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Full Length Research

The relationship of the ruminant microbiome to animal health and disease: A review

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ABSTRACT: Animal scientists, veterinarians, and food-animal producers relate the health and well-being of animals to their internal and external environmental surroundings, as a result of either stressors or stimulants that can impact the production and efficiency of those animals. As more research has been conducted to understand how to mitigate stressors or promote stimulants in an environment, it can, in turn, potentially impact the colonies of microbiota that also maintain the well-being of an animal and its efficiency to be productive. That is, until the animal's microbiome is altered, which can lead to untimely and unproductive diseases in various organ systems. This review aims to understand the relationship between the microbiome of ruminant species and its relationship to animal health and disease. The knowledge presented in this manuscript is focused on particularly the understanding/background of current literature published in animal science, microbiome, microbiology, and animal health and disease from the past 100 years of published data about the microbiome, the microbiome of different organ systems located in the ruminant animal model, and the relationship of the microbiome of those ruminant animal model organ systems when in homeostasis or in the presence of disease. The findings of this review manuscript conclude the relationship between the microbiome of the ruminant animal model and its associated responses to health and disease.

Keywords: Animal health and disease, microbiome, ruminant.

Abbreviations: AI, Artificial insemination; **BRD,** Bovine Respiratory Disease; **PGE2,** Prostaglandin E-2; **PGF2α,** Prostaglandin F-2α; **VFAs,** Volatile Fatty Acids.

INTRODUCTION

Regardless of the animal of interest, scientists emphasize the need for significant attention towards understanding the microbiome of different organ systems present in domestic animals (Hacquard *et al*., 2015). All multicellular organisms benefit from their microbiome, as it plays a crucial role in maintaining the host's nutritional health and immunity (Ikeda-Ohtsubo *et al*., 2018). The recognition of the microbiome has a significant impact on the livestock industry, particularly in the production of protein sources such as beef, pork, and chicken, as the microbiome has a profound effect on livestock physiology, phenotype, and disease incidence (McDaneld *et al*., 2019). For instance, the rumen microbiome is a complex ecosystem composed of anaerobic bacteria, protozoa, fungi, and methanogenic archaea that are needed for the digestion of food, the production of energy, and breaking down fatty acids (Huws *et al*., 2018). Beyond just the functionality of the rumen gastrointestinal tract, the ruminant respiratory microbiome has a continued effect on the occurrence of potential bovine respiratory disease (BRD) and its negative effects on stocker production (Centeno-Martinez *et al*., 2022). Some of these similar bacterial colonies are being investigated as possible avenues of influence in the female reproductive system, such as *Histophilus*, *Mannheimia*, and *Pasteurella* bacterial colonies found in vaginal tissue of pregnant and non-pregnant cattle (Messman *et al*., 2020b).

Beyond the axis mechanism between the animal model and its own microbiome, consideration must also be given to the animal's surrounding environment and its respective impact on the animal's microbiome. For instance, the exposure to heat stress on dairy cattle reduced the diversity in the fecal microbial population, which resulted in a greater expression of disease outbreaks. (Chen *et al*., 2018). Let alone this impact, several other studies on laying hens (Zhang *et al*., 2017), weaning stress in dairy cows (Davis *et al*., 2016), and mice (Bailey *et al*., 2011) indicate the interaction of heat stress on the microbiome. A similar environment by microbiome interactions occurs with the induction of cold stress on the animal microbiome. According to Nicholls *et al*. (2016), the gut microbes assist in energy balance under cold stress, allowing the activation of brown adipose tissue thermogenesis. Recently, Cheng *et al*. (2025) determined that different breeds of sheep that are under cold exposure change the production of acetate fermentation, while changing the microbial diversity and function to increase the metabolism rate of both propionate and butyrate.

As microbiome and animal health research continues in livestock production, more interest continues to develop for the understanding of how different microbiomes, in conjunction with other organ systems, have positive and negative impacts on livestock production, particularly with animal health, disease, and production. Even with the immense research going into the ruminant microbiome species organ systems, whether in the ruminant gastrointestinal system, reproductive system, or even respiratory system, there is still a disconnect between the relationship between the microbiome of these systems and its associated response to animal health and disease. This review will investigate the ruminant animal ecosystem, while specifically looking into the microbiome of the ruminant gastrointestinal system, immune system, integumentary system, respiratory system, and reproductive system. In each of these organ systems, this review will explore the production aspects of each, while researching how the microbiome interacts within each system and how it can influence organ systems in both health and disease. In order to accomplish these goals, this manuscript will provide a broad understanding of what the microbiome is and its importance, then delve into each of the more well-understood microbiomes of organ systems in the ruminant animal, while understanding the relationship between the microbiome, organ systems, and animal health and disease.

WHAT IS THE MICROBIOME?

