

Beyond AGPs: Controlling necrotic enteritis through gut health optimization



Antibiotic growth promoters (AGPs) have routinely been used in intensive poultry production for improving birds' performance. However, in recent years, reducing the use of [antibiotics in animal production has become a top priority](#), due to concerns about the development of antibiotic-resistant bacteria and mounting consumer pressure. Multiple countries have introduced bans or severe restrictions on the non-

therapeutic use of antibiotics, including in the US, where the Food and Drug Administration has implemented measures to curb the use of antibiotics since 2017.

However, the removal of AGPs poses challenges for poultry performance, including reduced feed efficiency, decreased daily weight gain, as well as higher mortality. Moreover, the withdrawal of AGPs in feed is widely recognized as one of the predisposing factors for necrotic enteritis (NE). NE is one of the most common and economically important poultry diseases, with an [estimated global impact of US\\$ 5 to 6 billion per year](#). As a result of withdrawing AGPs, the usage of therapeutic antibiotics to treat NE has increased. To break out of this vicious cycle and to secure the efficiency of poultry production, alternatives are needed that combat NE where it starts: in the gut.

Necrotic enteritis: a complex disease

NE is caused by pathogenic strains of *Clostridium perfringens* (CP): ubiquitous, gram-positive, spore-forming anaerobic bacteria. The spores of CP can be found in poultry litter, feces, soil, dust, and contaminated feed. Low levels of different CP strains are naturally present in the intestines of healthy birds, kept in check by a balanced microbiome. However, when gut health is compromised, [pathogenic strains can proliferate at the expense of unproblematic strains](#), resulting in clinical or sub-clinical NE.

Animals suffering from the clinical form show symptoms such as general depression, reluctance to move, and diarrhea, with mortality rates of up to 50%. Infected birds suffer from degenerated mucosa lesions in the small intestines. Even in its “mild”, subclinical form, which often goes unnoticed, the damage to the animals’ intestinal mucosa can result in permanently reduced performance and consequent economic losses for the producer.

Certain [predisposing factors](#) have been found to enable the proliferation of pathogenic strains in the gastrointestinal tract. Diet is a key example: the composition of the gut flora is directly linked to feed composition. High inclusion rates of cereals (barley, rye, oats, and wheat) that contain high levels of non-starch polysaccharides (NSPs), high levels of indigestible protein, and inclusion of proteins of animal origin (e.g. fishmeal) have been shown to predispose birds to NE.

A range of diseases (e.g. chicken infectious anemia, Gumboro, and Marek’s disease), but also other factors that have immunosuppressive effects, such as heat or cold stress, [mycotoxins](#), feed changes, or high stocking density, render birds more susceptible to intestinal infections. The single most prominent predisposing factor for the occurrence of NE is the [mucosal damage caused by coccidiosis](#).

Gut health is key to combating necrotic enteritis

To control NE, a holistic approach to optimizing the intestinal health of poultry is needed. It should take into account not only parameters such as diet, hygiene, and stress, but should also make use of innovative tools.

Phytomolecules, also known as secondary plant compounds, are essentially plants’ defense mechanisms against pathogens such as moulds, yeasts, and bacteria. [Studies have demonstrated the antimicrobial effects](#) of certain phytomolecules, including against antibiotic-resistant pathogens. Phytomolecules have also been found to boost the production of digestive enzymes, to suppress pro-inflammatory prostaglandins and have antioxidant properties. These features make them a potent tool for optimizing gut health, potentially to the point of replacing AGPs.

Can phytomolecules mitigate the impact of necrotic enteritis?

To study the impact of phytomolecules on the performance of broilers challenged with a NE-causing CP strain, a trial was conducted at a US-based research facility. In this 42-day study, 1050 male day-old Cobb 500 broiler chicks were divided into 3 groups, with 7 replicates of 50 chicks each.

On the first day, all animals were vaccinated against coccidiosis through a live oocyst spray vaccination. The experimental diets met or exceeded the National Research Council requirements, and were fed as crumbles/pellets. On days 19, 20, and 21, all pens, except the negative control group, were challenged with a broth culture of *C. perfringens*. A field isolate of CP known to cause NE (originating from a commercial broiler operation) was utilized as the challenge organism. On day 21, three birds from each pen were selected, sacrificed, group weighed, and examined for the degree of present NE lesions.

The positive control group received no supplements. The trial group received a synergistic combination of two phytogenic products containing standardized amounts of selected, microencapsulated phytomolecules: an in-feed phytogenic premix (Activo®, EW Nutrition GmbH) and a liquid complementary feed supplied via the drinking water (Activo® Liquid, EW Nutrition GmbH). The products were given at inclusion rates corresponding to the manufacturer's baseline antibiotic reduction program recommendations (Figure 1):

Figure 1: Trial design

The trial results indicate that the addition of phytomolecules helps to mitigate the impact of NE on broilers' performance. The group receiving Activo® and Activo® Liquid showed a better feed conversion (Figure 2) compared to the positive control group (NE challenge, no supplement). Also, better lesion scores were noted for animals receiving phytomolecules (0.7 and 1) than for the positive control group (1.6).

The most significant effect was observed concerning mortality: the group receiving Activo® and Activo® Liquid showed a 50% lower mortality rate than the positive control group (Figure 3). These results clearly indicate that phytomolecules can play an important role in mitigating losses due to NE.

Figure 1: Adjusted FCR

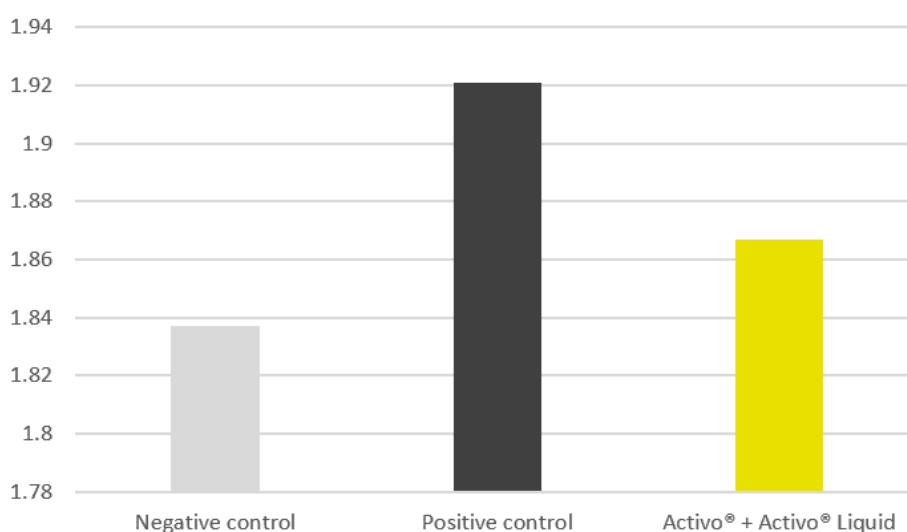
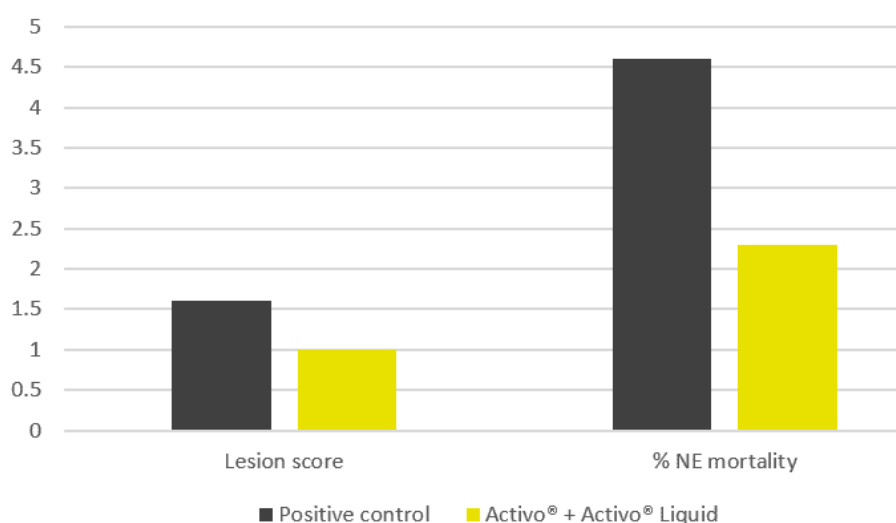


