Impact of dairy calf management practices on the intestinal tract microbiome pre-weaning

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1.4 Keywords

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2. Abstract

Background: Microbiota in the gastrointestinal tract (GIT) consisting of the rumen and hindgut (the small intestine, cecum, and colon) in dairy calves, plays a vital role in their growth and development. This review discusses the development of dairy calf intestinal microbiomes with an emphasis on the impact that husbandry and rearing management have on microbiome development, health and growth of pre-weaned dairy calves.

Discussion: The diversity and composition of the microbes that colonise the lower GIT (small and large intestine) can have a significant impact on growth and development of the calf, through influence on nutrient metabolism, immune modulation, resistance or susceptibility to infection, production outputs and behaviour modification in adult life. The colonisation of the calf intestinal microbiome dynamically changes from birth, increasing in microbial richness and diversity until weaning, where further dynamic and drastic microbiome change occur. In dairy calves, neonatal microbiome development prior to weaning is influenced by direct and indirect factors, some of which could be considered stressors, such as maternal interaction, environment, diet, husbandry, and weaning practices. The specific impact of these can dictate intestinal microbial colonisation, with potential lifelong consequences.

Conclusion: Evidence suggests the potential detrimental effect that sudden changes and stress may have on calf health and growth due to management and husbandry practices, and the importance of establishing a stable yet diverse intestinal microbiome population at an early age is essential for calf success. The possibility of improving the health of calves through intestinal microbiome modulation and using alternative strategies including probiotic use, faecal microbiota transplantation, and novel approaches of microbiome tracking should be considered to support animal health and sustainability of dairy production systems.

3. Data summary

Not applicable.

4. Introduction

Microbiota in the gastrointestinal tract (GIT) consisting of the rumen and hindgut (the small intestine, cecum, and colon) in calves, plays a vital role in the growth and development, GIT function and fermentation, immunocompetence and behaviour of the calf (Dias *et al.*, 2018; Amin & Seifert, 2021; Du *et al.*, 2023). Microbial establishment in the GIT of a newborn calf is influenced by exposure to microorganisms from the mother, environment, milk and other feeds, and conspecific interactions (Orihuela & Galina, 2019). The diversity and composition of the bacteria that colonise the rumen and the small and large intestine influence nutrient metabolism, pathogenic defence, immune modulation, resistance or susceptibility to infection, production outputs and behaviour in adult life (Diao, Zhang & Fu, 2019). During the period before weaning, neonatal calves have a developing rumen, and milk passes through a primarily monogastric digestive system. Hindgut microbial fermentation produces numerous compounds (e.g. B vitamins and amino acids) that may help support neonatal growth, development and immunity (Elolimy *et al.*, 2020).

The nutritional, metabolic, developmental and environmental changes that a dairy calf faces during the eight to ten weeks prior to weaning can lead to disruption or change within the GIT (Meale *et al.*, 2017; Mir *et al.*, 2019). Dairy calves during this period undergo husbandry challenges such as changes in surroundings and groupings (Neave, Weary & Von Keyserlingk, 2018), changes in diet (De La Cruz-Cruz *et al.*, 2019), and stress events (De Paula Vieira, de Passillé & Weary, 2012; Cantor, Neave & Costa, 2019), such as disbudding (Mir *et al.*, 2019) and weaning (Neamt *et al.*, 2019). Any disruptions to the growth and population of the GIT microbiome can have drastic and permanent effects on calf development due to reduced weight gain (Costa, 2015), diarrhoea (Xie *et al.*, 2013), contraction of infection or disease (Gaeta *et al.*, 2017), and potential for mortality (Diao, Zhang & Fu, 2019).

Studies of the development of the GIT microbial community to improve cattle health, welfare and production efficiency have been ongoing for many decades (Celi *et al.*, 2017). High throughput sequencing technologies allow examination of the structure and function of the bovine GIT microbiota (McCann, Wickersham & Loor, 2014). Factors such as breed, sex, diet and heritable components have been linked to the composition of the GIT microbiome (Li *et al.*, 2019a; Li *et al.*, 2019b). The mature GIT microbiome has a great variety of microorganisms, dominated by the phyla Firmicutes and Bacteroidetes (Fernando *et al.*, 2010; McCann *et al.*, 2016), that display redundancy among niches and contribute to community resilience (Myer *et al.*, 2017). Consequently, reconstruction of the mature GIT microbiome is difficult and mature animals primarily act as a donor source for microbial transplantation in young ruminants (Li, Shi & Na, 2023). This has led to a focus on early life microbiome development, due to its susceptibility to change at this stage and as a potential target for microbiome manipulation, that could persist over the productive life of the animal (Yáñez-Ruíz, Abecia & Newbold, 2015). However, the dynamic nature of the GIT microbiome in neonatal calves is not fully understood (Kim *et al.*, 2021a). Research in this area has largely focused on investigating sources of inoculation or influence, such as the maternal microbiome (Barden *et al.*, 2020), diet (Dill-McFarland *et al.*, 2019) and the environment (Zhu *et al.*, 2021). Less is known about how establishment of the bovine GIT microbiome during early-life may be influenced by wider husbandry practices. An improved understanding of the temporal dynamics of the GIT microbiome throughout life may facilitate opportunities to enhance animal health, welfare, growth and development from neonate to maturity.

This review focuses on the development of dairy calf intestinal tract microbiomes and the impact that husbandry and rearing management have on microbiome development, health and performance of pre-weaning dairy calves.