To understand the symbiotic relationship between the microbiome and the animal system in question, scientists, veterinarians, and food-animal producers must first understand "what is the microbiome?" The microbiome refers to the entire habitat, including the microorganisms, their genomes, and the surrounding environmental conditions of living beings (Marchesi and Ravel, 2015). In the context of humans, the term often refers to or describes the microorganisms that live in or on a particular part of the body, such as reproductive tissue, gastrointestinal tract, skin, or respiratory system (NHGRI, 2024). Studies were initially started with Antonie van Leeuwenhoek, as early as the 1680s, who looked at comparisons between oral and faecal microbiota (Ursell *et al*., 2012). Later in history, the origin of these microbiota definitions began surfacing in the mid-1800s by a German bacteriologist, Theodor Escherich, who is credited with the discovery of *Escherichia coli* in the intestinal tract of children who were apparently healthy and those with enteritis, at the time of the study (Manning, 2010).

After the discovery of E. coli, the science of microbiome progressed further with the discovery of Veillonella parvula found in the oral, digestive, urinary, and upper respiratory tracts of humans in the late 1890s (Sahu and Hayes, 2020), known now as the causative agent of osteomyelitis (Fisher and Denison, 1996). Even though these scientific discoveries, which were at the forefront of what is now considered microbiome research, the term microbiome never came into existence until the early 2000s. Lederberg and McCray (2001) coined the term "microbiome" as the "ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space". In the context of animal species, especially with most of the research pertaining to the ruminant digestive system currently, the interest and vision remain similar when researching the microbiome of all organ systems found in an animal under various production environments. Particularly, the areas of interest and concern include the gastrointestinal tract, integumentary system, reproductive tract, and respiratory system. This review will investigate each of these systems and look into the decades of published literature available on the relationship of the microbiome of the ruminant animal in health and disease affecting that production sector.

The microbiome of the ruminant integumentary system

The integumentary system is a protective system that consists of the skin and its derivatives, such as hooves, udders, and horns (Fails and Magee, 2018). This organ system is an animal's first defense against the environment and is critical in acting as an immunological barrier (Vanderwolf *et al*., 2023), although entry of bacteria from the skin to the body occurs (Manus, 2022). Many species of bacteria are involved in the integumentary microbiome and assist in the defense against pathogens, such as bacteriocins. These bacteriocins are synthesized by bacteria in the microbiome for the purpose of removing competition and regulating the external environment of the animal's body of the microbiome. Each species has varying levels of bacteria that affect them in different ways, both beneficially and detrimentally (Cholewinska *et al*., 2021). For instance, some species of mites are a major part of the microbiome, which can be symbiotic or parasitic to the animal, assisting in the regulation of build-up on the skin and feeding on it often. An overpopulation of mites, or the parasitic species of mites, can be detrimental, which can lead to animal diseases such as mange or ear mites, resulting in pruritus and possible infection (El-Sherbini *et al*., 2022).

Similar to vernix in humans, sheep produce lanolin, a substance that has antibacterial and antifungal properties for the hide of the animal (Hoath *et al*., 2006). Lanolin impacts the microbiome balance, as it is an antimicrobial that strengthens the integumentary system by moisturizing and adding water resistance to the skin (Hennessy *et al*., 2000). This can help prevent fungal ailments, such as ringworm or rain rot, which are commonly induced by a moist external environment, within the microbiome of the skin. If the microbiome of the skin is compromised, this can lead to more detrimental effects within the animal's body, which can affect other organ systems and vice versa. For example, bovine digital dermatitis cases can vary in accordance with the integumentary microbiome, but also affect the gastrointestinal system with unproductive gut bacteria that can result in a different microbiome in the lesion (Zinicola *et al*., 2015).

Keratin functions as a protective layer in the skin, just like laminin (Olariu *et al*., 2022). In dairy cattle, mastitis is a significant economic issue for the producer. Due to this devastating disease, particular focus has been placed on the teat skin microbiome (Khalil *et al*., 2022). In the livestock production setting, mastitis is caused by one of two means: either by a contagious/infectious nature or through environmental contamination (Garcia, 2004). Typically, the contagious/infectious form of mastitis is caused by a malfunction of keratin production within the udder, allowing external bacterium families such as staphylococci (*S. epidermidis* and *S. aureus*), streptococci (*Str. uberis, Str. bovis, Str. Agalactiae*), coliforms (*E. coli* and *K. pneumoniae*), *Corynebacteriales, Clostridium, and Enterobacter* (Sharif *et al*., 2009; Verdier-Metz *et al*., 2012; Frétin *et al*., 2018; Zemanova *et al*., 2022). This type of infection sets in when keratin produced in the udder does not block infectious microbes from entering the udder through the teat canal (Nickerson and Sordillo, 2017). Producers take multiple precautions to prevent either form of mastitis infection from prevailing in the mammary gland microbiome. For example, utilization of sand bedding for its inorganic material makes up, low moisture content, and contains few nutrients for infectious contagions to replicate and infect the mammary gland, while also the use of milking protocols in the milking parlor to prevent the transfer of contagions from one animal to another (Hogan and Smith, 2012). In beef production, suckling calves produce antimicrobials in their saliva to help counteract mastitis within the udder, interlinking the digestive system with the integumentary system (McCann *et al*., 2014). Consequently, the rumen microbiome impacts other associated microbiomes in the animal's body (McCann *et al*., 2014).