Figure 2: Lesion scores and mortality



Tackling necrotic enteritis in a sustainable way

In an age of AGP-free poultry production, a concerted focus on fostering animals' gut health is key to achieving optimal performance. This study strongly demonstrates that, thanks to their antimicrobial, digestive, anti-inflammatory and antioxidant properties, phytomolecules effectively support birds' intestinal health when challenged with NE. The inclusion of [Activo®](#) and Activo® Liquid, two phytogenic products designed to synergistically support birds during critical periods, resulted in improved feed conversion, better lesion scores, and 50% lower mortality.

In combination with good dietary, hygiene, and management practices, phytomolecules are therefore a potent tool for reducing the use of antibiotics: including Activo® and Activo® Liquid in their animals' diets allows poultry producers to reduce the incidence of NE, to mitigate its economic impact in case of outbreaks, and therefore to control NE in a sustainable way.

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Why we need to replace zinc oxide in tackling post-weaning diarrhea



Piglets experience significant stress when they are weaned from the sow and change diet, making them susceptible to gastrointestinal disorders. Primarily during the first two weeks after weaning, they are likely to suffer from post-weaning diarrhea (PWD). PWD is a significant problem for pig producers worldwide: it leads to severe dehydration, stunted growth and [mortality rates of up to 20-30%](#). Treatment and additional labor costs further squeeze farm profitability and necessitate unwanted antibiotic interventions.

Zinc oxide: an effective but highly problematic tool

Since the early 1990s zinc oxide (ZnO) has been used to control post-weaning diarrhea and promote growth in piglets, mainly at pharmacological dosages of 2500 to 3000ppm. Its mode of action is still not entirely understood; effects on [immune or metabolic processes, altered microbiota, or post-absorptive metabolism](#) are likely to play a role. What is clear is that the use of ZnO in European pig production has strongly increased since the EU banned the use of antibiotic growth promoters such as [colistin](#) in 2006 to curb the development of antimicrobial resistance.

Pigs depend on a continuous supply of zinc. Among other roles, this trace element constitutes a functional component of around 300 biochemical enzymes, making it pivotal to most metabolic processes, and by extension to optimal health, production and reproduction. [Modern pig diets thus include zinc supplementation](#) to meet the animals' requirements. The European Food Safety Authority (EFSA) currently suggests that [a total level of 150ppm](#) of zinc in feed matches the animals' physiological need for zinc. The EFSA's concerns are solely connected to the environmental concerns arising from pharmacological high dosages of ZnO.

These concerns are grave indeed: zinc is a heavy metal after all. Too much zinc is toxic for the animal, hence its physiology ensures that excessive zinc intake is excreted. The bioavailability and absorption of zinc from zinc oxide is particularly low. Therefore most of the zinc given to piglets in this way accumulates in their manure – which is widely used as an organic fertilizer for agricultural soils.

The continual application of manure gradually increases topsoil zinc concentrations; leaching and run-off then lead to contamination of groundwater, surface waters, and sediment. As zinc is non-volatile and non-degradable, it is only a matter of time before concentrations lead to ecotoxic effects, including food crops, aquatic life, and drinking water. Classic mitigation measures such as diluting the manure or keeping certain minimum distances between application areas and surface waters can only slow down the environmental accumulation of zinc, not prevent it.

EU ban: ZnO to be phased out by 2022

In 2017, the European Medicines Agency (EMA) – the EU agency responsible for the scientific evaluation, supervision and safety monitoring of medicines, including veterinary medicinal products – conducted an overall risk-benefit analysis for ZnO. It concluded that the benefits of preventing diarrhea in pigs did not outweigh the significant environmental risks caused by zinc pollution. By June 2022 [all EU member states will thus have to withdraw marketing authorizations](#) for veterinary medicinal products containing zinc oxide that are administered orally to food-producing species.

In its [decision](#), the EMA's Committee for Medicinal Products for Veterinary Use also points out the risk that, due to co-resistance, the use of zinc oxide might promote the development of antimicrobial resistance. High doses of zinc supplementation have been shown to [increase the proportion of multidrug-resistant *E. coli*](#) and [Salmonella](#), two of the most important pathogens in pig production.

What is more, studies show that [excessive zinc can accumulate in the liver, the pancreas, and blood serum](#), and that it [permanently reduces the lactobacilli population](#) of the gut flora. With what consequences for performance in the fattening phase? Hence, there are plenty of reasons why getting rid of zinc oxide is a good thing and will ultimately result in even better, more sustainable pig production – but, of course, only if effective replacement strategies to control PWD and boost piglet performance are in place.

Towards zero ZnO: smart feed additives optimize gut health

The search for ZnO alternatives takes us right back to the start, to the piglets' challenged gastrointestinal tract. During their first three months of life, [pigs' gastrointestinal system undergoes a complex maturation process](#) of its epithelial, immune, and enteric nervous systems. Only once all of these systems are fully developed is the gut capable of delivering its normal functions (digestion, nutrient absorption, immunity, etc.), while also providing an effective barrier against the pathogens, antigens, and toxins in the lumen.

Unlike in nature, where weaning occurs around the time when GIT functions have matured, weaning in commercial pig production takes place during this vulnerable developmental period. Post-weaning diarrhea is ultimately a consequence of intestinal dysbiosis, a state of imbalance in the intestinal microbiome which in turn is induced by the dietary, behavioral, and environmental stressors of the weaning phase (such as separation from the sow, vaccinations, transport, introduction of solid feed).

