Update on Coccidiosis in Dairy Calves

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Take Home Messages

- Eimeria parasites are ubiquitous and are present in all dairy herds. There are 16 Eimeria species recognized to date. Although largely specific to cattle, several species can infect bison and water buffalo. At present, only *E. bovis*, *E. zuernii* and *E. alabamensis* are thought to be capable of causing significant clinical disease in cattle.
- Clinical coccidiosis affects dairy calves typically between four and twelve months of age and adult dairy cattle are typically asymptomatic carriers. Disease risk is highest in indoor systems but can also occur at pasture, particular if stocking density is high with no pasture rotation. Disease occurs when environmental contamination with the infective sporulated oocysts is allowed to build up to high levels.
- Coccidiosis typically presents as a diarrhoeal disease that can vary from acute and severe to low grade and chronic. Sub-clinical impacts on calves such as reduced growth rates and food-conversion, impaired future fertility, and a predisposition to intercurrent disease can occur but the extent of this is poorly defined.
- Coccidiosis should be thought of as a disease where diagnosis, control and treatment are all considered at the group level.
- Diagnosis is based on fecal oocyst counts of groups of calves sharing an environment. Fecal oocyst counts > 500 oocysts/gram combined with classical clinical signs are generally used for diagnosis of acute cases. However, the identification of the Eimeria species involved is important to confirm diagnosis in less typical cases and chronic diarrhoea and to assess potential sub-clinical impacts. However, many diagnostic labs do not routinely offer Eimeria species identification and improved diagnostics is an important research priority.
- Control should centre on good husbandry and hygiene to prevent the build-up of environmental contamination and the exposure of calves to high levels of oocysts before they have had time to acquire immunity. Several pharmaceutical products are available for the prevention of coccidiosis in dairy calves but careful timing and duration of treatment is required.

What is Bovine Coccidiosis and What is its Cause?

Coccidiosis is a disease caused by single celled protozoan parasites of the genus Eimeria that can affect all species of domestic ruminants (cattle, bison, sheep goats, deer). Each different livestock species is infected by a different set of Eimeria species that are mainly host-specific. Thirteen different species of Eimeria are currently recognized to infect cattle, some of which can cause severe disease, others mild disease and some no disease essentially being thought to be commensals (Figure 1). Eimeria species that infect cattle are largely host-specific but several species, including the major pathogens *E. bovis*, *E. zuernii* and *E. alabamensis*, can infect closely related host species such as North American and European bison and water buffalo (Dubey, 1963; Bangoura, personal communication). The life cycle of Eimeria is complex and is summarized in figure 2 (Blake and Tomley, 2014). Essentially, following infection by ingestion of sporulated oocysts from the environment, the single celled sporozoites are released in the calf gastrointestinal tract and infect epithelial cells lining the small or large intestinal mucosa (depending on the particular species). There are then several rounds of multiplication in which very large numbers of parasites are produced that eventually break out of the host epithelial cells lysing them in the process. This can cause severe damage to the lining of the gut causing severe clinical signs, particularly if occurring in the large intestine. Clinical disease is typically manifested by diarrhea and can be either chronic and low grade or acute and severe (Figure 1A). In the case of dairy cattle, clinical disease is most commonly seen between four and 12 months of age (Keeton and Navarre, 2018). Disease can occur in calves indoors or outdoors but is generally a more common problem for calves during housed indoors. Although older cattle are often infected, disease is rare in adult cattle and generally a sign of other underlying disease problems.

