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Graduate Student Literature Review: Role of antioxidants in calf immunity, growth, and health*

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ABSTRACT

The neonatal period for dairy calves is crucial for immune, metabolic, and physical development, which opens a window of disease susceptibility. Although the industry has relied on tools such as colostrum and vaccination to support early life immunity, there are several challenges when vaccinating neonatal calves: (1) the inability to mount an effective immune response, (2) interference with maternal antibodies, and (3) oxidative stress (OS). Oxidative stress, which is characterized as an imbalance of pro-oxidants to antioxidants, results in cellular oxidative damage or dysfunction, or both.. Oxidative stress has become a topic of interest in the neonatal period because it negatively affects lymphocyte function, which might affect vaccine response. Widely studied in mature cattle, antioxidant supplementation has the potential to improve reduction–oxidation balance and immune response. Evidence supporting the use of antioxidants such as vitamins and minerals in neonatal calves is far scarcer but necessary to optimize immunity and disease resistance. This review summarizes research on the effect of antioxidant supplementation on calf immunity, health, and productivity and highlights remaining gaps in knowledge. Overall, micronutrient supplementation, including vitamins and minerals, in preweaning and postweaning calves improved immune responses but there is conflicting evidence supporting the subsequent positive effect on calf health and growth performance.

Key words: dairy calf, oxidative stress, trace minerals, vitamins

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INTRODUCTION

Despite drastic improvements in neonatal calf management in the past decades, the prevalence of morbidity and mortality remains high worldwide (Svensson et al., 2006; Windeyer et al., 2014; Abebe et al., 2023). It is estimated that preweaning calf mortality is 5% in the US with the 2 main causes being diarrhea and respiratory disease, 32% and 14.1%, respectively. Also, preweaning morbidity is estimated to be 33.8% in the US with more than 50% of calves showing signs of digestive illness (USDA, 2014). Similarly, preweaning mortality is estimated to be 7.8% to 11%, around 4%, and 5.5%, in Canada (OMAFRA, 2011), Europe (Hyde et al., 2020), and China (Zhang et al., 2019), respectively. Calf adverse health events are not only a financial burden to producers due to treatment cost but also negatively affect future production, as well as culling rate and replacement costs (Overton, 2020; Buczinski et al., 2021). Other financial considerations include veterinary and technician costs. Treatment costs for neonatal illnesses have increased over time; for example, the cost of a case of bovine respiratory disease increased from $14.7 (Kaneene and Scott Hurd, 1990) to $42.1 (Dubrovsky et al., 2020).

Calves are born immunologically naive, which compromises their ability to mount an effective immune response within the first weeks of life (Chase et al., 2008). Although colostrum is critical for transfer of maternal antibodies and immune cells, these maternal antibodies diminish endogenous antibody production in response to parenteral vaccination (Chase et al., 2008). Intranasal vaccination is used to stimulate mucosal immune response for antibody production and bypass maternal antibody interference (Hill et al., 2012). Regardless of vaccine administration, calves experience OS during the first few weeks of life (Abuelo et al., 2014), which can also adversely affect calves' ability to mount an immune response (Cuervo et al., 2021). Therefore, the need is critical for strategies that can improve vaccine responsiveness in neonatal calves.

The list of standard abbreviations for *Journal of Dairy Science* is available at adsa.org/jds-abbreviations-24.

Supplementary antioxidants have the potential to increase blood antioxidant capacity and improve reduction–oxidation (redox) potential, which might affect vaccine response. Examples of antioxidants used in calves include vitamins, trace minerals, and herbal plants and derivatives thereof (Spears and Weiss, 2008; Kuralkar and Kuralkar, 2021). Herbal plants, their extracts, and other derivatives can enhance antioxidant status, improve immune function, and increase ADG in preweaning calves (Hassan et al., 2020; Liu et al., 2021; Kumar et al., 2022; Nguse et al., 2022; Hu et al., 2023). For these products, however, ensuring composition consistency both from batch to batch and over time is problematical (Xie et al., 2007), they are not widely available worldwide, and based on each country's legislation, they might not be subject to regulations. Moreover, plant extracts can incorporate antinutritive compounds, and outbreaks of calf mortality associated with feeding some of these products have been reported (Wieland et al., 2015). Thus, although some plants and their extracts are effective in improving redox balance and immunity, more research is needed before their use can be widely recommended. Therefore, this review will focus on vitamins and trace minerals because these are more routinely available worldwide and more research has been accumulated over the past decades to provide evidence-based recommendations.

