Fighting antimicrobial resistance with immunoglobulins



By **Lea Poppe**, Regional Technical Manager On-Farm Solutions Europe, and **Dr. Inge Heinzl**, Editor

One of the ten global public health threats is antimicrobial resistance (AMR). Jim O'Neill predicted 10 million people dying from AMR annually by 2050 (O'Neill, 2016). The following article will show the causes of antimicrobial resistance and how antibodies from the egg could help mitigate the problem of AMR.

Global problem of AMR results from the incorrect use of antimicrobials

Antimicrobial substances are used to prevent and cure diseases in humans, animals, and plants and include antibiotics, antivirals, antiparasitics, and antifungals. The use of these medicines does not always happen consciously, partially due to ignorance and partially for economic reasons.

There are various possibilities for the wrong therapy

- 1. The use of antibiotics against diseases that household remedies could cure. A recently published <u>German study</u> (Merle et al., 2023) confirmed the linear relationship between treatment frequency and resistant scores in calves younger than eight months.
- 2. The use of antibiotics against viral diseases: antibiotics only act against bacteria and not against viruses. Flu, e.g., is caused by a virus, but doctors often prescribe an antibiotic.
- 3. Using broad-spectrum antibiotics instead of determining an antibiogram and applying a specific antibiotic.
- 4. A too-long treatment with antimicrobials so that the microorganisms have the time to adapt. For a long time, the only mistake you could make was to stop the antibiotic therapy too early. Today, the motto is "as short as possible".

Let's take the example of neonatal calf diarrhea, one of the most common diseases with a high economic impact. Calf diarrhea can be caused by a wide range of bacteria, viruses, or parasites. This infectious form can be a complication of non-infectious diarrhea caused by dietary, psychological, and environmental stress (Uetake, 2012). The pathogens causing diarrhea in calves can vary with the region. In Switzerland and the UK, e.g., rotaviruses and cryptosporidia are the most common pathogens, whereas, in Germany, E. coli is also one of the leading causes. To minimize the occurrence of AMR, it is always crucial to know which pathogen is behind the disease.

Prophylactic use of antibiotics is still a problem

- 1. The use of low doses of antibiotics to promote growth. This use has been banned in the EU now for 17 years now, but in other parts of the world, it is still common practice. Especially in countries with low hygienic standards, antibiotics show high efficacy.
- 2. The preventive use of antibiotics to help, e.g., piglets overcome the critical step of weaning or to support purchased animals for the first time in their new environment. Antibiotics reduce pathogenic pressure, decrease the incidence of diarrhea, and ensure the maintenance of growth.
- 3. Within the scope of prophylactic use of antimicrobials, also group treatment must be mentioned. In veal calves, group treatments are far more common than individual treatments (97.9% of all treatments), as reported in a <u>study</u> documenting medication in veal calf production in Belgium and the Netherlands. Treatment indications were respiratory diseases (53%), arrival prophylaxis (13%), and diarrhea (12%). On top, the study found that nearly half of the antimicrobial group treatment was underdosed (43.7%), and a large part (37.1%) was overdosed.

However, in several countries, consumers request reduced or even no usage of antibiotics ("No Antibiotics Ever" – NAE), and animal producers must react.

Today's mobility enables the spreading of AMR worldwide

Bacteria, viruses, parasites, and fungi that no longer respond to antimicrobial therapy are classified as resistant. The drugs become ineffective and, therefore, the treatment of disease inefficient or even impossible. All the different usages mentioned before offer the possibility that resistant bacteria/microorganisms will occur and proliferate. Due to global trade and the mobility of people, drugresistant pathogens are spreading rapidly throughout the world, and common diseases cannot be treated anymore with existing antimicrobial medicines like antibiotics. Standard surgeries can become a risk, and, in the worst case, humans die from diseases once considered treatable. If new antibiotics are developed, their long-term efficacy again depends on their correct and limited use.

