A 100-Year Review: Mastitis detection, management, and prevention¹

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ABSTRACT

Mastitis is the most frequent disease of dairy cows and has well-recognized detrimental effects on animal wellbeing and dairy farm profitability. Since the beginning of modern dairy farming, producers have sought effective methods to minimize the occurrence of mastitis in their herds. The objective of this paper is to review and highlight important advances in detection, management, and prevention of mastitis that have occurred since the first volume of the *Journal of Dairy Science* was published in 1917. Initial research efforts were directed at understanding the nature of pathogenic bacteria that were responsible for most intramammary infections. For decades, researchers worked to identify effective strategies to control mastitis caused by *Streptococcus agalactiae* and *Staphylococcus aureus*. To develop successful control programs, mastitis workers first had to identify mechanisms of infection, define the clinical and subclinical states of the disease, discover appropriate screening tests, determine likely points of exposure, identify pathogen-specific characteristics, and develop effective procedures for machine milking. Pioneering researchers eventually recognized that mastitis control was based on preventing new infections from occurring in healthy cows and reducing the duration that cows remained infected. Development of a control program that incorporated post-milking teat dipping, hygienic milking procedures, and strategic use of antibiotic therapy at dry-off resulted in widespread control of contagious pathogens. As herd management changed, researchers were tasked with defining control of mastitis caused by opportunistic pathogens originating from environmental sources. As mastitis pathogens have evolved, researchers have sought to define antimicrobial usage that will maintain animal wellbeing while minimizing unnecessary usage. During the last century, tremendous significant advances in mastitis control have been made but changing herd structure and more

rigorous processor standards ensure that mastitis will remain an important subject focus of future research.

Key words: mastitis, prevention, management, 100-year review, *Journal of Dairy Science*

INTRODUCTION

Historical evidence suggests that cows have been milked since at least 3100 BC (Nemet-Nejat, 1998) and it is likely that bovine mastitis has existed since that time. For millennia, the close contact required by hand milking allowed for easy detection of abnormalities of milk and the mammary gland, but little was known of the causes or management of mastitis. A more complete understanding of mastitis was not possible until the development of microscopes that allowed detection of microorganisms that are the primary etiological agents. The earliest mention of bovine mastitis in the *Journal of Dairy Science* (JDS) occurred in the third issue of 1917 and was focused on public health risks associated with high bacterial counts of raw milk. In that study, Breed and Brew (1917) described a method of grading dairy farms that included enumeration of bacteria in milk and noted that “long chain streptococci” were frequently found in large numbers, even when signs of inflammation were so slight that “farmers cannot be blamed for having saved the milk.” The authors reported bacteriological results from several surveys of raw milk cans and noted in one survey ($n = 9,387$ cans), that >20% of “high count milk” could be attributable to “udder problems.” During that period, streptococci were the primary known cause of mastitis and the concept of subclinical infections was just becoming known. Since then, pathogens, cows, and herd management have changed dramatically but mastitis remains an important disease of dairy cows. Hundreds of research and review articles with the topic of bovine mastitis have been published in JDS and the emphasis has broadened (Appendix Table A1). Effects of mastitis on public health, processing characteristics of milk, milk quality, animal wellbeing, and farm profitability have become well known. Quality standards for acceptable milk have progressed and concern about mastitis has expanded to include the effect of mastitis management programs on farm sustainability and consumer perceptions. The

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number of research articles in JDS that include content about mastitis has steadily increased from about 3 in 1917 to >100 in 2016. The purpose of this review is to highlight advances in detection, management, and prevention of mastitis with an emphasis on research published in JDS that has encapsulated our changing understanding of the disease.

DETECTION AND DIAGNOSIS

Pathogens Past and Present

In a comprehensive review, Plastringe (1958) noted that bacterial causes for mastitis were first advanced in the late 1800s. An early mastitis researcher (Murphy, 1947) defined a 3-phase process for development of mastitis based on (1) invasion of an organism (with or without establishment of infection), (2) infection (the bacteria became established in the gland), and (3) inflammation. This process continues to serve as the basis of our understanding of mastitis. Although numerous bacteria are recognized as able to cause IMI, initial emphasis of mastitis control was directed at pathogens that were known to spread among cows in a contagious manner when teats were exposed to bacteria in milk that originated from an infected mammary gland. For decades, *Streptococcus agalactiae* and *Staphylococcus aureus* were considered the most important contagious pathogens.

Streptococcus agalactiae and *Staphylococcus aureus*

Initial concern about bovine mastitis was based on public health and was directed at reducing bacterial counts of raw milk. Breed and Brew (1917) stated, “we have come to know that mastitis is a cause of high bacterial counts. The mastitis causing high bacterial counts has without exception been due to streptococci.” As the dairy industry progressed, a broader understanding of mastitis pathogens emerged. In a manuscript titled “A study of flaky milk,” Jones and Little (1927) reported observations of 20 instances where foremilk revealed “flocculent particles.” Although streptococci were the most prevalent bacteria identified, hemolytic staphylococci (most likely *Staph. aureus*) accounted for 20% of bacterial pathogens, and only 1 case failed to yield significant bacterial growth. That paper contributed to our understanding of mastitis as they correctly defined the abnormalities observed in milk as clumping of leucocytes as a result of inflammation caused by IMI. Although occurrence of large numbers of bacteria in milk was an obvious public health issue, researchers noted that not all of the bacteria originated from IMI

and that many aspects of mastitis remained obscure. By 1927, *Strep. agalactiae* was considered responsible for about 90% of IMI (Williams, 1927) and the subclinical condition was an important reason that milk was de-graded (from grade A to B). During this period, mastitis workers were struggling to find an efficient way to detect infected cows in order to maintain grade A status in infected herds (Williams, 1927). This issue remained important as the prevalence of IMI in the 1950s was estimated to approach 50% of cows and 25% of quarters (Plastringe, 1958). The emphasis on *Strep. agalactiae* as the most important cause of mastitis continued for several decades, although mastitis attributed to *Micrococcus pyogenes* (later defined as *Staph. aureus*) began to be recognized during the 1950s (Plastringe, 1958).

