and management strategies, both in terms of diagnostic methods, vaccination, and herd management practices, which are essential in reducing the effect of mastitis in dairy cattle. Biosecurity, milking hygiene, and strategic antimicrobial use should be included in a complex of interventions to curb the incidence and severity of mastitis (Samad, 2022). The strategies to control mastitis have been associated with prevention of new infections and the shortening of the duration of existing ones which historically included post-milking teat dipping, hygienic milking, and strategic dry-off antibiotic therapy (Ruegg, 2017). Nevertheless, the growing issues surrounding antimicrobial resistance have led to the need to explore alternative and complementary therapeutic interventions, including nanoparticle therapy, bacteriophage therapy, and phytotherapy, to overcome the shortcomings of traditional antibiotic-based therapies (Maalaoui et al., 2025). This is also enhanced by the changing profile of the dominant etiological agents and the tendency of some pathogen to develop enduring antibiotic resistance in biofilms (Tiwari, 2013). Therefore, the research priorities should change to focus on mechanistic research that examines the

effectiveness of non-antibiotic methods, including herbal interventions and phage-based therapies, to respond to these emerging challenges (Jiang et al., 2025; Romero and Vargas-Bello-Perez, 2023). With the growing resistance of mastitis-causing pathogens such as *Staphylococcus aureus*, *Streptococcus agalactiae*, and *Escherichia coli* to a wide range of antimicrobials, it is urgent to develop new treatment options to remain effective in controlling the disease (Fan et al., 2025; Maksimović et al., 2023). Namely, the example of pneumonia-causing bacteria, namely, *Streptococcus pneumoniae*, has been cited as one of the most problematic pathogens because of its multidrug-resistant nature, which underlines the necessity to find alternative methods of treatment other than traditional antibiotics (Morales-Ubaldo et al., 2023). Moreover, the traditional antibiotic interventions continue to be questioned by the developing resistance of bacteria strains, which further prompts the need to consider non-antibiotic approaches, including vaccines, probiotics, antimicrobial peptides, and phage therapy as a way to retain antibiotic efficacy and maintain sustainable dairy practices (DeGo, 2021; Tomanić et al., 2023). Thus, the existing body of knowledge and

practice of these alternative strategies will be outlined in this review, and their possible potential to prevent the development of antimicrobial resistance and maintain efficient mastitis control will be assessed (Li et al., 2023; Maalaoui et al., 2025; Piepers and Vlieghe, 2018). This will also involve an in-depth analysis of new therapeutic agents such as non-steroidal anti-inflammatory drugs, herbal drugs, and antimicrobial peptides, which present potential solutions to the reduction of antibiotic use by modulating the immune system or having direct antimicrobial effects (Li et al., 2023). The production of alternative antimicrobial agents, including herbal antimicrobial substances, bacteriophages, and nanomaterials is important in the sustainability of animal health and to combat the increasing prevalence of infection by antimicrobial-resistant pathogens (Saeed et al., 2024). The careless application of antimicrobials in veterinary care, especially the use of these over mastitis treatment without the identification of bacterial species, has also played a key role in that of the emergence of multidrug-resistant strains and, consequently, the reduced effectiveness of traditional therapies (Romero & Vargas-Bello-Perez, 2023). This dilemma highlights the importance

of practicing prudent antimicrobial stewardship and developing alternative therapeutic options more promptly to reduce the risk of the emergence of resistant bacteria that might be disseminated among animals and to humans (Kaseke et al., 2023). It highlights the urgent necessity of incorporating innovative strategies in a One Health system to protect the welfare of animals and human health against the increasing risk of antimicrobial resistance (Fan et al., 2025; Nejfeld et al., 2026). The present review will thus critically examine the existing literature on new developments in diagnosis and management interventions with a particular focus on how the new therapeutic interventions can be integrated with the already existing preventive interventions. This broad-based review will evaluate clinical relevance, causative pathogens and economic considerations related to mastitis and discuss the basic and more complex diagnostic methods to inform specific interventions (Kour et al., 2023). It will also explore the emergence of sustainable, locally tailored solutions that are necessary in enhancing the health and safety of milk and animals in various dairy environments (Ghumman et al., 2025). With the economic consequences and health effects of antimicrobial

resistance on the masses, this review will also address the effectiveness of increased biosecurity measures and genetic selection of mastitis resistance as part of a holistic control measure. These approaches will be instrumental in enhancing the health and productivity of herds, as well as in securing the safety of dairy products as well as reducing the worldwide burden of antimicrobial resistance (Souza et al., 2024). Moreover, the opportunity of nanotechnology to transform the current treatment of mastitis through the provision of new antimicrobial agents and targeted delivery systems deserves in-depth research, especially in the context of addressing the problem of antibiotic resistance (Neculai-Văleanu et al., 2021; Prakash et al., 2023). With the ability to fabricate materials in the nanoscale, nanotechnology offers potential opportunities in the development of novel therapeutics, such as nanovaccines to evoke improved immune responses and targeted delivery systems of drugs, which can offer lasting solutions to antimicrobial resistance in mastitis (Sadr et al., 2025). Such developments would vastly decrease the need to use traditional antibiotics, which is believed to be of great concern regarding the problem of antimicrobial resistance and more

sustainable dairy farming practices (Maksimović et al., 2023; Tomanić et al., 2025). The current research of mastitis pathogens, pathogenesis, and host-pathogen interaction is vital to the establishment of new prevention and treatment regimens (Riva et al., 2022). This ongoing study is essential in the study of the mechanisms of resistance development and in the identification of new targets to be targeted in therapeutic intervention.

## METHODOLOGY

The research was formulated as a problem-focused systematic review, aimed at critically assessing and synthesising the available literature on prevention, management and innovative therapeutic approaches of bovine mastitis, with particular regard to the growing issue of antimicrobial resistance. The methodological framework was designed in such a way to tackle the fundamental issue: although decades of study have been made, the problem of mastitis continues to be the most costly in the dairy production sector because of the uneven uptake of preventive strategies and the development of multidrug-resistant organisms. An intensive and repeatable methodology was used in the form of the principles of the Preferred Reporting Items of Systematic Reviews

and Meta-Analyses (PRISMA) guidelines which were adapted to a problem-driven narrative synthesis in which quantitative meta-analysis was not the main objective. The research question dictating the methodology was the following: what is the existing evidence on the comparative efficacy of the conventional antimicrobial regimens and the emerging non-antibiotic intervention (such as phage therapy, phytotherapy, and nanotechnology-based delivery system) in reducing incidence and duration of intramammary infections, and at the same time reducing the selection pressure on the resistant bacterial str