Different approaches are taken to fight AMR

There have already been different approaches to fighting AMR. As examples, the annually published MARAN Report compiled in the Netherlands, the EU ban on antibiotic growth promoters in 2006, "No antibiotics ever (NAE) programs" in the US, or the annually published "Antimicrobial resistance surveillance in Europe" can be mentioned. One of the latest approaches is an advisory "One Health High-Level Expert Panel" (OHHLEP) founded by the Food and Agriculture Organization of the United Nations (FAO), the World Organization for Animal Health (OIE), the United Nations Environment Program (UNEP), and the World Health Organization (WHO) in May 2021. As AMR has many causes and, consequently, many players are involved in its reduction, the OHHLEP wants to improve communication and collaboration between all sectors and stakeholders. The goal is to design and implement programs, policies, legislations, and research to improve human, animal, and environmental health, which are closely linked. Approaches like those mentioned help reduce the spread of resistant pathogens and, with this, remain able to treat diseases in humans, animals, and plants.

On top of the pure health benefits, reducing AMR improves food security and safety and contributes to achieving the <u>Sustainable Development Goals</u> (e.g., zero hunger, good health and well-being, and clean water).

Prevention is better than treatment

Young animals like calves, lambs, and piglets do not receive immunological equipment in the womb and need a passive immune transfer by maternal colostrum. Accordingly, optimal colostrum management is the first way to protect newborn animals from infection, confirmed by the general discussion on the <u>Failure of Passive Transfer</u>: various studies suggest that calves with poor immunoglobulin supply suffer from diarrhea more frequently than calves with adequate supply.

Especially during the immunological gap when the maternal immunoglobulins are decreasing and the own immunocompetence is still not fully developed, it is crucial to have a look at housing, stress triggers, biosecurity, and the diet to reduce the risk of infectious diseases and the need for treatments.

Immunoglobulins from eggs additionally support young animals

Also, if newborn animals receive enough colostrum in time and if everything goes optimally, the animals suffer from two immunity gaps: the first one occurs just after birth before the first intake of colostrum, and the second one occurs when the maternal antibodies decrease, and the immune system of the young animal is still not developed completely. These immunity gaps raise the question of whether something else can be done to support newborns during their first days of life.

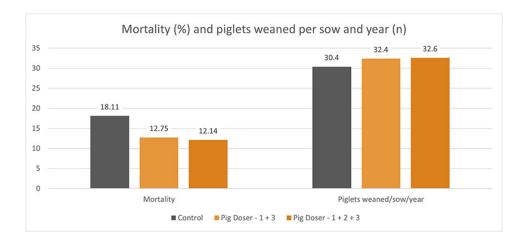
The answer was provided by Felix Klemperer (1893), a German internist researching immunity. He found that hens coming in contact with pathogens produce antibodies against these agents and transfer them to the egg. It is unimportant if the pathogens are relevant for chickens or other animals. In the egg, the immunoglobulins usually serve as an immune starter kit for the chick.

Technology enables us today to produce a high-value product based on egg powder containing natural egg immunoglobulins (IgY – immunoglobulins from the yolk). These egg antibodies mainly act in the gut. There, they recognize and tie up, for example, diarrhea-causing pathogens and, in this way, render them ineffective.

The efficacy of egg antibodies was demonstrated in different studies (Kellner et al., 1994; Erhard et al., 1996; Ikemori et al., 1997; Yokoyama et al., 1992; Marquart, 1999; Yokoyama et al., 1997) for piglets and calves.

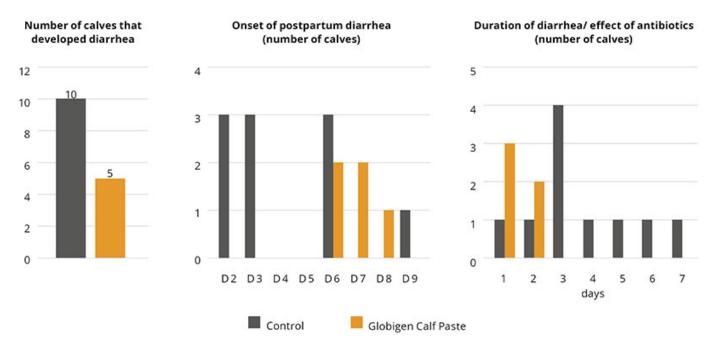
Trial proves high efficacy of egg immunoglobulins in piglets