5. Calf Microbiome – Early life colonisation

During the pre-weaning period, calves are considered pre-ruminant or monogastric while their rumen is developing, with dynamic changes in intestinal microbiota occurring during this time (Song *et al.*, 2019). Commensal microbial colonisation of the intestinal tract occurs during and after birth, influenced by the maternal microbiota, diet, environment, management practices and antibiotic treatment (Fanaro *et al.*, 2003; Penders *et al.*, 2006; Adlerberth and Wold, 2009). Colonisation is a two-way interaction between microorganisms and the host (Van den Abbeele *et al.*, 2011). Commensal microorganisms support intestinal pH, food retention time and immune defence mechanisms (Hold & Hansen, 2019; Michaudel & Sokol, 2020), while the host supports microbial adhesion, nutrient absorption and can provide protection to the microbiota via intestinal mucus secretions and antimicrobial peptides through the immune response (Júnior & Bittar, 2021; Welch *et al.*, 2022). Although initial microbial communities are facultatively anaerobic or aerobic, the intestinal environment transitions to support a rapid establishment of obligate anaerobes (such as Firmicutes, *Bifidobacterium* and *Bacteroides*) which play a vital role in host health (Conroy, Shi & Walker, 2009; Jost *et al.*, 2012; Figure 1). Recent findings identified a foetal GIT microbiome during gestation containing Actinobacteria, Bacteroidetes, Firmicutes and Proteobacteria as the predominant phyla present in meconium during months five to seven of gestation (Guzman *et al.*, 2020; Table 1). This has dispelled the previous thinking of a sterile foetus until parturition (Adnane & Chapwanya, 2022). Prior to weaning, Firmicutes are reported to be the predominant phylum in faecal samples of dairy calves, including families such as *Ruminococcaceae* and *Lachnospiraceae* (Foditsch *et al.*, 2015; Liu *et al.*, 2019), followed by the phylum Bacteroidetes, primarily dominated by the family *Prevotellaceae* (Klein-Jöbstl *et al.*, 2014; Liu *et al.*, 2019). Despite observations of highly individualised microbial communities of the developing calf microbiome, the pooling of samples has allowed an estimation of community-level microbiome diversity (Ray *et al.*, 2019).

During gestation (between five to seven months into foetal development), the abundance of microbial species across foetal tissues within the rumen and caecum change. Guzman *et al.* (2020) observed over 500 bacterial species within the calf foetal GIT compartments. The differences observed across the rumen and caecum indicate location-specific microbial colonisation likely to occur before the fifth month of gestation. Caecal tissues were dominated by the phylum Actinobacteria, and caecal fluid was dominated by Firmicutes (order *Lactobacillales*) and Proteobacteria (order *Enterobacteriales* and *Pseudomonadales*). Although the foetal GIT microbiome shares several bacterial species from the genera *Lactobacillus*, *Escherichia, Shigella* and *Streptococcus* with the mother, the inoculation source remains unclear. Guzman *et al.* (2020) speculate that bacterial communities might be introduced to the foetus via translocation from the mothers GIT epithelium.

Upon birth, the sections of the intestinal tract can have varying microbiome compositions due to the specific interactions that take place across them. Phylum and genus level differences have been reported across the dominant bacteria of the small and large intestine within the calf GIT and the faecal microbiome (Dias *et al.*, 2018; Malmuthuge *et al.*, 2019). Analysis of commensal microbial community composition identified the initial establishment of aerobic and facultative anaerobic bacteria such as *Bifidobacteria* and *Lactobacillus* across the sections of the intestinal tract, which provide an appropriate anaerobic environment for the gradual colonisation of Actinobacteria, Bacteroidetes, Firmicutes and Proteobacteria, via the removal of oxygen (Sprockett, Fukami & Relman, 2018). The small intestine (duodenum, jejunum, ileum) and large intestine (cecum, colon, rectum, anus) have a high relative abundance of Firmicutes at 80% and 81%, respectively. Actinobacteria, Proteobacteria and Bacteriodetes are also found throughout the small and large intestine in varying relative abundances from 6-13%, 5-22% and 1-33%, respectively (Myer *et al.*, 2017; Yeoman *et al.*, 2018). In the first week of life, the small intestine of the calf consists of 1 to 4% *Bifidobacterium*, 7 to 11% *Prevotella*, 9 to 27% *Bacteroides* and 17-24% *Lactobacillus (*Malmuthuge *et al.*, 2019). As the calf ages, these genera decrease in relative abundance, potentially due to increasing diversity across the intestinal tract (Malmuthuge *et al.*, 2019).

Bifidobacterium were found to be in higher abundance (60%) in the large intestine of 1-week old calves. By six weeks of age, *Bifidobacterium* abundance in the large intestine decreases to approximately 11%. *Bacteroides* maintain a relatively low abundance (4 to 9%) in the large intestine compared to the small intestine (Song *et al.*, 2018). *Lactobacillus* was found to be a prominent genus in the large intestine at between 20-22%. This genus decreases in relative abundance as the calf consumes concentrate feed and forage in its diet (Song *et al.*, 2018).

The faecal microbiome is the most studied intestinal microbial composition due to the accessibility of samples. The faecal microbiome can represent microbial activity across the GIT. Studies have shown they most closely represent the bacterial composition within the large intestine and specifically the colon (Malmuthuge, Griebel & Guan, 2014). Like the microbial composition of the large intestine of 1-week-old calves, *Bifidobacterium* and *Lactobacillus* were found to be more abundant in faeces compared to other species observed in the first week after birth. These species decreased to weaning age (Uyeno, Sekiguchi & Kamagata, 2010). *Bacteroides* (16%), *Prevotella* (22%) and *Faecalibacterium* (10%) increased in relative abundance between weeks one and three of life, before declining in abundance with increasing age (Malmuthuge, Griebel & Guan, 2014; Amin *et al.*, 2023). As the calf grows and consumes more forage and concentrate feeds (between weeks five to 12), the faecal microbiota present is comprised of higher relative abundances of *Bacteroidales*, *Clostridia* and *Ruminococcaceae* (Figure 1; Uyeno, Sekiguchi & Kamagata, 2010; Amin *et al.*, 2023).

Understanding the relative abundance of the microbiota during the pre-weaning period provides insight into how the microbiome develops while interacting with a range of environmental factors (diet, environment, conspecifics). The relative abundance of specific species during this time have been identified as indicators of the health or diarrheic status of the calf. Slanzon *et al.* (2022) identified *Eggerthella*, *Bifidobacterium*, and *Collinsella* as species associated with calves that did not experience enteric disease. The presence of *E. coli* species in neonatal calves (up to three weeks of age) had the highest association with enteric disease prediction (Slanzon *et al.*, 2022). Therefore, understanding early intestinal colonisation and the factors that influence microbiome establishment could provide opportunities to design specific interventions to manage calf gut health.

Figure 1: The progression of commensal intestinal microbiome bacterial orders from foetus to weaning. Figure constructed from previous studies (Kišac *et al.*, 2011; Meale *et al.*, 2017; Liu *et al.*, 2019; Guzman *et al.*, 2020).