PWD control thus starts with managing these stressors, which includes ensuring sufficient colostrum intake, gradual feed changes, and meticulous nursery hygiene. Critically, the weaning diet needs to optimally support gut health. Intelligent feed additive solutions are able to

- reduce the pathogenic load in the piglet's GIT,
- strengthen the piglet's maturing gut barrier functionality, and
- selectively induce the development of beneficial microorganisms within the microbiome.

A synergistic combination of phytomolecules, medium-chain fatty acids, glycerides of butyric acid, and prebiotics achieves these objectives in a reliable and cost-effective manner. Thanks to their antimicrobial, anti-inflammatory, and digestive properties these selected ingredients effectively support piglets during this critical phase of their postnatal gut development, while also boosting their feed intake.

In the past decade, the European pig sector has successfully adapted to the 2006 ban on antibiotic growth promoters through significant improvements in management and feed practices. Cutting out zinc oxide is an ambitious challenge – but with the support of targeted, functional feed additives, producers will be able to set their piglets up for a strong, sustainable, zero ZnO health and growth performance.

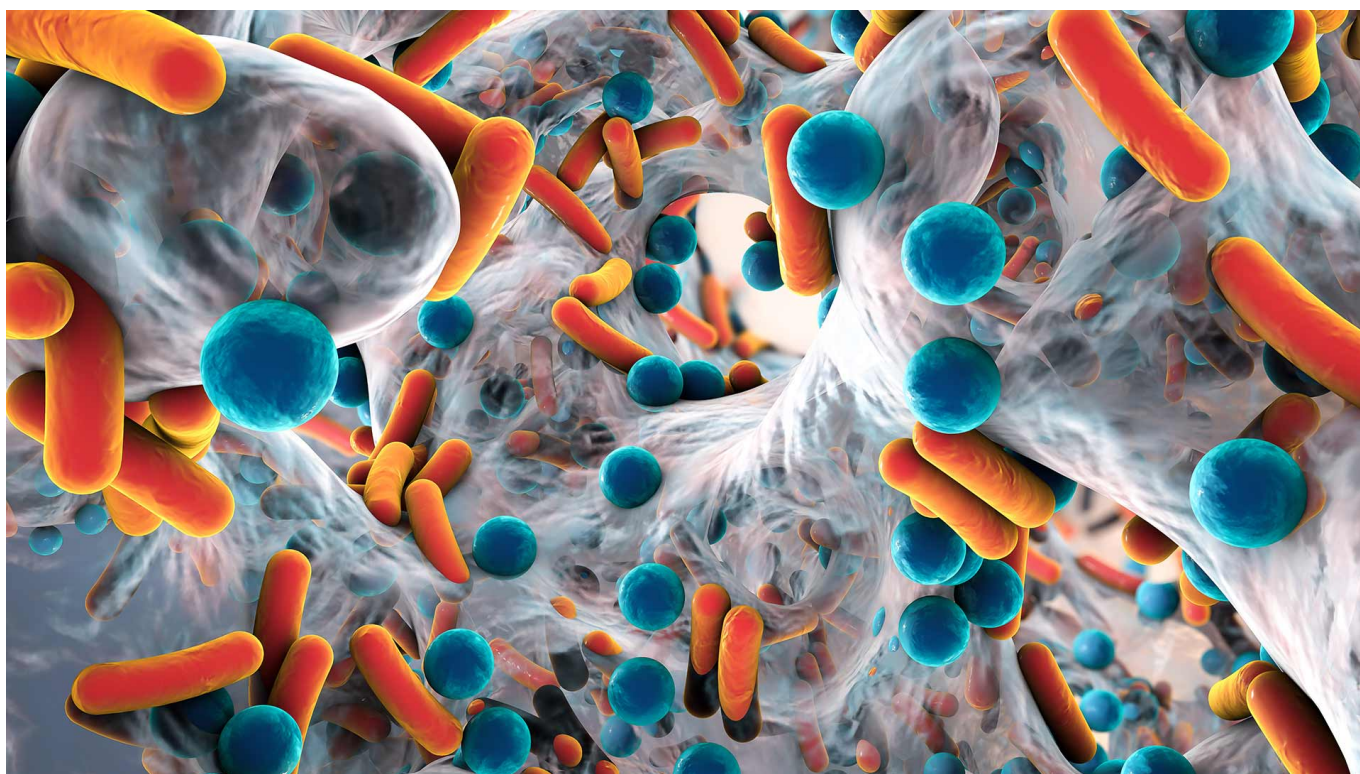
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Antibiotic reduction: The increased importance of high-level

biosecurity



Biosecurity is the foundation for all disease prevention programs (Dewulf, et al., 2018), and one of the most important points in antibiotic reduction scenarios. It includes the combination of all measures taken to reduce the risk of introduction and spread of diseases. It is based on the prevention of and protection against infectious agents by understating the disease transmission processes.

The application of consistently high standards of biosecurity can substantially contribute to the reduction of antimicrobial resistance, not only by preventing the introduction of resistance genes into the farm but also by lowering the need to use antimicrobials (Davies & Wales, 2019).

Lower use of antimicrobials with higher biosecurity

Several studies and assessments relate that high farm biosecurity status and/or improvements in biosecurity lead to [reduced antimicrobial use](#) (Laanen, et al., 2013, Gelaude, et al., 2014, Postma, et al., 2016, Collineau, et al., 2017 and Collineau, et al., 2017a). Laanen, Postma, and Collineau studied the profile of swine farmers in different European countries, finding a relation between the high level of internal biosecurity, efficient control of infectious diseases, and reduced need for antimicrobials.

Reports on reduction on antibiotic use due to farm interventions are also available. Gelaude, et al. (2014), evaluated data from several Belgian broiler farms, finding a reduction of antimicrobial use by almost 30% within a year when biosecurity and other farm issues were improved. Collineau et al. (2017) studied pig farms in Belgium, France, Germany, and Sweden, in which the use of antibiotics was reduced on average by 47% across all farms. The researches observed that farms with the most strict biosecurity protocols, higher compliance, and who also took a multidisciplinary approach (making other changes, e.g. in management and nutrition), achieved a greater reduction of antibiotic use.

Biosecurity interventions pay off

Of course, the interventions necessary to achieve an increased level of biosecurity carry some costs. However, the interventions have proven to also improve productivity. Especially if taken with other measures such as improved management of newborn animals and nutritional improvements. The same studies which report that biosecurity improvements decrease antibiotics use also report an improvement in animal performance. In the case of broilers, Laanen (2013) found a reduction of 0.5 percentual points in mortality and one point in FCR; and Collineau (2017) reported a reduction in mortality in pigs during both the pre-weaning and fattening period of 0.7 and 0.9 percentual points, respectively.

Execution

Although biosecurity improvements and other interventions necessary for antibiotic reduction programs are well known, continuous compliance of these interventions is often low and difficult. The implementation, application, and execution of any biosecurity program involve adopting a set of attitudes and behaviors to reduce the risk of entrance and spread of disease in all activities involving animal production or animal care. Measures should not be constraints but part of a process aimed to improve health of animals and people, and a piece of the multidisciplinary approach to reduce antibiotics and improve performance.