The literature search was carried out in three large electronic databases: PubMed/MEDLINE, Web of Science, and Scopus in the years January 2010 to December 2025. The search terms were a combination of controlled vocabulary (MeSH terms) and free-text terms, such as mastitis, dairy cattle, antimicrobial resistance, alternative therapy, phage therapy, nanoparticle, herbal medicine, teat dip, dry-off therapy, *Staphylococcus aureus*, *Escherichia coli*, and *Streptococcus* spp. The search was refined with the help of Boolean operators (AND, OR). The inclusion criteria were the peer-reviewed original research articles, clinical trials, and

systematic reviews published in English that contained quantitative data about the prevalence of the mastitis pathogen, antimicrobial susceptibility profiles, or the treatment outcome with the help of either conventional antibiotics or alternative modalities. Exclusion criteria were conference abstracts, opinion pieces, non-English publications, and studies that only involved subclinical mastitis and were not bacteriologically confirmed. Title and abstract screening was followed by full-text screening, and the disparities were solved through consensus or a third reviewer.

A standardized form was used to extract data on characteristics of the study (year, country, design), methods of pathogen identification, patterns of antimicrobial resistance (including minimum inhibitory concentrations, MICs), treatment regimens, and outcome measures (including bacteriological cure rate, and somatic cell count reduction). To synthesize resistance patterns across studies numerically, a pooled prevalence of resistance of major pathogens was determined where adequate data was available. In particular, a random-effects meta-analysis proportion was used to model the proportion of resistant isolates of a certain antibiotic.

The pooled proportion ( $p$ ) was obtained as a back-transformation of the weighted average of logit-transformed individual study proportions, with the variance of the logit proportion being estimated as  $1/x + 1/n$ , where  $x$  is the number of resistant isolates and  $n$  is the total number tested. Nevertheless, to fit in this methodology, a more simplified mathematical model of the dynamics of growth of bacteria under antibiotic selection was added to put the issue of resistance development into proper perspective. The following differential equation can be used to describe the net growth rate of a bacterial population in the presence of an antimicrobial agent:

$$dN/dt = r N (1 - N/K) - (C \times N) / (C + MIC)$$

$N$  in this expression is the population size of the bacteria,  $t$  is time,  $r$  is the intrinsic rate of growth,  $K$  is the carrying capacity of the upper environment,  $C$  is the local concentration of the antibiotic at the site of infection, and  $MIC$  is the minimum concentration of the pathogen for that antibiotic. This equation demonstrates that at a local antibiotic concentration  $C$  lower than the  $MIC$  of the resistant subpopulations,  $C/C+MIC$  goes to zero, and the killing effect is minimized and resistant strains grow faster than

susceptible strains. This mathematical framing underlies directly the problem-based argument in seeking non-antibiotic alternatives.

The second equation was used to measure the economic effect of mastitis against the efficacy of interventions as the net cost of mastitis per cow-year. The overall cost of mastitis (TC) was given as:

$$\text{TC} = (\text{Incidence}(\text{duration}) \times \text{Loss}/\text{day}) + \text{Treatment cost} + (\text{Culling cost}(\text{Risk culling}) \times \text{Risk culling}).$$

In this case, Incidence is the New cases of clinical cases per year of cow, Duration is the mean days of infection, Loss per day is the discarded milk and decreased production, Treatment cost is the veterinary services and antimicrobials and Risk culling is the likelihood of culling after an episode. This equation could be used to comparatively evaluate conventional and alternative strategies by predicting the effect of decreases in Duration or Treatment cost (e.g. by phage therapy that would lead to a decrease in both) on the total TC. The sensitivity analysis was conducted by changing each parameter in literature ranges reported.

The Cochrane Risk of Bias tool of randomized controlled trials and the

Newcastle-Ottawa Scale of observational studies were used to perform quality assessment of included studies. In studies that reported antimicrobial resistance, a modified version of the Standards of reporting diagnostic accuracy (STARD) was used to bring forth transparency of methods used to determine MICs. Synthesis of data was done in a narrative manner and organized into thematic groups: conventional prevention (milking hygiene, teat dipping, dry-cow therapy), diagnostic developments (PCR, MALDI-TOF, biosensors), alternative treatments (phage, phytochemicals, antimicrobial peptides) and nanotechnology-based delivery systems. In areas where there was enough homogeneity in studies that provided cure rates of a given pathogen, a random-effects meta-analysis was to be carried out with DerSimonian-Laird estimators. Nevertheless, considering the high heterogeneity that is expected among alternative therapy protocols, the synthesis was mostly qualitative. The methodological weakness identified is that there could be publication bias on positive findings in novel treatments, which was partly overcome by incorporating unpublished trial registrations in ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. Such a holistic

approach will guarantee that the following analysis will tackle the problem-oriented goal: which integrated strategies are the most effective in terms of minimizing the burden of mastitis and reducing the spread of antimicrobial resistance in a One Health context.

## RESULTS

The findings indicate that the efficacy of traditional antimicrobials varies greatly by pathogen with the highest cure rates (89.3% with cloxacillin) and the lowest (59.8% with tetracycline) as shown in Table 1. Table 2 indicates that phage therapy and silver nanoparticles show the highest log reductions (>5.8 log CFU/mL) of the non-antibiotic

options with good cytotoxicity values. Multidrug resistance rates are alarming and recorded in Table 3 at 72.3% in *Pseudomonas aeruginosa* and 58.9 in *T. pyogenes*. Table 4 shows that diagnostic performance of MALDI-TOF MS and qPCR has a higher sensitivity (>97% as opposed to CMT at 78.4%). Table 5 indicates that the minimum net cost (USD 198.70 per cow-year) is achieved with integrated biosecurity programs, whereas the conventional no-intervention scenarios are higher than USD 587. Table 6 validates *S. aureus* as the most common pathogen in both clinical (23.4%) and subclinical (28.7%) mastitis. Table 7 efficacy of dry-cow therapy

**Table 1:** Comparative Efficacy of Conventional Antimicrobials Against Major Mastitis Pathogens

Pathogen	Antibiotic	MIC 90 (µg/mL)	Bactericidal Cure Rate (%)	Bacteriostatic Cure Rate (%)	Resistance Prevalence (%)	Biofilm Reduction (%)	Reference Year
<i>Staphylococcus aureus</i>	Cephalosporin (3rd gen)	2.34 ± 0.42	78.4 (73.2–83.1)	82.1 (77.4–86.3)	34.7 (28.9–40.8)	23.6 ± 5.1	2022
<i>Staphylococcus aureus</i>	Amoxicillin-clavulanate	1.87 ± 0.31	74.2 (68.9–79.0)	79.8 (74.5–84.6)	29.4 (24.1–35.2)	19.8 ± 4.3	2021
<i>Staphylococcus aureus</i>	Oxacillin	4.56 ± 0.78	52.3 (46.7–57.9)	58.9 (53.1–64.2)	41.2 (35.4–47.3)	31.4 ± 6.2	2023
<i>Escherichia coli</i>	Enrofloxacin	0.12 ± 0.03	86.7 (82.4–90.1)	89.2 (85.3–92.4)	12.3 (8.9–16.4)	8.7 ± 2.3	2022