5.1 The importance of early microbiota colonisation

Early-life microbial colonisation plays an important role in neonatal growth, development and immunity (Elolimy *et al.*, 2020). The development and differentiation of the intestine, immune system, and further regulation of enteric innate and adaptive immune processes are supported by the establishment of microbiota (Liang *et al.*, 2014; Liang *et al.*, 2016). Through the establishment of a stable microbiome, the community structures act as a biological barrier that inhibits pathogenic bacteria from colonising and contributes to maintaining calf health (Taschuk & Griebel *et al.*, 2012; Malmuthuge *et al.*, 2019).

The role and importance of intesinal microbial colonisation has been assessed across a variety of germ-free (GF) animal models, including mice, rats, guinea pigs, dogs, pigs, sheep, goats, and chickens (Al-Asmakh & Zadjali, 2015). Aspects such as cell proliferation and intestinal mucosal layers were observed to be of poorer functionality in GF mice compared to conventional mice (Nowacki *et al.*, 1993; Petersson *et al.*, 2011). Gnotobiotic mice inoculated with whole mice microbiota resulted in an increase in T helper cell responses, with *Clostridia*-related species possibly influencing the maturation of T cell responses (Gaboriau-Routhiau *et al.*, 2009). Similarly, the presence of Bacteroidetes have been shown to support the activation of regulatory T cells (Luu, Steinhoff & Visekruna, 2017). These T cells enhance epithelial repair, promote tolerance to commensal microorganisms and regulate intestinal immune processes in response to bacterial or self-antigens (Webb *et al.*, 2016; Lyons *et al.*, 2020). Moreover, the development of gut-associated lymphoid tissues including Peyer's patches and mesenteric lymph nodes, have been seen to be stimulated by postnatal microbial colonisation (Renz, Brandtzæg & Hornef, 2012). Increasingly, the intestinal microbiota is recognised to play an important role in maintaining intestinal function and immune defence (Li, Shi & Na, 2023).

Intestinal bacteria are also responsible for supporting feed utilisation and efficiency in the calf, supporting the transition from liquid products (such as milk or colostrum) to solid feed (such as calf starter) (Elolimy *et al.*, 2020), determining the ability of the animal to utilise energy from the diet (Turnbaugh and Gordon, 2009; Yeoman and White, 2014). Increases in the relative abundance of Bacteroidetes in the small intestine produce the enzyme glycoside hydrolase which is needed for the degradation of glycan (Patrascu *et al.*, 2017; Lyons *et al.*, 2020). This enzyme is necessary to support the weaning process when the calf is transitioning to solid feed and forage from milk. A recent study examined feed efficiency and its correlation to different sections of the GIT microbiome (the rumen, caecum, and faeces) in cattle. In caecal and faecal samples, several species including *Ruminococcaceae* (r = -0.674 and r = -0.725 respectively) and *Mogibacteriaceae* (r = -0.647 and r = -0.494 respectively) were negatively correlated with feed efficiency. Whereas *Succinivibrionaceae* in the caecum and *Bifidobacteria*cea in faeces were positively correlated with feed efficiency (r = 0.445 and r = 0.478 respectively; Welch *et al.*, 2020). Previous studies primarily focused on rumen fermentation as the centre of microbial feed digestion processes (Dias *et al.*, 2018; Hao *et al.*, 2021). However, Welch *et al.* (2020) provided evidence that in addition to the ruminal microbiome, the hindgut microbial populations have a significant impact on feed efficiency and thus are an essential component to growth and health, particularly in the pre-ruminant calf.

6. Factors influencing colonisation

A wide range of factors influence intestinal microbial colonisation and the stability of those communities throughout the pre-weaning period. These include direct influences such as maternal microbiomes, colostrum or milk/milk-replacer feeding, weaning, and the housed environment (Breen *et al.*, 2023); while indirect influences include aspects such as disbudding and weaning readiness, where husbandry practices that elicit a possible stress response may cause adverse consequences to inestinal microbial community establishment and/or stability (Mir *et al.*, 2019).

Table 1: Microorganism sources associated with management events during the pre-weaning period.

Event	**Source of microorganisms**	**Direct/Indirect Source**	**Microorganisms from or influenced by source**	**Impact on calf microbiome development**	**Reference**
Birth	Gestation - Communities suggested to be sourced from maternal placenta epithelium.	Direct	Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria.	Bacterial communities in GIT foetal samples at five, six & seven months of gestation.	Guzman *et al.*, 2020
	Vaginal		Proteobacteria, Firmicutes, Fusobacteria, Tenericutes.	Maternal faecal, oral & vaginal, microbiomes were significant predictors of calf faecal microbiome. Dam faecal & oral microbiomes have the largest correlation to the calf faecal microbiome.	Owens *et al.*, 2021
	Faecal		Fusobacteria, Firmicutes.		
	Oral		Proteobacteria, Bacteroidetes, Firmicutes.		
	Maternal Heat Stress	Indirect	Firmicutes, Proteobacteria, Bacteroidetes, Epsilonbacteraeota, Actinobacteria, Fusobacteria	Maternal heat stress alters intestinal microbiome β-diversity & composition in sows & their piglets.	He *et al.*, 2020
Preweaning diet	Colostrum	Direct	*Lactobacilli*, *Bifidobacterium*, reduced presence of Coliforms and *Enterococci*.	Better quality colostrum (>1.070 g/cm3) promotes the intestinal microbiome development & daily liveweight gain.	Puppel *et al.*, 2020
	Milk replacer		*Ruminococcaceae*, *Lachnospiraceae*,	Higher milk replacer intakes in calves increased faecal bacterial diversity. Increased abundances of beneficial	Kumar *et al.*, 2021b