Designing effective biosecurity programs: consider five principles

When designing or evaluating biosecurity programs, we can identify five principles that need to be applied (Dewulf, et al., 2018). These principles set the ground for considering and evaluating biosecurity interventions:

1. Separation: Know your enemy, but don't keep it close

It is vital to have a good definition of the perimeter of the farm, a separation between high and low-risk animals, and dirty and clean internal areas on the farm. This avoids not only the entrance but the spread of disease, as possible sources of infection (e.g. animals being introduced in the herd and wild birds) cannot reach the sensitive population.

2. Reduction: Weaken your enemy, so it doesn't spread

The goal of the biosecurity measures is to keep infection pressure beneath the level which allows the natural immunity of the animals to cope with the infections (Dewulf, et al., 2018). Lowering the pressure of infection e.g. by an effective cleaning and disinfection program, by the reduction of the stocking density, and by changing footwear when entering a production house.

3. Focus: Hunt the elephant in the room, shoo

the butterflies

In each production unit, some pathogens can be identified as of high economic importance due to their harm and frequency. For each of these, it is even more important, to understand the likely routes of introduction into a farm and how it can spread within it. Taking into consideration that not all disease transmission routes are equally significant, the design of the biosecurity program should focus first on high-risk pathogens and transmission routes, and only subsequently on the ones lower-risk (Dewulf, et al., 2018).

4. Repetition: When the danger is frequent, the probability of injury is increased

In addition to the probability of pathogen transmission via the different transmission routes, the frequency of occurrence of the transmission route is also highly significant when evaluating a risk (Alarcon, et al., 2013). When designing biosecurity programs, risky actions such as veterinary visits, if repeated regularly must be considered with a higher risk.

5. Scaling: In the multitude, it is easy to disguise

The risks related to disease introduction and spread are much more important in big farms (Dorea, et al., 2010); more animals may be infected and maintain the infection cycle, also large flocks/herds increase the infection pressure and increase the risk by contact with external elements such as feed, visitors, etc.

Can we still improve our biosecurity?

Almost 100% of poultry and swine operations already have a nominal biosecurity program, but not in all cases is it fully effective. BioCheck UGent, a standardized biosecurity questionnaire applied in swine and broiler farms worldwide, shows an average of 65% and 68% in conformity, respectively, from more than 3000 farms between both species (UGent, 2020). Therefore, opportunities to improve can be found in farms globally, and they pay off.

To find these opportunities, consider three situations you need to know:

1. **Know your menace:** Identify and prioritize the disease agents of greatest concern for your production system by applying the principles of **focus** and **repetition**. Consider the size of the facility when evaluating risks applying the **scaling**
2. **Know your place:** Conduct an assessment of the facility. A starting point is to define the *status quo*. For that, operation-existing questionnaires or audits can be used. However, the “new eyes principle” should be applied and an external questionnaire such as BioCheck UGent (biocheck.ugent.be) is recommended. The questionnaire will help you identify gaps in your **biosecurity plan** as well as **processes** that may be allowing pathogens to enter or move from one location to another, and measures that can be implemented applying the principles of **separation** and **reduction**.
3. **Know your processes:** Implement processes and procedures that apply the biosecurity principles and help to eliminate, prevent, or minimize the potential of disease. A deep evaluation of the daily farm processes will aid in risk mitigation, considering, among others, movement of personnel, equipment, and visitors, the entrance of pets, pests and vermin, dealing with deliveries and handling of mortality and used litter.

Compliance – The weak link in biosecurity programs

Achieving systematic compliance of biosecurity protocols on a farm is a complex, interactive, and continuous process influenced by several factors (Delabbio, 2006) and an ongoing challenge for animal production facilities (Dewulf, et al., 2018). Thus, it is clear that the biosecurity plan can only be effective if everyone on the operation follows it constantly, i.e. if everyone performs in **compliance**.

Compliance can be defined as the extent to which a person's behavior coincides with the established rules. Thus, compliance with biosecurity practices should become part of the culture of the facility. Poor compliance in relation with biosecurity can be connected to:

- Lack of knowledge or understanding of the biosecurity protocols (Alarcon, et al., 2013; Cui & Liu, 2016; Delpont, et al., 2020)
- Lack of consequences for non-compliance (Racicot, et al., 2012a)
- A company culture of inconsistent or low application of biosecurity protocols (Dorea, et al., 2010)

In general terms, compliance with biosecurity procedures has been found to be incomplete in different studies (Delpont, et al., 2020; Dorea, et al., 2010; Gelaude, et al., 2014; Limbergen, et al., 2017). In one study (Racicot, et al., 2011) used hidden cameras, to assess biosecurity compliance in Quebec, Canada and found 44 different biosecurity fails made by 114 individuals (farm workers and visitors) in the participating poultry farms, over the course of 4 weeks; in average four mistakes were made per visit. The most frequent mistakes were ignoring the delimitation between dirty and clean areas, not changing boots, and not washing hands at the entrance of the barns; these three mistakes were committed in more than 60% of the occasions, regardless of being farm employees or visitors. These are frequent breaches not only of those farms in Quebec but found frequently in many animal production units around the world and have a high probability of causing the entrance and spread of pathogens.

How to create a high biosecurity culture: start now!

Creating, applying, and maintaining a biosecurity culture is the most effective way to make sure that compliance of the biosecurity program and procedures is high on the farm. Decreasing, therefore, the probability of entrance and spread of pathogens, reducing the use of antimicrobials, and maintaining animal health. Some actions are recommended in order to achieve a high biosecurity culture:

1. Name an accountable person

Every operation should have a biosecurity coordinator who is accountable for developing, implementing, and maintaining the biosecurity program.

This important position should be appointed having in mind that certain personality traits may facilitate performance and execution of the labor (Delabbio, 2006; Racicot, et al., 2012; Laanen, et al., 2014; Delpont, et al., 2020) such as responsibility, orientation to action, and being able to handle complexity. Additionally, expertise – years working in the industry y- and orientation to learn are strategic (Racicot, et al., 2012).

2. Set the environment

When the farm layout is not facilitating biosecurity, compliance is low (Delabbio, 2006), thus the workspace should facilitate biosecurity workflows and at the same time make them hard to ignore (Racicot, et al., 2011).

3. Allow participation

It is important to mention that not only the management and the biosecurity coordinator are responsible for designing and improving biosecurity procedures. Biosecurity practices must be owned by all the farm workers and should be the social norm.

The annual or biannual revision of biosecurity measures should be done together with the farm staff. This not only serves the purpose of assessing compliance but also allows the personnel to suggest measures addressing existing -often overlooked- gaps, and to be frank about procedures that are not followed and the reasons for it. At the same time, participation increases accountability and responsibility for the biosecurity program.

4. Train for learning

Don't take knowledge for granted. Even when a person has experience in farm work and has been working in the industry for several years, their understanding and comprehension around biosecurity may have gaps.