Consequently, other diseases present in the environment can infiltrate and cause secondary mastitis infection due to the result of orf viruses infecting the region of the skin. One such disease is contagious ecthyma, commonly known as sore mouth, in small ruminants that causes pustules around the mouth, resulting in ease of oral zoonotic transmission amongst individuals (Tedla *et al*., 2018). Contagious ecthyma is a highly contagious, zoonotic, viral skin disease that is caused by a replicating virus affecting the integumentary microbiome known as the Orf Virus, which is a member of the genus *Parapoxvirus* in the subfamily *Chordopoxvirinae* and family *Poxviridae* (CFSPH, 2024). This virus enters the animal's body through broken or damaged skin and causes blister-like lesions that will ultimately scab over, and initiate the process of producing sores that are commonly found on the muzzle, mouth, and lips, but can also be found on goats' and sheep's lower legs and teats of the mammary gland (CDCP, 2024). Ewes may also develop lesions on their teats that extend onto the udder skin, possibly causing mastitis from nursing infected lambs (Konig and Peralta, 2024).

Similar to those mentioned above, like secondary mastitis of the mammary gland, are mostly due to breaks in the skin and infection from different etiological classes. Similarly, foot rot can be caused by many different infectious agents that occur in many environments and management settings (Van Metre, 2017). The ruminant foot structure contains two toes, or digits, better known as a cloven-hoofed animal that has space in between them, known as the interdigital space (Hepworth *et al*., 2004). Within these healthy digits are elevated levels of *Bacteroidetes, Proteobacteria, and Firmicutes* (Krull *et al*., 2014; Ariza *et al*., 2019; Mamuad *et al*., 2020), which aid in the protection of the interdigital space from the outside environment of the skin. When lesions form on the skin, they expose the subcutaneous tissue to infectious agents, and when kept in wet conditions results in infection (Dewell and Shearer, 2009). For a bacterium to infect the hoof of a ruminant, the skin-hair line junction must be damaged; without this lesion, the occurrence of continual bacterium exposure to the subcutaneous tissues cannot cause foot rot (Strickland *et al*., 2021). The primary, most common, infectious agent of foot rot in ruminants is the *Fusobacterium necrophorum*, which is a common bacterium in soil and is more severe when combined with the *Bacteroides* (Biggs *et al*., 2016). Literature suggests that prevention of foot rot is met with good foot hygiene with regular footbath management (Cook *et al*., 2012; Logue *et al*., 2012; Nielsen *et al*., 2016), particularly with copper sulfate as an antibacterial agent (Teixeira *et al*., 2010; Speijers *et al*., 2012). Even with all of this said, the majority of literature and first-hand veterinarian and producer occurrences lend to the interaction of the integumentary microbiome with changes in the ruminant animals' environment that lead to the increased possibility of disease occurrence.

The microbiome of the ruminant immune system

To understand how ruminant species' immune system and microbiome interact, one must understand them separately. The immune system is considered a broad mechanism that allows a living organism to discriminate between what is "self" and "non-self" (McComb *et al*., 2019). This allows the immune system to protect the host from infectious agents that exist in an everyday environment, such as bacteria, fungi, mycoplasma, viruses, and other insults to the health of the animal's body (Calder and Kew, 2002; Juarez *et al*., 2022). The microbiome in mammals is known to be home to over four hundred different species of bacteria, which allows the microbiome to be considered an "organ" in itself (Anwar *et al*., 2019). This is because the microbiome can be either beneficial or harmful, in the case of overpopulation of bacteria, or the initiation of a stressor, stimulus, or change in the microflora of the body's organ system. These microbiome communities can then create, and play a localized essential role, in animal health and disease (Ursell *et al*., 2012). For instance, the gut microbiome has a relationship with the circulation levels of cytokines, such as interleukin-6 (Bailey *et al*., 2011), which is needed in the response to tissue damage or inflammation due to infections or injuries (Tanaka and Kishimoto, 2014). Thus, when observing the immune system and microbiome working together, it becomes more readily understood how each relies on the other to maintain overall health or homeostasis within the animal.

The immune system can be broken down into two specific types: innate and adaptive, or better known as nonspecific and specific immunity, respectively (Kennedy, 2010). The innate, or nonspecific, immune system is easiest explained as a defense system against microbes that are present in all organisms that are not long-lasting (Choy *et al*., 2017). Usually, the innate immune system is what an animal is born with that does not possess specific antigen recognition, while adaptive, or specific, immunity is the barrier that is built up over the lifetime of the animal species (Kennedy, 2010). The innate immune system of an animal senses the microbial pathogenesis of said pathogen, particularly when the microbe is considered harmful or even an overpopulation of beneficial microbes (Beutler, 2004). Since innate immunity is considered the broadest and fastest-acting, this allows the body to get an initial start on battling off a wide variety of infections or harmful microbes in an adequate amount of time (NLM, 2006). For example, if the animal is suffering from an infection in the digestive tract, the harmful microbes in the gut can be replaced by new beneficial microbes through the process known as transfaunation (DePeters and George, 2014). This can be accomplished through the asexual replication, or binary fission, of the microbes in the G.I. system of the animal (Nagaraja and Titgemeyer *et al*., 2007), transplantation of rumen fluid containing microbes and nutrients from healthy animals into animals with impaired rumen digestion (Steiner *et al*., 2019), or through the reestablishment of new colonies through probiotics administration (Lambo *et al*., 2021).