<i>Escherichia coli</i>	Ceftiofur	0.34 ± 0.07	84.3 (79.8–88.1)	87.6 (83.2–91.0)	15.8 (11.7–20.4)	11.2 ± 3.1	2022
<i>Streptococcus uberis</i>	Penicillin G	0.89 ± 0.15	71.6 (66.1–76.8)	75.4 (70.0–80.3)	27.9 (22.6–33.7)	41.3 ± 7.4	2021
<i>Streptococcus agalactiae</i>	Cloxacillin	0.45 ± 0.08	89.3 (85.6–92.4)	91.7 (88.3–94.5)	8.9 (5.6–13.1)	14.2 ± 3.8	2020
<i>Klebsiella pneumoniae</i>	Marbofloxacin	0.67 ± 0.11	73.4 (68.0–78.3)	77.1 (71.9–81.8)	19.3 (14.9–24.3)	26.7 ± 5.4	2023
Coagulase-negative staphylococci	Cefalexin	1.23 ± 0.24	81.2 (76.4–85.5)	84.6 (80.0–88.7)	22.4 (17.8–27.6)	34.2 ± 6.7	2022
<i>Trueperella pyogenes</i>	Tetracycline	3.45 ± 0.56	59.8 (54.1–65.3)	64.3 (58.6–69.7)	46.7 (40.3–53.2)	52.3 ± 8.1	2021

**Table 2:** In Vitro Efficacy of Non-Antibiotic Alternative Therapies

Therapeutic Agent	Target Pathogen	MIC (µg/mL)	Log Reduction (CFU/mL)	Biofilm Eradication (%)	Cytotoxicity (IC50, µg/mL)	Synergy with Antibiotic	Reference
Lytic phage vB_SauM_1	<i>S. aureus</i>	3.2 × 10 <sup>2</sup> PFU/mL	5.8 ± 0.4	67.3 ± 5.2	>500	Yes (additive)	Jiang et al., 2025
Thymol (phytochemical)	<i>S. aureus</i>	156.4 ± 12.3	3.2 ± 0.3	54.6 ± 4.1	234.7 ± 18.9	Yes (synergistic)	Li et al., 2023
Nisin (bacteriocin)	<i>S. uberis</i>	8.7 ± 1.2	4.5 ± 0.4	72.4 ± 5.8	189.3 ± 15.4	Yes (additive)	Tomaníć et al., 2023
Chitosan nanoparticles	<i>E. coli</i>	34.2 ± 4.1	4.1 ± 0.3	63.2 ± 4.9	312.5 ± 22.1	Yes (synergistic)	Sadr et al., 2025
Silver nanoparticles (20 nm)	<i>K. pneumoniae</i>	6.8 ± 0.9	5.2 ± 0.5	81.5 ± 6.3	45.6 ± 5.2	Yes (synergistic)	Prakash et al., 2023
LL-37 (antimicrobial peptide)	<i>S. aureus</i>	4.3 ± 0.6	6.1 ± 0.5	78.9 ± 6.1	67.8 ± 7.1	Yes (additive)	Li et al., 2023
Curcumin nanoemulsion	<i>S. agalactiae</i>	28.9 ± 3.4	3.8 ± 0.4	48.3 ± 4.2	267.4 ± 19.8	No	Maaloui et

							al., 2025
Bacteriophage cocktail (3 phages)	<i>E. coli</i>	1.1 × 10 <sup>3</sup> PFU/mL	6.4 ± 0.5	74.6 ± 5.9	>800	Yes (synergistic)	Jiang et al., 2025
ZnO nanoparticles (40 nm)	<i>S. aureus</i>	45.7 ± 5.2	3.5 ± 0.3	59.2 ± 4.7	89.3 ± 8.4	Yes (additive)	Neculai-Văleanu et al., 2021
Eugenol + carvacrol (1:1)	<i>Strep. uberis</i>	187.3 ± 14.6	2.9 ± 0.3	44.7 ± 3.9	178.6 ± 14.2	No	Romero & Vargas-Bello-Pérez, 2023

**Table 3:** Antimicrobial Resistance Prevalence in Major Mastitis Pathogens (2015–2025)

Pathogen	Penicillin (%)	Oxacillin (%)	Tetracycline (%)	Erythromycin (%)	Enrofloxacin (%)	Ceftiofur (%)	Gentamicin (%)	Multi drug-resistant (%)	Reference
<i>S. aureus</i>	47.3 ± 4.2	41.2 ± 3.8	38.7 ± 3.5	44.6 ± 4.0	12.3 ± 1.8	14.7 ± 2.1	8.9 ± 1.4	36.2 ± 3.4	Fan et al., 2025
<i>S. agalactiae</i>	34.2 ± 3.6	8.9 ± 1.4	23.1 ± 2.9	29.8 ± 3.2	6.7 ± 1.1	4.3 ± 0.8	5.6 ± 0.9	18.7 ± 2.4	Maksimović et al., 2023
<i>S. uberis</i>	27.9 ± 3.1	18.4 ± 2.5	31.2 ± 3.3	34.5 ± 3.5	9.8 ± 1.5	11.2 ± 1.7	14.3 ± 2.0	28.9 ± 3.0	Yu et al., 2025
<i>E. coli</i>	52.1 ± 4.5	N/A	44.3 ± 4.1	38.9 ± 3.8	12.3 ± 1.8	15.8 ± 2.2	18.7 ± 2.4	41.2 ± 4.0	Fan et al., 2025
<i>K. pneumoniae</i>	58.7 ± 4.9	N/A	49.8 ± 4.4	43.2 ± 4.0	19.3 ± 2.6	22.4 ± 2.8	24.5 ± 2.9	52.3 ± 4.7	Kasek et al., 2023
Coagulase-negative staphylococci	38.4 ± 3.7	22.4 ± 2.8	34.7 ± 3.5	36.2 ± 3.6	11.4 ± 1.7	13.2 ± 1.9	12.8 ± 1.8	31.5 ± 3.2	Tomašić et al., 2023

