



Improvement of gastrointestinal resilience in meat rabbits: a literature review

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Report 1488



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Foto voorkaft/front cover photo: zojuist gespeende konijntjes die hun nieuwe hok verkennen / recently weaned rabbits exploring their new pen.

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Samenvatting: Maagdarmkanaal (MDK)-gerelateerde gezondheidsproblemen komen veel voor bij konijnen en vormen één van de hoofdaanleidingen voor behandeling met antibiotica. De konijnensector heeft als ambitie het gebruik van antibiotica verder te reduceren en daarvoor is het voorkómen van MDK-gerelateerde problemen van groot belang. In deze literatuurstudie wordt een overzicht gegeven van het normaal functioneren van het MDK en worden verscheidene interventies voor het voorkómen van MDK-gerelateerde problemen besproken. Drie hoofdcategorieën van preventieve benaderingen worden besproken: 1) voer, 2) management en 3) dier-gerelateerde factoren. Voor wat betreft voer, kan een verhoogde weerbaarheid van het MDK mogelijk worden bereikt door rantsoenen met veel vezel, weinig ruw eiwit en met bepaalde voeradditieven te voeren, onder een voerbeperringsstrategie (qua voerhoeveelheid of tijds-toegankelijkheid). Voor wat betreft management, lijken factoren gerelateerd aan spenen, omgeving, huisvesting en reiniging, zoals bijvoorbeeld speenleeftijd, groepsgroottes, verschillende typen vloer en schoonmaakstrategieën, potentie te bieden voor het reduceren van MDK-gerelateerde problemen. Voor wat betreft dier-gerelateerde factoren, lijken er kansen te zijn voor het genetisch selecteren voor een hogere weerbaarheid tegen MDK-gerelateerde problemen. Alles tezamen genomen lijkt het erop dat er een brede range aan mogelijke benaderingen is, eventueel in onderlinge combinaties, om de weerbaarheid tegen MDK-gerelateerde problemen te verhogen en zo het antibioticagebruik in de konijnensector te reduceren.

Summary: Gastrointestinal disease is common in rabbits and is a major reason for treatment with antibiotics. The rabbit sector aims to reduce the use of antibiotics, and therefore prevention of gastrointestinal disease is of great importance. In this literature study, an overview of the normal functioning of the healthy gut of growing rabbits is provided, and different interventions for the prevention of gastrointestinal disease are discussed. Three main categories of preventative approaches are discussed: 1) feed, 2) management, and 3) animal factors. In terms of feed, an improved resistance to gastrointestinal disease may come from high fibre diets, low crude protein diets, the use of specific feed additives, and restricted feed provisioning (in time or quantity). In terms of management, weaning-, environment-, housing-, and sanitation-related factors appear to have potential for reducing the occurrence of gastrointestinal disease, including for example weaning age, group sizes, flooring types, and cleaning. In terms of animal factors, there appears to be potential for genetic selection for improved resistance to gastrointestinal disease. Overall, it appears that a range of approaches can be implemented, potentially in combination, to reduce the prevalence of gastrointestinal disease in rabbits, and the use of antibiotics in the rabbit sector.

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Foreword

Diergezondheid en antibioticagebruik zijn belangrijke maatschappelijke en bedrijfseconomische thema's in de konijnenhouderij. Het ministerie van LNV heeft Wageningen Livestock Research gevraagd in een tweejarig project het thema 'Darmgezondheid' verder uit te diepen, met als doel het optreden van darmaandoeningen te verminderen, en daarmee het antibioticagebruik verder terug te dringen. Darmaandoeningen zijn namelijk de belangrijkste aanleiding voor het inzetten van antibiotica.

Het project is ingevuld met twee invalshoeken:

- 1) Identificatie van risicofactoren en good practices die een handelingsperspectief voor de konijnenhouder of toeleverancier (voer, dier, materialen) hebben;*
- 2) Beter begrijpen van het uit balans raken van het verteringssysteem (dier en microbiom), en inzicht te krijgen hoe het systeem principieel robuuster / meer resiliënt te maken is.*

Voor dit tweede punt was uitdrukkelijk het verzoek ook te zoeken buiten de lijntjes, dus ook mogelijkheden die wat verder van de huidige praktijk staan te onderzoeken.

De belangrijkste werkvormen betroffen in eerste instantie literatuurstudie, interviews met deskundigen en gesprekken met konijnenhouders. In tweede instantie zijn hypothesen van mechanismen van ontsporing van het verteringsproces geformuleerd en experimenteel getoetst. Het huidige rapport is de verslaglegging van de literatuurstudie in relatie tot de eerste invalshoek, als weergave van de gepubliceerde kennis over darmgezondheid. Het maken van expliciete aanbevelingen voor de sector is geen onderdeel van dit rapport.

Afspraak was om nauw samen te werken met de sector en ook expertise van deskundigen van Universiteit Utrecht en Wageningen University te benutten. We zijn de betrokken konijnenhouders, dierenartsen, bedrijfsvoorlichters, nutritionisten en collega-onderzoekers erg erkentelijk voor hun loyale medewerking en advies.

Animal health and the use of antibiotics are important societal and business themes in the meat rabbit sector. The ministry of Agriculture, Nature and Food Quality has asked Wageningen Livestock Research to set up a two-year project to further investigate the theme 'gut health' in order to reduce the prevalence of gastrointestinal disease and, consequently, reduce the use of antibiotics. This is because gastrointestinal disease is common in rabbits and is a major reason for treatment with antibiotics.

The two main angles of the research project are:

- Identification of risk factors and good practices that provide a framework for action for rabbit farmers or suppliers (feed, animal, materials);
- To better understand the cause(s) of disorders of the digestive system (animal and microbiome), and to learn how we can improve the strength/resilience of the system.

For the second angle, the specific request was to think outside the box and also look at possibilities that deviate from current practice.

The most important working practices for this research project were initially literature study, interviews with professionals and conversations with rabbit farmers. In the second phase, hypotheses of mechanisms of derailment of the digestive process were formulated and tested experimentally. The current document is the report of the literature study in relation to the first research angle, and provides an overview of the published knowledge on rabbit gastrointestinal health. Providing explicit recommendations for the rabbit sector is outside the scope of this report.

The agreement was to work closely together with the sector and to make use of the expertise of professionals from the University of Utrecht and Wageningen University. We are grateful for the cooperation and advice from the rabbit farmers, veterinarians, information officers, nutritionists and colleague-researchers.

Summary

Voor een uitgebreide Nederlandstalige samenvatting, zie appendix 1 op pagina 44.

Gastrointestinal disease is common in rabbits and is a major reason for treatment with antibiotics. The rabbit sector aims to reduce the use of antibiotics, and therefore prevention of gastrointestinal disease is of great importance. In this literature study, an overview of the normal functioning of the healthy gut of growing rabbits is provided, and different interventions for the prevention of gastrointestinal disease are discussed. Three main categories of preventative approaches are discussed: 1) feed, 2) management, and 3) animal factors. In terms of feed, an improved resistance to gastrointestinal disease may come from high fibre diets, low crude protein diets, the use of specific feed additives, and restricted feed provisioning (in time or quantity). In terms of management, weaning-, environment-, housing-, and sanitation-related factors appear to have potential for reducing the occurrence of gastrointestinal disease, including for example weaning age, group sizes, flooring types, and cleaning. In terms of animal factors, there appears to be potential for genetic selection for improved resistance to gastrointestinal disease. Overall, it appears that there is a range of approaches that can be implemented, potentially in combination, to reduce the prevalence of gastrointestinal disease in rabbits, that can help reduce the use of antibiotics in the rabbit sector.

1 Introduction

Antibiotics are generally used to combat bacteria, and some antibiotics can also inhibit certain parasites. Although antibiotics are widely used to treat or prevent disease in production animals (McEwen & Fedorka-Cray, 2002), their use can have negative side effects for the animals and potentially also for human health (Chang et al., 2015). For example, bacteria may become resistant to antibiotics. As noted by Turnidge (2004), in intensive farming environments cross-infection between animals is common, infection vulnerability of the animals is high and there is often prolonged antibiotics use. This poses a risk for the emergence of resistant bacteria. Furthermore, antibiotics may not only affect the pathogen of interest, but can also cause dysbiosis, which is a perturbation of the number and composition of the microbiota and affects normal microbial balance (Connelly et al., 2017). Therefore, antibiotics use is under scrutiny and alternatives are needed. In the Netherlands, efforts are undertaken to reduce the use of antibiotics in animal production (SDa, 2022) and the use of antibiotics for preventive use is prohibited, only metaphylactic use is allowed (Rijksoverheid, 2022). One sector that currently aims to reduce antibiotics in the Netherlands is the meat rabbit sector.

To reduce the use of antibiotics in meat rabbits, it is important to first determine which diseases are the most common cause for treatment with antibiotics. In 2016, the Federation of Veterinarians of Europe (**FVE**) published a report on the use of antimicrobials (that is, any compound with a direct action on micro-organisms used for treatment or prevention of infections, including antibiotics and compounds that target parasites or yeasts for example) in food-producing animals in Europe and possible measures to reduce antimicrobial use (FVE, 2016). In this report, the provided information regarding rabbits was mostly based on expert opinion, due to limited formal data on antimicrobial use for rabbits being available. Although there are differences between countries in Europe, this report does provide indications of the main reasons for antibiotic treatments in rabbits. Young rabbits that just entered the fattening phase are noted to be especially vulnerable to intestinal diseases, which are a major cause of mortality and result in the increased need for antimicrobials in this phase (FVE, 2016). A study by Schwarz et al. (2021) on rabbit mortality on 32 rabbit farms in Switzerland indicated that intestinal diseases were the primary cause of death (68.2% of the mortalities). The main intestinal diseases were dysentery, intestinal coccidiosis and mucoid enteropathies (also known as epizootic rabbit enterocolitis (Bäuerl et al., 2014)), and the most frequent pathogens were *Eimeria* spp., *Escherichia coli* and *Clostridium perfringens* (Schwarz et al., 2021). It appears that gastrointestinal (**GI**) diseases are a key topic to focus on to reduce the use of antibiotics (or antimicrobials) in the rabbit sector (e.g., see SDa (2022)).

In this literature study, we aim to provide an overview of factors reported in literature that may contribute to improved GI health and resilience in meat rabbits, to subsequently aid in preventing the occurrence of GI disease and reducing the use of antibiotics in the meat rabbit sector. Making recommendations for the rabbit sector is outside the scope of this report. First, a short overview of the digestive system of rabbits in the healthy state is presented. Then the aetiology (where known) of several of the most prevalent intestinal diseases in rabbits will be discussed. It can be difficult to diagnose different intestinal diseases as multiple factors may be involved (Gidenne et al., 2010a), including the animal itself (e.g., age, genetics), environmental factors (e.g., nutrition, hygiene, stress) and the pathogenic agents (e.g., bacteria, viruses, parasites). Subsequently, different risk factors for GI disease are discussed, across three main categories: 1) feed, 2) management and 3) animal factors. Lastly, concluding remarks are provided.