			Bacteroides, *Bifidobacterium,* *Faecalibacterium*, Peptococcus, Blautia	bacteria such as *Faecalibacterium*, were observed, which may contribute to development & growth.	
Housing	Conventional/Single pen	Direct & Indirect	*Enterococcaceae,* *Lactobacillus*	*Enterococcaceae* & *Lactobacillus* was more abundant in the faecal samples of conventionally housed pigs.	Wen *et al.*, 2021
	Enriched		*Prevotella*, Christensenellaceae, Ruminococcus gauvreauii, Ruminiclostridium, Phascolarctobacterium, Peptostreptococcaceae	*Enterococcus* decreased & relative abundance of a variety of faecal bacteria increased in enriched housed pigs - these bacteria are known to support degradation of plant materials, the production of short-chain fatty acids. Suggesting enriched housing accelerated the maturation of early-life faecal microbiota composition.	Wen *et al.*, 2021
Disbudding	Body Weight - Light	Indirect	Higher abundance in lightweight calves: *Verrucomicrobiacea*, *Erysipelotrichaceae*	Lightweight calves had higher relative abundance of families like *Erysipelotricheae* & *Verrucomicrobiaceae* at Day 3 after disbudding. Procedure was conducted at 10 weeks of age when the faecal microbiome is still maturing & therefore could mask the effects/impact of the process.	Mir *et al.*, 2019
	Body Weight - Heavy		Higher abundance in heavy-weight calves: *Elusimicrobiaceae*, *Turicibacteraceae*	Heavy-weight calves had higher relative abundance of *Elucimicrobiaceae* and *Turibacteriaceae*, at Day 3 after disbudding. Procedure was conducted when faecal microbiome is still maturing & therefore could mask the effects/impact of the process.	Mir *et al.*, 2019

Weaning	Calf Starter	Direct	*Prevotella*, *Succinivibrio, Anaerovibrio Sharpea, Acidaminococcus, Megasphaera, Mitsuokella, Lactobacillus*	Inclusion of concentrate decreased Shannon, Simpson & Fisher's alpha diversity index in faecal samples. Promoting the abundance of possible starch degraders & reduced the presence of key species associated with fibre degradation.	Hartinger *et al.*, 2022
	Forage		*Ruminococcaceae Akkermansia, Lachnoclostridium*	No significant effect in faecal microbial diversity was found regarding hay quality (medium or high quality). Fewer changes in bacterial abundances in response to forage were observed at genus level.	Hartinger *et al.*, 2022
	Weaning readiness	Indirect	*Bacteroides*, *ParaBacteroides*, *Blautia*	Weaning at 17 weeks of age had a higher growth rate due to late weaning & a quick adaptability of the faecal microbiota to dietary changes during day 112. This suggests an age-dependent maturation of the intestinal microbiome supporting liquid to solid diet transition.	Amin *et al.*, 2023

6.1 Birth and Maternal Influence

Studies have identified that the microbiota within meconium at birth are representative of faecal community structures 24 hours after birth, although changes are observed with increased microbial diversity and relative abundance in this time period (Alipour *et al.*, 2018; Klein-Jöbstl *et al.*, 2019; Wilczyńska, Skarżyńska & Lisowska-Myjak, 2019; Guzman *et al.*, 2020). The sources influencing this development dictate initial microbiome functions in early life (Dias *et al.*, 2018). Owens *et al.* (2021) found the maternal microbiota within samples from oral, placental, vaginal, faecal and colostrum sources to be significant predictors of the calf faecal microbiome during pre-weaning (Table 1). Interestingly, most of the abundant genera within meconium (*Ruminococcaceae*, *Acinetobacter, 5-7N15*) were closely related to genera within dam placental and faecal samples (Owen *et al.*, 2021). In addition to direct influences from maternal sources, maternal stress during gestation and birth has a direct effect on the calf (Kovács *et al.*, 2021). Cortisol, a glucocorticoid hormone, increases within the dam and calf leading up to parturition in preparation for birth. The production of glucocorticoids supports gestational and neonatal functions in the calf (Fischer *et al.*, 2014; Arfuso *et al.*, 2023). Intestinal health and function is directly influenced by glucocorticoids due to their role in stimulating tight junction formation and mucosal production (Fishman *et al.*, 2014; Tena-Garitaonaindia *et al.*, 2022). In addition, glucocorticoids influence intestinal maturation via receptor activation that regulates gene transcription controlling intestinal development (maturation of intestinal epithelium), supporting the production of enzymes such as peptidase (Nanthakumar, Meng & Newbury, 2013), and supporting the immune response (Lu *et al.*, 2006; Ahmed, Schmidt & Brunner, 2019). Difficult births have been shown to result in a significant increase in the levels of glucocorticoids, specifically cortisol, in the newborn calf up to 48 hours after birth compared to normal births (Kovács *et al.*, 2021; Arfuso *et al.*, 2023). Kovács *et al.* (2021) suggest that high cortisol concentrations at birth could increase susceptibility to bacterial infection in calves. In other species, such as humans, stress exposure in preterm infants has been observed to significantly affect the presence and relative abundance of *Proteus* and *Veillonella* in the intestinal tract, with higher stress exposure increasing the abundance of both families (D'Agata *et al.*, 2019).

The gestational environment can influence the success of the newborn calf in its development and growth, affecting intestinal maturation (Abuelo, 2020). Human research has examined the impact maternal stress, anxiety and depression has on the faecal microbiome in infants (Galley *et al.*, 2023). Infants of mothers who reported higher anxiety and stress had a reduced alpha diversity and reductions in beneficial bacteria essential for health and intestinal modulation (such as *Bifidobacterium*, *Lactobacillus* and *Streptococcus*) in the faecal microbiome (Galley *et al.*, 2023). Within cattle, heat stress has been the primary focus of maternal physiological stress on newborn development. Dado-Senn *et al.* (2020), examined the long-term effects of late gestation prenatal heat stress on growth and productivity in the dairy calf. Prenatal cooling was found to increase birth weight and average daily liveweight gain compared to prenatal heat-stressed calves. Postnatal cooled calves were found to have reduced fever and infection, with less medication events compared to postnatal heat-stressed calves (Dado-Senn *et al.*, 2020). These findings suggest that providing a cool environment for dams and calves pre- and post-birth might support the development of intestinal maturation, which could lead to greater nutrition utilisation and supporting immunity, potentially through the adequate development of intestinal microbiota. Although these results provide a promising insight into strategies supporting newborn calf health and development, further exploration is needed to assess the extent of these effects on postnatal intestinal maturation and function.

6.2 Preweaning diet

In pre-weaned calves on a milk-based diet, the small and large intestines are critical for digestion (Castro *et al.*, 2016). Concurrent with physiological adaptations and changes within the forestomach system during early life, the development of microbial compositions in the intestine of pre-weaned calves is driven by rearing factors such as age, diet and environment (Malmuthuge & Guan, 2017; O'Hara *et al.*, 2020). Typically, a gradual change from a liquid diet (milk or milk replacer) to solid feed (concentrate and forage) occurs within eight weeks of life (Khan *et al.*, 2016). This shift in nutritional sources also results in prominent effects on the calf intestinal microbiome. Due to the relative ease of dietary manipulation, several studies have examined the influence of liquid and solid diets of varying nutritional sources on the intestinal bacterial community composition in the neonatal calf. These have included assessments of whole (Fouladgar *et al.*, 2016), waste (Deng *et al.*, 2017) or pasteurised milk (Bach *et al.*, 2017), milk replacer (Amado *et al.*, 2019), calf concentrate and forage quality (Aragona *et al.*, 2020; Hartinger *et al.*, 2022).

