The Changing Nature of Mastitis and Mastitis Treatments

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Introduction

Reducing mastitis has always been an important priority of dairy farmers; management of udder health has been influenced by continued evolution of dairy herd structure. In the U.S., the majority of milk is produced on farms that contain greater than 500 milking cows (http://www.nass.usda.gov/Quick_Stats/) and the presentation of mastitis on larger dairy farms has changed. As housing and management have become more intensive, the distribution of mastitis pathogens has changed. Larger farms have greater adoption of modern management practices that reduce transmission of subclinical infections (Rodrigues et al., 2005, Rowbotham and Ruegg, 2015). These improvements have contributed to control of *Staph. aureus* and near eradication of *Strep. agalactiae* and resulted in considerable decreases in bulk tank somatic cell counts (**SCC**; Figure1). While intensification has resulted in reduced bulk tank SCC, mastitis remains a significant challenge for many dairy farms. Increased animal densities and changes in dairy housing (Ericsson Unnerstad et al., 2009) have increased potential exposure to opportunistic intramammary pathogens that often present with mild clinical signs, and national surveys have indicated that the rate of clinical mastitis has consistently increased (Figure 1). In most larger herds, the majority of clinical cases are caused by opportunistic pathogens that originate from the environment (Oliveira et al., 2013). These trends are especially evident when reviewing microbiological results of milk samples obtained from cows with cases of clinical mastitis and one study reported that only about 35 of 741 cases of clinical mastitis occurring on 52 larger Wisconsin dairy farms were caused by Staph aureus (Oliveira et al., 2013). Recovery of "traditional" pathogens, such as *Strep. agalactiae* or *Staph aureus*, tends to more frequent in regions that are populated by a greater proportion of smaller herds that utilize tie stall facilities (Olde Riekerink et al., 2008) or herds that have failed to use well-known preventive strategies, such as comprehensive use of intramammary antimicrobials at dry off (Olde Riekerink et al., 2010). Understanding the changing nature of mastitis is necessary to manage it and the purpose of this paper is provide an update on current concepts of preventing and managing bovine mastitis.

Detection of Mastitis

Management of mastitis requires use of accurate detection and recording systems for both subclinical and clinical presentations of the disease. Without the use of routine SCC testing, effective management strategies for control of subclinical mastitis are extremely limited. On many farms, subtle signs of clinical mastitis are overlooked or disregarded by both humans and automated detection systems. Clinical mastitis is usually defined as the production of abnormal

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milk (with or without secondary symptoms), but the working definition of clinical mastitis varies greatly among farm workers. On large farms, detection of mastitis is usually dependent on the training and observational skills of the milking technicians.

Use of standardized case definitions for clinical mastitis is helpful for monitoring detection intensity and accuracy. Use of a 3-point scale based on clinical symptoms is practical, intuitive, simply recorded and can be an important way to assess detection intensity (Pinzon-Sanchez et al., 2011). In this system, a mastitis severity score of 1(mild) is assigned when abnormal milk is the only symptom, 2 (moderate) is assigned when abnormal milk is accompanied by localized udder symptoms (such as swelling or redness), and 3 (severe) is assigned when systemic symptoms, such as fever, anorexia, rumen stasis, or a large decrease in milk production are observed. Research has consistently indicated that severity of clinical mastitis is about 50% mild, 35% moderate, and 15% severe (Pinzon-Sanchez et al., 2011, Oliveira et al., 2013). When foremilk is not examined, approximately 50% of cases will not be detected and if the proportion of severe cases exceeds about 15%, it is a signal that detection intensity and case definition should be investigated.