One trial conducted in Germany showed promising results concerning the reduction of mortality in the farrowing unit. For the trial, 96 sows and their litters were divided into three groups with 32 sows each. Two of the groups orally received a product containing egg immunoglobulins, the EP -1 + 3 group on days 1 and 3 and the EP - 1 + 2 + 3 group on the first three days. The third group served as a control. Regardless of the frequency of application, the egg powder product was very supportive and significantly reduced mortality compared to the control group. The measure resulted in 2 additionally weaned piglets than in the control group.



Egg immunoglobulins support young dairy calves

IgY-based products were also tested in calves to demonstrate their efficacy. In a field trial conducted on a Portuguese dairy farm with 12 calves per group, an IgY-containing oral application was compared to a control group without supplementation. The test product was applied on the day of birth and the two consecutive days. Key observation parameters during a two-week observation period were diarrhea incidence, onset, duration, and antibiotic treatments, the standard procedure on the trial farm in case of diarrhea. On-farm tests to check for the pathogenic cause of diarrhea were not part of the farm's standards.



In this trial, 10 of 12 calves in the control group suffered from diarrhea, but in the trial group, only 5

calves. Total diarrhea and antibiotic treatment duration in the control group was 37 days (average 3.08 days/animal), and in the trial group, only 7 days (average 0.58 days/animal). Additionally, diarrhea in calves of the Globigen Calf Paste group started later, so the animals already had the chance to develop an at least minimally working immune system.

The supplement served as an effective tool to support calves during their first days of life and to reduce antibiotic treatments dramatically.

Conclusion

Antimicrobial reduction is one of the biggest tasks for global animal production. It must be done without impacting animal health and parameters like growth performance and general cost-efficacy. This overall demand can be supported with a holistic approach considering biosecurity, stress reduction, and nutritional support. Feed supplements such as egg immunoglobulins are commercial options showing great results and benefits in the field and making global animal production take the right direction in the future.

References upon request.

Calf diarrhea: types, causes, solutions



By Dr. Inge Heinzl, Editor, EW Nutrition

Diarrhea causes a higher workload, increased costs for treatment, losses, and, of course, lower benefits for the farmer. But not all diarrheas are equal. How do they differ, where do differences come from, and what can you do to protect your animals?



Diarrhea is a protective measure of the organism

In general, diarrhea is characterized by more liquid being secreted than being resorbed. However, diarrhea is not a disease but only a symptom. Diarrhea has a protective function for the organism: the higher liquid volume in the gut increases motility, and pathogens and toxins are more readily excreted.

Diarrhea can occur for several reasons. It can result from inadequate nutrition but also the reaction to an infection by pathogens such as bacteria, viruses, and protozoa.

Where does the fluid come from?

Depending on how the accumulation of fluid in the gut is generated, there are different kinds of diarrhea:

- In the case of secretory diarrhea, as the name says, the fluid accumulation comes from an increased secretion into the gut caused by toxins activating enzyme systems. The gut mucosa can no longer resorb this higher amount of liquid.
- When the animals suffer from malabsorptive diarrhea due to destroyed enterocytes and shortened villi, the enzyme activity and absorption capacity are reduced. Less liquid can be absorbed and has to be excreted via the gut.
- When inflammatory diarrhea occurs, the gut mucosa is damaged. Higher amounts of mucus, protein, and blood are released into the gut lumen.

Due to multiple infections, diarrhea often is a mixture of different forms.

Multiple causes can be responsible

For the occurrence of diarrhea, different causers can be a possibility. Besides infectious pathogens, also the feed must be considered.