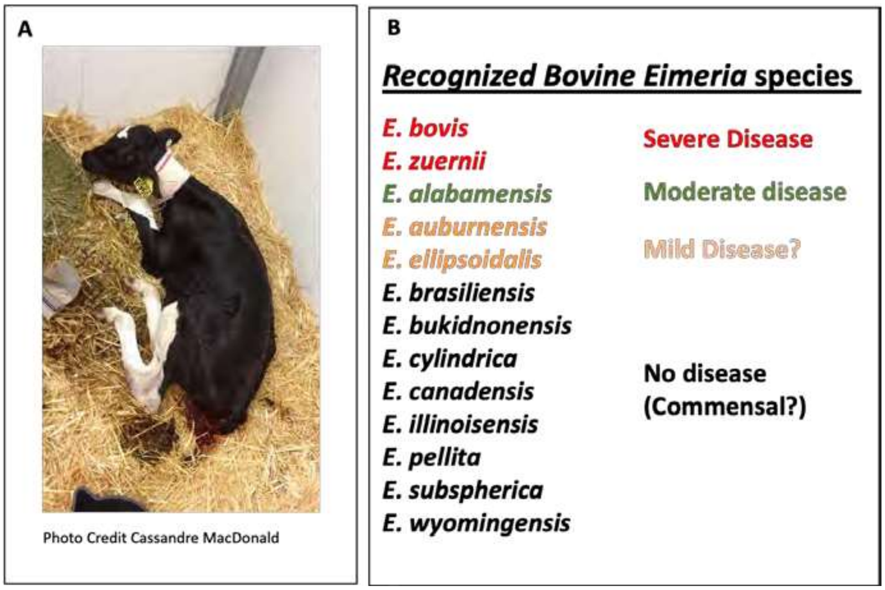

Figure 1: Panel A: Clinical coccidiosis in dairy calf. Panel B: Bovine Eimeria species

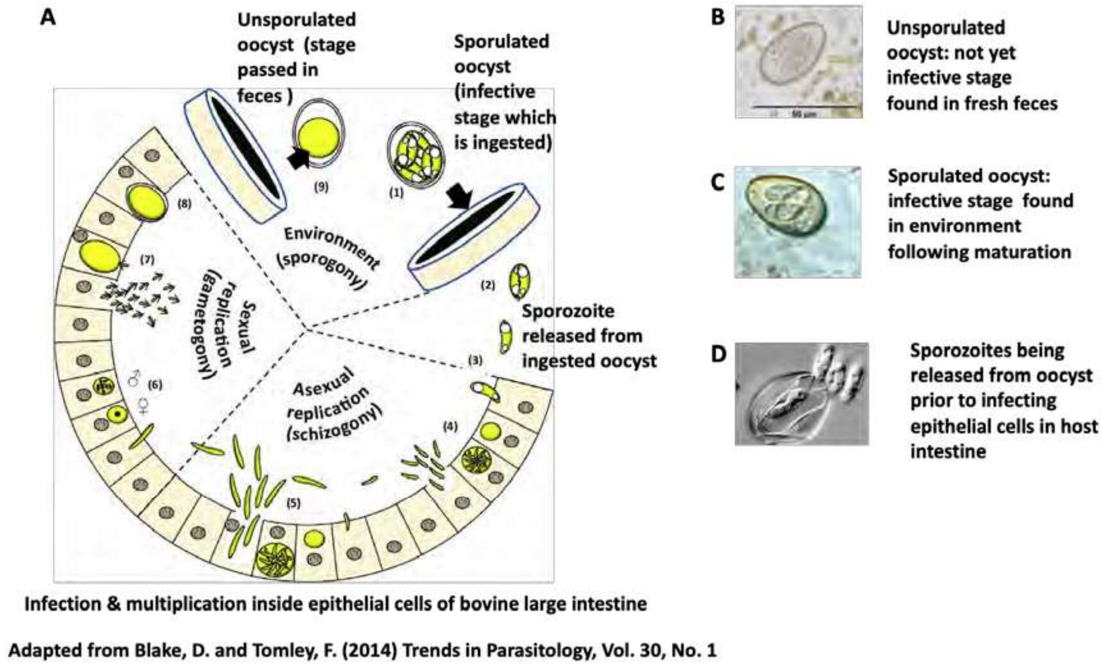

Figure 2: Panel A. Eimeria life cycle (Adapted from Blake and Tomley, 2014). Panel B. Unsporulated oocyst. Panel C. Sporulated oocyst. Panel D. Sporozoites being released from a sporulated oocyst.

