Mitigating Eimeria resistance in broiler production with phytogenic solutions

By Dr. Ajay Bhoyar, Global Technical Manager, EW Nutrition

In modern, intensive poultry production, the imminent threat of resistant Eimeria looms large, posing a significant challenge to the sustainability of broiler operations. Eimeria spp., capable of developing resistance to our traditional interventions, has emerged as a pressing global issue for poultry operators. The resistance of Eimeria to conventional drugs, coupled with concerns over drug residue, has necessitated a shift towards natural, safe, and effective alternatives.

Several phytogenic compounds, including saponins, tannins, essential oils, flavonoids, alkaloids, and lectins, have been the subject of rigorous study for their anticoccidial properties. Among these, saponins and tannins in specific plants have emerged as powerful tools in the fight against these resilient protozoa. In the following, we delve into innovative strategies that leverage the potential of these compounds, particularly saponins and tannins, to prevent losses by mitigating the risk of resistant Eimeria in poultry production.

Understanding resistant Eimeria in broiler

production

The World Health Organization Scientific Group (World Health Organization, 1965) developed the definition of resistance in broad terms as ‘the ability of a parasite strain to survive and/or to multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within the limits of tolerance of the subject’.

The high reproduction rate of *Eimeria spp.* allows them to evolve quickly and develop resistance to drugs used for their control. Moreover, the resistant strains of Eimeria can persist in the environment due to their ability to form resistant oocysts, leading to the re-infection of animals and further spread of resistant strains.

Resistant Eimeria strains present many challenges in modern poultry farming, significantly impacting overall productivity and economic sustainability. However, one of the primary challenges is the reduced efficacy of traditional anti-coccidial drugs.

Eimeria resistance occurs in different types

There are different possibilities as to why Eimeria are resistant to specific drugs.

Acquired resistance results from heritable decreases in the sensitivity of specific strains and species of Eimeria to drugs over time. There are two types of acquired resistance: partial and complete. These types depend upon the extent of sensitivity lost. There is a direct relationship between the concentration of the drug and the degree of resistance. A strain controlled by one drug dose may show resistance when a lower concentration of the same drug is administered.

Cross-resistance is the sharing of resistance among different compounds with similar modes of action (Abbas et al., 2011). This, however, may not always occur (Chapman, 1997).

Multiple resistance is resistance to more than one drug, even though they have different modes of action (Chapman, 1993).

Natural substances can bring back the efficacy of anticoccidial measures

It was found that if a drug to which the parasite has developed resistance is withdrawn from use for some time or combined with another effective drug, the sensitivity to that drug may return (Chapman, 1997).

Botanicals and natural identical compounds are well renowned for their antimicrobial and antiparasitic activity, so they can represent a valuable tool against Eimeria (Cobaxin-Cardenas, 2018). The mechanisms of action of these molecules include degradation of the cell wall, cytoplasm damage, ion loss with reduction of proton motive force, and induction of oxidative stress, which leads to inhibition of invasion and impairment of Eimeria spp. development (Abbas et al., 2012; Nazzaro et al., 2013). Natural anticoccidial products may provide a novel approach to controlling coccidiosis while meeting the urgent need for control due to the increasing emergence of drug-resistant parasite strains in commercial poultry production (Allen and Fetterer, 2002).

Saponins and Tannins: Nature’s Defense against

Eimeria Challenge

Phytogenic solutions, specifically those based on saponins and tannins, have recently surfaced as promising alternatives to mitigate the Eimeria challenge in poultry production. By harnessing the power of these natural compounds, poultry producers can boost the resilience of their flocks against the Eimeria challenge, promoting both the birds' welfare and the industry's sustainability.

Saponins are glycosides found in many plants with distinctive soapy characteristics due to their ability to foam in water. In the context of Eimeria, saponins can disrupt the integrity of the parasites' cell membranes. When consumed, saponins can interfere with the protective outer layer of Eimeria, weakening the parasite and rendering it vulnerable to the host's immune responses. This disruption impedes the ability of Eimeria to attach to the intestinal lining and reproduce, effectively curtailing the infection.

Tannins are polyphenolic compounds with astringent properties, occurring in various plant parts, such as leaves, bark, and fruits. Choosing the proper tannin at the right level and time is crucial to realize the benefits of tannin-based feed additives.

In the context of Eimeria, tannins exhibit several mechanisms of action. Firstly, they bind to proteins within the parasites, disrupting their enzymatic activities and metabolic processes. This interference weakens Eimeria, hindering its ability to cause extensive damage to the intestinal lining. Secondly, tannins are anti-inflammatory, reducing the inflammation caused by Eimeria infections. Additionally, tannins act as antioxidants, protecting the intestinal cells from oxidative stress induced by the parasite.

When incorporated into broilers' diets, saponins and tannins create an unfavorable environment for Eimeria, inhibiting their growth and propagation within the host. Moreover, these compounds fortify the broiler's natural defenses, enhancing its ability to resist Eimeria infections. By leveraging the innate properties of saponins and tannins, the impact of resistant Eimeria strains can effectively be managed and mitigated, fostering healthier flocks and sustainable poultry production.

What is Pretect D?

Pretect D is a unique proprietary blend of phytomolecules, including saponins and tannins, that supports the control of coccidiosis challenges in poultry production. It can be used alone or in combination with coccidiosis vaccines, ionophores, and chemicals as part of a shuttle or rotation program.

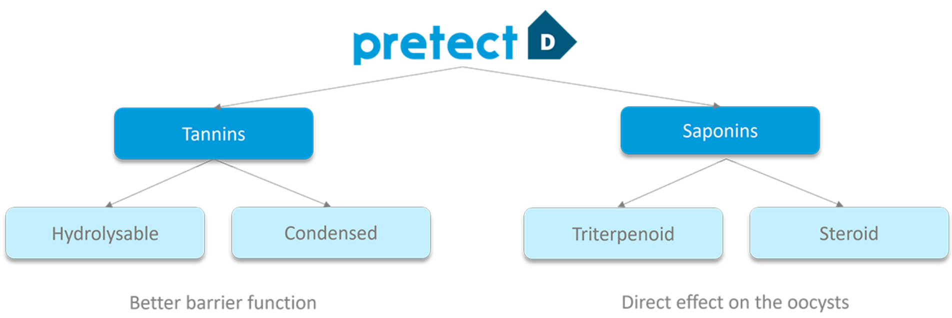


Fig.1. Key active ingredients of Pretect D

Modes of action of Pretect D

Pretect D exhibits multiple modes of action to optimize gut health during challenging times. Due to its anti-protozoal, anti-inflammatory, immunomodulatory, and antioxidant properties, it

a. effectively decreases oocyst excretion and disease spread
b. promotes restoring the mucosal barrier function and improves intestinal morphology
c. protects the intestinal epithelium from inflammatory and oxidative damage.

The beneficial effects of Pretect D

The beneficial effects of Pretect D's inclusion in the coccidiosis control program include improving overall gut health and broiler production performance.

In a challenge study with Cobb 500 broiler chicks under a mixed Eimeria inoculum challenge, it was evident that the group receiving Pretect D (@500g/ton) in the feed throughout the 35-day rearing period had less coccidia-caused lesions (D27) than the broilers challenged and fed control diets.