People are more likely to do something when they see evidence of the activity's benefit. Therefore, if workers are told about the effectiveness of the practices, showing the benefits of biosecurity and analyzing the consequences of non-compliance, they are most likely to follow the procedures (Dewulf, et al., 2018). Knowledge of disease threats and symptoms also improves on-farm biosecurity (Dorea, et al., 2010), thus workers should recognize the first symptoms of disease in animals and act upon them.

Discussion of 'What if...?' scenarios to gain an understanding of the key aspects of farm biosecurity should be held on a regular basis. Workers should see examples of the benefits of compliance – and risks of noncompliance – as part of their training.

5. Lead by example

A high biosecurity culture requires everyone to comply regardless of status.

Personnel practice of biosecurity procedures is not only affected by the availability of resources and training, but also by the position that management takes on biosecurity and the feedback provided. The management and owners must transmit a message of commitment to the farm personnel, owning and following biosecurity practices, procedures and protocols, giving positive and negative feedback on the personnel's compliance, supplying information on farm performance and relating it with biosecurity compliance and ensuring adequate resources for the practice of biosecurity (Delabbio, 2006).

When necessary, management also should enforce personnel compliance by disciplinary measures, firings, and creating awareness about the consequences of disease incidence. Nevertheless, the recognition of workers' contribution to animal health performance also has a positive impact on biosecurity compliance (Dorea, et al., 2010).

The bottom line

Biosecurity is necessary for disease prevention in any animal production system. Actions and interventions that prevent the entrance and spread of disease in a production unit have a pay-off as they often lead to performance improvements and lower antimicrobial use. Maintaining a successful production unit requires a multidisciplinary approach in which [biosecurity compliance](#) needs to be taken seriously and also actions to improve in other areas such as management, health, and nutrition.

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Necrotic enteritis: The complete overview



by Inge Heinzl, Marisabel Caballero, Ajay Bhoyar, EW Nutrition

Eliminating necrotic enteritis from your operations starts from a good understanding of what it is, how to prevent it, and how to mitigate its effects on your poultry production.



Necrotic enteritis is a poultry disease caused by an overgrowth of *Clostridium perfringens* type A, and to a lesser extent type C, in the small intestine. The toxins produced by *C. perfringens* also damage the intestinal wall. In general, it occurs in broiler chickens of 2-6 weeks of age. In subclinical forms, it is characterized by impaired digestion. Clinical forms lead to severe problems and increased flock mortality in a very short time.

Necrotic enteritis is the cause of USD 6 billion annual losses in global poultry production and this controllable disease is on the rise. One reason is the voluntary or legally required reduction of antibiotics in animal production. This trend is driven by the increasing occurrence of antimicrobial resistance, as well as by consumer demand. Another reason is the reduction of ionophores which, besides their activity against coccidia, also show efficacy against clostridia. When anticoccidial live vaccines are used, the application of these ionophores is not possible and clostridia / necrotic enteritis increase (Williams, 2005).

While this is a widespread problem in all poultry, for broilers in particular, necrotic enteritis and coccidiosis are the most significant health problem.

Clinical and subclinical forms of NE

The clinical form



(c) Rob Moore

...is characterized by acute, dark diarrhea resulting in wet litter and suddenly increasing flock mortality of up to 1% per day after the first clinical signs appear (Ducatelle and Van Immerseel, 2010), sometimes summing up to mortality rates of 50% (Van der Sluis, 2013). The birds have ruffled feathers, lethargy, and inappetence.

Necropsy typically shows ballooned small intestines with a roughened mucosal surface, lesions, and brownish (diphtheritic) pseudo-membranes. There is a lot of watery brown, blood-tinged fluid and a foul odor during post-mortem examination. The liver is dark, swollen, and firm, and the gall bladder is distended (Hofacre et al., 2018).

In the case of **peracute** necrotic enteritis, birds may die without showing any preliminary signs.

The subclinical form



When birds suffer from the subclinical form, chronic damage to the intestinal mucosa and an increased quantity of mucus in the small intestine lead to impaired digestion and absorption of nutrients resulting in poor growth performance.

The deteriorated feed conversion and the resulting decreased performance become noticeable around day 35 of age. As feed contributes approximately 65-75% of the input cost to produce a broiler chicken, poor feed conversion increases production costs and significantly influences profitability. Often, due to a lack of clear symptoms, this subclinical disease remains untreated and permanently impacts the efficiency of production.

Pathogens

Responsible for necrotic enteritis are Gram-positive, anaerobic bacteria, specific strains of *Clostridium perfringens* type A and, to a lesser extent, type C (Keyburn et al., 2008).

Clostridia primarily occur in the soil where organic substances are degraded, in sewage, and the [gastrointestinal tract of animals and humans](#). These bacteria produce spores, which are extremely

resistant to environmental impact (heat, irradiation, exsiccation) as well as some disinfectants, and can survive for several years. Under suitable conditions, *C. perfringens* spores can even proliferate in feed or litter.

Clostridium perfringens is a natural inhabitant of the intestine of chickens. In healthy birds, it occurs in a mixture of diverse strains at 10^2 - 10^4 CFU/g of digesta (McDevitt et al., 2006). The disease starts when *C. perfringens* proliferates in the small intestine, usually due to a combination of factors such as high amount protein, low immunity, and an imbalance in the gut flora. Then, the number rises to 10^7 - 10^9 CFU/g of digesta (Dahiya et al., 2005).

NetB, a key virulence factor for NE

To establish in the host, *Clostridium* Spp. and other pathogens depend on virulence factors (see infobox). These virulence factors include, for example, “tools” for attachment, evasion or suppression of the host’s immune system, “tools” for getting nutrients, and “tools” for entry into intestinal cells. Over the years, the α -toxin produced by *C. perfringens* was assumed to be involved in the development of the disease and a key virulence factor. In 2008, Keyburn and coworkers found another key virulence factor by using a *C. perfringens* mutant unable to produce α -toxin, yet still causing necrotic enteritis.

Thus, another toxin was identified occurring only in chickens suffering from necrotic enteritis: *C. perfringens* necrotic enteritis B-like toxin (NetB). NetB is a pore-forming toxin. Pore-forming toxins are exotoxins usually produced by pathogenic bacteria, but may also be produced by other microorganisms. These toxins destroy the integrity of gut wall cell membranes. The leaking cell contents serve as nutrients for the bacteria. If immune cells are destroyed, an immune reaction might be partially impacted (Los et al., 2013).

Additionally, pathogenic strains of *C. perfringens* produce bacteriocins – the most important being Perfrin (Timbermont et al., 2014) – to inhibit the proliferation of harmless *Clostridium* Spp. strains and to replace the normal intestinal flora of chickens (Riaz et al., 2017).

Examples of virulence factors

1. Adhesins

Enable the pathogen to adhere or attach within the target host site, e.g. via fimbria. Pili enable the exchange of RNA or DNA between pathogens.

2. Invasion factors

Facilitate the penetration and the distribution of the pathogens in the host tissue (invasion and spreading enzymes). For example: hyaluronidase attacking the hyaluronic acid of the connective tissue or flagella enabling the pathogens to actively move.