▪ Why Does Bovine Coccidiosis Occur and What are the Risk Factors?

Eimeria parasites are ubiquitous and most cattle are infected at some level with different mixtures of Eimeria species. Transmission is by oral ingestion of the infective stages (sporulated oocysts) from the environment that are present as the result of fecal contamination by infected animals (Figure 2, Panel A). The extent to which disease is likely to occur depends on which Eimeria species are present and on the balance between the level of environmental contamination with sporulated oocysts and the immune response of the calf. When relatively low numbers of sporulated oocysts are ingested, parasites complete their life cycle with insufficient damage to the intestinal mucosa to cause disease. Under these circumstances, the calf gradually becomes immune to the parasite with no clinical impacts and can then withstand future challenge even with higher numbers of oocysts. On the other hand, if a calf is exposed to large numbers of sporulated oocysts in the environment before immunity has had time to develop, the developing parasites can cause serious damage to the intestinal mucosa resulting in disease. Consequently, the risk of disease depends on how rapidly the numbers of sporulated oocysts build up in the environment relative to how quickly calves develop immunity.

The capacity for Eimeria oocysts to build up in the environment can be understood from the lifecycle that involves several rounds of multiplication, typically two rounds of asexual and one round of sexual reproduction depending on the species, through which a single ingested sporulated oocyst can result in many millions of oocysts being shed in the feces ((Figure 2 panel A). Experimental infections have shown that more than one million oocytes of *E. zuernii* can be shed in 1 gram of bovine feces (Bangoura and Daugschies, 2007).The time between sporulated oocysts being ingested and millions of oocysts then being shed in the feces is known as the pre-patent period and can vary between 7 and 23 days depending on the particular Eimeria species involved (Bangoura and Bardsley, 2020). Consequently, low levels of initial environmental contamination can build up to extremely high levels relatively quickly once calves become infected. The oocytes shed in the feces into the environment are not immediately infective but need to undergo several rounds of cell division inside the oocyst (a process called sporulation) before they become infective (Figure 2, panels B and C). This can take as little as two days under optimal conditions to several weeks depending on the temperature and relative humidity. Sporulated oocysts can remain viable and infectious for over a year and are resistant to freezing, extreme pH changes, and low oxygen but are damaged by ultraviolet light and dry conditions (Bangoura and Bardsley, 2020). Consequently, Eimeria oocysts build up the most rapidly in warm, moist, dark environments with high fecal contamination and minimal changes of bedding. The highest risk of disease occurs when susceptible (not yet immune) calves are kept in such conditions, particularly at high stocking densities. Once a calf has been exposed to sufficient oocysts, which may or may not cause disease as described above, it is generally solidly immune to future infection. However, immunity is specific to each Eimeria species and so a calf may succumb to disease several times in its life if different Eimeria species are involved.

▪ What are the Impacts of Bovine Coccidiosis in Dairy Calves?

Bovine coccidiosis can occur as sub-clinical, chronic or acute disease depending on the infection level and the particular Eimeria species involved (discussed further below). Acute disease can present as young as two months of age but is most common in calves from four to 12 months of age as a result of the severe damage and associated inflammation of the large intestinal mucosa. Acute coccidiosis is characterised by a hemorrhagic mucoid diarrhea where fresh blood and mucus are visible in the loose feces (Figure 1, Panel A). Calves can appear to be in severe discomfort exhibiting abdominal straining and, in severe cases, can become dehydrated and may die. A more gradual build-up of oocysts can cause chronic coccidiosis that varies from low-grade diarrhea to calves simply being in poor condition or failing to grow at the expected rate. Eimeria infections in poultry are known to predispose to other gastrointestinal diseases such as those of bacterial origin (Collier et al., 2008; Blake and Tomley, 2014). Given the damage, inflammation and breach of integrity of the intestinal mucosa caused by Eimeria infections, it seems likely that similar disease associations occur in cattle although little research has been done in this area. One interesting study from Japan showed an association between hemorrhagic enteritis caused by *Clostridium perfringens* and *Eimeria zurneii* infection which is very similar to that described in poultry coccidiosis (Kirino et al., 2015).

