(Review)

Healthy Cattle Microbiome and Dysbiosis in Diseased Phenotypes

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Abstract: Cattle farming is an ancient practice, with roots in the early Neolithic era that has retained its status in the food industry today, with global beef market revenue amounting to $385.7B, as of 2018. Hence, cattle maintenance is naturally essential to cater to nutritional requirements of modern civilization. This extensive review aims to provide a holistic overview of cattle microbiome, analysing the native microbial composition within respiratory tract, gastrointestinal tract, reproductive tract, and skin. The dysbiosis associated with various diseases such as bovine respiratory disease, bovine digital dermatitis, mastitis, Johne's disease, uterine diseases (metritis and endometritis) and metabolic disorders (ruminal acidosis and ketosis) has been discussed. Moreover, various non-antibiotic microbial therapies including phage therapy, prebiotics and probiotics have been examined as potential means to reduce disease-associated dysbiosis. In general, this review highlights the importance of the microbiome in maintenance of health in cattle and its potential in alleviating bovine diseases, with an aim to enhance cattle health and production.

Keywords: Microbiome, Cattle, Johne's disease, Dysbiosis, Mastitis

1. Introduction

Microbiome encompasses interactive and dynamic micro-ecosystem, established by the genetic elements, structures, and metabolites of a characteristic microbiota, inhabiting diverse ecological niches, including eukaryotic hosts. In eukaryotic host environments, the importance of microbiome in maintenance of physiological functionality has been signified by many researchers as a neglected niche [1]. The potential influence of cattle microbiome over its growth and immune system has been thoroughly investigated [2]. The commensal microbiota confers its beneficial effects to animal health through various mechanisms such as aid in digestion of host-indigestible plant fibre [3], and providing host with nutrients and energy sources (volatile fatty acids) [4], building units (carbohydrates, peptides, lipids)[1, 5], modulation of immune system via cytokines, antibodies and stimulation of immune cells [6], creating physical barrier between pathogens and immune cells, competing with the pathogens for adhesion niches and nutrients [50,51] and inhibiting the pathogenic growth by production of antimicrobial compounds, such as organic acids, hydrogen peroxide, bacteriocins, and biosurfactants [134] [49].

The holistic view of cattle microbiome indicates the colonization of skin, body cavities and mucosal surfaces related to the respiratory, gastrointestinal, and urogenital tracts by microbial communities [7-10]. The distribution varies throughout these organs,

depending on the host factors and distinct physiochemical properties of the colonization site [11]. Although cattle microbiome co-evolves with its host and is influenced by inter-microbial interactions, host attributes, and environmental factors [12], a core functional microbiome at any specific niche is more conservative [13]. However, during disease conditions, the delicate growth balance of microbial consortium is prone to intrusions, followed by either loss or gain of different microbial species leading to microbial imbalance known as dysbiosis [14]. Dysbiosis may cause or aggravate multiple disease phenotypes in cattle such as Johne's disease, uterine and metabolic diseases (ruminant acidosis) [15, 16]. To explore the therapeutic and prophylactic role of cattle microbiome, understanding of microbial composition particularly associated with health and disease phenotypes is paramount. This understanding could very well aid in laying out well-defined microbiome manipulation strategies for better health and production outcomes [17]. Therefore, this review aims at summarizing the natural bacterial microflora associated with healthy cattle microbiome and how the composition shifts in several disease conditions. Alternative therapeutics such as probiotics, prebiotics, and bacteriophages that have proven efficacy in combating dysbiosis have been discussed [18]

2. Development and succession of cattle microbiome with age

Since the microbiota are rapidly evolving and represent a dynamic ecosystem where the host factors play a crucial role in selection, adaptation, and stabilization of microbial communities, it would be prudent to observe the developmental changes in the microbial consortium throughout cattle lifespan [19]. Previous studies report significant fluctuations in microbiome throughout cattle's life-time [13, 20]. These changes could very well be influenced by infant transitions (weaning age, weaning strategy, mode of delivery and type of milk feeding), as well as environmental factors and host genetics [21, 22]. Soon after birth, the infant microflora starts to establish and is derived from mother's vaginal, skin and environmental microbiota [23], which implies that the mode of delivery either through natural (vaginal) or caesarean section (C-section) could be a deciding factor in harbouring initial infant microbiome [22]. Recent studies already observed a significant microbiome difference between these two modes of delivery; vaginal delivery developed a high species richness, evenness, and diverse microbiome in human and cattle infant as compared to C-section mode of delivery [13, 24]. Following vaginal delivery, the species belonging to the phylum Proteobacteria were most abundant in calves' rumen, in addition to increased relative abundance of gastrointestinal tract related genera Bifidobacteria and Bacteroides [25] and the vaginal tract associated genera Prevotella and Butyrivibrio spp. [13]. In contrast, the rumen of calves, delivered by C-section, are more likely to be colonized by species from the phylum Firmicutes, and the genera Peptostreptococcus and Dorea. The reduced colonization and low maternal microbial persistence over time in calves after C-section make them more prone to infections [13].

The new-born calves do not have a fully functional rumen, as the milk bypasses the rumen, reticulum, and omasum via oesophageal groove to the abomasum where it is enzymatically digested [26]. Milk could be the first substrate for rumen fermentation, which leads to alterations in the microbiota. In young ruminants shortly after birth, aerobic and facultative anaerobes gradually consume oxygen which contributes to the predominance of the anaerobes in rumen microbiome [20]. As shown in Figure 1, at first three days, rumen microbiota is dominated by Proteobacteria, Firmicutes (whereas Streptococcus represents 75% of the Firmicutes reads), and Bacteroidetes with varying minor contributions of other phyla including Actinobacteria, Fusobacteria, Tenericutes and Cyanobacteria [20, 27]. The microbiome abundance trend shifts from the phylum Proteobacteria that dominate for the first three days to Bacteroidetes, which dominate in the older group 3-12 days of age [20, 28, 29]. Another prominent microbial transition

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during early stages to adult development is characterized by the Verrucomicrobiaceae genus Akkermansia decline from 23-40% in the initial days to 2-4% (or not detected at all) at first month [13, 20]. Among the minor phyla, Actinobacteria mainly Actinomycetales and Fusobacteria are prominent in the new-borns [20]. Taxonomical diversity increases with age, especially upon the introduction of a new fermentation substrate i.e., solid food [30]. Prevotellaceae family is observed to be the most abundant family in the phylum Bacteroidetes from day 6 to 83 with 31 to 72% abundance, respectively [13, 20, 28].