3. Toxins

Damage the function of the host cells or destroy them (e.g. endotoxins – lipopolysaccharides, exotoxins)

4. Strategies of evasion

Enable the pathogen to bypass the strategies of defense of the immune system (e.g. antiphagocytosis factors provide protection against an attack by phagocytes; specific antibodies are inactivated by enzymes).

A chicken with **optimal gut health** may be less **susceptible to NE**. Additional **predisposing factors** are necessary to allocate nutrients and make the gut environment suitable for the proliferation of these pathogens, enabling them to cause disease (Van Immerseel et al., 2008; Williams, 2005).

Predisposing factors

Feed: composition and particle size

The role of feed in the development of necrotic enteritis should not be underestimated. This is where substances creating an intestinal environment favorable for *C. perfringens* come into play.

NSPs

Non-starch polysaccharides

Mode of action

- Increase viscosity
- Decrease passage rate
- Decrease digestibility of other nutrients
- Serve as nutrient

more nutrients available for *C. perfringens*

Stimulation of mucus production

anaerobic environment

Van der Sluis, 2013

Koldhaudal and Skjerve (1996); Annett et al. (2002)

Particle size

Not uniform particle size

Increased rates of NE

(Ranton et al., 1987)

Finely-ground

Mode of action

- gizzard size/activity ↓
- pH ↑, GIT transit time ↓

proliferation of pathogenic microbes

(*Salmonella*, *Campylobacter*, *Clostridium*...) ↓
(in comparison to coarse corn)

(Rouquette and Carré, 2008;
Santos et al., 2008;
Singh et al., 2014)

Excessive content of protein

Poorly digestible protein

Excessively high concentrations of zinc/glycine

Mode of action:

- high protein levels in the GIT
- act as substrate for the bacteria

shift in balance of intestinal flora

(Antonissen et al., 2016)

Mycotoxin contamination

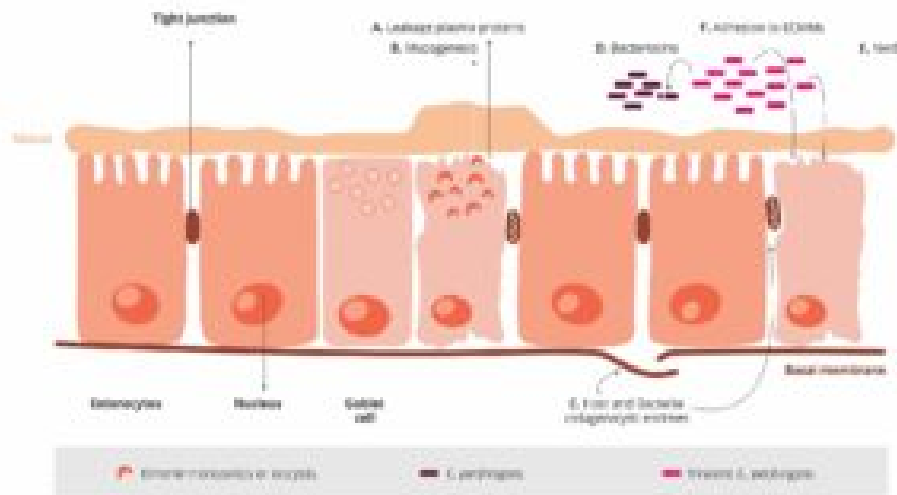
Mycotoxins harm gut integrity and create ideal conditions for the proliferation of *Clostridium perfringens*.

Mycotoxins do not have a direct effect on *C. perfringens* proliferation, toxin production, or NetB transcription. However, mycotoxins disrupt gut health integrity, creating a favorable environment for the pathogen. For example:

1. DON provides good conditions for proliferation of *C. perfringens* by disrupting the intestinal barrier and damaging the epithelium. The possibly resulting permeability of the epithelium and a decreased absorption of dietary proteins can lead to a higher amount of proteins in the small intestine. These proteins may serve as nutrients for the pathogen (Antonissen et al., 2014).
2. DON and other mycotoxins decrease the number of lactic acid producing bacteria indicating a shift in the microbial balance (Antonissen et al., 2016.).

Eimeria ssp.

An intact intestinal epithelium is the best defense against potential pathogens such as *C. perfringens*. Here, Coccidiosis comes into play. Moore (2016) showed that by damaging the gut epithelium, *Eimeria* species give *C. perfringens* access to the intestinal basal domains of the mucosal epithelium. Then, the first phase of the pathological process takes place and from there, *C. perfringens* invades the lamina propria. Damage to the epithelium follows (Olkowski et al., 2008). The plasma proteins leaking to the gut and the mucus produced are rich nutrient sources (Van Immerseel et al., 2004; Collier et al., 2008). A further impact of Coccidiosis is shifting the microbial balance in the gut by decreasing the number of e.g., *Candidatus savagella* which activates the innate immune defense.



1. *Eimeria* induce leakage of plasma proteins by killing epithelial cells
2. They enhance mucus production in the intestine

1+2 lead to an increase in available nutrients and create an environment favorable for the proliferation of *C. perfringens*.

Not only *Eimeria* Spp., also other pathogens (e.g. *Salmonella* Spp., Ascarid larvae, viruses) and agents, such as mycotoxins damaging the intestinal mucosa can pave the way for a *C. perfringens* infection.

Predisposing factors like wet litter, the moisture of which is essential for the sporulation of *Eimeria* Spp. oocysts, must also be considered as promoting factors for necrotic enteritis (Williams, 2005).

Immunosuppressive factors

Besides the already explained influencers feed, mycotoxins and coccidia, also other predisposing factors must be mentioned. In general, any factor which induces stress in the animals disrupts the balance of the intestinal flora. The resulting suppression of the immune system contributes to the risk of necrotic enteritis (Tsiouris, 2016). These factors include:

Bacteria: Shivaramaiah and coworkers (2011) investigated a neonatal *Salmonella typhimurium* infection as a predisposing factor for NE. The early infection causes significant damage to the gut (Porter et al., 1998) Additionally, Hassan et al. (1994) showed that the challenge with *Salmonella typhimurium* negatively impacted the development of lymphocytes which might also promote a colonization of *Clostridium perfringens*.

Viruses: Infectious Bursal Disease is known to increase the severity of infections with salmonella, staphylococci, but also clostridia. Another clostridia-promoting viral disease is Marek's Disease.

Stress: The intestinal tract is particularly sensitive to any type of stress. This stress can be caused by e.g. too high temperatures, high stocking densities, an abrupt change of feed.



Treatment

In acute cases, the farmer should consult a veterinarian and treat his birds.

It must be mentioned that, as the treatment takes place via feed or water, only birds which still consume water or feed may be treated.

Antibiotics

Antibiotics targeting Gram-positive bacteria are commonly used for the treatment of acute NE. The antibiotic choice shall be addressed by a veterinarian, taking into account mode of action and the presence of resistance genes in the farm/flock.