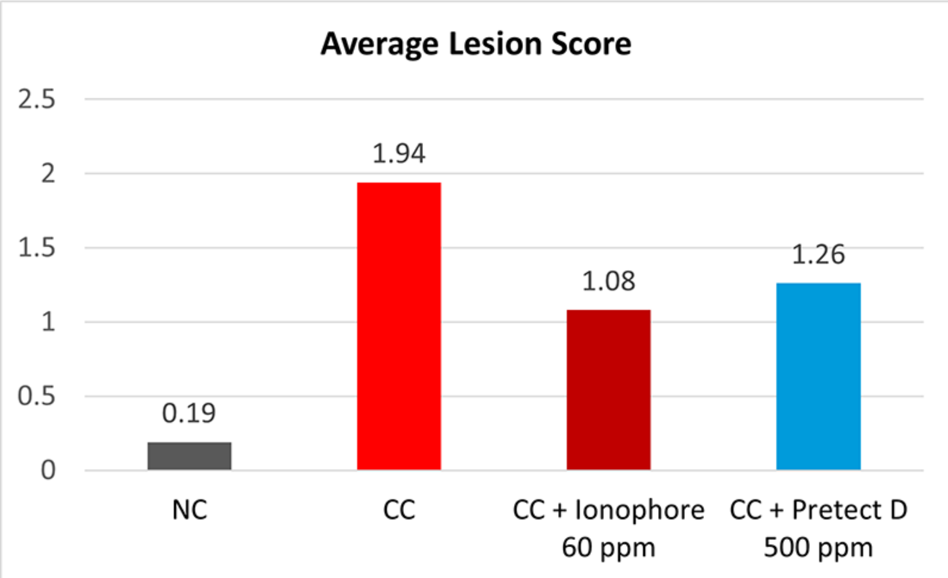
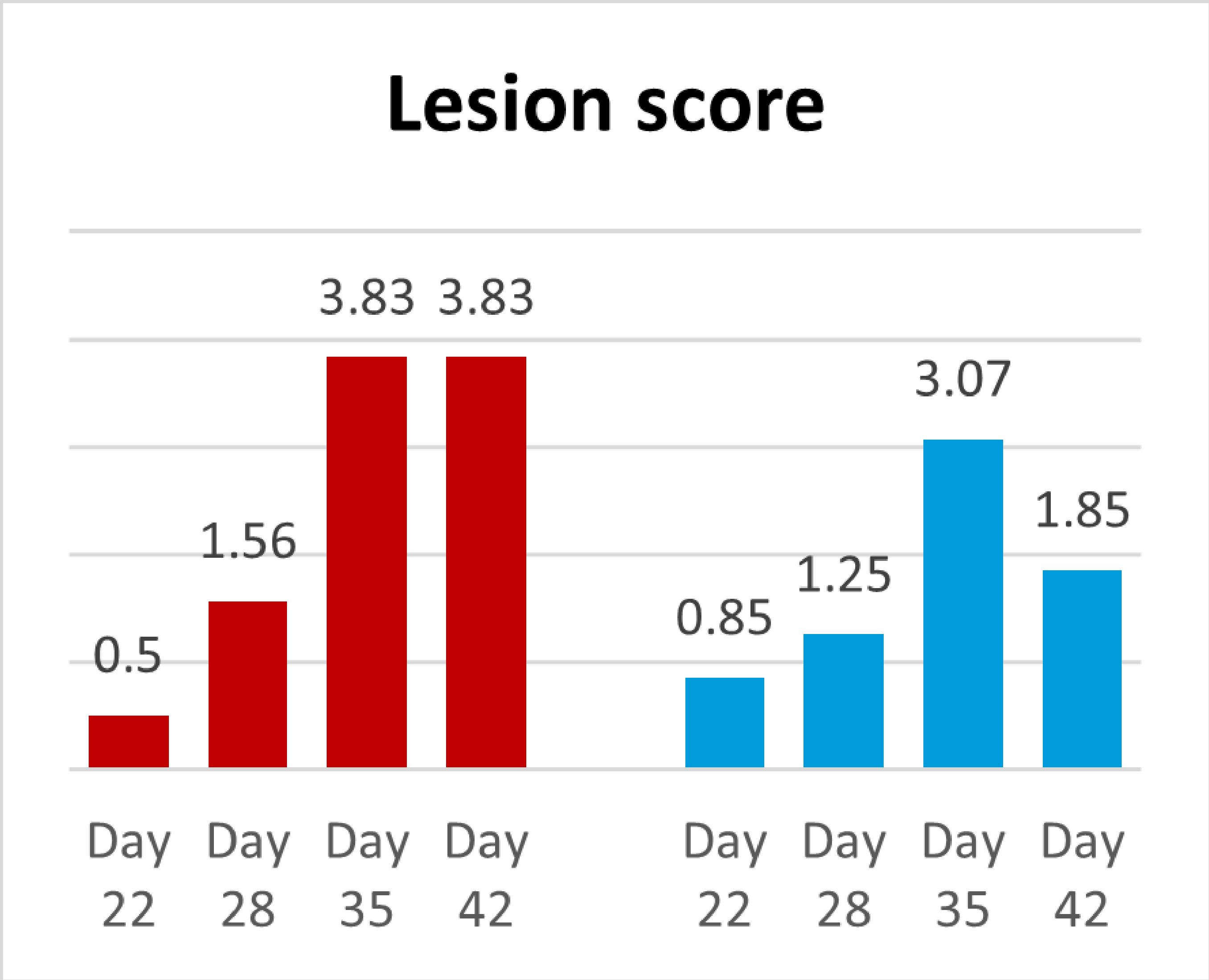


Fig. 2: Pretect D reduced coccidia-caused lesions in broilers

In another field study, a traditional anticoccidial program (Starter and Grower I feeds: Narasin + Nicarbazin, Grower II feed: Salinomycin, Finisher/ withdrawal feeds: No anticoccidial) was compared with a program combining anticoccidials with Pretect D (Starter and Grower I feeds: Narasin + Nicarbazin, Grower II and Finisher feeds: Pretect D). The addition of Pretect D significantly reduced OPG count and lowered the coccidiosis lesion score compared to the control (Fig. 3).


Lesion score
0.5
1.56
3.83
3.83
0.85
1.25
3.07
1.85
Day 22
Day 28
Day 35
Day 42
Day 22
Day 28
Day 35
Day 42

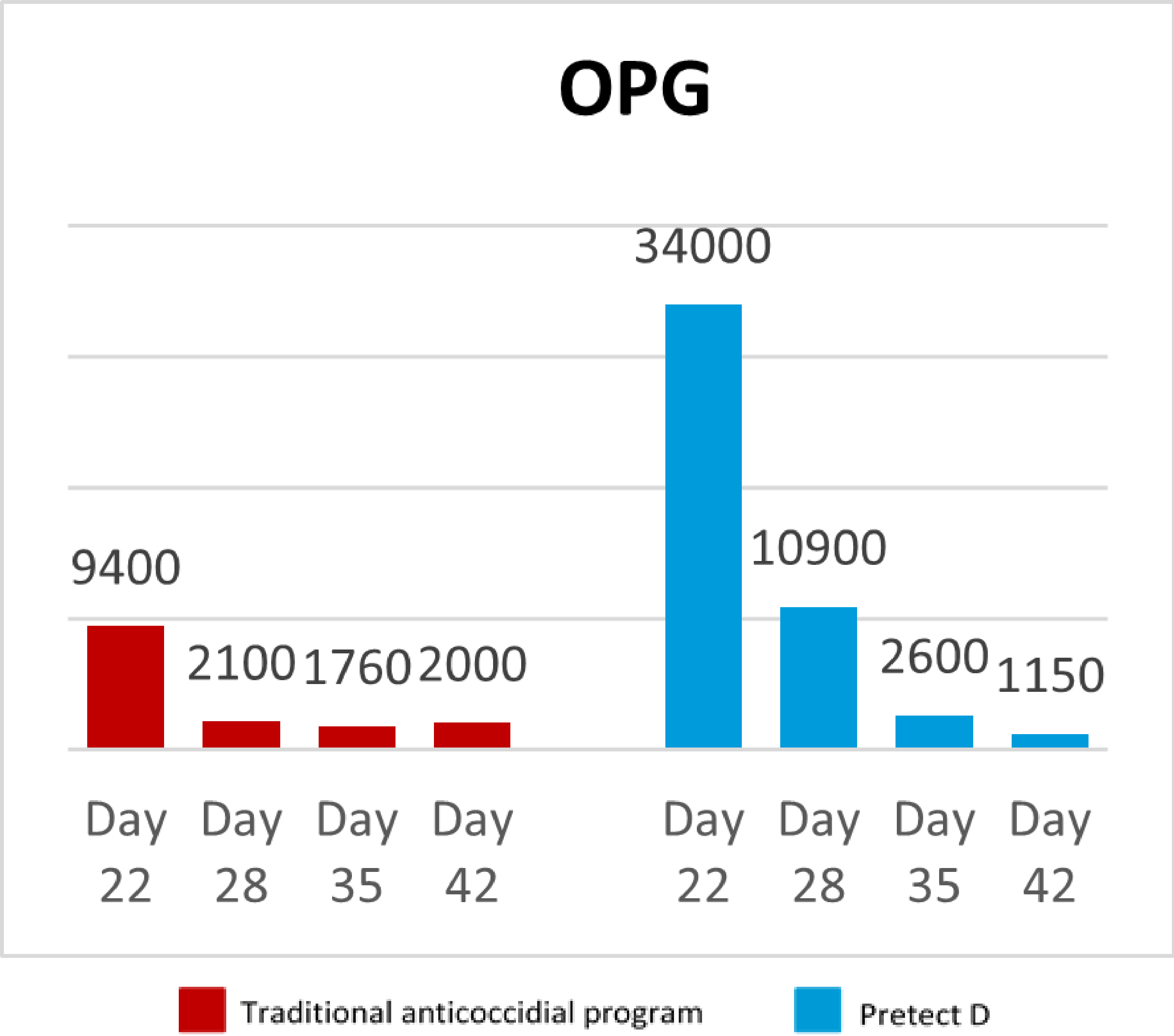
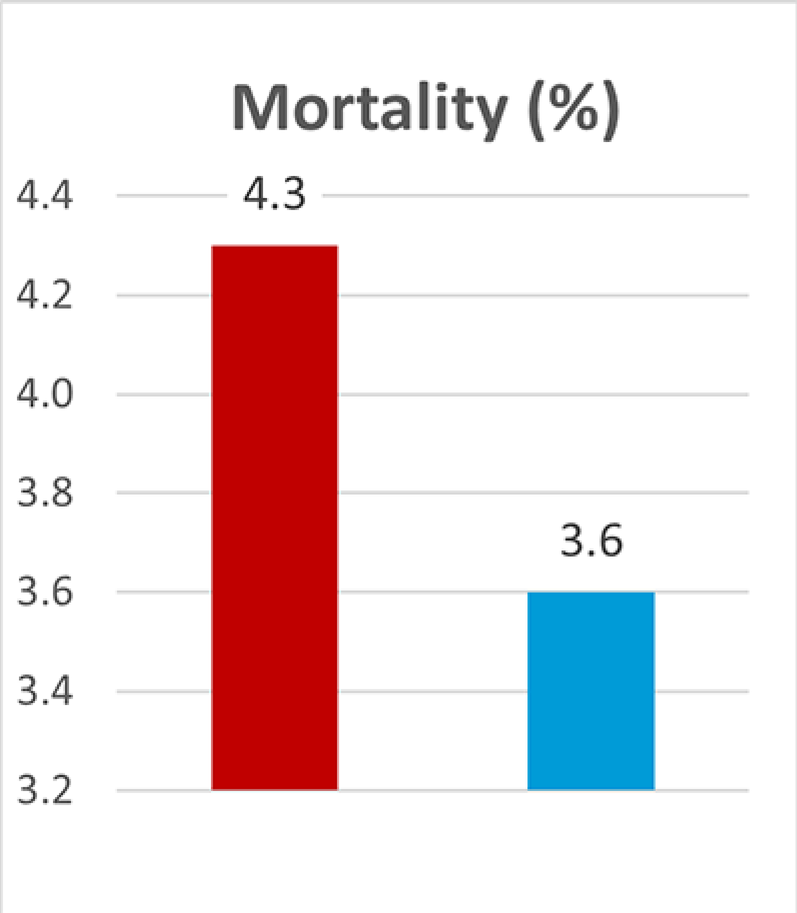
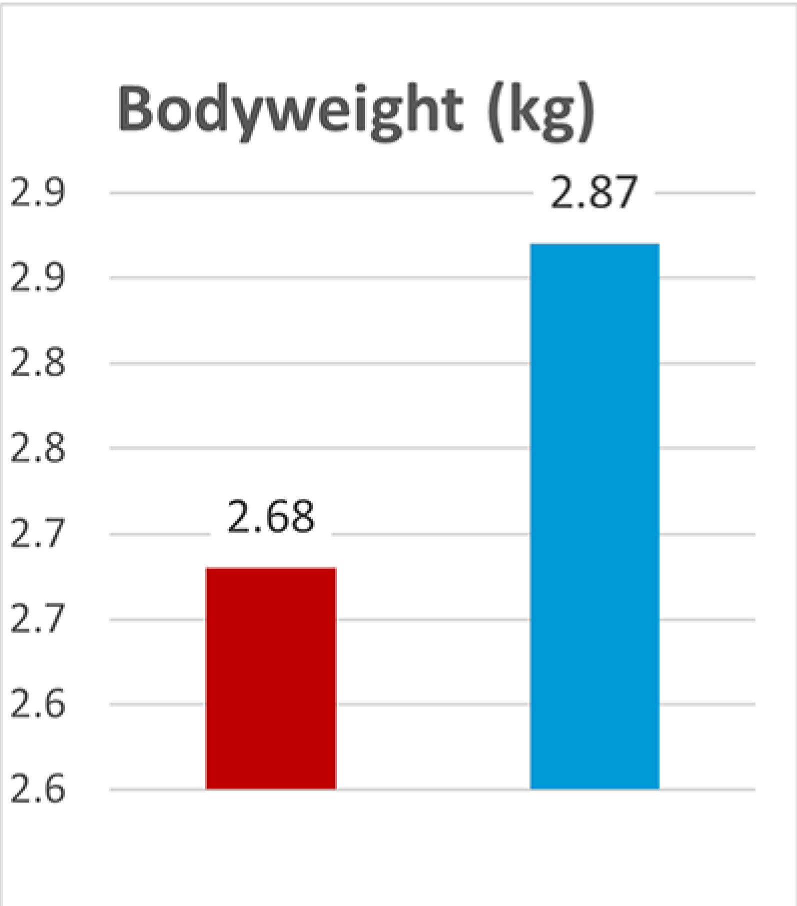