In 1956, at the annual meeting of the American Dairy Science Association, the committee on animal diseases reported that mastitis was “the most costly dairy cattle disease not under satisfactory control,” (Murphy, 1956). In a seminal paper titled “Mastitis—The struggle for understanding,” Murphy (1956) described years of experience with ineffective mastitis control programs in New York and Connecticut, and concluded that “the problem is larger than any single effort put forth toward its understanding.” He then presented 8 points to help define the disease (Table 1). These points serve as the basis of our modern understanding of the disease and succinctly define the challenges inherent in mastitis control. He noted that while >20 types of infections can cause mastitis, “at least 99% are caused by...*Str. agalactiae*, other streptococci, staphylococci and bacillary mastitis (including coliform, pseudomonas etc.).” He identified clinical, nonclinical, and severe states and noted that even though discrimination among pathogens could only be performed by laboratory testing, the clinical and nonclinical states did not occur at the same frequency for all pathogens. Murphy (1956) further stated that shedding (and the chance of negative cultures) varied among pathogens over time and emphasized the need for pathogen-specific control programs so that appropriate treatment could be applied to cows affected with *Strep. agalactiae* while calling for research to identify environmental sources of exposure for other pathogens.

Environmental Pathogens

Until the late 1970s, little emphasis was placed on gram-negative organisms as a cause of mastitis. Eberhart (1977) directed initial attention to the emergence of coliforms as mastitis pathogens and in 1979 a paper titled “Coliform mastitis—A review” was published in JDS by the Coliform Subcommittee of the Research

Committee of the National Mastitis Council (1979). This comprehensive review included a description of growth requirements of various coliform bacteria, mechanisms of IMI (with emphasis on exposure and movement through the teat canal), an explanation of pathogenesis (including recognition that magnitude of inflammation is dependent on host factors), an excellent portrayal of epidemiology and risk factors, and recommendations for a model control program. Publication of this review signaled awareness about the emerging importance of mastitis caused by opportunistic environmental organisms. In 1985, the importance of environmental mastitis was highlighted by a comprehensive symposium paper titled "Environmental mastitis: Cause, prevalence, prevention," (Smith et al., 1985). In that paper, progress in controlling contagious pathogens was contrasted with emergence of mastitis caused by environmental pathogens. They described results of a longitudinal study of a university herd that characterized microbiological characteristics, epidemi-

ology, control, and treatment of both gram-positive and gram-negative pathogens that originate primarily from environmental exposure (Smith et al., 1985). They recognized the importance of reducing teat-end exposure, highlighted differences in susceptibility among cows, and contrasted differences among gram-negative and gram-positive (primarily *Streptococcus* spp.) opportunistic pathogens. Differences among pathogens, the importance of IMI during the dry period, the high rate of spontaneous clearance of gram-negative IMI, and the increased rate of clinical cases (vs. subclinical IMI) associated with environmental pathogens were all thoroughly described. They correctly predicted the challenges of reducing environmental mastitis in herds that have effectively controlled contagious organisms and summarized recommendations for mastitis control that remain relevant for modern intensively managed dairy farms.

The same group (Hogan et al., 1989) later reported that herds with low SCC (indicating successful control

Table 1. Outline for the understanding of mastitis (reproduced from Murphy, 1956)

Disease forms based on laboratory cultures	Clinical stages based on barn observations				
	Non-clinical negative to barn tests*		Mild-clinical positive to barn tests only*		Severe-clinical; also swelling or general illness
Point 1. Each of the four forms of the disease can appear in each of the clinical stages.					
Point 2. Without laboratory cultures, the clinical stages of each form cannot be distinguished from one another.					
Streptococcal, <i>Strep. agalactiae</i>	Yes		Yes		Yes
Streptococcal, other	Yes		Yes		Yes
Staphylococcal	Yes		Yes		Yes
Bacillary	Yes		Yes		Yes
Point 3. The clinical stages do not occur with the same frequency in each form of the disease.					
Point 4. All forms of the disease may fluctuate between the clinical stages, except that severe-clinical mastitis due to <i>Strep. agalactiae</i> rarely occurs.					
Streptococcal, <i>Strep. agalactiae</i>	+++	↔	++	↔	Rare
Streptococcal, other	+++	↔	+	↔	+
Staphylococcal	++	↔	++	↔	+
Bacillary	+	↔	++	↔	++
Point 5. The four forms of the disease have different shedding characteristics.					
Streptococcal, <i>Strep. agalactiae</i> Long duration, positive most days	+++	↔	++	↔	Rare
Streptococcal, other Variable duration, positive most days	+++	↔	+	↔	+
Staphylococcal Variable duration, not positive every day	++	↔	++	↔	+
Bacillary Short duration, often negative when cultured	+	↔	++	↔	++
Point 6. The <i>Strep. agalactiae</i> form of the disease is the only one that can be eliminated from herds. This is economically worthwhile.					
Point 7. The habitat of these bacteria is the environment. It will be a monumental research task to discover their mode of operation. Until then they cannot be eliminated from herds.					
Point 8. By means of treatment and management, the clinical stages may be cured or forced temporarily into the nonclinical stages. At present, it is not known precisely which management practices are of true value.					

*Barn tests such as strip-cup, bromthymol-blue test, White-side test and the California Mastitis test (CMT).

of contagious mastitis pathogens) could experience serious udder health problems that are characterized by high rates of clinical cases. In the ensuing decades, this situation has become common. Between 1994 and 2001, isolation of *Strep. agalactiae* and *Staph. aureus* from milk samples submitted to the Wisconsin Veterinary Diagnostic Laboratory declined dramatically (Makovec and Ruegg, 2003) and gram-negative pathogens (or culture-negative results) have become the predominant results of milk samples obtained from cows experiencing clinical cases (Oliveira et al., 2013). National data collected for US herds has demonstrated considerable improvements in bulk tank SCC, reaching a milk-weighted average of 194,000 cells/mL in 2015 (USDA, 2015). In contrast, from 1996 to 2014, the reported incidence of clinical mastitis on US dairy farms increased from 13% (USDA, 1996a) to 25% (USDA, 2016). Although mastitis caused by *Staph. aureus* remains a challenge for some herds that have not effectively implemented well-known control strategies, a variety of opportunistic pathogens (i.e., *Enterobacteriaceae*, *Streptococcus* spp., CNS, *Lactococcus* spp., *Prototheca* spp., and others) are frequently identified as mastitis pathogens in modern dairy herds (Bradley and Green, 2001; Oliveira et al., 2013). Additional challenges with pathogens such as *Mycoplasma* spp. (Jasper, 1967; Fox, 2012) have been recognized as important for expanding herds, especially if animals are commingled from multiple locations. Identifying mechanisms to reduce exposure and enhance resistance to IMI caused by opportunistic and emerging organisms while also defining appropriate interventions for affected cows will continue to be a challenge for future farmers, veterinarians, and researchers.

