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NUTRITION: *Invited Review*

INVITED REVIEW: Strategic use of microbial-based probiotics and prebiotics in dairy calf rearing

L. R. Cangiano,[1]* T. T. Yohe,[1]* M. A. Steele,[1]† and D. L. Renaud[2]†
[1]Department of Animal Biosciences, Animal Science and Nutrition, University of Guelph, Guelph, Ontario, Canada N1G 1Y2; and [2]Department of Population Medicine, University of Guelph, Guelph, Ontario, Canada, N1G 2W1

ABSTRACT

Purpose: The objective of this narrative review was to describe the effect of microbial-based products, specifically pro- and prebiotics, on gut health, function, and disease prevention during early life and at weaning in dairy calves.

Sources: The main source of data and information compiled for this review was peer-reviewed literature.

Synthesis: Diarrhea is responsible for the majority of mortality and morbidity early in life. Pro- and prebiotics have recently been explored as mechanisms to promote gut health and decrease diarrhea in young calves. In addition, the change in calf diet, where there is a transition from a predominantly milk diet to a solid diet in a relatively short period of time, may also provide an opportunity to use microbial-based products.

Conclusions and Applications: Based on the current studies that have supplemented calves with pro- and prebiotics, the majority of responses in growth, feed efficiency, and health have either been nonsignificant (39/68, 32/70, and 15/68, respectively) or positive (22/68, 9/70, and 31/68, respectively). The results presented in this review highlight that health and growth were the most positively affected responses to supplementation and that most of the beneficial effects were observed when these products were supplemented during a bout of illness. It appears that pro- and prebiotic supplementation to calves is low risk with potentially positive benefits that are worthy of further investigation. Supplementation of pro- and prebiotics to young ruminants requires further investigation to better understand the underlying mechanisms responsible for the phenotypical responses observed to implement better supplementation strategies.

Key words: calf growth, calf health, antimicrobial, gut development

INTRODUCTION

Female dairy calves are crucial to the dairy herd and should be reared in a way that maintains good health, welfare, and the ability to produce milk. Similarly, for male dairy calves, opportunities to maximize growth and minimize health challenges are essential. Despite their undoubted importance, significant challenges remain around safely and effectively rearing male and female dairy calves. It is estimated that 5 to 6% of female dairy calves die during the preweaning period on farms in Canada and the United States (Urie et al., 2018; Winder et al., 2018a). Moreover, an estimated 33% of female dairy calves are treated once during the preweaning period on farms in the United States (Urie et al., 2018). Male dairy calves face even greater health disorders and diseases, with 4.3 to 9.6% of calves dying on veal farms in Canada and the United States (Pempek et al., 2017; Renaud et al., 2018), and 25 to 87% of calves treated at least once for disease on veal farms in Belgium and Canada (Pardon et al., 2012; Scott et al., 2019). Clearly, as mortality and morbidity are used as markers of welfare (Ortiz-Pelaez et al., 2008), there is a significant need to address these challenges to protect the long-term sustainability of the dairy, and associated, industries.

The high diarrhea incidence in calves is an area of concern that should be addressed immediately, as this disease is responsible for the majority of calf mortality and morbidity early in life (Urie et al., 2018; Scott et al., 2019). Diarrhea prevention should be emphasized, as calves that require treatment for diarrhea experience reduced growth, increased risk of mortality, increased age at first calving, and reduced first lactation milk production (Waltner-Toews et al., 1986; Svensson and Hultgren, 2008; Windeyer et al., 2014). Traditionally, oral antimicrobials are used to prevent diarrhea; however, the demonstrated variable efficacy of oral antimicrobials and concerns surrounding antimicrobial resistance make this an unsustainable option (Smith, 2015). Hence, alternative measures should be sought to combat this disease.

The past decade has been marked by great advances in our understanding of how the gut microbiota can affect

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*L. Rostoll Cangiano and T. T. Yohe contributed equally to this work.

†Corresponding authors: renaudd@uoguelph.ca and masteele@uoguelph.ca

gut health and disease. It is now becoming clear that the gut microbial community interacts closely with the host to influence intestinal physiology and the development of the immune system (Mazmanian et al., 2005; Peterson et al., 2007). The presence of specific bacteria with health outcomes are commonly reported in young mammal gastrointestinal research. For example, the prevalence of fecal *Bifidobacterium* and *Lactobacillus* has been shown to be a reliable indicator of infant gut health (Yoshioka et al., 1983; Harmsen et al., 2000). Similar microbial biomarkers have been uncovered in calves, namely the prevalence of *Faecalibacterium* in feces, which resulted in reduced diarrhea incidences and increased BW gains during the first weeks of life (Oikonomou et al., 2013). In addition, *Bifidobacterium*, and several genera from the *Bifidobacteriaceae* family, have been found to be more prevalent in healthy Holstein calves compared with diarrheic calves (Gomez et al., 2017). The factors that can alter the gut microbial community in the early life of the calf to benefit health are of great interest. The external factors that have been shown to induce these changes include diet, maternal factors, environment, and antibiotic treatment (Malmuthuge et al., 2015b). However, it is important to note that the host—especially the immune defense of the host—plays a substantial role in sculpting the gut microbiota and adaptive responses to gut health challenges and, thus, should not be overlooked.

Although there is a paucity of information about microbial colonization during the birthing process, there has been some characterization of how colostrum, milk, and solid feed affect the gut microbiota of calves. Malmuthuge et al. (2015a) noted that colostrum accelerates bacterial colonization in the small intestine. Delaying colostrum feeding by 12 h has been shown to reduce the prevalence of *Bifidobacteria* and *Lactobacillus* (beneficial bacteria) in the colon of dairy calves (Fischer et al., 2018). After colostrum feeding, during the preweaning period, milk accounts for a large proportion of bacterial substrates provided in the diet, and as such, the source of milk provided can alter bacterial colonization. Specifically, when calves are fed waste milk, which may contain residual levels of antimicrobials, lower levels of *Clostridales* and *Bacteroidales* are found in the feces, and gut microbial imbalances occur more often (Maynou et al., 2016; Van Vleck Pereira et al., 2016). The transition from milk feeding to solid feed during weaning is marked by some of the most dramatic anatomic and metabolic adaptations (Baldwin et al., 2004) in addition to large changes in the gut microbiome. In the case of the rumen, bacteria belonging to the *Bacteroidetes* phylum decreased and bacteria belonging to *Proteobacteria* and *Firmicutes* increased during weaning, demonstrating the effect that the solid feed transition can exert on the rumen microbiome (Li et al., 2012; Meale et al., 2017).

It has been widely characterized in infants and laboratory animals that the gut microbiome has greater plasticity in early life and microbial exposure and perturbations can have consequences related to health and development later in life. The same is thought to occur in calves, as the supplementation of prebiotics (Marquez, 2014) and probiotics (Abe et al., 1995) exert the greatest effects in the first weeks of life. This could be directly related to the instability of their microbial communities, whereas later in life the microbiome is stable and more difficult to influence (Malmuthuge et al., 2015b). Hence, manipulating the gut microbiome, which is a key factor influencing gut health (Bischoff, 2011), early in life could become an option to improve calf health through the use of microbial-based products (Malmuthuge and Guan, 2017). Specifically, pro- and prebiotics have recently been explored to promote gut health and decrease diarrhea in young calves. In addition, the change in calf diet, where there is a transition from a predominantly milk diet to a solid diet composed of rapidly fermentable carbohydrates, may also provide an opportunity to use microbial-based products. This strategy could aid in mitigating exposure of the developing rumen to harsh conditions and may help to prevent calves from experiencing events that negatively affect health and growth during and after weaning.

The objective of this narrative review is to describe the effect of microbial-based products, specifically pro- and prebiotics, on gut health, function, and disease prevention during early life and at weaning in dairy calves.

PROBIOTICS

Probiotics are defined as live strains of strictly selected microorganisms which, when administered in adequate amounts, confer a health benefit (e.g., decrease in diarrhea incidence) on the host (Markowiak and Śliżewska, 2017). Probiotics can refer to specific bacterial or fungal strains, microbial cultures, enzyme preparations, culture extracts, or a combination (Yoon and Stern, 1995). Young preruminants can be supplemented with probiotics in milk or starter feed to promote gut health, stimulate earlier solid feed consumption, and improve growth. The most commonly used probiotics fed to young calves are live yeast, mainly *Saccharomyces cerevisiae* (**SC**), yeast cultures of SC (Alugongo et al., 2017), and bacterial-based probiotics, such as *Lactobacillus* spp., *Enterococcus* spp., and *Bacillus* spp. (Uyeno et al., 2015).