Diagnosis of Etiology

Mastitis is caused by intramammary infection (**IMI**) and the agents are usually bacteria, thus appropriate treatment and control programs are based on understanding the etiological agent. On many modern dairy farms, subclinical mastitis is primarily caused by Gram-positive organisms [such as environmental *Streptococci* or coagulase negative staph (**CNS**) while the greatest proportion of milk samples from clinical cases are culture negative or Gram-negative. Of 741 cases of clinical mastitis that were cultured from 52 Wisconsin dairy herds, the most common bacteriological diagnoses were no bacterial growth (27% of cases) and *E coli* (23% of cases); *Streptococci* were isolated from about 13% of clinical cases and a further 17% of cases were caused by a variety of opportunistic organisms (Oliveira et al., 2013). While clinical signs may be suggestive of some pathogens, detection of mastitis is based on observation of non-specific signs of inflammation, and it is impossible to diagnose the cause based on observation of the milk, gland or animal. Thus, on modern dairy farms, increased use of milk culturing to direct mastitis control programs is recommended. When results of milk cultures are closely linked to treatment decisions, the value of culturing milk from cows with clinical mastitis is clearly evident to owners of larger herds. Of 325 large Wisconsin dairy herds recently surveyed, use of culture of milk from most or all clinical cases was 20%, 22%, 52%, and 75% of herds containing 200 to 499, 500 to 999, 1000 to 2000, and >2000 cows, respectively (Rowbotham and Ruegg, 2015 unpublished).

On a typical farm, about 50% of milk samples obtained from cows with subclinical mastitis and 25 to 40% of milk samples obtained from cases of clinical mastitis are microbiologically negative. The reason that cases are culture negative likely varies based on case presentation. Chronic subclinical cases have strong evidence of on-going inflammation that is most likely the result of persistent IMI. These cases are often false negatives because the inflammatory response has successfully reduced the number of organisms to below the normal detection limit (about 100 cfu/mL in most mastitis laboratories). Repeated culturing of ¼ milk samples may help arrive at a diagnosis for some of these cases. In contrast, in herds that have environmental mastitis problems, many mild and moderate clinical cases are caused

by opportunistic pathogens that have been successfully eliminated by a localized immune response. The clinical symptoms are observed after the immune system has responded and about 75 to 80% of these cases may actually be spontaneously cured of the IMI before detection of the symptoms. The only way to determine if the symptoms of mild and moderate mastitis are accompanied by active infection (and thus will benefit from antimicrobial therapy) is to perform microbiological analysis.

Epidemiology of Mastitis on Modern Dairy Farms

Bulk tank SCC have declined throughout the world, but the ability to maintain a low bulk tank SCC does not always indicate that mastitis is controlled. Even in regions that are known for producing high quality milk, about 15 to 20% of cows have monthly SCC values that indicate at least one mammary gland quarter is affected with subclinical mastitis. Accurate detection and recording of clinical mastitis and a review of management strategies used to reduce bulk tank SCC (such as use of quarter milkers or drying off of chronically affected quarters) are necessary to determine the magnitude of mastitis challenges on dairy farms. A study of large Wisconsin dairy herds with bulk tank SCC around 220,000 cells/mL indicated that there were approximately 40 clinical mastitis treatments per 100 lactating cows per year, with a range of 6 to 90 treatments per 100 cows per year (Oliveira et al., 2013). In spite of low bulk milk SCC, some of these herds had evidence of considerable mastitis problems. While the average herd withheld from sale about 1.8% of daily milk (from treatments), the maximum amount of daily milk withheld was 6.7%. Likewise, the average proportion of cows milking with <4 quarters was 4.7%; however, one herd reported that 30% of the cows had at least one non-functioning quarter. The shift to clinical mastitis (rather than subclinical disease) is primarily a response to changing exposures to pathogens.

Based on their primary reservoir and most likely mode of transmission, mastitis pathogens have typically been characterized as either "contagious" or "environmental." Using this traditional classification, the udder of cows with subclinical infections serves as the primary reservoir of contagious pathogens. Transmission of contagious pathogens occurs when teats of healthy cows are exposed to organisms in milk that originated from infected udders. The most common point of exposure is usually bacteria present in milk droplets on teat contact surfaces (such as milking inflations or milked leaked onto bedding surfaces). In the US, contagious mastitis pathogens commonly include *Staph aureus* and *Mycoplasma bovis*. However, transmission via a "contagious route" is possible for any microorganism that can cause persistent subclinical mastitis and shed sufficient colonies in milk to establish an infective dose. Thus, chronic subclinical infections with organisms such as *Prototheca zopfii* or *Klebsiella spp*, can also result in contagious transmission among cows.