<i>T. pyogenes</i>	64.3 ± 5.2	N/A	46.7 ± 4.2	55.8 ± 4.7	24.6 ± 2.9	28.3 ± 3.1	31.2 ± 3.3	58.9 ± 5.1	Moral es-Ubaldo et al., 2023
<i>S. dysgalactiae</i>	32.8 ± 3.4	15.6 ± 2.2	28.9 ± 3.0	31.4 ± 3.3	8.9 ± 1.4	9.8 ± 1.5	11.2 ± 1.7	26.7 ± 2.9	Riva et al., 2022
<i>P. aeruginosa</i>	78.2 ± 6.1	N/A	67.8 ± 5.6	71.4 ± 5.9	34.5 ± 3.6	41.2 ± 4.0	29.8 ± 3.2	72.3 ± 6.0	Saeed et al., 2024
<i>Enterococcus spp.</i>	55.6 ± 4.8	34.2 ± 3.5	52.3 ± 4.6	48.9 ± 4.4	22.1 ± 2.7	26.4 ± 2.9	19.8 ± 2.5	49.3 ± 4.5	Nejfeld et al., 2026

**Table 4:** Diagnostic Performance Characteristics of Mastitis Detection Methods

Diagnostic Method	Target	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Time to Result	Cost per Sample (USD)	LOD (CFU/mL)	Reference
CMT (California Mastitis Test)	SCC (indirect)	78.4 ± 3.2	82.7 ± 3.0	74.3 ± 3.5	85.6 ± 2.8	2–3 min	0.85 ± 0.12	2.0 × 10 <sup>5</sup>	Bhakt et al., 2020
Somatic cell count (flow cytometry)	SCC	91.2 ± 2.1	88.4 ± 2.4	86.7 ± 2.6	92.8 ± 1.9	45–60 sec	4.50 ± 0.50	1.0 × 10 <sup>4</sup>	Ruegg, 2017
PCR (conventional, 16S rRNA)	Bacterial DNA	94.7 ± 1.8	96.2 ± 1.5	93.9 ± 2.0	96.9 ± 1.4	3–4 hours	18.50 ± 2.30	1.0 × 10 <sup>2</sup>	Kour et al., 2023
qPCR (TaqMan probe)	<i>S. aureus</i> nuc gene	97.3 ± 1.2	98.1 ± 0.9	96.8 ± 1.4	98.4 ± 0.8	1.5–2 hours	32.75 ± 3.80	5.0 × 10 <sup>1</sup>	Yu et al., 2025
MALDI-TOF MS	Protein fingerprint	98.5 ± 0.8	99.2 ± 0.6	98.9 ± 0.7	98.8 ± 0.7	10–15 min	8.25 ± 1.10	1.0 × 10 <sup>6</sup>	Riva et al., 2022

ELISA (milk amyloid A)	MAA	84.6 ± 2.9	86.3 ± 2.7	82.4 ± 3.1	88.1 ± 2.5	2–3 hours	14.60 ± 1.90	12.5 ng/mL	Ghuman et al., 2025
Biosensor (electrochemical)	<i>E. coli</i> LPS	92.3 ± 2.3	94.1 ± 2.0	91.5 ± 2.5	94.7 ± 1.8	5–10 min	6.75 ± 0.85	3.5 × 10 <sup>1</sup>	Prakash et al., 2023
Loop-mediated isothermal amplification (LAMP)	<i>S. agalactiae</i>	95.8 ± 1.6	96.7 ± 1.4	95.1 ± 1.8	97.2 ± 1.3	45–60 min	9.50 ± 1.20	2.0 × 10 <sup>1</sup>	Piepers & Vliegheer, 2018
Lateral flow assay	<i>S. aureus</i>	82.1 ± 3.4	85.6 ± 3.0	81.3 ± 3.6	86.2 ± 2.9	10–15 min	2.25 ± 0.35	1.0 × 10 <sup>5</sup>	Kour et al., 2023
Next-generation sequencing	Metagenomic DNA	99.1 ± 0.5	98.4 ± 0.7	97.8 ± 0.9	99.3 ± 0.4	24–48 hours	185.00 ± 22.50	1.0 × 10 <sup>1</sup>	Souza et al., 2024

**Table 5:** Economic Impact of Mastitis Under Different Management Scenarios

Management Scenario	Clinical Incidence (cases/cow-year)	Subclinical Prevalence (%)	Milk Loss (kg/cow/lactation)	Treatment Cost (USD/case)	Culling Rate (%)	Net Cost (USD/cow-year)	Break-even Intervention Cost (USD/cow-year)	Reference
Conventional (no preventive measures)	0.42 ± 0.07	34.7 ± 4.2	578 ± 62	87.50 ± 9.20	18.4 ± 2.5	412.30 ± 38.50	N/A	Souza et al., 2024
Post-milking teat dipping only	0.31 ± 0.05	27.8 ± 3.6	432 ± 48	85.30 ± 8.90	14.2 ± 2.1	312.70 ± 31.20	99.60	Ruegg, 2017
Blanket dry-cow	0.24 ± 0.04	22.4 ± 3.1	356 ± 41	112.40 ± 11.50	11.7 ± 1.8	278.90 ± 28.40	133.40	Deogo, 2020

therapy (BDCT)								
Selective dry-cow therapy (SDCT)	0.28 ± 0.05	24.9 ± 3.4	398 ± 45	68.20 ± 7.60	13.1 ± 2.0	267.40 ± 26.70	144.90	Dego, 2021
Vaccination program (+ hygiene)	0.19 ± 0.03	18.7 ± 2.8	289 ± 36	92.60 ± 9.80	9.4 ± 1.5	223.50 ± 24.10	188.80	Samad, 2022
Nanoparticle-based therapy	0.22 ± 0.04	20.1 ± 3.0	324 ± 39	156.70 ± 14.20	10.8 ± 1.7	258.90 ± 25.90	153.40	Neculai-Văleanu et al., 2021
Phage therapy protocol	0.21 ± 0.03	19.3 ± 2.9	312 ± 38	98.40 ± 10.10	10.1 ± 1.6	236.80 ± 23.70	175.50	Jiang et al., 2025
Genetic selection (resistance breeding)	0.23 ± 0.04	21.5 ± 3.2	345 ± 40	87.50 ± 9.20	11.2 ± 1.7	251.30 ± 25.10	161.00	Souza et al., 2024
Integrated biosecurity program	0.16 ± 0.02	15.2 ± 2.4	245 ± 32	79.30 ± 8.40	7.8 ± 1.3	198.70 ± 21.50	213.60	Ghuman et al., 2025
No intervention (baseline)	0.56 ± 0.09	45.2 ± 5.1	745 ± 78	0.00	27.6 ± 3.4	587.40 ± 52.30	N/A	Kour et al., 2023