Live Yeast and Yeast Culture

Yeast are single-celled microorganisms and members of the fungi kingdom. The most extensively used probiotic strain of yeast for farm animals is SC. There are several yeast products in the market, including live yeast (**LY**) and yeast cultures (**YC**). Live yeast products are fermentable living yeast that have been dried and typically contain at least 10 × 10^9 LY cells per gram, and YC are products of yeast fermentation and include the media they are grown in (AAFCO, 2013). It is important to note that even though YC is classified as a probiotic, it also contains cell-wall components and cell constituents such us β-glucans and oligosaccharides, which are considered prebiotics in nature and possess various biological functions that contribute to the effects exerted by LY (Spring et al., 2000; Davis et al., 2004).

Effects on Growth and Performance

The effects of supplementing LY and YC on DMI are summarized in Table 1, based on a total of 17 studies that measured DMI. Six of the studies showed an increase in starter intake, whereas 11 showed no differences. With respect to growth performance, responses to supplementation follow a similar pattern to that observed for DMI, and the effects are summarized in Figure 1. The inconsistency in growth and DMI response might be attributed to different strains, yeast products (LY or YC), health status of the animals, route of delivery (milk vs. starter feed), or insufficient replicates to show performance responses (Kim et al., 2011).

The most significant effects of supplementation of yeast products during the preweaning phase have been reported when included in the diet of animals during stressful periods, promoting optimal maturation of the rumen microbiota and reducing risk of pathogen colonization (Chaucheyras-Durand and Durand, 2010). Specifically, calves supplemented with a YC in starter (Harris et al., 2017) or milk replacer (**MR**; Brewer et al., 2014) that were orally challenged with S*almonella enterica* had greater starter intake, ADG, and improved fecal consistency than control calves. Furthermore, calves supplemented with *Saccharomyces cerevisiae boulardii* (**SCB**) in MR, a subspecies of SC, had no drop in ADG when experiencing diarrhea compared with control calves that experienced a severe drop in growth performance during a diarrheic episode (Villot et al., 2019). When the same SCB strain was fed to healthy calves, no effects were observed on growth performance (He et al., 2017). In addition, calves with failed transfer of passive immunity supplemented with SC in the starter also had improved performance compared with control calves (Galvão et al., 2005).

Yeast products have been found to aid in preventing microbial imbalances and enhance microbial activity in young ruminants. In a study with gnotobiotic lambs, Chaucheyras-Durand and Fonty (2002) showed that inoculation with SC increased cellulolytic bacteria and fibrolytic enzymes, influenced the establishment of ciliated protozoa in the rumen, reduced lactate synthesis, and enhanced lactate utilization in vitro. This suggests that SC may stabilize rumen pH, an important factor for cellulolytic bacteria to thrive in the early rumen conditions. Several new studies have reinforced the concept that LY and YC supplementation can improve rumen development. Specifically, these studies have found that supplementing YC in MR or starter feed leads to an increase in *Butyrivibrio* and decreased *Prevotella* richness in rumen fluid, which resulted in increased butyrate production, papillae length (Xiao et al., 2016), and rumen weight (Harris et al., 2017). However, others found that the supplementation of YC had no effect on rumen development or rumen pH (Lesmeister et al., 2004; Xiao et al., 2016). The differences observed between studies might be attributed to the type of yeast product fed, LY versus YC. In addition, the starter composition, specifically its fiber content, may influence results because diet composition affects the capacity of yeast products to modify rumen microbiota and, specifically, to stimulate fibrolytic bacteria (Callaway and Martin, 1997). Furthermore, one important factor to consider is the route of delivery of the product because it is more likely to have an effect on rumen function when delivered in the starter, as opposed to milk, which will bypass the rumen into the abomasum (Hill et al., 2009).

Effects on Health

The most consistent response of yeast supplementation is associated with a reduction in the incidence and severity of diarrhea. Calves with failed transfer of passive immunity supplemented with SC had fewer days with diarrhea (Galvão et al., 2005). Furthermore, calves supplemented with YC had better fecal and overall health scores (Magalhães et al., 2008; Kim et al., 2011; Harris et al., 2017), reduced rates of mortality and diarrhea cases, and a tendency to reduce the presence of a fever (Magalhães et al., 2008). In addition, supplementation of SCB in MR was associated with a lower incidence of severe diarrhea and a tendency to reduce antibiotic treatments (Villot et al., 2019). Clearly, these beneficial effects on health result in increased profitability, even without improvements in growth performance, due to a reduction of rearing costs (Magalhães et al., 2008).

Supplementation of YC and LY have been shown to reduce diarrhea by preventing pathogenic bacteria from binding to intestinal epithelial cells or by modulating gut mucosal immunity (Davis et al., 2004; Wang et al., 2008). In addition, supplementation of YC has been shown to improve intestinal development with increased villus height and villus height-to-crypt ratio in all segments of the small intestine (Xiao et al., 2016), and increased villi length and crypt depth in the ileum (Harris et al., 2017). The majority of the gut has only one layer of cells that separates the lumen of the intestine, and supplementation with YC could improve gut barrier integrity, leading to reduced infiltration of toxic luminal antigens and bacteria (Kvidera et al., 2017; Liehr et al., 2017). However, in a recent study conducted by Pisoni and Relling (2020), calves supplemented with YC showed no improvement in gut barrier function, possibly due to high diarrhea incidence during this particular study. Supplementation of SCB to calves from birth to one week of life has recently been shown to enhance production and release of secretory IgA in the ileum and colon with no effects on immune function at the systemic level (Villot et al., 2020). Secretory IgA contributes to the establishment of a healthy microbiota, shaping commensal microbiota, while limiting pathogen growth (Pabst et al., 2016; Mantis et al., 2011).

Table 1. Summary of growth, health, and gut development responses in calf studies utilizing different probiotics based on yeast culture or live yeast

	Effects in response to[2]					
Yeast[1]	**Weight gain**	**Feed efficiency**	**Health**	**Gut development**	**Remark**	**Reference**
YC	++	NS	NS	NS	Fed in starter feed.	Lesmeister et al., 2004
SC	++	NS	++	n/a	Fed in starter. Increased starter intake. Fewer days with diarrhea.	Galvão et al., 2005
YC	NS	NS	n/a	+	Fed in starter feed. Improved rumen development.	Kaldmäe et al., 2008
YC	NS	NS	++	n/a	Fed grain feed. Reduced incidence of diarrhea and mortality rates. Tendency to improve neutrophil function.	Magalhães et al., 2008
SC and SCB	NS	NS	NS	n/a	Oral administration in sterile water twice daily.	Pinos-Rodríguez et al., 2008
LY	NS	NS	++	n/a	LY product fed in starter feed. Improved fecal scores.	Hill et al., 2009
YC	++	NS	n/a	n/a	YC fed in starter feed	Zhou et al., 2009
YC	NS	NS	n/a	+	Fed in starter feed. Improved microbial cellulolytic activity.	Hučko et al., 2009
YC	NS	NS	++	n/a	Fed in starter feed. Improved humoral response to vaccine challenge. Low replication to assess growth performance.	Kim et al., 2011
YC	++	NS	++	++	Fed in both MR[3] and starter. Reduction in diarrhea. Improved rumen development and reduced pathogen intestinal colonization.	Brewer et al., 2014
YC	NS	NS	NS	n/a	SCB yeast culture fed with starter.	Huuskonen and Pesonen, 2015
SCB	NS	NS	NS	n/a	Fed in MR. Low incidence of diarrhea.	He et al., 2017
YC	n/a	n/a	n/a	+++	Fed in starter. Increased rumen papillae length and increased villus height in all segments of the gastrointestinal tract.	Xiao et al., 2016
YC	NS	NS	+	+	Fed in MR or MR and starter. Increased starter intake when fed in both MR and starter.	Harris et al., 2017
SCB	+	NS	++	n/a	Fed in MR. Lower incidence of severe diarrhea, and reduction of diarrhea treatments.	Villot et al., 2019
YC	NS	NS	NS	n/a	Fed in starter. No effects on gut permeability in diarrheic calves.	Pisoni and Relling, 2020

[1] YC = yeast culture; SC = *Saccharomyces cerevisiae*; SCB = *Saccharomyces cerevisiae boulardii*; LY = live yeast.

[2] Either positive (+) or negative (−) effects are noted with magnitude of change explained here: + = $P \geq 0.05$ but ≤0.10, ++ = $P \leq 0.05$, and +++ = $P \leq 0.01$. An NS denotes no change, and an n/a denotes the variable was not measured.

[3] MR = milk replacer.

