dairy

MDPI

Review

An Evaluation of Nutritional and Therapeutic Factors Affecting Pre-Weaned Calf Health and Welfare, and Direct-Fed Microbials as a Potential Alternative for Promoting Performance—A Review

Sarah J. Davies [1], Giulia Esposito [1,2], Clothilde Villot [3], Eric Chevaux [3] and Emiliano Raffrenato [1,4,*]

[1] Department of Animal Sciences, Stellenbosch University, Stellenbosch 7600, South Africa
[2] Department of Veterinary Science, University of Parma, 43126 Parma, Italy
[3] Lallemand SAS, F-31702 Blagnac, France
[4] Research and Development RUM&N Sas, 42123 Reggio Emilia, Italy
* Correspondence: emiliano@sun.ac.za; Tel.: +39-339-832-9053

Simple Summary: This review aims to provide a comprehensive evaluation of the nutritional management strategies that may increase a calf's susceptibility to morbidity and mortality, the efficacy and sustainability of antibiotics as a tool for managing calf health and welfare, and the potential for direct-fed microbials (DFM) as an alternative therapy for promoting calf wellbeing. The first line of intervention for improving calf welfare should be the optimization of the nutritional management strategies that are employed. Thereafter, additives that support the development of the growing calf can be further investigated. The literature reviewed indicates that there is an increased research interest in the administration of DFMs to pre-weaned calves.

Abstract: The priority for calf rearing has been to maintain good health and welfare in order to promote and sustain future production. However, there have been numerous reports of undesirable levels of morbidity and mortality amongst pre-weaned calves. This may be mitigated or exacerbated by nutritional management practices. Some areas of concern include colostrum feeding, utilization of waste milk, and restrictive milk feeding regimes. Antibiotics may be prescribed at lethal or sub-inhibitory doses to treat or prevent disease. However, extensive antibiotic use may disrupt the gastrointestinal microbiota and aid in expanding the antibiotic resistant gene pool. In an attempt to reduce the use of antibiotics, there is a demand to find alternative performance enhancers. Direct-fed microbials, also known as probiotics, may comply with this role. A DFM consists of live microorganisms that are biologically active and able to confer health benefits onto the host. Lactic acid bacteria have been the most frequently investigated; however, this field of research has expanded to include spore-forming bacteria and live yeast preparations. This review aims to provide a comprehensive evaluation of the nutritional management strategies that may increase a calf's susceptibility to morbidity and mortality, the efficacy and sustainability of antibiotics as a tool for managing calf health and welfare, and the potential for DFMs as a supportive strategy for promoting calf wellbeing.

Keywords: pre-weaned calf; morbidity and mortality; calf welfare; nutritional management; antibiotics; direct-fed microbials; probiotics

Citation: Davies, S.J.; Esposito, G.; Villot, C.; Chevaux, E.; Raffrenato, E. An Evaluation of Nutritional and Therapeutic Factors Affecting Pre-Weaned Calf Health and Welfare, and Direct-Fed Microbials as a Potential Alternative for Promoting Performance—A Review. *Dairy* **2022**, *3*, 648–667. https://doi.org/10.3390/dairy3030045

Academic Editor: Burim Ametaj

Received: 21 May 2022
Accepted: 29 August 2022
Published: 6 September 2022

1. Introduction

Within the dairy industry, female calves are destined to become replacement heifers; therefore, the priority is to maintain good health and welfare in these animals to preserve them for good milk production in the future. The male calves are generally sold soon after birth, to be reared for veal or beef, and the aim is for them to have good growth and minimal health complications [1]. However, there have been numerous reports of

undesirable levels of morbidity and mortality amongst pre-weaned calves. As a result, there has been a heightened interest in the management of these animals from birth until weaning. All aspects of traditional calf rearing have been under scrutiny to determine the consequences that it may have on calf performance, particularly health and growth [2] and, subsequently, future production and profitability [3].

In dairy-production systems, the pre-weaning phase is considered to be the time from birth until the calf is completely weaned off of milk or milk replacer. An industry target for weaning is usually at 8 weeks of age or at the time at which calves double their birth weight [4]. It has been found that improved health and growth during this time period has, in fact, significant effects on life-long health and production [3]. This was demonstrated in the studies of Raeth-Knight et al. [5] and Soberon et al. [6], which found that an increased growth rate during the pre-weaning phase was associated with a decreased age at first calving and increased milk production during the first lactation, respectively. Additionally, Soberon et al. [6] found that calves receiving antibiotic treatments for respiratory disease had a significantly lower yield in milk production in the first lactation.

The pre-weaning period is considered to be a critical period in which calves are exceptionally susceptible to diseases [7]. This is attributed to the fact that calves are confronted with the challenges of a naïve immune system [8] and an immature digestive tract [9]. During this time, the risk of morbidity and mortality may be increased or diminished by calf management strategies [3]. Although different aspects of calf management have been investigated in the past years (i.e., housing, bedding, etc.), nutritional management strategies are still considered to be crucial, since they have the potential of programming the calf, i.e., the manner of colostrum and milk feeding can greatly influence the development of immunity, growth, and gut maturation [9,10].

Morbidity and mortality statistics are commonly used parameters to gauge the standard of calf rearing and animal welfare [11]. As a benchmark, the Dairy Calf and Heifer Association [12] has set the target of reducing morbidity and mortality to 25% and 5%, respectively. However, globally, these levels of morbidity and mortality are still not achieved [13,14]. In calf studies, the United States Department of Agriculture (USDA) is frequently cited for their estimates of pre-weaned calf morbidity and mortality, which are derived by their National Animal Health Monitoring System (NAHMS). National estimates for these parameters were last reported in 1992 [15] and 2007 [16]. In these two studies, morbidity was reported at 36.1 and 38.5%, respectively, and mortality was reported at 8.4 and 7.8%, respectively. In 2014, another study was published that consisted of a calf component, which looked at calf morbidity and mortality in dairy operations in 13 of the major dairy States. In this study, morbidity and mortality estimates were 33.8 and 5%, respectively [13]. Digestive diseases and disorders remain the most common reported cause of morbidity and mortality, accounting for approximately 56% of all sick calves and 32% of all deaths [3].

Probiotics have been reviewed for their modes of action [17] and effects on cattle health and production [18]. Specific yeast additives and derivatives [19] and, in particular, the *Saccharomyces* genus [20] have also been reviewed to determine animal responses and health. Furthermore, live yeast additives have already been reviewed for their effect on the rumen microbiota and, subsequently, ruminant health and production [21]. In the context of calf nutrition, probiotics (including live yeast strains), prebiotics, and oligosaccharides have recently been reviewed for their effect on calf growth and health [1,22]. In another review, the effects of yeast additives, live yeast, and yeast cultures on pre-weaned calf performance were investigated. Although probiotics have already been reviewed, these papers did not investigate other management practices that may influence calf performance and welfare. Therefore, the purpose of this review was to evaluate literature to (1) determine if on-farm nutritional management practices may jeopardize calf health and welfare, (2) understand the effects of antibiotic administration strategies on calf performance, and (3) determine if DFMs

can ameliorate calf welfare and reduce antibiotic administration by improving overall calf health and performance.

2. Implications of Calf Nutritional Management on Welfare

A calf's susceptibility to morbidity and mortality may be mitigated or exacerbated by a number of management factors that are applied over three main developmental periods, namely the in utero, neonatal, and pre-weaning phases [10,23]. Poor management of any of these phases can have negative implications on calf health by increasing the incidences of disease, such as diarrhea and bovine respiratory disease [24]. The incidence of disease may be difficult to avoid if the dam or calf have been mismanaged during either of the first two phases. However, calf welfare during the pre-weaning phase is also considered to be one of the main factors associated with morbidity and mortality [25]. According to the globally accepted "five freedoms" [26] and the European Welfare Quality® protocol, adequate calf welfare encompasses good health; comfort; adequate nutrition for maintenance and growth; the ability to express natural behavior; and the absence of pain, fear, and distress [27]. As previously acknowledged, calves are highly susceptible to diseases, in particular digestive disorders. Therefore during the pre-weaning phase, calves are constantly at risk of having a compromised welfare status due to digestive diseases and disorders [28].

However, digestive diseases can be mitigated by the nutritional management of the calf [29]. With this being said, from birth, the nutritional management of the calf includes fast diet transitions [30]. Therefore, one area of concern includes the management of the liquid diet of calves, i.e., colostral and post-colostral. This includes the provision of colostrum, utilization of waste milk, and restrictive feeding [31].

2.1. Colostrum

The most conspicuous factor influencing calf morbidity and mortality is the successful acquisition of passive immunity [32,33]. According to Lora et al. [34] the rate of failure of passive immunity (FPI) is likely to influence the occurrence of digestive diseases amongst pre-weaned calves. Calf studies within the last two decades report FPI rates ranging from 12.1 to 19.1% [35,36], as opposed to an older survey, which reported a rate of 40% [15]. However, Fischer et al. [29] suspect that the most recent statistics are not a true reflection of the actual rate of FPI because only healthy calves were evaluated. In reality, the rate of FPI may be much higher and might explain why there is still a high proportion of pre-weaned calf morbidities and mortalities caused by digestive diseases. This may motivate further investigation into colostrum management to ensure that digestive diseases are lowered.

It is already well known that feeding colostrum is associated with achieving successful passive immunity (SPI) [29]. After the ingestion of colostrum, immunoglobulins are actively absorbed from the small intestine and into blood circulation by pinocytosis [37]. The acquired immunoglobulins, predominantly immunoglobulin G (IgG), provide immunocompetence and protect the calf from disease [38]. Therefore, colostrum management may be regarded as the first step in preventing digestive diseases. Optimal IgG absorption encompasses the method and timing of colostrum feeding and the volume and quality of colostrum based on the IgG concentration and bacterial count [39]. Gut closure appears to be the greatest threat for preventing the absorption of IgG from the small intestine.

Until recently, it was recommend that calves should ingest colostrum before gut closure [40], which was considered to be at 24 h after birth [41]. However, Fischer et al. [42] demonstrated that the time for optimal IgG absorption is shorter than was popularly believed and that colostrum should be provided immediately after birth and not beyond 6 h post-partum. In addition to timing, the volume of colostrum fed should be taken into account. According to Godden et al. [43], it is preferable to feed larger volumes of colostrum, because it allows for a greater mass of immunoglobulins to be delivered to the

small intestine to be absorbed. In order to manage the timing and volume offered, the method of colostrum feeding has to be considered [39].