The effect of micronutrient supplementation on calves' immunity and health is an emergent area of research and has not been summarized previously. Therefore, this review will summarize research on micronutrient supplementation in dairy calves in the context of their developing immune system and response to vaccination. Current gaps in knowledge and future research directions will also be presented in this review.

CALF IMMUNE DEVELOPMENT AND EARLY LIFE CHALLENGES

Immune Development and Vaccination Challenges

Calves are born immunologically naive, meaning they rely on an external source to provide necessary immunologic protection (Chase et al., 2008). Colostrum intake provides neonatal calves with antibodies, cytokines, and immune cells, including leukocytes. Although the necessary immune components are present in neonatal calves, it can take up to a few months for functional application of these cells to mature (Chase et al., 2008). During the neonatal period, calves experience high metabolic demands to support growth, with target ADG greater than 0.68 kg/d (Hyde et al., 2022). Immune development and the energy demand for quick growth contributes to the window of disease susceptibility that challenges calves in early life.

Vaccination is also used to help mitigate calfhood disease, specifically respiratory disease, within the first weeks of life. There are several challenges when vaccinating young calves, including maternal antibody interference and oxidative stress (**OS**). Maternal antibodies inhibit or prevent the function of host B cells, which are responsible for endogenous antibody production, by binding to B cells and blocking antigen recognition, reducing the efficacy of parenteral vaccination (Brüggemann and Rajewsky, 1982; Chase et al., 2008). To circumvent interference from maternally derived antibodies, intranasal vaccination, which targets mucosal surface antibody production, has become a popular protocol to prevent respiratory disease in neonatal calves. Although using intranasal vaccines directly targets the mucosal surface, acting as a first line of defense, the protection provided does not cover the full duration of disease susceptibility (Ellis et al., 2013). Aside from route of vaccine administration, OS is an emerging field of research because it might affect calves' ability to respond to pathogen exposure by reducing lymphocyte functions that are essential for an effective response to vaccines (Cuervo et al., 2021). Therefore, the potential use of antioxidants to improve redox balance and mitigate OS might improve vaccine response. Furthermore, the combination of intranasal vaccination and antioxidant supplementation might help mitigate 2 of the most influential challenges of vaccinating neonates.

Oxidative Stress During the Neonatal Period

At birth, mammals are exposed to an oxygen-rich environment for the first time, increasing endogenous production of reactive oxygen species (**ROS**; Wiedemann et al., 2003). Briefly, research in humans reports that oxygen exposure at birth results in increased OS for up to 4 wk (Vento et al., 2001). Increased OS might affect cell development and cell death (Saugstad, 2003). Similar findings have been reported in calves (Gaál et al., 2006). Calves have higher blood concentrations of ROS in comparison to their dams after birth and before colostrum ingestion (Gaál et al., 2006). Colostrum intake further contributes to circulating ROS concentrations right after birth because it contains pro-oxidants (Kankofer and Lipko-Przybylska, 2008). Just as colostrum is a source of pro-oxidants, it is also a source of antioxidants (Kankofer and Lipko-Przybylska, 2008). However, concentrations of antioxidants in colostrum are less than the concentrations of antioxidants in milk (Kankofer and Lipko-Przybylska, 2008). Thus, calves might be at greater risk for developing OS when fed colostrum compared with normal milk. However, differences in antioxidant status assessment methodology might lead to varying results. As such, antioxidant status in milk and colostrum should be cautiously interpreted, considering the methodology used. Therefore, introduction to an oxygen-rich environment, as well as colostrum intake, could overwhelm the available antioxidant capacity. Other stressors during early life such as metabolic demands for growth (Hyde et al., 2022) and disease susceptibility contribute to the risk of OS. In fact, calves face a greater imbalance of total pro-oxidants to available antioxidant defenses than transition cows (Gaál et al., 2006; Abuelo et al., 2014), supporting the contention that OS might play a key role in preweaning calf health. The ratio of pro-oxidants to antioxidants is known as the oxidant status index (**OSi**) and is a validated tool to assess redox balance in cattle (Abuelo et al., 2013). Potential sources of variation in OSi in calves must be considered. For example, the redox balance of colostrum is associated with the calves' redox status in the first weeks of life (Abuelo et al., 2014). Therefore, differences in the volume and duration of feeding of colostrum, as well as the colostrum redox profile, might influence the oxidative status of the calves. Also, the redox status of the cow during late gestation also affects their offspring's oxidative balance (Ling et al., 2018). Thus, factors that can affect the pregnant dam's redox balance, such as parity, feeding practices, and other stressors, including cold/heat stress, vaccination, or disease, can ultimately affect the OS status of the newborns and, subsequently, increase their susceptibility to diseases by compromising their immune responses (Cuervo et al., 2021).