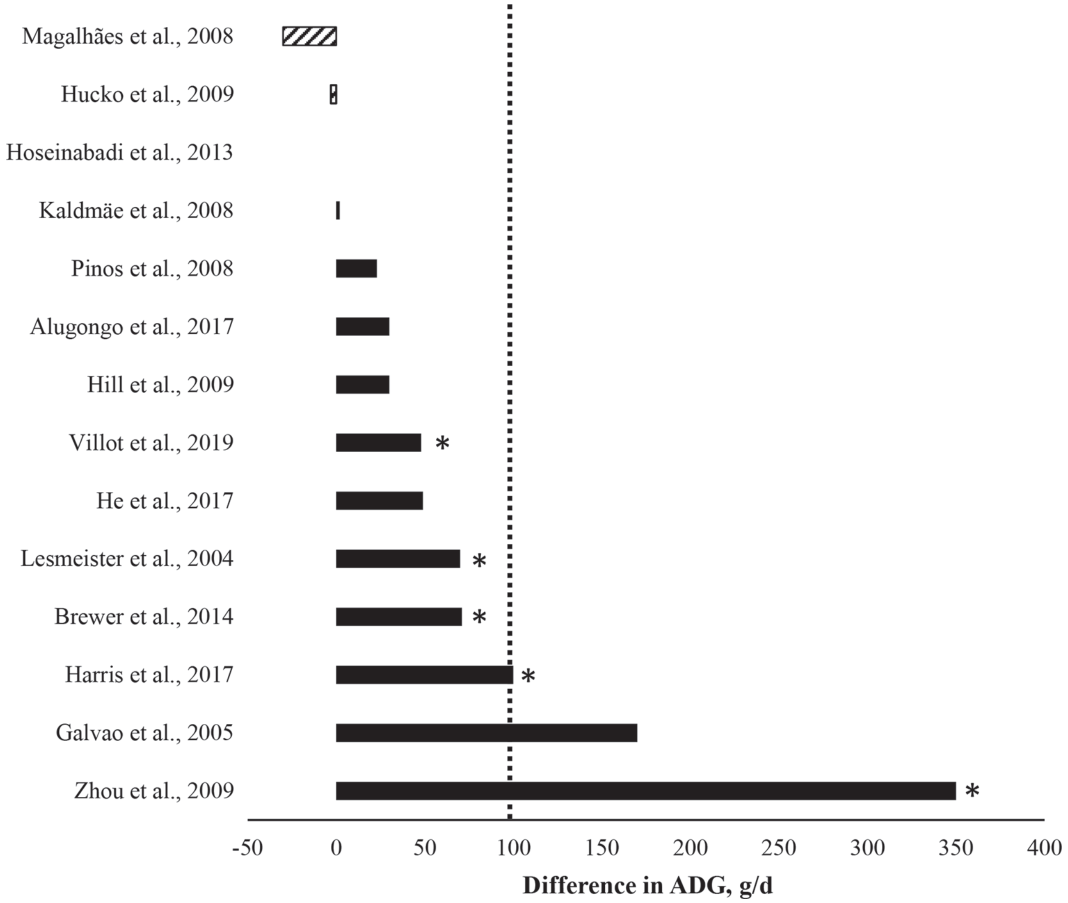

Figure 1. Summary of difference in ADG response between control and yeast-supplemented calves. Significant difference between control and prebiotic-supplemented calves from each study is indicated by * ($P \leq 0.05$), with the average ADG difference across all studies indicated by the dotted line.

In a similar study with veal calves, the supplementation of SCB in milk increased butyric acid–producing bacteria and *Lactobacillus*, along with a reduction of *Colinsella*, a bacterium previously correlated with increased intestinal permeability (Villot et al., 2019). Furthermore, control diarrheic calves tended to have a greater relative abundance of *Escherichia-Shigella*. Last, supplementation of a YC has been shown to affect immune function at a systemic level, with improved humoral responses to a vaccination challenge (Kim et al., 2011) and greater leukocyte counts and leukocyte-to-neutrophil counts following supplementation (Harris et al., 2017). Furthermore, neutrophil function was observed to be slightly improved (Magalhães et al., 2008).

Taken together, supplementation of yeast products has the ability to modulate gut microbial composition and enhance gut humoral immunity, effects that ultimately translate into a reduction in diarrhea and improvements in growth performance (Abu-Tarboush et al., 1996; Villot et al., 2019).

Bacterial-Based Probiotics

Bacterial-based probiotics (**BBP**) are widely used in preweaned calves, mainly to improve gut health, reduce diarrhea, and improve growth (Table 2). Some commonly used BBP bacterium are *Lactobacillus* spp., *Bifidobacterium* spp., *Bacillus* spp., and *Enterococcus* spp. Supplementation of BBP have been shown to limit pathogen invasion by providing a stable, nutrient-rich environment for gut microbiota, thereby enhancing host digestive efficiency and mucosal immunity (Uyeno et al., 2015; Ma et al., 2018).

Effects on Growth and Performance

As observed for yeast supplementation, BBP supplementation resulted in inconsistent growth responses; however, in studies where positive growth responses were observed, this result usually occurred when calves experienced high diarrhea incidences (Timmerman et al., 2005; Frizzo et al., 2010; Zhang et al., 2019; Table 2). Of the 11 studies evaluating the growth performance of BBP supplementation in preweaned calves, 5 showed a significant positive effect on ADG (Figure 2), whereas the remaining studies showed no effect. In a study conducted by Frizzo et al. (2011), supplementation during the preweaning period of a probiotic composed of 3 lactic acid–producing bacteria (**LAB**) strains of bovine origin (*Lactobacillus casei* DSPV 318 T, *Lactobacillus salivarius* DSPV 315 T, and *Pediococcus acidilactici* DSPV 006 T) improved starter

Table 2. Summary of growth, health, and gut development responses in calf studies using different bacteria-based probiotics

	Effects in response to[1]					
Lactic acid–producing bacteria	**Weight gain**	**Feed efficiency**	**Health**	**Gut development**	**Remark**	**Reference**
Multistrain LAB[2]	++	NS	+++	n/a	Four experiments were performed with a multistrain *Lactobacillus* probiotic.	Timmerman et al., 2005
Multistrain LAB	+++	NS	+++	n/a	3 lactic acid–bacteria strains.	Frizzo et al., 2010
Multistrain LAB	NS	NS	NS	n/a	Follow-up study with the same 3 lactic acid bacteria, no effects found.	Frizzo et al., 2011
Multispecies BBP[3]	n/a	n/a	+++	n/a	Meta-analysis composed of 15 different experiments and 965 calves.	Signorini et al., 2012
Multistrain LAB	NS	++	++	n/a	Multispecies probiotic: *Lactobacillus plantarum* + *Bacillus subtilis*.	Zhang et al., 2016
Lactobacillus rhamnosus	+++	NS	++	++	Increase VFA production and microbial diversity.	Zhang et al., 2019
Multispecies BBP	NS	n/a	++	n/a	Multispecies probiotic bolus for the treatment of diarrhea.	Renaud et al., 2019
Multispecies BBP	+++	n/a	n/a	n/a	Multispecies probiotic. 96 heifer calves fed with automated feeder.	Cantor et al., 2019
Multistrain LAB	++	n/a	NS	n/a	Improved final BW.	Bayatkouhsar et al., 2013
Multispecies BBP	n/a	n/a	++	n/a	Improved cellular immunity.	Qadis et al., 2014
Bacillus spp.	n/a	n/a	++	n/a	*Bacillus*-based probiotic provided in electrolytes to scouring calves. Improved cellular and innate immunity.	Novak et al., 2012
Lactobacillus acidophilus	n/a	n/a	n/a	++	Improved gut bacterial community structure, reducing pathogenic load.	Fomenky et al., 2018
Multispecies BBP	++	++	NS	n/a	Improved milk intake, ADG, and feed efficiency.	Soto et al., 2014
Multispecies BBP	NS	NS	NS	n/a		Riddell et al., 2010
Faecalibacterium prausnitzii	++	n/a	++	n/a		Foditsch et al., 2015
Multispecies BBP	NS	NS	++	n/a	Jersey calves challenged with *Salmonella* Typhimurium. Reduction in inflammatory markers.	Liang et al., 2020

[1] Either positive (+) or negative (−) effects are noted with magnitude of change explained here: ++ = $P \leq 0.05$ and +++ = $P \leq 0.01$. An NS denotes no change, and an n/a denotes the variable was not measured.

[2] Multistrain LAB = probiotic consisting of a combination of *Lactobacillus* species.

[3] Multispecies BBP = probiotic consisting of a combination of more than one species of bacteria.

consumption and stimulated earlier starter consumption, resulting in enhanced growth performance. However, in a follow-up study evaluating the same multistrain probiotic, no differences were observed in growth parameters, demonstrating that the effects of probiotic supplementation are highly variable depending on environmental factors, pathogen load, and animal stress (Frizzo et al., 2011). In a multi-experimental study supplementing a combination of 5 *Lactobacillus* strains and *Enterococcus faecium* during the preweaning period, improved growth occurred during the first 2 wk of life, when animals experienced the highest incidence of digestive and respiratory disorders (Timmerman et al., 2005), emphasizing that probiotic supplementation works best during periods of high stress.