Fig.3. Pretect D reduced broilers' coccidiosis lesion score and OPG count

Consequently, broilers receiving Pretect D showed better overall production performance.


Mortality (%)
4.4
4.2
4.0
3.8
3.6
3.4
3.2
4.3
3.6


Bodyweight (kg)
2.9
2.9
2.8
2.8
2.7
2.7
2.6
2.6
2.68
2.87

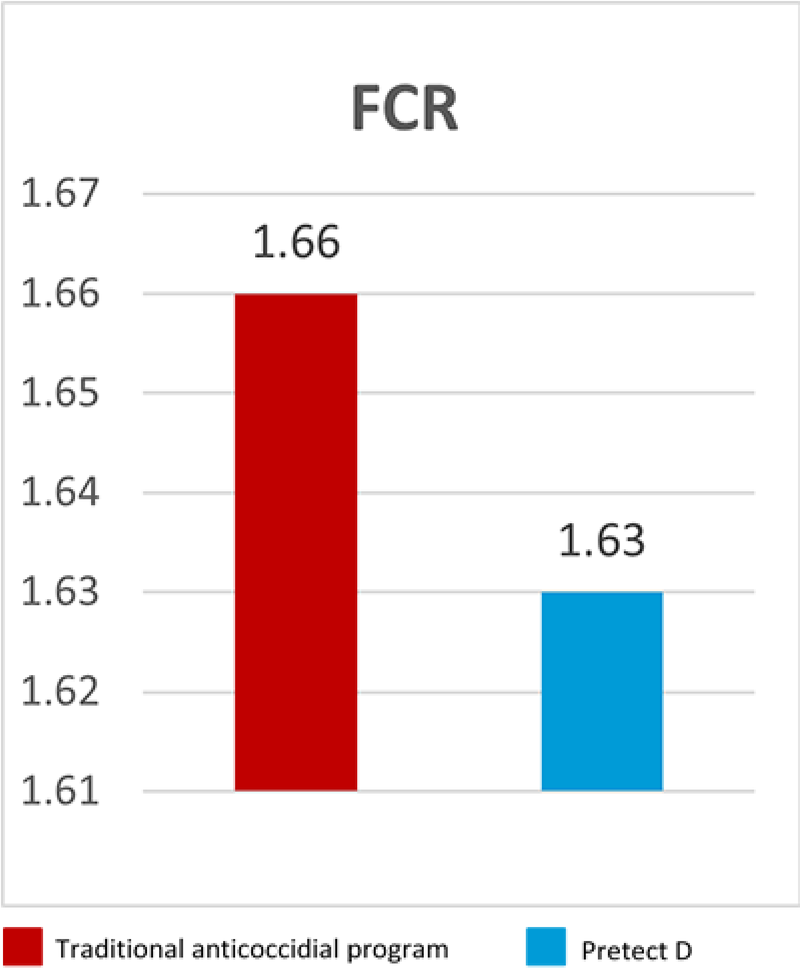


Fig. 4. Overall improved production performance by Pretect D

Pretect D: Application Strategies

The introduction of an effective phytogenic combination in the coccidiosis control program can help mitigate the drug resistance issue. Such a natural anticoccidial solution can be used as a standalone, preferably in less challenging months, as well as in combination with chemicals (shuttle/ rotation) or a coccidiosis vaccine (bio-shuttle), reducing the need for frequent drug use.

Shuttle programs are commonly employed for managing coccidiosis, and they yield a satisfactory level of success. Within these programs, multiple drugs from distinct classes of anticoccidials are administered throughout a single flock. For instance, one class of drug is utilized in the starter feed, another in the grower stage, reverting to the initial class for the finisher diet and concluding with a withdrawal period.

In rotation programs, anticoccidial drugs are alternated between batches rather than within a single batch.

Conclusions

Coccidiosis is considered one of the most economically significant diseases of poultry and the development of anticoccidial resistance has threatened the profitability of the broiler industry. Therefore, regularly monitoring Eimeria species to develop resistance against different anticoccidial groups is crucial to managing resistance and choosing an anticoccidial. It would be rewarding to use an effective phytogenic solution in the coccidiosis control program as a strategic and tactical measure and to focus on such integrated programs for drug resistance management in the future.

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Coccidiostats in the European Union: Challenges and Perspectives

*by **Twan van Gerwe**, DVM PhD (EBVS), Technical Director, EW Nutrition*

Controlling coccidiosis has been and continuous to be a major concern for poultry operations. However, for decades, some of these control measures have been taking an increasingly visible toll on the overall health of the flocks, the economics of poultry production, and the environment itself. Regulations have been put in place to defend consumer health and animal welfare while maintaining profitability in poultry production.

In the European Union and elsewhere, coccidiostats or anticoccidials are an essential means of control and are categorized either as feed additives or as veterinary medicinal products. The category is dictated by the pharmacologically active substance, mode of action, pharmaceutical form, target species and route of application.

In the European Union, there are currently 11 different coccidiostats which have been granted 28 different authorizations as feed additives allowed for specific usage in chickens, turkeys, and rabbits.

Coccidiostats: the basics

Compounds designed to kill the coccidial population are known as coccidiocidal; those designed to prevent the replication and development of coccidia are known as coccidiostats. Quite often, coccidiostat or anticoccidial is the term used to describe both categories.

Coccidiostats are antimicrobial compounds which either inhibit or destroy the protozoan parasites that cause coccidiosis in livestock. Each coccidiostat has individual inhibitory mechanisms. In the case of ionophores, the compounds affect transmembrane ion transport. In the case of synthetic compounds, the molecules' mode of action is varied and, in some cases, not even entirely known (Patyra et al., 2023).

The production, manufacture, and marketing of coccidiostats, premixes with coccidiostats, and feed with coccidiostats are regulated by the Regulation (EC) No 183/2005 of the European Parliament and of the Council of 12 January 2005 laying down requirements for feed hygiene.

Coccidiostat categories

Coccidiostats fall under two categories:

Ionophores

Ionophores, sometimes called polyether ionophore antibiotics, are substances which contain a polyether group and are of bacterial origin. They are produced by fermentation with several strains of *Streptomyces* spp and *Actinomadura* spp. Six substances are allowed in the EU:

- monensin sodium (MON)
- lasalocid sodium (LAS)
- maduramicin ammonium (MAD)
- narasin (NAR)
- salinomycin sodium (SAL)
- semduramicin sodium (SEM)

Synthetic

Synthetic compounds include:

- decoquinate (DEC)
- diclazuril (DIC)
- halofuginone (HFG)
- nicarbazin (NIC)
- robenidine hydrochloride (ROB)

EU authorizations for ionophores are granted under specific conditions of usage, including animal category, minimum and maximum dosage, MRL (Maximum Residue Limits), and withdrawal periods.

Regulation (EC) No 1831/2003 [13] of the European Parliament and of the Council of 22 September 2003 distinguishes between coccidiostats and antibiotics used as growth promoters. Unlike the antibiotic growth promoters (forbidden in the EU since 2006), whose primary action site is the gut microflora, coccidiostats only have a secondary and residual activity against the gut microflora. That still signals that they have the potential to trigger resistance and to alter the natural balance and immune response of the farmed animals. Their potential to cause resistance has been widely acknowledged by science and practitioners alike (see below).

Why were some antimicrobial growth promoters withdrawn in 1997-1998 – but not others?