Antioxidant supplementation can improve redox balance and reduce OS by improving antioxidant capacity. In mature dairy cattle, substantial evidence shows the beneficial effects of antioxidant supplementation on redox balance, health, and production outcomes (Abuelo et al., 2015). In calves, however, OS is still an emerging area of research and hitherto findings of antioxidant supplementation trials in calves have, to our knowledge, not been summarized. Thus, our aim is to collate the current knowledge of the effects antioxidant supplementation on calf immunity, health, and growth performance.

ANTIOXIDANT SUPPLEMENTATION

Antioxidant Function

The antioxidant defense system is made of both enzymatic and nonenzymatic components, including antioxidant enzymes such as superoxide dismutase (**SOD**), glutathione peroxidase, catalase, as well as vitamins and trace minerals (Ighodaro and Akinloye, 2018). An antioxidant is defined as a compound that prevents oxidation of molecules and the consequent damage (Halliwell and Gutteridge, 2007). Table 1 summarizes the antioxidant supplementation trials conducted in calves thus far, including supplementation dosage, based on search terms specific to this review. The micronutrients used included Se, Cu, Zn, Mn, Cr, vitamin A, vitamin E, and vitamin D. Vitamins and minerals were selected for this review based on available information regarding requirements, regulations, and approved supplementation. The authors would like to direct the readers to the review article of Spears and Weiss (2008) for more information regarding the specific antioxidant function of the micronutrients listed. Other supplements with antioxidant properties, such as herbal plant extracts, are outside the scope of this review because they are not widely available worldwide or with consistent compositions. Moreover, they are often used as a dietary supplement that relies on a mature rumen. This review focuses on the preweaning period when the rumen is still developing. As such, we have discussed in detail the parenteral or liquid feeding supplementation with vitamins and trace minerals.

Current literature evaluating the effect of antioxidant supplementation on calves' redox balance is scarce. A recent study supplemented dairy calves with injectable antioxidants (Se, Cu, Zn, Mn or Se, and vitamin E) at birth and assessed their redox balance through the OSi (Nayak and Abuelo, 2021). This study found that injectable antioxidants at birth improve redox balance, shown as a decrease in OSi, throughout the first 2 weeks of life. However, this proof-of-principle study used a limited sample size. Therefore, the evidence that injectable antioxidant supplementation might improve redox balance in neonatal calves should be further explored. Although current evidence investigating the effects of antioxidant supplementation on redox balance is limited, total antioxidant status is often measured as a response to antioxidant supplementation. A study supplementing 7 mo-old calves with vitamins and trace minerals (Se, Cu, Zn, Mn, vitamin A, and vitamin E) reported increased total antioxidant status in supplemented calves compared with control calves 60 d after weaning (Mattioli et al., 2020). Antioxidant status alone is an important indicator of immune response, but research suggests that both antioxidant status and pro-oxidant production are essential to appropriately assess and understand redox biology (Costantini and Verhulst, 2009). Therefore, further research is required to expand current knowledge of redox balance in calves.

Table 1. Reported effects of calf antioxidant supplementation on immune, health, and performance outcomes[1]