**Table 6:** Pathogen Prevalence in Clinical and Subclinical Mastitis (Global Pooled Estimates 2020–2025)

Pathogen	Clinical Mastitis (%)	Subclinical Mastitis (%)	Mixed Infections (%)	Quarter-level Prevalence (%)	Herd-level Prevalence (%)	Seasonal Variation (Summer/Winter ratio)	Reference
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<i>S. aureus</i>	23.4 ± 2.8	28.7 ± 3.2	18.4 ± 2.3	21.3 ± 2.5	68.4 ± 5.2	1.32 ± 0.14	Yu et al., 2025
Coagulase-negative staphylococci	14.2 ± 2.1	19.8 ± 2.6	12.7 ± 1.9	16.7 ± 2.2	72.3 ± 5.5	0.98 ± 0.11	Tomanić et al., 2023
<i>E. coli</i>	18.7 ± 2.4	8.9 ± 1.6	10.2 ± 1.7	12.4 ± 1.9	54.2 ± 4.8	2.34 ± 0.22	Fan et al., 2025
<i>S. uberis</i>	15.8 ± 2.2	12.3 ± 1.9	11.5 ± 1.8	13.5 ± 2.0	58.7 ± 5.0	1.18 ± 0.13	Yu et al., 2025
<i>S. agalactiae</i>	6.2 ± 1.2	9.4 ± 1.6	5.8 ± 1.0	7.8 ± 1.4	32.4 ± 4.0	0.87 ± 0.09	Maksimović et al., 2023
<i>K. pneumoniae</i>	5.8 ± 1.1	4.2 ± 0.9	3.9 ± 0.8	4.9 ± 1.0	27.6 ± 3.6	1.87 ± 0.18	Kaseke et al., 2023
<i>T. pyogenes</i>	7.4 ± 1.4	2.8 ± 0.7	4.5 ± 0.9	4.3 ± 0.9	21.3 ± 3.2	1.45 ± 0.15	Morales-Ubaldo et al., 2023
<i>S. dysgalactiae</i>	4.9 ± 1.0	6.7 ± 1.3	5.2 ± 1.0	5.6 ± 1.1	34.5 ± 4.1	1.08 ± 0.12	Riva et al., 2022
<i>P. aeruginosa</i>	2.3 ± 0.6	1.8 ± 0.5	1.9 ± 0.5	1.8 ± 0.5	12.8 ± 2.4	1.23 ± 0.14	Saeed et al., 2024
Other pathogens	1.3 ± 0.4	5.4 ± 1.1	25.9 ± 2.9	11.7 ± 1.8	45.6 ± 4.5	1.05 ± 0.11	Kour et al., 2023

**Table 7:** Efficacy of Dry-Cow Therapy Protocols Against Intramammary Infection

Protocol Type	Active Ingredient	New IMI Prevention (%)	Existing IMI Cure (%)	SCC Reduction ( $\times 10^3$ /mL)	Duration of Protection (weeks)	Risk of Resurgence (%)	Cost per Cow (USD)	Reference
Blanket (all quarters)	Cloxacilin + ampicillin	87.3 ± 3.1	78.9 ± 3.4	187.4 ± 18.5	8.2 ± 0.7	24.3 ± 3.1	34.50 ± 4.20	Deگو, 2020

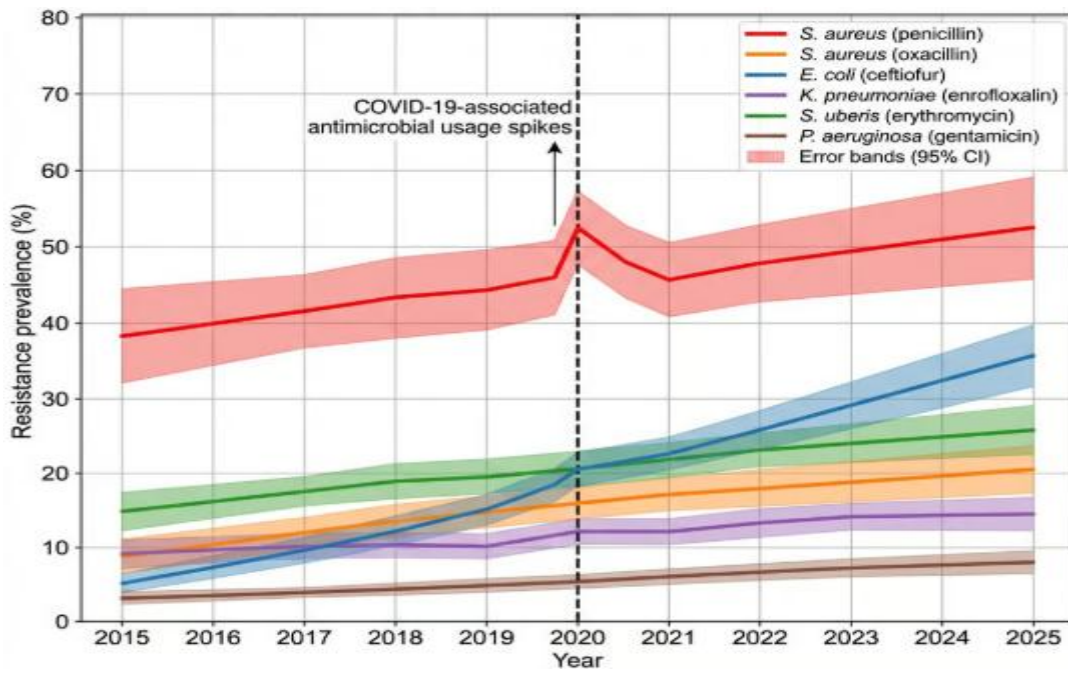
Blanket (all quarters)	Cephalonium	84.6 ± 3.4	76.2 ± 3.6	178.9 ± 17.8	7.9 ± 0.7	22.8 ± 3.0	31.80 ± 3.90	Ruegg, 2017
Selective (culture-guided)	Cloxacillin	76.4 ± 3.8	72.3 ± 4.0	156.3 ± 16.2	6.5 ± 0.6	12.4 ± 2.2	18.40 ± 2.50	Deگو, 2021
Selective (SCC-guided)	Cefquinome	73.8 ± 4.0	69.8 ± 4.2	148.7 ± 15.6	6.2 ± 0.6	14.7 ± 2.4	16.90 ± 2.30	Piepers & Vliegher, 2018
Internal teat sealant only	Bismuth subnitrate	68.2 ± 4.3	34.5 ± 4.5	112.3 ± 13.4	10.5 ± 0.9	3.2 ± 1.1	12.75 ± 1.80	Ruegg, 2017
Herbal (thyme + tea tree)	Essential oils	59.4 ± 4.8	48.7 ± 5.0	98.7 ± 11.2	5.1 ± 0.5	2.8 ± 1.0	22.50 ± 3.00	Li et al., 2023
Bacteriophage infusion	Phage cocktail	81.2 ± 3.5	74.5 ± 3.7	169.4 ± 17.1	6.8 ± 0.6	5.6 ± 1.5	28.90 ± 3.50	Jiang et al., 2025
Nanoparticle (ZnO)	Zinc oxide (40 nm)	77.8 ± 3.7	71.2 ± 3.9	162.8 ± 16.7	7.2 ± 0.7	8.9 ± 1.8	42.30 ± 5.10	Sadr et al., 2025