Diagnosis and Impact of Mastitis

Leukocyte Counting. Development of reliable tests for detection of mastitis was a priority for early researchers who wanted to ensure public safety, produce high-quality dairy products, and have a practical means of managing affected cows (Halversen et al., 1934; Shaw et al., 1937). Detection methods that were evaluated included direct microscopic examination of milk for bacteria, enumeration of milk leukocytes, microbial culture, and detection of various abnormal milk constituents (such as chloride content; Halversen et al., 1934). Leukocyte counting rapidly emerged as a practical and repeatable test but general ignorance about the nature of inflammatory responses to IMI made it difficult for early researchers to agree upon an apparently healthy threshold. Although thresholds used for defining mastitis were highly variable (reaching 3,000,000 cells/mL), an early comparative study noted that most milk samples from apparently healthy

glands contained <100,000 cells/mL and identified approximately 200,000 to 250,000 cells/mL as a reasonable threshold for discriminating healthy and abnormal milk samples (Prouty, 1934). However, this threshold was not adopted uniformly for many years, probably because the overall prevalence of cows with subclinical infections was quite high and researchers could not arrive at a consensus for defining normal milk. For many years, the threshold of 500,000 cells/mL combined with isolation of >200 cfu/mL of pathogenic bacteria was commonly used to define subclinical mastitis (Plastridge, 1958).

By 1953, the incidence of subclinical mastitis was found to explain almost 80% of the leukocyte count of milk that was delivered to processors, and this study set the stage for use of leukocyte counting as a herd management tool (MacLeod et al., 1953). The ensuing development of the California Mastitis Test (CMT; Schalm and Noorlander, 1957) and the Wisconsin Mastitis Test (Postle, 1964) provided inexpensive and rapid methods to detect and manage subclinical infections but these tests required producers to collect milk and subjectively evaluate results, thus limiting their applicability. The development of faster and more automated methods to enumerate somatic cells in milk was an area of intense research during the 1960s (Paape et al., 1965). As methods to measure SCC were developed, regulatory authorities began to set limits for bulk tank SCC. In the United States, a maximum bulk tank SCC (1,500,000 cells/mL) was first imposed in 1967. The limit was decreased several times and was stabilized at 750,000 cells/mL in 1993. Limits in northern European countries were much lower; in 1992, the European Union adopted a limit of 400,000 cells/mL, which has become the global standard for milk that is used for products destined for international markets.

Emphasis on reducing bulk tank SCC required identification of infected cows and led to the important step of incorporating SCC tests in monthly DHI programs (Funk et al., 1967). The modern era of managing udder health using monthly SCC testing of individual cows was initiated and, eventually, SCC values came into routine use as a mastitis management tool (Reneau, 1986). The use of monthly SCC values was a departure from previous programs that defined mastitis based almost exclusively on culture of milk samples. Learning how to correctly interpret SCC required knowledge of immunology and physiology, and a comprehensive review of milk SCC published in 1994 remains a relevant reference for understanding factors that influence these values (Harmon, 1994). Today, use of SCC of individual cows is a well-accepted tool that mastitis workers continue to fine tune as pathogens and market needs evolve.

Impact of Mastitis. The negative effects of clinical mastitis were obvious, but the full impact of the disease only gradually became known. Although early researchers recognized that mastitis impeded curd formation (Hansen et al., 1934) and resulted in reduced milk yield (Shaw and Beam, 1935; White et al., 1937), the effect of subclinical mastitis on product quality, milk yield, and overall productivity was not easy to quantify until methods of accurately detecting subclinical infections were developed. The development of the somatic cell score (Ali and Shook, 1980; Wiggans and Shook, 1987) allowed researchers to quantify the linear relationship between subclinical mastitis and reduced milk production. Determining that each 1-unit increase in SCS (or doubling of SCC above 50,000 cells/mL) resulted in a constant production loss (−91 and −181 kg per lactation for parity 1 and >1, respectively) allowed producers to understand the tremendous effect of subclinical mastitis on herd productivity. These values continue to form the basis for estimating the economic impact of mastitis on dairy farms.

Inflammation was known to be detrimental to the mammary gland, but the effect of mastitis beyond the udder did not become apparent until researchers began focusing on environmental pathogens. As researchers studied mastitis caused by gram-negative pathogens, experimental studies indicated that endotoxin could reduce fertility (Gilbert et al., 1990), and several observational studies were subsequently performed to explore this relationship. Initially, researchers recognized that the occurrence of clinical mastitis caused by both gram-negative and gram-positive pathogens resulted in reduced conception rates and increased days to conception (Barker et al., 1998). This research was followed by a study that identified similar detrimental effects for cows affected with subclinical mastitis during the early breeding period (Schrack et al., 2001). Since that time, numerous researchers have confirmed that even relatively modest levels of inflammation can affect fertility, and the effect of inflammation caused by mastitis beyond the mammary gland continues to be an important area of research (Lavon et al., 2011, 2016; Hudson et al., 2012; Fuenzalida et al., 2015).

MANAGEMENT

Definition of Modern Mastitis Control

In 1956, Murphy defined the problem of mastitis (Murphy, 1956; Table 1) but presciently noted that treatment would not be the solution and called for research to define the value of various unproven management practices. Mastitis workers recognized that mastitis was a multifactorial disease but they lacked

research that allowed them to prioritize the effect of various preventive practices. In the next decade, UK researchers from the National Institute for Research in Dairying evaluated a management program that focused on understanding the dynamics of IMI (Figure 1; Dodd et al., 1964). They arrived at the simple equation that the percent of infected quarters within a herd was a function of the rate of new infections and the duration of those infections (Figure 2; Dodd et al., 1964). They noted that treatment was effective for reducing duration (and controlling *Strep. agalactiae*) but was of little value for eliminating staphylococcal infections, thus emphasis was directed at reducing the rate of new IMI. While Neave and Dodd were experimenting with the impact of various management practices (Neave et al., 1966), they correctly noted that, “it means that the control is going to depend on being able to persuade thousands of people of different abilities to conform to particular work patterns.” Four decades later, researchers continue to study methods to persuade farmers to improve mastitis management (Valeeva et al., 2007).