Study	Animals supplemented	Antioxidant supplement	Immune outcomes[2]		Health outcomes[2]		Performance outcomes[2]	
			Measured	Findings	Measured	Findings	Measured	Findings
Reddy et al. (1985)	7 calves	Vitamin E, 1,400 mg orally weekly for 12 wk	Serum vitamin E every 2 wk for 12 wk Serum metabolic biomarkers every 2 wk starting at wk 4- 12 wk	Serum vitamin E higher in high oral group at wk 4 Serum vitamin E higher in injectable group at wk 2, 4, 6, and 8 No differences in creatinine, glucose, phosphorus, calcium, urea nitrogen, chloride, sodium, potassium, albumin, and total protein	Fecal consistency twice daily	No difference in fecal consistency	Weekly weight	A trend was identified for greater weight gain in supplemented calves
	7 calves	Vitamin E, 2,800 mg orally weekly for 12 wk						
	7 calves	Vitamin E, 938 mg i.m. weekly for 12 wk						
Reddy et al. (1986)	7 calves	Vitamin E, 1,400 mg orally weekly for 12 wk	Plasma protein and packed cell volume Lymphocyte stimulation Infectious bovine rhinotracheitis virus replication. Serum antibody titers (IgG and IgM)	Lymphocyte stimulation was higher for calves given the high amount of oral supplementation and for injected calves than for unsupplemented calves No differences in concentrations of IgG1 and IgG2 among treatments IgM was higher at wk 6 in calves given the high amount of oral supple- mentation than in all other calves At wk 12, the high oral group and calves given injections inhibited infectious bovine rhinotracheitis viral replication in tissue cultures	—	—	—	
	7 calves	Vitamin E, 2,800 mg orally weekly for 12 wk						
	7 calves	Vitamin E, 938 mg i.m. weekly for 12 wk						
Richeson and Kegley (2011)	30 crossbred calves	0.11 mg/kg Se, 0.22 mg/kg Cu, 0.44 mg/kg Zn, and 0.44 mg/kg Mn s.c. at 199 kg	—	—	Daily health scores Treatment of BRD	Rate of BRD morbidity was less Fewer calves required second treatment for BRD		
	30 crossbred calves	0.11 mg/kg Se, 0.35 mg/kg Cu, 1.1 mg/kg Zn, and 0.22 mg/kg Mn s.c. at 199 kg			—	—		
Arthington et al. (2014)	75 crossbred beef calves	0.11 mg/kg Se, 0.33 mg/kg Cu, 1.32 mg/kg Zn, and 0.22 mg/kg Mn s.c. at birth	Trace mineral status was assessed in liver biopsy samples on d 150, 200, and 250	Greater concentrations of liver Cu and Se and lesser liver Fe concentrations compared with control	—		BW was recorded at birth and on d 100, 150, 200, and 250 (weaning)	No differences in BW gain
Teixeira et al. (2014)	395 Holstein heifers	0.11 mg/kg Se, 0.33 mg/kg Cu, 1.32 mg/kg Zn, and 0.22 mg/kg Mn s.c. at 3 d and 30 d old	Blood samples at 7, 14, 35 d old to measure antioxidant enzyme activity and neutrophil//monocyte function	Increased neutrophil activity Greater glutathione peroxide activity on d 14	Incidence of disease in first 50 d of life	Reduced incidence of diarrhea Reduced incidence of combined pneumonia or Otis or both		

Continued

Table 1 (Continued). Reported effects of calf antioxidant supplementation on immune, health, and performance outcomes[1]

Study	Animals supplemented	Antioxidant supplement	Immune outcomes[2]		Health outcomes[2]		Performance outcomes[2]	
			Measured	Findings	Measured	Findings	Measured	Findings
Palomares et al. (2016)	15 calves	0.11 mg/kg Se, 0.33 mg/kg Cu, 1.32 mg/kg Zn, and 0.22 mg/kg Mn s.c. at 3.5 mo old and 3 wk later	Weekly blood samples to measure antibody titers to BVDV1	Increased antibody titers to BVDV1 28 d post priming vaccination				
Bittar et al. (2018)	30 Holstein calves	0.11 mg/kg Se, 0.33 mg/kg Cu, 1.32 mg/kg Zn, and 0.22 mg/kg Mn s.c. at weaning and 3 weeks later	Serum neutralizing antibody titers to *M. haemolytica* and *P. multocida* Antigen induced PBMC proliferation Interferon g production	Increased fold change in antibody titers against *M. haemolytica* Augmented PBMC proliferation upon antigen stimulation				
Kargar et al. (2018a)	24 Holstein calves	0.05 mg Cr/kg BW	Blood metabolites and antioxidant enzymes	No differences	Health status observed daily including fecal scores Behavioral data	Increased feed intake Decreased respiration rate	Weight at birth and monthly. Body measurements at birth and weekly	No differences
Kargar et al. (2018b)	12 Holstein calves	0.05 mg Cr/kg of BW	Serum concentrations of glucose and insulin at 63 and 91 d old	Increased insulin concentrations Increased insulin-to-glucose ratio	Health parameters such as temperature Behavioral data	Increased feed intake	Weight recorded at birth and weekly	Greater ADG
Bates et al. (2019)	435 Friesian-Jersey cross calves	0.02 mg Zn, 0.05 mg Cu, 0.15 mg Se, 0.075 mg Mn, and 0.15 mg Cr s.c. within 24 h of birth			Morbidity Mortality	Reduced morbidity and mortality from birth to 140 d	Growth rate	No difference in ADG
Mousavi et al. (2019a)	24 Holstein calves	0.05 mg Cr/kg of BW	Blood collected on d 63, 77, and 91 of life to assess blood metabolite, hormones, and antioxidant enzymes IVGTT	Increase in serum catalase No difference in other blood metabolites or hormones No difference in plasma glucose and insulin	Health status including fecal score was observed	Tendency for lower fecal scores in supplement group	Growth rate	No difference in growth performance
Mousavi et al. (2019b)	12 Holstein calves	0.05 mg Cr/kg of BW	Blood collected every 2 wk to assess various blood parameters such as glucose and cholesterol Blood also used to assess antioxidant status such as catalase	Minor effects on antioxidant status and glucose-insulin kinetics	Health status observed daily	Decreased days with pneumonia Faster recovery from disease	Weight collected at birth and weekly	Improved weight gain
Leslie et al. (2019)	418 Holstein calves	0.33 mg Se and 0.01 mg vitamin E s.c. at birth	—		Fecal score observed at 1, 2, and 7 wk old Mortality rate Fecal pathogen excretion Odds of being treated for disease	No treatment effect on fecal score or mortality Protective effect against rotavirus Reduced odds of treatment for diarrhea		