‘Nervous coccidiosis’ is an unusual clinical syndrome that occurs in North American beef calves, typically in feedlots during the winter, and is characterized by neurological signs including hyperactivity and epileptiform seizures with up to 50% mortality of affected animals (Reppert and Kemp, 1972; Bangoura and Bardsley, 2020). The cause is unknown but Eimeria-related toxins or metabolic disturbances have been implicated. This syndrome has been reported in dairy breeds but does not appear to be common in dairy calves (Bangoura, personal communication).

Assessment of the economic impacts of bovine coccidiosis in dairy cattle is poorly researched. A 1980 study estimated that bovine coccidiosis was responsible for a ~US$723 million loss worldwide (Lassen and Ostergaard, 2012; Bangoura and Bardsley, 2020). Losses are associated with clinical disease outbreaks including loss of production, mortalities and the costs of treating and managing affected animals as well as others in the group. Sub-clinical disease is likely to have the biggest economic impact for the industry although this is poorly defined. Such costs include those associated with exacerbation of other gastrointestinal diseases, lower feed conversion efficiency, lower growth rates and lower future fertility and milk production (Lassen and Ostergaard, 2012). Although the use of in-feed ionophores and anticoccidials currently reduces some of these potential impacts, animals with high oocyst counts and clinical disease outbreaks still occur. Furthermore, the ongoing debate regarding the prophylactic use of pharmaceuticals in food producing animals, the status of anticoccidials as antimicrobials and the trend towards more organic systems are all likely to increase the importance of sub-clinical and clinical coccidiosis in dairy calves over the coming years.

▪ How is Bovine Coccidiosis Diagnosed?

Coccidiosis is diagnosed by the detection of Eimeria oocytes in fresh feces using fecal floatation methods, similar to those used to detect roundworm eggs (Figure 2B). Diagnosis should be made on a group basis because oocyst counts can vary widely between individual calves within a group (Figure 3). Consequently, samples should be taken from multiple animals in the group (preferably ten or more) including those showing no clinical signs and affected animals.

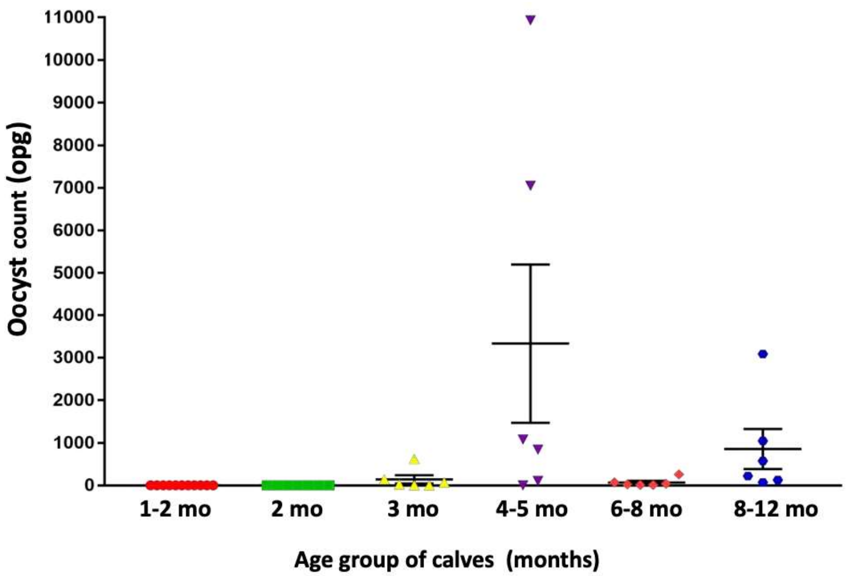

Figure 3: Eimeria oocyst counts in fecal samples taken from individual dairy calves from a farm in western Canada. Each age group was kept in separate pens. opg = oocysts per gram. No clinical signs were apparent in any of the calves.