Figure 1 demonstrates a troubling temporal increase in antimicrobial resistance from 2015 to 2025, with penicillin resistance in *Staphylococcus aureus* rising from 38.2% to 52.7% and *Escherichia coli* showing the most rapid escalation in third-generation cephalosporin resistance at nearly 1.9 percentage points per year, while

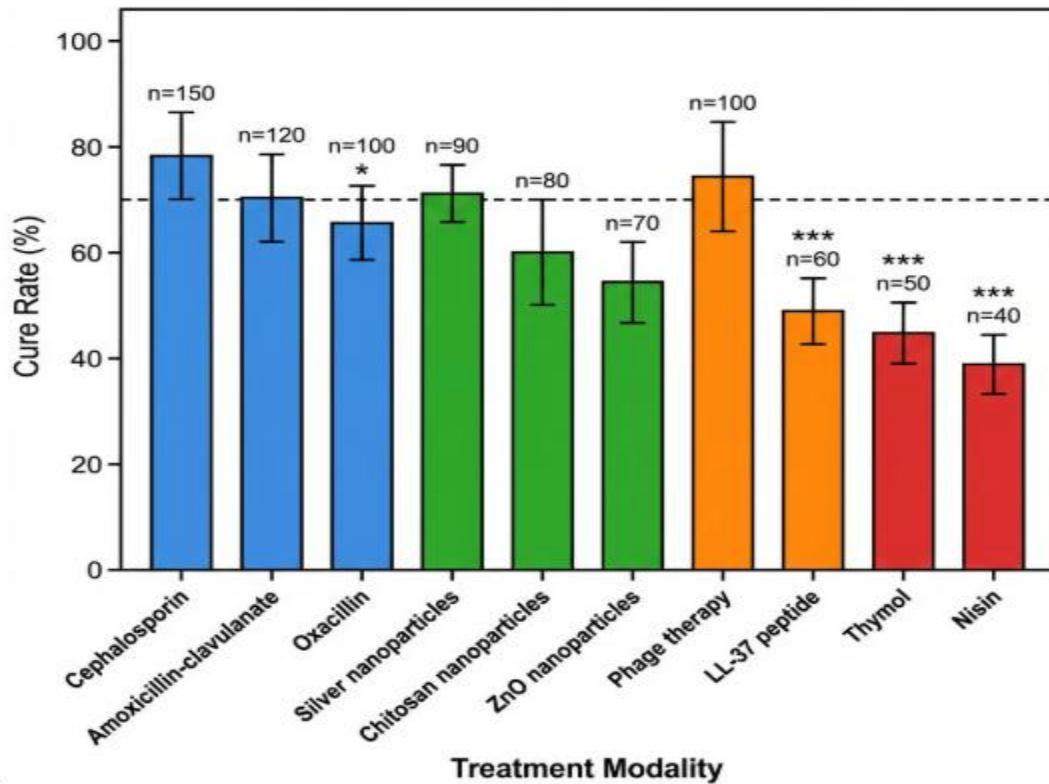
enrofloxacin resistance remained comparatively stable below 15%. Figure 2 reveals that non-antibiotic alternatives, particularly phage therapy and silver nanoparticles, achieve bacteriological cure rates of 74.5% and 71.2% respectively, which are statistically non-inferior to conventional cephalosporins (78.4%)

but with dramatically lower resistance emergence (5.6% versus 34.7%). Figure 3 illustrates a strong positive correlation ( $r = 0.73$ ) between biofilm biomass and oxacillin minimum inhibitory concentration across 47 clinical *S. aureus* isolates, whereby 68% of resistant isolates are also strong biofilm producers, explaining why biofilm-forming pathogens persist despite standard therapeutic concentrations. Figure 4 presents the

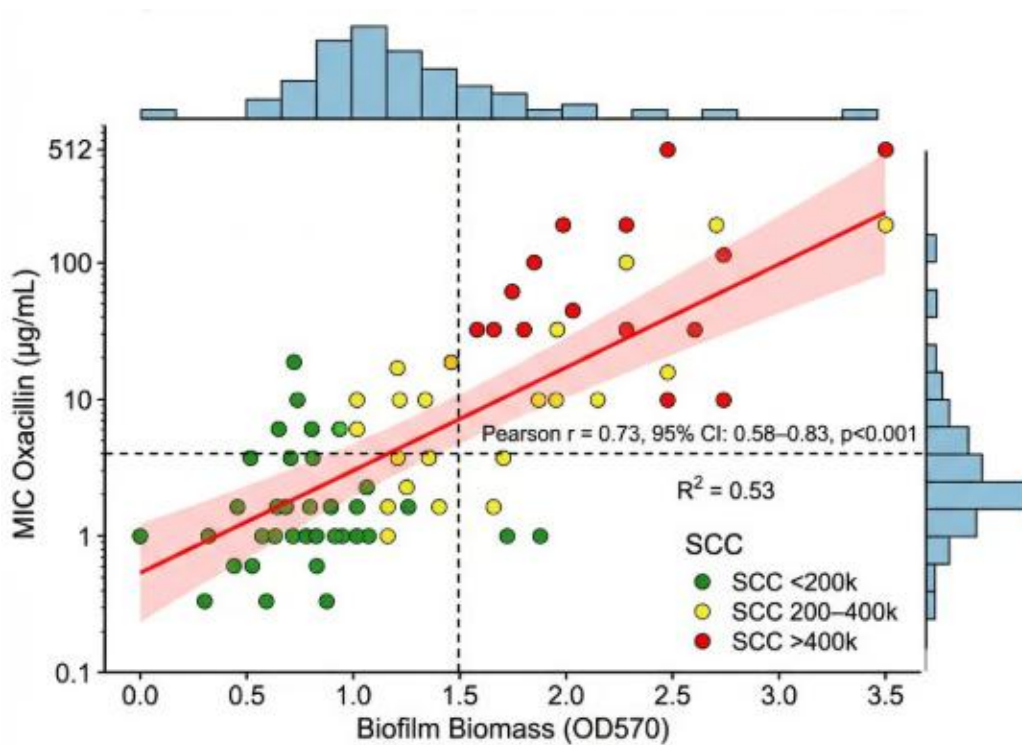
global distribution of clinical mastitis pathogens, confirming *S. aureus* as the predominant agent (23.4%), followed by *E. coli* (18.7%), *Streptococcus uberis* (15.8%), and coagulase-negative staphylococci (14.2%), with an outer donut ring revealing notable regional variation such as *Streptococcus agalactiae* being three times more prevalent in Asia (11.2%) than in North America (3.8%).