In 1969, JDS published a series of symposium papers that described progress in mastitis control (Dodd et al., 1969; Neave et al., 1969; Norcross and Stark, 1969; Philpot, 1969; Read, 1969). The series was introduced by Frank Dodd, who is recognized as an important pioneer in the field of mastitis control. He summarized data from a longitudinal study of 721 cows in 14 herds (Dodd et al., 1969). At the beginning of the study, 57% of the cows were affected with subclinical mastitis, 80% of which was attributed to either streptococci or staphylococci. Throughout the yearlong study, they characterized the dynamic nature of new infections, occurrence of clinical mastitis (in cows with IMI), and the effect of various treatment strategies on reducing overall prevalence. They also experimented with various management practices that were referred to as a “hygiene system.” They commented that the ideal mastitis control program “must cost much less than the losses caused by the disease, it must be relatively easy to carry out, there should be good experimental evidence that the control works under a range of conditions, and it must be obvious to the farmers who adopt the method that clinical mastitis is much reduced.” In an accompanying paper, Neave et al. (1969) described results of field experiments that evaluated the effect of applying a “full hygiene system.” They described results of a series of experiments and field trials that systematically evaluated use of premilking teat disinfection with individual towels, use of milking gloves, sanitation of teat cups, and efficacy of post-milking teat dip. They reported that a program of “partial hygiene” (the preceding steps without the practice of sanitizing the teat cups between cow milking) resulted

Figure 1. Possible sequence of events in development of infection and mastitis. Reprinted from Dodd et al. (1964) with permission.

in a 44% reduction in new infection rates (Table 2) and advocated use of antibiotic therapy at dry-off to further reduce infections. In the coming years, this plan was widely adopted as the basis of modern mastitis control and the work of Dodd and Neave greatly contributed to improving udder health and milk quality throughout the world. Their work soon led the recently formed National Mastitis Council to develop a mastitis control program known as the “5-Point Plan” that is the basis for controlling contagious mastitis and includes (1) effective post-milking teat dipping, (2) use of antibiotic dry cow therapy in every quarter at the end of each lactation, (3) appropriate treatment of clinical cases, (4) culling of chronically affected cows, and (5) maintenance of milk equipment to ensure stable teat end vacuum.

Antimicrobial Therapy

During the pre-antibiotic era, little could be done with cows that developed IMI and little was known on how to limit transmission. Early researchers determined that periodic examination of milk, followed by segregation and selective culling of affected cows, could be used to establish herds free of *Strep. agalactiae* (Plastring et al., 1936). However, this control strategy was difficult to implement and when antimicrobials became available researchers rapidly began experiments to determine how to use them. Despite administration of massive doses (that resulted in toxicity in several cows), initial studies with oral sulfanilamide failed to achieve effective concentrations in blood or milk and the researcher noted that “treatment with sulfanilamide was successful in restoring normal flow and normal appearance of milk...but it did not eliminate the streptococci from

the udder, nor prevent later acute attacks (Gildow et al., 1938).” This comment is the first indication that clinical impressions can be misleading in determining efficacy of antimicrobial compounds and illustrate the difficulty of separating the occurrence of inflammation from active IMI. Experiments with intramammary penicillin began in the 1940s and the in vitro efficacy of penicillin against gram-positive mastitis organisms was established by 1945 (Seeley et al., 1945). Even in the early years, researchers were aware that treatment using penicillin was much more efficacious against *Strep. agalactiae* than staphylococcal infections (Seeley et al., 1945). The ineffectiveness of controlling mastitis based on treatment of clinical cases was noted very early in the paper by Murphy (1956) and summarized with the memorable statement that “the utter futility of thinking that mastitis can be controlled by the treatment of clinical mastitis only should be obvious. This is merely cutting the tops off the weeds and leaving the roots.” However, despite variable success and limited understanding of effective means to reduce new infections, use of antibiotics to treat mastitis was rapidly adopted for both lactating and dry cows. Mastitis remains the most common bacterial disease on most dairy farms, and consequently, mastitis treatment and prevention account for the majority of antimicrobials administered to adult dairy cows (Pol and Ruegg, 2007b; Saini et al., 2012; González Pereyra et al., 2015; Kuipers et al., 2016; Stevens et al., 2016). Such use is of increasing concern to consumers and public health authorities, and additional research is required to define appropriate antimicrobial usage that balances animal wellbeing with societal concerns about the role that farm use of antimicrobials plays in development of antimicrobial resistance.

Table 2. Results of field trials that compared normal herd management (control) to a full or partial hygiene program, showing the proportionate reduction (%) in new infection rate with the 3 hygiene systems (reproduced from data in Table 4 in Neave et al., 1969); significant results are shown in bold

Trial ¹	Hygiene comparison ²	Decrease in new infections	Decrease in new <i>Staphylococcus aureus</i> infections	Decrease in new streptococcal infections
MFE ₁	Full vs. control	45 (45)³	33 (41) ³	60 (62)³
MFE ₂	Full vs. control	58	62	70
MFE ₂	Partial vs. control	44	55	63
MFE ₂	Full vs. partial	25	17	19

¹MFE₁ = first field experiment, using 14 herds for 12 mo; MFE₂ = second field experiment, using 15 herds for 18 mo.

²Full hygiene = teat cups pasteurized, udders disinfected with separate udder cloths or towels, and teat dip. Partial hygiene = teat cups not disinfected, disinfectant with separate udder cloths or towels, and teat dip. Control = teat cups not disinfected, udders washed with water and common cloth, and no teat dip.

³After adjustment for the mean number of infected quarters at the start.

Figure 2. Factors influencing the average level of infection in a herd: prevention of new infection and reduction of duration of infections. Reprinted from Dodd et al. (1964) with permission.

Antibiotic Treatment During Lactation. By 1969, use of antibiotic therapy was well established, and a review article titled “Role of therapy in mastitis control” was published as part of the ADSA mastitis symposium (Philpot, 1969). As appropriate for this period, the emphasis was on treatment of IMI caused by *Strep. agalactiae* and *Staph. aureus*. Recommendations about treatment of subclinical mastitis included a preference for intramammary administration of broad-spectrum drugs suspended in relatively small volumes of aqueous vehicles. Although use of antibiotics to treat mastitis was common, the limitations of therapy were well known by this time. Philpot (1969) emphasized that the excellent prognosis for treatment of *Strep. agalactiae* was partially because of the location of the infection in the milk duct system. In contrast, when referring to *Staph. aureus*, he reported that the “prognosis regarding therapy is disappointingly low” because the organisms “penetrate the duct walls of the udder and become established in numerous foci.” He further stated, “tissue barriers within the udder are of infinitely greater importance in therapeutic failures than the matter of drug resistance.” Although he documented that a single treatment of penicillin would result in elimination of about 90% of IMI caused by *Strep. agalactiae*, he cited 5 studies indicating an expected efficacy of 50% for treatment of staphylococcal IMI. Importantly, this is the first publication that includes recommendations to review individual animal factors (age, stage of lactation, level of milk production, pedigree, and the severity of infection) before deciding to use antibiotics to treat cows affected with *Staph. aureus*. Three decades later, these recommendations were validated in research evaluating factors associated with bacteriological cure of mastitis caused by *Staph. aureus* (Sol et al., 1997, 2000; Barkema et al., 2006). Similar to Philpot (1969), these studies confirmed low bacteriological cure rates (30–50%) and indicated that age of the cow, SCC, infection in the front quarters, and stage of lactation were the most important determinants of successful outcome. More recently, a highly cited review about cow, pathogen, and treatment factors that contribute to therapeutic success of cows infected with *Staph. aureus* again emphasized that only selected animals will respond to antibiotic therapy (Barkema et al., 2006). Philpot (1969) concluded his paper with the following statement that is as relevant today as it was when originally published (capitalized as in original citation): “Therapy can be a valuable adjunct to an effective program of mastitis control. It should be employed, however, with a full awareness that IT IS LESS THAN DESIRABLY EFFECTIVE IN ELIMINATING MANY EXISTING INFECTIONS AND THAT IT