2 The digestive system of rabbits

Rabbits have a highly complex GI tract, that makes up around 10-20% of their body weight (Meredith, 2010). Rabbits are herbivorous hindgut fermenters (Bäuerl et al., 2014) and they are adapted to digesting high fibre diets that largely consists of grass (Meredith, 2010). Rabbits have a high daily feed intake (65-80 grams per kilogram body weight; Carabaño et al., 2010) and a high metabolic rate, and so the food passes through the GI tract rapidly and, in this process, fibre is quickly eliminated from the digestive tract (Meredith, 2010; Rees Davies & Rees Davies, 2003). Rabbits perform caecotrophy, that is, eating of soft faeces. This contributes to completion of the digestion of vegetable components and facilitates assimilation of proteins and other nutrients that are synthesised by caecal bacteria (Bäuerl et al., 2014). Moreover, gut bacterial populations are maintained through caecotrophy (Bäuerl et al., 2014). Disruption of the digestive process can quickly result in GI disease (Bäuerl et al., 2014).

2.1 General gastrointestinal physiology

2.1.1 Stomach

Rabbits have a simple, glandular stomach, that serves as a reservoir for ingesta (Chen & Quesenberry, 2006). The positioning of the part of the stomach that is attached to the oesophagus (i.e., the cardia) renders rabbits unable to vomit (Chen & Quesenberry, 2006). The stomach is large, thin-walled, and virtually never empty, containing food, caecal pellets and hair that has been ingested (Meredith, 2010). It holds about 15% of the total GI contents (Chen & Quesenberry, 2006). The fundic region of the stomach, next to the cardia, serves as a storage for caecotrophs, after caecotrophy occurred (Carabaño et al., 2010). The pH of the stomach is very low (pH 1-2) in adult rabbits during ingestion of food, resulting in most microbial organisms being killed, and a nearly sterile stomach and small intestine (Meredith, 2010; Rees Davies & Rees Davies, 2003). In the stomach, the hydrolysis of protein starts, except for the mucus cover of the caecotrophs (Rees Davies & Rees Davies, 2003; see also section **2.1.3 Large intestine**). Ingesta remain in the stomach for approximately three to six hours, before being gradually pushed into the small intestine through strong stomach contractions in short burst (Lebas et al., 1997).

2.1.2 Small intestine

The stomach is followed by a small intestine of around 3 m in length (Carabaño et al., 2010). The stomach contents entering the small intestine are diluted by bile, the first intestinal secretions and pancreatic juice (Lebas et al., 1997). The liver secretes bile into the small intestine, containing bile salts and multiple organic substances that aid in digestion (Lebas et al., 1997). Rabbits have a small pancreas, that produces trypsin, chymotrypsin and carboxypeptidases, which are released into the intestinal lumen (Rees Davies & Rees Davies, 2003). Moreover, the pancreas forms an important source of bicarbonate ions, which contribute to the neutralization of the acidic chyme from the stomach (Rees Davies & Rees Davies, 2003). In the duodenum and jejunum, most of the digestion of carbohydrates and simple proteins takes place. The trypsin, chymotrypsin and carboxypeptidases, together with intestinal aminopeptidases, aid in the completion of protein digestion. The monosaccharides and amino acids that result from the digestion, as well as volatile fatty acids (**VFAs**), vitamins, and digested microbial organisms, are absorbed through the jejunal brush border (Rees Davies & Rees Davies, 2003). At the distal end of the ileum, the sacculus rotundus forms the ileo-caecal junction, and has an immunological function (Rees Davies & Rees Davies, 2003; Arrazuria et al., 2018). After about one and a half hour in the small intestine, any particles that are not broken down move into the caecum and colon (Lebas et al., 1997; Cheeke, 1994).

2.1.3 Large intestine

Rabbits have a large caecum that holds about 40% of the total GI contents (Chen & Quesenberry, 2006). The particles that were not broken down in the small intestine and were passed to the caecum remain there for 2 to 12 hours, during which time bacterial enzymes work on the particles (Lebas et al., 1997). The caecum serves as an anaerobic fermentation chamber, where the ingesta, as well as mucopolysaccharides secreted from the mucosa, form an important carbohydrate source for caecal fermentation (Rees Davies & Rees Davies, 2003). The caecum's microbial flora contributes to the breakdown of ammonia, urea, proteins, enzymes from the small intestine, and cellulose (Rees Davies & Rees Davies, 2003). The resulting products from this process are the protein and enzyme structures of the microbiota itself (obtained later through the process of caecotrophy), as well as by-products in the form of VFAs that are absorbed through the caecal and colonic walls (Rees Davies & Rees Davies, 2003). The remaining contents of the caecum, consisting of not yet broken down food particles and bacteria that developed in the caecum, are then moved to the colon (Lebas et al., 1997). The colon of rabbits consists of different parts. There is a short proximal colon, followed by a muscular thickening, the fusus coli, and then the distal colon (Rees Davies & Rees Davies, 2003). The fusus coli has a role as a pacemaker for peristaltic wave initiation and in the separation of indigestible fibre from digestible components (Rees Davies & Rees Davies, 2003; Ruckebusch & Fioramonti, 1976). Through colonic and caecal motility, food components are sorted into digestible and indigestible (Meredith, 2010; Rees Davies & Rees Davies, 2003). Indigestible fibre is required for stimulating the normal gut motility, but has no nutritional value, and is therefore quickly eliminated in the form of hard faecal pellets (Meredith, 2010). The digestible components are moved backwards from colon to caecum and are fermented there

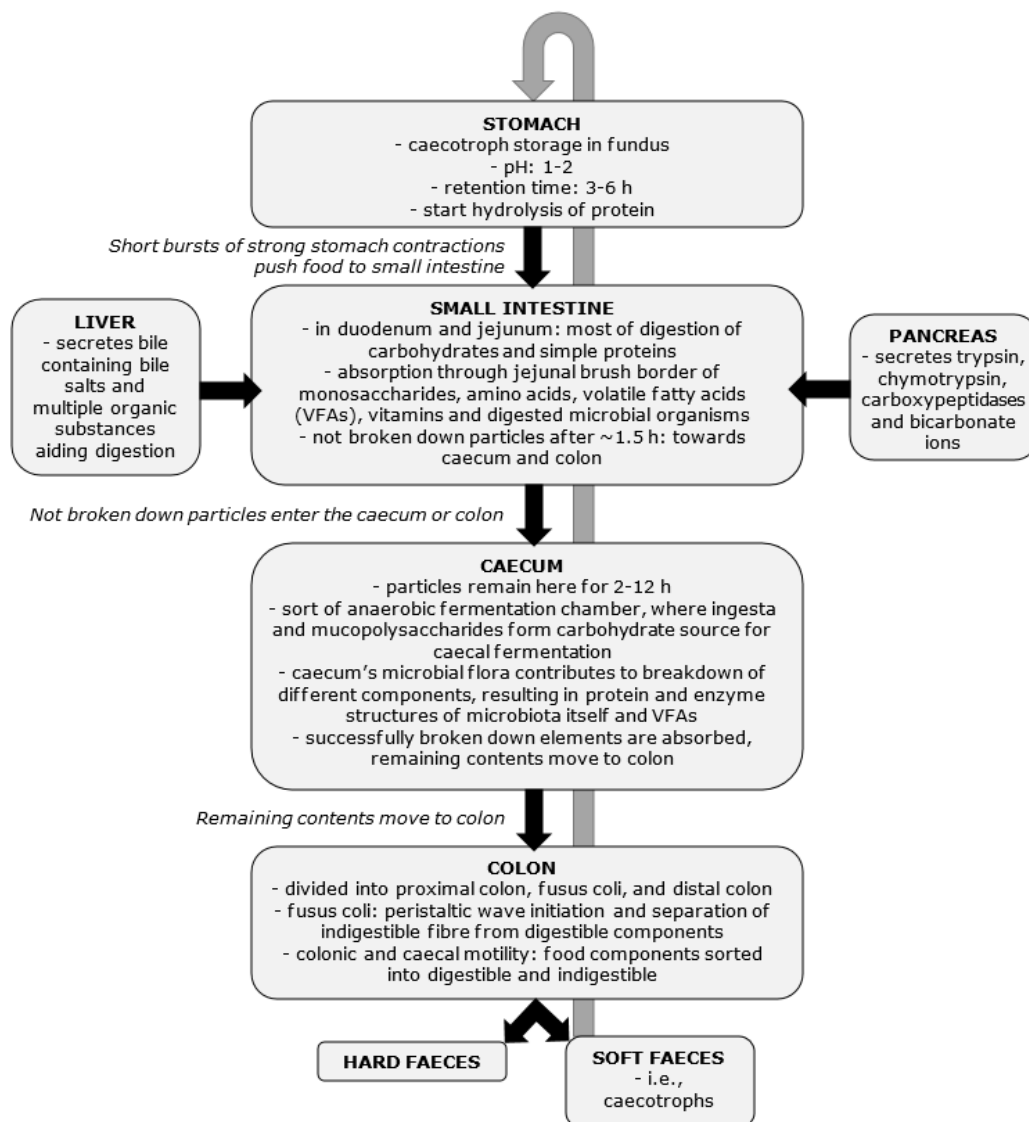


Figure 2.1 Schematic overview of the digestive process in rabbits. References provided in the main text.

(Meredith, 2010). Depending on the timing of entering the proximal colon, few biochemical changes to the caecal contents take place and the colon wall secretes mucus, that starts to capsule the contents, forming soft pellets (Lebas et al., 1997). Soft caecal pellets are expelled from the anus at approximately three to eight hours after eating, and these are eaten directly from the anus (i.e., caecotrophy). These soft pellets then go through the same digestive process as normal feed does (Lebas et al., 1997). Some parts of the feed (or soft pellets) may go through this process multiple times, so the total digestive process lasts around 18 to 30 hours (Lebas et al., 1997). The process of caecotroph excretion follows a circadian rhythm and is paired with a reduced feed intake and an absence of hard faeces excretion (Carabaño et al., 2010). Caecotrophy mainly takes place during the light period, while feed intake and hard faeces excretion mainly take place during the night (Carabaño et al., 2010). When feed access is not *ad libitum*, the rhythm of excretion changes depending on the time of feed distribution (Carabaño et al., 2010).

A schematic overview of the digestive process in rabbits is shown in **Figure 2.1**.

2.1.4 Sensitivity of the digestive tract

The complexity of the rabbit GI tract means that disturbances of the precarious balance can have severe consequences (Meredith, 2010). For example, GI stasis is a serious problem in rabbits, and is a consequence of reduced, or absent, motility and peristaltic movement (Meredith, 2010). Multiple factors affect GI motility, including diet, the autonomic nervous system, and prostaglandins and other hormones (Meredith, 2010). This means that, among other things, indigestible fibre can have an effect on gut movement (Meredith, 2010). The autonomic nervous system and adrenal glands are thought to be involved in the regulation of the fusus coli, and this might be the reason why rabbits are prone to stress-related GI disease (Rees Davies & Rees Davies, 2003): hypersecretion of adrenalin, associated with stress, results in a slowing down of the digestive activity and hereby poses a risk for digestive trouble (Lebas et al., 1997). Other risk factors for reduced GI motility include anorexia, chronic dehydration, environmental stressors (such as a changed diet or housing), pain and ingestion of toxins (Meredith, 2010).