Continued

Table 1 (Continued). Reported effects of calf antioxidant supplementation on immune, health, and performance outcomes[1]

Study	Animals supplemented	Antioxidant supplement	Immune outcomes[2]		Health outcomes[2]		Performance outcomes[2]	
			Measured	Findings	Measured	Findings	Measured	Findings
Bates et al. (2020)	15 dairy calves	0.02 mg Zn, 0.05 mg Cu, 0.15 mg Se, and 0.075 mg Mn s.c. at 2 wk and 6 wk old	Neutrophil and monocyte function Gamma interferon release Antibody titers Micronutrient concentrations	Increase in cells phagocytosing Increase in number of bacteria ingested per cell No difference in gamma interferon response or antibody titers No treatment effect on micronutrient concentrations				
Opgenorth et al. (2020)	8 calves	60 mL of fish and flaxseed oil and 200 mg of vitamin E in colostrum at birth	Polyunsaturated fatty acids, oxidant status, total protein, and vitamin E blood concentrations on d 1, 2, 4, 7, 14, 21 of age Colostrum was sampled from each calf's first feeding to assess antibody concentrations and polyunsaturated fatty acids	No differences in serum total protein Increased concentrations of vitamin E and decreased OSi in first wk of life	Daily health scores	No differences in prevalence of diarrhea or other signs of disease	Weights and hip height weekly	No differences in rate of growth
Vedovatto et al. (2020)	Nellore calves	0.11 mg/kg Se, 0.33 mg/kg Cu, 1.32 mg/kg Zn, and 0.22 mg/kg Mn s.c. at 8 mo old	Blood samples collected on d 0, 7, 21, 64 to assess antioxidant enzymes, leukogram, erythogram, and platelets	Increased super dioxide dismutase on d 7 Increased glutathione peroxide on d 7 and 21 Greater leukocyte concentrations on d 64				
Nayak and Abuelo (2021)	7 Holstein calves	0.11 mg/kg Se, 0.33 mg/kg Cu, 1.32 mg/kg Zn, and 0.22 mg/kg Mn s.c. at birth	Weekly nasal anti-BHV1 and -BRSV IgA following intranasal vaccine at birth	Increased IgA concentrations Faster IgA production				
	7 Holstein calves	0.08 mg/kg Se and 4.16 mg/kg vitamin E s.c. at birth						

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Table 1 (Continued). Reported effects of calf antioxidant supplementation on immune, health, and performance outcomes[1]

Study	Animals supplemented	Antioxidant supplement	Immune outcomes[2]		Health outcomes[2]		Performance outcomes[2]	
			Measured	Findings	Measured	Findings	Measured	Findings
Wo et al. (2022)	12 Holstein calves 12 Holstein calves	80 mg zinc metallothionine (ZM) orally for 28 d 80 mg zinc propionate (ZP) orally for 28 d	Weekly blood samples collected to measure serum zinc, antioxidant properties, plasma immunoglobulin and cytokine concentrations	Increased serum zinc concentrations Increased concentrations of metallothionine and total antioxidant capacity in ZM group Increase in plasma IgG and IgM	Fecal consistency was scored to determine incidence of diarrhea	Reduction of incidence of diarrhea	BW and other growth measures recorded at birth and weekly	Increase in ADG
Kumar et al. (2023)	10 Hariana calves	0.15 mg Cr-picolinate /kg BW	Blood collected on d 0, 30, 60, 90 to assess glucose, insulin, cortisol, superoxide dismutase, catalase, total antioxidant status, total immunoglobulin, IgG, Ca, P, Fe, and Cr Blood also used to assess IVGTT and OLTT	Increase in insulin sensitivity Tendency to reduce serum cortisol	Health scores observed daily	Improved fecal scores. Lower incidence and duration of diarrhea	Weight was recorded at the beginning of the study and every 2 wk	No effect on growth performance