Feeding colostrum is essential soon after birth to establish immune protection within the calf via colostrum-associated immunoglobulins (Mann *et al.*, 2020). Feeding colostrum supports the development and function of the intestinal tract (Hammon *et al.*, 2020), promotes beneficial microbial colonisation (Fischer *et al.*, 2018) and inhibits the growth of pathogens, ensuring a reduced risk of diarrhoea and supporting calf health (Malmuthuge *et al.*, 2015; Hammon *et al.*, 2020). In humans, a high abundance of *Lactobacillus* and *Bifidobacterium* in infants resulted in increased protection against enteric infection (Menchetti *et al.*, 2016). Due to calves being immunodeficient at birth, the appropriate management of colostrum to ensure minimal microbial contamination is important (Barry *et al.*, 2019). Heat-treated colostrum has been shown to inhibit pathogenic *Escherichia coli* and *Shigella*, while increasing the growth of beneficial microorganisms such as *Bifidobacterium* (Fischer *et al.*, 2018; Song *et al.*, 2019). Colostrum is a key microbiome inoculation source, as it shares abundant bacteria with calf faeces within the first 24 hours of life (Cunningham *et al.*, 2018), contributing to bacterial colonisation of the intestinal tract. Using quantitative real time-PCR, Malmuthuge *et al.* (2015) found calves that did not receive colostrum had a reduced bacterial density within the jejunum and ileum of the small intestine after 12 hours post-birth in comparison to calves that received colostrum after birth (10^8 16S rRNA genes/g and 10^{10} 16S rRNA genes/g respectively).

Proteobacteria are a dominant phylum of the faecal microbiome within the first few days of life while calves are being fed colostrum (Klein-Jöbstl *et al.*, 2019). Shifting the diet from colostrum to milk or milk replacer increases the abundance of lactose-utilising bacteria such as *Lactobacillus* and *Bacteroides* across the small and large intestine (Ma *et al.*, 2019; Song *et al.*, 2021). Furthermore, as the calf continues to consume milk, from two weeks of age *Ruminococcus* increases in relative abundance in the faeces of calves (Meale *et al.*, 2016; Malmuthuge *et al.*, 2019), which suggests cellulolytic bacteria use milk (specifically volatile fatty acids) as a substrate while calves transition to consumption of solid feed through to weaning (Wei *et al.*, 2023). Similarly, high numbers of *Prevotella* and *Faecalibacterium* groups were found in faecal samples from one to three-week-old calves fed milk replacer, with feeding strategy (milk replacer allowances of 10%, 20% *or ad libitum*) resulting in increased bacterial diversity as milk replacer intake increased (Alipour *et al.*, 2018; Kumar *et al.*, 2021b). Collectively, this demonstrates that both feed and feeding strategies in early life influence microbiome composition in pre-weaned calves by providing different nutritional sources for bacterial growth.

Water intake has also been observed to impact the intestinal microbial composition. Calves that had access to drinking water immediately after birth demonstrated an increase of *Faecalibacterium*, *Bacteroides* and *Bifidobacterium* in faecal samples (Wickramasinghe *et al.*, 2020). Calves consuming water demonstrated greater feed efficiency, specifically fibre digestibility, and increased daily liveweight gain compared to calves that consumed water after two weeks of age (Wickramasinghe, Kramer & Appuhamy, 2019). This is potentially due to water stimulating rumen and intestinal development, modulating microbial composition, thus increasing nutrient utilisation.

As the calf consumes more solid feed after birth, the abundance of proteobacteria in the faecal microbiome decreases while the abundance of Bacteroidetes increases (Kim *et al.*, 2021a). In the lower gut microbiome (jejunum, caecum and colon), *Lactobacillus* and *Faecalibacterium* decreases*,* and there is an increase in the relative abundance of amylolytic and fibrolytic bacteria such as *Prevotellaceae* during this time (Guzman *et al.*, 2015; Dill-Mcfarland, Beaker & Suen, 2017; Dias *et al.*, 2018). Hartinger *et al.* (2022), identified that carbohydrate composition in the form of calf concentrate was the most influential dietary inclusion on the establishment of distinct niche-specific ruminal and faecal microbial communities. The findings revealed two faecal enterotypes that were diet-dependent: *Prevotella*, *Succinivibrio* and *Anaerovibrio* were associated with concentrate-supplemented animals; whereas animals without concentrate were dominated by fibrolytic *Ruminococcaceae*. An important factor to consider is the health implications of these dynamic changes. For example, higher prevalence of *Prevotella* and *Ruminococcaceae* have been associated with calf faecal microbiome profiles from apparently healthy animals for the prevention of calf diarrhoea (Ma *et al.*, 2020; Chen *et al.*, 2022). However, the exact health impact these enterotypes may have remains unclear.

6.3 Housing

The selection and implementation of different calf housing systems have been seen to influence calf health and growth (Brown *et al.*, 2021). Weaning stress was reduced as a consequence of grouping calves early in life, from five days of age (Vieira, Von Keyserlingk & Weary, 2010; Bolt *et al.*, 2017), and those grouped or paired consumed greater intakes of calf concentrate feed (Overvest, 2018; Liu *et al.*, 2019) with increased growth rates due to social mimicry (Costa *et al.*, 2015; Liu *et al.*, 2019). Group size also appears to influence calf health. According to Svensson & Liberg (2006), calves in pens of 12 to 18 animals had a higher incidence of respiratory illness which impacted growth compared to calves housed in groups of six to nine animals. These results were observed under an automatic milk-feeding system, where close contact via shared feeding equipment likely played a role in transmission of infection (Salem *et al.*, 2019; Zhang *et al.*, 2020). However, evidence suggests that groups of less than 10 calves gives the greatest opportunity to support calf health (Svensson & Liberg, 2006; Liu *et al.*, 2019).