In most developed dairy regions, udder health programs are increasingly focused on mastitis caused by environmental pathogens. The term "environmental pathogen" refers to mastitis caused by opportunistic bacteria that often reside in the housing area of cows. Common pathogens include both Gram-negative bacteria (such as *E. coli* and *Klebsiella spp*.) and Gram-positive bacteria (such as *Strep. uberis* and other *Streptococcal* like organisms). Opportunistic pathogens tend to be less adapted to survival in the udder and IMI often triggers sufficient inflammation to result in visually apparent mild or moderate clinical signs. Bedding materials, and moisture or manure in animal walkways are common reservoirs and

controlling environmental mastitis is based on reducing exposure of teats of the most susceptible cows.

The duration of infection with environmental pathogens varies among pathogens (Smith et al., 1985) and can be associated with the degree of host adaptation of the pathogen. Some environmental pathogens (such as most *E. coli*), are truly opportunistic and the immune response is usually successful in eliminating these pathogens after a brief period of mild clinical disease. Other environmental pathogens (such as many IMI caused by *Streptococci* or *Klebsiella spp*.) seem to have become more host adapted and may present as mild clinical cases that appear to resolve when in actuality the case has returned to a subclinical state. Control of mastitis caused by environmental pathogens can be more complex than control of mastitis caused by bacteria usually considered to be contagious. Bedding materials, moisture, mud, and manure in housing areas of cows are common reservoirs for these pathogens and controlling them requires reducing exposure of teats of the most susceptible cows.

Risk Factors for Intramammary Infection

Environmental Risk Factors

Manure handling, type of bedding, and stall maintenance all have significant impacts on exposure of teats to mastitis pathogens. While many bedding materials initially have relatively low bacterial populations, organic matter in some bedding contains nutrients that support bacterial growth and results in exposure of teats to a great variety of potential mastitis pathogens. This is especially true of recycled manure which is very rich in nutrients that support growth of fecal organisms. A recent observational study of large Wisconsin dairy farms demonstrated lower rolling herd average (**RHA**), greater SCC, more treated cows, and a greater proportion of cows with non-functional quarters in herds that used manure based bedding as compared to herds that used sand (Rowbotham and Ruegg, 2015). In general, the number of Gram-negative bacteria (often associated with shorter duration infections and occurrence of clinical mastitis) is greater in organic bedding materials (such as recycled manure solids) as compared to new sand bedding. However, the number of opportunistic Gram-positive bacteria (often associated with longer duration subclinical infections) can be quite significant in recycled sand, and IMI with these organisms may contribute to increased bulk tank SCC (**BTSCC**).

The number of bacteria recovered from teat skin is typically 2 to 3 log units (100 to 1000 times) less than that found in bedding, indicating potentially greater risk of IMI for quarters exposed to bedding that contains greater quantities of bacteria. A linear relationship between exposure to bacteria in bedding and rate of Gram-negative clinical mastitis has been demonstrated but that association was relatively weak and the authors of the study cautioned that <16% of variation in clinical mastitis rate could be attributed to differences in bedding bacterial count (Hogan et al., 1989). Exposure to bacteria alone doesn't necessarily result in IMI. For all infectious diseases, exposure to a pathogen is necessary for infection, but mastitis is a multifactorial disease and other risk factors are needed for exposure to result in mastitis. Factors that influence the risk of infection with opportunistic pathogens include management factors, such as design and usage of stalls, management of bedding (including particle size and content of moisture and organic matter), adequacy of milking procedures, and gentleness of milking. Important cow-level factors include anatomical characteristics of the udder and teats. While exposure is important, risk of IMI is also influenced by the ability of the cow to mount

an effective and rapid immune response after bacteria have penetrated the teat orifice.

Cow Level Risk Factors

Reducing risk of opportunistic IMI is based on reducing exposure to potential pathogens, but risk of developing mastitis is not equal among animals because different groups of cattle have differing abilities to withstand environmental challenges. The ability to resist and respond to infection is influenced by both stage of lactation and parity. As compared to older animals, cows in first and second lactation have reduced risk of developing clinical mastitis caused by opportunistic pathogens (Zadoks et al., 2001; Pantoja et al., 2009; Pinzon-Sanchez and Ruegg, 2011). Stage of lactation is also a risk factor for development of clinical mastitis and the disproportionate occurrence of clinical mastitis in early lactation is a hallmark of mastitis caused by environmental pathogens (Oliveira et al., 2013). It is well documented that leaking milk, high daily milk yield, and reduced immunological capabilities are associated with increased risk of clinical mastitis (Schukken et al., 1990) and all of these characteristics are more common in early lactation. While exposure to opportunistic environmental pathogens can occur throughout the lactation cycle, cows initiating lactation are less able to withstand exposure to microorganisms because of innate immune suppression.