[1]PubMed was used to search for clinical trials and randomized controlled trials from 1946 to 2023 with the following key terms: (trace minerals OR vitamins OR micronutrients OR selenium OR zinc OR copper OR manganese OR chromium) AND (calf OR cattle OR dairy) AND (immunity OR health OR growth).

[2]Outcomes presented as compared with the unsupplemented control of the study. BHV1 = bovine herpesvirus type 1; BRD = bovine respiratory disease; BRSV = bovine respiratory syncytial virus; OSi = oxidant status index; PBMC = peripheral blood mononuclear cells; ZM = zinc metallothionine; ZP = zinc propionate; IVGTT = intravenous glucose tolerance test; OLTT = oral lactose tolerance test.

Antioxidant Supplementation Effect on Calf Immunity

Few studies have evaluated the effect of micronutrient supplementation on both the innate and adaptive immune response of calves. Common immune function markers include leukocyte concentrations, white blood cell function, and antioxidant enzyme activity such as SOD and glutathione peroxide. Bovine viral diarrhea virus directly targets platelets, and therefore, platelets are often measured as immune response in viral challenge studies. In a recent study, weaned calves (7 mo old) supplemented with injectable trace minerals (**ITM**; Se, Cu, Zn, and Mn) concurrent with a modified live virus vaccine against bovine herpes virus 1, bovine viral diarrhea virus types 1 and 2, bovine respiratory syncytial virus, and parainfluenza 3 virus showed increased platelet counts post bovine viral diarrhea virus challenge compared with other groups (Bittar et al., 2020). Similarly, another study reports a tendency for increased platelet counts in association with increased antioxidant enzyme production in calves supplemented with ITM (Se, Cu, Zn, and Mn) at 8 mo old compared with control calves (Vedovatto et al., 2020). A decrease in platelet counts has been reported to have an association with bovine viral diarrhea virus 2 infection in calves (Rebhun et al., 1989; Walz et al., 2001; Bittar et al., 2020). Therefore, micronutrient supplementation is suggested to have improved the immune response of these calves to support the viral challenge because platelet counts were higher in calves receiving the supplement.

A few studies also report an increase in activity and concentrations of antioxidant enzymes in both neonatal dairy and weaned beef calves supplemented with the same ITM compared with control calves (Teixeira et al., 2014; Vedovatto et al., 2020). Similarly, a study looking at dairy heifers reports an increase in serum catalase concentrations during the postweaning period when supplemented with chromium in starter feed (Mousavi et al., 2019a). In addition, neonatal calves supplemented with ITM (Se, Cu, Zn, and Mn) exhibit increased neutrophil function, specifically a greater percent of neutrophils showing phagocytosis activity compared with unsupplemented calves (Teixeira et al., 2014; Bates et al., 2019). Overall, robust evidence exists to suggest that ITM supplementation improves innate immunity in both neonatal calves and weaned calves.

Although evidence supporting trace mineral supplementation in calves is becoming more available, research exploring vitamin supplementation is more limited. However, evidence suggests positive effects of vitamin supplementation on immunity in mature cows, for example, as (1) enhanced neutrophil function (Hogan et al., 1990, 1992), (2) increased concentrations of antioxidant enzymes (Jin et al., 2014), and (3) increased serum concentrations of IgA (Jin et al., 2014). The extent to which these positive effects can be seen in the immature immune system of neonatal calves remains unexplored. However, there are dietary vitamin supplementation studies (Table 1) that suggest positive effects on calf performance, metabolism, and immunity (Reddy et al., 1985; Reddy et al., 1986; Opgenorth et al., 2020) but further research on parenteral vitamin supplementation in calves is required.