The method of colostrum feeding is an incremental factor in providing a sufficient concentration of IgG to the intestinal lumen within the critical time frame. Allowing calves to suckle has been discouraged. This is largely due to the fact that there is a greater chance of delayed suckling and colostrum consumption [31]. However, according to the Nation Animal Health Monitoring System (NAHMS) [13], only a minority, approximately 17%, of calves are left to suckle. Therefore, rates of FPI and digestives diseases cannot be solely attributed to calves suckling. Although the manual feeding of colostrum, by a nipple bottle, bucket, or esophageal tube, is considered to be more desirable, there are additional factors to take into account. For instance, the volume of colostrum provided should be considered. When feeding small volumes of colostrum, it is preferable to utilize a nipple bottle or bucket to ensure that all of the milk reached the abomasum and intestines. If larger volumes of milk are provided, then it may also be appropriate to use an esophageal feeder, where a portion of the milk will enter the reticulorumen and will be delayed in reaching the abomasums [43].

According to the authors Godden et al. [37], the quality of colostrum, including IgG concentration and bacterial count, is also important for the active absorption of maternal immunoglobulins. There are several available strategies for optimizing the quality of colostrum. In particular, it is suggested that, excluding the dam effect (age, parity, and breed), other factors, such as the length of the dry period, season of calving, vaccinal status of the dam, and nutrition during the periparturient period, can affect the colostrum IgG concentration. However, these factors are relevant to the management of the dam as opposed to the newborn calf. Therefore, more focus will be given to management practices that can be applied if there is a shortage of high-quality colostrum and the influence of the bacterial count on colostrum quality.

In case there is a shortage of colostrum with sufficient concentrations of IgG, there are various management strategies that can be utilized. According to Cardoso et al. [44], this the use of colostrum supplements and replacers. One strategy not mentioned in the aforementioned review, but often used at the farm-level to overcome the issue of poor-quality colostrum is the use of high-quality colostrum from other cows within the farm. This can be easily achieved by storing surplus high-quality colostrum produced by other cows at −20 °C, which can then be used after thawing to feed newborn calves.

Another factor that may influence SPI is the colostral bacterial count. It is postulated that the bacterial contamination of colostrum may interfere with IgG absorption, and this may occur because colostral antibodies bind to bacteria [45]. Unacceptably high levels of bacteria, more than 100,000 colony-forming-units (CFU)/mL total plate count or 100,000 CFU/mL total coliform count, may bind to IgG and hinder absorption [37]. On the farm, colostrum contamination can be prevented by practicing good hygiene during collection and feeding, prohibiting prolonged exposure to ambient temperatures, and in some cases by appropriate heat treatment of colostrum. Heat treatment should not damage the IgG molecules; therefore, it is advisable to use a lower temperature for a longer time (i.e., 60 °C for 60 min) [37].

Based on the most recent literature of colostrum management, it is advised that calves should be provided with colostrum consisting of no less than 50 g/L of IgG at a volume of approximately 8.5–10% of the birth weight within 2 h after birth [37,46]. If these recommendations are met, it is likely to reduce the risk of an FPI.

Although, FPI has been regarded to be the main reason for the high occurrence of digestive diseases in calves, there may be another factor that is equivocally import; this includes the bacterial colonization of the intestines [47]. The composition of the intestinal bacterial community has been shown to be correlated with the incidence of diarrhea. Calves that have a higher proportion of *fecalibacterium* in the feces during the first week of life have been shown to have a lower occurrence of diarrhea [48]. Therefore,

colostrum-management strategies for promoting SPI should also be reviewed for the influence that they have on the bacterial colonization in the gut. It is possible that colostrum may provide two equivocally important protective mechanisms, SPI and microbial colonization.

2.2. Waste Milk

Unsalable milk is often used to describe the term "waste milk". It may consist of low-quality colostrum, transition milk, and milk from morbid cows consisting of high somatic cell counts or antibiotic residues [49]. Waste milk may be utilized as the liquid diet for pre-weaned calves, because it is deemed to be economically favorable. However, milk derived from infected cows may increase the risk of pathogen transmission, posing a direct threat to calf health [31]. In an attempt to minimize the pathogen load, it is preferable to pasteurize waste milk before feeding it to calves. In some cases, this has been successful in eliminating *Mycobacterium paratuberculosis* and *Mycoplasma* species [50,51]; however, others have reported that it is not completely effective in destroying pathogenic organisms [52]. Alternatively, ultraviolet light treatment may also be used to control the bacterial count in waste milk; however, it is not able to completely eliminate the presence of pathogens [53]. The antibiotic residues that may be present in waste milk can also have an impact on calf health and welfare. Trace amounts of antibiotics in the calves' diet may disrupt the microbiota in the gastrointestinal tract (GIT), thereby negating the physiological and immunological development of the calf [49]. Due to the risk of pathogen transmission [31] and exposure to antibiotic residues [49], it is recommended that waste milk should not be fed to pre-weaned calves. However, it appears to remain a common practice in the dairy industry; in a nationwide study conducted in the United States, it was found that 40.1% of calves were fed whole or waste milk [54]. Whereas, a smaller study conducted in Chile found that 51.7% of the calves that were included were fed unpasteurized waste milk [55].

However, the term waste milk is often used ambiguously, without clarifying its composition, i.e., transition milk or mastitic milk. It may be helpful to refer to these two types of unsalable milk separately, since they are likely different in composition and the effect that they will have on calves. Transition milk is the milk produced by the cow on the second to sixth milking after producing colostrum. Transition milk is unique in that it differs from colostrum and mature milk, containing an intermediary amount of bioactive compounds [29], such as of sialylated oligosaccharides [56] and insulin-like growth factor 1 [57]. Transition milk may be beneficial in assisting with the early development and maturation of the GIT; however, there is currently no evidence to support this idea [29].

2.3. Post-Colostral Milk Feeding Strategies

There is a lot of variation in calf nutritional management between different farms; differences are usually present in the feed composition and plane of nutrition [58]. Traditionally, calves have been fed according to a restrictive milk feeding regime, which allows only the daily provision of restricted amounts of whole milk or milk replacer solids (10% of birth weight) [59]. The reasoning is that if calves consume less milk, they will consume more grain and forage, thereby promoting earlier rumen development and greater post-weaning growth [60]. The development of the rumen is an important part of the GIT maturation in calves and is considered to be important for upholding good welfare [61]. However, it has been found that the consumption of solid feed in the first three weeks of life is negligible and that digestion may be impaired due to an underdeveloped rumen [14]. This may put calves in restrictive feeding regimes at risk of being underfed. Upon reviewing literature on calf feeding strategies, Khan, et al. [60] found that in order to improve calf performance and welfare, it may be more beneficial to provide milk volume at 20% of their body weight per day (dry solids at 2% of their body weight per day).

Underfeeding calves is likely to infringe directly on welfare by imposing distress due to hunger [62]. The presence of stress may enhance or suppress immunity. Enhanced immunity is likely to occur in the presence of a short-term acute stressor. Whereas prolonged chronic stress may induce a continuous glucocorticoid release, which may depress the activity of the immune system and increase disease susceptibility [63]. It is unclear whether or not restrictive feeding would illicit an acute or chronic stress response in calves. However, it has been found that calves receiving lower planes of milk during the pre-weaning phase have elevated neutrophil L-selectin protein concentrations, which may indicate that their immune system was more active [64]. It is speculated that the increased activity of the immune system was related to non-nutritive suckling and exposure to environmental microorganisms as opposed to the presence of stress [64].

Feeding higher planes of milk has been shown to positively improve growth during the pre-weaning phase [65]. However, some calves have been shown to have a loose fecal consistency [66]. In another study, calves that were provided with non-restricted quantities of milk also appeared to have a loose fecal consistency; however, no difference in fecal dry matter between the calves on a restrictive and non-restrictive diet was observed [67]. It is possible that calves receiving more milk only appeared to have loose feces, due to the greater provision of fluids [68], but did not in fact have any GI infection. The authors suggest that fecal scores cannot be used alone in determining the status of GI health. When implementing an intensive milk feeding protocol for the purpose of promoting early growth, dietary protein and energy should be taken into consideration. It may not be appropriate to simply increase the volume of a conventional milk replacer meant for a restrictive milk feeding protocol, because it might result in insufficient protein for lean tissue growth and the excess energy, which may be converted to fat [58].

The prevention of calf morbidity and mortality should start with the implementation of a nutritional management program that ensures the successful acquisition of passive immunity, prevents excessive exposure to pathogens, minimizes disturbances in the gastrointestinal (GI) microbiota, and promotes satiety by meeting the appropriate nutritional requirements. If these milestones are achieved, it is likely to promote calf welfare by improving health, providing adequate nutrition, encouraging natural feeding behavior, and reducing the occurrence of distress. There are additional management strategies that may be utilized to further assist in controlling or preventing morbidity and mortality. This may include a sound antibiotic treatment program for infectious diseases and the administration of DFMs to further aid in preventing pathogen overgrowth and microbial disturbances.

3. Antibiotics

Antibiotics have been frequently used as a tool for managing calf health. Historically, it was commonly used for prophylactics, a mode of antibiotic administration that allows sub-inhibitory doses to promote health and growth, thereby preventing the occurrence of disease. This was first established during the 1950s, in which different types of tetracycline antibiotics were highly beneficial for improving growth and health [53]. Thereafter, it was also found that a combination of oxytetracycline hydrochloride and neomycin sulphate supplemented to the liquid diet of calves was beneficial for promoting calf performance [32,69,70]. Alternatively, producers would also use unsalable waste milk, consisting of antibiotic residues, as a more economical and convenient liquid diet for calves [71,72]. The antibiotic residues consisted primarily of penicillin, cephalosporin, and tilmicosin. Antibiotics are also frequently used to treat infectious diseases; on some farms, all of the calves with respiratory symptoms and three quarters of the calves with diarrhea receive treatment [73]. In calf rearing, macrolides, florfenicol, penicillin, and fluroquinolones are commonly used to treat and prevent bovine respiratory disease (BRD) [74]. Conversely, diarrheic calves are com-

monly treated with broad-spectrum β-lactam antibiotics, i.e., amoxicillin, potentiated sulfonamides, and cephalosporins [75].

Although some of the pioneer studies have reported that prophylactic antibiotic programs are beneficial for improving growth and health, not all these results were in fact statistically significant [70,72]. Furthermore, therapeutic and sub-therapeutic doses of oxytetracycline hydrochloride alone or in combination with neomycin sulphate have shown no improvement in starter intake, growth, and the incidence of diarrhea [76–78]. It is worth noting that intestinal infections that are accompanied with diarrhea, may be caused by various enteric pathogens including viruses, bacteria and protozoa [79]. Therefore, due to the nature of the infection (i.e., viral or protozoan), milk replacer supplemented with antibiotics may be ineffective in controlling the incidence of the intestinal disease [77]. In addition to this, studies looking at the effect of antibiotics commonly found in waste milk have also found no improvement in these parameters [80,81]. In some cases, calves receiving these drugs have experienced a reduction in growth and an increase in diarrhea incidences [32,49].