The prophylactic use of antibiotics is not recommended and many countries have already banned it in order to reduce [antimicrobial resistance](#) (AMR).

Antimicrobial Resistance (AMR)

Some bacteria are less sensitive to certain antibiotics due to genetic mutations. They are able to:

- stimulate the production of enzymes, which break down or modify the antibiotics and inactivate them (1).
- eliminate entrances for antibiotics or promote the development of pumps, which discharge the antibiotic before taking effect (2).
- change or eliminate molecules to which the antibiotic would bind (targets for the antibiotics).

This means that, when the corresponding antibiotics are used, bacteria resistant against these antibiotics survive. Due to the fact that their competitors have been eliminated they are able to reproduce better.

Additionally, this resistance may be transferred by means of “resistance genes”

- to daughter cells
- via their intake from dead bacteria (3)

- through horizontal gene transfer (4)
- through viruses (5)

Every application of antibiotics promotes the development of resistance (Robert Koch Institute, 2019). A short-term use, [better biosecurity](#), or an application at low dosage give the bacteria a better chance to adapt.

Bacteriophages

Experimental use of phage treatments have shown to be effective in reducing disease progression and symptoms of necrotic enteritis (Miller et al., 2010). By oral application of a bacteriophage cocktail, Miller and coworkers could reduce mortality by 92% in *C. perfringens* challenged broilers compared to the untreated control.

Mode of action: the endolysins, highly evolved enzymes produced by bacteriophages, are able to digest the bacterial cell wall for phage progeny release (Fischetti, 2010). However, phages are still not approved by the EFSA.

Prevention

Preventing a disease is always better – and more cost-effective – than its treatment.

How, then, should it be done?

Preventing the conditions that favor the proliferation of *Clostridium perfringens* and strengthening the host's immune response lowers the probability of disease.

Besides eliminating the predisposing factors, the main targets are:

- Balance of the [gut flora](#)
- Optimization of gut function and integrity
- Maintenance of immunity

Biosecurity

There is evidence that most *Clostridium* strains isolated from birds suffering from necrotic enteritis could induce the disease experimentally, while strains isolated from healthy birds cannot. This confirms that only specific strains are problematic (Ducatelle and Van Immerseel, 2010).

It is therefore of the highest importance to avoid introducing these pathogenic strains to the farm.

- Strict [biosecurity](#) measures!
- Separate clothing, boots, and hand washing/disinfecting facilities in each poultry house
- More than 14 days of down time between flocks

Specific measures against coccidiosis

1. Vaccination

According to parasitologists, 7 to 9 *Eimeria* species are found in chickens, and they do not cross-protect against each other. An effective vaccination must contain sporulated oocysts of the most critical pathogenic *Eimeria* species (*E. acervulina*, *E. maxima*, *E. tenella*, *E. necatrix*, and *E. brunetti*). The more species contained in the vaccine, the better. However, if not applied the correct way, vaccines can be

ineffective or cause reactions in the birds that might lead to NE (Mitchell, 2017).

2. Anticoccidials

Alternate use of chemicals (synthetic compounds) and ionophores (polyether antibiotics) with different modes of action is important to avoid development of resistance.

Ionophores have a specific mode of action and kill oocysts before they are able to infect birds. Being very small, ionophore molecules can be taken up and diffused into the outer membrane of the sporozoite. There, it decreases the concentration gradient leading to an accumulation of water within the sporozoite causing its bursting.

Diet

Minimizing non-starch polysaccharides (NSPs) in cereals



To prevent a “feeding” of *Clostridium perfringens*, high content of water-soluble but indigestible NSPs such as wheat, wheat by-products, and barley should be avoided or at least minimized. Additionally, xylanases should be included in the feed formulation to reduce the deleterious effects of NSPs and improve feed energy utilization. Instead of these cereals, maize could be included in the diet. It is considered a perfect ingredient in broiler diets due to its high energy content and high nutrient availability.

Formulating low protein diets/diets with highly digestible amino acids

Feeding low-protein diets supplemented with crystalline amino acids might be beneficial to reduce the risk of necrotic enteritis (Dahiya et al., 2007). To improve protein digestibility and therefore reduce the proliferation of *C. perfringens*, proteases may be added to the feed.

Avoiding/Minimizing poor quality fats / animal fats in the diet

These fats tend to increase the count of *Clostridium perfringens*; thus, they should be replaced by higher quality and/or vegetable fats, respectively.

Feed form

In terms of feed form, Engberg et al. (2002) found that birds fed pellets showed a reduced number of *Clostridium perfringens* in the caeca and the rectum than mash-fed birds. Branton and co-workers (1987) reported a lower mortality by feeding roller-milled (coarsely ground) than hammer-milled feed.

Additives

Additives can be used either to prevent the proliferation of *Clostridium perfringens* or to change the environmental conditions in a way that proliferation of *C. perfringens* is prevented.

Probiotics

These live microbial supplements can be used to help to establish, maintain or re-establish the intestinal microflora.

Mode of action:

- compete with pathogenic bacteria for substrates and attachment sites
- produce antimicrobial substances inhibiting the growth of pathogenic bacteria (Gillor et al., 2008)
- bind and neutralize enterotoxins (Mathipa and Thantsha, 2017)
- promote immune function of the host (Yang et al., 2012)

Prebiotics

- These feed ingredients serve as substrates to promote beneficial bacteria in the intestine.

Mode of action:

- D-mannose or fructose, starches non-digestible by birds, selectively stimulate the growth and the activity of the “good” gut flora
- Fructooligosaccharides decrease *C. perfringens* and *E. coli* in the gut and increase the diversity of *Lactobacillus* Spp. (Kim et al., 2011)
- Galactooligosaccharides, in combination with a *B. lactis* based probiotic, have been reported to selectively promote the proliferation of *Bifidobacterium* ssp. (Jung et al., 2008).

Organic acids

Organic acids are often used in animal diets to improve intestinal health.

Mode of action:

- decreased pH promotes beneficial bacteria
- caprylic acid suppresses *C. perfringens*, but also *Salmonella* Spp. by inhibiting their utilization of glucose (Skrivanova et al., 2006)
- lauric, citric, oleic and linoleic acid as well as medium-chain fatty acids (C8-C14) impede the growth of *C. perfringens*

Phytomolecules

[Phytomolecules](#), also known as secondary plant compounds, have been used against pathogens for centuries. In general, two subgroups of these substances are known as effective against *Clostridium perfringens*:

Tannins

- Many studies have shown the efficacy of tannins against different pathogens such as helminths, *Eimeria*, viruses, and bacteria
- Extracts from the chestnut and quebracho trees are effective not only against *C. perfringens*, but also its toxins (Elizando et al., 2010)
- Activity of tannins against *Eimeria* (Cejas et al., 2011) and *Salmonella* Sp., two predisposing factors for NE.

Essential Oils

- Their hydrophobic characteristic enables them to interact with the lipids of the membrane of *C. perfringens*.
- They can incorporate into the bacterial membrane and disrupt its integrity.
- This increases the permeability of the cell membrane for ions and other small molecules such as ATP, leading to the decrease of the electrochemical gradient above the cell membrane and the loss of the cell's energy equivalents.