2.2 Feed intake patterns

Gidenne et al. (2010b) described the feeding behaviour of domesticated rabbits in detail. Kits spend very little time suckling and they generally have only a single milk meal per day. In the first week postnatal, they drink around 15% of their live weight in milk per day. In this first week, they may also ingest some hard faeces from the doe. Then, the milk intake increases and peaks between 17 and 25 days of age. After 20 to 25 days, the milk production of the doe decreases and, in commercial systems, rabbits are then commonly weaned between 28 and 35 days of age. From around 16 to 18 days of age, the kits start to eat substantial quantities of solid feed and in the fourth week of life the ingestion of solid feed is larger than the milk consumption (in terms of grams of fresh matter per day). After weaning, the daily feed intake increases with metabolic live weight and then stabilizes at around five months of age. The timing of the start of caecotrophy is not fully known, but the intake of soft faeces increases until two months of age, before stabilizing. Rabbits split their solid feed intake into around 40 meals per day at six weeks of age, and slightly fewer when they are older. When a pelleted diet is supplied, rabbits of six weeks of age spent a bit more than three hours per day on feeding, and for older rabbits this decreases to less than two hours. The intake of solid feed fluctuates across the day. Of the total solid feed intake, more than 60% is consumed during the dark period, when a 12-h light, 12-h dark schedule is implemented. A peak in intake is observed around an hour before the start of the dark period. In domesticated rabbits, there are no prolonged periods of no feed intake anymore, with over 20 meals of dry feed in a day and the consumption of caecotrophs. In situations in which only a limited amount of feed is provided, rabbits tend to consume their daily allocation within a few hours. Moreover, if there is restricted access to the feeder in time (but not a restricted amount of feed), with access of less than 14 to 16 hours per day, the feed intake is reduced (Lebas (2007) in Gidenne et al. (2010b)). The restricted access does not reduce the total number of meals per day, but the meals are closer together in time, yet not significantly longer in duration, due to the restricted time available for eating.

3 Common gastrointestinal diseases in rabbits

Gastrointestinal disease is common in rabbits and, as mentioned earlier, is the primary cause of death on rabbit farms (Schwarz et al., 2021). Two of the most common GI diseases in rabbits are coccidiosis and epizootic rabbit enteropathy, and these are discussed in more detail below.

3.1 Coccidiosis

Coccidiosis is a disease caused by protozoan parasites (Balicka-Ramisz et al., 2020; Harcourt-Brown, 2002). Rabbits with an acute infection show inappetence, weight loss, depression and (sometimes haemorrhagic) diarrhoea, whereas rabbits with subclinical coccidiosis may show a reduced feed conversion (Harcourt-Brown, 2002). Protozoan parasites are common in rabbits and around 87 protozoan parasite species from six genera (*Cryptosporidium*, *Eimeria*, *Isospora*, *Besnoitia*, *Sarcocystis* and *Toxoplasma*) are known to infect rabbits (Duszynski & Couch, 2013). In rabbit breeding, *Eimeria* are most common and they develop in the epithelial cells of the digestive system (Licois, 2004). Coccidiosis mostly occurs in the intestine, although there is one *Eimeria* species that affects bile ducts and causes so-called hepatic coccidiosis (Harcourt-Brown, 2002). Here we will only focus on intestinal coccidiosis. For rabbits, there are multiple pathogenic *Eimeria* species that alone or in mixed infections can cause intestinal coccidiosis. There is no cross-immunity, meaning that rabbits with immunity to one species of *Eimeria* will not per definition be immune to another *Eimeria* species (Harcourt-Brown, 2002; Licois, 2004). It appears that almost all rabbits, regardless of which species and wild or domestic, are infected with coccidia, usually with multiple coccidian species (Duszynski & Couch, 2013). It is likely that all rabbits at some point in their life become infected (Duszynski & Couch, 2013). Mainly young animals become ill, whereas adults are often carriers of the disease and may spread oocysts (Duszynski & Couch, 2013). These oocysts show a high resistance in the environment, to time and chemical agents (Licois, 2004). The disease can spread via such contaminated environments and especially intensive, damp and dirty environments put rabbits at risk of coccidiosis (Harcourt-Brown, 2002). Rabbits can become infected through ingestion of sporulated oocysts in their water or feed (Duszynski & Couch, 2013). Currently, there is no vaccine for coccidiosis commercially available (Hamid et al., 2021). At present, coccidiosis can be controlled through adequate hygienic management and the use of anticoccidial drugs (Pakandl, 2009).

3.2 Epizootic rabbit enteropathy (ERE)

Epizootic rabbit enteropathy (**ERE**) is also known as enterocolitis (Van den Hof & Maertens, 2014), mucoid enteropathy (Bäuerl et al., 2014) or mucoid enteritis (Puón-Peláez et al., 2018). ERE is an acute and contagious digestive pathology, that is marked by a range of symptoms that are not specific for ERE (Licois et al., 2005; Puón-Peláez et al., 2018). The symptoms may include a rambling noise when animals are grasped and slightly shaken, abdominal bloating, caecal impaction, diarrhoea, presence of mucus under cages, increased mortality, anorectic behaviour (and possible consequent dehydration and weight loss), and gnashing of teeth (Licois et al., 2005; Van den Hof & Maertens, 2014; Puón-Peláez et al., 2018). ERE often presents in combination with other infections (Van den Hof & Maertens, 2014), and samples from the field (i.e., practice) are often contaminated by opportunistic pathogens, such as coccidia and *E. coli* (Licois et al., 2005). Consequently, the diagnosis of ERE is difficult to make. ERE is mostly seen in rabbits between six and eight weeks old (Licois et al., 2005; Van den Hof & Maertens, 2014). The cause of ERE is not completely known yet (Van den Hof & Maertens, 2014). However, it is now generally assumed that some form of microbial origin is involved (Puón-Peláez et al., 2018). Different studies have suggested different pathogenic agents, either in terms of general presence or in terms of an imbalance in their numbers when they are naturally present, including *Clostridium* spp., *Bacteroides* spp., *Blautia* spp., *Dorea* spp., *Bacillus* spp.,

Fusobacterium spp., *Eimeria* spp., *Escherichia coli* and more (reviewed in Puón-Peláez et al. (2018); Djukovic et al., 2018). Marlier et al. (2006) aimed to reproduce ERE through inoculating specific-pathogen-free (**SPF**) rabbits with 1) different pools of cultivable bacterial strains or 2) caecal content samples from diseased rabbits. The isolated pathogens did not reproduce the disease, whereas the caecal content samples did reproduce the disease. The exact aetiological agent of ERE remains yet unknown, although a bacterial infectious origin is suspected (Djukovic et al., 2018). Although the incidence of mortality from ERE can be reduced through, for example, an altered diet or improvement of hygienic measures (see section **4. Preventing gastrointestinal disease**), ERE still presents in most farms and is generally controlled through the use of antibiotics (Van den Hof & Maertens, 2014; Licois et al., 2006).

4 Preventing gastrointestinal disease

A major way to reduce the use of antibiotics in the rabbit sector would be to prevent GI diseases from occurring. Harcourt-Brown (2002; figure 10.1 therein) provides a very useful overview of the GI disease pathway, about which a lot is known. However, we are really focused on the prevention side of GI disease, and thus aim to provide more insight into the risk factors for the development of GI disease (the left-hand side of figure 10.1 in Harcourt-Brown, 2002). In this section, we discuss different ways in which the occurrence of (symptoms of) GI disease can be prevented. Maintaining gut health is complex, as it relies on a fine balance between the mucosa, the gut microbiota and environmental factors such as diets (Abecia et al., 2017). Moreover, recording gut health, or health in general, is challenging, as there is no true measurement of health, apart from absence of disease as an indicator. Therefore, our main focus here lies on examining the effects of different approaches for avoiding disease symptoms. It is important to keep in mind that it is not known whether animals that do not show symptoms are completely healthy and how 'far away' they are from getting ill or showing symptoms (i.e., animals might have an underlying health issue that has not (yet) resulted in the animal showing symptoms). We can only observe indicators for 'somewhat ill' or 'severely ill' animals, but not for 'fully healthy' animals.

Three main possible approaches for preventing GI disease are 1) feed, 2) management and 3) animal factors, and these are discussed in more detail below. An overview of the risk factors discussed in this review, and their overall relationships with the occurrence of gastrointestinal disease, is shown in **Figure 4.1**. Generally, a combination of reduced individual resilience and increased pathogen pressure (indicated with × in **Figure 4.1**) is expected to result in an increased risk of gastrointestinal disease.

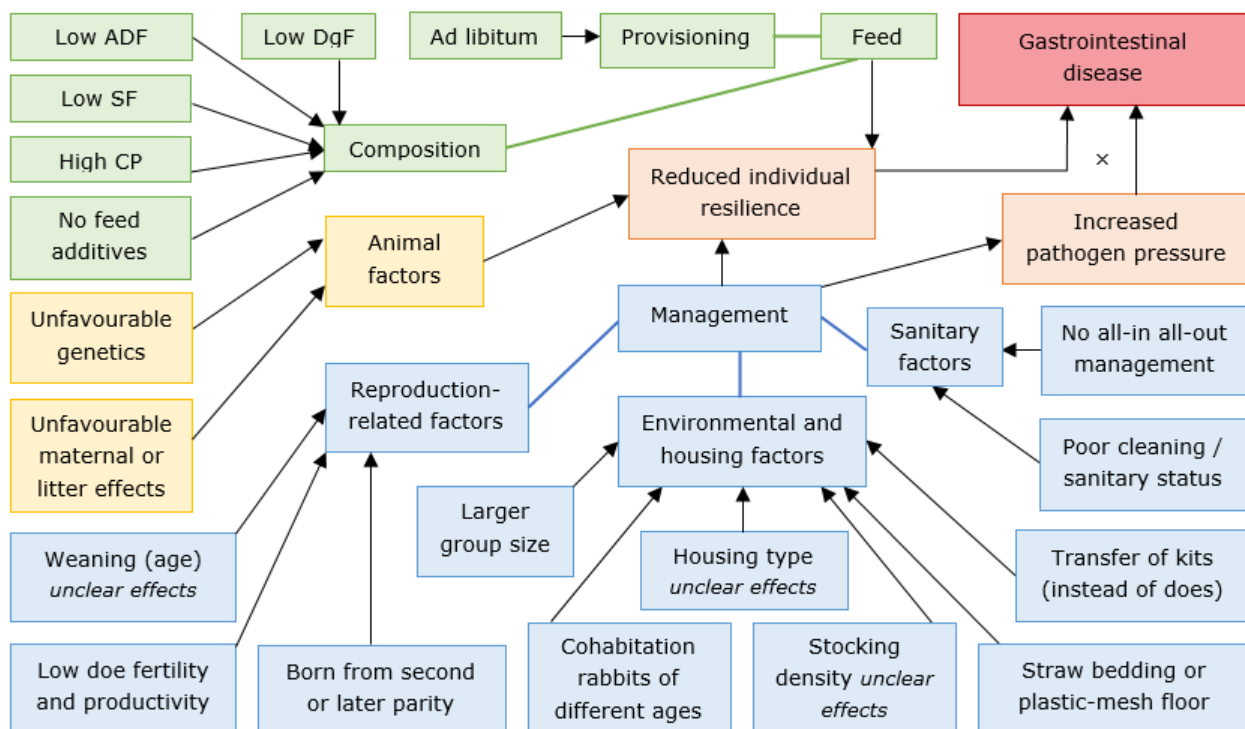


Figure 4.1 Overview of the risk factors discussed in this review and their overall relationships with the occurrence of gastrointestinal disease. Green boxes are linked to feed-related factors, yellow boxes are linked to animal-related factors and blue boxes are linked to management-related factors. References provided in the main text.