Although most have underscored the role of BBP on gut health, some reports have demonstrated an effect on modulation of rumen function. *Lactobacillus rhamnosus* supplementation for 6 wk during the preweaning period resulted in greater microbial diversity in the rumen, altering the dominant bacteria order and relative abundance of bacterial families present in ruminal fluid (Zhang et al., 2019). As a result, total VFA production and microbial protein concentration were increased, and ruminal pH was reduced, compared with control calves. However, it is important to note that the improvements in rumen function might stem from increased starter intake rather than a direct effect of BBP on rumen development.

Effects on Health

In a meta-analysis conducted by Signorini et al. (2012) including 15 trials and 965 calves, supplementation of LAB reduced the relative risk of diarrhea compared with control calves, although significant variability between studies was observed. Most of the variability observed was due to the type of milk fed to calves (whole milk or MR), with most of the positive responses coming from studies where calves were fed whole milk. The variability in response depending on the source of milk might be attributed to difference in pathogen load between MR and whole milk (Selim and Cullor, 1997). In addition, the response was dependent on the type of inoculum, with only multistrain inocula having a positive effect on diarrhea levels.

Some evidence demonstrates that the supplementation of BBP to calves with diarrhea could result in positive effects, as calves dosed with a multispecies bolus of *Pediococcus acidilactici*, *Enterococcus faecium*, *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum* had a faster resolution of diarrhea than calves that only received a placebo (Renaud et al., 2019). Furthermore, Zhang et al. (2019) observed that supplementation of *Lactobacillus rhamnosus* was able to reduce fecal scores in preweaned Holstein calves. Several mechanisms have been proposed to explain the effects of BBP on resolution of diarrhea; however, their mode of action is not fully under-

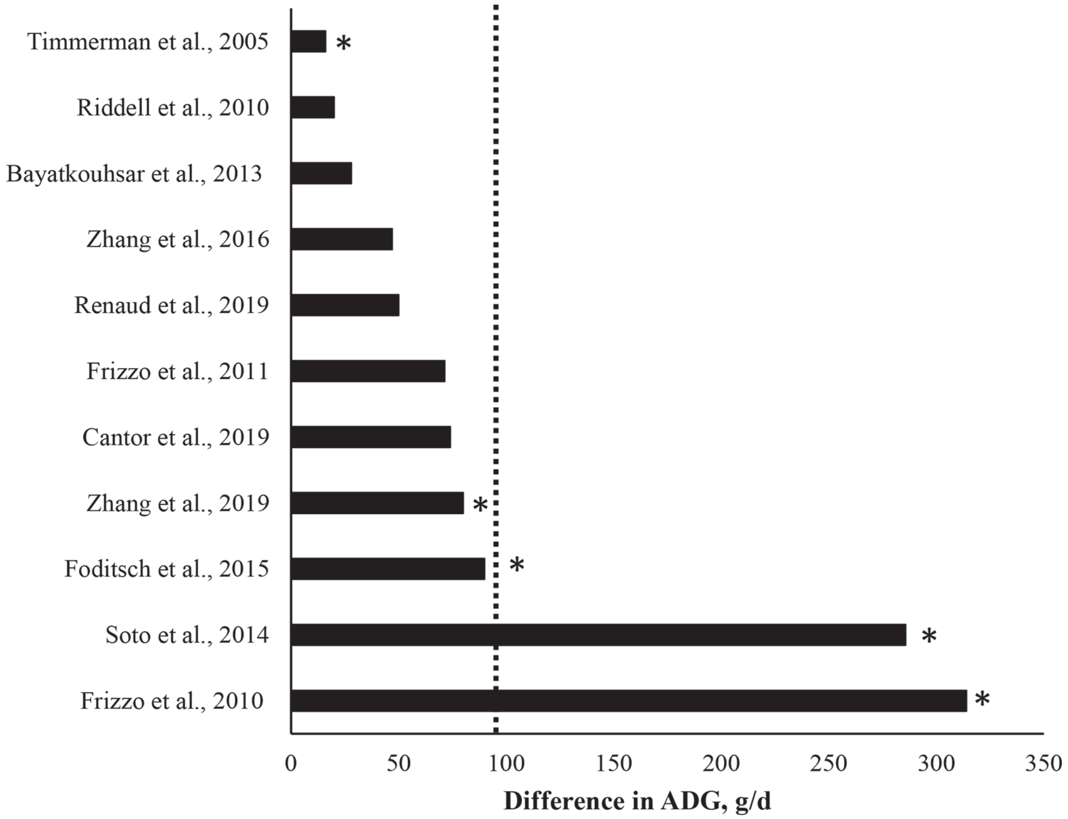

Figure 2. Summary of difference in ADG response between control calves and calves supplemented with lactic acid–producing bacteria. Significant difference between control and prebiotic-supplemented calves from each study is indicated by * ($P \leq 0.05$), with the average ADG difference across all studies indicated by the dotted line.

stood and most of the studies have been conducted with nonruminant animals. Furthermore, many of the effects are dependent on the specific bacterium family and strain used (Newbold et al., 1995), and a combination of different bacteria can result in additive effects. The proposed mechanisms can be divided into 3 main categories: (1) direct interaction with host cells, (2) inhibition of pathogen growth, and (3) modulation of the host immune responses.

Bacteria-based probiotics have been shown to directly interact with the host, modulating the gut immune response, leading to increased mucin production by goblet cells, enhancing barrier function by increasing tight junctions and promoting regulation of the inflammatory response (Aragon et al., 2010; Cazzola et al., 2010; Wang et a., 2019). Lactic acid–producing bacteria can decrease gut pH by production of lactic acid, creating a more favorable condition for commensal microorganisms. Furthermore, BBP can produce and release antimicrobial peptides, such as bacteriocins in the gut lumen, or out-compete pathogens for nutrients or adhesion sites, thereby decreasing the risk of pathogen infections (Isolauri et al., 2001; La Ragione and Woodward, 2003; Servin, 2004). Most of these findings come from monogastric or rodent models but might explain the phenotypic responses observed in LAB-supplemented calves.

Last, the health benefits of LAB supplementation might not be only constrained to the lower gut, as LAB supplementation has been reported to modulate systemic immune function, improving humoral and cell-mediated immunity as indicated by increased T and B cell activity and lower cortisol levels in blood (Qadis et al., 2014; Zhang et al., 2016). In a recent study conducted by Liang et al. (2020), calves challenged with *Salmonella Typhimurium* and fed a BBP blend of *Lactobacillus casei* and *Enterococcus faecium* strains had reductions in blood inflammatory markers and a reduction in rectal temperature when compared with control calves that did not receive the probiotic blend. These results showing that BBP supplementation can affect cell function in distant tissues outside the gastrointestinal tract are promising; however, more studies are required to better understand how probiotic–host interaction at the gut mucosal surface translate into systemic modulation of immune function of the growing calf.

Conclusion

Probiotic supplementation seems to offer some beneficial effects that promote animal growth while reducing digestive disorders. However, we observed significant variability among studies, and it appears that most of the beneficial effects are observed when supplemented during stressful conditions. Part of the variation between studies can be attributed to differences in environmental and management factors between studies such as the type of milk fed (whole milk vs. MR), pasteurization, and the incidence of disease and pathogen load on the farm (Klein-Jöbstl et al., 2014). Furthermore, even if BBP and yeast supplementation had similar effects in terms of diarrhea resolution and growth parameters, the underlying mechanisms of action seem to differ. Further investigation is needed in young ruminants to understand the phenotypical responses observed to better formulate and target probiotic supplementation strategies. Yeast supplementation showed improvements in starter intake, possibly as a function of improved fiber digestion, and mild improvement in rumen development in early life. Furthermore, the route of delivery seems to be critical and most of the effects on starter intake are observed when fed in starter rather than in milk. This suggests that it might be advantageous to include them in feeding programs to promote starter intake, especially when animals are weaned early. In the case of BBP supplementation, most of the effects observed appear to be postruminal, having marked effects on lower gut health and reducing diarrhea cases.

Last, the mode of action of BBP might be species and strain specific; therefore, supplementation of multispecies and multistrain BBP typically result in improved beneficial effects on the host due to a combination of their different effects. Further research is needed to better formulate probiotic products that can harvest the different metabolic activities of multispecies and multistrain probiotics to the benefit of the host.