Anatomical characteristics of the udder and teat are known risk factors for IMI. Cows with larger udders are at increased risk of IMI as are cows with udder hygiene scores (**UHS**) that indicate dirtier udders (scores 3 or 4 on a 4-pt. scale) (Barkema et al., 1999, Schreiner and Ruegg, 2003). Udders become dirty as a consequence of a number of routine management decisions. Risk factors for "dirty udders" were evaluated on 79 commercial Wisconsin dairy farms (Salgado and Ruegg, data unpublished).The farms included 11,200 lactating cows housed in both freestalls (n = 51 herds) and tie stall barns (n = 28). There was no difference in the proportion of clean UHS (77%) based on type of facility. For animals housed in tie stalls, the risk of dirty udders was increased 1.5 times when stalls were cleaned <2 times per day, 4.5 times when stall beds were scored as dirty, and >10 times when a large proportion of the cows had loose manure. For animals housed in freestalls, the risk of dirty udders was increased 1.8 times when organic bedding materials were replenished less than daily, 4 times when stall beds were scored as "dirty," >10 times when a large proportion of the cows had loose manure, 2.5 times when cows had access to outdoors, and >10 times as barns were increasingly overstocked. This data reinforces the role of facility management and cow comfort in reducing risk of environmental mastitis.

Changing Concepts of Mastitis Control

On modern dairy cattle farms, most antibiotics are administered to treat sick animals but some are used for prevention of disease during high risk periods. Almost all conventional dairy farms report some regular usage of antibiotics (Zwald et al.; 2004 Oliveira, 2013). Nationally, in 2007, about 7, 3, 7, and 16% of adult dairy cows were treated for foot infections, pneumonia, metritis, or mastitis, respectively (USDA, 2009). When antibiotic treatments are summed up, research has demonstrated that each adult cow receives about 5 defined daily doses per year (Pol and Ruegg, 2007; Saini et al., 2012). In a recent study of large dairy farms in Wisconsin (Oliveira and Ruegg, 2014), a dramatically greater proportion of animals were treated for mastitis (40 treatments/100 cows/yr) as compared to reproductive disorders (13 treatments/100 cows/yr), respiratory disease (4 treatments/100 cows/

yr), lameness (5 treatments/100 cows/year), or digestive problems (2 treatment/100 cows/yr) (data not presented in original study). This data indicates that efforts to reduce antibiotic usage on dairy farm must be targeted on prevention and appropriate treatment of mastitis. Several important principles should be considered before using antibiotics for treatment of mastitis.

Antibiotics should not be used for cows that are unlikely to benefit. Cows that have a previous diagnosis of mastitis caused by a refractory pathogen (*Mycoplasma bovis*, *Staph aureus*, *Prototheca*, *Serratia*, etc.) should not receive antibiotics as they are unlikely to be effective. Likewise, it is unusual for antibiotic therapy to be effective for cows that have chronic symptoms of mastitis (>3 cases of clinical mastitis (**CM**) during the current lactation or >4 months of SCC > 200,000 cells/mL). In these instances, abnormal milk should be discarded until it returns to normal (usually about 4 to 6 days) and "watchful waiting' should be performed (frequent observation of the cows behavior and symptoms) to detect the rare instances where the severity of the case progresses.