DOES NOT PRECLUDE THE DEVELOPMENT OF MOST NEW INFECTIONS.”

As coliform mastitis was recognized as an emerging problem, researchers began to evaluate the unique challenges in treating these infections. Although it was recognized that many cases were not severe, defining effective treatment of peracute and acute cases was a high priority and almost no controlled studies were available to guide treatment decisions (Coliform Subcommittee of the Research Committee of the National Mastitis Council, 1979). Initially, recommendations for treatment were empirical and included frequent milk out, systemic and intramammary administration of antibiotics, supportive fluid, and anti-inflammatory therapy. The authors noted that approved antibiotics with gram-negative spectrum were not available. Thus, choices of antibiotics included drugs that were soon to be banned for use in dairy cows (such as chloramphenicol) and other drugs that did not have Food and Drug Administration–approved withholding periods (Coliform Subcommittee of the Research Committee of the National Mastitis Council, 1979). Until the 1990s, few trials were performed to validate recommendations for treatment of coliform mastitis but initial experiments indicated that antimicrobial therapy did not improve outcomes of mastitis caused by *Escherichia coli* (Pyörälä et al., 1994) and challenged prevailing concepts of how mastitis should be treated. The important role of the host immune response in clearance of coliform infections (rather than antibiotic therapy) has been highlighted by an important body of research (Burvenich et al., 2003, 2007). Although some broader spectrum drugs later became available, the increased proportion of culture-negative clinical cases and increased diversity of etiological agents have encouraged development of selective treatment protocols (Lago et al., 2011a,b). Current recommendations for treatment of clinical mastitis are based on targeted antibiotic usage for most gram-positive cases while allowing time for spontaneous cure of most other cases (Ruegg, 2017). With increasing pressure to reduce antibiotic usage on dairy farms, additional research is needed to develop evidence-based treatment protocols that use antibiotics appropriately and can be practically applied on a variety of dairy farms.

Dry-Cow Antibiotic Therapy. Early mastitis workers recognized that about 50% of cows had IMI so use of antibiotic therapy to reduce duration of IMI was recommended as part of a comprehensive mastitis control program (Neave et al., 1969). The cost of discarded milk and the risk of milk residues (Albright et al., 1961) were recognized as limitations to using antibiotics to treat the large proportion of infected lactating cows so

Table 3. Numbers of new IMI detected during 2 trials to evaluate use of comprehensive dry cow antibiotic therapy and milking hygiene (reproduced from data in Tables 2 and 5 in Eberhart and Buckalew, 1972)

Trial ¹	Group ²	Period	Quarters infected					Total	No. of new IMI/cow-year
			<i>Streptococcus agalactiae</i>	<i>Staphylococcus aureus</i>	Other streptococci	Coliform	Other		
1	Control	Lactating	53	51	25	13	4	146	1.50
		Dry	4	12	12	12	0	40	
		Total	57	63	37	25	4	186	
	Treatment	Lactating	14	50	40	27	2	103	1.03
		Dry	2	0	7	10	2	21	
		Total	16	20	47	37	4	124	
2	Control	Lactating	17	1	9	9	1	37	0.98
		Dry	2	1	3	1	1	8	
		Total	19	2	12	10	2	45	
	Treatment	Lactating	0	4	9	3	0	16	0.48
		Dry	0	1	3	4	0	8	
		Total	0	5	12	7	0	24	

¹Trial 1 used 3 herds with about 60 cows per group; trial lasted 2 yr and prevalence of IMI at start of trial was characterized as high. Trial 2 used 2 herds with about 40 cows per group; trial lasted 60 wk and prevalence of IMI at start of trial was characterized as low.

²Control = no post-milking teat dipping and no dry period antibiotic therapy; teats were disinfected before milking and forestripped, and cases of clinical mastitis were treated with antibiotic. Treatment = teats received post-milking disinfection using iodine-based teat dip; all quarters were treated with antibiotic during wk 1 and 2 after dry off; teats were disinfected before milking and forestripped, and cases of clinical mastitis were treated with antibiotic.

use of antibiotic dry-cow therapy (**DCT**) was explored. Researchers had already established that cows were at risk of acquiring IMI during the dry period, and additional benefits of reducing new IMI during this period were hypothesized (Neave et al., 1950). Similar to current concerns about giving antibiotics to animals that may not be infected, early researchers disagreed about which cows should be treated. Some authorities were recommending treatment of all quarters of all cows whereas others believed that only infected cows should be treated (Philpot, 1969). Shortly after DCT was initiated, Natzke (1971) reviewed potential methods of selecting cows for dry treatment. After comparing bacterial culture, use of screening tests (such as CMT), and review of clinical mastitis history, he stated that the limited sensitivity of each of those methods led to the conclusion “that the treatment of all quarters of all cows at the time of drying off is the preferred system...” The effectiveness of DCT (combined with teat dipping) was subsequently demonstrated conclusively by several field studies. Use of teat-dipping and comprehensive DCT was shown to reduce new IMI by about 50% in herds with both high and lower prevalence of existing IMI (Table 3), but the authors noted that “other streptococci” were not effectively controlled and one herd that started the trial with high prevalence of IMI experienced increased infections caused by coliform bacteria (Eberhart and Buckalew, 1972). Results of a later study comparing comprehensive DCT to selective DCT (cows selected based on history of clinical mastitis) demonstrated considerably reduced clearance of infections,

increased new IMI, and increased cases of clinical mastitis in cows that were in the selective treatment group (Ward and Schultz, 1974), and use of comprehensive DCT became established as an important component of mastitis control in dairy herds in North America and the United Kingdom. While researchers continued to debate the use of antibiotics in apparently uninfected glands (Rindsig et al., 1978; Poutrel and Rainard, 1981; Schultze, 1983), US dairy farmers rapidly adopted the practice of comprehensive DCT; by 1996, about 77% of farmers used antibiotic DCT in all quarters of all cows at dry-off (USDA, 1996b). In contrast, during the same period, dairy herds in Scandinavia had lower rates of IMI and preferred use of selective dry-cow programs (Schultze, 1983).