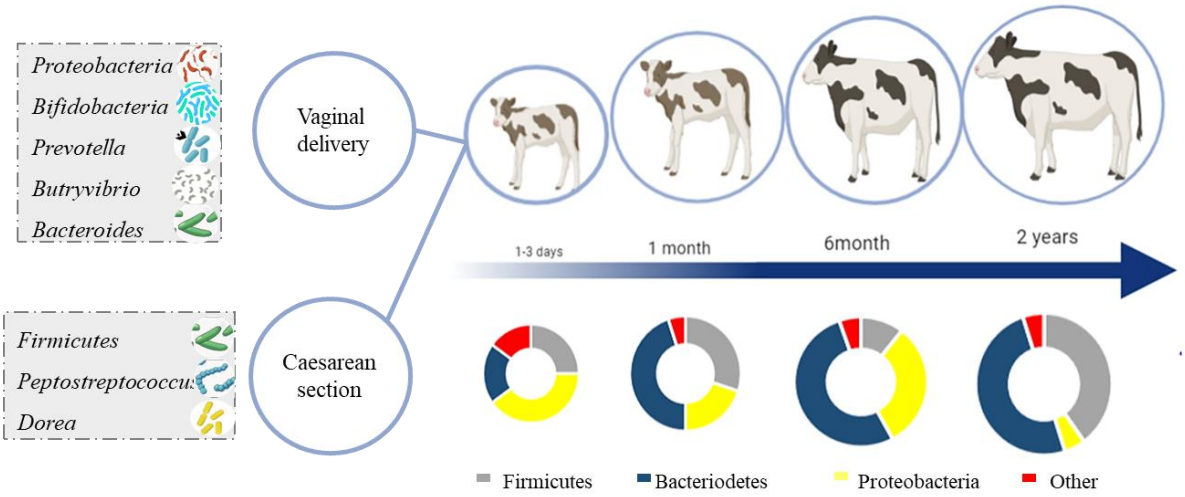

Figure 1. Dynamics of bacterial communities across different ages [20, 28]

3. Healthy cattle microbiome composition

3.1 Respiratory tract microbiome

The respiratory tract harbours distinct microbial ecosystems of nostrils, nasopharynx, hard plate, oropharynx, tonsils, trachea, and lungs [31]. Overall, healthy cattle respiratory tract microbiome could be attributed to six phyla, namely Proteobacteria, Firmicutes, Tenericutes, Actinobacteria, Fusobacteria, and Bacteroidetes [32]; though the relative abundance of each phylum varied across individual organs. Tenericutes dominated the distal trachea to the lung except the secondary bronchi of the left and right caudal lobes, which were colonized mainly by Actinobacteria [31]. Proteobacteria prevailed in the nostrils, nasopharynx, and oropharynx, whereas Firmicutes were extensively present on the floor and hard palate of the mouth and Fusobacteria colonized the tonsils. At the genus level, Mycoplasma, Moraxella, Streptococcus, Fusobacterium and Streptomyces were the most abundant along the respiratory tract with uneven distribution as following: Mycoplasma predominated the trachea, lung, nostril, and nasopharynx; Streptococcus was observed to be most abundant on the floor and hard plate of the mouth; Bibersteinia was localized in oropharynx; and Fusobacterium dominated the tonsils [31].

3.2 Gastrointestinal microbiome

Given the significance of oral health in organisms, extensive studies have been devoted to investigating human, cat, sheep, and dog oral microbiome [33-35]. Most studies on cattle oral health are limited to dental formulas and diseases, and not a lot of data is available regarding oral microbiome. Recently, it was reported that the most prevalent genera associated with healthy cattle oral cavity are Arcobacter, Gastranaerophilales,

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Planifilum, Escherichia-Shigella, Actinobacteria, Burkholderia, and Pseudomonas genera (Figure 2). Interestingly, studies pertinent to periodontitis reported that healthy samples demonstrate low intra-sample variability and clustered separately from disease-prevalent samples [36].

3.3 Rumen microbiome

The ruminal stomach is compounded with four compartments, the pre-stomach (reticulum, rumen, omasum) and the true stomach (abomasum) [37]. Being the largest compartment of the stomach, the complexity of the microbial ecosystem allows rumen to utilize fibre rich diets in addition to complex carbohydrates [38], resulting in digestion of 60-70% of the ingested cellulose [1]. Bacteria are the most abundant prokaryotes which constitute more than 95% of the ruminal microbiota at a cellular density of 1010-1011 cells/g [2]. The most abundant phylum in the rumen is Bacteroidetes (with genus Prevotella comprising 45-57% of total 16S rRNA sequences and 90% of Bacteroidetes population), followed by 28% of phylum Firmicutes. Furthermore, genera Dialister, Succiniclasticum, Ruminococcus, Butyrivibrio and Mitsuokella represented more than 1% of the total bacterial genera in the rumen [39].

3.4 Small intestine

The main function of the small intestine is absorption of protein and carbohydrates [1] and it consists of duodenum, jejunum and the ileum, which vary in their function and microbial communities. Interestingly, one study reported that phylum Firmicutes dominated within all sections of cattle gastrointestinal tract except jejunum, where Proteobacteria dominated. Enterobacteriaceae were highly abundant within small intestine, while jejunum was enriched by Ruminococcus, Acetitomaculum, and Lachnospiraceae [40]. Compared to the rumen, the relative abundance of the phylum Bacteroidetes significantly decreased (0.4-1.1%) while that of phylum Firmicutes elevated drastically, reaching up to 80% of relative abundance. Studies based on low abundance phyla Actinobacteria (6-13%), Proteobacteria (0.8-5.8%) and Tenericutes (0.4-4%) have also been reported. Furthermore, other significant genera pertinent to the small intestine include Ruminococcus, Butyrivibrio, Lactobacillus, Bulleidia, Mogibacterium, Mitsuokella, and Propionibacterium [39].

3.5 Large intestine

Bacterial colonization in the cecum, colon and rectum is estimated to be 1012 to 1014 cell/ml [1]. The large intestine plays an important role in water absorption and digestion as 30% of the cellulose digestion takes place in the large intestine [1, 41]. Different regions of the large intestine represent distinct microbial intensity and diversity in their corresponding microbiota. In the cecum, Firmicutes have been the predominant phylum reaching up to 81% of the total phyla while Bacteroidetes contributes to 18-26%. Spirochetes, Tenericutes, and Actinobacteria have also been reported in the cecum. Furthermore, Prevotella, Turicibacter, Coprococcus, Ruminococcus, Dorea, Blautia, Clostridium, and Oscillospira have been the most abundant genera in the cecum [39]. Similar to cecum, the colon contains phylum Firmicutes as 81% of microbial relative abundance, followed by Bacteroidetes at 21-33%. Moreover, Spirochetes, Tenericutes, Proteobacteria, Actinobacteria, and Fibrobacteres have been in greatest abundance among the rest of 23 phyla. Whereas the most abundant genera were Prevotella, Ruminococcus, Coprococcus, Dorea, Turicibacter, Blautia, Oscillospira, and Parabacteroides [39, 42]. Similarly, the rectum has also been dominated by the phylum Firmicutes. Moreover, the genera that dominated rectum were Clostridium, Roseburia, Osillospira, Succinivibrio, Ruminococcus, Bacteriodes, Prevotella, Blautia, Coprococcus, and Turicibacter [43].

3.6 Reproductive tract microbiome

Reproductive efficiency greatly influences overall productivity of cattle and regulation of health and homeostasis. In that perspective, the need for understanding the reproductive tract microbiome becomes greatly significant [44]. Despite the availability of the advanced next generation sequencing techniques (NGS), the healthy cattle reproductive tract microbiota is not fully understood due to lack of definitive research. Insights in the healthy reproductive tract

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microbiome would greatly improve and influence the cattle reproduction, maternal, and neonatal health related medicinal or therapeutic practices [45].