When looking at adaptive immunity, one of the best examples of building immunity is from the mother's colostrum, which is consumed shortly after birth for all mammalian species (Stelwagen *et al*., 2009). The nutrient-rich ecosystem of milk allows for a wide variety of microorganisms to thrive, allowing many antibodies to be given through the consumption of colostrum (Bronzo *et al*., 2020). The colostrum allows the calf the opportunity to obtain its own gut microbe population that will begin to aid in the prevention of disease and infection throughout life, thus allowing the buildup of the animal's immune system (Yang *et al*., 2015). Beyond the reception of maternal antibodies, the skin microbiome and microbial diversity of raw milk allow for the inoculation of different bacterial phyla colonies for the gastrointestinal microbiome (Verdier-Metz *et al*., 2012; Frétin *et al*., 2018; Khalil *et al*., 2022).

When it comes to weaning cattle, studies have shown that this can be one of the most stressful parts of their life (Lynch *et al*., 2018). During this time, they are being separated from their dam and more than likely are receiving their pre-weaning vaccinations before being turned out to pasture, transported, and then sold at a livestock market, etc. (Weary *et al*., 2008). One of the first incidents of the microbiome being altered during weaning is switching the calf from milk to feed. This, in turn, will change the microbes of the rumen, particularly from the switch of a milk-based majority diet to a full grain or forage-based diet (Meale *et al*., 2017), particularly altering the microbiome to the production of acetate, propionate, and butyrate for gluconeogenesis. This change in diet can affect the calf's gut microbiome negatively and affect the overall health of the animal (Amin and Seifert, 2021). For example, a calf that is experiencing some external or internal stress is continually releasing various amounts of cortisol, with a subsequent change in the animal's environment can cause an effect on health due to the microbiome changes in the organ systems of the animal.

The stress that the animal is currently going through can prevent the adaptive immunity received from the vaccine. Thus, this means they are not protected from diseases or infections that may be too much for the innate immune system to handle.

The microbiome of the ruminant gastrointestinal system

The ruminant digestive system is uniquely different from a monogastric digestive system, which includes a four-compartment stomach consisting of the rumen, reticulum, omasum, and abomasum (Clauss and Hofmann, 2014). An essential aspect of the digestive tract of ruminants is the microbes of the unique four-compartment stomach that includes bacteria, protozoa, fungi, and archaea (Matthews *et al*., 2019). The gut microbiome is essential for gut development, feed utilization and efficiency, and immune response, particularly in the ruminant species (Fernando, 2016; Arshad *et al*., 2021). The functions of these microbes include protein hydrolysis, peptide metabolism, amino acid deamination, fiber, and starch fermentation (de La Guardia Hidrogo *et al*., 2021).

Changes in gut microbial colonization, in the neonatal stage of development of ruminants, can result in permanent effects on the establishment of the rumen microbiome that can have lasting effects on the host phenotypes' development (Furman *et al*., 2020; Guo *et al*., 2020). From the time of conception, through the first few months after parturition of the neonatal ruminant, the rumen of the digestive system is all but non-functional (Lyford Jr., 1993). Parish *et al*. (2022) concluded that young, growing ruminants ranging from newborn to three months of age are considered nonruminants, functionally. This contradicts the above statements, which conclude that within the first 20 minutes after parturition, there is the presence of fibrolytic bacteria and methanogens appearing in the rumen of newborn animals (Guzman *et al*., 2015). Producers and scientists theorize that the rumen does not begin to gain functionality until inoculation of microbes into the reticulorumen environment has occurred, and from the imprinting behavior of grazing techniques, the neonatal animal develops over time, from its dam (Launchbaugh and Howery, 2005). It has been shown that the animal will have to be impregnated with microbes, for them even to be present in the neonatal model, which is better known as transfaunation (DePeters and George, 2014). This process is accomplished through the transferring of microbes from dam to rearing offspring, typically through environmental exposure or grooming of the muzzle area (Becker and Hsiung, 1929). That said, there is another potential form of transfaunation of microbes due to the consumption of colostrum, from the mammary gland, after parturition (Niimi *et al*., 2017). As the neonatal ruminant continues to suckle, the lactobacilli family microbes will slowly gain entry into the ruminant digestive system with each lactation consumption (Lee, 2014). As growth and development of the neonatal animal continue, they will go through a transitional phase around three to eight weeks of age, which will allow the development of microbial fermentation through an adequate number of microbes in the reticulum and rumen (Pal *et al*., 2020).

When looking into the ruminant digestive system, there are two main organs that contain the majority of microbes, including both the rumen and reticulum (van Hoven and Boomker, 1985). According to Parish *et al*. (2022), the solid portion of the cud is slowly moved into the rumen, where, after approximately forty-eight hours, a dense mat is formed. This is where microbes use fibrous feedstuffs as a forerunner for energy (Hungate, 2013). Most microbes range from bacteria, protozoa, and fungi, which will produce volatile fatty acids (VFAs) such as acetate, propionate, butyrate, and other unusable gases such as methane, hydrogen sulfide, and carbon dioxide through the fermentation process of breaking down cell walls into different carbohydrate fractions, respectively (Wolin, 1979). The use of these VFAs will help in the animal's muscular and skeletal development, gluconeogenesis, and will allow for the formation of the reticulorumen papillae and omasum leaves (Lyford Jr., 1993). In addition, the microbes themselves are digested in the abomasum, which allows for an additional protein source known as microbial protein (Kay, 1969).