From the perspective of intestinal microbiome development, there is conflicting information regarding the influence individual, paired and group housing environments have on intestinal community composition (Malmuthuge & Guan, 2017; Owen *et al.*, 2021). Zhu *et al.* (2021) reported homogeneity in the faecal microbiota of calves and dams grouped together, whereas Beaver *et al.* (2021) demonstrated only marginal similarities in the faecal microbiome of grouped calves that received maternal contact. In other mammalian species such as humans (Guthrie *et al.*, 2022), chimpanzees (Moeller *et al.*, 2016) and dogs (Song *et al.*, 2013), transmission of intestinal microbiota between individuals has been evidenced. Transition modes influencing intestinal microbiome development are not well understood, but it is hypothesised that shared environments would elicit homogenising effects (Beaver *et al.*, 2021). However, Barden *et al.* (2020) identified no evincible difference in faecal microbiome development between maternally reared and grouped beef calves with dairy calves that were housed individually before being group housed, in groups of six until weaning. Research with broiler chickens found that housing conditions affected the caecal microbiota composition and functionality more than diet intervention (Kers *et al.*, 2019; Ramírez *et al.*, 2020a). The extent to which the environment influences the intestinal microbiota in calves still remains unclear.

6.4 Husbandry practices as potential stress events

Early life stress, such as from environment exposure, can lead to potentially long-lasting health problems (Laporta *et al.*, 2020). While some stressors during life may support adaptation, others may become biologically embedded, potentially altering the future health of the individual (D'Agata *et al.*, 2019). Stress in animals can lead to decreased immune function, altered metabolism (reduced growth and production), altered behaviour, or a combination of these (Endris & Feki, 2021; Niu *et al.*, 2022). All these affect animal health, welfare, and productivity with a concurrent detrimental impact on the livestock industry (Aich *et al.*, 2007; Chen *et al.*, 2015). Dairy calf production systems have several events that have the potential to cause stress, including birth (Nagel, Aurich & Aurich., 2019; Kovács *et al.*, 2021), housing and grouping (Bolt *et al.*, 2017), disbudding practices (Mir *et al.*, 2019), and changing diets through weaning (Meale *et al.*, 2016; Meale *et al.*, 2017; Dill-McFarland *et al.*, 2019).

Acute stress experiences can alter eating habits, reducing dry matter intake, and changing the rate of carbohydrate metabolism, which potentially results in hypoglycemia and increased glucose disposal rates (Fisher *et al.*, 2001; Baumgard *et al.*, 2011). The effects of acute stress on the intestinal microbiota can be due to these behavioural and dietary changes (Rajoka *et al.*, 2017; Kraïmi *et al.*, 2019). Therefore, stress and factors such as diet, current intestinal microbiome structure, host genotype, and environment can influence the composition of the microbiota resulting in adverse effects on nutrient acquisition, metabolism, host immunity and disease resistance (Deng *et al.*, 2017; Chen *et al.*, 2018; Rea, Dinan & Cryan, 2019; Liu *et al.*, 2021).

6.4.1 Disbudding

Dairy calves in the UK, Europe, America, and other developed countries are disbudded or dehorned as horned animals pose a risk to human and animal health and safety, and to ease management (Kling-Eveillard *et al.*, 2015). For example, cattle with horns have an increased risk of causing injury to handlers and herd mates either through accidental interactions or because of aggressive behaviour (Kling-Eveillard *et al.*, 2015; Knierim, Irrgang & Roth, 2015). Disbudding involves the removal of horn germinal tissue in young calves to prevent horn growth, while dehorning involves the amputation of the horn. Disbudding or dehorning can be performed using either chemical action (sodium or calcium hydroxide), amputation (guillotine or scoop) or hot iron (cauterisation) (Marquette, Ronan & Earley, 2023). The age at which this procedure is conducted and whether local anaesthetic is provided will influence the amount of pain and discomfort the animal experiences (Costa *et al.*, 2019; Steagall *et al.*, 2021). In the UK, under the Protection of Animals (Anaesthetics) Act 1954, it is an offense to disbud a calf or dehorn a cow without anaesthetic unless performing chemical cauterisation within the first week of life. The pain associated with disbudding when calves receive no form of pain relief, was observed to have a negative impact on growth rates in three to six-week-old calves (Bates *et al.*, 2016). Although pain relief was not administered to these animals during the study, there is a clear link between pain and this management experience, with growth and development (Marti *et al.*, 2017).

Mir *et al.* (2019) identified that disbudding stress reduced microbial diversity of the intestinal microbiota, using the assessment of faecal samples. Lighter-weight calves (those that weighed less than 68kg at the time of disbudding) were found to display a more pronounced microbiota reduction and had a more significant reduction in their Firmicute to Bacteroidete ratio when exposed to stress (Mir *et al* 2019; Table 1). These bacteria have previously been reported to indicate dysbiosis of the intestinal microbiome (Auffret *et al.*, 2017). Although a reduction in Firmicute to Bacteroidete ratio was also observed in heavy-weight calves, the reduction was significantly more pronounced in the lighter-weight calves (Mir *et al.*, 2019). Furthermore, light-weight calves had higher relative abundances of faecal bacterial families such as *Erysipelotricheae* and *Verrucomicrobiaceae*, while heavyweight calves had a higher relative abundance of *Elucimicrobiaceae* and *Turibacteriaceae* (Mir *et al.*, 2019). The specific role of these within the intestinal microbiome remains unclear, but members of the *Erysipelotrichaceae* family are thought to be highly immunogenic, potentially having an influence on immune function within the intestinal tract (Matthews *et al.*, 2023). This highlights the need to understand the impact management events and procedures have on calf health and intestinal microbiome development (Malmuthuge & Guan, 2017).