PREBIOTICS

Prebiotics are defined as substrates that are selectively used by host microorganisms, conferring a health benefit to the host (Markowiak and Śliżewska, 2017). Compared with probiotics, prebiotics are nonviable substrates that serve as nutrients for healthy microbes (e.g., LAB and *Bifidobacteria*) and can be used to defend against pathogens and modulate the immune system (Gibson et al., 2017). In young ruminants, prebiotics have been shown to have effects on growth, feed efficiency (**FE**), and health. The most commonly used prebiotics fed to calves are oligosaccharides (**OS**), which comprise the major prebiotic group, and β-glucans. Unlike probiotics, the mechanisms by which prebiotics exert their effect have been relatively unexplored in ruminant models. However, potential mechanisms have been suggested in monogastrics, including changes in intestinal microbiota, immunomodulation, nutrient absorption effects, and pathogen inhibition (Markowiak and Śliżewska, 2017). It is worth noting that although "prebiotics" has been a term used for the past few decades, the definition of what constitutes a prebiotic has evolved. In recent years, there has been an effort to better characterize metabolites and cell-wall components derived from either living or nonliving microbes with particular interest in the term "postbiotic" (reviewed by Aguilar-Toala et al., 2018). For the sake of clarity and familiarity with the subject, we have decided to use the term "prebiotic" throughout this review with the knowledge that other definitions may also be appropriate for these compounds.

Fructooligosaccharides

Fructooligosaccharides (**FOS**) are a family of OS consisting of one glucose molecule linked to several fructose molecules via β-(2–1) or β-(2–6) bonds. Some variations of FOS include inulin and short-chain FOS (**scFOS**), which are found in vegetables, such as onions and Jerusalem artichokes, or produced via transfructosylation of sucrose via β-fructosidase, respectively (Wang et al., 1999; Singh et al., 2017). The use of FOS as a prebiotic is similar to other prebiotics, as it has been shown to support growth of LAB (Sghir et al., 1998; Menne et al., 2000). However, FOS has the unique ability to prevent the adhesion of *E. coli* and *Salmonella* to the intestinal epithelium (Hartemink et al., 1997; Benyacoub et al., 2008) and has been shown to reduce *E. coli* growth when added to a coculture with LAB (Vongsa et al., 2016).

Effects on Growth and Performance

The effects of supplementing FOS on growth are summarized in Table 3. Four of the 7 studies that measured growth showed an increase in growth, whereas 3 showed no differences (Figure 3). With respect to FE, 2 of the 4 studies measuring FE observed an improvement in calves supplemented with FOS (or a FOS variation) compared with controls, whereas a decrease in FE was also found in another study (Table 3). There is a lack of data throughout these studies measuring the effects of FOS on LAB or other potential beneficial bacteria throughout the gut; however, differing results were found with respect to gut development. Grand et al. (2013) fed scFOS at 6 g/d and found a tendency for increased fecal butyrate concentrations compared with controls, which may be a sign of enhanced gut development (Gorka et al., 2018). Conversely, Masanetz et al. (2010) found tendencies for shorter villi in the jejunum and less proliferation in the ileum of calves supplemented with 2% inulin in their MR, suggesting decreased intestinal development compared with control calves. Interestingly, both Masanetz et al. (2010) and Grand et al. (2013) observed an improvement in FE, which suggests that regardless of gut development, the inclusion of FOS in the diet may allow more energy to be absorbed, contributing to more efficient calf growth.

Effects on Health

Only 2 studies measured the health effects of feeding FOS, with both reporting positive results (Table 3). Quigley et al. (2002), who fed FOS with bovine serum sprayed on MR, reported a tendency for reductions in fecal scores, scouring days, days offering electrolytes, and antibiotic treatments compared with control calves. Pineda et al. (2016) found lower mortality, fewer antibiotic treatments, and lower mean fecal scores in inulin-supplemented compared with control calves. Interestingly, Pineda et al. (2016) also saw a decrease in respiratory scores in inulin-supplemented calves. It is difficult to interpret immune parameter data when it is not coupled with health records; however, 2 studies evaluated the immunity of calves supplemented with FOS. Kaufhold et al. (2000) supplemented FOS in whole milk or MR and observed an increase in total leukocytes during wk 12 and an increase in eosinophils during wk 13 in blood compared with control calves. As recent evidence has demonstrated, eosinophils communicate in both the innate and adaptive immune system (Wen and Rothenberg, 2016); thus, the increase in eosinophils may improve the calf's ability to respond if an infection occurs. Masanetz et al. (2011) found that calves supplemented with 2% inulin had a decreased number of thrombocytes and an increase in the gene *PECAM1*, which is important for transmigration of leukocytes (Wakelin et al., 1996).

The utility of FOS based on the current data seems to support the role of FOS as an effective prebiotic for growth, FE, and health in calves. While certain studies observed no differences, which would suggest utilizing FOS is unnecessary, it is worth noting that the true benefit of FOS (or other prebiotics) may not be recognized until a calf is in a state of distress or illness, which has not been the focus of many studies utilizing FOS in calf diets.

Galactooligosaccharides

Galactooligosaccharides (**GOS**) are created from lactose and contain repeating galactose molecules via β-(1–3) and β-(1–4) linkages. More specifically, GOS are typically created at scale from β-galactosidase–treated whey permeate that has been filtered from whey leftovers during cheese manufacturing (Vera et al., 2016). Galactosyl-lactose (**GL**) is similar to GOS in structure, in that it is a trisaccharide containing 2 galactose and 1 glucose molecule. The usefulness of GOS stems from its similarity to OS found in milk, which has been shown to promote beneficial bacteria in the lower gut (Malmuthuge et al., 2015a), and thus, it is used as a prebiotic in calf diets.

Effects on Growth and Performance

Mixed results on growth and FE were found in the 3 studies that evaluated GOS/GL products. One study found an increase in growth and tendency for improved FE (Quigley et al., 1997), whereas the others found either decreased growth (Castro et al., 2016) or FE (Senevirathne et al., 2019) in supplemented calves (Table 3). Senevirathne et al. (2019) fed a condensed whey soluble (**CWS**) product to calves before and after weaning, which increased di- and oligosaccharide concentrations (including GL), and increased starter and total DMI overall. However, these differences did not translate to higher levels of growth and supplemented calves had reduced FE postweaning. The exact amount of GOS fed in the CWS in Senevirathne et al. (2019) is unclear, but it appears that Quigley et al. (1997) fed the lowest amount of a GOS supplement (GL) at 1% DM of MR, whereas the other studies likely fed the GOS at 3.35% DM or greater, which could indicate that high levels of GOS may have a negative effect on

Table 3. Summary of growth, health, and gut development responses in calf studies using different prebiotic supplements

	Effects in response to[2]					
Prebiotics used[1]	**Weight gain**	**Feed efficiency**	**Health**	**Gut development**	**Remark**	**Reference**
Oligosaccharides						
CO	++	++	NS	n/a	Feed efficiency was improved after weaning.	Hasunuma et al., 2011
CO	NS	n/a	n/a	n/a		Uyeno et al., 2013
CO	+	n/a	n/a	n/a	Beef calves weaned between 3 and 4 mo.	Kido et al., 2019
scFOS	+	n/a	n/a	n/a		Kaufhold et al., 2000
Inulin	+, NS	NS, NS	++, ++	n/a, n/a	2 experiments were performed where FOS was fed in milk replacer.	Quigley et al., 2002
Inulin	NS	+	n/a	–, –	Inulin calves tended to have decreased jejunal villus lengths and proliferative ileal cells.	Masanetz et al., 2010
scFOS	NS	+	n/a	n/a		Grand et al., 2013
Inulin, serum proteins	+	+++, – –	+++	n/a	Feed efficiency was increased in FOS calves in wk 1 but decreased in wk 2–4.	Pineda et al., 2016
scFOS	NS	n/a	n/a	n/a		Pantophlet et al., 2016
Inulin	+++	n/a	n/a	n/a		Jonova et al., 2018
Galactosyl-lactose	++	+	+	n/a		Quigley et al., 1997
GOS	– – –	n/a	– – –	++	Jejunal villus length and colon crypt depth were increased in GOS calves.	Castro et al., 2016
CWS	NS	– –	+++	n/a	G:F was reduced after weaning in CWS-fed calves, whereas mean fecal scores after weaning were decreased in CWS calves.	Senevirathne et al., 2019
MOS	NS	n/a	+++	n/a		Heinrichs et al., 2003
MOS	NS	–, – –	NS	n/a		Terre et al., 2007
MOS	NS	NS	++	NS	Jersey calves had increased BW in wk 9; both Jersey and Holstein calves had decreased mean fecal scores.	Hill et al., 2009
MOS	NS	n/a	++	n/a		Morrison et al., 2010
MOS	NS	n/a	++	n/a	Mean fecal score was decreased in MOS-supplemented calves during wk 1.	da Silva et al., 2012
MOS	+++	+++	+++	n/a	Crossbred Holstein calves were used.	Ghosh and Mehla, 2012
MOS	++	n/a	n/a	n/a	Increased ADG in wk 7 and 8 of trial.	Roodposhti and Dabiri, 2012
MOS	+	NS	++	n/a		Heinrichs et al., 2013
MOS	NS	NS	NS	n/a		Kara et al., 2015
MOS, probiotics, fibrolytic enzymes	NS	NS	+++	n/a		Marcondes et al., 2016
YCW	NS	NS	++	n/a	Mean fecal score was decreased in YCW-supplemented calves during wk 3.	Froehlich et al., 2017