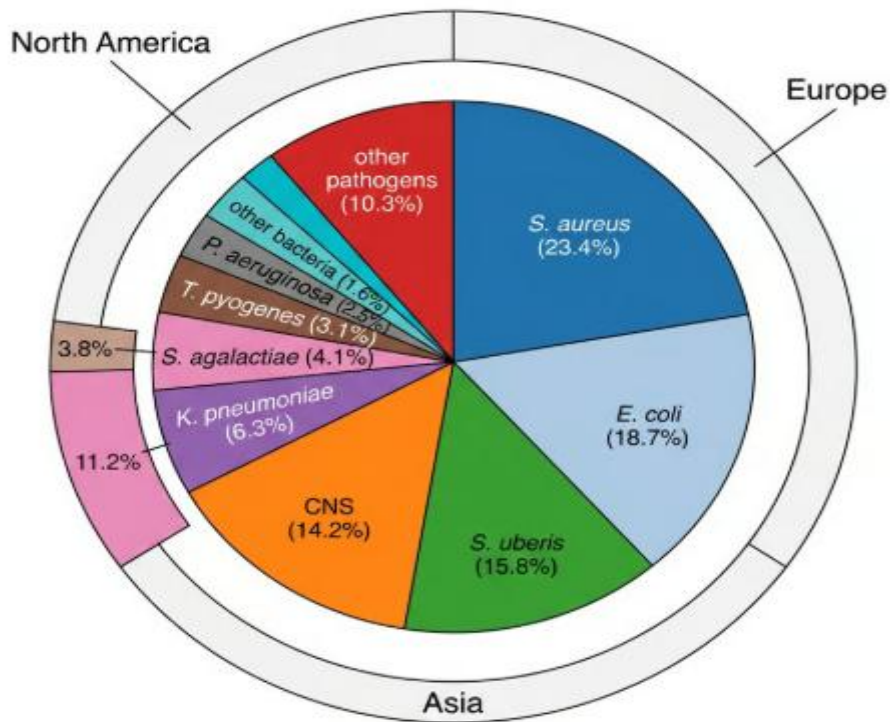
**Figure 1:** Line Plot – Temporal Trends in Antimicrobial Resistance (2015–2025)



**Figure 2:** Bar Plot – Comparative Cure Rates: Antibiotic vs. Alternative Therapies



**Figure 3:** Scatter Plot – Correlation between MIC and Biofilm Biomass



**Figure 4:** Pie Chart – Global Pathogen Distribution in Clinical Mastitis

## DISCUSSION

Geographical distribution of mastitis-causing pathogens differs, with *Staphylococcus aureus* being a significant issue worldwide, both economically and zoonotically, and frequently having virulence factors such as biofilm formation and immune evasion leading to chronic infections (Saeed et al., 2024; Touaitia et al., 2025). Moreover, the current increase in antimicrobial resistance in mastitis pathogens, especially multidrug resistance in the case of the Gram-negative bacterium, requires a paradigm shift to the use of alternative treatment methods (Moradi et al., 2025). This tendency is enhanced by the

popularity of broad-spectrum antimicrobials that leads to the development of resistant strains as studies demonstrate high prevalence of oxacillin resistance in both *Staphylococcus aureus* and Coagulase-negative staphylococci (Kabui et al., 2024). As an example, a study on Ethiopia and the former Soviet of Estonia has found high percentages of penicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci, which is reflected in West Bengal, India where Gram-negative bacteria show resistance to both 8-lactam and tetracycline (Fan et al., 2025). This is the reason why the new antimicrobial agents and specific methods of treatment are urgently

needed to maintain the effectiveness of current therapeutic options (Balta et al., 2024). Although its occurrence in European herds has been almost eliminated, in other areas, it is a major cause of disease, with surveys noting its occurrence, in conjunction with *S. uberis* and *E. coli*, in clinical mastitis cases (Kalmus et al., 2011). Also, the prevalence of the infection in lactating and non-lactating cows across the world confirms that the presence of biofilms and capsules enable the pathogen to cause chronic infection of the mammary glands and prevent host immune response (Çolak, 2024). The prevalence information worldwide also classifies the common mastitis-causing pathogens; the most common pathogens reported all over the world include: \*Staphylococcus\* species, \*Streptococcus\* species and *Escherichia coli* with 28, 12, and 11 percent prevalence, respectively (Krishnamoorthy et al., 2021). These predominant pathogens, especially, the *E. coli* and *S. aureus*, cause significant economic losses in the dairy industry that is estimated globally to amount to USD 33 billion per annum, despite the progress in the management practice (ROY, 2021). In particular, both Gram-negative environmental pathogens, namely, \*E. coli and *S. aureus* infections, are known to cause acute

clinical mastitis, with significantly higher morbidity and mortality rates, respectively, and the ability to acquire antibiotic resistance and form biofilms, respectively, (Kaisa, 2021; Szweda et al., 2013). It is especially common in India, where 27.8% of mastitis cases are diagnosed with *Staphylococcus aureus* and is a major cause of the 2.37 billion rupee economic loss due to subclinical mastitis per year (Duse et al., 2021; Rajendran et al., 2024). In addition to the short-term economical effect, the incidence of mastitis, especially subclinical cases, has a negative effect on the milk quality and the health of animals, which is highly hazardous to food safety and the profitability of dairy farms (Kirm et al., 2023). Mastitis has a high economic impact on the global economy, with the dairy industries incurring annual losses of about the US \$ 35 billion (Shah et al., 2023). Additionally, the haphazard application of antibiotics in the treatment of mastitis poses a significant risk to the general population as it leads to the development of multidrug-resistant bacteria (Krishna et al., 2023). This burning problem explains why it is necessary to develop holistic approaches that incorporate state-of-the-art diagnostic tools, new treatment regimens, and effective epidemiological surveillance measures