Five designated “antibiotic feed additives” were prohibited in 1997-98: Avoparcin, Bacitracin zinc, Spiramycin, Virginiamycin, and Tylosin phosphate. The EU withdrew their authorization in order to “help decrease resistance to antibiotics used in medical therapy”. The motivation specified that these antibiotics belonged to classes of compounds also used in human medicine.

On the other hand, the EU at the time allowed the remaining antibiotics for use in feed as they did not belong to classes of compounds used in human medicine. That, of course, did not mean that resistance did not develop in birds.

The Commission did acknowledge the need to phase out the remaining antibiotics. At the same time, it stated that the use of coccidiostats would not presently be ruled out “even if of antibiotic origin” (MEMO/02/66, 2022). The reason was that “hygienic precautions and adaptive husbandry measures are not sufficient to keep poultry free of coccidiosis. Modern poultry husbandry is currently only practicable if coccidiosis can be prevented by inhibiting or killing parasites during their development.”

In other words, the Commission acknowledged that the only reason ionophores were still authorized was that it believed there were no other means of controlling coccidiosis in profitable poultry production.

What issues are raised by current coccidiosis control measures?

In its 2022 Position Paper on Coccidia Control in Poultry, the European Veterinaries Federation states that "challenges in coccidia control are due to parasitic and bacterial drug (cross-)resistance. Coccidiostats also interact with other veterinary medicinal products and have a secondary residual activity against gram-positive bacteria" (FVE, 2022).

Resistance

Ever since 1939, when sulphanilamide was shown to cure coccidiosis in chickens, the industry increased the use of similar (chemical) compounds. It quickly added sulfaquinoxaline, then nitrofurazone and 3-notroroxarsone, amprolium and nicarbazin (Martins et al., 2022).

Prior to the introduction of the first ionophore, monensin, in the early 1970s, producers only had synthetic (non-ionophores) coccidiostats, characterized by rapid parasite resistance development. With the addition of ionophores, poultry operations started to rotate products between production cycles, or to use shuttle programs, with the express purpose of controlling the development of resistance. Synthetic compounds can, however, result in increased resistance in the long run (Martins et al., 2022). Moreover, studies in farmed animals indicate that sometimes even single use of antibiotics can promote the selection of resistant bacterial strains.

Another issue is the design of the rotation system, which, some researchers claim, could only delay the appearance of resistance (Daeseleire et al., 2017).

To make matters worse, for instance in the case of broilers, coccidiostats are generally administered throughout life to protect against re-infection. This may also lead to the next item on the list.

Residues

Regulation (EC) No 1831/2003 establishes Maximum Residue Limits (MRLs) for residues of an additive in relevant foodstuffs of animal origin. The goal is to control the use of coccidiostats in feed and ensure that there is no excess residue that ends up on the consumers' plate.

Broilers can be fed with coccidiostats throughout life, with the exception of a certain withdrawal period before slaughter. Cross-contamination of feed batches and residue formation in edible tissues of nontarget species represent valid concerns for end consumers.

Coccidiostats in food have been regulated in the Commission Regulation (EC) No 124/2009, including maximum levels for meat ranging between 2 µg/kg (monensin, salinomycin, semduramycin, and manduramycin) and 100 µg/kg (nicarbazin in liver and kidney). However, Daeseleire et al. state that “in the period 2011–14, noncompliant results were reported for maduramycin, monensin, diclazuril, lasalocid, nicarbazin, robenidine, salinomycin, narasin, semduramicin, decoquinate, halofuginone, and toltrazuril. The matrices/animals species affected were in descending order eggs, poultry, farmed game, horses, pigs, and sheep/goat (EURL workshop, 2015)”. Residues in eggs are widely seen as a serious concern (Bello et al., 2023). The fact that regulations are in place constitute no safeguard against defective practices.

What alternatives to coccidiostats does the EU support?

Vaccination

Coccidiosis vaccines have been in use for the last three decades. They are based on precocious oocysts and are commonly used in breeding and laying birds, and the use in broilers is steadily increasing. There is a limited number of vaccines authorized in the EU. As vaccines are relatively costly to apply, vaccination is typically performed during 2-3 cycles only, afterwards reverting to the use of coccidiostats, which leads to a suppression of the precocious vaccine-origin strains, allowing persistent coccidiostat-resistant field strains to flourish.

Herbal products (phytomolecules)

Phytomolecules have been widely used for a variety of poultry gut health issues. Their usage in flocks at risk of coccidiosis is predicated on their ability to strengthen the natural defenses of the animal. Infection severity and consequences depend to a large extent on co-infections, gut health, and the general immunity of the bird.

Prescription veterinary medicines

Toltrazuril, amprolium, and some sulfamides (sulfamiderazin, sulfadimethoxin, trimethoprime) are used against (clinical) coccidiosis outbreaks. However, these medicines are also prone to triggering resistance and should not be widely used. Moreover, they are used when coccidiosis is already manifest on the farm, so they do not prevent economical and performance losses.

Other research

There is limited research on acidifiers, enzymes, prebiotics or probiotics acting as defenses against infection. Furthermore, oocysts are highly resistant to the common disinfectants, but there are some highly specialized types available. In general, producers are reluctant to use these methods as their benefits are limited or indemonstrable.

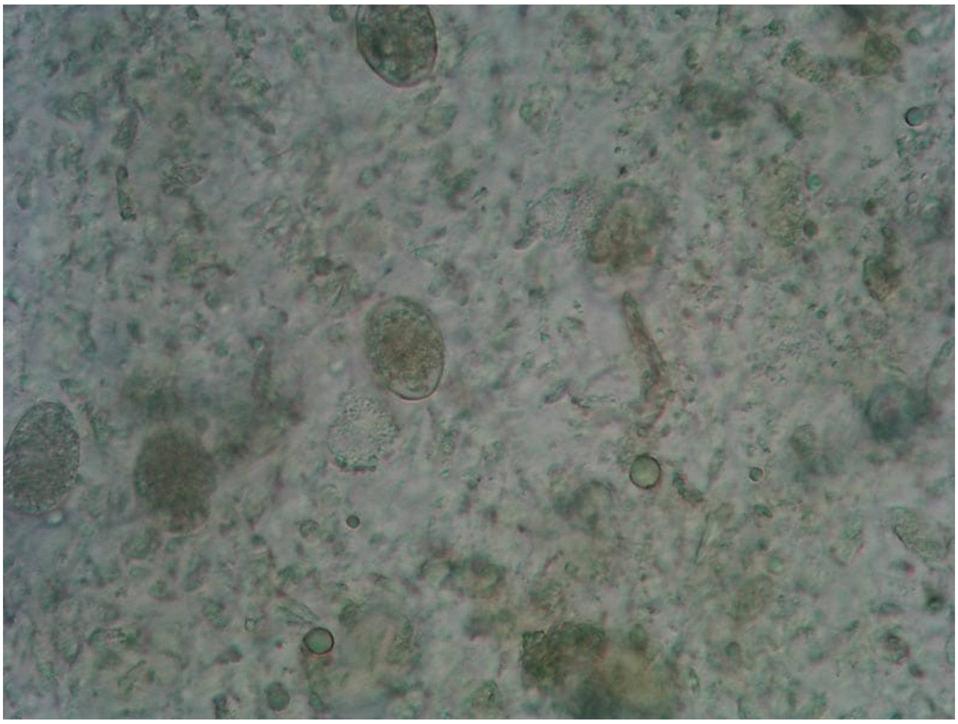
Genetic selection of the animals is also unable to offer solutions for the moment.

Ionophores as antibiotics: The U.S. case

Ionophores have demonstrated antibacterial activity (e.g., Rutkowski and Brzezinski, 2013). As opposed to their regime in the EU, where they are allowed as feed additives, in the United States, coccidiostats belonging to the polyether-ionophore class (ionophores) are not allowed in NAE (No Antibiotics Ever) and RWA (Raised Without Antibiotics) programs.

Instead of using ionophores, coccidiosis is approached by NAE/RWA US producers with a veterinary-led combination of live vaccines, synthetic compounds, phytomolecules, and farm management.

What are the perspectives of coccidiosis control?



In 2019, The European Medicines Agency (EMA) published the new Veterinary Medicinal Products Regulation (EU2019/6), emphasizing the necessity of fighting antimicrobial resistance. In response to the VMP Regulation, in November 2022, the FVE (European Veterinaries Federation) recommended tackling coccidiosis through “a combination of holistic flock health management, optimized stocking density, litter management, feeding and drinking regime as well as nutraceuticals, accompanied by appropriate biosecurity measures, vaccination and coccidiostats, where indicated”.

In its position paper, FVE advocates a “prudent and responsible use of coccidiostats”, as well as monitoring of polyether ionophores coccidiostats sales through ESVAC (European Surveillance of Veterinary Antimicrobial Consumption). European Union past experiences show that strong urges for monitoring are usually implemented and signal a need for regulation. As other countries and regions have shown excellent productivity in the absence of ionophores, it may be that, sooner or later, the EU will revise its lax attitude and embrace a stricter control of antimicrobial resistance.

FVE also recommends the development of rapid, low-cost and especially quantitative diagnostic tests for ongoing surveillance and monitoring purposes. Through fast, reliable, on-site oocyst counts, producers can cut cost and time resources and improve reaction time to preserve the health of their flocks.

From a scientific perspective, considering the range of micro-organisms affected, ionophores can be seen as antibiotics, with the usual associated risks for cross-resistance or co-selection (Wong 2019). While their current status in the European Union represents a concession to the economic security of a large and important industry, best practices in other regions show that coccidiosis can be approached holistically with solutions that reduce antimicrobial resistance and support the profitability of poultry operations.

Bio-shuttle with natural anticoccidial additives: the all-encompassing solution

As producers optimize the use of biological interventions such as vaccines, their effect on broiler performance becomes more predictable and constant.