Continued

Table 3 (Continued). Summary of growth, health, and gut development responses in calf studies using different prebiotic supplements

	Effects in response to[2]					
Prebiotics used[1]	Weight gain	Feed efficiency	Health	Gut development	Remark	Reference
MOS	NS	n/a	n/a	+++	Rumen papillae and jejunal villus lengths were increased in MOS calves.	Alves Costa et al., 2019
MFOS	NS	n/a	n/a	NS		Alves Costa et al., 2019
Unknown or other						
BC	NS	n/a	NS	n/a		Castro-Hermida et al., 2001
Commercial product	NS	NS	NS	n/a	It contained fermentation products of *Lactobacillus gasseri* OLL2716 and *Propionibacterium freudenreichii* ET-3.	Heinrichs et al., 2009
Lactulose	NS	NS	n/a	++, +	Lactulose calves had increased jejunal villus lengths and tended to have more proliferative ileal cells.	Masanetz et al., 2010
Commercial product	NS	+	NS	n/a		Quezada-Mendoza et al., 2011
SRB	NS	n/a	–	n/a		Velasquez-Munoz et al., 2019
Polysaccharides						
BG, ascorbic acid	NS	NS	n/a	n/a		Eicher et al., 2010
BG[3]	NS	NS	++	n/a	Mean fecal score was decreased in BG-supplemented calves during wk 3.	Kim et al., 2011
Kraft pulp	NS	n/a	n/a	n/a	Beef calves weaned between 3 and 4 mo.	Kido et al., 2019
BG	– – –	n/a	–	n/a		McDonnell et al., 2019

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[1] The term listed is how the prebiotic was described in the manuscript, but the grouping in the table is based on structure similarities. CO = cellooligosaccharides; scFOS = short-chain fructooligosaccharides; GOS = galactooligosaccharides; CWS = condensed whey solubles that are created enzymatically and contain a variety of di- and oligosaccharide compounds (e.g., galactosyl-lactose); MOS = mannanoligosaccharides; YCW = yeast cell wall (described as mannanoligosaccharide product in the paper); MFOS = mannan and fructooligosaccharides; BC = β-cyclodextrin; SRB = heat-stabilized rice bran; BG = β-glucans.

[2] Either positive (+) or negative (−) effects are noted with magnitude of change explained here: 1 = $P \geq 0.05$ but ≤ 0.10, 2 = $P \leq 0.05$, and 3 = $P \leq 0.01$. An NS denotes no change, and an n/a denotes the variable was not measured.

[3] A hydrolyzed yeast product was used in this study containing 10–12% β-glucan.

calf growth. However, Castro et al. (2016) did measure an increase in jejunal villi length and colon crypt depth in GOS-supplemented calves, suggesting an overall improvement in intestinal health, despite decreased growth, even when GOS was supplemented at higher levels.

Effects on Health

Of the studies that evaluated health, 2 found that health was improved in supplemented calves (Quigley et al., 1997; Senevirathne et al., 2019), whereas one reported negative results (Castro et al., 2016; Table 3). Castro et al. (2016) found increased LAB in the colon of GOS-fed calves compared with control; however, this difference was short lived and did not translate to improvements in intestinal health, as GOS calves in this study had an increased number of days with diarrhea. It should be noted that the authors suggested the cause of diarrhea to be osmotic in nature instead of health related. In contrast, Quigley et al. (1997) observed that calves supplemented with GL experienced fewer days with diarrhea, and Senevirathne et al. (2019) found lower mean fecal scores after weaning in GL-fed calves, which suggests an improved intestinal microbial community able to prevent pathogens from causing diarrhea.

While there have been suggested benefits of colostral and milk OS in both ruminants and nonruminants (ten Bruggencate et al., 2014; Malmuthuge et al., 2015a; Song et al., 2019), the effects of GOS/GL in calf diets are conflicting. Evidence of GOS/GL altering microbial popula-

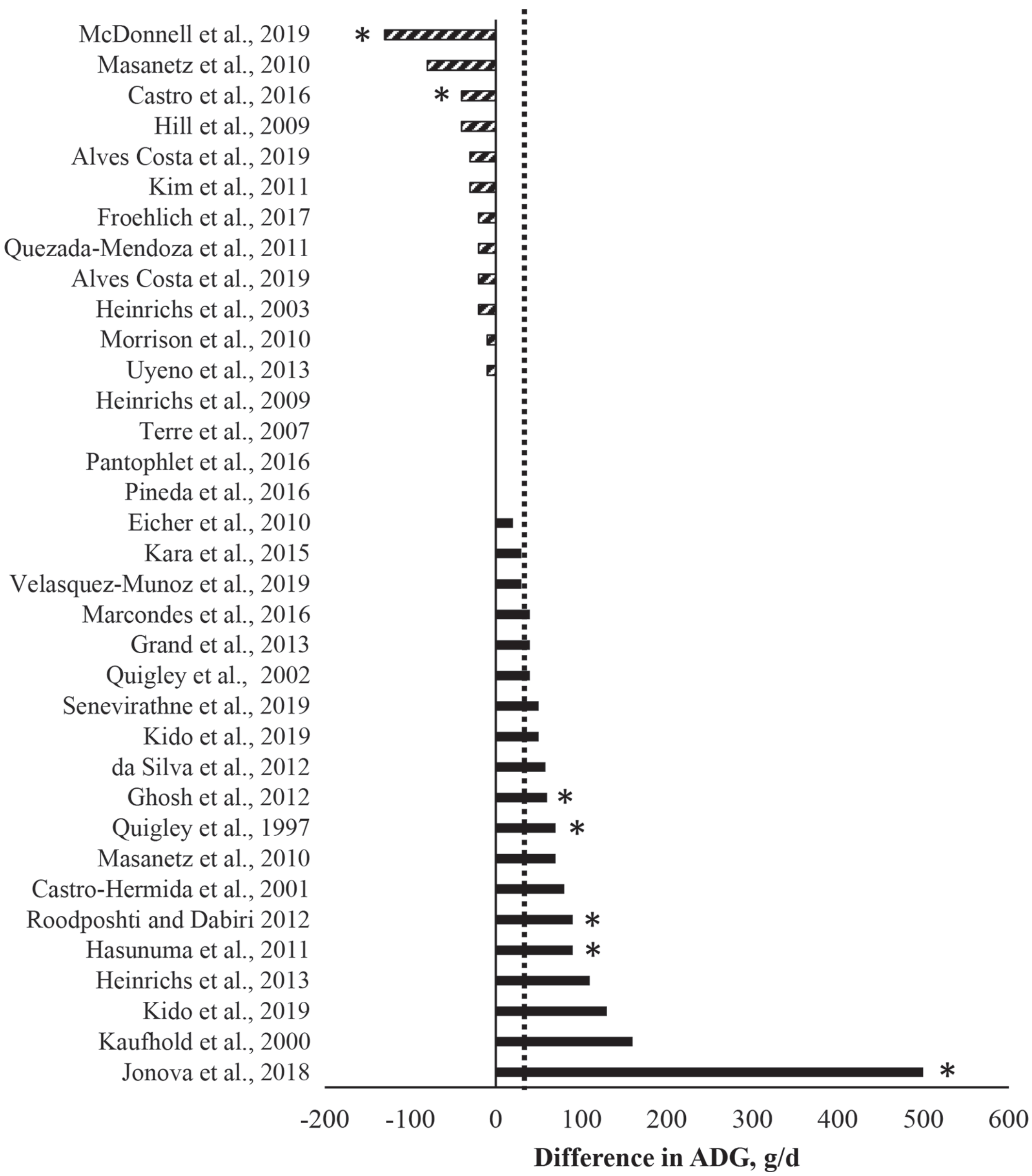

Figure 3. Summary of difference in ADG response between control and prebiotic-supplemented calves. Significant difference between control and prebiotic-supplemented calves from each study is indicated by * ($P \leq 0.05$), with the average ADG difference across all studies indicated by the dotted line.

tions and subsequently improving calf growth and health is lacking and warrants further investigation.