Although antibiotics were widely regarded as an optional performance enhancer for pre-weaned calves [82], the results from these studies do not provide enough evidence to suggest that they are suitable for that role.

The possible growth-promoting effects of antibiotics have been attributed to mechanisms that modify the GI microbiota [81]. This includes inhibiting pathogen growth and infectious diseases, diminishing the presence of growth-depressing microbial metabolites, reducing the amount of nutrients utilized by commensal microbes and, subsequently, dissipating the thickness of the GI tract, allowing for improved nutrient absorption [83]. However, there is speculation that this may actually have negative implications on calf health due to disruptions in the GI microbiota, leaving permanent changes in the community structure [49]. For instance, a commonly used broad-spectrum antibiotic, oxytetracycline, has been shown to significantly reduce the abundance of *Lactobacilli* in the GIT [84]. The resident GI microbial community has a mutualistic relationship with the host and has been shown to be a crucial constituent in the development of local and systemic immunity [85].

In calf studies, therapeutic and non-therapeutic doses of antibiotics have been shown to have no effect on community structure and species diversity [76]. Conversely, calves receiving waste milk with antibiotic residues have had distinctly different microbial communities, although most of the differences were only at the genus-level [80]. Contrary to this, Penati et al. [49] observed that antibiotic residues in waste milk had a detrimental effect on microbial richness and diversity, to the extent that they disrupted the community structure at the phylum-level. The greater degree of dysbiosis may have been due to higher antibiotic concentrations. It appears that antibiotic residues in waste milk, which are unregulated and frequently differ in concentration, may pose a greater risk of dysbiosis in the GI microbiota of calves. However, it is unclear if metaphylactic and prophylactic antibiotic administration has the same effect. Additionally, the GI microbiota consists of various microorganisms, apart from bacteria, such as viruses, fungi, and protozoa. It may be important to investigate if changes in the bacterial community may cause any changes in the community structure of these organisms [49].

Several studies have expressed concerns over the occurrence of antibiotic-resistant genes in calves receiving antibiotics. Langford et al. [71] found that increasing concentrations of penicillin residues in milk subsequently increased the level of resistance amongst the fecal bacteria. Resistant bacteria were stable and persistent in the microbial community, even after receiving untreated milk for four consecutive days. It has also been found that treating sick calves with cephalosporin and the prophylactic addition of oxytetracycline hydrochloride and neomycin sulphate to milk replacer significantly increases the level of resistance in the fecal *E. coli* community. In addition to this, the *E. coli* community also showed resistance to multiple antimicrobials that were not even used on the experimental

farm [86]. This suggests that the prophylactic use of antibiotics does increase the abundance of antibiotic-resistant bacteria.

These findings on antibiotic-resistant genes do support research efforts to reduce the use of antibiotics in the dairy industry. According to Gomez et al. [75], there are three strategies for reducing antibiotic use, that is by (1) preventing disease, (2) reducing the total mass of antibiotics used, and (3) refining antibiotic stewardship. As mentioned before, the second point is already in practice, since there is already a global movement towards reducing the use of antibiotics for prophylactics (as a performance enhancer). However, the first and third points do need to be further addressed. It is apparent that not all farms utilize a sound antibiotic program for the treatment of diseases. This may result in antibiotics being used excessively or incorrectly (i.e., incorrect drug or dose). This may be prevented by utilizing an antibiotic protocol that targets specific disease signs in calves. In terms of disease prevention, the influence of nutritional management practices has already been discussed to some extent in this review. However, it is also worth noting that housing and hygiene also play an important role. Additionally, preventing disease and improving health creates an opportunity to further investigate supportive strategies, such as DFM administration.

4. Direct-Fed Microbials (Probiotics)

When looking at the mammalian GIT, the mucosal layer and resident microbiota are together incremental in preventing infection [87]. The microbial community resides in close proximity with the mucosa, and under the right circumstances, a mutualistic relationship exists between these two entities [88]. The microbiota assist the host in digesting feed, combating pathogens, and in regulating the mucosal immune system [87,89]. The mucosal layer regulates the GIT conditions by monitoring the activities of the epithelial and immune cells; in doing so, it assists in maintaining a favorable environment for a stable microflora [90]. Any dysfunction in either of these systems is likely to disrupt this symbiosis and ameliorate the local defense mechanisms of the host, increasing the risk of local and systemic infections [87]. Prophylaxis through intervention of the mucosa may be inaccessible; however, the microbiota is more pliable and may be manipulated by various external and internal factors [91,92]. Therefore, strategies which improve gut health by the way of manipulating the GIT microflora [84] are of interest for improving overall calf health.

At maturity, the GI microbiota accommodates a diverse ecosystem of microorganisms, including bacteria, viruses, fungi, archaea, and protozoa, with bacteria being the most abundant [92,93]. However, during infancy it is less complex and has to undergo continuous changes in composition during the first months of life [84]. It is often during this transitional state in which the microbiota are less resilient to disruptions that may cause a dysbiosis [49]. Dysbiosis is likely to increase the risk of pathogens colonizing the GIT and cause enteric infections [18]. As a result, calves are frequently predisposed to diarrhea, which also puts them at risk of diminished digestion and absorption of nutrients and compromised growth [94]. Mechanisms for manipulating and stabilizing the intestinal microbiota have become a focus point [29]. Live microbial additives, such as DFMs, may have the potential to fulfill this role.

A DFM consists of live microorganisms that may improve the health of the host when administered in sufficient doses [95], this may include prokaryotic or eukaryotic organisms, such as bacteria or yeast [96]. It is recommended that a DFM should contain a sufficient number of viable microorganisms; this should be no less than the suggested minimum level (SML) of 10^6 CFU/mL or g [97]. Furthermore, an ideal DFM should be non-toxic and non-pathogenic, able to tolerate gastric acid, inhibit pathogen growth, and enhance the defense mechanisms of the immune system [17]. Lactic acid bacteria, consisting of the genera *Lactobacillus*, *Bifidobacterium*, and *Enterococcus* (Table 1), have been the most frequently investigated as DFMs due to their natural presence in a healthy GI microbiota [98]. However, this field of research has expanded to include foreign

microorganisms, namely some spore-forming *Bacillus* species- and *Saccharomyces*-based live yeast preparations (Table 1).

Different DFMs may have different modes of action [1], and these mechanisms may not be attributed to an entire species but instead are unique to given strains within a species [89]. Lactic acid bacteria are commonly characterized by strains that exert a competitive pressure on pathogens by utilizing available nutrients, occupying epithelial binding sites and lowering the intestinal pH. Alternatively, some strains of the *Bacillus* genus inhibit pathogens by producing antimicrobials and non-toxic spores, which stimulate the immune system [98]. Strains of live yeast, which are significantly larger in size than bacteria, are also able to promote a protective barrier by preventing pathogens from colonizing the epithelial mucosa. Additionally, strains of *S. cerevisiae var. boulardii* have been shown to neutralize toxins and stimulate a pro-inflammatory response in the event of a bacterial infection [96].

In calf studies, it was commonly perceived that there was incongruent evidence for the efficacy of DFM administration. Some researchers would report positive results, whereas others would find no significant effects [99]. However, a recent systematic review by Alawneh, et al. [22] has shown that there is sufficient evidence to suggest that DFMs are able to improve pre-weaned calf performance; however, there is still not enough evidence to suggest that they promote health by enhancing the immune system or stabilizing the microbiota. Discrepancies in results are often attributed to differences in the health status of the maternal herd and calf-management practices, all of which are critical constituents in promoting calf performance [100]. Microbial properties (Table 1), including strain, dosage, and form of administration, are also considered to alter the success of the DFM [99]. As previously mentioned, the microbial properties are specific to the strain, not species [89]. For example, the species *L. acidophilus* is commonly considered to be a DFM [77], but not all strains of *L. acidophilus* necessarily exert a probiotic effect. Therefore, it is also important for researchers to specify the strain that is being investigated in order to improve the consistency between studies.

Table 1. DFMs that have been investigated for effects on calf performance, listed in chronological order.

Direct-Fed Microbial	Source	CFU/g or mL	Per Calf per Day	Calves/ Group	Calf Starter Consumption	Weight Gain	Health	
Multistrain: *L. acidophilus*, *L. lactis*, and *B. subtilis*	ND	2.2×10^9, 2.2×10^6, 1.1×10^9	10 g	28	NS	NS	NS	[101]
B. subtilis	ND	1.24×10^{10}	10 g	28	NS	NS	NS	[101]
Multistrain: *L. acidophilus* and *Streptococcus faecium*	ND	1×10^9	1 g	T1: 53 T2: 25	NS	NS	NS	[102]
L. acidophilus	ND	5×10^7	1 mL	20	NS	↑ Average daily gain **	NS	[103]
Multistrain: *L. acidolphilus*, *B. subtilis*, *B. licheniformis*, and *L. lactis*	ND	3.3×10^8	10 g (7 days) 5 g (18 days)	14	NS	NS	NS	[104]
L. acidolphilus	ND	2×10^{10}	10 g	14	NS	NS	NS	[104]