The current common practice of rotating coccidiostats fails to take advantage of the milder precocious Eimeria population that has developed within the broiler house. Instead, the use of new, natural feed additives with anticoccidial activity that is directly related to the coccidiostat-resistant Eimeria (field) strains, as well as the precocious Eimeria strains, can help to maintain a favorable ratio between mild precocious and more virulent field strains. This can help increase the number of cycles that benefit from the vaccinations applied, even when discontinuing vaccination. Careful monitoring of oocyst shedding patterns, preferably accompanied by gut health and coccidiosis lesion scoring and performance monitoring, can guide the producer on the right time to restart vaccination and repeat the same rotation program.

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The future of coccidiosis control

*By **Madalina Diaconu**, Product Manager Pretect D, EW Nutrition and*
***Twan van Gerwe**, Ph.D., Technical Director, EW Nutrition*

With costs of over 14 billion USD per year (Blake, 2020), coccidiosis is one of the most devastating enteric challenges in the poultry industry. With regard to costs, subclinical forms of coccidiosis account for the majority of production losses, as damage to intestinal cells results in lower body weight, higher feed conversion rates, lack of flock uniformity, and failures in skin pigmentation. This challenge can only be tackled, if we understand the basics of coccidiosis control in poultry and what options producers have to manage coccidiosis risks.

Current strategies show weak points

Good farm management, litter management, and coccidiosis control programs such as shuttle and rotation programs form the basis for preventing clinical coccidiosis. More successful strategies include disease monitoring, strategic use of coccidiostats, and increasingly coccidiosis vaccines. However, the intrinsic properties of coccidia make these parasites often frustrating to control. Acquired resistance to available coccidiostats is the most difficult and challenging factor to overcome.

Optimally, coccidiosis control programs are developed based on the farm history and the severity of infection. The coccidiostats traditionally used were chemicals and ionophores, with ionophores being polyether antibiotics. To prevent the development of resistance, the coccidiostats were used in shuttle or rotation programs, at which in the rotation program, the anticoccidial changes from flock to flock, and in the shuttle program within one production cycle (Chapman, 1997).

The control strategies, however, are not 100% effective. The reason for that is a lack of diversity in available drug molecules and the overuse of some molecules within programs. An additional lack of sufficient coccidiosis monitoring and rigorous financial optimization often leads to cost-saving but only marginally effective solutions. At first glance, they seem effective, but in reality, they promote resistance, the development of subclinical coccidiosis, expressed in a worsened feed conversion rate, and possibly also clinical coccidiosis.

Market requests and regulations drive coccidiosis control strategies

Changing coccidiosis control strategies has two main drivers: the global interest in mitigating antimicrobial resistance and the consumer's demand for antibiotic-free meat production.

Authorities have left ionophores untouched

Already in the late 1990s, due to the fear of growing antimicrobial resistance, the EU withdrew the authorization for Avoparcin, Bacitracin zinc, Spiramycin, Virginiamycin, and Tylosin phosphate, typical growth promoters, to "help decrease resistance to antibiotics used in medical therapy". However, ionophores, being also antibiotics, were left untouched: The regulation (EC) No 1831/2003 [13]of the European Parliament and the Council of 22 September 2003 clearly distinguished between coccidiostats and antibiotic growth promoters. Unlike the antibiotic growth promoters, whose primary action site is the gut microflora, coccidiostats only have a secondary and residual activity against the gut microflora. Furthermore, the Commission declared in 2022 that the use of coccidiostats would not presently be ruled out "even if of antibiotic origin" (MEMO/02/66, 2022) as "hygienic precautions and adaptive husbandry measures are not sufficient to keep poultry free of coccidiosis" and that "modern poultry husbandry is currently only practicable if coccidiosis can be prevented by inhibiting or killing parasites during their development". In other words, the Commission acknowledged that ionophores were only still authorized because it believed there were no other means of controlling coccidiosis in profitable poultry production.

Consumer trends drove research on natural solutions

Due to consumers' demand for antibiotic-reduced or, even better, antibiotic-free meat production, intensified industrial research to fight coccidiosis with natural solutions has shown success. Knowledge, research, and technological developments are now at the stage of offering solutions that can be an effective part of the coccidia control program and open up opportunities to make poultry production even more sustainable by reducing drug dependency.

Producers from other countries have already reacted. Different from the handling of ionophores regime in the EU, where they are allowed as feed additives, in the United States, coccidiostats belonging to the polyether-ionophore class are not permitted in NAE (No Antibiotics Ever) and RWE (Raised Without Antibiotics) programs. Instead of using ionophores, coccidiosis is controlled with a veterinary-led combination of live vaccines, synthetic compounds, phytomolecules, and farm management. This approach can be successful, as demonstrated by the fact that over 50% of broiler meat production in the US is NAE. Another example is Australia, where the two leading retail store chains also exclude chemical coccidiostats from broiler production. In certain European countries, e.g., Norway, the focus is increasingly on banning ionophores.

The transition to natural solutions needs knowledge and finesse

In the beginning, the transition from conventional to NAE production can be difficult. There is the possibility to leave out the ionophores and manage the control program only with chemicals of different modes of action. More effective, however, is a combination of vaccination and chemicals (bio-shuttle program) or the combination of phytomolecules with vaccination and/or chemicals (Gaydos, 2022).

Coccidiosis vaccination essentials

When it is decided that natural solutions shall be used to control coccidiosis, some things about vaccination must be known:

1. There are different strains of vaccines, natural ones selected from the field and attenuated strains. The formers show medium pathogenicity and enable a controlled infection of the flock. The latter, being early mature lower pathogenicity strains, usually cause only low or no post-vaccinal reactions.
2. A coccidiosis program that includes vaccination should cover the period from the hatchery till the end of the production cycle. Perfect application of the vaccines and effective recirculation of vaccine strains amongst the broilers are only two examples of preconditions that must be fulfilled for striking success and, therefore, early and homogenous immunity of the flock.
3. Perfect handling of the vaccines is of vital importance. For that purpose, the personnel conducting the vaccinations in the hatchery or on the farms must be trained. In some situations, consistent high-quality application at the farm has shown to be challenging. As a result**,** interest in vaccine application at the hatchery is growing.

Phytochemicals are a perfect tool to complement coccidiosis control programs

As the availability of vaccines is limited and the application costs are relatively high, the industry has been researching supportive measures or products and discovered phytochemicals as the best choice. Effective phytochemical substances have antimicrobial and antiparasitic properties and enhance protective immunity in poultry infected by coccidiosis. They can be used in rotation with vaccination, to curtail vaccination reactions of (non-attenuated) wild strain vaccines, or in combination with chemical coccidiostats in a shuttle program.

In a recent review paper (El-Shall et al., 2022), natural herbal products and their extracts have been described to effectively reduce oocyst output by inhibiting Eimeria species' invasion, replication, and development in chicken gut tissues. Phenolic compounds in herbal extracts cause coccidia cell death and lower oocyst counts. Additionally, herbal additives offer benefits such as reducing intestinal lipid peroxidation, facilitating epithelial repair, and decreasing Eimeria-induced intestinal permeability.

Various phytochemical remedies are shown in this simplified adaptation of a table from El-Shall et al. (2022), indicating the effects exerted on poultry in connection to coccidia infection.

Bioactive compound	Effect
Saponins	*Inhibition of coccidia:* By binding to membrane cholesterol, the saponins disturb the lipids in the parasite cell membrane. The impact on the enzymatic activity and metabolism leads to cell death, which then induces a toxic effect in mature enterocytes in the intestinal mucosa. As a result, sporozoite-infected cells are released before the protozoa reach the merozoite phase.*Support for the chicken:* Saponins enhance non-specific immunity and increase productive performance (higher daily gain and improved FCR, lower mortality rate). They decrease fecal oocyst shedding and reduce ammonia production.
Tannins	*Inhibition of coccidia:* Tannins penetrate the coccidia oocyst wall and inactivate the endogenous enzymes responsible for sporulation.*Support for the chicken:* Additionally, they enhance anticoccidial antibodies’ activity by increasing cellular and humoral immunity.
Flavonoids and terpenoids	*Inhibition of coccidia:* They inhibit the invasion and replication of different species of coccidia.*Support for the chicken:* They bind to the mannose receptor on macrophages and stimulate them to produce inflammatory cytokines such as IL-1 through IL-6 and TNF. Higher weight gain and lower fecal oocyst output are an indication of suppression of coccidiosis.
Artemisinin	*Inhibition of coccidia:* Its impact on calcium homeostasis compromises the oocyst wall formation and leads to a defective cell wall and, in the end, to the death of the oocyst. Enhancing the production of ROS directly inhibits sporulation and also wall formation and, therefore, affects the Eimeria life cycle.*Support for the chicken:* Reduction of oocyst shedding
Leaf powder of Artemisia annua	*Support for the chicken:* Protection from pathological symptoms and mortality associated with Eimeria tenella infection. Reduced lesion score and fecal oocyst output. The leaf powder was more efficient than the essential oil, which could be due to a lack of Artemisinin in the oil, and to the greater antioxidant ability of A. annua leaves than the oil.
Phenols	*Inhibition of coccidia:* Phenols change the cytoplasmic membrane’s permeability for cations (H+ and K+), impairing essential processes in the cell. The resulting leakage of cellular constituents leads to water unbalance, collapse of the membrane potential, inhibition of ATP synthesis, and, finally, cell death. Due to their toxic effect on the upper layer of mature enterocytes of the intestinal mucosa, they accelerate the natural renewal process, and, therefore, sporozoite-infected cells are shed before the coccidia reaches the merozoite phase.

Table 1: Bioactive compounds and their anticoccidial effect exerted in poultry

Consumers vote for natural – phytochemicals are the solution

Due to still rising antimicrobial resistance, consumers push for meat production without antimicrobial usage. Phytomolecules, as a natural solution, create opportunities to make poultry production more sustainable by reducing dependency on harmful drugs. With their advent, there is hope that antibiotic resistance can be held in check without affecting the profitability of poultry farming.