Mannanoligosaccharides

Mannanoligosaccharides (**MOS**) are derivatives of the cell walls of *S. cerevisiae* and are known to contain repeating mannose units via α-(1–2) and α-(1–3) linkages. It is the most commonly used prebiotic and has been shown to competitively bind pathogenic bacteria (Spring et al., 2000; reviewed in Spring et al., 2015), highlighting the positive role MOS can exert in calf diets.

Effects on Growth and Performance

Of the 13 studies that evaluated the effect of MOS supplementation on growth, 3 found a measurable improvement in growth in MOS-supplemented calves, whereas the other studies noted no difference compared with control calves (Table 3). With respect to FE, one study found a positive effect on FE, one study found a negative effect on FE, and 5 studies found no difference between MOS-supplemented and control calves (Table 3). An increase in DMI was only observed in 2 studies (Heinrichs et al., 2003; Terre et a., 2007), where there was an increase in starter intake without improved growth in MOS-supplemented calves, ultimately leading to decreased FE. Although no differences in intake or growth were noted in calves fed MOS in milk, an increase in rumen papillae length and jejunal villi height was found (Alves Costa et al., 2019). The increased intestinal villi height was likely the result of enhanced growth of the intestinal epithelium due to an increase in substrate availability from bacteria utilizing MOS. However, it is unclear how MOS supplementation led to ruminal papillae differences observed by Alves Costa et al. (2019).

Effects on Health

Improved health seems the most consistent response for calves supplemented with MOS. Of the 10 studies to assess health, 8 found a positive effect of MOS supplementation and the other 2 found no differences compared with controls (Table 3). Heinrichs et al. (2003) found a greater probability of normal fecal scores, a decrease in diarrhea severity, and faster recovery to normal fecal consistency in MOS-supplemented calves. Fecal scores were also lower in MOS-supplemented Holstein calves in other studies (Hill et al., 2009; Morrison et al., 2010; Ghosh and Mehla, 2012; Heinrichs et al., 2013). Marcondes et al. (2016) fed a blend of MOS, probiotics, and fibrolytic enzymes and also observed lower fecal scores. These results might not be completely attributable to the MOS, but nevertheless demonstrate the potential synergistic effects of pro- and prebiotics that should be further explored. It has been suggested that MOS may help prevent attachment of pathogenic species in the lower gut (Spring et al., 2000), although 2 studies noted no differences in *E. coli*, *Clostridium perfringens*, or *Cryptospordium* spp. fecal counts between control or MOS-supplemented calves (Terre et al., 2007; Kara et al., 2015). Froehlich et al. (2017) measured a lower mean fecal score during wk 3 in calves supplemented with 2 g/d of a yeast cell-wall product containing MOS, and da Silva et al. (2012) also measured a lower mean fecal score during wk 1 in calves supplemented MOS in their MR. There was little assessment of the immune response in calf studies utilizing MOS; however, a single study noted no differences in leukocytes or IgG levels in the blood, demonstrating that the immune system of calves was not altered due to MOS supplementation (Roodposhti and Dabiri, 2012).

Compared with the other prebiotics used in calf studies, MOS has a clear and consistent benefit on health (mainly digestive health), which suggests that it is worth including in calf diets. This value is further highlighted by Ghosh and Mehla (2012), who calculated an improvement in feed cost per kilogram gain for calves supplemented with MOS. Overall, these results underpin the benefit of MOS to calf growth and health, although how MOS exerts these beneficial effects still needs to be elucidated.

β-Glucans

There are many variations of β-glucans (**BG**), with the main sources coming from plant and fungal cell walls. β-Glucans are polysaccharides of glucose that differ in their arrangement of β-glycosidic bonds [e.g., baker's yeast: β-(1–3) and β-(1–6), cellulose: β-(1–4), or cereal grains: β-(1–3) and β-(1–4)] and are used in food, cosmetic, and health products for humans, as well as feed additives for livestock animals (Zhu et al., 2016). In this review, we found it difficult to interpret and synthesize results from research studies that used BG, as it originates from a multitude of different sources. However, the studies discussed provided information on the source of BG, which helped to compare results between studies. While BG may be controversial to include as a prebiotic for ruminants, it has demonstrated prebiotic effects in humans (reviewed by Roberfroid et al., 2010) and other nonruminants (Snart et al., 2006; Pieper et al., 2008; Cox et al., 2010), which may explain the few studies that have investigated BG in calves that have undeveloped rumens and have a metabolism more similar to that of a nonruminant early in life. As this field of research advances, a more appropriate definition of a prebiotic may not include BG for ruminants, but at present, we have included studies that have used BG sourced from both microbiota and plants in calf diets.

Effects on Growth and Performance

The effects of BG on growth and FE are highlighted in Table 3, with a total of 4 studies measuring these parameters. The results were mixed, with no differences found in 3 studies and, in a single study, a substantial decrease in growth was observed in BG-supplemented calves. It should be noted that both Eicher et al. (2010) and Kim et al. (2011) supplemented calves with BG from the yeast cell wall and Kido et al. (2019) used kraft pulp, whereas McDonnell et al. (2019) demonstrated negative effects in growth by supplementing BG containing 10% laminarin [β-(1–3) and β-(1–6)-glucopyranose bonds] and 8% fucoidan [typically α-(1–3)-fucopyranose or α-(1–3) and α-(1–4) fucopyranose], which are extracted from brown algae (Kadam et al., 2015; Luthuli et al., 2019). An explanation for this difference between BG from the yeast cell wall or kraft pulp and brown algae may be due to an aversion to the taste of brown algae, which was demonstrated by Erickson et al. (2012), who noted calves preferred a textured starter compared with the same starter mixed with brown algae meal. In addition, McDonnell et al. (2019) noted a decrease in starter DMI throughout the trial, which taken together, suggest BG from brown algae may not be a suitable choice for promoting weight gain.

Effects on Health

Similar to growth, there were mixed results between studies in terms of health. Of the 3 studies that reported health data, one found improved health measures (Kim et al., 2011), another found no differences (Kido et al., 2019), and the other found a tendency for greater mean fecal scores in BG calves throughout the trial (McDonnell et al., 2019; Table 3). With respect to immune function, Eicher et al. (2010) found that although general health scores were not measured in the study, leukocyte phagocytosis of *Staphylococcus aureus* was decreased. Moreover, the percentage of calves that were positive for *Escherichia coli* O157:H7 on d 7 was greater in calves supplemented with the 2% BG or 70% BG product compared with control calves. Furthermore, McDonnell et al. (2019) found a decrease in cell-mediated and humoral immune responses in the BG and noted greater plasma haptoglobin in BG calves. Kim et al. (2011) also noted increased haptoglobin in BG-supplemented (hydrolyzed yeast containing 10–12% BG) calves; however, this could have been due to a response that occurred after the vaccine challenge. Several positive effects, however, were noted by Kim et al. (2011). Specifically, an increased production of total serum IgA (both bacterial-specific and viral-specific IgA) as well as increased neutrophils, neutrophil:lymphocyte ratio, and serum lactoferrin in calves challenged with a live bacterial and viral vaccine and supplemented with BG in a starter. This suggests that the BG in the starter boosted the immune response to the vaccine, potentially conferring additional protection against disease. Similarly, Eicher et al. (2011) fed MR with 70% BG from a SC extract and found a tendency for increased gene expression of toll-like receptor 4 (**TLR4**) and interleukin-12 (**IL12**) in the lung of BG-supplemented calves, suggesting that calves fed BG had improved responses to a potential infection in the lung.

Taken together, the growth and health results of studies utilizing BG in calves were inconclusive but suggest that BG used from yeast cell wall or kraft pulp is more effective than BG from brown algae based on growth, health, and immune measurements taken.

Cellooligosaccharides

The group of cellooligosaccharides (**CO**) are similar to BG in that they are composed of repeating units of β-(1–4)-glucopyranose, but they differ in length, where OS (including CO) have shorter chain lengths of glucose monomers—typically in the 3 to 10 range. Unlike BG that occur naturally and are extracted from the cell wall of plants or fungi, CO are prepared via acid hydrolysis of isolated cellulose and have been shown to promote the growth of LAB (Kontula et al., 1998).

Effects on Growth and Performance

The effect of CO on growth and FE is more promising than BG, as 2 of the 3 studies observed a positive effect on growth, and one found improved FE (Table 3). The study by Uyeno et al. (2013) was the only study that found CO supplementation did not improve growth or FE; however, an increase in fecal numbers of the butyric acid–producing *Clostridium coccoides-Eubacterium rectale* group and fecal butyrate was found in CO-supplemented calves, which may have resulted in enhanced gut development (Gorka et al., 2018). Whereas Uyeno et al. (2013) demonstrated the role of CO as a fermentation substrate for cellulolytic bacteria in the lower gut, Kido et al. (2019) demonstrated the role of CO fermentation in the rumen of beef calves, where ruminal short-chain fatty acids were increased during weaning at 4 mo of age and subsequently had a tendency for increased ADG after weaning compared with control calves. Hasunuma et al. (2011) did not measure gut development but found a tendency for increased insulin-like growth factor-1 (**IGF-1**), which has been shown to be an important somatotropic axis hormone involved in calf growth (Blum et al., 2007).