3.7 Female reproductive tract

Significant differences in bovine reproductive tract microbiome are linked with the type of breed [46], different anatomical regions [9], and the physiological status [47]. Four major phyla found in cattle vagina have been reported by several studies namely Firmicutes, Bacteroidetes, Proteobacteria [9, 46-48], and Actinobacteria [9, 48]. The predominant genera reported were Aeribacillus, Bacillus, Clostridium, Ruminococcus, Rikenella, Alistipes, Eubacterium, and Prevotella [47, 48]. The cattle uterus contains the uterine body and two uterine horns; and each horn has its oviduct [49]. A concept of the sterile uterine system has been challenged by several studies [50]. Uterus microbiome is present before the occurrence of pregnancy when the female reaches the reproductive maturity, and it is maintained throughout pregnancy. The major phyla colonizing the uterus reported for five pregnant and 10 virgin cows were Firmicutes, Bacteroidetes, and Proteobacteria [51]. Another study by Clemmons et al. 2017 compared the healthy microbiome communities in bovine vagina and uterus for non-pregnant cows after insemination. They reported that Firmicutes was the most dominant phyla in both uterus and vagina; with the vagina containing a higher abundance of mentioned phylum than the uterus. The next phyla, in order of abundance, were Proteobacteria, followed by Actinobacteria, and Bacteroidetes. At the genus level, the vagina showed the highest abundance of an undetermined genus pertinent to order Bacteroidales. The next in order of abundance was genus 5-7N15 pertinent to family Bacteroidaceae, followed by Oscillospira, Butyrivibrio, Ureaplasma, Campylobacter, Dorea, CF231 (pertinent to family Paraprevotellaceae), Clostridium, Helcococcus, and Corynebacterium. Alternatively, the uterus contained a dominating abundance of Corynebacterium, Ureaplasma, Staphylococcus, Microbacterium, Butyrivibrio, and Helcococcus [9].

3.8 Bull reproductive tract

Selection of the bulls is a vital practice for successful reproduction in the cattle industry [52]. Despite the microbial significance in maintenance of fertility and reproduction health, the research data found on bull reproductive tract microbiome remains nominal. A study published in 2019 investigated the microbiome of penis and prepuce [53]. According to the authors, the most abundant phyla were Firmicutes, Fusobacteria, Bacteroidetes, Proteobacteria, and Actinobacteria. Community composition was consistent with clustering patterns and low and high diversity clusters were identified at the genera level. For low diversity samples, Bradyrhizobium had constantly been detected, whilst the high diversity samples exhibited multiple genera. The dominant colonizers in the prepuce were Bacteriodes, unclassified Ruminococcaceae, Histophilus, and Streptobacillus [54].

3.9 Skin microbiome

Skin is a potent physical barrier against pathogenic invasion, environmental factors, and physical trauma [44]. Skin microbiome is considered important to understand the host evolutionary history and disease association. Some interesting studies sought to analyse changes in human and cattle skin microbial communities caused by close environmental contact and reported a weak correlation in characterization of cattle skin microbiome, much focus has been reserved for teat skin microbiome, particularly as it related to raw milk microbial diversity. Some of the major taxa found to be associated with teat skin, were Corynebacteriales, Clostridium, Atopobium, Bifidobacteriales, Lachnospiraceae, and Coriobacteriia as well as Pediococcus, Aerococcus, Staphylococcus, Pantoea, Enterobacter, Enterococcus, and Proteobacteria [55, 56]. Several commensal microbial species associated with teat skin are not common in milk, indicating a breakdown of microbial flow from teat skin to milk [56]. Ample research has been devoted to characterization of microbiome of digits as well [57]. Healthy digits have been characterized by elevated levels of phyla Proteobacteria, Bacteroidetes, and Firmicutes [58-60]. Furthermore, Actinobacteria and Spirochetes have also been detected in healthy digits [58]. A study by Mamuad et al. 2020, indicated two more phyla that preceded the aforementioned phyla in abundance. The study reported Tenericutes and Bacteroidetes, with 14.1% and 11.8% mean abundance respectively [60]. The families commonly found in healthy skin belong to Ruminococcaceae, Aerococcaceae, Corynebacteriaceae, and Moroxillaceae [59].

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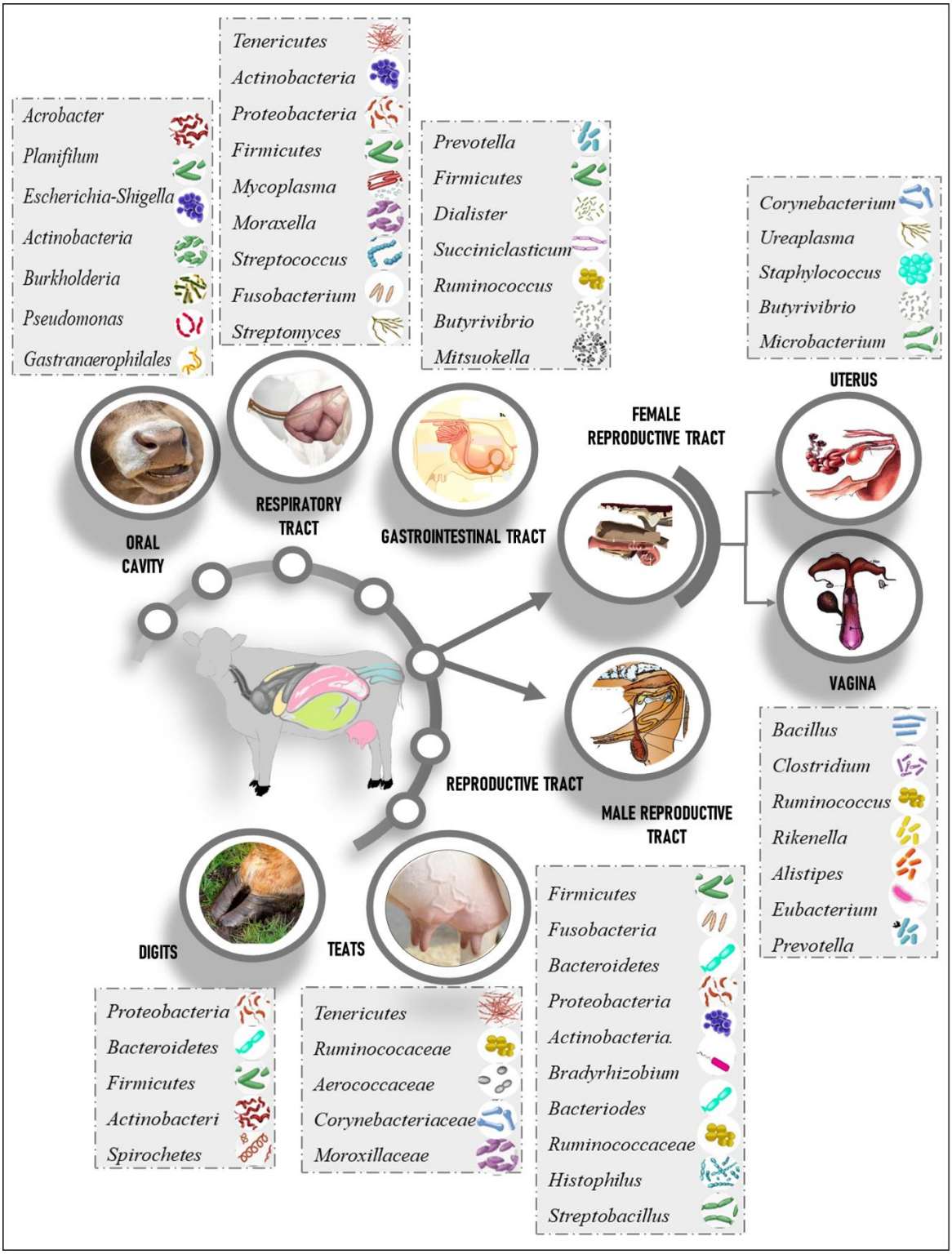

Figure 2. Variation in healthy cattle microbiome at different organs. Predominant bacteria in skin, reproductive organs, oral cavity, gastrointestinal tract, and respiratory tract are shown. [9, 31, 36, 47, 48, 54-56, 59, 190].