Interpretation of fecal oocyst counts can be difficult, particularly for chronic disease or when assessing the risk of sub-clinical production impacts. Although there are 13 recognized Eimeria species that can infect domestic cattle, only two are considered to cause severe disease (*E. bovis* and *E. zuernii*), most commonly affecting housed calves, and one causing moderate disease (*E. alabamensis*) that can also cause problems in calves at pasture (Figure 1B). Two other species are considered to be potential mild pathogens *(E. ellipsoidalis* and *E. aubernensis*) with the rest assumed to be non-pathogenic and essentially commensal. However, there has been limited research into many of these Eimeria species and so their true potential for clinical impacts or predisposition to other diseases is still poorly understood. Infections in dairy calves are typically mixtures of pathogenic and presumed non-pathogenic strains (Figure 4). Consequently, high fecal oocyst counts do not necessarily suggest an imminent disease risk if they mainly comprise presumed non-pathogenic species although such counts should be taken as a flag that housing, husbandry and hygiene procedure are conducive to a build-up of Eimeria oocysts in the environment. Consequently, it is critical, both for clinical diagnosis and for routine monitoring, to take into account which species are present and in what proportions. For cattle, counts > 500 oocysts per gram of feces of one or more pathogenic species are potentially clinically significant (Joachim et al., 2018). Even in the absence of clinical signs, finding counts of > 500 oocysts of pathogenic Eimeria species in several animals in a group should raise concerns of a potential imminent disease risk. Lower counts of several 100 oocysts per gram of pathogenic species are warnings that further monitoring and preventive measures are likely required. In the example provided in Figure 4 for Pen 1, an oocyst count of > 2000 opg comprising mainly *E. alabamensis* could result in mild diarrheal disease or mild negative impacts on growth. Although the oocyst counts in pens 3 and 4 are below 500 opg they comprise mainly *Eimeria bovis*, which is a severe pathogen, and so there is potential for more severe disease or growth impacts to occur if counts rise and so careful monitoring is recommended.

The determination of the species of Eimeria present is traditionally achieved by detailed microscopic examination of oocysts following their sporulation in the lab. However, this is a highly specialized and extremely time-consuming technique and not routinely performed in many diagnostics labs. Consequently, diagnosis is often presumptive based on total oocyst counts and there is relatively little surveillance data available on the prevalence and infection intensities of the different bovine Eimeria species in Canadian dairy cattle. We are currently undertaking research to develop molecular diagnostic methods, based on polymerase chain reaction and next-generation amplicon sequencing methods for both surveillance and diagnostics similar to approaches we have previously applied to parasitic nematodes of cattle (Avramenko et al., 2015, 2017). These approaches have great potential to improve the accuracy and scalability of species-specific diagnostics tests in bovine coccidiosis.