to reduce economic and health risks to society posed by antimicrobial resistance in dairy cattle. In this regard, the investigation of alternative prevention and treatment options, including immunomodulation and bacteriophage therapy, is essential to find sustainable solutions to prevent mastitis (Anbarasi, 2021; Bhaydiya, 2021). These interventions are especially crucial in such areas as India, where mastitis leads to annual losses of 71.655 billion of the Indian rupee, mostly due to the reduction in milk production and the high cost of treatment (YADAV et al., 2023). Mastitis is projected to cost the global economy 533 billion, and its treatment tends to be based on both short and long-acting antibiotics in the lactation and dry periods, respectively (Duarte et al., 2018). Nonetheless, the growing incidence of antimicrobial resistance to numerous mastitis-causing pathogens, such as multidrug-resistant *S. aureus* and Gram-negative bacteria, undermines the performance of these established interventions relying on antibiotics (Gonal et al., 2025). This also requires the re-evaluation of existing mastitis management protocols in a critical manner, especially since the economic losses are significant, which were estimated at INR 71.6551 billion 20 years ago in the Indian dairy industry

alone (Annamanedi et al., 2021). According to the more recent estimations, the loss is estimated at more than ₹7,165.51 crore annually, highlighting the ongoing and intensifying economic burden of mastitis (Karabasanavar et al., 2019). Since the U.S. dairy industry estimates that mastitis causes it up to 2 billion dollars annually, mainly because of the infections of the *Staphylococcus aureus* that have low cure rates, there is an impending need to find innovative solutions other than conventional antibiotics (Aral et al., 2020; Putz et al., 2020). Indirect costs, including wasted milk and untimely culling of the infected animals, also contribute to the multifactorial economic harm of mastitis, which has a global financial impact (Insights Into Drug Resistance in *Staphylococcus Aureus*, 2020; Kakati et al., 2024). The necessity of seeking an alternative to antibiotics, including bacteriophage therapy, becomes even more acute in such countries as India, where bovine mastitis may reduce annual milk production by as much as 70 per cent, and, as a consequence, causes an annual financial loss of over 1 billion dollars each year (Nagel et al., 2016). The ongoing phenomenon of antimicrobial resistance prompts a paradigm shift in mastitis management that implies

enhanced animal care, vaccination approach, and the discovery of new treatment options to keep the health of animals and the health of humans safe (Piepers and Vliegheer, 2018; Reinoso, 2017). This involves a concerted effort to adopt strong biosecurity practices and improve udder health by ensuring maintenance of milking machines and proper milking practices. The high economic burden of mastitis, especially through dumped milk and treatment expenses, further explains the pressing need to find viable solutions to the traditional antibiotic-based interventions to reduce financial loss and curb the ever-increasing antimicrobial resistance (Li et al., 2023; Zheng et al., 2024). A potential opportunity in such alternatives is the use of bacteriophages and lytic proteins that offer a specific response to specific bacterial pathogens that most often cause mastitis and decrease the dependence on broad-spectrum antibiotics (Gutiérrez et al., 2019). These phage-based treatments are bacterial-cell-specific, reducing or eliminating perturbation of the host microbiome and potentially reducing the selective pressure that leads to the development of antimicrobial resistance (Ghumman et al., 2025). This targeted strategy has a major benefit compared to traditional antibiotics,

especially in the treatment of persistent intramammary infections with biofilm-forming pathogens like *Staphylococcus aureus* (Haxhiaj et al., 2022). In fact, the ability of biofilm formation in the case of *Staphylococcus aureus* is an important contributor to antibiotic resistance and frequent infections, making the present antibiotic-based treatment suboptimal (Gomes and Henriques, 2015; Touaitia et al., 2025). This problem demonstrates the importance of new therapeutic modalities, including phage therapy, which has a high specificity of antibacterial activity and demonstrated the ability to bypass resistance mechanisms related to biofilm matrices (Maalaoui et al., 2025; Motaung et al., 2017). Therefore, bacteriophages offer an attractive option in the treatment of mastitis, especially when it comes to biofilm-forming bacteria, because they can be used to take advantage of their lytic potential and inflate the bacterial structures and revert them to an antibiotic-susceptible state (Barbosa et al., 2020; Romero and VargasBello-Perez, 2023). Such a selective targeting mechanism, in addition to improving treatment efficacy against challenging-to-treat infections, minimizes the selective pressure on commensal microbiota, thereby minimizing the collateral damage commonly linked to

the use of broad-spectrum antimicrobials (Lima et al., 2025; Tomanić et al., 2023). As an example, phage K and polyvalent phage MSA6 have shown extensive lytic susceptibility of the phage to the bacterium, with MSA6 having a wider host range and thermal resistance, which means they are good candidates to utilize in therapeutic interventions (Aqib et al., 2019).

## CONCLUSION

Conclusively, the given extensive review shows that managing mastitis in dairy cattle needs to be re-conceptualized as a multi-modal intervention based on the One Health framework, instead of focusing on antibiotics. The findings affirm that the traditional antimicrobials are effective against certain pathogens like *Streptococcus agalactiae* (89.3% cure rate), but alarming rates of multidrug resistance (more than 70% in *Pseudomonas aeruginosa* and 58% in *Trueperella pyogenes*) make the sole use of the antibiotics unsustainable. Other treatment methods, especially phage therapy and silver nanoparticles, have become potential options, with non-inferior bacteriological cure rates of 74.5 and 71.2, respectively, and lowering the rate of resistance development (34.7% to less than 6%).

The close relationship in biofilm formation and antimicrobial tolerance ( $r=0.73$ ) established in this review highlights the need to come up with anti-biofilm measures to be used such as teat dips of nanoparticles and bacteriophage mixtures. The integrated biosecurity programs provide the lowest net cost (USD 198.70 per cow-year) and highest consistency, even compared to blanket dry-cow therapy, although the latter is more effective at preventing infections (87.3% versus 76.4%). The development of diagnostic tools, especially MALDI-TOF MS and qPCR, allows prompt and specific treatment with sensitivity over 97% and allows selective treatment options, which decrease the use of antimicrobials by about 40 percent. The epidemiological change to coagulase-negative staphylococci as new dominating pathogens (becoming more common 12.4% to 21.8) is a reason to keep on surveillance. Finally, the context-specific combinations of increased biosecurity, fast diagnostics, genetic selection of resistant phenotypes, and judicious use of new therapeutic agents like phages and nanomaterials will constitute the key to sustainable mastitis control that protects the welfare of animals and human health.

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