As researchers learned more about the high risk of mastitis during the nonlactating period, it became evident that antibiotic DCT was not able to prevent new IMI entirely during the periparturient period (Oliver and Sordillo, 1988). The combination of concern about widespread use of antibiotics and the desire to better reduce IMI during the dry period resulted in development and commercial introduction of a nonantibiotic internal teat sealant (Woolford et al., 1998; Hillerton and Kliem, 2002; Huxley et al., 2002), which was rapidly adopted as an adjunct to antibiotic DCT. The continued decline of IMI caused by *Strep. agalactiae* and *Staph. aureus* and availability of a nonantibiotic alternative to prevent new IMI have again ignited debate and research about selective DCT (Halasa et al., 2010; Cameron et al., 2014; Scherpenzeel et al., 2014).

Economic models have demonstrated that the decision to use either selective or comprehensive antibiotic DCT is highly farm specific (Huijps and Hogeveen, 2007) but it is likely that governmental regulations encouraging reduced antibiotic usage will result in less use of comprehensive antibiotics at dry-off in the future.

PREVENTION

Effect of Milking Machines and Milking Management

Machine Milking. During the century covered by this review, methods of milking and milking management underwent revolutionary changes that go far beyond the scope of this paper. The tremendous progress during this period is illustrated by comments of Witzel (1956), who reviewed advances in dairy farm engineering in JDS for the 50th anniversary of the founding of the American Dairy Science Association. He noted that in 1950, the average herd size was 6 cows and, although 93% of farms had electrical power, only 51% of cows were machine milked. As milking machines rapidly replaced hand milking, researchers became concerned that the machines could cause irritation and serve as fomites for spreading mastitis among cows (Cone, 1942). Research was needed to determine how milking machines functioned relative to the physiology of milk secretion and how adoption of machine milking would influence the risk of mastitis.

Early innovative studies about machine milking were performed by Espe and Cannon (1942), who injected barium into the teat sinus and took a series of radiographs that illustrated functioning of the teat sphincter. These experiments contributed greatly to our understanding of the mechanics of the teat and illuminated the mechanism of bacterial penetration through the streak canal. As research progressed, effects of vacuum level, vacuum stability, and milking duration on risk of mastitis were identified (Mochrie et al., 1953a,b; Eberhart et al., 1968). Eventually, investigators determined that both vacuum fluctuations and milking duration should be minimized to reduce the risk of new IMI associated with liner slips (Baxter et al., 1992).

A decade-by-decade review of progress in machine milking research was published in JDS by Thompson (1981) for the 75th anniversary of the founding of the American Dairy Science Association. Thompson (1981) reviewed advances in development of milking machines and highlighted research about the important association between milking vacuum and IMI. He concluded his review by emphasizing the increasing role for automation in the milking process. He noted that the automatic detacher had been the most important development in milking automation, predicted that sensors would

be developed that would result in “further automation not only of milking tasks but also of management data recording and analysis.” In the decades since his review, automatic milking systems have become commonplace in many regions but effective use of data from the systems is still not optimized (Jacobs and Siegford, 2012). Detection of mastitis and maintaining udder health in automated milking systems remains challenging, and the role of the “competent” herds person in managing udder health remains as important today as in past decades (Hovinen and Pyörälä, 2011).

A later reviewer (Spencer, 1998) defined the role of the milking machine in maintaining udder health. By this time, many herds had controlled *Strep. agalactiae* and *Staph. aureus*, and the prevalence of IMI had declined. Advances in milking machines had greatly improved vacuum stability, and installation standards for milking systems had been developed. While Spencer (1998) noted that the milking machine could influence new IMI by serving as a fomite, allowing cross-infections within cows, damaging teat sphincters or creating teat impacts, he was one of the first to point out that the milking machine is rarely a direct cause of new IMI. He cited research that demonstrated that only 6.6% of new IMI were accounted for by milking machine factors and concluded that there was no convincing evidence linking the milking machine to the overall prevalence of herd infection (Spencer, 1998).

Milking Management. As milking machines became popular, defining appropriate milking procedures was an important priority. Early mastitis workers had studied physiological mechanisms of milk secretion and ejection, and “pituin” (oxytocin) was identified as a substance that could positively stimulate milk flow (McCandlish, 1918). As milking machines were adopted, factors that could influence milk ejection were studied. In one remarkable experiment, the effect of fright on milk ejection was evaluated by placing a cat on the back of a cow and exploding paper bags every 10 s for 2 min (the authors noted that “later the cat was dispensed with as unnecessary”; Ely and Petersen, 1941). This work clearly demonstrated that fear had a significant effect on reducing milk ejection. This was a potentially important finding because incomplete milking of cows chronically infected with *Strep. agalactiae* was soon shown to result in increased occurrence of clinical mastitis (Schalm and Mead, 1943). This study had a lasting effect influence on milking management. Although the authors did not report milk yield of cows enrolled in their experiment, the volume of milk left in the udder (about 1 kg) was probably close to 15 to 20% of the normal daily milk yield of cows of that period. The authors did not report negative effects in cows free of IMI, but this fear—that leaving milk in the

udder led to mastitis—persisted and likely encouraged widespread use of excessively long attachment times for decades to follow.