4. Cattle diseases associated with microbiome dysbiosis

4.1 Bovine respiratory disease BVD

Bovine respiratory disease (BVD) is a complex multifactorial disease associated with host susceptibility, pathogenic load, and environmental stimuli [61]. BVD is a major concern in producers worldwide due to the high treatment costs as well as high morbidity and mortality rate [62]. Among the environmental factors, it has been demonstrated that transportation stress as well as temperature fluctuations and ventilation play a crucial role in aggravating the disease [63]. Dysbiosis has been reported to be one of the hallmarks of disease [7]. Disease conditions are exacerbated through infections and immune system suppression caused by bovine viral diarrhoea virus (BVDV), bovine respiratory syncytial virus (BRSV) and parainfluenza type 3 virus (PI3) [64]. According to previous studies, the most commonly described bacterial communities in BVD comprised of *Mycoplasma spp*., particularly *Mycoplasma bovis*, *Mannheimia haemolytica*, and *Pasteurella multocida* [65, 66]. Many studies have also reported the natural abundance of these bacteria in the healthy respiratory tract microbiome. Nevertheless, these species are classified as opportunistic [67] and their relative abundances are higher in diseased animals as compared to the healthy counterparts. For instance, the abundance of *Mycoplasma* and *Mannheimia* has increased substantially over time in infected calves, though some studies also report rise in *Moraxella spp.*, indicating its role in the pathogenesis of BVD [64, 65]. *Pseudomonas fluorescens* abundance has also been significantly higher in BDV infected calves, however, its contributing role in respiratory disease remains unclear [65]. Recent studies in healthy calves reported the abundance and probiotic effect of *Lactobacillus lactis* and *Lactobacillus casei* colonization against *M. haemolytica* growth which has also been proved in vitro [66].

4.2 Bovine digital dermatitis

Bovine Digital Dermatitis (DD) is characterized by painful ulcerative lesions that might persist in chronic disease [68] and has been a major cause of cow lameness. Being a highly prevalent infectious disease, DD causes major economic losses in dairy herds worldwide and affects animal health, productivity, and welfare [69]. It is a genetic, multifactorial disease, influenced by both environmental as well as pathogenic involvement [70]. Disease pathogenesis is still not fully understood, though a number of research papers have been published since its first description in 1974 [59]. Several studies have frequently identified spirochetes from *Treponema* genus as a major pathogen in DD lesions [58, 59, 70-72]. A distinct six phylogroups were highly associated with the disease and classified as *Treponema phagedenis, Treponema medium*, *Treponema putidum*, *Treponema denticola*, *Treponema matophilum*, and *Treponema paraluiscuniculi* groups [73]. Despite the continual presence of *Treponema spp.* In DD lesions, the DD disease phenotype could not be reproduced by using *Treponema* pure culture [74]. Other identified microbes included *Mycoplasma spp., Fusobacterium necrophorum, Bacteroides spp., Porphyromonas levii* [59, 71], *Prevotella spp., Corynebacterium spp.,* and *Tissierella spp.* [58]. These evidences suggested potential association of these bacteria with the disease pathogenesis as secondary opportunistic pathogens [75]. A metagenomic study by Zinicola et al. 2015, could not detect any viral or fungal DNA in the DD lesions and thus presently, it cannot be linked to the disease [72, 75]. The positive response against antibiotic treatment also indicated the bacterial nature of the disease [74]. A correlation has been proposed between the main pathogen *Dichelobacter nodosus* involved in bovine foot rot and DD lesions by several studies [76, 77]. Nevertheless, this correlation was negated by another study that reported a lack of presence of *D. nodosus* in Swiss cattle affected by DD [78]. Another study by Krull et al. 2014 stated the presence of *D. nodosus* in DD lesions but no statistical significance was reported [59]. The *Treponema spp.* Were also observed within rumen and faecal microbiome of infected cattle [72]. Another study suggested that foremilk and udder cleft skin might be an important reservoir for *Trepenoma spp.* [79].

4.3 Mastitis

Mastitis is characterized by an inflammatory response to the intramammary infection that disturbs the physical barrier of the mammary quarters [80]. This disease is a major economic burden in dairy industry worldwide, affecting animal health and productivity [81]. Mastitis has been classified into two subgroups based on the severity of the disease (clinical and subclinical). Observable physiological changes in the milk and udder are a consequence of clinical mastitis while in subclinical mastitis no symptoms are observed, despite the presence of pathogens [82]. Mastitis's aetiological agent usually has a microbial origin that involves various bacterial species. The major pathogens included *Staphylococcus aureus, Streptococcus agalactiae*, *Escherichia coli*,

Streptococcus dysgalactia, *Mycoplasma spp.,* whilst the minor pathogens were represented by coagulase negative *staphylococci* and *Corynebacterium spp*. [83]. Environmental pathogens including *Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Enterobacter aeorogenes, Streptococcus uberis Pseudomonas spp.,* and *Prototheca* have also been involved in mastitis pathogenesis [81, 84]. NGS has made a transition from identifying a single organism to characterizing the aetiological microbiome associated with mastitis infection [85]. Recent studies reported that alteration in the mammary gland microbiome (dysbiosis) is related to mastitis; whether the dysbiosis is a sequence or consequence of mastitis is still a debate [86-88]. An increased microbial load and relative reduction in bacterial diversity has been reported in mastitis milk [89]. This can be attributed to increased amount of pathogenic colonization with progression of infection, accompanied with reduction in the healthy commensal bacteria. Altering the intramammary commensal bacteria has a deleterious effect on mammary gland homeostasis [90]. Shifts in milk microbiome have been observed in healthy cows and those infected with mastitis. Phylum *Firmicutes* have dominated the healthy milk and the usual most abundant phyla were *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria* [86, 91]. In contrast a higher representation of *Proteobacteria* was over observed in mastitis milk [86]. Hoque et al. 2019 identified 26 unreported strains associated with mastitis, namely the strains belonging to genera *Acinetobacter*, *Pseudomonas, Streptococcus, Corynebacterium Staphylococcus, Enterococcus, Bacillus*, and *Escherichia* [86].