Similar to cell-mediated immune responses, there is evidence suggesting that antioxidant supplementation improves humoral immunity. Two studies supplementing 3.5 mo-old bull calves with ITM (Se, Cu, Zn, and Mn) concurrent with a modified live virus parenteral vaccine for bovine herpes virus 1, bovine viral diarrhea virus, and parainfluenza 3 virus and a parenteral bacterin for *Mannheimia haemolytica* and *Pasteurella multocida* reported increased and faster antibody production to bovine viral diarrhea virus 1 and *M. haemolytica* (Palomares et al., 2016; Bittar et al., 2018). Similarly, a study supplementing 7 mo-old calves with vitamins and trace minerals (Se, Cu, Zn, Mn, vitamin A, and vitamin E) reported higher serum antibody titers to bovine herpes virus 1 (Mattioli et al., 2020). Nevertheless, there is also some contradicting evidence that found no difference in antibody production, specifically for *Salmonella* spp., in calves treated with ITM (Se, Cu, Zn, Mn, and Cr) at 2 wk old compared with control calves (Bates et al., 2020). A potential explanation for this difference in antibody production reported could be the age at which calves were studied and the virus or bacteria of interest. Calves that are 3.5 mo old would be expected to have a more mature and robust immune response compared with 2-wk-old calves (Chase et al., 2008); thus resulting in noticeable serum antibody responses in calves with the more mature immune system but not in calves in the first weeks of life. The authors claim that the ELISA used to assess salmonella antibody titers was not appropriate because of the IgG molecule binding sites potentially being blocked by IgM and reducing optical density, therefore underestimated the immune response. However, increased nasal secretion of IgA against bovine herpes virus 1 and bovine respiratory syncytial virus were found in calves up to 1 mo old that were supplemented at birth with injectable antioxidants (Se, Cu, Zn, Mn or Se, and vitamin E) compared with control calves (Nayak and Abuelo, 2021). This could suggest that antioxidant supplementation can improve the immune responses in neonatal calves but interference of maternally-derived antibodies could have masked some of the results in studies using parenteral vaccines in newborn calves. Altogether, there is substantial evidence in the literature to support supplementation of antioxidants to improve both innate and adaptive immunity in calves.

Antioxidant Supplementation Effect on Calf Growth and Health Status

Calf Growth. Beyond improvements in immune parameters as a consequence of antioxidant supplementation to calves, it is important to explore the extent to which these immune changes translate into improved growth and health. Growth is commonly assessed in calves because it is an indicator of future performance and production (Van De Stroet et al., 2016). Despite age at supplementation (birth to 9 mo), numerous studies report no difference in ADG between calves supplemented with antioxidants (Se, Cu, Zn, Mn, Cr, and vitamin E) and control calves (Arthington et al., 2014; Teixeira et al., 2014; Bates et al., 2019; Leslie et al., 2019; Vedovatto et al., 2020), suggesting that antioxidant supplementation does not affect growth performance during the pre- or postweaning period. Conversely, a feedlot study reported greater ADG in crossbred calves receiving ITM (Se, Cu, Zn, and Mn) compared with control calves throughout the 55-d trial (Richeson and Kegley, 2011). Also, a study supplementing newborn dairy calves with zinc reported an increase in ADG compared with control calves (Wo et al., 2022). Similarly, studies looking at dairy heifers reported increased ADG during the preweaning and postweaning period when supplemented with chromium, liquid and solid, compared with control (Kargar et al., 2018b; Mousavi et al., 2019b). It is possible that the difference in results presented is due to differences in breed as well as differences in supplementation type, dose, or source of mineral. Overall, there is not consistent evidence to suggest that antioxidant supplementation influences ADG in calves throughout the pre- or postweaning period.