The association between bacterial colonization of teat skin and development of IMI has been well established and use of management practices that reduce bacterial contamination of teat ends is a fundamental aspect of mastitis control. Dodd et al. (1964) and Neave et al. (1969) established the importance of postmilking teat disinfection for control of contagious pathogens. In a comprehensive review of postmilking teat disinfection, Pankey et al. (1984) stated, “postmilking teat antisepsis is regarded as the single most effective practice for prevention of IMI of lactating dairy cows” but cautioned that it was not equally effective against coliforms and many streptococci. Smith et al. (1985) concurred and noted that postmilking teat disinfection did not effectively control environmental pathogens. As environmental mastitis emerged, researchers began to investigate other preventive strategies. Historically, premilking sanitation had usually been performed by washing udders and teats with water or disinfectants, but Galton et al. (1984, 1988) demonstrated that premilking disinfection of teats (not udders) followed by effective drying dramatically reduced development of IMI caused by *Streptococcus uberis*. In a field trial, Pankey et al. (1987) demonstrated a 51% reduction in new IMI caused by streptococci and coliforms when pre-dipping was combined with “good udder preparation.” “Good udder preparation” included teat sanitation, drying using a single-service towel, forestripping, and application of a pre-dip sanitizer for a minimum of 30 s. Pankey (1989) later recommended standardization of premilking procedures and use of proper udder hygiene at every milking. In the United States, regulatory requirements state that teats must be sanitized and dried before milking, and farmers rapidly switched from washing udders to the process of good udder preparation (including pre-dipping and drying teats). National statistics indicate that use of premilking teat sanitation with a dip cup (or spray) followed by drying increased from 58 to 85% of farmers between 1996 (USDA, 1996b) and 2014 (USDA, 2016). Although geographical differences exist in adoption of pre-dipping and other premilking procedures, it is likely that processor preferences for milk with little bacterial contamination, sediment, or residues will continue to encourage adoption of increasingly stringent teat preparation practices.

Other Important Preventive Strategies

Genetic Selection for Mastitis Resistance. The ability to use genetic selection to reduce mastitis has gradually evolved. As part of their pioneering work,

Murphy et al. (1944) observed differences in the rate of IMI among separate cow families of equal productivity within a single herd and noted that heritable differences in susceptibility may contribute to development of IMI. Early estimates of heritability of mastitis ranged from 0.27 (Legates and Grinnells, 1952) to 0.38 (Lush, 1950), but progress toward selection of mastitis resistance was impeded by differences in definition of the disease and by the lack of testing programs. Advancements in genetic selection for mastitis resistance were not possible until widespread adoption of SCC testing in DHI programs. Selection for mastitis resistance was encouraged because genetic increases in milk yield were shown to be correlated with increased susceptibility to mastitis (Shook and Schutz, 1994). Somatic cell scores (Ali and Shook, 1980) were incorporated into US selection indices in 1994 (Schutz, 1994). Although improving mastitis resistance has not been the highest priority of US dairy farmers, considerable progress has occurred in other countries (Heringstad et al., 2008), and future innovations in genomic selection technologies will likely be used to accelerate genetic gains in resistance to mastitis (Vukasinovic et al., 2017).

Supplementation with Vitamin E and Selenium. The role of nutritional management in development of mastitis has long been controversial and difficult to separate from other confounding effects. Plastringe (1958) erroneously suggested that feeding high-concentrate diets was a risk factor for mastitis but direct effects of nutrition on mastitis were not reported until Smith and coworkers (1985) performed experiments that demonstrated that dietary deficiencies of selenium and vitamin E increased incidence and duration of clinical mastitis. Initial experiments were supported by later field studies (Erskine et al., 1987; Weiss et al., 1990) that demonstrated increased subclinical and clinical mastitis in selenium-deficient herds. Researchers performed experiments that demonstrated the essential role of these nutrients in maintaining effective neutrophil function (Grasso et al., 1990; Hogan et al., 1990b, 1993). The important role of vitamin E and selenium in maintaining udder health are now well established and this work contributed to both dietary modification and important knowledge about neutrophil function.

Immunization. The development of effective vaccines to protect cows from developing new IMI has been a goal of numerous mastitis workers. Although vaccines have been used to effectively control other bacterial diseases of dairy cows, the nature of mastitis poses numerous challenges to their success. Mastitis is caused by a variety of evolving bacterial pathogens with strains that vary among farms and over time. The site of IMI within the mammary gland, virulence

characteristics, and immunogenic capabilities all vary among pathogens. Initial vaccine research was directed toward development of vaccines against *Strep. agalactiae* and *Staph. aureus* and although potential efficacy was shown in laboratory experiments, early field trials failed to demonstrate that immunization could reduce new IMI (Oehme and Coles, 1967; Mellenberger, 1977). While several *Staph. aureus* vaccines have been commercialized, successful control of these organisms has been achieved in many regions without use of immunization based on adoption of the well-known principles first described by Dodd et al. (1964).

In contrast to vaccines directed at gram-positive pathogens, experimental challenges and field trials were able to demonstrate acceptable efficacy of a gram-negative core-antigen vaccine (Hogan et al., 1990a, 1992a,b, 1995), and several vaccines are marketed to help dairy farmers control symptoms of mastitis caused by gram-negative bacteria. Gram-negative vaccines are based on a highly conserved core antigen of lipopolysaccharide, thus avoiding the problem of variation in bacterial strains among farms. Similar to vaccines directed at gram-positive pathogens, vaccination with gram-negative vaccines does not have a large effect on reducing new IMI but does significantly reduce the development of clinical signs. In contrast to mastitis caused by *Staph. aureus*, most IMI caused by coliform bacteria develop clinical signs that account for most of the economic and welfare losses associated with these infections. The ability of vaccinated cows to more rapidly clear infections and prevent progression to the clinical state has resulted in widespread usage of these vaccines. The quest for efficacious vaccines continues to be a research priority (Piepers et al., 2017), and contemporary researchers are using advances in immunology to test new vaccines against *Staph. aureus*, environmental streptococci, and other pathogens.

Mastitis in Primigravid Heifers. Until recently, primigravid heifers were not considered affected by mastitis. Although Schalm (1942) recognized that inter-sucking among calves increased risk of postcalving mastitis caused by *Strep. agalactiae*, almost no attention was placed on IMI in heifers until Oliver and Mitchell (1983) reported results of a small study in which they recovered a high frequency of staphylococci from mammary secretion collected in the prepartum period. Subsequent field surveys indicated wide geographical differences in prevalence and type of pathogen based on region and time of sampling (Fox et al., 1995). A high prevalence of IMI caused by *Staph. aureus* was initially reported for prepartum heifers in the southern United States (Trinidad et al., 1990), and led to experiments to identify appropriate interventions. Nickerson et al. (1995) summarized experiments conducted to define

prevalence and control of IMI in dairy heifers. In contrast to that in mature cows, the use of antimicrobial therapy in prepartum heifers was found to be highly efficacious in reducing IMI caused by *Staph. aureus*, and this strategy remains a tool for herds experiencing significant problems with this issue.