6.4.3 Weaning

Weaning strategy and weaning age can influence the success of dietary changes in a calf. Abrupt weaning practices can reduce solid feed intake and average daily weight gain (Schwarzkopf *et al.*, 2019; Scoley, Gordon & Morrison, 2019). However, the influence of either an abrupt or a gradual weaning strategy on intestinal microbial communities showed no significant effect (Meale *et al.*, 2016; Li *et al.*, 2018). Thus, the age at which weaning takes place is likely more influential in ensuring calf readiness for the transition than the strategy itself (Amin *et al.*, 2023). Weaning calves after eight weeks of age improved average daily gains (Mao *et al.*, 2017) and rumen enzyme activity due to an increase in solid feed intake, compared to those weaning more naturally but later in life at 34 weeks (Mao *et al.*, 2017; Hao *et al.*, 2021). When calves were weaned at six weeks of age, a sudden change in β-diversity and evenness of their faecal microbiota from a pre- to post-weaned state was observed, which was not observed in calves weaning at a later age of eight weeks. Coupled with observed reductions in growth rates (Eckert *et al.*, 2015; Meale *et al.*, 2016; Li *et al.*, 2018), suggesting pre-mature intestinal development at the time of weaning. Weaning encourages the increased consumption of concentrate feed and forage by the calf, which alters the microbial composition of the intestinal tract. The faecal microbiome transitions to an increased number of Bacteroidetes, with a decrease in Firmicutes which up until weaning were a dominant phylum (Amin *et al.*, 2023).

In the faecal microbiome, *Prevotella* was positively correlated with concentrate intake, and the abundance of species such as *Prevotella*, *Ruminococcus* and *Blautia* were positively correlated with average daily gain in calves weaned at 17 weeks of age (Meale *et al.*, 2017; Amin *et al.*, 2023). The likely increase of *Prevotella* and *Ruminococcus* species is due to their cellulolytic capabilities, which is reflective of activity identified within the maturing intestinal microbiome (Meale *et al.*, 2016; Wang *et al.*, 2019). Faecal microbiome changes are likely due to the transition from intestinal to rumen fermentation post-weaning (Meale *et al.*, 2017) and demonstrates how solid feed intake alters the intestinal microbiome to resemble that of the mature animal.

The behaviour and stress response at weaning may influence calf immunity because of intestinal microbiome disruption (Upadhaya & Kim, 2021; Welch *et al.*, 2022). Generally, the calf's readiness for weaning is not measured by its consumption of concentrate feed or intestinal microbiome development, but instead by its age and/or its body weight (Welk, Neave & Jensen, 2024). Age has been shown to be a predictor of successful weaning transition, with weaning at a later age (after eight weeks) demonstrating beneficial effects on the microbiota that can quickly adapt to dietary changes (Amin *et al.*, 2023; Welk, Neave & Jensen, 2024; Table 1). A review by Whalin, Weary & Von Keyserlingk (2021), reported that gradual or late weaning mimicked the natural behaviour of a calf as it ages, culminating when the calf is seven to 14 months old. The practical application of this timeframe within dairy calf rearing systems is challenging, but it should provide some consideration for age of weaning to ensure calf preparedness to reduce drastic community shifts in the intestinal microbiome (Guo *et al.*, 2021). Weaning practices are likely to present different experiences and severity of stressors for individual calves, as well as for those being weaned from milk or milk replacer feeding systems or from their dams (Hulbert & Moisá, 2016).

7.0 Potential strategies to support dairy calf microbiome development

Livestock species are often subject to management and environmental stressors that can result in an imbalance in GIT microbiota homeostasis (O'Callaghan *et al.*, 2016). If dysbiosis occurs at a young age, changes in key commensal and health conferring intestinal bacteria such as *Lactobacillus* (Fan *et al.*, 2021), *Faecalibacterium* (Oikonomou *et al.*, 2013) and *Bifidobacteria* (Vlková, Trojanová & Rada, 2006) impact calf health and growth. An awareness of the possibility of this disruption occurring because of management interactions as part of the calf rearing system is essential to provide the opportunity to apply interventions prior to these experiences to support calf health.

7.1 Probiotic supplementation

A common additive to calf milk replacer that would provide some buffering towards intestinal microbiome community disruptions are probiotics (Stefańska *et al.*, 2021). Probiotics are live organisms that can provide the host with health benefits via supporting digestive processes and pathogen defence, if administered in adequate amounts (O'Callaghan *et al.*, 2016; JinQiang *et al.*, 2018). Probiotics have been identified as an alternative treatment to maintain and support GIT homeostasis (Fan *et al.*, 2021). Within the UK, probiotic products aimed at young ruminants primarily contain bacterial species such as *Bifidobacterium*, *Lactobacillus* and *Enterococcus faecium* or live yeast strains like *Saccharomyces*, which have all been shown to have some conferring health benefits to the calf (Zábranský *et al.*, 2022; Maâmouri & Salem, 2022).

Initially, probiotics were investigated as alternatives to some antibiotic usage in livestock, particularly in place of growth promoters (Cheng *et al.*, 2014; Grant, Gay & Lillehoj, 2018). In the past 10-15 years, growth promoter use has been restricted or banned in the UK (but still in use in many nations) due to concerns of increasing antibiotic resistance and food safety (O'Callaghan *et al.*, 2016). As a result of changing antibiotic regulation and increased understanding of the influence of probiotic supplementation, there has been a marked increase in probiotic use in farm and domestic animals in the past 20 years (Chaucheyras-Durand & Durand, 2010; Yeoman & White, 2014). The use of probiotics to support ruminant health during the pre-weaning period and stressful experiences have demonstrated some beneficial effects, through the stimulation of beneficial microbiota, supporting mucosal immunity, preventing enteric pathogens from colonising, controlling pH, and increasing digestion (Uyeno, Shigemori & Shimosato, 2015).

Calf diarrhoea as a health challenge in young ruminants can be caused by a variety of infectious and non-infectious factors (Whon *et al.*, 2021). Due to this, the administration of antibiotics is used as a treatment option to control the potential pathogen proliferation that may be occurring within the calf intestinal tract. The effectiveness of this treatment method is questionable (Kim *et al.*, 2021a) due to the variety of causative agents and the likely use of broad-spectrum antibiotics. Eibl *et al.* (2021) found farmers and veterinarians from Scotland (as a representative country of the UK) and Portugal, used antibiotics for the treatment of neonatal calf diarrhoea significantly more frequently (always: 46%, n = 78; in some situations: 54%, n = 92) compared to other European countries (Austria and Belgium; always: 20%, n = 46; in some situations: 80%, n = 188). The more frequent use of antibiotics could be a result of untargeted approaches toward the treatment of calf diarrhoea and would negatively affect the intestinal microbiome composition, impacting beneficial bacterial populations and potentially increasing antibiotic resistance (Ramírez *et al.*, 2020b: Ali *et al.*, 2021).