Table 1. *Cont.*

Direct-Fed Microbial	Source	CFU/g or mL	Per Calf per Day	Calves/ Group	Calf Starter Consumption	Weight Gain	Health	
Multistrain: *L. acidophilus* W55, *L. salivarius* W57, *L. paracasei spp. Paracasei* W56, *L. plantarum* W59, *Lactococcus lactis* W58, and *Enterococcus faecium* W54.	NCS	1×10^9 cfu/kg of BW	T1 & T2: 45 mL T3 & T4: 45, 50, 60 and 80 mL	T1: 72 T2: 31 T3: 24 T4: 24	↑ Feed efficiency *	↑ Weight gain *	NS	[105]
Multistrain: *L. sanfranciscensis*, *L. bifermentans*, *L. viridescens*, *L. confuses*, *L. kefiri* or *L. reuteri*, *L. fermentum*	CS	1×10^9	45, 50, 60 and 80 mL	T3: 24 T4: 24	↑ Feed efficiency *	↑ Weight gain *	↓ Incidence and duration of diarrhea **	[105]
Saccharomyces cerevisiae CNCM I-1077	NCS	10×10^9	0.5 g	13	↑ Starter DM intake and feed efficiency **	↑Weight gain **	↓ Days with diarrhea	[106]
S. boulardii CNCM I-1079	NCS	10×10^9	0.5 g	13	NS	NS	↓ Days with diarrhea	[106]
S. cerevisiae CNCM I-1077	NCS	2×10^{10}	1 g	8	↑ Starter DM intake **	NS	NS	[107]
S. boulardii CNCM I-1079	NCS	2×10^{10}	1 g	8	NS	NS	NS	[107]
Bacillus licheniformis and Bacillus subtilis	NCS	1.28×10^9/kg	In the milk replacer powder: 400 g/t	32	↑ Starter DM intake **	↑ Weight gain **	NS	[100]
Multistrain: *L. casei* DSPV 318T, *L. salivarius* DSPV 315T, and *Pediococcus acidilactici* DSPV 006T	CS	1×10^9 kg/ calf/day	40 mL	18	NS	NS	NS	[99]
Multistrain: *L. casei* DSPV 318T, *L. salivarius* DSPV 315T, and *Pediococcus acidilactici* DSPV 006T	CS	1×10^9 kg BW/calf/day	40 mL	8	↑ Starter DM intake **	↑ Average daily gain **	↓ Fecal consistency index **	[108]
B. subtilis natto	NCS	1×10^{10}	10 mL	6	↑ Feed efficiency **	↑ Average daily gain **		[109]
B. lichenformis and B. subtilis	NCS	1×10^9		20	NS	NS	NS	[98]
Multistrain: *L. acidophilus*, *L. casei*, *Bifidobacterium bifidium*, and *Enterococcus faecium*	ND	2×10^8	2 g	8	NS	↑ Final body weight ** ↑ Final wither height and hip height ** ↑ Final body weight **		[110]

Table 1. *Cont.*

Direct-Fed Microbial	Source	CFU/g or mL	Per Calf per Day	Calves/ Group	Calf Starter Consumption	Weight Gain	Health	
Multistrain: *L. acidophilus* PTCC 1643, *L. rhamnosus* PTCC 1637, *L. casei* PTCC 1608, and *L. delbrueckii* PTCC 1333	NCS	2×10^8	2 g	8	NS	↑ Final wither height and hip height **		[110]
Multistrain: *L. johnsonii* CRL1693, *L. murinus* CRL1695, *L. mucosae* CRL1696, and *L. salivarius* CRL1702	CS	1×10^9	10 mL	26			↓ Mortalities ** ↓Antibiotic treatments ** ↑Health index**	[111]
Multistrain: *Pediococcus acidilactici*, *Enterococcus faecium*, *L. acidophilus*, *L. casei*, *Bifidobacterium bifidum*	ND	43.4×10^9	4 g	100		NS	↓ Duration of diarrhea **	[112]
S. boulardii CNCM I-1079	NCS	1×10^9	5 g	42	NS	NS	↓ Severity of diarrhea ** ↓ Antibiotic treatments **	[30]
S. boulardii CNCM I-1079	NCS	2×10^{10}	Low: 0.5 g Medium: 1 g High: 2 g	4	↑ Starter DM intake **	NS	↓ Fecal scores **	[113]
S. boulardii CNCM I-1079		10×10^{10}	5 g	80	NS	NS	NS	[114]
		20×10^{10}	10 g	80	NS	↑ Weight gain **	NS	
Multistrain: *B. subtilis* (DSMZ 5750), *B. licheniformis* (DSMZ 5749), and *Enterococcus faecium.*	NCS	3.2×10^{10}, 3.2×10^{10} and 5×10^{10} Per kg	20 g	8	NS	NS	NS	[115]
Multistrain: *L. sporogenes*, *Enterococcus faecalis*, and *Bifidobacterium bifidum*	ND	4.1×10^7	3 g	40		↑ Average daily gain **	NS	[116]
Multistrain: *L. casei* PKM B/00103, *L. salivarius* PKM B/00102, *L. sakei* PKM B/00101.	CS	1×10^{11}	250 mg	11	NS	NS	↓ Severity of diarrhea ***	[117]

T: trial; CS: calf-specific; NCS: not calf-specific; ND: not determined or not described; NS: not significant; * ($0.05 < p < 0.1$); ** ($p < 0.05$); *** ($p < 0.0001$); ↑: increase; ↓: decrease.

Upon evaluating the literature, it is evident that lactic acid bacteria (LAB) were the first microorganisms of interest, in particular, the species *L. acidophilus*. It appears, that the earliest studies reported incongruent effects of DFMs on calf-performance parameters. For example, when 10 g of a multistrain LAB probioitic was reconstituted in milk, no effects on calf performance were observed [101]. However, it is unclear if this dosage was for the entire treatment group or individual calves. If it was the former, then it could mean the calves received considerably lower doses as opposed to some of the more recent studies. Since the dosage is an important requirement determining the efficacy of

a DFM, this should be taken into account. Alternatively, a significant improvement in average daily gain was found when calves were fed *L. acidophilus* [103]. However, when *L. acidophilus* was fed at a higher dose, no significant effects were reported [102,104]. These discrepancies could be due to the use of a medicated milk replacer, consisting of oxytetracycline and neomycin sulphate, or waste milk. Oxytetracycline is a broad spectrum antibiotic, and it has been shown to significantly reduce the abundance of *Lactobacilli* in the GIT of calves [118]; therefore, it is possible that it intereferes with the efficacy of the *L. acidophilus* DFM. In the aforementioned studies, the strain of the microorganisms was often not specified, and it is unclear how the various microorganisms were selected. As previously suggested, this might explain why DFMs appear to have incongruent results.

In more modern studies, after the year 2000, many of the LAB DFMs consisted of multiple species and strains. A majority of these studies have reported a positive improvement in calf performance; however, there are two studies where no improvement was found [99,104]. It is worth noting that in one of these studies, the calves were provided with a medicated milk replacer [104]. Several studies have reported an attenuation in the intensity of diarrhea [105,108,111,112,117], which may suggest that some strains of LAB are effective in maintaining a stable microflora, thereby preventing enteric infections [119]. Four of these studies utilized strains that were isolated from calf fecal samples. This may support the idea that host-specific strains have a greater probiotic effect than non-host- specific strains. This idea was further investigated by Timmerman et al. [105], where a host-specific and non-host-specific DFM were fed to calves. The non-host-specific DFM was able to reduce the incidence of severe diarrhea; however, unlike the host-specific DFM, it was unable to reduce the incidence of mild nutritional diarrhea [105].

Additionally, growth and intake were also influenced by LAB DFMs. In some cases, ADG was improved [105,108,116], or alternatively, final body weight, whither, and hip height were improved [110]. Starter dry matter intake [108] and feed efficiency were also improved [105].

A DFM product consisting of *B. subtillus and B. licheninformis* has been shown to significantly increase starter feed and energy intake [100]. However, this DFM has not shown any improvement in feed efficiency [98,100]. Alternatively, a different type of *Bacillus* DFMs, consisting of *B. subtilis natto,* significantly enhanced feed efficiency. The improvement in feed efficiency was associated with better growth, and this was also correlated with an earlier weaning age. Additionally, increased levels of serum IgG and interferon-γ were observed [109]. This may suggest that the non-toxic spores may have the ability to stimulate cell-mediated immunity. It is worth noting that the stimulation of the immune system is expected to reduce an animal's growth potential and subsequently feed efficiency [88]. However, this was not the case in the aforementioned study. There are few studies which demonstrate a significant effect on the occurrence of diarrhea, except for two studies in which a multi-strain *Bacillus* DFM and a single-strain DFM (*B. amyloliquefaciens*) reduced the occurrence and the number of days with diarrhea, respectively [109,115].

In comparison to bacterial DFMs, there are relatively fewer studies on yeast-based DFMs. There are several calf studies which investigated the use of a yeast culture (YC); however, those which utilized a live yeast additive are sparse. It is important to distinguish between a YC and a live yeast additive, such as an active dry yeast (ADY) [120]. An ADY is the most commonly used live yeast additive. It contains a high number of viable fermentable cells, approximately 15 to 25 billion CFU/g, in which the metabolic activity is preserved, and therefore, it meets the minimum requirements of a DFM (SML of 10^6 CFU/mL or g) [19,97]. Viable yeast products, such as an ADY, are used as an inoculant to produce a YC. Therefore, after fermentation is complete, there may be some residual viable cells in the product; however, it is unlikely that it meets the suggested minimum

level of a DFM. As a result, a yeast culture cannot be classified as a DFM; however, it may be considered to be a prebiotic [82,105].

It appears that these two types of yeast additives are not always clearly differentiated, since YC supplements are often erroneously referred to as DFMs [105]. In this review, only live yeast additives, i.e., ADYs, were considered to be a DFM and were investigated.

In calf nutrition, two strains of *Sacharomyces cerevisiae* origin have been of interest, namely the Pasteur Institute CNCMI-1077 of *S. cerevisiae* and the Pasteur Institute CNCMI-1079 of *S. cerevisiae var. boulardii.* The Pasteur Institute CNCMI-1077 strain has been established as suitable feed additive in ruminant nutrition [107] for its ability to promote an increased DMI, rumen pH, and volatile fatty acids and organic matter digestibility in dairy cattle receiving high concentrate diets [21,121]. In pre-weaned calves, this is the first strain of live yeast to be investigated, and it has been shown to successfully promote DMI, body weight gain, feed efficiency, and plasma glucose levels [106]. Alternatively, in another study, it did not have a significant effect on body weight gain and feed efficiency. It did, however, significantly increase rumen ammonia N, propionate, and butyrate [107]. This strain appears to positively modify rumen fermentation, although it is unclear to what extent it may also impact calf performance.

It appears that the research interest has moved towards the Pasteur Institute CNCMI-1079 strain of *S. cerevisiae var. boulardii.*

A few emerging studies have focused on the use of *Saccharomyces cerevisiae var. boulardii* due to its reputation as an anti-diarrheal treatment in humans and animals [20,122]. Galvão et al. [106] and Villot et al. [30] observed that *S. cerevisiae var. boulardii,* containing the Pasteur institute CNCM-1077 strain, diminished the duration or severity of diarrhea, respectively. This was also accompanied by a reduction in the administration of antibiotic treatments. Furthermore, it has also been found that this particular strain assists diarrheic calves in maintaining the same dry matter intake (DMI) and growth rate as the non-diarrheic calves [30]. These results may be associated with the ability of the Pasteur Institute CNCMI-1079 strain to promote a stable microbiota consisting of beneficial LAB. This was observed by one study in which a greater proportion of *Lactobacilli* were found in the feces of calves; this may suggest that the growth of *Lactobacilli* in the GIT was promoted [123]. Additionally, Fomenky et al. [124] observed that this strain enhanced neutrophil activity, including phagocytosis and oxidative burst capacity. As mentioned before with the *Bacillus*-based DFM, an immune response is expected to reduce calf growth and feed efficiency [88]. If this strain does have the potential to stimulate innate immunity, then the maintained DMI and growth of diarrheic calves, as observed by Villot et al. [30], may be of interest.