4.1 Feed

Meat rabbits are often fed *ad libitum* (although in the Netherlands feed restriction is often applied, see section **4.1.2 Feed provisioning**) with at least two different diets over time, one for the post-weaning period (from approx. 30-35 to 45-50 days of age) and one for the fattening period (from approx. 45-50 days of age onwards) (Tazzoli, 2012). As mentioned earlier, in the post-weaning period rabbits appear to be most susceptible to digestive disease. Potentially, this is linked to the immaturity of the gastrointestinal tract around, and soon after, weaning (e.g., the colonization and development of a new caecal microbial flora, the start of the caecotrophy mechanism and potential damage to the intestinal mucosa caused by the change from a liquid to a solid diet), as suggested by Tazzoli (2012). Feeding strategies can strongly affect GI health in rabbits. The feeding strategy can aid in competitive exclusion among bacteria (i.e., non-pathogenic species predominate over pathogenic species) and promote the development of intestinal barrier mechanisms (Tazzoli, 2012), and hereby improve GI resilience. Both the feed composition and the feed provisioning may play a role and are discussed in more detail below.

4.1.1 Feed composition

The composition of the feed can affect GI health. The caecal microflora's fermentative activity plays a large role in rabbits' health and it is generally thought that an active symbiotic microflora can aid in the prevention of development of a pathogenic microflora (Jehl & Gidenne, 1996). Changes in diet composition can alter the nature of the digesta that enter the caecum for digestion, which might in turn affect the microflora and microflora activity (Jehl & Gidenne, 1996). The diet, or an imbalance in nutrients in the diet, should not be viewed as a primary cause of digestive health problems (Gidenne et al., 2010a; Martínez-Vallespín et al., 2011), but (imbalances in) the diet can result in an increased susceptibility to digestive disease (Gidenne et al., 2010a), as it has been mentioned that alterations in gut microbiota might be a primary cause of digestive pathologies (Chamorro et al., 2007). A nutritionally balanced diet can aid in the prevention of digestive disorders through two main mechanisms (Chamorro et al., 2007). First, balanced diets can promote a lower retention time of digesta in the digestive tract. Long retention times should be avoided, as these may contribute to a destabilization of the caecal microbial activity and may hereby favour digestive troubles (Gidenne et al., 2010a). In terms of the mechanism behind this observation, Gidenne et al. (2010a)

Box 1. Dietary fibre components

Although an exact definition of dietary fibre is still under debate, in animal nutrition dietary fibres may include cell wall polysaccharides such as cellulose, hemicelluloses and pectic substances, as well as other components that are only fermented by the microbiota, such as oligosaccharides and resistant starch (Gidenne, 2015). A distinction can be made between different dietary fibre components. Total dietary fibre (**TDF**) is a major component of commercial rabbit diets, constituting around 35-50% of the as-fed diet (Trocino et al., 2013). A large part of the TDF, around 65-90%, consists of insoluble dietary fibre (**IDF**), which is seen as the most important fibre fraction (Gidenne, 2015; Trocino et al., 2013). Soluble dietary fibre (**SDF**) is the TDF minus the IDF, and is a minor fraction of the TDF, around 10-35% (Trocino et al., 2013). A further subdivision can be made within the IDF. Neutral detergent fibre (**NDF**) is estimated to make up 27-42% of the dry matter of a complete growing rabbit feed (Gidenne, 2003) and acid detergent fibre (**ADF**) is estimated to make up 16-21% of the dry matter of a complete growing rabbit feed (Gidenne, 2003). There are large differences in the digestibility of the different dietary fibre fractions (see **Table B1**, from Gidenne (2015)), and digestible fibre (**DgF**) is defined as the sum of hemicelluloses (that is, NDF - ADF) and (water-insoluble) pectin (Gidenne, 2003).

Table B1 Whole tract digestibility coefficients for different fibre fractions (from Gidenne (2015)).

Dietary fibre fraction	Whole-tract digestibility coefficients
Neutral detergent fibre	10-60%
Cellulose	5-25%
Hemicelluloses	20-60%
Water-insoluble pectins	30-80%
Uronic acids	30-85%
Soluble fibre	70-90%
Lignin	x-15%

x = unclear in original publication.

speculate that the low caecal turnover of digesta may result in an insufficient supply of substrates for the fibrolytic flora. Second, balanced diets can cause a lower flow of easily available substrates into the fermentative area. Different dietary components have been observed to be related to digestive health problems, and are discussed below. It is important to keep in mind that the effects of different feed component levels in a diet may be difficult to disentangle, as a change in the level of one component per definition results in changing relative levels of other feed components.

4.1.1.1 Fibre

An important feed component for rabbits is dietary fibre (see **Box 1**) and a correct dietary fibre balance constitutes a possible way of avoiding pre-emptive antibiotics use (Gidenne, 2015). Fibre has an important role in the normal functioning of the rabbit digestive system, and the presence of indigestible fibre is seen as the main driving force for the rabbit gastrointestinal system (Rees Davies & Rees Davies, 2003). **Figure 4.2** shows the expected positive effects of sufficient fibre in the diet and the negative effects of a fibre deficiency in the diet. First of all, fibre is needed to regulate intestinal motility in rabbits (Acedo-Rico et al., 2010) and reduced digestible fibre levels can result in increased retention times of digesta (Gidenne et al., 2004a; Perez et al., 2000; Gidenne et al., 2010a). Increased retention times, and the associated low caecal turnover of digesta, are hypothesized to potentially result in an insufficient supply of substrates for the fibrolytic flora, hereby destabilizing the caecal microbial activity (Gidenne et al., 2010a). Furthermore, lower levels of digestible fibre have been linked to a reduced caecal microbial activity, based on observations of lower caecal VFA concentrations (Jehl & Gidenne, 1996; Gidenne et al., 2004b), and rabbits fed a high fibre diet showed a

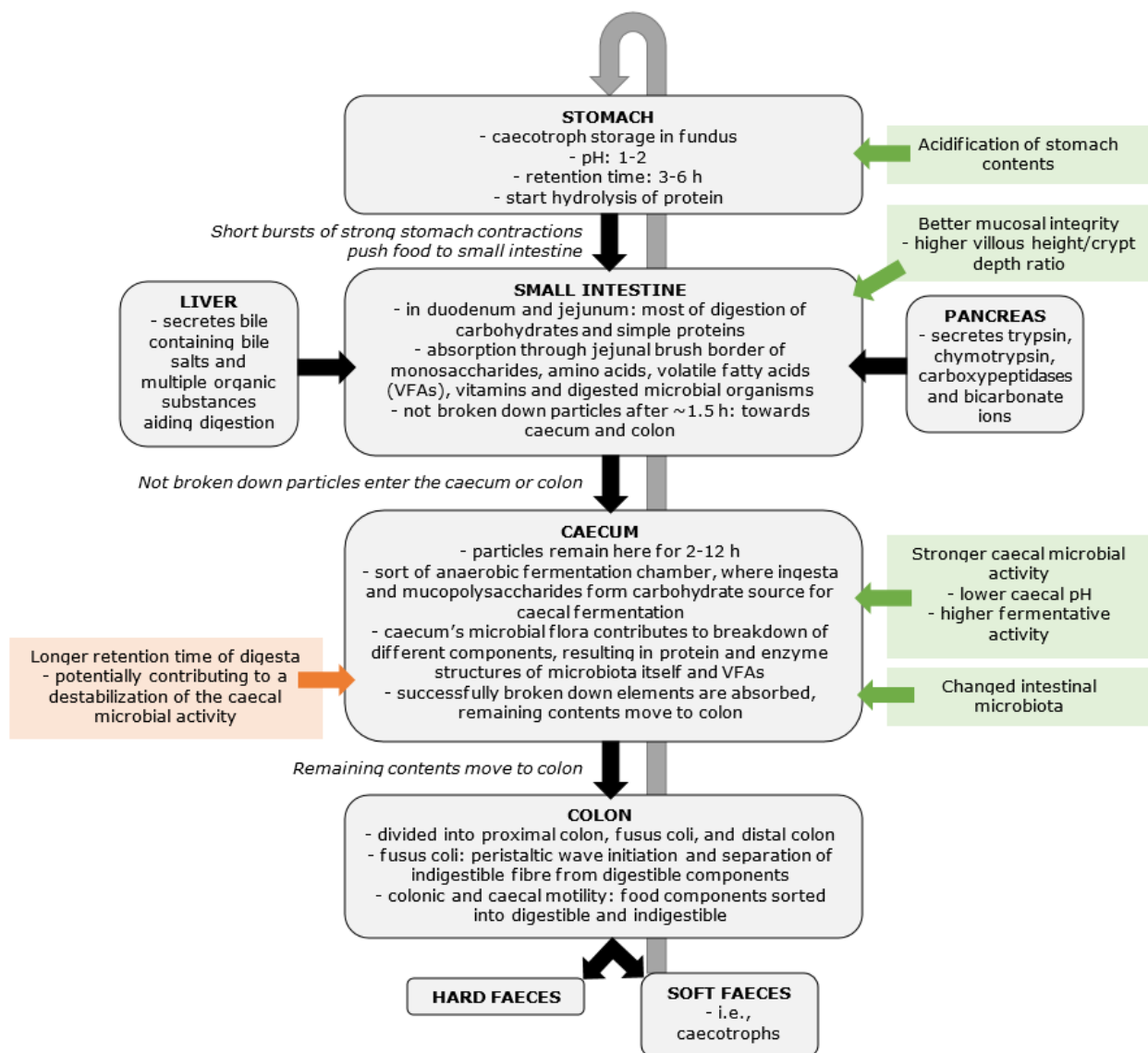


Figure 4.2 Expected effects of fibre on digestive functioning. Orange boxes indicate effects of too little fibre, green boxes indicate effects of more fibre. See main text for references.

higher fermentative activity and a lower caecal pH, suggesting a stronger caecal microbial activity (Gidenne & Licois, 2005). Moreover, higher neutral detergent soluble fibre (**NDSF**) levels have been linked to a higher villous height/crypt depth ratio in the jejunum (indicative of mucosal integrity), sucrase specific activity and starch digestibility (Gómez-Conde et al., 2007). Furthermore, a tendency has been observed for a lower ileal frequency of *C. perfringens*, *Butirivibrio fibrosolvens* and *Campylobacter* spp. and for a lower *C. perfringens* and *Campylobacter* spp. caecal frequency for higher NDSF levels (Gómez-Conde et al., 2007). Lastly, it has been suggested that the positive effect of fibre may come from the protective effect of the associated acidification of the stomach contents and from the changed intestinal microbiota (Gómez-Conde et al., 2009).