Calf Health. There is also conflicting evidence on the effect of antioxidant supplementation on calf morbidity and mortality. A few studies report calves supplemented with ITM (Se, Cu, Zn, and Mn) had lower prevalence of diarrhea and respiratory disease throughout the preweaning period (Teixeira et al., 2014; Bates et al., 2019). For example, the prevalence of diarrhea in calves supplemented with ITM within 24 h of birth was 4.9%, in contrast with the 10.6% diarrhea risk in unsupplemented control calves (Bates et al., 2019). Similarly, compared with control calves, ITM calves exhibited lower morbidity (15.6 vs. 7.5%) and mortality (3.2 vs. 1.8%) within the first 48h after birth (Bates et al., 2019). In contrast, another study found no differences on mortality or preweaning treatment between calves supplemented with selenium and vitamin E at birth and their control counterparts (Leslie et al., 2019). This study, however, reported a 4% decrease in the odds of diarrhea in supplemented calves but no differences on likelihood of experiencing respiratory disease. A feedlot study reports that crossbred calves supplemented with ITM (Se, Cu, Zn, and Mn) 1 d post arrival had lower rates of bovine respiratory disease morbidity compared with control calves (Richeson and Kegley, 2011). As such, fewer ITM calves required a second treatment of antibiotics for respiratory disease. Similarly, studies looking at dairy heifers reported a decrease in the number of days of diarrhea and treatment duration during the preweaning period when supplemented with chromium (Kargar et al., 2018a; Kumar et al., 2023). Potential limitations to the studies reviewed and a few potential explanations for differences in results presented include (1) different micronutrients supplemented, some including vitamins and others not, (2) calf management (dairy vs. feedlot), and (3) prevalence of disease at each farm or region. Because of a lack of evidence-based protocols, the timing of supplementation and dose vary throughout the different studies, which could contribute to the inconsistencies of growth and health results. The studies referenced range from 1 to 39 farms, in various geographical regions worldwide. As such, there is a chance for great variability in the prevalence of disease in each study. Further research is required to determine appropriate supplementation strategies, including frequency and dose, to potentially improve calf growth, morbidity, and mortality. Potential strategies for exploration include comparison of supplementation type (vitamins, minerals, or both), optimizing timing of supplementation to target times of susceptibility (neonates, weaning, transportation, and so on), and considering supplementation differences based on breed (dairy vs. beef).

FUTURE DIRECTIONS

The literature suggests that antioxidant supplementation can improve calf immunity but there are contradictory findings regarding the extent to which this translates into improved calf health and growth. When pursuing future research, it is important to consider potential confounders in calf health such as management practices (e.g., housing, feeding, and sanitation), environment conditions (season), or disease incidence on farm. Throughout the studies conducted to date (Table 1), there was a great variation in the type of antioxidant supplemented (e.g., vitamins, minerals, or both) as well as the age at supplementation. Currently, there are several commercial parenteral formulations containing combinations of micronutrients with antioxidant properties that could be used in calves. However, these products have not been compared to date and a gap in knowledge still exists regarding the best supplementation formulations and regimens for optimal calf immunity, health, and growth. Providing evidence-based supplementation protocols could allow practical application of antioxidant supplementation to improve calf immunity and health.

Hitherto, most of the micronutrient supplementation studies have been conducted in older, weaned calves. In dairy calves, however, the window of greater disease susceptibility is between 2 and 4 wk of age due to waning passive immunity concurrently with a still-developing active immunity (Hulbert and Moisa, 2016). Thus, further research is required to optimize antioxidant supplementation in neonatal and preweaning claves to improve immunity at this critical time.

Last, OS causes immune dysfunction in calves and antioxidant therapy improves immune responses through its mitigation of OS (Abuelo et al., 2019). However, most of the calf antioxidant supplementation studies did not adequately assess the animals' oxidant status or degree of oxidative damage, which would be required to assess the effectiveness of the intervention. Thus, it is unclear if some of the discrepancies among studies could be due to the supplementation strategy used failing to reduce OS. Therefore, new supplementation studies should include an assessment of OS. Ultimately, more research is still needed to provide evidence-based guidance on the levels and timing of supplementation of young dairy calves that provide an effective improvement of the animals' health and performance.

CONCLUSIONS

This review summarizes the importance of antioxidant supplementation in calves. Although limited evidence is available in neonates, current literature suggests that antioxidant supplementation can improve calf immunity throughout the pre- and postweaning periods. Furthermore, there is conflicting evidence on the effect of antioxidant supplementation on calf health and growth performance. Age at supplementation; type of supplementation, such as trace minerals, vitamins, or a combination; and appropriate assessment of oxidant status are potential areas of investigation to expand upon current findings. Combined efforts between researchers and veterinarians are crucial for expanding the knowledge of and appropriately using antioxidant supplementation in the cattle industry.

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Abbreviations used: BHV1 = bovine herpesvirus type 1; BRD = bovine respiratory disease; BRSV = bovine respiratory syncytial virus; ITM = injectable trace minerals; IVGTT = intravenous glucose tolerance test; OLTT = oral lactose tolerance test; OS = oxidative stress; OSi = oxidant status index; PBMC = peripheral blood mononuclear cells; ROS = reactive oxygen species; SOD = superoxide dismutase; ZM = zinc metallothionine; ZP = zinc propionate.

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