A majority of the papers that were reviewed looked at the effect of supplementing the DFM to milk or milk replacer. This feeding protocol is used for the purpose of targeting intestinal health in pre-ruminant calves [18]. However, there is potential for DFMs to also be utilized as an additive for promoting rumen development in calves. DFMs, such as *Megasphaera elsdenii*, are used in ruminant nutrition for the purpose of improving rumen fermentation [18]. This particular DFM has been shown to improve feed intake and rumen development in pre-weaned calves [125]. The Pasteur Institute CNCMI-1077 strain of *S. cerevisiae* has also been shown to increase DMI, feed efficiency [106], and volatile fatty acid production [107]. Studies targeting rumen development have supplemented the calf starter feed with a DFM. Therefore, it appears that there are two distinct roles for DFMs in calf nutrition, and each requires different feeding protocols and DFM strains. We suggest that DFM protocols should be refined and specialized to target intestinal health in pre-ruminant calves and rumen development in the ruminant calves. It is likely that the DFMs that encourage starter intake and rumen development will become increasingly important, especially due to an increase in the popularity of enhanced milk feeding regimes.

In general, it appears that the different types of DFMs have the potential to bring about similar improvements in calf performance, although it may be achieved through different modes of action. Lactic acid bacteria seem to stabilize the resident microflora, which subsequently influences the health, growth, and vivacity of the calf. Alternatively, the *Bacillus*-based DFMs utilize non-toxic spores, which have been shown to stimulate cell-mediated immunity and promote calf performance, i.e., feed intake, feed efficiency, and growth. The yeast-based DFMs are dynamic and have been shown to stimulate innate immunity and promote *Lactobacilli* growth in the GIT, which has been shown to assist diarrheic calves in maintaining the same DMI and growth rate as non-diarrheic calves. It is of interest that *Bacillus*- and *S. cerevisiae var. boulardii*-based DFMs have been shown to promote immune responses and either maintain or even promote calf performance.

It is frequently suggested that the positive effects of DFMs are only visible when calves are stressed or under poor management conditions. However, although some current management practices in intensive farms may exacerbate stress, the pre-weaning period will always be a considerably stressful time. This may be due to exposure to the *exutero* environment after birth [67], dam separation, rapidly changing diets, and early weaning. Although a number of studies have shown that DFMs are able to support calves during stress exposure, such as heat stress [113] and FPI [106], DFMs should not be seen as a supportive therapy for calves that are poorly managed. Instead, DFMs should be seen as an additional measure to support calf performance during an already challenging time period. As a recommendation, DFMs should be administered as soon as possible, before the onset of disease or infections, in order to be efficiently utilized [100]. Some studies suggest that it may be beneficial to start administration as soon as the first colostrum meal [103,116,117].

5. Conclusions

High levels of morbidity and mortality diminish the welfare of pre-weaned calves. Nutritional management strategies may exacerbate digestive diseases and infringe on calf welfare if they result in FPI, exposure to harmful pathogens, antibiotic residues, and distress. The first line of intervention for improving calf welfare should be the improvement of the nutritional management strategies that are employed. Although, the concept of SPI is well understood, the true proportion of calves that receive SPI is not clearly defined. This should be elucidated to help understand if it could be linked with the high levels of digestive diseases in calves. Furthermore, colostrum should also be considered for its role in the colonization of the GIT. Waste milk is considered to be unfavorable for calves; however, transition milk may be beneficial for the development of the GIT. Numerous studies suggest that calves should be fed non-restrictive milk diets in order to promote growth and health. Although antibiotics have been traditionally viewed as a viable growth promoter or performance enhancer for calves, there is in fact insufficient evidence to suggest that it is an effective performance-enhancer. Additionally due to the risk associated with antibiotic-resistant bacteria, antibiotic stewardship should be improved so that it can be preserved for the therapeutic treatment of infectious diseases. Alternatively, different types of DFMs may be suitable for promoting calf performance and GI health. Multi-strain DFMs, especially those of calf origin, and live yeast additives have shown similar improvements in fecal scores, growth, and feed efficiency. Direct-fed microbials have been shown to be especially beneficial for calves exposed to stress; however, DFMs should not be simply seen as a supportive therapy for calves that are poorly managed. Instead DFMs should be viewed as an additional measure to support calves during a challenging developmental period. There is potential for this field to be refined to develop specialized feeding protocols to target pre-ruminant and ruminant calves.

Author Contributions: Conceptualization, S.J.D., G.E., C.V., E.C. and E.R.; writing—original draft preparation, S.J.D.; writing—review and editing, S.J.D., G.E., C.V., E.C. and E.R.; supervision, G.E. and E.R.; project administration, G.E., C.V., E.C. and E.R. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: Lallemand SAS supported the first author's internship but no conflict of interest is reported for this article.

References

1. Cangiano, L.R.; Yohe, T.T.; Steele, M.A.; Renaud, D.L. Invited Review: Strategic use of microbial-based probiotics and prebiotics in dairy calf rearing. *Appl. Anim. Sci.* **2020**, *36*, 630–651. [CrossRef]
2. Lorenz, I.; Mee, J.F.; Earley, B.; More, S.J. Calf health from birth to weaning. I. General aspects of disease prevention. *Ir. Vet. J.* **2011**, *64*, 9. [CrossRef] [PubMed]
3. Urie, N.; Lombard, J.; Shivley, C.; Kopral, C.; Adams, A.; Earleywine, T.; Olson, J.; Garry, F. Preweaned heifer management on US dairy operations: Part V. Factors associated with morbidity and mortality in preweaned dairy heifer calves. *J. Dairy Sci.* **2018**, *101*, 9229–9244. [CrossRef] [PubMed]
4. Hulbert, L.E.; Moisá, S.J. Stress, immunity, and the management of calves. *J. Dairy Sci.* **2016**, *99*, 3199–3216. [CrossRef] [PubMed]
5. Raeth-Knight, M.; Chester-Jones, H.; Hayes, S.; Linn, J.; Larson, R.; Ziegler, D.; Ziegler, B.; Broadwater, N. Impact of conventional or intensive milk replacer programs on Holstein heifer performance through six months of age and during first lactation. *J. Dairy Sci.* **2009**, *92*, 799–809. [CrossRef]
6. Soberon, F.; Raffrenato, E.; Everett, R.W.; Van Amburgh, M.E. Preweaning milk replacer intake and effects on long-term productivity of dairy calves. *J. Dairy Sci.* **2012**, *95*, 783–793. [CrossRef]
7. Alimirzaei, M.; Alijoo, Y.A.; Banadaky, M.D.; Eslamizad, M. Effects of intensified or conventional milk feeding on pre-weaning health and feeding behavior of holstein female calves around weaning. *Vet. Res. Forum* **2020**, *11*, 311–318. [CrossRef]
8. Cortese, V.S. Neonatal Immunology. *Vet. Clin. N. Am. Food Anim. Pract.* **2009**, *25*, 221–227. [CrossRef] [PubMed]
9. Diao, Q.; Zhang, R.; Fu, T. Review of strategies to promote rumen development in calves. *Animals* **2019**, *9*, 490. [CrossRef]
10. van Niekerk, J.K.; Fischer-Tlustos, A.J.; Wilms, J.N.; Hare, K.S.; Welboren, A.C.; Lopez, A.J.; Yohe, T.T.; Cangiano, L.R.; Leal, L.N.; Steele, M.A. ADSA Foundation Scholar Award: New frontiers in calf and heifer nutrition—From conception to puberty. *J. Dairy Sci.* **2021**, *104*, 8341–8362. [CrossRef]
11. Santman-Berends, I.M.G.A.; Buddiger, M.; Smolenaars, A.J.G.; Steuten, C.D.M.; Roos, C.A.J.; Van Erp, A.J.M.; Van Schaik, G. A multidisciplinary approach to determine factors associated with calf rearing practices and calf mortality in dairy herds. *Prev. Vet. Med.* **2014**, *117*, 375–387. [CrossRef] [PubMed]
12. DCHA. *Gold Standards*, 2nd ed.; Dairy Calf and Heifer Association: Madison, WI, USA, 2014.
13. USDA. *Dairy 2014 Health and Management Practices on U.S. Dairy Operations*; United States Department of Agriculture: Washington, DC, USA, 2014.
14. Hammon, H.M.; Liermann, W.; Frieten, D.; Koch, C. Review: Importance of colostrum supply and milk feeding intensity on gastrointestinal and systemic development in calves. *Animal* **2020**, *14*, S133–S143. [CrossRef] [PubMed]
15. USDA. *Transfer of Maternal Immunity to Calves: National Dairy Heifer Evaluation Project*; United States Department of Agriculture: Washington, DC, USA, 1993.
16. USDA. *Dairy 2007 Heifer Calf Health and Management Practices on U.S. Dairy Operations*; United States Department of Agriculture: Washington, DC, USA, 2007.
17. Ma, T.; Suzuki, Y.; Guan, L.L. Dissect the mode of action of probiotics in affecting host-microbial interactions and immunity in food producing animals. *Vet. Immunol. Immunopathol.* **2018**, *205*, 35–48. [CrossRef] [PubMed]
18. Uyeno, Y.; Shigemori, S.; Shimosato, T. Effect of Probiotics/Prebiotics on Cattle Health and Productivity. *Microbes Environ.* **2015**, *30*, 126–132. [CrossRef] [PubMed]
19. Shurson, G.C. Yeast and yeast derivatives in feed additives and ingredients: Sources, characteristics, animal responses, and quantification methods. *Anim. Feed Sci. Technol.* **2018**, *235*, 60–76. [CrossRef]
20. Garcia-Mazcorro, J.F.; Ishaq, S.L.; Rodriguez-Herrera, M.V.; Garcia-Hernandez, C.A.; Kawas, J.R.; Nagaraja, T.G. Review: Are there indigenous Saccharomyces in the digestive tract of livestock animal species? Implications for health, nutrition and productivity traits. *Animal* **2019**, *14*, 22–30. [CrossRef] [PubMed]