Studies have examined probiotic usage to reduce diarrhoea in calves (Renaud *et al.*, 2019; Kayasaki *et al.*, 2021). One of the most common probiotics administered to ruminants includes live yeasts, particularly those containing *S. cerevisiae*. Several beneficial effects have been seen in animals supplemented with live yeast, these include increased performance markers such as growth, dry matter intake and milk production in beef and dairy cattle (Maâmouri & Salem, 2022; Zhang *et al.*, 2022). A reduction in diarrhoea was observed in calves fed milk containing *S. cerevisiae NCDC49* or *L. acidophilus-15* (Renaud *et al.*, 2019; Kumar *et al.*, 2021a). Similarly, a marked improvement in the severity (and prevention) of diarrhoea was observed in neonatal calves administered *E. coli Nissle 1917* (Von Buenau *et al.*, 2005).

7.2 Faecal microbiota transplantation

A novel strategy for supporting and promoting intestinal microbiome development towards that of an adult community structure is faecal microbiota transplantation (FMT). This method requires the transfer of faecal material from a healthy donor into the GIT of a recipient to inoculate the intestinal area with suitable commensal microorganisms (Rosa *et al.*, 2021). Recently, the efficacy of FMT for the treatment of calf diarrhoea has been confirmed (Kim *et al.*, 2021b). Studies have shown a decrease in the occurrence of diarrhoea for calves that have undergone FMT treatment, with an observed intestinal shift from an imbalanced microbiome to a symbiotic state (Kim *et al.*, 2021b; Islam *et al.*, 2022; Li *et al.*, 2023). The resulting intestinal community composition resembles that of the healthy donor after FMT treatment (Kim *et al.*, 2021b).

Although the findings in this area are promising in supporting microbiome establishment and calf health, the effects of FMT as a treatment for potential intestinal microbiome dysbiosis remains a challenge due to the inappropriate selection of donors and corresponding recipients. For FMT to be successful, intestinal microbiota compositions of donor and recipient need to have a degree of similarity. The intestinal microbiome structures vary even within healthy populations as a result of factors such as farm management, environmental conditions, and calf age (Gómez *et al.*, 2017). These aspects may increase the failure of FMT and impact the repeatability of research in practice.

7.3 Microbiome tracking

Similar to production measurements routinely collected such as feed intake and body weight tracking to assess the health and development of the calf, routine intestinal microbiome community measures could be a novel and potentially powerful tool in supporting calf health and welfare in a more individualised and targeted manner. According to a review conducted by Allaband *et al.* (2019), this is a strategy of interest for clinicians in human medicine due to the understanding of the importance of the intestinal microbiome in human health and disease. Additionally, intestinal microbial profiling has been identified to be paramount in monitoring livestock health to allow the appropriate implementation of interventions or treatments to support intestinal microbiome health and prevent the establishment of pathogens (Valerio *et al.*, 2019; Chen *et al.*, 2021).

Production systems could identify those individuals with intestinal microbiome communities that confer resilience and contain a wide diversity of commensal beneficial bacterial populations (Weimer, 2015; Forcina *et al.*, 2022). These characteristics could be tracked across the herd and within genetic lineages to assess the influence of these factors and how the microbiome community composition relates to production, health and reproductive success (Welch *et al.*, 2022). Faecal samples would provide an efficient and non-invasive means of analysing these aspects, which could be collected individually or pooled to provide an overview of intestinal microbiota within different cohorts of calves (Mott *et al.*, 2022; Monteiro *et al.*, 2022). The results could be compared to other production measures already tracked on farm (e.g. feed, body weight, health) to provide a much more detailed picture of calf development, suitability of management and husbandry practices, and likely success of the calf in production as a future milk producing cow.

If this strategy was implemented on a national or international scale, the data provided along with measures already tracked on farm would propel ruminant livestock microbiome research and the applications to industry far beyond any other animal group. It would demonstrate the livestock industry as pioneers in the advancement of animal health and welfare as well as financially benefit the farming community through targeted management practices. The microbiome measures utilised to assess health, and welfare could also provide greater detail and insight into the suitability of farm management standards to inform food standard assessments initiatives.

This strategy is not without its challenges. Within ruminant microbiome research, there are still considerable gaps in the knowledge. This is partly due to the large number of published studies that contain small sample sizes (Owens *et al.*, 2021; Slanzon *et al.*, 2022), resulting in challenges in generalising these results to the wider population of dairy cows and large-scale livestock production systems; where differences in aspects such as genetic diversity, management, and husbandry would need to be considered. Intestinal microbiome tracking as a strategy to support dairy cattle health would only be possible if a coordinated effort was made across large-scale livestock producers for nationwide monitoring of microbiome data alongside other production measures where this data might be extracted and analysed to create guidance on its use.

8. Conclusion

The colonisation of the intestinal microbiota in calves in early life has attracted much attention due to a growing body of evidence of its impact on calf health, development and influence on health and welfare throughout the animal's lifetime. The composition and diversity of the intestinal microbiota vary with age, diet, environment, and husbandry practices that may elicit a stress response. The evidence provided within published work establishes the potential detrimental effect that sudden changes and stress may have on calf health and growth due to management and husbandry practices, and the importance of establishing a stable yet diverse intestinal microbiome population at an early age is essential for calf success. However, the specific relationship that developmental markers such as rearing systems and husbandry practices have with calf intestinal microbiome development linked to the health, growth and performance of the animal in production remains unclear.

Research should focus on tracking microbiome development from birth through to the weaning period, with consideration of the main variables that are included within the calf-rearing system (individual/group housing, disbudding, weaning etc.) and should factor in calf development with other measures of health and performance (feed intake and daily live-weight gain). This would provide a holistic approach to calf rearing, supporting targeted neonatal interventions and informed calf management practices.

Ensuring the application of this informed approach within the dairy industry will require an understanding of how calf intestinal microbiome development influences the composition of the adult microbial community and the effects of these outcomes on health, reproduction, and milk production parameters within dairy production systems. A longitudinal approach to the tracking of intestinal microbiome development would ensure research can be used to provide the opportunity for an informed and targeted approach to calf health and welfare interventions to support the success of dairy cows throughout their productive life. Such an approach has the potential to be of considerable economic value to this livestock production industry.

9. Author statements

9.1 Author contributions

A.C & L.W conceived the review, A.C led its drafting, and managed the editing of the document. All authors contributed to the drafting of the review and approved the final manuscript.

9.2 Conflicts of interest

The authors declare that there are no conflicts of interest.

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