The link between (different types of) fibre levels and gastrointestinal health has been examined in multiple studies. In these studies, the fibre/starch ratios are commonly changed. Therefore, it can be difficult to separate the effects of increased fibre versus reduced starch. Moreover, altered diets can result in increased or decreased feed consumption, which may also affect gastrointestinal health (see section **4.1.2 Feed provisioning**).

Digestible fibre (DgF)

Gidenne (2015) reviewed the effects of dietary fibres in rabbits and noted that, based on results from several studies, the post-weaning mortality rate (from digestive disorders measured from weaning to slaughter, on at least 40 rabbits/diet) reduced with increasing digestible fibre in diets. Similar to Gidenne (2015), **Figure 4.3** shows a visualisation of the relationship between DgF and mortality, based on results from several studies. As mentioned earlier, changing the level of one feed component per definition results in a change in the level of other components. In the case of DgF, often the ratio with starch is altered. For example, Perez et al. (2000) examined four diets with different levels of DgF (24.9%, 21.7%, 18.7% and 14.9% (Gidenne & Perez, 2000)), where DgF was replaced by starch. For each diet, over 500 rabbits were included. They observed that, across the whole fattening period, the weight gain was the same for all diets, but the feed consumption was lower when the starch content was higher (16-24% instead of 12%) and the DgF was lower (14.9-21.7% instead of 24.9%). Moreover, the mortality rate by digestive disorders increased with reduced DgF levels, and thus increased starch levels (see also **Figure 4.3**). Gidenne (2015) also noted the difficulty with separating the effects of DgF and starch in diets and posed the question whether digestive health problems are linked to a fibre deficiency or a carbohydrate overload in the caecum, or perhaps a combination of both. It was concluded that mainly fibre intake plays a role, and not so much starch (Gidenne, 2015), based on the results of several other studies. For example, Gidenne et al. (2005) examined

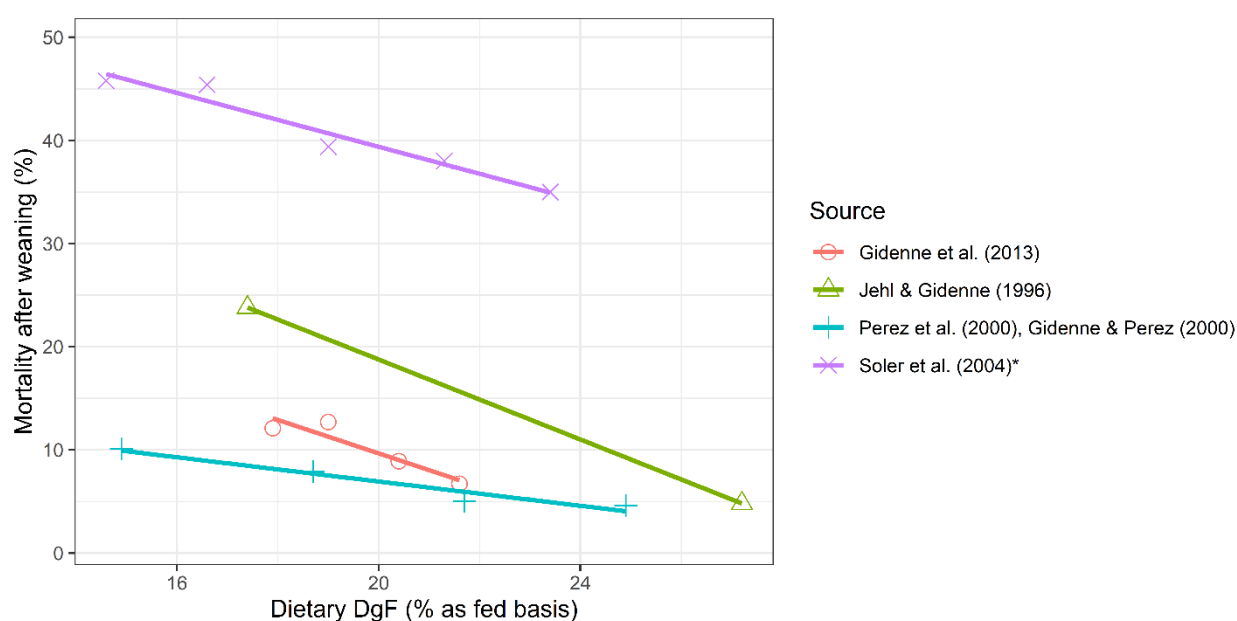


Figure 4.3 Visualisation of the relationship between dietary digestible fibre (DgF) and mortality rates after weaning in rabbits. Based on Gidenne (2015), with adaptations, using results from Gidenne et al. (2013), Soler et al. (2004), Gidenne & Perez (2000), Perez et al. (2000), Jehl & Gidenne (1996). *Average taken of two comparable diets in terms of DgF/starch ratio, but with different animal fat levels.

four *ad libitum* fed diets with different sources, but not levels, of starch that differed in intestinal digestion rates. They observed no statistically significant differences in mortality rates by digestive disorders across the four starch sources and no relationship between mortality and ileal starch concentration. Overall, increased DgF in rabbit diets appears to contribute to a reduced incidence or severity of digestive disease.

Acid detergent fibre (ADF)

Several studies specifically assessed the impact of lower or higher ADF levels on GI health. Gidenne & Licois (2005) studied, among other things, the effects of an *ad libitum* low or high fibre diet on the response to an enteropathogenic *E. coli* challenge. The low fibre diet was proportionally reduced in terms of the different fibre fractions (that is, the proportions of the different types of cell wall polysaccharides remained similar), with 120 g/kg ADF in the low fibre diet and 200 g/kg ADF in the high fibre diet. At the same time, the level of starch was increased from 100 g/kg to 300 g/kg, resulting in a four-fold reduced ADF/starch ratio. The digestible protein/digestible energy was controlled to have a similar digestible protein supply in the diets (Gidenne & Licois, 2005). They provided multiple litters with one of the two diets, from 21 days old onwards. The rabbits were subsequently weaned at 28 days old and part of the groups were inoculated with *E. coli* O103. In the non-inoculated control groups, mortality from acute diarrhoea was low and not different between the two diets. However, across the period from 28 to 70 d, there was a trend for a higher morbidity level for the low fibre diet group. In the *E. coli* inoculated rabbits, there was a numerical (but not statistically significant) difference in mortality from diarrhoea, with a higher mortality in the rabbits fed the low fibre diet. For morbidity, a similar trend was observed. In the period from 7 to 14 days after inoculation, the mean frequency of rabbits with a high *E. coli* flora, over 10^5 colony-forming units per g, was higher in the low fibre group (65.0%) than in the high fibre group (26.7%). This suggests that rabbits fed a low fibre diet experience a greater negative impact of *E. coli* inoculation on their digestive health (Gidenne & Licois, 2005). It is important to remember that there was also variation in the fibre/starch ratio, but the effect of starch on caecal microbial activity and flora was thought to be negligible in comparison with the effect of fibre (Gidenne & Licois, 2005). This positive effect of higher ADF levels was also observed in other studies. For example, Bennegadi et al. (2001) studied the impact of a fibre deficient diet, as well as sanitary status (see section 4.2.3.2 Sanitary status), on non-specific enteropathy from weaning (28 d) to slaughter (70 d). They worked with *ad libitum* fed diets, of which one was a standard diet with an ADF fraction of 19% and the other one was a fibre deficient diet with an ADF fraction of 9%, i.e., the acid detergent fibre level was around 50% lower in the deficient diet than in the standard diet. Both these diets had wheat and dehydrated alfalfa as the main starch and fibre sources, and the origin and proportions of the fibre fraction and the ratio of digestible protein over digestible energy were similar (Bennegadi et al., 2001). They observed that there was no effect

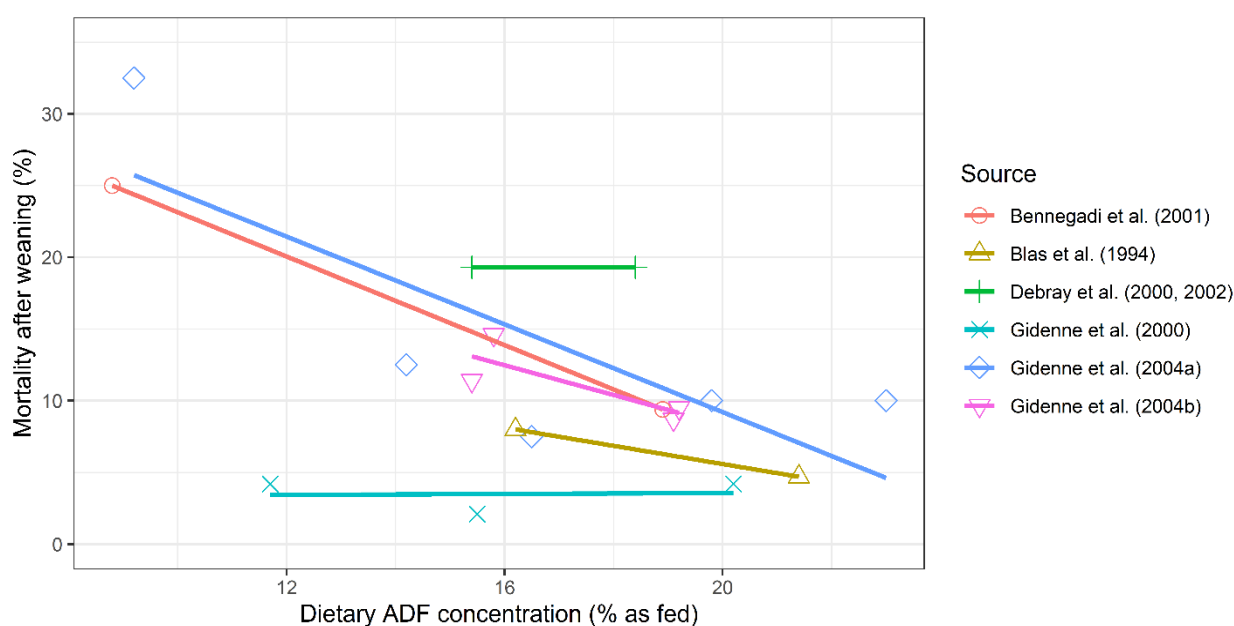


Figure 4.4 Visualisation of the relationship between dietary acid detergent fibre (ADF) and mortality rates after weaning in rabbits. Based on Gidenne (2015), with adaptations, using results from Bennegadi et al. (2001); Blas et al. (1994); Debray et al. (2000; 2002); Gidenne et al. (2000, 2004a, 2004b).

of diet on morbidity. However, the mortality and health risk index (the sum of morbid and dead animals, with each animal deducted only once and categorised either as dead or morbid) was higher for the rabbits on the fibre deficient diet (Bennegadi et al., 2001). Gidenne (2015) reviewed the relationship between dietary ADF concentration and mortality after weaning, based on the results of a range of studies, and noted that within typical dietary ADF ranges (15-22%) there was large variation in mortality rate, but within studies increased ADF tended to reduce mortality (see **Figure 4.4**; adapted from Gidenne (2015)). Overall, increased ADF in rabbit diets appears to contribute to a reduced incidence or severity of digestive disease.