21. Chaucheyras-Durand, F.; Walker, N.D.; Bach, A.; Wallace, R.J.; Colombatto, D.; Robinson, P.H. Effects of active dry yeasts on the rumen microbial ecosystem: Past, present and future. *Anim. Feed Sci. Technol.* **2008**, *145*, 5–26. [CrossRef]
22. Alawneh, J.I.; Barreto, M.O.; Moore, R.J.; Soust, M.; Al-harbi, H.; James, A.S.; Krishnan, D.; Olchowy, T.W.J. Systematic review of an intervention: The use of probiotics to improve health and productivity of calves. *Prev. Vet. Med.* **2020**, *183*, 105147. [CrossRef]
23. Klein-Jöbstl, D.; Iwersen, M.; Drillich, M. Farm characteristics and calf management practices on dairy farms with and without diarrhea: A case-control study to investigate risk factors for calf diarrhea. *J. Dairy Sci.* **2014**, *97*, 5110–5119. [CrossRef]
24. Zhao, W.; Choi, C.Y.; Li, G.; Li, H.; Shi, Z. Pre-weaned dairy calf management practices, morbidity and mortality of bovine respiratory disease and diarrhea in China. *Livest. Sci.* **2021**, *251*, 104608. [CrossRef]
25. Von Keyserlingk, M.A.G.; Rushen, J.; De Passillé, A.M.; Weary, D.M. Invited review: The welfare of dairy cattle-Key concepts and the role of science. *J. Dairy Sci.* **2009**, *92*, 4101–4111. [CrossRef] [PubMed]
26. Introduction to the Recommendations for Animal Welfare. In *Terrestrial Animal Health Code*; 2021; p. 4.
27. Welfare Quality. *Welfare Quality Assessment Protocol for Cattle*; Lelystad, The Netherlands, 2009.
28. Barrington, G.M.; Parish, S.M. Bovine neonatal immunology. *Vet. Clin. N. Am. Food Anim. Pract.* **2001**, *17*, 463–476. [CrossRef]
29. Fischer, A.J.; Villot, C.; van Niekerk, J.K.; Yohe, T.T.; Renaud, D.L.; Steele, M.A. INVITED REVIEW: Nutritional regulation of gut function in dairy calves: From colostrum to weaning. *Appl. Anim. Sci.* **2019**, *35*, 498–510. [CrossRef]
30. Villot, C.; Ma, T.; Renaud, D.L.; Ghaffari, M.H.; Gibson, D.J.; Skidmore, A.; Chevaux, E.; Guan, L.L.; Steele, M.A. Saccharomyces cerevisiae boulardii CNCM I-1079 affects health, growth, and fecal microbiota in milk-fed veal calves. *J. Dairy Sci.* **2019**, *102*, 7011–7025. [CrossRef] [PubMed]
31. Vasseur, E.; Borderas, F.; Cue, R.I.; Lefebvre, D.; Pellerin, D.; Rushen, J.; Wade, K.M.; De Passillé, A.M. A survey of dairy calf management practices in Canada that affect animal welfare. *J. Dairy Sci.* **2010**, *93*, 1307–1315. [CrossRef] [PubMed]
32. Berge, A.C.B.; Lindeque, P.; Moore, D.A.; Sischo, W.M. A clinical trial evaluating prophylactic and therapeutic antibiotic use on health and performance of preweaned calves. *J. Dairy Sci.* **2005**, *88*, 2166–2177. [CrossRef]
33. Lorenz, I. Calf health from birth to weaning—An update. *Ir. Vet. J.* **2021**, *74*, 5. [CrossRef]
34. Lora, I.; Gottardo, F.; Contiero, B.; Dall Ava, B.; Bonfanti, L.; Stefani, A.; Barberio, A. Association between passive immunity and health status of dairy calves under 30 days of age. *Prev. Vet. Med.* **2018**, *152*, 12–15. [CrossRef]
35. Shivley, C.; Lombard, J.; Urie, N.; Weary, D.; von Keyserlingk, M. Management of preweaned bull calves on dairy operations in the United States. *J. Dairy Sci.* **2019**, *102*, 4489–4497. [CrossRef]
36. Beam, A.L.; Lombard, J.E.; Kopral, C.A.; Garber, L.P.; Winter, A.L.; Hicks, J.A.; Schlater, J.L. Prevalence of failure of passive transfer of immunity in newborn heifer calves and associated management practices on US dairy operations. *J. Dairy Sci.* **2009**, *92*, 3973–3980. [CrossRef] [PubMed]
37. Godden, S.M.; Lombard, J.E.; Woolums, A.R. Colostrum Management for Dairy Calves. *Vet. Clin. N. Am. Food Anim. Pract.* **2019**, *35*, 535–556. [CrossRef] [PubMed]
38. Weaver, D.M.; Tyler, J.W.; VanMetre, D.C.; Hostetler, D.E.; Barrington, G.M. Passive transfer of colostral immunoglobulins in calves. *J. Vet. Intern. Med.* **2000**, *14*, 569–577. [CrossRef] [PubMed]
39. Lopez, A.J.; Heinrichs, A.J. Invited review: The importance of colostrum in the newborn dairy calf. *J. Dairy Sci.* **2022**, *105*, 2733–2749. [CrossRef] [PubMed]
40. Franklin, S.T.; Amaral-Phillips, D.M.; Jackson, J.A.; Campbell, A.A. Health and Performance of Holstein Calves that Suckled or Were Hand-Fed Colostrum and Were Fed One of Three Physical Forms of Starter 1. *J. Dairy Sci.* **2003**, *86*, 2145–2153. [CrossRef]
41. Stott, G.H.; Marx, D.B.; Menefee, B.E.; Nightengale, G.T. Colostral Immunoglobulin Transfer in Calves I. Period of Absorption. *J. Dairy Sci.* **1979**, *62*, 1632–1638. [CrossRef]
42. Fischer, A.J.; Song, Y.; He, Z.; Haines, D.M.; Guan, L.L.; Steele, M.A. Effect of delaying colostrum feeding on passive transfer and intestinal bacterial colonization in neonatal male Holstein calves. *J. Dairy Sci.* **2018**, *101*, 3099–3109. [CrossRef] [PubMed]
43. Godden, S.M.; Haines, D.M.; Konkol, K.; Peterson, J. Improving passive transfer of immunoglobulins in calves. II: Interaction between feeding method and volume of colostrum fed. *J. Dairy Sci.* **2009**, *92*, 1758–1764. [CrossRef]
44. Cardoso, C.L.; King, A.; Chapwanya, A.; Esposito, G. Growth and Puberty of Calves—A Review. *Animals* **2021**, *11*, 1212–1224. [CrossRef]
45. Gelsinger, S.L.; Gray, S.M.; Jones, C.M.; Heinrichs, A.J. Heat treatment of colostrum increases immunoglobulin G absorption efficiency in high-, medium-, and low-quality colostrum. *J. Dairy Sci.* **2014**, *97*, 2355–2360. [CrossRef]
46. Conneely, M.; Berry, D.P.; Murphy, J.P.; Lorenz, I.; Doherty, M.L.; Kennedy, E. Effect of feeding colostrum at different volumes and subsequent number of transition milk feeds on the serum immunoglobulin G concentration and health status of dairy calves. *J. Dairy Sci.* **2014**, *97*, 6991–7000. [CrossRef]
47. Malmuthuge, N.; Griebel, P.J.; Guan, L.L. The gut microbiome and its potential role in the development and function of newborn calf gastrointestinal tract. *Front. Vet. Sci.* **2015**, *2*, 1–10. [CrossRef]
48. Oikonomou, G.; Teixeira, A.G.V.; Foditsch, C.; Bicalho, M.L.; Machado, V.S.; Bicalho, R.C. Fecal Microbial Diversity in Pre-Weaned Dairy Calves as Described by Pyrosequencing of Metagenomic 16S rDNA. Associations of Faecalibacterium Species with Health and Growth. *PLoS ONE* **2013**, *8*, e63157. [CrossRef] [PubMed]