Abnormal milk is a visible indication that the cow's immune system has responded to an infection. Much antibiotic usage associated with mastitis cannot be justified because the infective bacteria is often gone before the inflammation is detected or the mastitis is caused by a type of bacteria that is unlikely to respond to the types of drugs that are available. In most modern dairy herds, clinical mastitis is caused by a diverse group of opportunistic pathogens and at least 20 to 25% of milk samples are culture negative at the time that the case is detected. Depending on specific virulence factors, organisms infect different locations in the udder, have differing abilities to cause illness in the cow, and differ in the expected rate of spontaneous bacteriological cure. Thus, identification of type of bacteria causing the infection is important to properly select an antibiotic (if needed) and to determine the best duration of therapy. Additionally, many characteristics of the cow are known to influence the probability of successful immune responses and cure after intramammary infections (Burvenich et al., 2003; Pinzon-Sanchez and Ruegg, 2011). Parity, stage of lactation, and history of previous clinical or subclinical mastitis cases are all factors that should be considered before using an antibiotic to treat a case of clinical mastitis.

Criteria for justifiable antibiotic usage

1. *Antibiotic usage should involve veterinary guidance*. On most farms, many mastitis treatments involve extralabel use of drugs. Extralabel drug usage must be supervised by a local veterinarian that has a proper veterinary client patient relationship (**VCPR**). Criteria for establishing a proper VCPR are codified by state and federal regulations, but the American Association of Bovine Practitioners (**AABP**) has guidelines that identify critical components of that relationship (http://www.aabp.org/resources/aabp_guidelines/vcprguidelinefinal11-2013.2.pdf). To maintain consumer confidence, farmers should work closely with their local veterinarians to deliver treatment protocols that are compliant with FDA regulations and meet general principles of appropriate antibiotic usage (Weese et al., 2013).

2. *Antibiotics should only be used when there is a reasonable likelihood that a bacterial infection is present.* This criteria cannot be met for most of the 25 to 40% of CM cases that are culture negative when detected and alternative ways to manage these cases should be considered. When possible, use of

rapid culturing methodologies is encouraged to identify active IMI.

3. *Narrow spectrum antibiotics that are less critical for treating human illnesses should be used as a first choice.* The World Health Organization has classified antibiotics based on their importance for treating human illnesses (Anonymous, 2012). Most intramammary (**IMM**) products available in the US, are not high priority drugs for treatment of human illnesses and only ceftiofur (a third generation cephalosporin) is listed as high priority and critically important for human use. Depending on the intrinsic susceptibility of bacteria, antibiotics are classified as either narrow or broad spectrum. Narrow spectrum drugs are usually active against either Gram-positive or Gram-negative bacteria, whereas broad spectrum drugs have activity against both types of organisms. When possible, narrow spectrum drugs are preferred as they have less potential for selection for resistance and are usually less critical for human health needs (Weese et al., 2013). Most approved IMM products are considered narrow spectrum and use of the broader spectrum IMI drugs should be reserved for cases that will benefit.

4. *Antibiotics should be used for as short a duration as possible.* In general, duration of antibiotic treatment should be kept as short as possible to minimize economic losses associated with milk discard while maximizing the probability of achieving bacteriological cure (Pinzon-Sanchez and Ruegg, 2011). The appropriate duration of antibiotic treatment for CM is not well-defined and varies depending on etiology. Different pathogens have varying abilities to infect mammary gland tissue. Some pathogens preferentially infect superficial mucosal surfaces, while other pathogens have the ability to deeply infiltrate mammary gland secretory tissue. There is considerable evidence that extended duration antibiotic therapy increases bacterial cure of invasive pathogens (such as *Staph aureus* and some environmental *Streptococci spp*.) (Oliver et al., 2004a; Oliver et al., 2004b). However, no research has indicated that extended duration therapy improves clinical outcomes of mastitis caused by non-invasive pathogens (such as CNS or most *E. coli*). Use of extended duration therapy to treat these types of pathogens significantly increases costs without improving economic outcomes (Pinzon-Sanchez and Ruegg, 2011). For mastitis caused by invasive pathogens, the duration of therapy should be extended, but for other etiologies, short duration is recommended.When extended therapy is considered, veterinarians should assess the ability of farm personnel to perform aseptic infusions as extended IMI treatment is associated with an increased risk of infection from opportunistic pathogens.