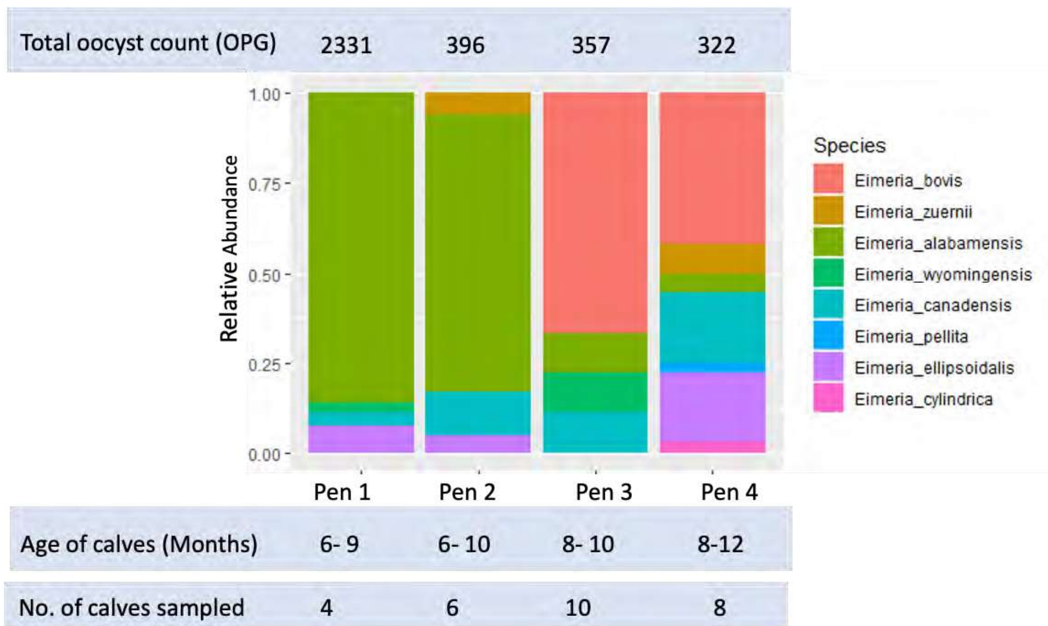

Figure 4: Eimeria oocyst counts and species proportions based on morphology of 100 sporulated oocysts following harvesting from pooled fecal samples from 4 different pens of calves from the same western Canadian dairy farm. Credits: Thanks to Dr. Berit Bangoura and Dr. Rao Parimasetti for the morphological identification and data analysis.

▪ How is Coccidiosis Prevented?

Eimeria parasites are ubiquitous in calves and routine fecal examination will generally detect oocysts present in some individuals, particularly in calves housed indoors. It is practically impossible to achieve an 'Eimeria- free' environment in the standard husbandry conditions used for either beef or dairy cattle. Indeed, it may be undesirable to eradicate all Eimeria species because some may be part of the normal commensal gut flora. Instead, the aim should be to minimize the build-up of sporulated oocysts in the environment and allow the gradual acquisition of immunity to reduce the risk of disease outbreaks or sub-clinical production loss. The most important control measures are good hygiene and husbandry practices including ensuring good colostrum intake, sufficient clean bedding with timely removal, prevention of fecal soiling of food troughs and water sources and separating groups of calves by age with all-in all-out systems using good disinfection and cleaning between batches of calves. Bleach-based disinfectants are partially, but not completely, effective at destroying Eimeria oocysts, which highly resistant and long lasting in the environment (up to over a year; Bangoura and Bardsley, 2020). Consequently, physical removal of bedding with thorough removal of debris (e.g., steam cleaning) is important, particularly in herds with a history of problems. For calves on pasture, a proportion of oocysts will survive the winter on pastures and so annual rotation of grazing should be considered if stocking densities are high or there is a history of disease. Routine monitoring of calves to determine oocyst counts can be a valuable tool to assess disease risk and the effectiveness of management practices, particularly for herds with a history of disease problems. As discussed earlier, it is important to test multiple animals in a group (ideally 10 to 20 calves) because there is a high degree of variance in the oocyst shedding of individual animals (Figure 3). Fecal samples taken from individual calves, either fresh from the bedding or per rectum, can be pooled in the lab and a group oocyst count determined to save on diagnostic costs.