What poultry producers need to know about coccidiosis control

By Madalina Diaconu, Product Manager Pretect D, and Dr. Ajay Awati, Global Category Manager Gut Health & Nutrition, EW Nutrition

Coccidiosis is one of the most devastating enteric challenge in the poultry industry costing over over 14 billion US$ per year (Blake et al., 2020). In the early days of intensive poultry production, outbreaks of *Eimeria tenella*, were most destructive. *Eimeria tenella* is a coccidia species that causes severe haemorrhages and hypovolemic shock, leading to a fatal outcome for the affected bird.

Poultry producers need to control the performance and welfare issues caused by subclinical coccidiosis

Understanding and managing coccidiosis in poultry

However, today, subclinical coccidiosis accounts for even more of production losses due to intestinal cells injuries: lower body weights, higher feed conversion rates, lack of flock uniformity, failures on skin pigmentation and, at the end mortality. Variation in the supply and quality of animal feed exacerbates the issue and compromises farm profitability even more. To tackle this challenge, we need to understand the basics of coccidiosis control in poultry and what options producers have to manage coccidiosis risks.

From *Eimeria* infection to disease

Coccidiosis is a disease caused by protozoan parasites, mainly of the genus *Eimeria*, that are located in the small and large intestines. Being very resistant and highly contagious, these protozoa are easily transmitted by various routes (via feed, litter, water, soil, material, insects, and wild animals).

Coccidia are present in all livestock species. However, the infection is particularly severe in poultry. The health consequences can be significant: loss of appetite, reduction in feed intake, increased FCR, enteritis, hemorrhagic diarrhea, and mortality. The most common species of *Eimeria* in broilers are: *E. acervulina, E. mitis, E. maxima, E. brunetti, E. necatrix, E. praecox,* and *E. tenella.* They are widely found in broiler productions across the globe (McDougall & Reid, 1991).

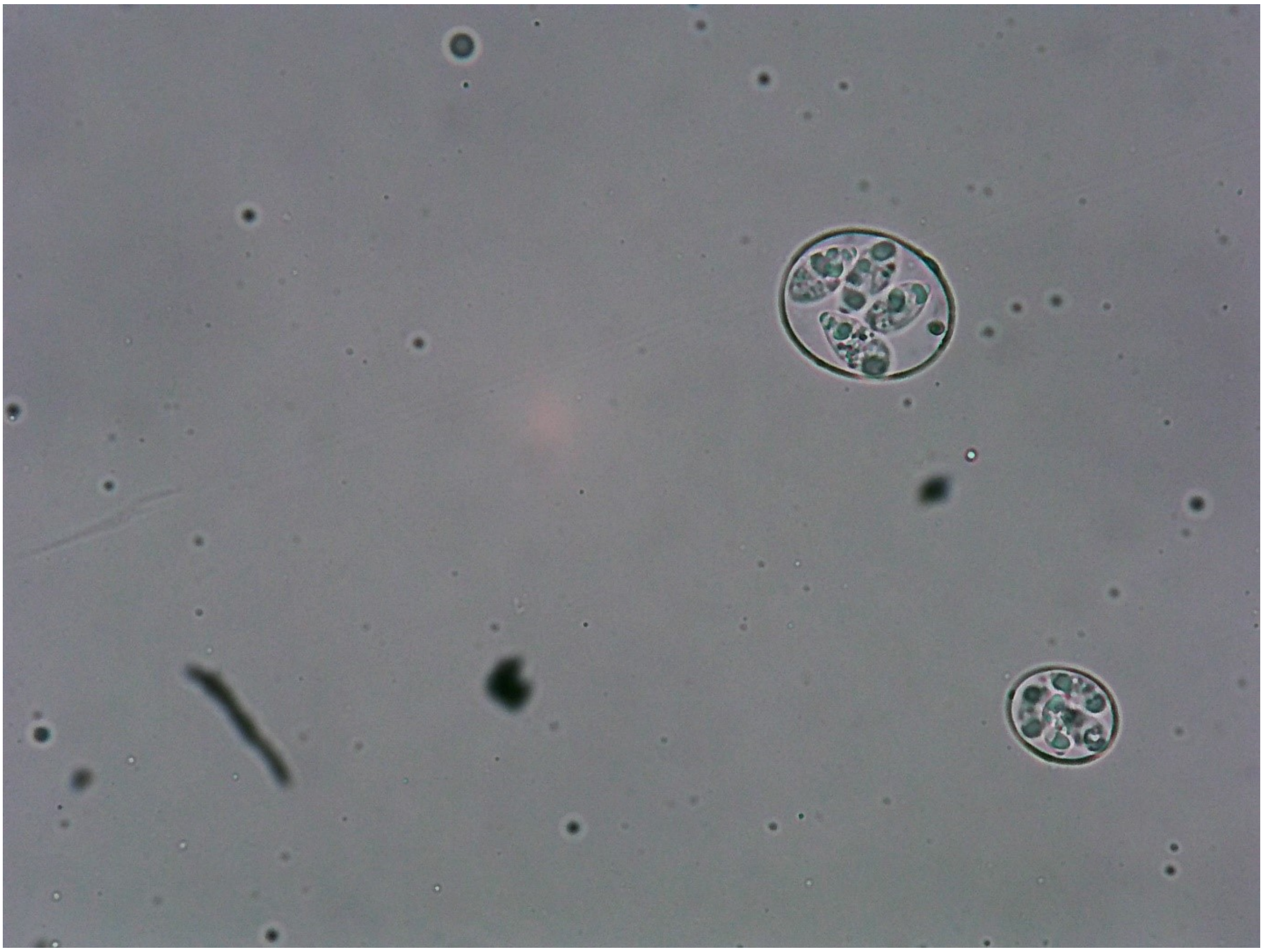

Figure 1: Sporulated oocyst of Eimeria maxima and E. Acervulina (40 x)

The pathogenesis of infection varies from mild to severe and is largely dependent on the magnitude of infection. Coccidiosis outbreaks are related to multiple factors that, together, promote a severe infestation in the farm.

Within poultry, the highest economic impact is in broilers, where the most common species of Eimeria are *E. acervulina, E. maxima, E. tenella* and *E. necatrix,* which all show high virulence. However, pathogenicity is influenced by host genetics, nutritional factors, concurrent diseases, age of the host and the particular species of the *Eimeria* (Conway & McKenzie, 2007).

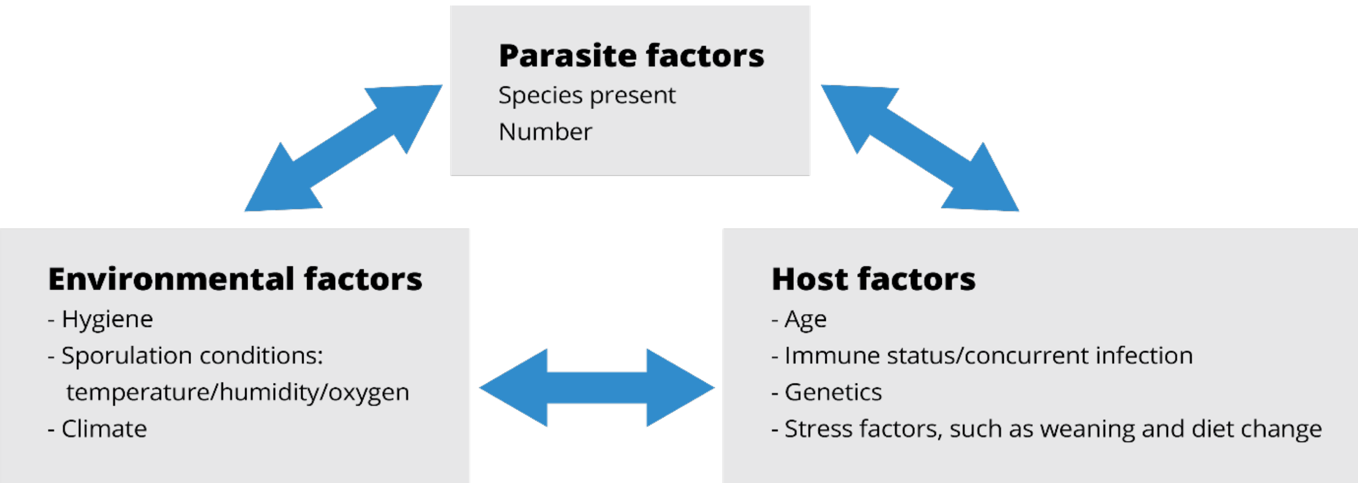

Figure 2: Interaction of factors that promote coccidia outbreaks

The *Eimeria* infection starts with the ingestion of protozoa that are at a sporulated stage. Once inside the gut, the protozoa liberate the sporozoites. This infective form can get into enterocytes and then begin a massive reproduction, killing thousands of intestinal cells. (Olabode et al., 2020; Shivaramaiah et al., 2014)