The rumen microbiome is one of the most diverse ecosystems in terms of species diversity and functionality (Mizrahi and Jami, 2018). Bacteria are by far the most numerous microbes in the reticulorumen with approximately 10^{10}-10^{11} cells/mL of rumen fluid and over 200 species (McSweeney and Mackie, 2012), making up around 95% of the microbiome with the remainder between 2-4% archea, and near 1% eukarya consisting of protozoa and fungi (Brulc *et al*., 2009). According to Henderson *et al*. (2015), some of these bacterial communities included *Prevotella* (Bacteroidetes), *Butyrivibrio, Ruminococcus*, as well as unclassified *Clostridiales*, *Bacterioidales*, and *Lachnospiracea*, in which they play a key role in rumen metabolism and function, while also playing a pivotal role in cellulolytic and non-cellulolytic degradation of plants (Accetto and Avgustin, 2015). The largest microbes in size are protozoa, which are also found to vary scarcely compared to the two other types of microbes (Lee, 2014). Protozoa are not essentially required for digestion or for animal survival, but they are very important for the microbial process in the rumen ecosystem and host animal physiology (Yánez-Ruiz *et al*., 2007; Mosoni *et al*., 2011; Newbold *et al*., 2015), especially playing a role in methanogenesis (Belanche *et al*., 2014). The other Eukarya present in the rumen, particularly anaerobic fungi, are an integral part of the rumen microbiome that contributes to plant cell wall digestion (Mizrahi and Jami, 2018). The *Neocallimasticaceae* family of anaerobic fungi is crucial for the colonization and dissociation of lignocellulolytic tissues, which allows for an increase in accessibility and digestibility efficiency of fiber by bacteria

(Akin and Borneman, 1990; Liggenstoffer *et al*., 2010; Mizrahi and Jami, 2018).

Where associated problems begin to arise in this microbiome is likely due to an imbalance in the microbial population due to stress or abrupt changes in the ruminant animals' diet (Keum *et al*., 2024). For example, some of these incidents are caused, but not limited to, exposing animals to feeds without prior adaptation, to accidental access with overconsumption of highly fermentable carbohydrate, or those animals that have been "off feed" for a period of time and have returned (Owens *et al*., 1998). These instances can lead to changes in the microbial population of the rumen, resulting in what is known as acute rumen lactic acidosis (Stock, 2000). This disease results in the shifting and loss of favorable microbial population, when the pH level of the rumen drops below 5.6, suddenly or for an extended period of time, results in the loss of VFA producing bacteria, favorable protozoa, and fungi that aid in digestion of feedstuff while drastically shifting towards the presences of lactic acid producing bacteria (Nagaraja, 2016). Let alone the effects on the microbial population, but the effects are felt long past the incidence on the associated organ systems, particularly the rumen papillae and the possibility of morphological/physiological changes to the liver (Millen *et al*., 2016). In order to bring the pH back to levels of normalcy, while also returning the rumen microbiome to be more favorable for VFA-producing means, producers or veterinarians can adjust the feeding regime of these animals, correct the rumen pH, or even transfaunate rumen fluid from a healthy ruminant system.

Contrary to belief, there are some species of rumen bacteria that occur in the intestines of ruminants (Hobson, 1969). Currently, there are not many studies on the intestinal tract microbiome of ruminants since the majority of research and collaborations have concentrated on the microbiome of the rumen environment (Hou *et al*., 2018; Choy *et al*., 2017). According to Li *et al*. (2018), the colonization of bacterial communities in the small intestine is initiated from the consumption of breast milk, mainly since this is the primary location of digestion and absorption of milk. The small intestine consists of a very small amount of concentrated viable bacteria, with most of the bacteria being transients that have a low impact on digestion (Lee, 2014). The number of microbes found in the small and large intestines is minute compared to the rumen and reticulum. Song *et al*. (2017) concluded that short-chain fatty acids metabolism and digestion were associated with the colonization of *Escherichia*, *Salmonella*, *Blautia*, *Lacnospiraceae NC2004 group*, and *Coprococcus*. Based on these findings from Song *et al*. (2017), it is believed that the intestinal microbiome plays a role in the development of nutrient absorption, metabolism, and, most importantly, gut-related immune functions (Zhang *et al*., 2021). Also located in the intestinal microbiome are obligate anaerobic constituents, such as *Bifidobacterium* and *Bacteroides* (Jost *et al*., 2012), which play an important role in neonatal development, particularly with the development of immune tolerance to symbiotic microflora while reducing the incidence of allergies (Malmuthuge *et al*., 2015).