49. Penati, M.; Sala, G.; Biscarini, F.; Boccardo, A.; Bronzo, V.; Castiglioni, B.; Cremonesi, P.; Moroni, P.; Pravettoni, D.; Addis, M.F. Feeding Pre-weaned Calves with Waste Milk Containing Antibiotic Residues Is Related to a Higher Incidence of Diarrhea and Alterations in the Fecal Microbiota. *Front. Vet. Sci.* **2021**, *8*, 650150. [CrossRef]
50. Butler, J.A.; Sickles, S.A.; Johanns, C.J.; Rosenbusch, R.F. Pasteurization of discard mycoplasma mastitic milk used to feed calves: Thermal effects on various mycoplasma. *J. Dairy Sci.* **2000**, *83*, 2285–2288. [CrossRef]
51. Stabel, J.R. On-farm batch pasteurization destroys Mycobacterium paratuberculosis in waste milk. *J. Dairy Sci.* **2001**, *84*, 524–527. [CrossRef]
52. Godden, S.M.; Smith, S.; Feirtag, J.M.; Green, L.R.; Wells, S.J.; Fetrow, J.P. Effect of on-farm commercial batch pasteurization of colostrum on colostrum and serum immunoglobulin concentrations in dairy calves. *J. Dairy Sci.* **2003**, *86*, 1503–1512. [CrossRef]
53. Kertz, A.F.; Hill, T.M.; Quigley, J.D.; Heinrichs, A.J.; Linn, J.G.; Drackley, J.K. A 100-Year Review: Calf nutrition and management. *J. Dairy Sci.* **2017**, *100*, 10151–10172. [CrossRef]
54. Urie, N.J.; Lombard, J.E.; Shivley, C.B.; Kopral, C.A.; Adams, A.E.; Earleywine, T.J.; Olson, J.D.; Garry, F.B. Preweaned heifer management on US dairy operations: Part I. Descriptive characteristics of preweaned heifer raising practices. *J. Dairy Sci.* **2018**, *101*, 9168–9184. [CrossRef]
55. Calderón-amor, J.; Gallo, C. Dairy calf welfare and factors associated with diarrhea and respiratory disease among chilean dairy farms. *Animals* **2020**, *10*, 1115. [CrossRef]
56. Fischer-Tlustos, A.J.; Hertogs, K.; van Niekerk, J.K.; Nagorske, M.; Haines, D.M.; Steele, M.A. Oligosaccharide concentrations in colostrum, transition milk, and mature milk of primi- and multiparous Holstein cows during the first week of lactation. *J. Dairy Sci.* **2020**, *103*, 3683–3695. [CrossRef]
57. Blum, J.W.; Hammon, H. Colostrum effects on the gastrointestinal tract, and on nutritional, endocrine and metabolic parameters in neonatal calves. *Livest. Prod. Sci.* **2000**, *66*, 151–159. [CrossRef]
58. Drackley, J.K. Calf Nutrition from Birth to Breeding. *Vet. Clin. N. Am. Food Anim. Pract.* **2008**, *24*, 55–86. [CrossRef]
59. Khan, M.A.; Bach, A.; Weary, D.M.; von Keyserlingk, M.A.G. Invited review: Transitioning from milk to solid feed in dairy heifers. *J. Dairy Sci.* **2016**, *99*, 885–902. [CrossRef]
60. Khan, M.A.; Weary, D.M.; von Keyserlingk, M.A.G. Invited review: Effects of milk ration on solid feed intake, weaning, and performance in dairy heifers. *J. Dairy Sci.* **2011**, *94*, 1071–1081. [CrossRef]
61. Stull, C.; Reynolds, J. Calf Welfare. *Vet. Clin. N. Am. Food Anim. Pract.* **2008**, *24*, 191–203. [CrossRef]
62. von Keyserlingk, M.A.G.; Weary, D.M. A 100-Year Review: Animal welfare in the Journal of Dairy Science—The first 100 years. *J. Dairy Sci.* **2017**, *100*, 10432–10444. [CrossRef]
63. Carroll, J.A.; Forsberg, N.E. Influence of Stress and Nutrition on Cattle Immunity. *Vet. Clin. Food Anim. Pract.* **2007**, *23*, 105–149. [CrossRef]
64. Ballou, M.A.; Hanson, D.L.; Cobb, C.J.; Obeidat, B.S.; Sellers, M.D.; Pepper-Yowell, A.R.; Carroll, J.A.; Earleywine, T.J.; Lawhon, S.D. Plane of nutrition influences the performance, innate leukocyte responses, and resistance to an oral *Salmonella enterica* serotype Typhimurium challenge in Jersey calves. *J. Dairy Sci.* **2015**, *98*, 1972–1982. [CrossRef]
65. Rosenberger, K.; Costa, J.H.C.; Neave, H.W.; von Keyserlingk, M.A.G.; Weary, D.M. The effect of milk allowance on behavior and weight gains in dairy calves. *J. Dairy Sci.* **2017**, *100*, 504–512. [CrossRef]
66. Quigley, J.D.; Hill, T.M.; Dennis, T.S.; Suarez-Mena, F.X.; Schlotterbeck, R.L. Effects of feeding milk replacer at 2 rates with pelleted, low-starch or texturized, high-starch starters on calf performance and digestion. *J. Dairy Sci.* **2018**, *101*, 5937–5948. [CrossRef]
67. Liang, Y.; Carroll, J.A.; Ballou, M.A. The digestive system of 1-week-old Jersey calves is well suited to digest, absorb, and incorporate protein and energy into tissue growth even when calves are fed a high plane of milk replacer. *J. Dairy Sci.* **2016**, *99*, 1929–1937. [CrossRef]
68. Nonnecke, B.J.; Foote, M.R.; Smith, J.M.; Pesch, B.A.; Van Amburgh, M.E. Composition and functional capacity of blood mononuclear leukocyte populations from neonatal calves on standard and intensified milk replacer diets. *J. Dairy Sci.* **2003**, *86*, 3592–3604. [CrossRef]
69. Morrill, J.L.; Dayton, A.D.; Mickelsen, R. Cultured Milk and Antibiotics for Young Calves. *J. Dairy Sci.* **1977**, *60*, 1105–1109. [CrossRef]
70. Quigley, J.D.; Drewry, J.J.; Murray, L.M.; Ivey, S.J. Body Weight Gain, Feed Efficiency, and Fecal Scores of Dairy Calves in Response to Galactosyl-Lactose or Antibiotics in Milk Replacers. *J. Dairy Sci.* **1997**, *80*, 1751–1754. [CrossRef]
71. Langford, F.M.; Weary, D.M.; Fisher, L. Antibiotic resistance in gut bacteria from dairy calves: A dose response to the level of antibiotics fed in milk. *J. Dairy Sci.* **2003**, *86*, 3963–3966. [CrossRef]
72. Berge, A.C.B.; Moore, D.A.; Besser, T.E.; Sischo, W.M. Targeting therapy to minimize antimicrobial use in preweaned calves: Effects on health, growth, and treatment costs. *J. Dairy Sci.* **2009**, *92*, 4707–4714. [CrossRef]
73. O'Keefe, O.C.; Moore, D.A.; McConnel, C.S.; Sischo, W.M. Parenteral Antimicrobial Treatment Diminishes Fecal Bifidobacterium Quantity but Has No Impact on Health in Neonatal Dairy Calves: Data from a Field Trial. *Front. Vet. Sci.* **2021**, *8*, 1–15. [CrossRef]
74. Foditsch, C.; Pereira, R.V.V.; Siler, J.D.; Altier, C.; Warnick, L.D. Effects of treatment with enrofloxacin or tulathromycin on fecal microbiota composition and genetic function of dairy calves. *PLoS ONE* **2019**, *14*, e0219635. [CrossRef]
75. Gomez, D.E.; Arroyo, L.G.; Renaud, D.L.; Viel, L.; Weese, J.S. A multidisciplinary approach to reduce and refine antimicrobial drugs use for diarrhoea in dairy calves. *Vet. J.* **2021**, *274*, 105713. [CrossRef]

76. Keijser, B.J.F.; Agamennone, V.; Van Den Broek, T.J.; Caspers, M.; Van De Braak, A.; Bomers, R.; Havekes, M.; Schoen, E.; Van Baak, M.; Mioch, D.; et al. Dose-dependent impact of oxytetracycline on the veal calf microbiome and resistome. *BMC Genom.* **2019**, *20*, 65. [CrossRef]
77. Donovan, D.C.; Franklin, S.T.; Chase, C.C.L.; Hippen, A.R. Growth and health of Holstein calves fed milk replacers supplemented with antibiotics or enteroguard. *J. Dairy Sci.* **2002**, *85*, 947–950. [CrossRef]
78. Thames, C.H.; Pruden, A.; James, R.E.; Ray, P.P.; Knowlton, K.F.; Lin, J.; Zurek, L.; Pristas, P.; Liu, J. Excretion of antibiotic resistance genes by dairy calves fed milk replacers with varying doses of antibiotics. *Front. Microbiol.* **2012**, *3*, 139. [CrossRef] [PubMed]
79. Cho, Y.-I.; Yoon, K.-J. An overview of calf diarrhea—Infectious etiology, diagnosis, and intervention. *J. Vet. Sci.* **2014**, *15*, 1–17. [CrossRef] [PubMed]
80. Van Vleck Pereira, R.; Lima, S.; Siler, J.D.; Foditsch, C.; Warnick, L.D.; Carvalho Bicalho, R. Ingestion of Milk Containing Very Low Concentration of Antimicrobials: Longitudinal Effect on Fecal Microbiota Composition in Preweaned Calves. *PLoS ONE* **2016**, *11*, e147525. [CrossRef] [PubMed]
81. Li, J.H.; Yousif, M.H.; Li, Z.Q.; Wu, Z.H.; Li, S.L.; Yang, H.J.; Wang, Y.J.; Cao, Z.J. Effects of antibiotic residues in milk on growth, ruminal fermentation, and microbial community of preweaning dairy calves. *J. Dairy Sci.* **2019**, *102*, 2298–2307. [CrossRef]
82. Alugongo, G.M.; Xiao, J.; Wu, Z.; Li, S.; Wang, Y.; Cao, Z. Review: Utilization of yeast of Saccharomyces cerevisiae origin in artificially raised calves. *J. Anim. Sci. Biotechnol.* **2017**, *8*, 1–12. [CrossRef]
83. Gaskins, H.R.; Collier, C.T.; Anderson, D.B. Antibiotics as growth promotants: Mode of action. *Anim. Biotechnol.* **2002**, *13*, 29–42. [CrossRef] [PubMed]
84. Malmuthuge, N.; Guan, L.L. Understanding the gut microbiome of dairy calves: Opportunities to improve early-life gut health 1. *J. Dairy Sci.* **2017**, *100*, 5996–6005. [CrossRef]
85. Wu, S.; Zhang, F.; Huang, Z.; Liu, H.; Xie, C.; Zhang, J.; Thacker, P.A.; Qiao, S. Effects of the antimicrobial peptide cecropin AD on performance and intestinal health in weaned piglets challenged with *Escherichia coli*. *Peptides* **2012**, *35*, 225–230. [CrossRef]
86. Berge, A.C.B.; Moore, D.A.; Sischo, W.M. Field trial evaluating the influence of prophylactic and therapeutic antimicrobial administration on antimicrobial resistance of fecal *Escherichia coli* in dairy calves. *Appl. Environ. Microbiol.* **2006**, *72*, 3872–3878. [CrossRef]
87. Bischoff, S.C. Gut health: A new objective in medicine? *BMC Med.* **2011**, *9*, 24. [CrossRef] [PubMed]
88. Celi, P.; Cowieson, A.J.; Fru-Nji, F.; Steinert, R.E.; Kluenter, A.M.; Verlhac, V. Gastrointestinal functionality in animal nutrition and health: New opportunities for sustainable animal production. *Anim. Feed Sci. Technol.* **2017**, *234*, 88–100. [CrossRef]
89. Altomare, R.; Damiano, G.; Gioviale, M.C.; Palumbo, V.D.; Maione, C.; Spinelli, G.; Sinagra, E.; Abruzzo, A.; Monte, G.L.; Tomasello, G.; et al. The intestinal ecosystem and probiotics. *Prog. Nutr.* **2016**, *18*, 8–15.
90. O'Callaghan, T.F.; Ross, R.P.; Stanton, C.; Clarke, G. The gut microbiome as a virtual endocrine organ with implications for farm and domestic animal endocrinology. *Domest. Anim. Endocrinol.* **2016**, *56*, S44–S55. [CrossRef]
91. Kogut, M.H.; Arsenault, R.J. Editorial: Gut health: The new paradigm in food animal production. *Front. Vet. Sci.* **2016**, *3*, 10–13. [CrossRef]
92. Gomez, D.E.; Galvão, K.N.; Rodriguez-Lecompte, J.C.; Costa, M.C. The Cattle Microbiota and the Immune System: An Evolving Field. *Vet. Clin. N. Am. Food Anim. Pract.* **2019**, *35*, 485–505. [CrossRef]
93. Freestone, P.P.E.; Sandrini, S.M.; Haigh, R.D.; Lyte, M. Microbial endocrinology: How stress influences susceptibility to infection. *Trends Microbiol.* **2008**, *16*, 55–64. [CrossRef]
94. Oanh, T.L.; Dart, P.J.; Harper, K.; Zhang, D.; Schofield, B.; Callaghan, M.J.; Lisle, A.T.; Klieve, A.; Mcneill, D.M. Effect of probiotic Bacillus amyloliquefaciens strain H57 on productivity and the incidence of diarrhoea in dairy calves. *Anim. Prod. Sci.* **2017**, *57*, 912–919. [CrossRef]
95. Fioramonti, J.; Theodorou, V.; Bueno, L. Probiotics: What are they? What are their effects on gut physiology? *Best Pract. Res. Clin. Gastroenterol.* **2003**, *17*, 711–724. [CrossRef]
96. Czeruka, D.; Piche, T.; Rampal, P. Review article: Yeast as probiotics -Saccharomyces boulardii. *Aliment. Pharmacol. Ther.* **2007**, *26*, 767–778. [CrossRef]
97. de Araújo Etchepare, M.; Nunes, G.L.; Nicoloso, B.R.; Barin, J.S.; Moraes Flores, E.M.; de Oliveira Mello, R.; Ragagnin de Menezes, C. Improvement of the viability of encapsulated probiotics using whey proteins. *LWT* **2020**, *117*, 108601. [CrossRef]
98. Riddell, J.B.; Mcleod, K.R.; de Cv, S.A. Addition of a Bacillus based probiotic to the diet of preruminant calves: Influence on growth, health, and blood parameters. *Int. J. Appl. Res. Vet. Med.* **2010**, *8*, 78–85.
99. Frizzo, L.S.; Bertozzi, E.; Soto, L.P.; Sequeira, G.J.; Rodriguez Armesto, R.; Rosmini, M.R. Studies on translocation, acute oral toxicity and intestinal colonization of potentially probiotic lactic acid bacteria administered during calf rearing. *Livest. Sci.* **2010**, *128*, 28–35. [CrossRef]
100. Kowalski, Z.M.; Górka, P.; Schlagheck, A.; Jagusiak, W.; Micek, P.; Strzetelski, J. Performance of Holstein calves fed milk-replacer and starter mixture supplemented with probiotic feed additive. *J. Anim. Feed Sci.* **2009**, *18*, 399–411. [CrossRef]
101. Jenny, B.F.; Vandijk, H.J.; Collins, J.A. Performance and Fecal Flora of Calves Fed a Bacillus subtilis Concentrate. *J. Dairy Sci.* **1991**, *74*, 1968–1973. [CrossRef]