Soluble fibre (SF)

Gidenne (2015) also reviewed the relationship between dietary SF and mortality after weaning. No clear relationship between post-weaning mortality and SF level was observed (Gidenne, 2015). In line with this, Farias-Kovac et al. (2020) examined whether earlier-reported positive effects of soluble fibre were influenced by the level of insoluble fibre. They used four diets, with two levels of insoluble fibre and soluble fibre, and observed no effect on mortality, although it must be noted that mortality was generally low (<1%). Other studies do show positive effects, of increased neutral detergent soluble fibre. Gómez-Conde et al. (2007) studied the effect of the NDSF level on gut barrier function in weaned rabbits. They worked with three *ad libitum*-fed diets, with either 79, 103 or 131 g NDSF per kg as-fed. They examined, among other things, the mortality from weaning until 63 days of age. The animals were fed one of the experimental diets for the first two weeks after weaning (at 25 d), followed by a commercial feed. They observed that the mortality decreased with increased NDSF, and that most of the dead rabbits showed signs of ERE being the underlying cause of death. Using the same diets, Gómez-Conde et al. (2009) observed mortality rates across the whole fattening period of 14.4%, 8.5% and 5.3% for the diets with 79, 103 and 131 g NDSF per kg dry matter, respectively. Delgado et al. (2018) studied the effects of dietary supplementation with SF (low: 7.8% and high: 13%) and the reduction of the n-6/n-3 fatty acid ratio (high: 13.4/1 and low: 3.5/1), both separately and in combination, on mortality, among other things. They examined weaned rabbits from a farm that was affected by ERE and observed that the increased SF resulted in a reduced mortality from weaning until 39 days of age, but not from 39 to 62 days of age. Across the full experimental period (27-62 d), the mortality was lower for the high SF diet (24.1%) compared to for the low SF diet (38.3%). There was no effect of the n-6/n-3 fatty acid ratio on mortality. It was concluded that SF has a role in reducing and delaying the mortality rate of rabbits affected by ERE, although the authors did note that the feed intake was lower for the rabbits on the high SF diet which may have contributed to the health improvement (Delgado et al., 2018). Overall, it appears that high fibre diets potentially contribute to a reduced incidence or severity of digestive health problems.

Fibre particle size

Not only the fibre level, but also the fibre particle size can affect gastrointestinal functioning and health. As mentioned earlier, in the colon mechanical separation of the digesta takes place (Carabaño et al., 2010). Water-soluble substances and fine particles of less than 0.3 mm are moved back towards the caecum, and coarse particles of more than 0.3 mm move to the distal colon (Carabaño et al., 2010). Studies have indicated that fibre particle size has an effect on mean retention times in rabbits. For example, Gidenne et al. (1991) examined faecal digestibility and retention times in adult rabbits fed diets with different levels of plant cell walls (lucerne meal; 48.5% and 76.5%) and different degrees of grinding (1 mm and 3 mm; **Figure 4.5**). They observed that the higher level of lucerne meal resulted in better digestion of glucose and xylose and a reduction in mean retention time across the whole digestive tract and across the caeco-colic segment. Moreover, the smaller particle size resulted in lower cell wall digestion and increased mean retention times, across the whole digestive tract as well as across the ileo-rectal segment. They furthermore observed higher starch concentrations in the terminal ileal contents in the low fibre diet. García et al. (1999) also studied the effect of fibre source, and its associated differences in particle size (with fine particles defined as <0.315 mm and large particles defined as >1.25 mm), on retention times in rabbits. They observed that the caecal mean retention time was positively correlated with the proportion of fine particles and negatively correlated with the proportion of large particles. They discuss that this observation links to the fact that small particles move back to the caecum, whereas large particles move to the distal colon (see section **2.1.3 Large intestine**). As discussed earlier, long retention times may contribute to a destabilization of the caecal microbial activity and may hereby favour digestive troubles (Gidenne et al., 2010a). It has been reported that with a large proportion (>78%) of fine particles (<0.315), there is an increase in accumulation of digesta in the caecum (Nicodemus et al. (1997) in De Blas et al. (1999)). Therefore, it appears that

having sufficient large particles is beneficial for gastrointestinal health in rabbits. Indeed, it has been indicated that fibre particle size can affect mortality rates in rabbits. For example, Sobri et al. (2019) examined the effect of NDF level and fibre particle size (exact sizes not given) on, among other things, mortality and number of *E. coli* in rabbits during the postweaning period. They observed that particle size was linked to a difference in number of *E. coli* bacteria in the caecum contents, and that there was an interaction effect between NDF level and fibre particle size in the observed cumulative mortality from 5 to 12 weeks of age. However, other studies observed no effects of particle size on mortality in rabbits (e.g., Nicodemus et al., 2004; Nicodemus et al., 2006; Laudadio et al., 2009).

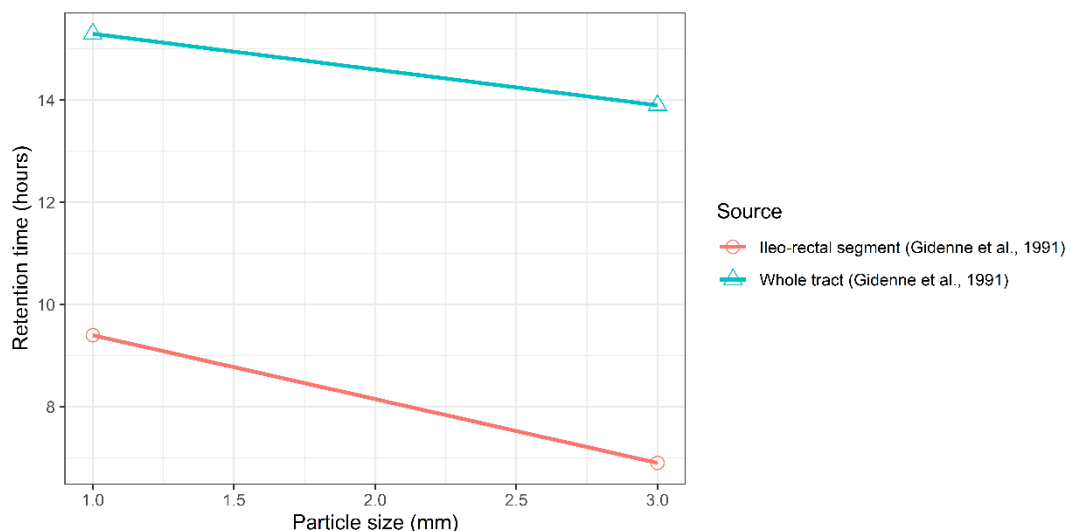


Figure 4.5 Visualisation of the relationship between particle size and retention time in rabbits. Based on Gidenne et al. (1991).

4.1.1.2 Starch

Starch is the main energy source in rabbit feed (El-Tahan et al., 2012). The digestion of starch mainly takes place in the small intestine and starch that is not digested there is generally quickly hydrolysed and fermented in the caeco-colic segment by the microbiota (Blas & Gidenne, 2010). However, it has been hypothesised that too much starch potentially results in a starch overload in the hindgut (Blas et al., 1994). This subsequently may result in an undesirable fermentation and growth of caecal microflora (Blas et al., 1994). Especially in young rabbits, an excessive flow of starch into the caecum could negatively affect the fibrolytic flora (Perez et al., 2000).

Several studies examined the effect of the level of starch in rabbit diets on mortality. Blas et al. (1994) studied rabbits on two different *ad libitum* diets, one with 16.4% starch and 15.3% crude fibre and one with 24.8% starch and 11.6% crude fibre. Both diets had maize and alfalfa hay as the main starch and fibre sources. The rabbits were weaned at 28 d and then fed with one of the two diets for 21 days, and their mortality was recorded. The rabbits on the lower starch and higher fibre diet showed a lower mortality (4.7% versus 8.0%, respectively). However, effects of starch may depend on what feed component is used as a replacement for starch, and also interactions with genetics are important to keep in mind. García-Quirós et al. (2014) studied three different genetic rabbit lines (see section **4.3.1 Genetic variability**) and, at the same time, examined the effects of two diets, one with animal fat and one with cereal starch as the main energy source. They studied, among other things, the mortality by digestive disorders and morbidity across the growing period and observed that there was no difference in mortality and morbidity between the two diets. However, an interaction was observed between diet and genetic line, with rabbits from a line selected for high average daily gain from week 4 to 9 of life showing a higher mortality on the animal fat diet than on the cereal starch diet (García-Quirós et al., 2014). Moreover, the source of the starch might play a role. Gidenne et al. (2005) examined whether the quality of the dietary starch affected, among other things, mortality in rabbits. Four diets with different starch origins were used: wheat, barley, maize, and extruded maize. The starch, protein and fibre levels were kept the same across diets and the diets were fed *ad libitum* from weaning to slaughter. They recorded the mortality of the rabbits, which was noted to always be caused by acute digestive disorders, and observed that, across the full fattening period, the mortality was lower for rabbits fed with wheat than for rabbits fed with maize as the main starch source. Overall, the effects of

starch in diets remain somewhat unclear, but it appears that a reduction in fibre plays a larger role than the increase in starch (reviewed by Gidenne (2015)).

4.1.1.3 Protein

Young rabbits have relatively high protein and amino acid requirements, as these are needed for tissue accretion, as well as renewal and growth of the intestinal mucosa (Lebas and Laplace (1972) in De Blas et al. (2012)). However, too much protein in rabbit diets may have negative effects. It has been shown that a higher ileal flow of protein results in an increase in microbial proliferation in the hindgut of rabbits (Catala and Bonnafous (1979) in Gidenne et al. (2010a)). When the availability of substrates for microbial growth increases as a consequence of too much protein in the diet, the prevalence of pathogenic microbes may increase (Gidenne et al., 2010a), including *Clostridia* and *E. coli* (Haffar et al. (1988) and Cortex et al. (1992) in Gidenne et al. (2010a)). Low crude protein diets, on the other hand, have been linked to a reduced frequency of *C. perfringens* detection (Chamorro et al., 2007).