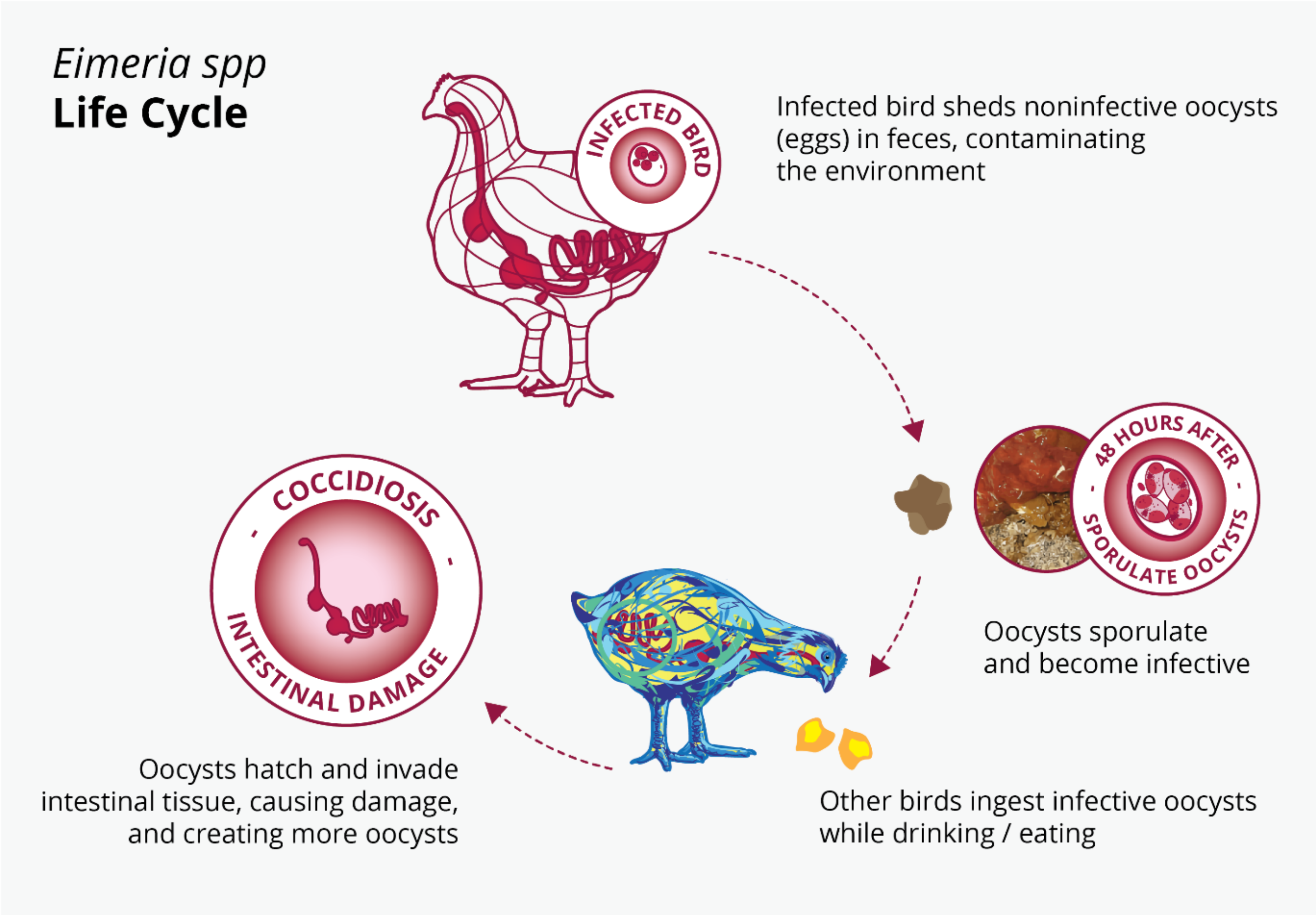

Figure 3: Eimeria spp. life cycle

The reproduction potential depends on the coccidia species. *E. acervulina, E. mitis and E. praecox* have the highest reproduction rate. This characteristic is closely related to their short life cycle.

In broilers, coccidiosis usually occurs after 21 days of age. The infection spreads gradually from day 1 already, depending on species of Eimeria and their virulence. A typical progression of coccidiosis in broilers is shown in Figure 4.

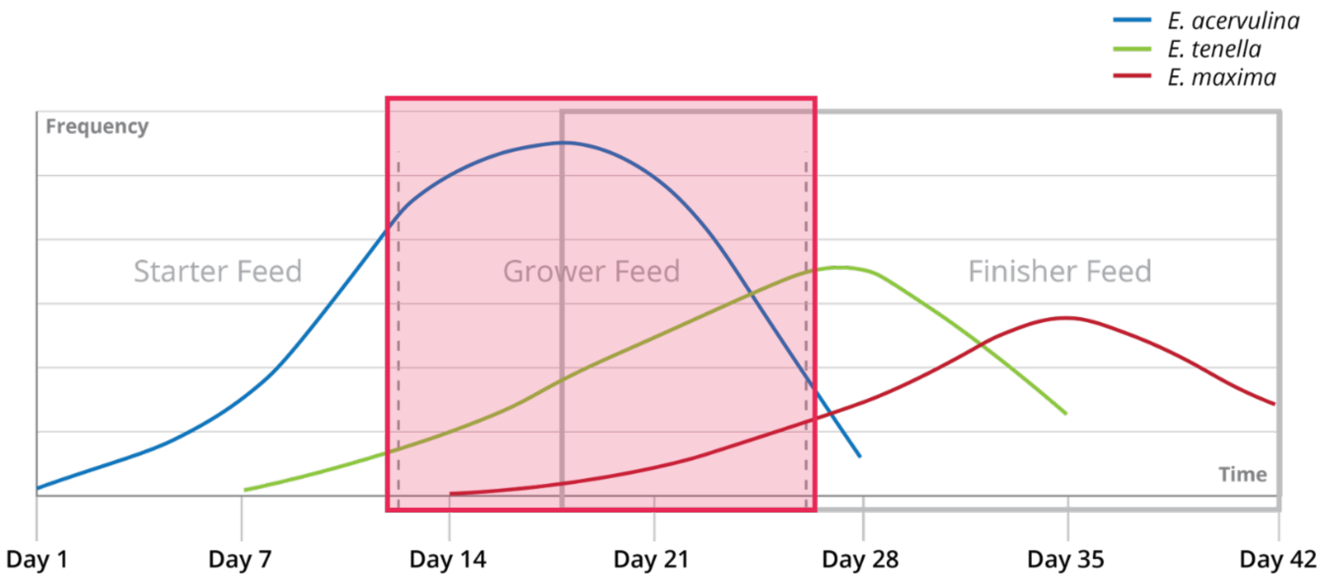

Figure 4: Typical development of a coccidia infection in relation to broiler feed phases

Coccidiosis control in poultry: Strategy guidelines

The intrinsic characteristics of coccidiosis makes this parasite unique and many times frustrating to control. Resistance to available coccidiostats makes this task even harder. Good farm management, litter hygiene, and the use of control coccidiosis programs such as shuttle and rotation are functional measures to prevent clinical coccidiosis. Successful control strategies specifically recognize the importance of monitoring, use anticoccidial drugs wisely, and include vaccines where applicable.

Monitoring

The first step is to establish a strict monitoring program in all stages of production, including the feed mill. It is important to verify that therapeutics are included in the feed in an adequate form and quantity, and that the follow-up in the field takes place.

Field monitoring should be frequent and in line with the operation's coccidiosis management program. Field monitoring is a complementary work that collates clinical, necropsy, and faeces findings to closely track the disease situation.

Coccidiosis control in poultry operations needs to include rigorous monitoring

Anticoccidial drugs

Since the middle of the 20th century, chemotherapeutic agents have offered the best way to control coccidia. However, unbridled use of anti-coccidial drugs and the emergence of the new resistant field strains of coccidia have made it increasingly challenging to control coccidiosis with commonly available coccidiostat drugs.

The coccidiostats have been classified in two groups: ionophores, molecules obtained from microbiological fermentation, and chemicals, synthetic compounds. The mode of action of ionophores is to interfere with the membrane ion exchange, killing the extracellular stages (sporozoites and or merozoites) as they expend energy to maintain the osmotic balance. Chemical compounds can have an anticoccidial effect even on extracellular and intracellular stages (Sumano López & Gutiérrez Olvera, 2005).

However, resistance development is limiting their effectiveness, and certain compounds cannot be used in older birds or in hot environments. Moreover, government regulations often include anti-coccidial drugs in bans on antibiotics use. This does not mean that these drugs are not crucial to controlling this disease, but it is important to use alternative tools: they help make a coccidiosis control program not only less dependent on anticoccidial drugs but also more robust.

Vaccines

There are two commercial kinds of coccidia vaccines; the first one uses natural strains. These *Eimeria* are selected from field outbreaks, show a medium pathogenicity, and allow for a controlled replication of a coccidia infection. The second kind of vaccines include attenuated strains; these are precocious strains and birds usually show low or no post-vaccinal reactions.

The management of coccidia vaccines is the principal challenge for using this tool to control coccidia. Special vaccination training is required at the hatchery, which then needs a follow-up on the farm. In the field, this follow-up and the alignment of all the protocols has proven challenging for many producers.

Managing coccidiosis in poultry: Next steps

The limitations chemotherapy and vaccines have led to a surge in the quest for effective natural solutions. Recent research into plant-derived phytochemicals shows that these compounds have properties that make them an interesting tool against coccidiosis (cf. Cobaxin-Cárdenas, 2018). Knowledge, research, and technological developments are now ready to offer solutions that can be an effective part of coccidia control programs. These natural solutions create opportunities to make poultry production more sustainable by reducing dependency on harmful drugs.

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ABF poultry production: How to keep coccidiosis in check

By T.J. Gaydos

Coccidiosis control consists of programs, including ionophores, chemical coccidiostats, vaccines, and gut health-promoting natural products. Sometimes, these are combined (Noack, Chapman, and Selzer, 2019). Antibiotic-free (ABF) production requires new approaches – this article will look at how different solutions can be successfully implemented.

Meticulous coccidiosis management in ABF productions is crucial to safeguard animal welfare and performance.

What makes up a successful coccidiosis control program for ABF systems?

When managing a poultry program without antibiotics in the U.S., where ionophores are classified as antibiotics, the only available tools for coccidiosis control are vaccines, chemical coccidiostats, and natural products supporting gut health during challenging times.