1. Bacteria often produce toxins

E. coli is a common agent of the gut microflora and in general it is harmless. However, E. coli can also be the cause of different types of diarrhea, depending on the virulence factors. Virulence factors of E.coli are, e.g., fimbria for the attachment to intestinal receptors or the ability to produce toxins influencing the secretion of ions and liquids. Example: enterotoxic E. coli (ETEC) F5 and F41 occurring during the first days of life.

In general, Salmonella plays a secondary role in calf diarrhea. Of the Salmonella serovars, mainly S. Typhimurium and S. Dublin are found in calves. Salmonella produces enterotoxins that attack the intestinal wall.

Clostridia infections belong to the most expensive ones in cattle farming globally. In herbivores, clostridia are part of the normal flora of the gastrointestinal tract; only a few types can cause severe disease. In calves, the necrotizing toxin-producing Clostridium perfringens can lead to enterotoxaemia manifesting in acute bloody diarrhea.

2. Viruses cause lesions in the gut

Rotavirus, which occurs mainly during the 5th -15th day of life, is the most common viral pathogen causing

diarrhea in calves and lambs. If more enterocytes are destroyed than regenerated by the organism, the resorption surface in the gut decreases. With increasing age, animals develop immunity against this pathogen.

Coronavirus usually attacks calves at the age of 5 - 21 days (mainly correlated with the decreasing concentration of antibodies in maternal milk). They cause similar lesions in the intestine as rotavirus but additionally lead to necrosis of the crypts in the large intestine. The digestive and absorptive function is lost, resulting in reduced reabsorption of fluids. 3 to 20 % of diarrhea arising in calves is caused by Coronavirus.

3. Protozoa can lead to malabsorptive diarrhea

Cryptosporidium parvum (mainly 1-2 weeks after birth) belongs to the coccidia and is presumed to be the most common pathogen to cause diarrhea (prevalence up to more than 60 %) in calves. Cryptosporidium is transmitted via oocysts found in feces and on the farm equipment. Cryptosporidia destroy the microvilli in the gut, the function of the gut mucosa is reduced, the resorption area decreases. Consequence: loss of enzyme activity and, therefore, an insufficient breakdown of sugar and protein, resulting in malabsorption.

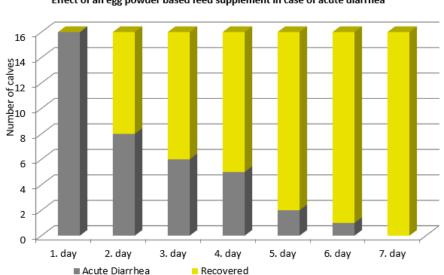
4. Calves need their special feed

In general, raw materials which cannot be well digested by the calf (mainly soya products, often used in milk replacers) or which cause allergy can cause diarrhea in calves. Also, antibiotics can lead to an imbalance of the intestinal flora, destruction of the villi, and malabsorptive diarrhea.

Trial shows promising results in the field

A field study with the egg powder-based product Globigen Dia Stop was conducted with 16 calves suffering from diarrhea. They were fed twice daily 50 g of Globigen Dia Stop stirred into the milk replacer.

Result (fig. 1): already one day after the first application of Globigen Dia Stop, 50 % of the calves recovered. After seven days, all calves overcame diarrhea. On average, one calf needed 2,4 treatments to show a full recovery from diarrhea (\triangleq 1,25 treatment days).



Effect of an egg powder based feed supplement in case of acute diarrhea

Egg immunoglobulins support against diarrhea

Egg immunoglobulins can effectively support calves in their fight against diarrhea. Immunoglobulins can act against bacteria, parasites, and viruses, not only against bacteria as antibiotics do. With egg immunoglobulin-based products, the farmer has a tool at his disposal that is easy to handle and does not require a withdrawal period. As there is no danger of the generation of resistance, these products are ideal for reducing the use of antibiotics in animal production.