There are currently no vaccines available for bovine coccidiosis, but several pharmaceutical compounds can be used in prevention (Noack et al, 2019). In Canada the pharmaceuticals for bovine coccidiosis prevention are typically administered as feed additives over a period of several weeks (Figure 5). These fall into two broad categories: coccidiostatic compounds that prevent parasite multiplication and allow the calf immune response to kill the parasites (amprolium, decoquinate, and sulfonamides) and coccidiocidal compounds that directly kill the parasites (either ionophores such as monensin and lasalocid or the symmetric triazine, toltrazuril). These different drugs have different modes of action and act on different stages of the parasite life cycle (Noack et al, 2019). Those that target the early stages (sporozoites and merozoites) are typically used for prevention (as opposed to treatment) whereas those that target multiple stages can be used for both prevention and treatment (Figure 5). The principal of control is essentially one of metaphylaxis rather than prophylaxis; it is better that animals are already infected with Eimeria before the drug administration is initiated to allow immunity to develop before infection levels reach a point where there is intestinal damage. All animals in the group need to be treated to reduce overall environmental contamination. This can be achieved in weaned animals by putting drugs such as lasalocid, monensin or decoquinate in the feed or in the water supply for at least 28 days. Shorter treatment periods run the risk of simply delaying parasite development, leading to disease outbreaks in older animals. Decoquinate is preferred in younger calves (less than four months of age) because there is a toxicity risk with ionophores such as monenesin in this age group (Ensley, 2020). Another strategy is to use toltrazuril, which is different to the other drugs in that it is given as a single oral dose. The drug is highly effective against all the different internal stages of the parasite and is used strategically as a single dose timed several weeks before the major risk period occurs, i.e., during the pre-patent period. The aim is to have allowed the infection to progress sufficiently to allow immunity to develop but break the lifecycle before disease and larger levels of environmental contamination occur. Little research has yet been conducted on drug resistance in bovine Eimeria. However, given how commonly it occurs in poultry Eimeria species to most classes of anticoccidials it seems likely it will be present in bovine Eimeria (Noack et al., 2019). One recent case report of interest is the development of toltrazuril resistance in Eimeria in sheep in Norway (Odden et al., 2018).

▪ How are Clinical Coccidiosis Cases and Outbreaks Managed?

The focus should always be on prevention as opposed to treatment of clinical disease because once clinical signs are apparent significant intestinal damage has already occurred. Severely affected animals are a mortality risk and may only partially recover having subsequent poor growth and fertility due to long term damage of the gastrointestinal tract. When disease outbreaks occur, coccidiosis should be thought of as a group or herd disease. If one, or several, calves in a group show clinical signs, then others in the same group sharing the environment will be exposed to the same infection levels and so are both at risk of disease and are also contributors to environmental contamination. Consequently, all animals in a group should be treated, not just those with clinical signs. Several drugs are available for treating clinical cases in Canada with the most commonly used being amprolium or toltrazuril (Figure 5). Toltrazural is effective against all the different parasite stages inside the host and treatment can reduce the severity and duration of diarrhea in clinical cases and a significant reduction in oocyst shedding of treated animals. Treating the whole group early, when only a few individuals are showing clinical signs, may prevent clinical disease in those individuals still in the pre-patent phases of infection. It is also important to remove the animals from the contaminated environment or, if not possible, to clean the environment of contaminated bedding to prevent further infection. Clinically affected individuals should ideally be separated from the rest of the group and given supportive oral and parenteral fluid therapy as necessary. The density of the remaining animals in the pens should reduced if at all possible.

	Parasite Stage Targeted	Route of administration	Primary Use
Lasalocid (Bovatec, Avatech)	Sporozoites & merozoites	In-feed	Prevention
Monensin (Rumensin, Coban)	Sporozoites & merozoites	In -feed	Prevention
Decoquinate (Deccox)	Sporozoites	In- Feed or milk	Prevention
Amprolium (Amprol, Apromed)	2nd generation Schizonts	In-feed or water	Mainly Treatment
Toltrazuril (Baycox)	All intracellular stages	Oral suspension (single dose)	Prevention and Treatment

Figure 5: Pharmaceutical agents licensed for bovine coccidiosis control in Canada

▪ Future Directions and Research Priorities

There has been remarkably little research on bovine coccidiosis relative to its importance. In many cases, control is largely achieved by the inclusion of ionophores or other anticoccidial agents in calf rations or water supplies. Disease problems are only likely to increase in the future as trends to move away from the prophylactic use of pharmaceuticals in food producing animals continue. There are many research questions and tools that are needed in this area including the following:

Some Required Research and Control Tools

- Improved tools for routine diagnostics and surveillance
- Vaccines against the most pathogenic bovine Eimeria species

Some Key Research Questions

- What are the prevalence and infection intensities of the different Eimeria species in different age groups, production systems and geographical areas?
- What is the pathogenicity of the less studied bovine Eimeria species?
- What is the extent of sub-clinical impacts of Eimeria infections in dairy calves?
- To what extent does Eimeria infection predispose to, or exacerbate, other gastrointestinal diseases in dairy calves?
- How do Eimeria communities impact the dairy calf microbiome and what role does this play in health and disease?

- To what extent is drug resistance developing to the different anticoccidial compounds in bovine Eimeria species?

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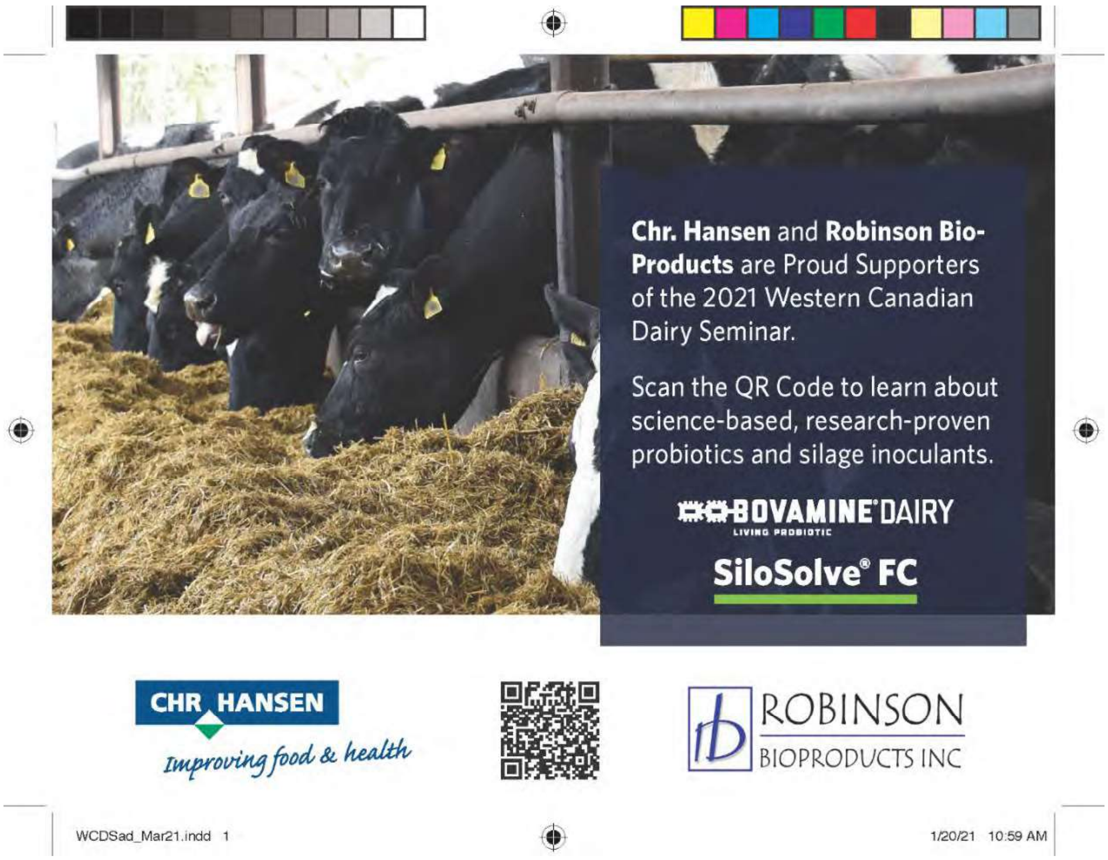
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