Several studies examined the effect of (crude) protein on digestion and mortality. Chamorro et al. (2007) examined the effects of crude protein (**CP**) on digestion in weaned rabbits. They formulated four diets, with similar fibre and energy content, that differed in dietary level and apparent ileal digestibility of protein: 1) high protein high lucerne-hay (**HPHL**), low protein high lucerne-hay (**LPHL**), low protein medium lucerne-hay (**LPML**), and low protein low lucerne-hay (**LPLL**), the last two of which had soy-bean protein concentrate partially replacing lucerne hay. Rabbits were provided *ad libitum* with these diets for the first two weeks after weaning at 25 days, followed by a commercial diet. Part of the animals also received antibiotics in their drinking water. They observed that none of the diets resulted in a change in the biodiversity of the ileal microbiota, but the antibiotic supplementation in the water led to a reduction. Antibiotic supplementation also reduced the mortality rate. Within the medicated rabbits, it was observed that the LPHL diet was associated with lower mortality than the HPHL diet across the full fattening period (1.9% versus 9.6%, respectively). The same was observed for non-medicated animals, with a mortality of 20.0% for the LPHL group and of 32.9% for the HPHL group. No effect of substitution of lucerne hay with soy-bean concentrate on mortality was observed. Not only the level but also the source of protein (and its associated digestibility) can affect digestive troubles. Gutiérrez et al. (2003) examined the effects of different vegetal protein concentrates on digestion in early-weaned rabbits. They used four isonutritive diets where about 30% of the total dietary CP came from either soya bean meal, soya bean protein concentrate, sunflower meal or a combination of soya bean meal and potato protein concentrate, in which the concentrates were highly digestible in comparison to the non-concentrates. For two weeks after weaning (at 25 d), rabbits were fed with these diets, followed by a commercial feed until slaughter age (60 d). Across the period from 25 to 60 d of age, the mortality differed between the diets, with a significantly higher mortality for the diet with the combination of soya bean meal and potato protein concentrate than for the other three diets (34.6% versus 13.6-19.9%). García-Ruiz et al. (2006) examined the effect of isonutritive diets with soybean meal or sunflower meal, as well as enzyme supplementation (no enzyme, protease addition or protease and xylanase addition; so six diets in total) on digestion in rabbits. They had 30 rabbits per diet, that were weaned at 35 d and then received the diets for four weeks. Across the period from 35 to 63 d, there was a tendency for a higher mortality for the soybean meal-fed rabbits, compared to the sunflower meal-fed rabbits. The authors suggested that the lower mortality for the sunflower meal-fed rabbits may have been linked to a lower daily ileal CP flow. It must be noted, however, that soybean meal-fed rabbits also had a higher feed intake, which may also affect digestive health (see section **4.1.2 Feed provisioning**).

4.1.1.4 Additive effects of feed composition changes

Up to this point, we have seen that high fibre and low crude protein appear to contribute to reduced digestive disease. However, a question that might follow from this is whether the effects of fibre and protein are interchangeable or additive. A study by Martínez-Vallespín et al. (2011) might shine more light on this. They studied rabbits on eight different diets (**Table 1**), where starch was partially replaced by ADF or NDSF and/or the crude protein content was reduced. Both rabbit does and young rabbits were studied and, among other things, the mortality in an ERE context was determined. On d 17 of the lactation, females and their litters were separated, to avoid free suckling, and were brought together for a short time once a day until weaning at d 28 of the lactation. The rabbits were fed *ad libitum* with one of the experimental diets from d 21. After weaning, the young rabbits were housed in individual or collective cages and continued receiving the experimental diet until 49 d, from which point onwards they received a non-medicated commercial

finishing diet. **Table 1** shows the mortality rates of the growing rabbits, per diet. The mortality was high in the first three weeks after weaning due to an ERE outbreak. All three dietary adjustments resulted in a reduced mortality, and the effects appeared to be additive, as the mortality rate was lowest in the high-ADF/high-NDSF/low-CP diet (**Table 1**). After switching back to a commercial diet, no differences in mortality were observed (**Table 1**). Overall, this indicates that increased levels of (low- and/or high-)digestible fibre replacing starch in diets, as well as a reduction in crude protein content, contribute to a reduced mortality in an ERE context.

Table 1 Overview of the diets and mortality in the study of Martínez-Vallespín et al. (2011). Adapted from Martínez-Vallespín et al. (2011).

Diet	LLH	HLH	LHH	HHH	LLL	HLL	LHL	HHL
ADF level	Low	High	Low	High	Low	High	Low	High
NDSF level	Low	Low	High	High	Low	Low	High	High
Crude protein level	High	High	High	High	Low	Low	Low	Low
Mortality rate 28-49 d of age (experimental diet) in % ¹	71.6 ^a	68.3 ^a	58.6 ^b	43.4 ^{cd}	51.4 ^{bc}	41.8 ^d	42.8 ^d	29.2 ^e
Mortality rate 49-60 d of age (commercial finishing diet) in %	1.0	6.9	6.5	2.0	5.8	1.3	3.0	3.2

¹ Means not sharing any common superscript are significantly different, with $p < 0.05$.

4.1.1.5 Feed additives

There are several non-therapeutic alternatives for in-feed antibiotics, including pro- and prebiotics, organic acids, plant extracts, and enzymes (Maertens, 2007). These feed additives may positively impact gastrointestinal health. For the purpose of providing a general overview, we mainly based this section on two relevant review papers (Maertens (2007) and Falcão e Cunha et al. (2007)), even though these are somewhat older. Providing a detailed overview of different feed additive products for rabbits is outside the scope of this report, but some examples are given below.

Probiotics

Probiotics are live micro-organisms that contribute to the intestinal microbial balance of their host (Maertens, 2007). As summarized in Kaur et al. (2002), probiotics are thought to act through, among other things, 1) competitive exclusion of enteric pathogens, 2) inhibiting the growth of potential pathogens through production of lactic acid, bacteriocin and more, and 3) increased turnover of enterocytes. Most commonly, strains of gram-positive bacteria, such as *Bacillus*, *Enterococcus*, *Lactobacillus* and *Streptococcus*, or yeasts are used (Maertens, 2007). Falcão e Cunha et al. (2007) reviewed the effects of probiotics on mortality in rabbits. Of the 16 studies they discussed, 7 showed a positive effect of probiotics (lower mortality, determined as absolute percentage difference in mortality between the treatment and the control), 6 did not show an effect and 3 showed a negative effect on mortality (higher mortality). It must, however, be noted that in the discussed studies, the probiotics were generally provided from around 28 d old onwards and under a range of circumstances (e.g., under experimental or under commercial conditions, with optimal housing conditions or with less favourable housing conditions, and more). Also Maertens et al. (2006) noted inconsistent results of probiotics. Such inconsistent results were noted by Maertens (2007) to not be surprising, as the gut ecosystem is complex. An added difficulty for implementation in practice is that the probiotics need to survive the feed preparation and storage conditions (Maertens, 2007).

Prebiotics

Prebiotics are feed ingredients that are not digested by the animal's enzymes, but that can stimulate certain, already-present, intestinal microbes that have potential benefits for the health of the host (Falcão e Cunha et al., 2007; Maertens, 2007). Generally, prebiotics are carbohydrates, mainly oligosaccharides (Maertens, 2007). Compared to probiotics, prebiotics have two major benefits: 1) there are no issues with the processing of the feed or the acid environment of the stomach, and 2) no foreign microbial species are introduced into the rabbit gut (Falcão e Cunha et al., 2007). For fructo-oligosaccharides (**FOS**), no clear effects on mortality in growing rabbits have been observed (reviewed in Falcão e Cunha et al. (2007)). However, Morisse et al. (1993) examined the effects of *E. coli* infection in rabbits with or without FOS supplementation in their feed. They observed no differences in mortality, but did observe that the animals receiving FOS supplementation showed, among other things, a lower pH, a rise in total VFA, a decrease in ammonia production and an increase in saprophytic *E. coli* counts in the caecal contents, all characteristic of

healthy rabbits (Morisse et al., 1993). Moreover, within the surviving rabbits, the number of animals showing diarrhoea was lower in the FOS-supplemented group. In terms of α -galacto-oligosaccharides (**GOS**), Gidenne (1995) reported negative results. Gidenne (1995) studied rabbits in a 2 x 2 design, with normal and low fibre diets, and with or without GOS supplementation. An increased morbidity and a trend for an increased mortality between weaning and slaughter were observed for rabbits fed a diet with GOS supplementation. Most of the mortalities were linked to acute diarrhoea. No significant effects on feed intake, feed conversion, growth or VFA were observed. Gidenne (1995) stated that the negative effects of GOS remain to be investigated in more detail, but that it appears that the negative effects were not due to a carbohydrate overload in the hindgut. Other studies observe positive effects of GOS. Peeters et al. (1992) examined the effects of GOS supplementation, in relation to an enteropathogenic *E. coli* infection. They observed no effects of GOS supplementation on, among other things, weight gain and feed intake. However, they did observe that the GOS supplementation was linked to some improvement in terms of diarrhoea between 7 and 10 days after infection with *E. coli* and to an increase in VFA and caecal pH. They concluded that their results suggested that GOS provides some protection against the effects of an *E. coli* infection. To summarize, the reported effects of prebiotics are sometimes contradictory and more research is required to examine the potential of prebiotics in more detail.

Organic acids

The addition of organic acids may also benefit gut health, although their exact mode of action is not yet completely understood, partly due to the complexity of the rabbit digestive system (Falcão e Cunha et al., 2007). There are several hypothesised ways in which the consequent acidification may contribute to gut health (Falcão e Cunha et al., 2007): 1) acid may replace gastric hydrogen chloride, contributing to activation of proteolytic enzymes, denaturation and unfolding of feed protein, and contributing to the barrier effect against microorganisms that enter with the feed, 2) residual antimicrobial effects in the lower gut, 3) specific trophic effects on the intestinal mucosa, and 4) organic acids may act as nutrients. There are few studies, and with inconsistent results, on organic acids for rabbits (Falcão e Cunha et al., 2007; Maertens et al., 2006). A few studies have, however, observed a positive effect of organic acid on mortality in rabbits. For example, Skřivanová & Marounek (2002) examined the effects of caprylic acid supplementation (0, 2 or 5 g/kg) in the feed of rabbits. They observed a reduced mortality for the rabbits that received caprylic acid at 5 g/kg, in comparison to rabbits that received no caprylic acid. Also in a later study using caprylic and capric acid supplementation, a lower mortality (necropsy results showed enteritis and pathological changes of organs, watery gastric content with mucous, and cachexy as underlying causes) was observed for the rabbits that received the supplementation (Skřivanová & Marounek, 2006).

Plant extracts

Plant extracts may also be used as an alternative to antibiotics and are increasingly used in animal nutrition (Dalle Zotte et al., 2016). Nevas et al. (2004) studied the antibacterial properties of thirteen different essential oils against twelve bacterial strains, using an agar diffusion approach. They observed that among others *C. perfringens* was relatively sensitive to essential oils, whereas *E. coli* was relatively resistant, and that oregano, savory and thyme showed the broadest antibacterial activity. However, in practice, the efficiency of such essential oils may be lower than *in vitro*, as the feed composition may affect the antimicrobial activity (Nevas et al., 2004). *In vivo* applications of herbs and spices for rabbits are limited and the effects are not completely clear (Dalle Zotte et al., 2016). However, some studies indicate positive effects of dietary supplementation with herbs and spices. Krieg et al. (2009) studied the effect of a herbal feed additive (a mixture of onion, garlic, caraway, fennel, gentian, melissa, peppermint, anise, oak bark and clove; 300 mg/kg feed) on rabbit performance, digestive disorders and intestinal microbiota. They observed that the rabbits that received the supplementation showed a lower prevalence of digestive disorders and related mortality. Moreover, a reduced microbial diversity in the caecum was observed for the rabbits that received the supplementation. Placha et al. (2013) studied the effects of thyme oil supplementation. They observed that the supplementation of thyme oil resulted in a strengthened intestinal barrier integrity and in enhanced blood phagocytic activity. Other studies, however, do not observe positive effects of plant extracts for rabbits. For example, Botsoglou et al. (2004) studied the effects of dietary supplementation (0, 100 or 200 ml/kg) with oregano oil in rabbits, and observed no effects on the performance of the rabbits.