Article initially published in NutriNews

IgYs support calves in case of diarrhea



By Lea Poppe, Technical Manager - Europe, EW Nutrition

Humans and animals protect themselves against diseases with specific antibodies (immunoglobulins). They receive antibodies from their mother or a vaccination (passive immunity) or produce them themselves after contact with a pathogen (active immunity). To be protected by a high passive immunity during the first weeks of life, a calf must receive high-quality colostrum with a sufficient amount of farm-specific antibodies as early as possible after

birth.



Undersupply with immunoglobulins lowers later performance

In 2015, the Ludwig Maximilian University of Munich examined the immunoglobulin supply of 1,242 newborn calves. This study showed that more than half of the calves were undersupplied: 23% severely (<5mg IgG / ml blood serum) and 36% slightly undersupplied (5-10mg IgG/ml). The supply situation was only satisfactory in 41% of the calves (> 10 mg IgG/ml).

Undersupply results in higher susceptibility to disease, higher mortality, and lower daily weight gain. This entails increased rearing costs. Besides, only healthy calves can achieve their full potential as adult animals. For example, when a calf experiences even mild diarrhea, it is expected to produce 344 kg less milk the first lactation (Welsch, 2016). Possible causes of diarrhea are infectious factors such as viruses (rota, coronaviruses), bacteria (*E. coli*) and parasites (cryptosporidia), but also non-infectious factors such as poor husbandry and feeding errors.

Survey confirms: Calves lack sufficient amounts of immunoglobulins

In December 2020, EW Nutrition conducted a telephone survey among 55 dairy cattle consultants and veterinarians from Spain, Germany, France, Poland, and Great Britain to review calves' passive immunity.

This survey confirmed that calves lack sufficient amounts of immunoglobulins: 69.1% of respondents thought that calves were undersupplied. 76.4% of them saw a clear connection between early-occurring

diarrheal diseases and calves' insufficient passive immunity. Respondents came to these conclusions even though more than half of them thought that colostrum quality had not deteriorated during the last years (56.4%).

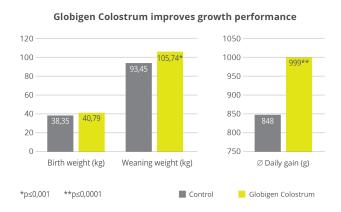
Immunoglobulins from the egg help calves against diarrhea

Egg immunoglobulins offer one way to support calves in case of diarrhea. Chickens form antibodies (IgY from "Immunoglobulins in Yolk") against all disease pathogens they encounter and release them into the egg as an immunological starting aid for the chick. It does not matter whether the disease is relevant to poultry or cattle.

These antibodies can be used to improve poor-quality colostrum or to support the calf during acute diarrhea. Studies show that egg immunoglobulins act in calves' intestines, where they can bind and block diarrhea pathogens (Ikemori et al., 1992).

IgY add value to colostrum

A feeding study with 39 female newborn calves took place on an 800-cow dairy farm in Brandenburg, Eastern Germany. The objective was to examine whether the lgY-containing complementary feed <u>Globigen Colostrum</u> effectively supports calves during the first critical period. For the experiment, all calves were given high-quality colostrum (4L within 2 hours after birth). During the first 5 days of life, the 19 calves in the test group additionally received 100g of the complimentary feed stirred into the colostrum (day 1) or the mixed colostrum (days 2 – 5).



Result: The daily weight gain for the test group was 18% higher than in the control group (+ 151g). This resulted in 13% higher weaning weights (see above).

Three calves in the control group had mild diarrhea; in the test group, only one calf. However, antibiotics did not have to be used to treat the diarrhea.