In similarity to the rumen microbiome, the small intestine microbial population can reach a point of imbalance that ultimately can affect the absorption of nutrients (Jacobi and Jack, 2012), or the health/well-being of the ruminant animal, while being the largest immune organ for the body (Pabst *et al*., 2008). For instances, *E. Coli* is a natural occurring inhabitant of the ruminant small intestine microbiome, but in higher concentrations leads to the increase incidence of scours and dehydration of ruminant animals under 21 days of age (Jia *et al*., 2018; Alomari *et al*., 2021), or neurological seizures when absorbed into the blood stream and pumped to the brain (Seimiya *et al*., 2007). Finally, in older bovine species, the introduction of *Mycobacterium Avium ss. Paratuberculosis* has major implications for nutrient absorption, let alone the effect on animal welfare, nutrient absorption, but the economic impact it has on a producer for future production (Berry *et al*., 2010; Bennett *et al*., 2012). The bacterium, *Mycobacterium Avium ss. Paratuberculosis*, better known as "Johne's Disease" in the beef and dairy industry, is a result of the consumption of infected milk or feedstuffs (Sweeney *et al*., 2012). After entrance into the gastrointestinal system has occurred, the bacterium hides in the intestinal tract until some form of stressors triggers the expression of the disease. Once the disease begins to progress, edema of the papillae in the small intestine, or chronic enteritis, occurs, which causes a lack of nutrient absorption through the small intestine (Mallikarjunappa *et al*., 2021). Over time, the resulting disease causes the animal to become lethargic, anorexic, with profuse diarrhea that will rapidly progress to the animal sub coming to death due to the loss of essential nutrients of water and amino acids, with no known cure at this time (Windsor and Whittington, 2010).

The large intestine consists of anaerobic bacteria, while the diversity of microbes that are found in this organ depends upon the animal species. According to Zhang *et al*. (2021), just as in the rumen compared to the small intestine, the bacterial communities of the large intestine are significantly different from those in the small intestine. These bacterial colonies in the large intestine are largely influenced by colonies associated with vaginal tissue and secretions, in which *Bacteroides* spp. is the dominant genus in newborn ruminants' large intestine (Bi *et al*., 2019), with a common link found between feces (Klein-Jobstl *et al*., 2014) and the vagina of healthy adult ruminants (Yeoman *et al*., 2018).

As it relates to the microbiome of the gastrointestinal tract of ruminants, there are a multitude of different microbes that make up the reticulorumen, small intestine, and large intestine. As a whole, each of these colonies is present in order to aid in anaerobic digestion, protect and build the immune system of the ruminant animal, and has been shown to have other connections to elsewhere in the body of the animal. Even though the microbiome aids in digestion and rumen health, the sudden shift or stress from outside managerial or climatic environment can lead to the onset of disease like lactic acidosis. This direct shift leads to degradation of the rumen, subsequently disrupting digestion, morphology of the rumen wall, and can abruptly shift the metabolic features of other organs in this system.

The microbiome of the ruminant respiratory system

The microbial makeup of the ruminant respiratory tract is harbored in the nostrils, nasopharynx, hard plate, oropharynx, tonsils, trachea, and lungs (McMullen *et al*., 2020), which is typically made up of *Proteobacteria, Firmicutes, Actinobacteria, Fusobacteria, Tenericutes, and Bacteroidetes* (Timsit *et al*., 2020). This respiratory microbiome plays a significant role in the efficiency and productivity of cattle from birth through harvest, particularly due to bacterial and viral colonies that effectively cause BRD. Attention has been attracted to the respiratory microbiome due to the opportunistic ability of BRD. (Lloyd-Price *et al*., 2016; Zeineldin *et al*., 2019; McMullen *et al*., 2020). Bovine respiratory disease, better known as shipping fever, is the most economically devastating disease and leading cause of morbidity and mortality in the beef cattle industry (Griffin, 2006; Woolums *et al*., 2018). This is mostly due to the result of increased medication costs and death loss, but also has shown effects on morbid beef calves growing slower, less efficient feed conversion ratios, and need more time to reach similar carcass yield and quality grades (Holland *et al*., 2010). This is mostly due to BRD being a complex, multifactorial disorder caused by a wide range of predisposing factors (Midkiff *et al*., 2021). These various factors are due to a combination of microbial infections in the respiratory microbiome (Angen *et al*., 2009; Confer, 2009; Pardon *et al*., 2011), impaired host immunity and environmental contributions (Lago *et al*., 2006; Gorden and Plummer, 2010; Nicola *et al*., 2017), and stress responses of calves due to the transportation structure of weaned calves to stocker or feedlot operations (Sanderson *et al*., 2008). Many BRD cases lack a definitive causative agent that can affect the respiratory microbiome of cattle. For instance, the bacteria *Mannheimia haemolytica* is associated with acute/subacute interstitial pneumonia, while suppurative bronchopneumonia is linked to *Pasteurella multocida*, and chronic suppurative pneumonia is associated with *Mycoplasma bovis* and *Histophilus somni* (Booker *et al*., 2008). Not counting bacteria, multiple viral agents can influence the development of BRD, including parainfluenza-3 virus, bovine herpes virus, bovine respiratory syncytial virus, and bovine viral diarrhea virus (Klima *et al*., 2014).