Recent studies suggested that gut microbiome dysbiosis played an important aetiological role in intramammary infections (IMI) [92]. In a study by Ma Chen et al. 2018, it was proposed that the intestinal microbiota can induce mastitis. To examine this suggestion, the researchers induced IMI by faecal transplantation from a cow suffering from mastitis to the germ-free mice, which led to the development of mastitis symptoms [93]. Interestingly, a promising result was obtained when probiotics were introduced in mice, parallel with inoculation of faecal microbiota of infected cattle. A relatively great relief from mastitis symptoms were observed in the probiotics-treated mice group. In this group, a functional shift in the intestinal microbiota was also observed to a state different from healthy and diseased microbiota, which approved the author's supposition regarding correlation of intestinal microbiota in mastitis induction [93]. Another supportive investigation revealed that gut microbiota dysbiosis could aggravate *S. aureus* mastitis severity and the blood-milk barrier permeability. These effects were reversed when faecal microbiota transplant from healthy mice was applied [94]. Nevertheless, correlation between the gut microbiome and mastitis may also be affected by other factors. One study found out that the overproduction of lipopolysaccharides (LPS) by the rumen, translocated into the blood and disturbed the blood-milk barrier by accumulating in the mammary glands. Consequently, inducing IMI in subacute rumen acidosis (SARA) infected cows, which eventually increased the severity of mastitis infection [92]. Ruminal short chain fatty acids (SCFAs) have a protective effect towards the blood-milk barrier, and therefore against IMI [95].

4.4 Johne's disease

Johne's disease, a chronic incurable infectious intestinal disease, is characterized by persistent diarrhoea that leads to malnutrition, emaciation, and significant economic losses in the livestock industry worldwide [96, 97]. Johne's disease is caused by a slow-growing non motile mycobacteria—*Mycobacterium avium subsp. Paratuberculosis* (MAP) [98]. MAP is also being investigated in correlation with human Crohn's disease [97, 99-101]. The pathological similarities between Johne's and Crohn's disease affirmed these speculations [102]. Recent studies suggested that gastrointestinal microbiome dysbiosis facilitated MAP infection and aggravated disease severity [15, 103]. However, a very limited number of investigations on cattle have been reported so far.

A study by Fecteau et al. in 2016 compared the faecal microbiome communities between MAP infected, exposed, and negative controls. A distinct bacterial community has been observed in MAP infected group compared to negative and exposed samples (which showed similarity to each other). A relative increase in the phylum *Actinobacteria* and *Proteobacteria* escorted with a significant decrease in the phylum *Bacteroidetes* and *Firmicutes* abundance. Interestingly, the genus *Arthrobacter* has dominated the phylum *Actinobacteria* in all positive samples [103].

Another study investigated the faecal and ileal microbiota during early infection with MAP. The faecal microbiota showed a relative decrease in the genera *Verrucomicrobia* and *Akkermansia*. *Planococcaceae* and *Paraprevotellaceae* showed higher abundance in the infected samples. Analysis of ileal microbiota showed less abundance of phylum *Proteobacteria* in MAP infected calves. Moreover, changes in the microbiome induced functional changes in its metabolites, thus an increased level of metabolism was observed in MAP negative calves. However, increased lysine and histidine metabolism pathways have been associated with MAP infection [15].

4.5 Uterine diseases

Metritis and endometritis are the most important postpartum uterine diseases, affecting up to 40% of dairy cattle [104, 105]. Uterine diseases are a major economic concern directly affecting animal overall health, milk production, and reproductive performance [106]. Metritis is an inflammation of the uterine wall, which is characterized by systematic signs of illness. The symptoms, such as fever and toxaemia usually occur during the first 21 days after parturition [107]. Endometritis is an inflammation in the inner lining of the uterus without signs of systematic illness, it can occur in or after the 21 post-partum. Endometritis is classified into clinical and subclinical types [107, 108]. Uterine diseases are multifactorial where environmental factors affect the occurrence of the disease and host defence plays an important role against bacterial pathogens [109]. Cow uterus is exposed to bacterial contamination during calving and up to two weeks postpartum. A healthy cow immune system can resist pathogenic colonization. However, failure to resist the pathogenic colonization leads to disease progression [110]. Several risk factors, including parity, dystocia, retinal placenta, abortion, twins, and calving season, play a role in triggering uterine diseases [111]. Culture-dependent studies have identified pathogenic bacteria associated with uterine infections from diseased cows. *Trueperella pyogenes* and *Escherichia coli,* in addition to gram negative pathogens *Porphyromonas levii*, *Fusobacterium necrophorum*, *Prevotella melaninogenica* and *Bacteroides spp.* were frequently isolated [112-115]. *Trueperella pyogenes* is usually diagnosed in clinical endometritis [115, 116]. *Escherichia coli* is also reported as one of the major pathogens in uterine infections [117]. Piersanti et al. 2019 reported that these two pathogens can induce Endometritis in Holstein Friesian model [116]. Whereas *Porphyromona, Bacteroides*, and *Fusobacteria* have been associated with metritis [109]. However, a dysbiosis in the microbiota is observed in the infected uterus [118]. This dysbiosis is characterized by a decrease in diversity and richness of bacterial communities, and therefore, a loss of heterogeneity [109]. Increased abundance of *Bacteroidetes* and *Fusobacteria* and decrease in *Proteobacteria* were observed in metritis cow [16, 113]. The ecological interaction between bacteria seems to be important in the development of metritis, such as the increased abundance of the genes of *Fusobacterium* of the *Bacteroides spp*. is an essential hallmark. Furthermore, *Helcococcus*, *Porphyromonas*, and *Filifactor* were also found to be associated with metritis [113]. Moreover, the uterine microbiota of clinical endometritis (CE) cows exhibited an increased abundance of *Fusobacterium*, *Trueperella*, and *Peptoniphilus*, whilst subclinical endometritis (SE) cows almost lacked the aforementioned phyla [115].

Proteobacteria, Bacteroidetes, and *Fusobacteria* have been identified as uterine disease risk factors. Cows with retained placenta and healthy cows exhibit the same total bacterial count in the first days postpartum. However, *Bacteroidetes* and *Fusobacteria* tend to be in higher abundance after day-7 in the cows with retained placenta, postpartum fever assisted parturition and twin delivery. *Proteobacteria* were found to be more abundant in metritis. The author concluded that the total bacterial load and the microbiome composition is associated with specific risk factors of uterine disease [112].

4.6 Metabolic disorders

4.6.1 Ruminal acidosis

Ruminal acidosis is a gastrointestinal metabolic disease that affects feedlot and dairy cattle. The prognosis predicts intensive feeding of a high carbohydrate diet by cattle, leading to accumulation of short-chain fatty acids, lactic acid and LPS in the rumen [119]. This results in an extreme drop of rumen pH reaching <5.8 for at least 3 hours in a day [120]. There are two forms of ruminal acidosis; clinical (acute) and subclinical ruminal acidosis (SARA) [121]. Disease sequelae includes lameness, liver abscesses, paint brush haemorrhage, weight loss, scouring and epistaxis apart from deleterious effects on the reproductive system [23, 122]. Ruminal acidosis is the most important

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disorder of the dairy industry as it causes low milk production, low milk protein and fat leading to huge economic losses [122].

Rumen microbial community alterations are observed in association with rumen acidosis [123]. Alteration in the protozoa communities are marked by severe reduction or elimination in protozoa [23]. Rumen bacterial diversity and richness reduction has also been associated with the disease [124]. Changes in *Firmicutes* to *Bacteroidetes* ratio have also been reported, resulting in a decrease in *Bacteroidetes* and cellulolytic bacteria as well as an increase in starch fermenting bacteria [21, 125]. Plaizier et al. 2017 reported an equal relative abundance in *Firmicutes* and *Bacteroidetes* in the rumen which indicated a reduction in *Bacteroidetes* phylum [125].