IgY to reduce neonatal diarrhea

The IgY-based product <u>Globigen Calf Paste</u> was tested on two dairy farms in Russia. These trials focused on reducing neonatal diarrhea, which occurs in the first 2 to 3 weeks of life. The product, a 30ml oral syringe with a dosing ring, was administered at a rate of 10ml per day for the first three days of life. On the first farm in the Belgorod region, the trial and control groups consisted of 11 calves each. On the 10th day of

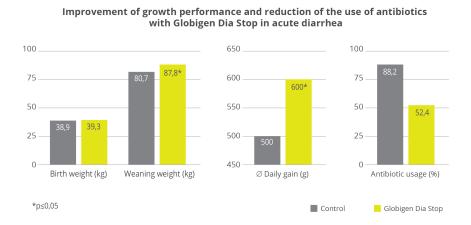
life, the diarrhea incidence per group was checked: while 73% of the calves in the control group had diarrhea, requiring antibiotics, only 1 calf of the trial group had diarrhea, and no antibiotic treatment was needed. On the second farm in the Moscow region, where the groups encompassed 20 calves each and observations took place on the 5th day of life, results were similar: 75% of the control animals suffered from diarrhea, but just 3 calves in the trial group showed signs of diarrhea.

IgY support calves with acute diarrhea

In another trial, carried out with 38 calves on a dairy farm with 550 cows in North Rhine-Westphalia, Western Germany, the dietetic feed supplement Globigen Dia Stop was tested. This product is also based on egg immunoglobulins.

Only calves showing newborn diarrhea were used for this experiment. When diarrhea occurred, the 21 calves in the test group received 50g <u>Globigen Dia Stop</u> twice a day in addition to their milk drink. The diseased calves in the control group (17 calves) were given a rehydration solution, stirred into water, twice a day.

If the diarrhea could not be stopped after four days in the calves of either group, the animals were treated by a veterinarian.



Result: In the test group, 100g (+ 20%) and thus significantly higher daily gains were achieved, which led to a 9% higher weaning weight. Furthermore, over 40% fewer calves had to be treated with antibiotics in the Globigen Dia Stop group than in the control group. (see above)

Conclusion: Egg immunoglobulins support gut health

The results of these studies indicate that the administration of egg antibodies (IgY) to calves supports intestinal health and has a positive effect on calves' performance. <u>Globigen supplementation</u> can likely reduce diarrhea incidence and severity, especially in the critical first phase of the calves' life – thus ensuring high performance in the long term.

Diarrhea in calves: Causes, consequences, prevention



by Judith Schmidt, ProductManager On Farm Solutions, EW Nutrition

Although diarrhea is called a factor disease, strictly speaking, it is not a disease but a symptom. Diarrhea can be a protective function of the body. With the higher fluid volume in the intestine and its increased peristalsis, pathogens and toxins are excreted.



Common causes of diarrhea

Despite various electrolyte drinks available from the veterinarian or in stores, too many calves still die as a consequence of diarrhea. The economic damage for the farms is immense.

The causes of the occurrence of diarrhea are diverse. Infectious causes such as viruses, parasites, bacteria, fungi, and non-infectious causes such as insufficient colostrum supply, feeding, and housing have a significant influence.

The diet of the newborn calf has a significant influence on scours. The following factors are decisive:

- The immune status of the calves
- Inadequate/incorrect preparation of the liquids
- Inadequate drinking hygiene

The development of diarrhea

In the first three weeks of life, diarrheal diseases are the most common and economically impactful diseases in newborn calves. In the first weeks of life, 75 to 85 % of calf diseases are related to diarrhea. The reason for this is that calves are born without immune protection. Their immunity is primarily built up in the first twelve hours by the supply of colostrum. After that, the intestinal barrier is barely passable for the antibodies.

The four most important pathogens are Rotavirus and Coronavirus, Cryptosporidium, and E.coli. These pathogens damage the intestinal lining, leading to water and minerals not being absorbed from the intestine into the blood. The minerals, instead of being assimilated, are lost and eliminated through feces.

Bacteria such as E.coli attach to the intestinal wall and produce toxins. Viruses, on the other hand, penetrate the intestinal wall in order to multiply. Both of them result in damages to the intestinal wall, which can allow fluids to leak out. The result is diarrhea.

Symptoms of diarrhea

The most important symptoms are:

- Sunken eyes as an expression of dehydration
- Reduced intake of fluids
- Lying down
- Low temperature
- Cold body surface
- Apathy or even coma

Types of diarrhea

There are different types of diarrhea, mainly the secretory and the malabsorptive form. Because of frequent mixed infections, the two forms of scours are often mixed.