5. *Characteristics of affected cows should be reviewed before antibiotics are administered.* The purpose of antibiotics is to help the cow's immune response successfully eliminate IMI and many characteristics of the cow are known to influence the probability of successful immune response (Burvenich et al., 2003). Thus, an assessment of the cow's ability to mount an immune response should be performed as part of the medical exam. Characteristics related to a healthy immune response include age, stage of lactation, negative energy balance, history of previous treatments, and environmental factors (such as heat-stress). Older cattle (>3rd parity) often have poorer responses to treatment as compared to younger cattle (Hektoen et al., 2004; McDougall et al., 2007a; McDougall

et al., 2007b). A history of chronically increased SCC is also associated with poorer prognosis after mastitis therapy (Bradley and Green, 2009; Pinzon-Sanchez and Ruegg, 2011). Cows in the immediate post-partum period are known to be immunosuppressed and heat stress can reduce the ability of the cow to respond to an IMI (do Amaral et al., 2011). Before administration of antibiotics, farmers should review the medical history of the cow and assess if she has risk factors that indicate antibiotics may be beneficial. For example, short-duration IMI antibiotics may be considered for CM occurring in valuable older cows that have non-severe Gram-negative mastitis in the immediate post-partum period. Conversely, "watchful waiting" may be considered for CM occurring in older cows that have a long history of repeated non-severe cases.

6. *Extralabel use should be avoided when on-label use is a possibility.* Extralabel use of intramammary products includes use for durations or dosing intervals that are not explicitly listed on the product label. These deviations from label guidelines are common for mastitis treatment and may be justifiable for some drugs but must be done under veterinary supervision. Extralabel use of parenteral antibiotics to treat mastitis is not unusual (Raymond et al., 2006; Pol and Ruegg, 2007; USDA, 2009; Oliveira and Ruegg, 2014) but should be restricted to justifiable cases, such as cows affected with severe mastitis.

Conclusion

Mastitis remains the most frequent and costly disease of dairy cows and is the most common reason that antimicrobials are administered to adult dairy cows. On modern dairy farms, mastitis is caused by an increasingly diverse group of pathogens. The separation between "contagious" and "environmental" organisms is not complete and many organisms can be transmitted in either manner. Detection systems for mastitis must include methods to detect both subclinical and clinical disease and should include severity scoring of clinical cases. It is not possible to determine etiology without microbiological examination of aseptically collected milk samples.

To control mastitis and use appropriate treatments, etiology must be determined. The worldwide dairy industry is continuing to rapidly change and to ensure the continued production of high quality milk mastitis control strategies must also progress.

References

Anonymous. 2012. Critically important antimicrobials for human health - 3rd rev. WHO. http://apps.who.int/iris/bitstream/handle/10665/77376/9789241504485_eng.744FE0F57DE2C9E514653F5?sequence=1

Barkema, H.W., Y.H. Schukken, T.J.G.M. Lam, M.L. Beiboer, G. Benedictus, and A. Brand. 1999. Management practices associated with the incidence rate of clinical mastitis. J. Dairy Sci. 82(8):1643-1654.

Bradley, A.J. and M.J. Green. 2009. Factors affecting cure when treating bovine clinical mastitis with cephalosporin-based intramammary preparations. J. Dairy Sci. 92(5):1941-1953.

Burvenich, C., V. Van Merris, J. Mehrzad, A. Diez-Fraile, and L. Duchateau. 2003. Severity of E. coli mastitis is mainly determined by cow factors. Vet. Res. 34(5):521-564.

do Amaral, B.C., E.E. Connor, S. Tao, M.J. Hayen, J.W. Bubolz, and G.E. Dahl. 2011. Heat stress abatement during the dry period influences metabolic gene expression and improves immune status in the transition period of dairy cows. J. Dairy Sci. 94(1):86-96.

Ericsson Unnerstad, H., A. Lindberg, K. Persson Waller, T. Ekman, K. Artursson, M. Nilsson-Ost, and B. Bengtsson. 2009. Microbial aetiology of acute clinical mastitis and agent-specific risk factors. Vet. Microbiol. 137(1-2):90-97.

Hektoen, L., S.A. Odegaard, T. Loken, and S. Larsen. 2004. Evaluation of stratification factors and score-scales in clinical trials of treatment of clinical mastitis in dairy cows. J. Vet. Med. A. Physiol. Pathol. Clin. Med. 51(4):196-202.