Besides their direct effect on *Clostridium* Spp., a lot of phytomolecules [improve gut health](#) and help to prevent a proliferation of *Clostridium* ssp. and therefore necrotic enteritis.

Mycotoxin/bacterial toxin binders

These binders have two modes of action:



- Binding mycotoxins, damage of the intestinal epithelium can be reduced or even prevented, so that the preconditions for *Clostridium* proliferation are not generated.
- Binding toxins produced by *Clostridium perfringens* can reduce the occurrence or severity of lesions:

Alpha-toxin (phospholipase C) hydrolyses membrane phospholipids and damages erythrocytes, leucocytes, myocytes, and endothelial cells and causes their lysis (Songer, 1996). This leads to necrosis and tissue damage.

- Binding NetB toxin, the key virulence factor, could reduce the severity of necrotic enteritis.

Conclusion

The ever-growing trend of reduced antibiotic and ionophore use is contributing to an increased incidence of necrotic enteritis in poultry production.

The subclinical form of necrotic enteritis generally goes unnoticed, resulting in poor feed efficiency and is a major cause of financial losses to poultry producers.

Maintaining optimum [gut health](#) is key to preventing the occurrence of necrotic enteritis. In the era of antibiotic-free poultry production, [alternatives](#) acting against this pathogenic bacterium and also against its predisposing factors must be considered to control this devastating disease.



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Challenging times for broilers? Phytomolecules, not antibiotics, are the answer



*by **Ajay Bhojar**, Global Technical Manager, EW Nutrition*

Anyone working with today's fast-growing broiler chicken knows that it is a sensitive creature – and so is its gut health. Thanks to continuous improvements in terms of [genetics and breeding](#), nutrition and feeding, as well as general management strategies, broiler production has tremendously upped performance and efficiency over the past decades. It is estimated that, between 1957 and 2005, the [broiler growth rate increased by over 400%, while the feed conversion ratio dropped by 50%](#).

These impressive improvements, however, have come at the cost of intense pressure on the birds' digestive system, which needs to process large quantities of feed in little time. To achieve optimal growth, a broiler's [gastrointestinal tract \(GIT\)](#) needs to be in perfect health, all the time. Unsurprisingly, enteric

diseases such as [necrotic enteritis](#), which severely damages the intestinal mucosa, hamper the intestines' capacity to absorb nutrients and induce an inflammatory immune response.

The modern broiler's gut - a high-performing, but sensitive system

However, in a system as high performing as the modern broiler's GIT, much less can lead to problems. From when they are day-old chicks up to slaughter, broilers go through several challenging phases during which they are more likely to show impaired gut functionality, e.g. after vaccinations or feed changes. [Good management practices go a long way towards eliminating unnecessary stressors](#) for the animals, but some challenging periods are unavoidable.

The transition from starter to grower diets is a classic situation when nutrients are very likely to not be well digested and build up in the gut, fueling the proliferation of harmful microbes. Immunosuppressive stress in combination with an immature intestinal microflora results in disturbances to the bacterial microbiota. At "best", this entails temporarily reduce nutrient absorption, in the worst case the birds will suffer serious intestinal diseases.

Phytomolecules - the intelligent alternative to antibiotics

To safeguard performance during stressful periods, poultry producers need to anticipate them and proactively provide effective gut health support. For many years, this support came in the form of antibiotic growth promoters (AGP): administered prophylactically, they were effective at keeping harmful enteric bacteria in check. However, due to grave concerns about the [development of antimicrobial resistance](#), non-therapeutic antibiotics use has been banned in many countries. Alternatives need to focus on improving feed digestibility and strengthening gut health, attacking the root causes of why the intestinal microflora would become unbalanced in the first place.

Phytomolecules are secondary metabolites active in the defense mechanisms of plants. Studies have found that certain phytomolecules [stimulate digestive enzyme activities](#) and stabilize the gut microflora, "leading to improved feed utilization and less exposure to growth-depressing disorders associated with digestion and metabolism" (Zhai et al., 2018). With other trials showing [positive effects on broilers' growth performance and feed conversion](#), the research indicates that phytomolecules might also specifically support chickens during challenging phases.

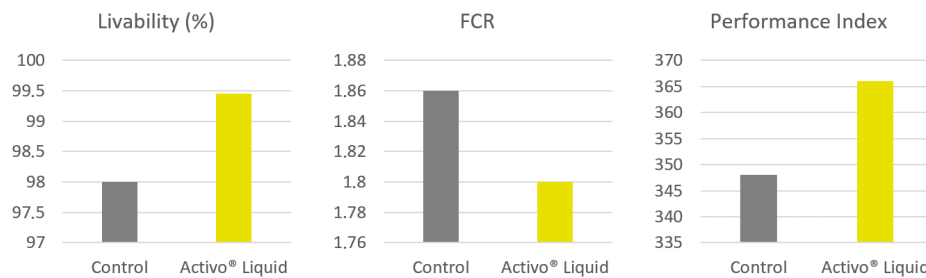
The effect of phytomolecules on broilers during a challenging phase

A study was conducted over a period of 49 days on a commercial broiler farm of an AGP-free integration operation in Japan. The farm reported gut health challenges in the second and third week of the fattening period due to vaccinations and changes to the animals' diets. The trial included 15504 Ross 308 broilers, divided into two groups. The negative control group included a total of 7242 birds, kept in another house.

All the birds were fed the standard feed of the farm. The trial group (8262 birds) received Activo® Liquid, which contains a synergistic combination of phytomolecules, administered directly through the drinking water. Activo® Liquid was given at an inclusion rate of 200ml per 1000L of water (3.3 US fl oz per gallon of stock solution, diluted at 1:128), from day 8 until day 25, for 8 hours a day.

The results are summarized in Figure 1:

Figure 1: Improved broiler performance for Activo® Liquid group (day 49)



The Activo® Liquid group clearly showed performance improvements compared to the control group. Livability augmented by 1.5%, while the feed conversion rate improved by 3.2%. This resulted in a more than 5% higher score in terms of the performance index.

Challenging times? Tackle them using phytomolecules

Poultry producers take great care to eliminate unnecessary sources of stress for their birds. Nonetheless, during their lifecycle, broiler chickens face challenging periods during which the balance of the intestinal microflora can easily become disturbed, with consequences ranging from decreased nutrient absorption to full-blown enteric disease.

The trial reviewed here showed that, after receiving Activo® Liquid, broilers raised without AGPs showed encouraging performance improvements during a challenging phase of feed changes and vaccinations. Likely thanks to the activation of digestive enzymes and a stabilization of the gut flora, the broilers showed improved livability and feed conversion, thus delivering a much more robust performance during a critical phase of their lives. In times where the non-therapeutic use of antibiotics is no longer an option, phytomolecules allow poultry farmers to effectively support their animals during challenging times.

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Photo Source: [Aviagen](#)

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