102. Higginbotham, G.E.; Bath, D.L. Evaluation of Lactobacillus Fermentation Cultures in Calf Feeding Systems. *J. Dairy Sci.* **1993**, *76*, 615–620. [CrossRef]
103. Cruywagen, C.; Jordaan, I.; Venter, L. Effect of Lactobacillus acidophilus Supplementation of Milk Replacer on Preweaning Performance of Calves. *J. Dairy Sci.* **1996**, *79*, 483–486. [CrossRef]
104. Quintero-Gonzalez, C.I.; Comerford, J.W.; Varga, G.A. Effects of Direct-Fed Microbials on Growth, Health, and Blood Parameters of Young Holstein Calves. *Prof. Anim. Sci.* **2003**, *19*, 211–220. [CrossRef]
105. Timmerman, H.M.; Mulder, L.; Everts, H.; Van Espen, D.C.; Van Der Wal, E.; Klaassen, G.; Rouwers, S.M.G.; Hartemink, R.; Rombouts, F.M.; Beynen, A.C. Health and growth of veal calves fed milk replacers with or without probiotics. *J. Dairy Sci.* **2005**, *88*, 2154–2165. [CrossRef]
106. Galvão, K.N.; Santos, J.E.P.; Coscioni, A.; Villaseñor, M.; Sischo, W.M.; Catharina, A.; Berge, B. Effect of feeding live yeast products to calves with failure of passive transfer on performance and patterns of antibiotic resistance in fecal Escherichia coli. *Reprod. Nutr. Dev.* **2005**, *45*, 427–440. [CrossRef]
107. Pinos-Rodríguez, J.; Robinson, P.H.; Ortega, M.E.; Berry, S.L.; Mendoza, G.; Bárcena, R. Performance and rumen fermentation of dairy calves supplemented with Saccharomyces cerevisiae1077 or Saccharomyces boulardii1079. *Anim. Feed Sci. Technol.* **2008**, *140*, 223–232. [CrossRef]
108. Frizzo, L.S.; Soto, L.P.; Zbrun, M.V.; Bertozzi, E.; Sequeira, G.; Armesto, R.R.; Rosmini, M.R. Lactic acid bacteria to improve growth performance in young calves fed milk replacer and spray-dried whey powder. *Anim. Feed Sci. Technol.* **2010**, *157*, 159–167. [CrossRef]
109. Sun, P.; Wang, J.Q.; Zhang, H.T. Effects of Bacillus subtilis natto on performance and immune function of preweaning calves. *J. Dairy Sci.* **2010**, *93*, 5851–5855. [CrossRef]
110. Bayatkouhsar, J.; Tahmasebi, A.M.; Naserian, A.A.; Mokarram, R.R. Effects of supplementation of lactic acid bacteria on growth performance, blood metabolites and fecal coliform and lactobacilli of young dairy calves. *Anim. Feed Sci. Technol.* **2013**, *186*, 1–11. [CrossRef]
111. Maldonado, N.C.; Chiaraviglio, J.; Bru, E.; De Chazal, L.; Santos, V.; Nader-Macías, M.E.F. Effect of milk fermented with lactic acid bacteria on diarrheal incidence, growth performance and microbiological and blood profiles of newborn dairy calves. *Probiotics Antimicrob. Proteins* **2018**, *10*, 668–676. [CrossRef] [PubMed]
112. Renaud, D.L.; Kelton, D.F.; Weese, J.S.; Noble, C.; Duffield, T.F. Evaluation of a multispecies probiotic as a supportive treatment for diarrhea in dairy calves: A randomized clinical trial. *J. Dairy Sci.* **2019**, *102*, 4498–4505. [CrossRef] [PubMed]
113. Lee, J.-S.; Kacem, N.; Kim, W.-S.; Peng, D.Q.; Kim, Y.-J.; Joung, Y.-G.; Lee, C.; Lee, H.-G. Effect of Saccharomyces boulardii Supplementation on Performance and Physiological Traits of Holstein Calves under Heat Stress Conditions. *Animals* **2019**, *9*, 510. [CrossRef]
114. Renaud, D.L.; Shock, D.A.; Roche, S.M.; Steele, M.A.; Chevaux, E.; Skidmore, A.L. Evaluation of Saccharomyces cerevisiae boulardii CNCM I-1079 fed before weaning on health and growth of male dairy calves. *Appl. Anim. Sci.* **2019**, *35*, 570–576. [CrossRef]
115. Mandouh, M.I.; Elbanna, R.A.; Abdellatif, H.A. Effect of Multi-species Probiotic Supplementation on Growth Performance, Antioxidant Status and Incidence of Diarrhea in Neonatal Holstein Dairy Calves. *Int. J. Vet. Sci.* **2020**, *9*, 249–253. [CrossRef]
116. Zábranský, L.; Poborská, A.; Malá, G.; Gálik, B.; Petrášková, E.; Kernerová, N.; Hanušovský, O.; Kučera, J. Probiotic and prebiotic feed additives in Calf nutrition. *J. Cent. Eur. Agric.* **2021**, *22*, 14–18. [CrossRef]
117. Stefańska, B.; Sroka, J.; Katzer, F.; Goliński, P.; Nowak, W. The effect of probiotics, phytobiotics and their combination as feed additives in the diet of dairy calves on performance, rumen fermentation and blood metabolites during the preweaning period. *Anim. Feed Sci. Technol.* **2021**, *272*, 114738. [CrossRef]
118. Oultram, J.; Phipps, E.; Teixeira, A.G.V.; Foditsch, C.; Bicalho, M.L.; Machado, V.S.; Bicalho, R.C.; Oikonomou, G. Effects of antibiotics (oxytetracycline, florfenicol or tulathromycin) on neonatal calves' faecal microbial diversity. *Vet. Rec.* **2015**, *117*, 598. [CrossRef] [PubMed]
119. Signorini, M.L.; Soto, L.P.; Zbrun, M.V.; Sequeira, G.J.; Rosmini, M.R.; Frizzo, L.S. Research in Veterinary Science Impact of probiotic administration on the health and fecal microbiota of young calves: A meta-analysis of randomized controlled trials of lactic acid bacteria. *Res. Vet. Sci.* **2012**, *93*, 250–258. [CrossRef]
120. Geng, C.-Y.; Ren, L.-P.; Zhou, Z.-M.; Chang, Y.; Meng, Q.-X. Comparison of active dry yeast (*Saccharomyces cerevisiae*) and yeast culture for growth performance, carcass traits, meat quality and blood indexes in finishing bulls. *Anim. Sci. J.* **2016**, *87*, 982–988. [CrossRef] [PubMed]
121. Desnoyers, M.; Giger-Reverdin, S.; Bertin, G.; Duvaux-Ponter, C.; Sauvant, D. Meta-analysis of the influence of Saccharomyces cerevisiae supplementation on ruminal parameters and milk production of ruminants. *J. Dairy Sci.* **2009**, *92*, 1620–1632. [CrossRef] [PubMed]
122. Stier, H.; Bischoff, S.C. Influence of saccharomyces boulardii CNCM I-745 on the gut-associated immune system. *Clin. Exp. Gastroenterol.* **2016**, *9*, 269–279. [CrossRef] [PubMed]
123. Fomenky, B.E.; Chiquette, J.; Bissonnette, N.; Talbot, G.; Chouinard, P.Y.; Ibeagha-Awemu, E.M. Impact of Saccharomyces cerevisiae boulardii CNCMI-1079 and Lactobacillus acidophilus BT1386 on total lactobacilli population in the gastrointestinal tract and colon histomorphology of Holstein dairy calves. *Anim. Feed Sci. Technol.* **2017**, *234*, 151–161. [CrossRef]

124. Fomenky, B.E.; Chiquette, J.; Lessard, M.; Bissonnette, N.; Talbot, G.; Chouinard, Y.P.; Ibeagha-Awemu, E.M. *Saccharomyces cerevisiae* var. boulardii CNCM I-1079 and Lactobacillus acidophilus BT1386 influence innate immune response and serum levels of acute-phase proteins during weaning in Holstein calves. *Can. J. Anim. Sci.* **2018**, *98*, 576–588. [CrossRef]
125. Muya, M.C.; Nherera, F.V.; Miller, K.A.; Aperce, C.C.; Moshidi, P.M.; Erasmus, L.J. Effect of Megasphaera elsdenii NCIMB 41125 dosing on rumen development, volatile fatty acid production and blood β-hydroxybutyrate in neonatal dairy calves. *J. Anim. Physiol. Anim. Nutr.* **2015**, *99*, 913–918. [CrossRef]