Hogan, J.S., K.L. Smith, K.H. Hoblet, D.A. Todhunter, P.S. Schoenberger, W.D. Hueston, D.E. Pritchard, G.L. Bowman, L.E. Heider, B.L. Brockett, and et al. 1989. Bacterial counts in bedding materials used on nine commercial dairies. J. Dairy Sci. 72(1):250-258.

McDougall, S., K.E. Agnew, R. Cursons, X.X. Hou, and C.R. Compton. 2007a. Parenteral treatment of clinical mastitis with tylosin base or penethamate hydriodide in dairy cattle. J. Dairy Sci. 90(2):779-789.

McDougall, S., D.G. Arthur, M.A. Bryan, J.J. Vermunt, and A.M. Weir. 2007b. Clinical and bacteriological response to treatment of clinical mastitis with one of three intramammary antibiotics. N. Z. Vet. J. 55(4):161-170.

Olde Riekerink, R.G.M., H.W. Barkema, D.F. Kelton, et al. 2008. Incidence rate of clinical mastitis on Canadian dairy farms. J. Dairy Sci. 91:1366-1377.

Olde Riekerink, R.G.M., H.W. Barkema, D.T. Scholl, et al. 2010. Management practices associated with the bulk-milk prevalence of Staphylococcus aureus in Canadian dairy farms. Prev. Vet. Med. 97:20-28.

Oliveira, L., C. Hulland, and P. L. Ruegg. 2013. Characterization of clinical mastitis occurring in cows on 50 large dairy herds in Wisconsin. J. Dairy Sci. 96:7538-7549.

Oliveira, L., and P. L. Ruegg. 2014. Treatments of clinical mastitis occurring in cows on 51 large dairy herds in Wisconsin. J. Dairy Sci. 97:5426-5436.

Oliver, S.P., B.E. Gillespie, and J.J. Headrick SJ, et al. 2004. Efficacy of extended ceftiofur intramammary therapy for treatment of subclinical mastitis in lactating dairy cows. J. Dairy Sci. 87:2393-2400.

Pantoja, J.C.F., C. Hulland, and P.L. Ruegg. 2009. Somatic cell count status across the dry period as a risk factor for the development of clinical mastitis in the subsequent lactation. J. Dairy Sci. 92(1):139-148.

Pínzon-Sanchéz, C., and P.L. Ruegg. 2011. Risk factors associated with short-term post-treatment outcomes of clinical mastitis. J. Dairy Sci. 94:3397-3410.

Pol, M., and P.L. Ruegg. 2007. Treatment practices and quantification of antimicrobial drug usage in conventional and organic dairy farms in Wisconsin. J. Dairy Sci. 90:249-261.

Raymond, M.J., R.D. Wohrle, and D.R. Call. 2006. Assessment and promotion of judicious antibiotic use on dairy farms in Washington state. J. Dairy Sci. 89(8):3228-3240.

Rodrigues, A.C., D.Z. Caraviello, and P.L. Ruegg. 2005. Management of Wisconsin dairy herds enrolled in milk quality teams. J. Dairy Sci. 88(7):2660-2671.

Rowbotham, R.F. and P.L. Ruegg. 2015. Association of bedding types with management practices and indicators of milk quality on larger Wisconsin dairy farms. J. Dairy Sci. 98(11):7865-7885.

Saini,V., J.T. McClure, D. Leger, et al. 2012. Antimicrobial use on Canadian dairy farms. J. Dairy Sci. 95:1209-1221.

Schreiner, D.A., and P.L. Ruegg. 2003. Relationship between udder and leg hygiene scores and subclinical mastitis. J. Dairy Sci. 86(11):3460-3465.

Schukken, Y.H., F.J. Grommers, D. Vandegeer, H.N. Erb, and A. Brand. 1990. Risk-factors for clinical mastitis in herds with a low bulk milk somatic-cell count 1. Data and risk-factors for all cases. J. Dairy Sci. 73(12):3463-3471.

Smith, K.L., D.A. Todhunter, and P.S. Schoenberger. 1985. Environmental mastitis: Cause, prevalence, prevention. J. Dairy Sci. 68:1531-1553.

USDA. 2009. Dairy 2007, Part V: Changes in dairy cattle health and managment practices in the United States, 1996-2007. C. USDA:APHIS:VS, ed, Fort Collins, CO.