Several studies evaluated the composition and functional activity of ruminal microbiota challenged with SARA. Microbiome dysbiosis was indicated by a decrease in cellulolytic bacteria including *Fibrobacter succinogenes*, *Ruminococcus albus*, *Streptococcus bovis* ,*Butyrivibrio fibrisolvens Prevotella bryantii, Selenomonas ruminantium* and *Ruminococcus bicirculans* in association with the acidotic challenge [126, 127]. *Streptococcus*, *Lactobacillus Succiniclasticum,* and *Clostridium* levels were increased during ruminal acidosis [27, 127]. Enrichment in carbohydrate-, amino acids-, energy-, vitamin co-factor- metabolism pathways in addition to biofilm formation pathways [126] and high concentration of LPS have also been reported to be associated with SARA. Inflammation induced by ruminal LPS over activate nuclear factor kappa-B and mitogen-activated protein kinase inflammatory pathways and significantly increased proinflammatory cytokine synthesis [119].

4.6.2 Ketosis

Acetonemia is a metabolic disorder that occurs in dairy cattle during early lactation period, affecting cattle health, fertility, and milk production. The disorder occurs when energy demands exceed energy intake, resulting in negative energy balance [128, 129].

Ketosis often occurs when high glucose demand is fulfilled through adipose utilization as an energy source. However, fat mobilization can lead to an increase in non-esterified fatty acid concentration in blood [128]. Longer periods of high blood concentrations of non-esterified fatty acids can impair the liver function, which leads to partial oxidation of non-esterified fatty acids. Consequently, overproduction and accumulation of ketone bodies, predominantly Beta-hydroxybutyrate (BHB), cause ketosis [130]. BHB levels can be used as a biomarker for ketosis diagnosis. Cows experiencing BHB levels higher than 1.4 mmol/L are usually diagnosed with ketosis [120].

Ketosis can result in less dry matter intake, reduction in milk production and weight loss. Some cows also develop neurological disorders, excitable uncoordinated and aggressive behaviour. Furthermore, ketosis may be a risk factor for mastitis [131].

Shifts in the microbiome in cows with ketosis have been detected by qPCR, T-RFLP and 16S rRNA sequencing. An increase in phyla *Firmicutes* and *Proteobacteria* was detected in cows with ketosis. A significant decrease in *Euryarchaeota* was also reported with elevated levels of *A. lipolytica, P. bryantii, M. elsdenii* and *Lachnospiraceae* in ketosis [132]. Also, genus *Ruminococcaceae*, *Methanobrevibacter*, *Erysipelotrichaceae*, and *Atopobium* were rarefied in ketosis [23, 132].

Disease	Significant changes in the microbiome	Reference

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Bovine respiratory disease	↑Mycoplama bovis	[65, 66]
	↑Mannheimia haemolytica	
	↑Pasteurella ultocida	
	↑Mycoplasma	
Mastitis	↑Staphylococcus aureus	[83, 84, 86]
	↑Streptococcus agalactiae	
	↑Escherichia coli	
	↑Klebsiella	
	↑Streptococcus dysgalactia,	
	↑Corynebacterium bovis	
Johnes Disease	↑Arthrobacter	[15, 103]
	↑Bacillus	
	↑Enterococcus	
	↑Camobacterium	
	↑Desemzia	
	↑Trichococcus	
	↑Planococcaceae	
	↓Paraprevotellaceae	
	↓ Faecalibacterium	

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	↓Akkermansia	
Metritis and endometritis	↑Trueperella pyogenes	[16, 109, 112, 114, 115]
	↑Escherichia coli	
	↑Porphyromonas levii	
	↑Fusobacterium necrophorum	
	↑Prevotella melaninogenica	
	↑Bacteroides spp	
Bovine digital dermatitis		[58]
	↑Treponema spp	
	↑Fusobacterium spp	
	↑Mycoplasma spp	
	↑Porphyromonas spp	
	↑Prevotella spp	
	↑Corynebacterium spp	
	↑Tissierella spp	
Rumen Acidosis	↓ Bacteroidetes	[27, 126, 127]
	↓Fibrobacter succinogenes	
	↓Ruminococcus albus	
	↓Ruminococcus bicirculans	
	↓Butyrivibrio fibrisolvens	
	↑Prevotella bryantii	
	↑Selenomonas ruminantium	
	↓ Streptococcus	

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	↑Lactobacillus	
	↑Succiniclasticum	
	↑Clostridium	
Ketosis	↑Lachnosparaceae	[23, 132]
	↑A. lipolytica,	
	↑P. bryantii	
	↑ M. elsdenii	
	↓Ruminococcaceae	
	↓Methanobrevibacter	
	↓Erysipelotrichaceae	
	↓Atopobium	
	↓ F. succinogenes	
	↓ Butyrivibrio proteoclasticus	
	↓Euryarchaeota	

Table 1. Significant transitions in microbiome associated with cattle disease.

5. Non-antibiotics microbial therapy

5.1 Probiotics

Probiotics are live microorganisms associated with human and animal health which confer a beneficial influence to the health when administrated in sufficient quantities [133]. To deliver this beneficial impact, the microorganisms should be alive, and the administration should be in effective doses to ensure abundance of the microorganisms [134]. Probiotics can exert their

beneficial effect through various mechanisms. They can modulate the host microbiota by competing with pathogens over the adhesion sites and nutrients [135]. Moreover, probiotics maintain intestinal homeostasis, resulting in improvement of barrier function [136]. Furthermore, they can produce antimicrobial metabolites, including lactic acid, diacetyl and antimicrobial peptides, such as bacteriocins, known to inhibit competing bacteria [137]. In other cases, probiotics can directly interact with the host cells to modulate the immune system [138, 139]. The most common types of microorganisms in probiotics are safe, food-grade bacteria related to genera lactic acid bacteria (LAB), *Lactobacillus*, and *Bifidobacterium* [140]. Apart from them, *enterococcus* and *streptococcus* form part of probiotics as well [141].

Since rumen acidosis is the most important disorder in dairy cattle, studies infusing probiotics for treatment of rumen acidosis were a reasonable choice. Goto et al. 2016 reported that the introduction of a probiotic cocktail (Miyarisan pharmaceutical Co., Ltd., Tokyo, Japan) including *L. plantarum*, *E. faecium,* and *C. butyricum* for 7 days can improve the pH and lactic acid level [142]. Yeast has also been incorporated within probiotics in cattle as various studies provide sufficient evidence of its beneficial impact against ruminal acidosis [123, 126]. Mohammed et al. 2017. reported that Saccharomyces cerevisiae supplementation can reduce subacute rumen acidosis, but it did not reduce acute acidosis [123].