Effects on Health

Unlike growth measurements, no differences were found with respect to total fecal score or days experiencing diarrhea in CO-supplemented calves when compared with controls in Hasunuma et al. (2011), whereas general health was not assessed by Uyeno et al. (2013) or Kido et al. (2019; Table 3).

Utilizing CO as a supplement in calf diets showed positive signs for calf growth, while health and microbial measurements were not affected. The source of cellulose used to synthesize CO was not discussed in any study included, but like BG, the source of the prebiotic used may have underlying effects that we are unable to observe presently. Studies utilizing CO in calf diets seem to provide their biggest effect via promoting microbial fermentation and subsequent short-chain fatty acids that promote gut and overall calf growth.

Other Prebiotic Compounds

Studies have used proprietary products or prebiotics that have not been well-defined in the literature, but given that they were discussed as prebiotics, they have been included in this review. Some of the examples listed in Table 3 are not well described, and others, like lactulose (disaccharide containing galactose and fructose) and β-cyclodextrin [**BC**; an OS that has 7 glucose units joined in a cyclic α-(1–4) manner] have been included as they do not fit well in other categories. Ultimately, they have been included in this review because they are believed to act in a prebiotic manner and have been used in calf studies.

Effects on Growth and Performance

Only one study in this category showed a positive response, which was a tendency to increase FE in calves (Quezada-Mendoza et al., 2011; Table 3). Masanetz et al. (2010) fed lactulose at 2% of the MR diet and found a tendency for calves to have more proliferative ileal cells, which suggests lactulose promoted intestinal growth; however, this did not translate to overall growth. The lack of replication using these products in calves may explain the lack of growth response in the other studies and suggests further investigation is required to accurately assess these compounds as prebiotic supplements in calf diets.

Effects on Health

Similar to growth and performance measures, there was a minimal effect on health, with only one study observing a negative effect (Table 3). The one negative result was observed by Velasquez-Munoz et al. (2019), who fed a compound believed to have prebiotic properties, heat stabilized rice bran (**SRB**), at 10% caloric intake/d for 28 d. The authors demonstrated a reduced number of days to first moderate diarrhea event, and an increased number of days were needed to recover from a diarrhea event in the supplemented group. The authors posited that the diarrhea occurring in SRB calves was the result of increased osmolality due to lack of digestion of SRB in MR. Increased fecal IgA may suggest an enhanced humoral immunity, which was found by Heinrichs et al. (2009), who fed a proprietary prebiotic product; however, no differences in health observations or lymphocyte populations were noted. The authors speculated that the excellent health of the calves used in the study may have prevented any noticeable differences and suggests that prebiotics might be more appropriate for unhealthy calves. Castro-Hermida et al. (2001) administered BC to calves orally, and although no differences in diarrhea incidences were observed, there was a decrease in *Cryptosporidium* oocyst shedding in the feces of calves administered BC. Masanetz et al. (2011), who supplemented lactulose, measured a decrease in immune activation via decreased IL2RA and tumor necrosis factor gene expression in the lower gut compared with control calves.

Taken together, the prebiotic results in this section demonstrate no promising effects on calf health or growth. Considering the large body of evidence underpinning lactulose as a positive prebiotic in monogastrics, there may be some usefulness in ruminants that has not yet been explored. The other compounds did not prove useful either, but as previously mentioned, lack of repetition or utilizing stressful or challenging situations may potentially explain why positive effects were not identified in this review.

Conclusion

When considering the prebiotic studies evaluated as part of this review, it seems clear that there are no prebiotics boasting substantial evidence of positive effects on calf growth, health, or immune status. There is more evidence to support the use of MOS in calf diets compared with other compounds, but it is worth noting that the majority of studies have been conducted using MOS. In addition, the mechanisms of action for these prebiotics is severely understudied, with the main connection to any positive health benefit currently being "prebiotics promote growth of beneficial bacteria." Although this statement is true, there are also cellular-level mechanisms involving epigenetic regulation and leukocyte activity that might play critical roles. Future work should look beyond growth and observable health parameters to focus on how and why compounds, such as OS, improve gut development and immune response. Furthermore, future work should also address when is the most appropriate time to use a prebiotic compound to receive the maximum return on investment (e.g., either prevention or treatment of a gastrointestinal illness).

FUTURE RESEARCH

Research synthesis is a fundamental component of science, with systematic reviews and meta-analyses becoming more common approaches to synthesize research in animal science. However, incomplete reporting in primary studies is a common finding that limits the ability of these systematic reviews to answer relevant questions (Ali Naqvi et al., 2018; Winder et al., 2018b). Specifically, in a meta-analysis evaluating microbial-based products, 18 out of 32 trials were excluded due to lack of information needed to conduct the analysis (Signorini et al., 2012). A study completed in 2019 also found that many areas of experimental design were not reported or incompletely described in many dairy science articles (Winder et al., 2019). Hence, there is a need to adhere to reporting guidelines for authors, reviewers, and editors, such as the Reporting Guidelines for Randomized Controlled Trials for Livestock and Food Safety (REFLECT), which was developed through consensus of experts to improve reporting in livestock trials (Sargeant et al., 2010). Improved reporting will ultimately allow for a better understanding of the efficacy of pro- and prebiotics and increase the value of the work that is being conducted.

In addition to following REFLECT principles, ensuring proper and consistent sample collection and analysis is essential to making proper comparisons between studies investigating mode of action. In particular, when researchers pursue the underlying mode of action of microbial-based solutions, the intensity of the sampling becomes more complex. To gain more insight into how the probiotics and prebiotics change the microbiome and host, many researchers have adopted "omic" approaches and next-generation sequencing. Although these approaches have been insightful, a large degree of variability exists in sample collection, processing, and laboratory analysis. With respect to assessing the changes in the microbial community of the gut, the locations and types (fluid digesta, solid digesta, attached to digestive tract) of samples in the literature are inconsistent. This is commonly shown in medical research, where the preparation, handling, and storage of human gut samples significantly affects the results (Gorzelak et al., 2015). Once the sample has been taken, the extraction method, clone library construction, DNA sequencing procedures, and data analysis pipelines are all different between studies. Adding to this problem is the overarching lack of existing databases to identify microorganisms and function of unclassified reads that still exist in cattle and calves (Malmuthuge et al., 2015b). Although new sequencing technologies boast great potential to improve our knowledge about microbial-based solutions in calves, consistency between research groups will be the key to making swift progress in this field. Moreover, to fully uncover how probiotic and prebiotic technologies can positively affect health and performance, researchers must look beyond characterization of the microbial community. The effect on the host—especially immune function—needs to be considered in studies investigating mode of action. More studies need to evaluate host–microbial interaction with integrated omic approaches to characterize the host and the microbes (Ma et al., 2018).

APPLICATIONS

It is worth noting that based on the study results included in this review, there have been limited negative responses in growth (2/68), FE (4/70), health (3/68) and gut development (2/70). Growth, FE, and gut development responses to pro- and prebiotic supplementation resulted in marginal positive responses (22/68, 9/70, and 11/70, respectively), with many results demonstrating a nonsignificant effect (39/68, 32/70, and 3/70, respectively). With respect to health, many studies (31/68) had positive responses and only 15 out of 68 did not show a difference. Taken together, it appears that using pro- and prebiotics in calf diets demonstrates the most beneficial effects on calf health, with growth being the next area most positively affected. Without formal, rigorous statistical testing, it would be inappropriate to make conclusions from these response proportions, but they do suggest that pro- and prebiotics should be further studied in calves to determine the most appropriate times for supplementation. As discussed earlier and signified by the large number of positive health responses, one time to study may be when the disease burden is high. There is a lack of data on whether it is most beneficial to supplement calves with pro- and prebiotics prophylactically or therapeutically, and future studies should investigate these areas further. Specifically, studies using models of experimentally induced enteric infections could provide useful information regarding timing and duration of pro- and prebiotic supplementation. Also, although rarely addressed in the literature and not in this review, proper mixing and administration of pro- and prebiotic supplements is an important consideration that should be addressed in future studies to confirm consumption. Last, although health may be the most positively affected response in the current data, there may be subsequent positive effects on growth, as calves will not have to partition energy for immune responses or have a reduction in feed intake.

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ORCIDS

M. A. Steele https://orcid.org/0000-0001-6941-6205