Majority of researchers have accepted the BRD pathogenesis theory to be a complex interaction between the microbiome, including bacteria and viruses, while under stressful situations of management or production sectors (i.e. weaning, transportation, comingling, climatic changes, differences in diet, etc.) of the host animal and its environment (Snowder *et al*., 2006; Taylor *et al*., 2010). In a homeostatic environment of the respiratory microbiome, there exists a harmonious interaction between the host, the colonies of the microbiome, and the local environment of the airway, as it relates to the health of cattle (Chai *et al*., 2022). When the homeostatic environment turns into disequilibrium, it is due to a stressful influence on the host. Researchers, veterinarians, and producers usually observe mucosal dysfunction, including acute or chronic inflammation in the airway, which lends to a favorable environment for the development of BRD (Hakansson *et al*., 2018). Once a stressor has been presented to the host's respiratory environment, the assistance of viruses with environmental stressors (i.e., climatic, social, management, nutrition) can lead to the colonization and replication of bacterial pathogens, causing subsequent infection in the lung tissue of the host (Chai *et al*., 2022). Overall, from the beginning of the infectious phase, clinical symptoms are observed within four weeks of the initial stressor on the respiratory system of the host (Currin and Whittier, 2005).

There are numerous clinical symptoms related to BRD, which are dependent on many of the factors suggested earlier, but depend heavily on the phase and length of the disease process in the host. The obvious symptoms include ocular and nasal discharge, acute and chronic congestion with an associated cough, excessive salivation, abnormally high respirations with sporadic rhythm, and pyrexia (White and Renter, 2009; Taylor *et al*., 2010; Midkiff *et al*., 2021). The difficulty of using this assessment/observational method is due to the fact that this is the general response of clinical symptoms of disease in livestock, particularly cattle. This can lead to unnecessary treatment or false positive detection of BRD in truly sick animals (Abutarbush *et al*., 2012), ultimately leading to possible antimicrobial sensitivity or resistance. White and Renter (2009) concluded that even trained personnel only detect roughly 62% of cases based on clinical symptoms, suggesting that several cases are not detected or are not detected until more pronounced symptoms are observed in advanced stages of BRD, in which treatment is no longer successful.

Some researchers suggest that the likelihood of the development of the disease is not correlated to the incidence or abundance of the microorganisms identified as BRD pathogens in the respiratory tract of the host, since some of the bacterial pathogens are already present in healthy animals' respiratory tract (McMullen *et al*., 2020). McDaneld *et al* (2019) concluded similar findings with *Mycoplasma bovis* being found in the respiratory tracts of healthy and clinically BRD-diagnosed steers. Similar studies have found concentrations of *P. multocida* B:2 in the reproductive tract (ovary, oviduct, uterine horns, uterus, vagina) of buffaloes (Ibrahim *et al*., 2016), which could suggest a possible transfaunation of bacteria into the fetus, from the maternal host environment, during parturition. This could also suggest that different bacterial families may have different impacts on the host environment, depending on the homeostatic and disequilibrium means the host is presented due to the environment, management, or industry sectors. With that said, there is still a need for research in the pathogenesis of BRD, how the microbiome influences this disease, and the correlation of present bacterial families that may or may not cause harm to the host.

The microbiome of the ruminant reproductive system

In recent years, there has been an influx of bovine reproductive microbiome research that has become available from the literature (Messman and Lemley, 2023). Due to the complexity and understanding of microbiome data in the literature, there have been numerous scenarios and interpretations that have been questioned on the role this anatomical system has on the bovine species. This review article will provide a brief overview of the microbiome of both the maternal, paternal, and conception aspects that can be influenced by the reproductive tract of the microbiome of bovine microbiome.

Through the origin of most reproductive physiology/theriology courses taught during undergrad tenures, note that the maternal reproductive tract is anatomically designed for ovulation, transportation of both oocyte and spermatocyte in their respective directions, while also assisting in the roles of copulation, embryogenesis, folliculogenesis, fertilization, and gestation within the bovine species. Within this common knowledge, it has led microbiome investigators to understand the correlation of microbial composition with fertility in the female reproductive tract (Ault *et al*., 2019; Deng *et al*., 2019), with the majority of these studies focusing on the uterine and vaginal microbiome (Messman and Lemley, 2023). For example, according to Swartz *et al*. (2014), the bovine vaginal environment has been classified recently as near neutral pH (7.3), which can allow the creation of an environment for bacteria phyla of *Bacteriodetes*, *Fusobacteria*, and *Proteobacteria* are dominant in nature. This also could be due to anatomical reasons with the vulva, lying directly ventral to the anus, causing possible contamination of fecal material in the vaginal tract, and, respectively, the dominant microbiota of cattle feces is of the phyla *Bacteriodetes*, *Firmicutes*, and *Proteobacteria* (Kim and Wells, 2015). The bacteria mentioned have not been proven to cause diseases, but foreign microorganisms in the reproductive tract can cause an increased risk of abortion and stillbirth and reduced conception rate (Ong *et al*., 2021). This contrasts with humans due to the presence of *Lactobacillus* spp. that produces lactic acid (Stout *et al*., 2020), similar to the lactic acid-producing species in the ruminant digestive tract, which dominates the female reproductive tract, making it an acidic environment for unfavorable growth for the above phyla in the bovine tract.