Secretory diarrhea

The binding of toxins to the enterocytes' cell surface receptors activates enzyme systems that lead to increased fluid secretion in the intestine. The intestinal lining can no longer absorb this increased fluid influx. The trigger for this can be, for example, an E.coli infection.

Malabsorptive diarrhea

The erythrocytes are destroyed and the villi are reduced in size. There is a loss of the microvilli. The result is a lower enzyme activity and resorption capacity. By this reduction in villi length, less fluid can be absorbed and has to be excreted through the intestine.

Importance of the colostrum supply

Low colostrum intake or a low quality of colostrum at birth results in the failure of passive transfer (FPT) due to the inadequate ingestion of colostral immunoglobulins. FPT is associated with an increased risk of mortality and decreased health status.

Adequate transfer of maternal immunoglobulins is associated with short- and long-term health advantages. These advantages are created by reducing pre- and post-weaning mortality due to infectious diseases, as well as by increasing daily weight gain, feed efficiency, fertility, and milk production in first and second lactation.

Colostrum is the elixir of life for newborn calves. As already mentioned, calves are born without their own active immune protection. Their immune system develops slowly. In order to obtain a first passive immunization, early administration of high-quality colostrum (≥ 50 mg lgG/ml) is of the highest importance.

The colostrum should be administered to calves as early as possible, but latest 4 to 6 hours after birth. The reason for early administration of colostrum is that the amount of immunoglobulins decreases with the passage of time after birth and with an increased milking number.

By the twelfth week, the calf has fully developed its own stable immune system and is therefore able to produce its own antibodies.

Economic consequences of diarrhea

The consequences of diarrhea and the associated costs should not be underestimated. Even a mild form of diarrhea costs the farmer money:

	Course of diarrhea			
	Heavy diarrhea		Light diarrhea	
	In €	In %	In €	In %
Costs for Vet Costs for drugs, electrolytes	75 € 72 €	56	45 € 30 €	69
Additional rearing days Additional rearing costs	9 days 30,60 €	12	4 days 13,60 €	13
Mortality rate Costs for mortality	13 % 48 €	18	2 % 7,40 €	7
Additional labor farmer Additional costs for labour	2,5 h 37,50 €	14	0,8 h 12 €	11
Overall costs	263,10 €		108,00 €	

How to avoid diarrhea in calves

It is primarily essential that the calf is protected from fluid losses and that active diarrhea is avoided. Measures can be taken in advance to prevent the newborn calves from diarrhea:

- Cleaning the calving pen after each calving
- Bringing the calves into cleaned and disinfected boxes
- Regularly checking the quality of colostrum

But the most important basic requirement for a healthy start into life is to give 2 to 4 liters of colostrum within the first six hours of life. In addition to the timing, the quality of the colostrum is crucial. To that end, EW Nutrition developed a colostrum enhancer that improves colostrum management.

IgY can bind foreign substances like bacteria or viruses in the gut, which improves gut health and increases weight gain. The natural <u>egg immunoglobulins</u> act like maternal colostrum and bind to the pathogen epitopes. After that, the blocked pathogens cannot bind to the intestinal wall, preventing damage to the intestinal wall. Field studies prove the product's efficacy, showing an 18 % higher daily weight gain and a 13 % higher weaning weight compared to the control group. Additionally, the IgG contained in Globigen Colostrum help you avoid a failure of passive transfer (FPT).

The application of <u>Globigen Colostrum</u> is very user-friendly and simple, as it can be mixed directly into the colostrum of the mother cow.

Higher profit through improved calf performance

The benefits of Globigen Colostrum are:

- Improved calf performance
- Lower incidence of diarrhea
- Improved weight gain
- Higher profit

The timely and adequate supply of colostrum is the most important factor in preventing infection-related calf diseases. Therefore, it is necessary to ensure that calves receive sufficient antibodies from the cow's colostrum in the first days after birth.

References available upon request