In line with the global efforts to reduce antibiotics usage, researchers have applied probiotics as potential alternative approach for preventing and controlling mastitis [143, 144]. LAB based probiotics have successfully stimulated the host immune response which may be approved as non-antibiotic mastitis therapy [134]. A study by Pellegrino et al. 2017 investigated the immunomodulatory effect of *L. perolens* CRL1724 and *L. lactis subsp. lactis* CRL1655. When inoculated in healthy cows during dry-off period, the study demonstrated an increase in immunoglobulin (Ig) G in milk and blood samples. Moreover, they were able to recognise *S. aureus* isotopes against which probiotics were established as a measure for preventing mastitis infection during dry off period [145]. Furthermore, a study conducted by Souza et al. 2018 showed that in event of *S. aureus* infection, *L. casei* BL23 exhibited anti-inflammatory properties on infected bovine mammary epithelial cells and did not obstruct the induction of host cell defensins [146]. A study by Wallis et al. 2018 assessed 13 LAB strains for their ability to form biofilms, producing a barrier against the pathogens and adhere to bovine glandular mammary epithelium. The biofilm formation and adherence were observed in all the strains, both characteristics showed strain dependency [134, 147]. Another study by the same group investigated the ability of five LAB strains to remove and replace the biofilm formed by pathogenic staphylococci. All five strains were able to remove the staphylococcal biofilm [148]. To assess the potential probiotic potential of *Lactococcus lactis* LMG 7930, Armas et al. 2017 examined it's *in vitro* potential against ten mastitis-causing pathogens. The strain showed antagonistic properties against many of the pathogens such as *S. agalactiae* and *S. aureus* strains. Interestingly, the probiotic strain was adhesive to bovine mammary epithelial cells. On the other hand, the strain did not significantly affect pathogen invasion although it tends to decrease the internalization in some strains. The author suggested further studies to assess the strain safety and efficiency in the field [149]. Another study by Pellegrino et al. 2019 selected two strains *Lactobacillus lactis subsp. lactis* CRL 1655 and *Lactobacillus perolens* CRL 1724 based on their adhesion patterns to bovine teat canal epithelial cells (BTCEC), ability to co-aggregate and inhibit the pathogenesis. The characteristics of these two strains suggested that they may be a good candidate for mastitis prevention during dry-off period [150]. A unique effort has been made in a study by Yu et al. 2017 to compare a commercial disinfectant with probiotic disinfectant made up of two strains *L. plantarum* IMAU 80065, and IMAU10155 combination. The study showed a gradual decrease in the SCC (somatic cell count; an indicator of milk quality) following the cleaning protocol. Also, it was lower in the LAB group than the commercial disinfectant. The complete 16S rRNA sequencing of raw milk samples revealed substantial diversity in microbial make-up within samples. The authors suggested that the probiotic disinfectants can replace chemical disinfectant [151].

Additionally, utilization of LAB has been evaluated as a potential preventive method against upper respiratory tract infection (bovine respiratory disease) caused by the *M. haemolytica* associated pathogen cluster [58, 78]. In a study by Amat et al., 2020 inter-nasal inoculations with four different species namely *L. amylovorus*, *L. buchneri*, *L. curvatus* and *L. paracasei*, isolated from healthy calves had been done to investigate their longitudinal effect on the nasopharyngeal microbiome. A significant decrease in *M. haemolytica*, owing to the colonization resistance had been reported [32, 152]. Another promising study introduced *Dietzia spp*. as potential probiotics, to

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inhibit *Mycobacterium avium subsp. Paratuberculosis* (MAP) and Johne's disease *in vitro* [153]. Probiotics had been administered to impede the development of Johne's disease, following MAP infection, in the susceptible calf. For this study, *Dietzia subsp*. C79793-74 had been introduced in antibiotic free milk feed for a 60-day period. None of the 10 treated calves developed the symptoms as they aged, in contrast to the untreated group in which seven out of eight developed MAP symptoms. Moreover, a group was treated with combination of *Dietzia* and tetracycline, as *Dietzia* has proven sensitivity to tetracycline contamination. This group also exhibited a high infection rate (six out of eight were infected), which signified that good practices were required alongside probiotic administration [154].

Metritis affects up to 40% of the dairy herd and is usually treated with antibiotics [155]. But recently, intravaginal introduction of several LAB strains have been used to prevent or reduce the incidence of postpartum uterine infections [156]. As reported by Deng et al. 2015, the intravaginal administration of a cocktail of LAB composed of *Lactobacillus sakei* FUA 3089, *Pediococcus acidilactici* FUA 3138 and FUA 3140 resulted in a lower uterine infection and an overall improvement in local and systematic immune response [157]. Another study suggested that the therapeutic potential of a LAB combination consisting of *Lactobacillus rhamnosus*, *Pediococcus acidilactici*, *Lactobacillus reuteri*, and *Lactobacillus sakei* showed reduced inflammation in uterus against endometrium inflammation and *E. coli* infection [158] [159].

The calf diarrhoea has a high incidence especially in the first 4 weeks of a calves' life, resulting in a high mortality and morbidity rate [160]. The long-term, broad-spectrum antibiotics have conventionally been applied as therapy for the disease [161]. However, the probiotic research has been implemented recently for preventing and controlling the disease. Renaud et al. 2019 reported a reduction in the duration of diarrhoea in calves treated with multispecies probiotic bolus (MSP). MSP contained *Pediococcus acidilactici, Lactobacillus acidophilus*, *Lactobacillus casei, Enterococcus faecium, Bifidobacterium bifidum*, peptide extract, enzyme blend, killed yeast extract, dried whey, and natural flavors. The authors recommended further investigations to assess clinical and economic relevance [162].

Another study suggested the administration of fermented milk with LAB strains for diarrhoea treatment. The strains were a combination of *Lactobacillus murinus* CRL 1695, *Lactobacillus mucosae* CRL 1696, *Lactobacillus johnsonii* CRL1693 and *Lactobacillus salivarius* CRL 1702. The result was a significantly low mortality and morbidity rate, reported in calves treated with fermented milk and LAB as compared to the control group. However, the viable bacterial number showed no difference between the two groups [163]. The study by Fukuda et al. 2019 examined a commercial probiotic product (Bio Three for animal, Toa pharmaceutical Co., Ltd., Tokyo, Japan) comprised of *Bacillus mesentericus*, *Clostridium butyricum* and *Enterococcus faecalis;* orally administrated for eight days. The antibiotic-treated group was medicated with ampicillin (Kyritsuseiyaku, Tokyo, Jaban) for the first five days, followed by kanamycin sulfate (Meiji Seika co., Tokyo, Japan) administration till eighth day. The results showed no significant differences in faecal score between the two treatment regimes, leading to the confirmation that probiotics can be an alternative therapy to antibiotic treatment [161].

5.2 Phage therapy

Bacteriophages are viruses acting as intracellular parasites, that infect bacteria to replicate within the bacterial cell [164]. The phages can replicate through either lytic (virulent) or lysogenic (temperate) cycle. These mechanisms play a paramount role in phage therapeutic potential. In the lytic cycle, the virus infects the bacteria and kill the cell [165]. Whereas, in the lysogenic cycle, the virus can either lysogenize the host cell by integrating its genome into the host genetic material or move to the lytic cycle [166]. The phages are extremely diverse in nature [167], thus highly specific in infecting their bacterial hosts [168].