Weese, J.S., S.W. Page, and J.F. Prescott. 2013. Antimicrobial stewardship in animals. Pages 117-133 in Antimicrobial Therapy. S. Giguere, J.F. Prescott, and P.M. Dowling, ed. Wiley Blackwell, Ames, IA.

Zadoks, R.N., H.G. Allore, H.W. Barkema, O.C. Sampimon, G.J. Wellenberg, Y.T. Grohn, and Y.H. Schukken. 2001. Cow- and quarter-level risk factors for Streptococcus uberis and Staphylococcus aureus mastitis. J. Dairy Sci. 84(12):2649-2663.

Zwald, A., P.L. Ruegg, J.B. Kaneene, L.D. Warnick, S.J. Wells, C. Fossler and L. Halbert. 2004. Management Practices and reported antimicrobial usage on conventional and organic dairy herds. J. Dairy Sci. 87:191-201.

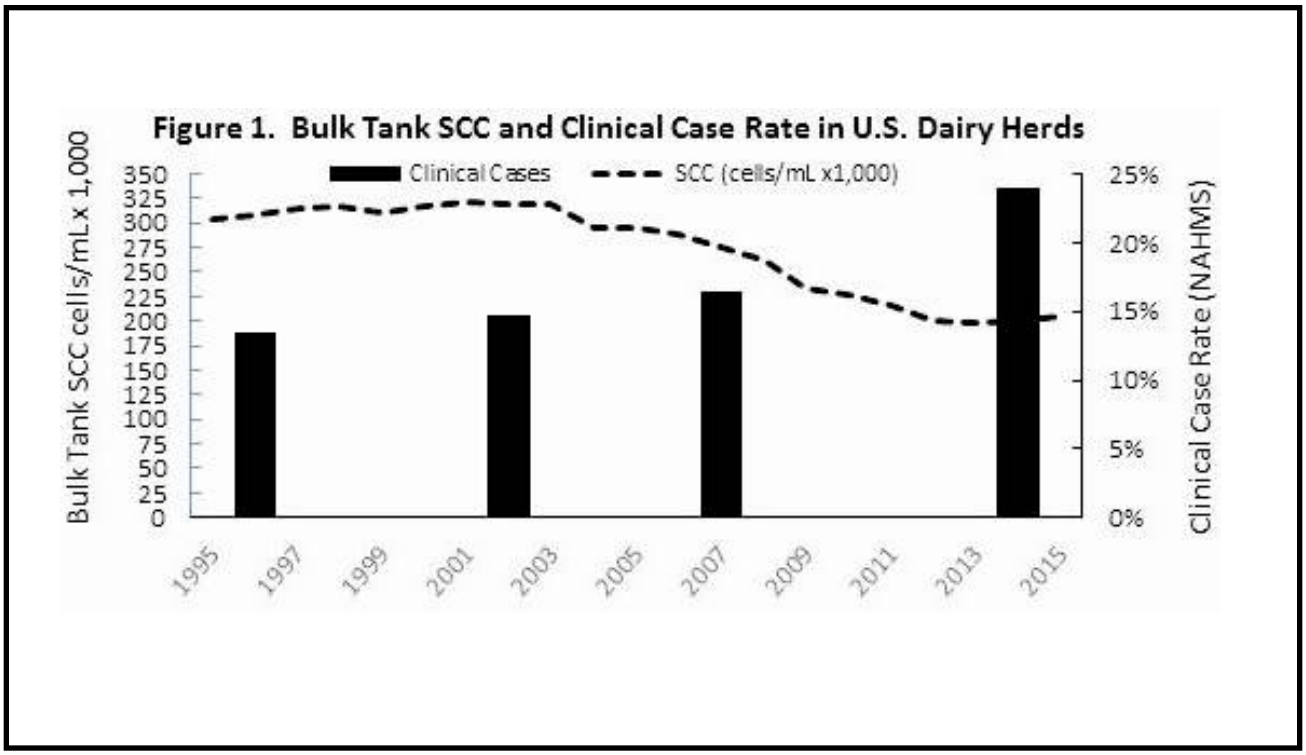

Figure 1. Data from: https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/monitoring-and-surveillance/nahms.