More recently, a comprehensive review about mastitis in dairy heifers was published (De Vliegher et al., 2012). In that paper, prevalence studies conducted from around the world were summarized, indicating that although primigravid heifers have a relatively low prevalence of infection with major pathogens, many are colonized by CNS (De Vliegher et al., 2012). Interestingly, IMI in dairy heifers caused by CNS have a high rate of spontaneous cure and do not usually have a negative effect on productivity, making the use of prepartum antibiotic treatment unnecessary in most herds. The authors of that review recommended prevention-based measures such as fly control, avoidance of inter-sucking, and assurance of hygienic and comfortable housing areas. Although considerable progress has been made in defining heifer mastitis, future research is needed to define epidemiological characteristics and to better understand the effect of IMI caused by CNS.

SUMMARY AND FUTURE DIRECTIONS

During the last century, researchers have characterized the nature of IMI, determined mechanisms of the inflammatory response, developed effective mastitis control programs that have been widely adopted throughout the world, and, in many regions, have virtually eradicated the pathogen (*Strep. agalactiae*) that was responsible for the vast majority of mastitis in the first half of this century. The effects of mastitis on productivity, reproductive performance, and product quality have been quantified. Diagnostic tools (such as SCC testing) have been developed that allow producers to identify subclinically infected cows and use targeted management strategies to reduce spread of contagious pathogens. As herd sizes grew and management intensified, researchers recognized emergence of opportunistic pathogens that often result in clinical cases. Tremendous advances in milking machines and milking management have resulted in wide adoption of highly functioning milking systems and standardized milking procedures. Limitations of antimicrobial therapy have been recognized but use of antibiotics to treat cows affected with some pathogens remains an important tool for mastitis control. During the period that this review covers, the effect that mastitis researchers have had on improving milk quality and dairy farm productivity is truly remarkable.

In 1958, Plastring published a review of bovine mastitis in JDS (Plastring, 1958) that summarized current mastitis research and included the following disclaimer: “A complete review is beyond the scope of this communication...” That disclaimer is even more applicable to the current review. An enormous volume of important research has been conducted in the 58 years since that statement was made. In the century covered by this review, numerous researchers have contributed to progress in controlling mastitis. I have attempted to summarize advances in the detection, prevention, and management of bovine mastitis and I have focused on papers published in JDS that helped illustrate how our understanding of mastitis has evolved. Important research has necessarily been excluded, simply due to the constraints of space. I encourage current mastitis researchers to reacquaint themselves with the historical research that has strengthened our knowledge and ability to manage this important disease.

In spite of tremendous progress, in most regions, mastitis remains the most economically significant bacterial disease of dairy cattle, and continued advances in mastitis control are necessary to ensure sustainability of dairy farming worldwide. Most countries have eliminated production controls and globalization has had a tremendous impact on quality standards. The ability to participate in global dairy trade is increasingly dependent on production of milk that meets stringent quality standards that are defined by milk processors rather than government regulators. In emerging dairy regions, there is a need to provide infrastructure and training to help farmers efficiently adopt proven management strategies that minimize development of new IMI and result in production of high quality milk. Investments in defining mastitis control strategies for minor dairy species (such as dairy sheep, goats, and buffalo) are also needed.

In developed dairy regions, intensification of herd management has resulted in new challenges for producers. Studies are needed to fully define risk factors and control strategies for emerging pathogens (such as *Prototheca*, *Mycoplasma bovis*, and others). Research using new diagnostic methods and molecular technologies is needed to fully understand the ecology and control of microbes that reside in the dairy ecosystem and are potential etiologic agents for mastitis. The issue of antimicrobial resistance and societal pressures to reduce antimicrobial therapy on dairy farms will grow in importance, and research defining appropriate use of antimicrobials is a high priority. Standardization of methods used to evaluate efficacy of mastitis treatments is needed to identify when antimicrobial usage is truly beneficial. Continued investment in research to develop alternatives to antimicrobials is required and

more emphasis should be directed at methods of improving mastitis resistance.

Limitations in labor supplies have already contributed to increased use of automation, and this trend will likely accelerate. Increased use of automatic milking systems and incorporation of automation into milking parlors requires research on optimization and effective use of data originating from these systems. All of these research priorities require effective means to communicate and persuade farmers of their utility, thus continued development of mechanisms for knowledge transfer are necessary to fully capture the value of future research gains.

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APPENDIX

Table A1. Timeline of significant advances in detection, management, and prevention of mastitis

Date	Milestone	Reference
1917	Streptococci from infected udders are identified as cause of high bacterial counts in milk.	Breed and Brew, 1917
1927	“Flaky” milk appearance is associated with bacterial inflammation caused by staphylococci and streptococci.	Jones and Little, 1927
1937	Occurrence of subclinical mastitis is shown to reduce milk yield.	White et al., 1937
1942	Anatomic and physiologic aspects of teat sphincter are described.	Espe and Cannon, 1942
1945	In vitro study demonstrates the efficacy of penicillin against gram-positive mastitis pathogens.	Seeley et al., 1945
1950	Heritability of susceptibility to mastitis is estimated.	Lush, 1950
1953	Leukocyte count of bulk milk is shown to predict prevalence of subclinical mastitis in herd.	MacLeod et al., 1953
1956	Pathogen-specific characteristics of infection and disease presentation are first defined.	Murphy, 1956
1957	Development of California Mastitis Test.	Schalm and Noorlander, 1957

Continued

Table A1 (Continued). Timeline of significant advances in detection, management, and prevention of mastitis

Date	Milestone	Reference
1961	National Mastitis Council is formed to unify recommendations for mastitis control.	
1967	First US limit on bulk tank SCC is set at 1,500,000 cells/mL.	
1969	Seminal works on control of <i>Streptococcus agalactiae</i> and <i>Staphylococcus aureus</i> through hygiene and management are published.	Dodd et al., 1969; Neave et al., 1969
1971	Use of comprehensive antibiotic treatment at dry off is promoted.	Natzke, 1971
1982	Linear relationship between SCC and milk yield loss is demonstrated.	Ali and Shook, 1980
1984	Epidemiology and control of environmental mastitis is defined.	Smith et al., 1985
1992	Efficacy of <i>Escherichia coli</i> core antigen vaccine is demonstrated.	Hogan et al., 1992a,b
1994	Mastitis is included in genetic selection indices in United States.	
1995	IMI in prepartum heifers is recognized.	Nickerson et al., 1995
1998	Mastitis shown to reduce fertility.	Barker et al., 1998
1998	Efficacy of internal teat sealants in preventing mastitis is demonstrated.	Woolford et al., 1998
2001	Era of molecular diagnostic tests begins.	Phuektes et al., 2001
2002	Antibiotic usage on farms and possible linkages with antibiotic resistance emerges as an important issue.	Erschine et al., 2002; Pol and Ruegg, 2007a,b
2012	Most US producers are required to meet European Union SCC standard of 400,000 cells/mL.	