In cattle, bacteriophages have been an attractive alternative to the antibiotic usage, as investigated by many researchers [169]. Many *in vitro* and mouse models show promising results for bacteriophage therapy potential. However, a few clinical studies have been conducted [170]. The phages have been widely introduced against mastitis pathogens such as staphylococcus, *E. coli*, and Streptococci [144]. Studies on utilizing bacteriophages for treating mastitis caused by *S. aureus* reported the lytic phage SA isolated from purified sewage water to be active against six *S. aureus* strains out of 13. The highest lytic activity was recorded at pH 7 in 37ºC [171]. In another study, SA

phage exhibited a relatively narrow host range against 10 *S. aureus* strains compared to SA2, and SNAF phages. Remarkably, phage SNAF exhibited a significant growth reduction in *S. aureus* compared to SA and SA2 phages [172]. A strong lytic activity of SAJK-IND phage reached 100% against *S. aureus* isolated from mastitis milk, as reported by Ganaie et al. 2018 However, using only MSP exhibited just 40% lytic activity against the same isolates [173]. Another study investigated a mixture of three phages, STA1.ST29, EB1.ST11, and EB1.ST27 against *S. aureus* from pasteurized as well as raw bovine mastitis milk. The results reported that the bacteriophage mixture significantly reduced *S. aureus* in the pasteurized milk [174].

Various laboratory models have been used to evaluate the effectiveness of bacteriophages as a treatment in many studies. Iwano et al. 2018 reported that the lytic phage ΦSA012 and ΦSA039 were effective against 93 *S. aureus* strains and six MRSA strains. Furthermore, studies investigated the effectiveness of phage ΦSA012 and ΦSA039, *in vivo* using mouse model. ΦSA012 showed a higher effectiveness in reducing *S. aureus* proliferation and consequently mammary gland inflammation [175]. The cocktail bacteriophages are more effective than single phage, as reported by a study by Geng et al. 2020, investigating the efficiency of lytic phage cocktail vGSM-A1 and vBSP-A2 in the mouse model [176].

Other studies used bacteriophages against *E. coli*. Porter et al. 2016 demonstrated the effectiveness of a cocktail of four bacteriophages against *E. coli* through several *in vitro* tests and reported a significant reduction in *E. coli* adhesion and intracellular survival. Moreover, the phage was able to inhibit *E. coli* growth when challenged by 1.6 $*10^3$ cfu/ml [177]. A more recent study by Da Silva et al. 2018, evaluated the effect of UVF13 phage against *E. coli* in induced mastitis in a murine model. The result indicated a 10-fold reduction in bacterial load in the phage-treated group [178].

Escherichia coli and *Trueperella pyogenes* are among the main pathogens driving metritis [109]. Despite the effectiveness of bacteriophage therapy against *E.coli* [178], the intrauterine administration of bacteriophages did not affect the uterine pathogens [170]. However, the administration of UFV13 can reduce the *T. pyogenes* adhesion and therefore, can disturb the biofilm formation [179].

The phage derived endolysins have also been proposed as a potential antimicrobial agent. In a study by Zhou et al. 2017, the lytic enzyme LysKΔamidase exhibited a broad lytic activity against 137 methicillin-resistant and susceptible staphylococci isolated from bovine mastitis milk samples and human patients [180]. Another study by Fan et al. 2016 investigated trx-SA1 endolysin isolated from *S. aureus* bacteriophage IME-SA1 as a possible treatment for bovine mastitis. The results showed that trx-SA1 could control mild infection of clinical mastitis [181]. An interesting result had been obtained from one study by Scholte et al. 2018 which used PlyC, peptidoglycan hydrolysed derived from streptococcus C1 bacteriophage against *streptococcus uberis* cell wall. The study reported that a low dose of PlyC 1.0 μg/ml can induce a lytic activity [182].

Bacteriophages have also been used against *M. haemolytica*, a bacterium that is implicated in bovine respiratory disease pathogenesis. However, none of the studies have reported a promising result against *M. haemolytica* [32].

5.3 Prebiotics

Prebiotics are defined as organic nutrients that are indigestible by animal's upper gastrointestinal tract enzymes but can be digested by one or a limited cohort of gut bacteria and consequently increase their growth and activity. The cumulative effect is an improvement of host's health [183, 184]. The most used prebiotics in animals are manno-oligosaccharides, fructo-oligosaccharides, and trans-galacto-oligosaccharides. Prebiotics can reduce the attachment of pathogenic bacteria and improve the immune response in cattle [185]. In a study by Grispoldi et al. 2017, the introduction of prebiotics in Holstein Friesian diet resulted in reduction of *E. coli* prevalence [186].

6. Future perspectives

In this review, we endeavour to summarize the microbiota composition and diversity related to cattle niches, as well as its contribution to animal health and production. The commensal microbiota composition is directly affected by various environmental and host factors, for

instance, the initial infant microflora is derived from mother's vaginal, skin and environmental microbiota [23] and the rumen of calves, delivered by C-section, are more likely to be colonized by species from the phylum *Firmicutes* instead of *Proteobacteria* [13, 24]. It implies that characterization of native colonized microbiome should be analysed in relation to the potential microbial sources such as water, feed, soil, air, animal handling conditions etc., and the host characters to be considered are cattle age, breed, immunity etc. The association studies considering more variables would sort out similar set of phylogenetic and functional biomarkers among consensus microbiome for a specific niche or organ. For analysis of complete microbiome, microbiome-wide association studies (MWAS) can be undertaken with reference to select host and environmental parameters [1].

Moreover, the lack of consistency within reported predominance of bacterial phyla within healthy cattle microbiome results in ambiguity. This uncertainty points towards an inevitable need to establish improved standardized methods for characterizing whole cattle metagenome at the omics level. This characterization will lead to a deeper understanding of conserved functional pathways within varying cattle species around the world. Therefore, substantiating the concept of a standardized probiotics therapy that can be administered alongside traditional therapies for effective treatment. The knowledge based on microbial shifts within diseased and healthy microbiota, can be utilized to understand and exploit commensal relationships within various microbes. The healthy microbiota can be selected for their prognostic effect, as candidates for preventive probiotics[6].

In light of the commensal relations within microbiota that generates synergistic benefits for cattle, the researchers must focus on selecting and optimising the most effective microbial combination. These combinations will relieve dysbiosis during disease conditions. Once these combination therapies are established, their efficacy within clinical trials can be initiated to standardize the dosage, time, and other parameters[187-189].

7. Conclusion

The review has aimed to build a case for combination therapies that benefit from prebiotic and probiotic therapies alongside traditional antibiotic medicines. The diseases characterized by dysbiosis are promising targets for such an approach. The bioceutical or neutraceutal therapies have shown promising physiological benefits in humans already. With deeper understanding of cattle microbiome, these therapies can be extended to all cattle management systems for improved cattle health and lifespan.

Understanding the cattle microbiome is critical for maintenance of cattle health and productivity. A holistic knowledge of cattle microbiome, has potential to generate a myriad of benefits, not limited to economic, therapeutic, industrial setups. Despite the advancements in sequencing technologies, our understanding of complexities of microbiome diversity and interactions with host remains superficial. Understanding the native microbial composition within could help in designing preventive and therapeutic approaches against the dysbiosis associated with various diseases. Although the research gaps are filling up rapidly and promising results have been elucidated in several studies pertinent to microbiome manipulation, more research is needed before microbiome can be exploited for effective disease prevention and treatment strategies. Hence, prolonged, horizontal studies with a large sample size are recommended to provide more precise explanations of the mechanisms influencing microbiome composition, diversity, and function.

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