- The use of a chemical-only program is possible and often successful. Still, the choice of chemicals is limited, and the risk of building resistance must always be considered and managed through the appropriate rotation of active ingredients.
- A second option is a coccidiosis vaccine with or without chemical coccidiostats. This is an excellent long-term option but the most difficult to manage.
- A third effective option is a coccidiosis vaccine combined with the use of phytomolecule-based solutions contributing to the coccidiosis control program and delivering improved gut health.

What do most ABF newcomers do?

When making the transition from conventional to ABF production, broiler producers usually try:

1. A chemical coccidiostat program,
2. A bio-shuttle program: a coccidiosis vaccine, followed by a chemical coccidiostat, or
3. Phytomolecule-based feed additives; typically, in combination with a coccidiosis vaccine or chemical program.

When the operation can master managing the coccidiosis vaccine and other husbandry challenges, the optimal solution is the combination of vaccination and phytomolecule-based feed supplements.

Why a combination?

A coccidiosis control program based on vaccination begins in the hatchery and continues through live production. Its success relies on many moving parts working in sync to produce the desired result of early uniform immunity to coccidiosis. Phytomolecule-based products additionally can support the animals in terms of gut health, oxidative balance, and immunity.

Vaccination success depends on attention to detail

If one decides to use vaccination for coccidiosis control, the following points must be considered to achieve high effectiveness.

Vaccine storage – the right temperature is crucial

Proper storage is essential for all vaccines. In general, coccidiosis vaccines should be stored between 2° to 7°C (35° to 45°F), but optimally, one asks the vaccine manufacturer for product-specific directions. Coccidiosis vaccines must not freeze. Freezing will severely damage or kill the oocysts, thus significantly reducing efficacy. It is also important to ensure that there are no cold spots in the refrigerator. Hence, vaccines should be stored in the middle of a shelf with air space around or in a foam-insulated place inside the fridge.

For monitoring the temperature, an analog high/low thermometer should be placed by the vaccine. The temperature should be recorded, and the thermometer reset daily. To minimize the risk of administering a frozen vaccine, it is recommended to put freeze indicators outside the boxes. If, despite all these measures, vaccines are suspected to have frozen, segregate the suspect product and contact the supplier for assistance.

Vaccine administration – mind an even distribution for all steps

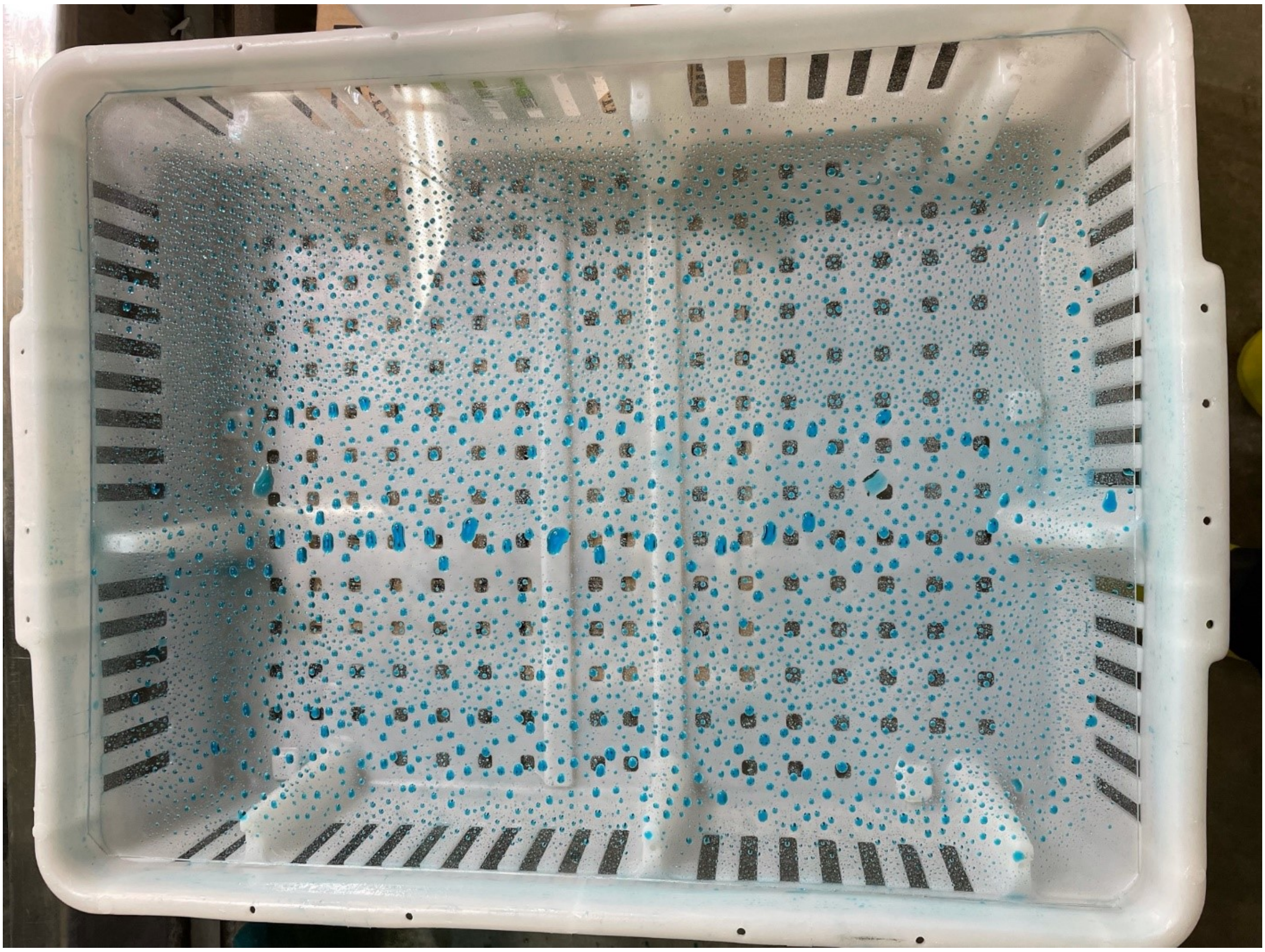
The goal of vaccination is to build early and uniform immunity in all chickens, which is achieved by exposure to repeated cycles of coccidia replication in the intestine.

1. Even distribution of the oocysts in the vaccine

It is essential to ensure that all oocysts flow from the bottle into the distribution jug when mixing the vaccine. The oocysts should be well-mixed and then must be constantly agitated to remain suspended in solution. The most common way to suspend oocysts is to use a small air pump to bubble the vaccine, creating turbulence.

2. Even spraying of the vaccine onto the chicks

The next important step is to ensure that the chicks are evenly covered with the vaccine. When in doubt, run a chick box through the spray cabinet, collect the nozzles' output, and measure the volume sprayed. To check the spray pattern, set a piece of clear hard plastic on top of the pegs in the chick basket and run the box through the spray cabinet. Evaluate the spray pattern on the plastic sheet and adjust as needed to ensure an even spraying. The spray pattern should be checked every time a new batch of vaccines is mixed.



Even spraying of coccidiosis vaccine can be easily tested using a clear plastic sheet.

3. A similar amount of vaccine intake for all chicks

Coccidiosis vaccines must be preened and consumed to be effective. Adding a dye to the spray compatible with the vaccine will help stimulate the birds to preen. A well-lit and temperature-controlled processing and holding area will promote preening behavior. Tongues should be checked regularly to ensure that chicks consume the vaccine. At a minimum, check ten birds per basket and ten baskets per lot. More than 98% of birds should have evidence of vaccine consumption within 10-15 minutes post-vaccination.

Chick vitality is a critical success factor in an ABF program. Healthy chicks perform better in the field. In the context of a coccidiosis vaccine, they are more apt to preen, more likely to consume food and water quickly, and less likely to excessively pick at the litter.

A dye helps to evaluate if the coccidiosis vaccine was evenly sprayed across all chicks.

Uniform immunity through effective farm management

A successful coccidiosis vaccination program achieves uniform immunity against coccidia, which slowly develops from the hatchery. For this purpose, birds must be evenly spread throughout all stages of growth to seed the litter evenly with oocysts and to have even coccidiosis pressure in all parts of the house.

Time management allows even immunization

Birds should be turned out from half to full house between 9 and 11 days. This schedule allows the birds to excrete the first round of oocysts and for the oocysts to sporulate and be consumed by the birds.

The birds need to be moved to full house before they secrete the second round of oocysts. This will allow the oocysts to be spread uniformly in the house. Coccidia reproduce exponentially and the second round of oocyst production is significantly more numerous than the first.

It is possible to brood birds in the full house while on coccidiosis vaccine. Still, it is complicated to manage the coccidiosis cycling because bird density is generally too low to ensure that birds effectively cycle the vaccine strain oocysts.

Litter consistency is decisive

Litter management is essential to control the cycling of coccidiosis because one stage of the life cycle of coccidia occurs in the litter. Litter moisture of 25% is ideal. When litter is squeezed in a fist, it should briefly form and immediately break apart. If it stays formed, it is too wet. If the litter is free-flowing and dusty, it is too dry for adequate sporulation.

Non-antibiotic supplements support coccidiosis management

Managing coccidiosis cycling requires attention to detail and is probably the most challenging part of adequately managing an ABF program. All farms are not equal and need to be supervised according to their specific needs. The use of non-antibiotic feed and water additives can help control coccidiosis and other enteric diseases.

Some non-antibiotic supplements have anticoccidial (e.g. amprolium, saponins, tannins) or antibacterial (e.g., plant extracts) activity. When used correctly, these may improve the performance of birds in a vaccination or chemical-based coccidiosis control program. Other non-antibiotic alternatives such as probiotics, prebiotics, organic acids, and yeast cell wall extracts have been shown to improve gastrointestinal health. The combination of excellent animal husbandry and the correct feed/water additive program is the key to success.

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