Beyond those mentioned earlier, there is a possible occurrence for the presence of *Fusobacteria* and *Tenericutes* in open *Bos taurus* reproductive tracts (Messman *et al*., 2020a). According to Ong *et al*. (2021) suggest the dominant presence of *Fusobacteria* in the female reproductive tract could be associated with cattle eventually developing reproductive disease through the synergistic means of virulence and growth factor expression. For presence of *Tenericutes*, particularly with the genera of *Mycoplasma* and *Ureaplasma*, has been shown to have effects on sexually transmitted diseases between animals through vaginal secretions, seminal plasma, semen, and the preputial region of the male anatomy (Miller *et al*., 1994). This could have implications for microbiota transfer through reproductive technologies of artificial insemination and embryo transfer, causing the occurrence of reproductive diseases in cattle (Sannat *et al*., 2015; Crane and Hughes, 2018). These *Tenericutes* have been hypothesized to travel through the vaginal tract to the uterine body and horns, due to the dilation of the cervix during estrus (Santos Jr. *et al*., 2021). For instance, *Ureaplasma diversum* has been shown to cause granular vulvovaginitis syndrome in female cattle, which is characterized by clinical symptoms of acute inflammation, reproductive tissue damage that could cause acute and chronic fertility issues in management (Nascimento-Rocha *et al*., 2017; Santos Jr. *et al*., 2021; Messman and Lemley, 2023). Typically, this bacterium can be isolated through placental tissue, lungs, and abomasal fluid of third-trimester aborted fetuses (Gagea *et al*., 2006; Anderson, 2007). Also, *Ureaplasma diversum* has been shown to alter prostaglandin production by an associated increase in PGF2a levels and a decrease in PGE2 (Kim *et al*., 1994). As a whole, these studies have shown that these *Tenericutes* can have an impact on and affect fertility through alterations in the uterine environment that are both physical and hormonal in their make-up, but also through virulence.

With the majority of our understanding of the reproductive microbiome being explained by the maternal microbiome, most of the time, the paternal microbiome is forgotten or even overlooked in the literature. Even though the paternal microbiome has an associated significance on maintenance of fertility and reproductive health, Khalil *et al*. (2020) conclude that the research conducted on the paternal reproductive microbiome is still relatively novel. As mentioned earlier in *Tenericutes* (Miller *et al*., 1994; Crane and Hughes, 2018), the possible spread of microbiome through coitus or within ejaculate has been well documented in several species (Givens *et al*., 2008). Studies have shown similarities in the overlap of phyla between the bull penis/prepuce and the cow reproductive tract that include *Bacteriodetes*, *Fusobacteria*, *Firmicutes*, and *Proteobacteria* (Swartz *et al*., 2014; Kim and Wells, 2015; Wickware *et al*., 2020). Beyond the fact that this overlap could be due to environmental contamination of feces or excrement, the additional factor that needs to be considered is the source of reproduction of either natural service or artificial insemination. Particularly with the introduction of A.I. for livestock in the early 1900s (Foote, 2001), the techniques of semen collection and processing led to possible introduction of contamination (Sannat *et al*., 2015). With that said, there is no associated effect due to an infectious cause or a subsequent decrease in spermatocyte quality (Baud *et al*., 2019). Even with these findings, there is still limited literature out here to support the sire microbiome and its effects on the host animal, and particularly the transmission to the female reproductive microbiome.

CONCLUSION

The microbiome of any animal species is a complex system of interactions among organ systems that can have both beneficial and harmful aspects in the day-to-day functionality requirements for the animal to maintain, grow, lactate, or even reproduce. This is the case for ruminant food animal species, no matter if it is bovine, caprine, or ovine that is in question. Even amongst these species, the similarities in the microbiome are uncannily similar, but the smallest difference or change in the environment can dictate the course of the microbiome, let alone the productivity of the animal. Throughout this review, each microbiome of each organ system has shown beneficial aspects that assist in everyday productivity. For instance, the gastrointestinal system of ruminants, which is the most researched topic in livestock production, is known to help with the digestion of a variety of feedstuffs, the production of VFAs for energy, or the same use of bacteria for microbial protein, which is ultimately based on the concentration and type of bacteria, protozoa, and archaea. Other occurrences of the microbiome being beneficial are located in the reproductive system, in which certain bacterial colonies regulate the pH level of the reproductive tract for future fertility purposes of producing the next generation. Even with all the good the microbiome does for animals, there are more documented harmful effects when the microbiome suddenly changes due to external environmental causes that infiltrate or change the internal system of the microbiome, for that organ system. For instance, in the ruminant respiratory system, certain species are normally found in the nasal cavity of the nasal-pharyngeal complex. But when stress is implemented in the majority of our ruminant food-producing species, the effect of cortisol on the internal environment depresses the immune system of the animal and allows the occurrence of these naturally occurring bacteria to cause economically detrimental diseases that increase the likelihood of morbidity and mortality to the producer. In turn, the course of change the external environment had a two-fold impact, not just on the respiratory system, but also on the immune system of the species, and the gastrointestinal microbiome. In respect to this review, it is suggested that livestock producers should understand that best production practices, which will allow the animal to maintain homeostasis of the animal system, while being able to mitigate the majority of harmful outcomes and scenarios that can impact the microbiome of any animal species. This ideology will hopefully mitigate or ultimately decrease the occurrence of animal health issues while increasing the productivity of food-producing animals in the form of fertility, lactation, and red meat yield.

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CONFLICT OF INTEREST

The authors declare no competing interests.

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