Enzymes

Enzymes are proteins that can catalyse certain chemical reactions with only minimum energy waste (Cachaldora et al., 2004). Falcão e Cunha et al. (2007) note, in their review, that most studies from around the turn of the century were unable to detect significant effects of enzymes on rabbit performance. However, some studies did report positive effects of enzyme supplementation. For example, Cachaldora et al. (2004) examined the efficacy of supplementation with an amylase, β -glucanase and β -xylanase enzyme complex. They provided three diets, with 0, 400 or 500 ppm of this complex, which were also medicated with an antibiotic, bacitracine. They observed that the supplementation with this enzyme complex reduced the mortality rate of the rabbits in a situation where there was a high incidence of intestinal disorders and mortality. In the earlier-mentioned study by García-Ruiz et al. (2006), enzyme supplementation with either protease or protease and xylanase was studied, as well as different diets (discussed earlier). They observed a trend for a reduced mortality across the full fattening period when enzymes were supplemented, but only in interaction with the source of protein: the difference was detected in sunflower-based diets in comparison to the control diet, but not in soybean-based diets. Gutiérrez et al. (2002) examined, among other things, the effects of enzyme supplementation, using an enzyme complex consisting of endo-1,3-beta-glucanase, endo-1,4-beta-xylanase, α -amylase and pectinase. They observed that the enzyme supplementation lowered mortality across the full fattening period, and suggested that this was potentially linked to the decrease in ileal starch concentration that was also observed.

Combined approaches

There are also indications that specific combinations of feed additives can aid in digestive health in rabbits. For example, Liu et al. (2018) studied the effect of supplementation with two combinations of feed additives: a stimulatory combination (**combination I**), consisting of 1×10^9 cfu/kg *Bacillus subtilis* in combination with 2 g/kg FOS, and an inhibitory combination (**combination II**), consisting of 2 g/kg acidifier (mixture of formic acid, acetic acid and ammonium formate) and 0.6 g/kg essential oil (mixture of thyme and thymol oil). Based on these combinations, they examined five experimental groups and observed, among other things, that the mortality rate was lower for all four treatment groups in comparison to the control group (see **Table 2**, where several statistically significant differences between the treatments are shown (adapted from Liu et al. (2018))). Overall, it appeared that the paired treatments (I-II and I-II-I; see **Table 2**) had similar or better effects on decreasing the mortality rate in rabbits in comparison with only combination II or the addition of zinc bacitracin, and that these groups had better intestinal morphology than the other groups. This shows that combinations of feed additives, also in time, might have potential to positively impact gastrointestinal health in rabbits. Overall, more research into the potential of feed additives for practical implementation is required, but there appears to be potential to reduce the incidence and severity of digestive disorders in rabbits through the use of feed additives.

Table 2 Overview of the treatments, mortality and diarrhoea rates, and bacterial counts in the study of Liu et al. (2018). Adapted from Liu et al. (2018). Means in the same row not sharing any common superscript (indicated with a, b or c) are significantly different, with $p < 0.05$.

	Control ¹	ZnB ²	II ³	I-II ⁴	I-II-I ⁵
Mortality rate (36-77 d, %)	20.08 ^a	9.92 ^b	12.50 ^b	12.50 ^b	6.25 ^b
Diarrhoea rate (15-35 d, %)	2.81 ^a	1.93 ^a	1.52 ^{ab}	1.50 ^{ab}	1.02 ^b
Diarrhoea rate (36-77 d, %)	3.35 ^a	3.39 ^a	3.29 ^{ab}	3.11 ^{ab}	3.00 ^b
<i>E. coli</i> ileum (35 d, 10^4 cfu/g content)	6.44 ^a	5.67 ^b	5.64 ^b	5.82 ^b	5.69 ^b
Bacteriodes-Prevotella caecum (77 d, 10^4 cfu/g content)	10.35 ^{bc}	10.11	10.20	10.48 ^{ab}	10.53 ^a
NH ₃ -N (35 d, mM)	17.35 ^a	10.70 ^b	11.56 ^b	11.95 ^b	11.47 ^b
Total volatile fatty acid (35 d, mM)	9.47 ^b	12.38 ^a	12.66 ^a	13.24 ^a	12.99 ^a
Acetic acid (35 d, mM)	7.84 ^b	9.95 ^a	10.17 ^a	11.95 ^a	11.03 ^a
Valeric acid (35 d, mM)	0.15 ^b	0.20 ^b	0.29 ^a	0.31 ^a	0.30 ^a
Crypt depth (77 d, μ m)	104.34 ^a	109.19 ^a	98.35 ^{ab}	94.73 ^{ab}	85.66 ^b
Villi height/crypt depth ratio (35 d)	6.04 ^b	7.01 ^b	6.81 ^b	8.40 ^a	8.35 ^a
Villi height/crypt depth ratio (77 d)	5.25 ^b	5.54 ^b	5.54 ^b	6.29 ^{ab}	6.89 ^a

¹ Basal diet; ² Addition of 0.1 g/kg bacitracin zinc in basal diet; ³ Addition of combination II (see main text); ⁴ Addition of combination I (see main text) during days 15–35 and addition of combination II during days 36–77; ⁵ Supplemented with combination I during days 15–35 and 57–77, supplemented with combination II during days 36–56.

4.1.2 Feed provisioning

Different studies report positive effects of specific feed provisioning strategies on gastrointestinal health, such as feed restriction strategies or timing-based strategies, that are discussed in more detail below.

4.1.2.1 Feed restriction strategies

There are strategies that directly implement a feed restriction, through a limited provisioning of feed, a limited feeding access time (but see section **Timing-based strategies**), or restricted access to water (see e.g., Boisot et al. (2005)). A potential difficulty with such strategies, however, are animal welfare concerns. According to Gidenne et al. (2012), through feed restriction the Freedom from Hunger and Thirst, part of the Five Freedoms (FAWC, 1993), is potentially no longer met. The Freedom from Pain, Injury or Disease, however, may be better met (Gidenne et al., 2012). This may result in an animal welfare dilemma, and therefore other strategies to improve gastrointestinal health may be preferred. Here, we provide a (non-exhaustive) overview of the observed effects of feed restriction on gastrointestinal health.

Gidenne et al. (2009a) examined the effects of different levels of feed restriction on, among other things, digestive health. They assessed treatment groups that were fed *ad libitum* and treatment groups with different levels of feed restriction, including diets of 90%, 80%, 70% and 60% of *ad libitum*, respectively. These diets were provided as a daily meal for 21 days after weaning, after which all animals were fed *ad libitum* again. The health status of the animals was monitored, and mortality and morbidity were noted to always be caused by acute digestive disorders (diarrhoea, caecal impaction). The mortality and morbidity rates were observed to not be different for the *ad libitum* and 90% group. During the post-weaning period, the mortality was lower in the 80%, 70% and 60% groups compared to the *ad libitum* and 90% groups. For the 70% and 60% groups, the morbidity after weaning was also reduced. However, after all rabbits were fed *ad libitum* again, this positive effect of a reduced feed intake did not persist, as there no longer were differences in mortality and morbidity between the treatment groups. Over the full fattening period, this resulted in a lower mean mortality and morbidity rate for the 80%, 70% and 60% groups compared to the *ad libitum* and 90% groups (Gidenne et al., 2009a), see also **Figure 4.6**. An often-noted downside of feed restriction is the potential subsequent lower daily gain, resulting in lower slaughter weights at the given slaughter age. To address this, as well as the earlier-discussed positive effects of increased digestible fibre,

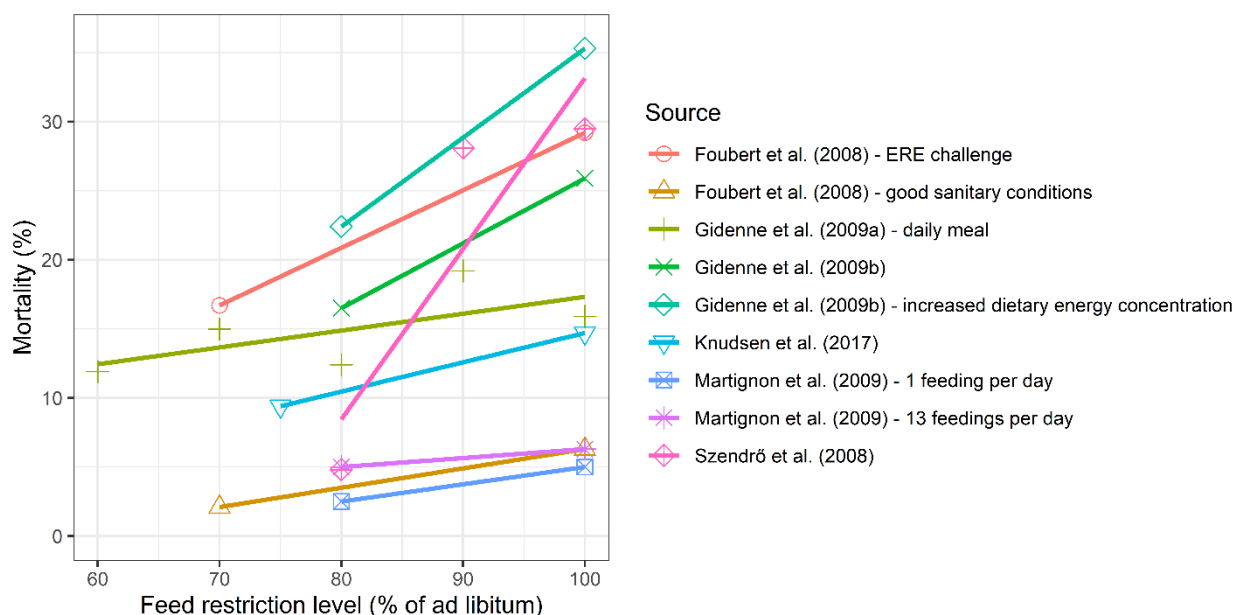


Figure 4.6 Visualisation of the relationship between feed restriction level and mortality after weaning. Based on Gidenne et al. (2009a) across both restriction and AL period; Martignon et al. (2009) across the restriction period; Szendrő et al. (2008) across the period from one week after weaning until slaughter (but the highest feed restriction group in this study received the diet with the highest dietary fibre content); Foubert et al. (2008) across both restriction and AL period, groups that also received water restriction excluded; Gidenne et al. (2009b) across both restriction and AL period; Knudsen et al. (2017) across both restriction and AL period and averaged across two different diets.

Knudsen et al. (2017) examined the use of high energy diets in which the DgF to starch ratio was increased, with equivalent ADF levels. Rabbits were fed one of two diets that either had starch or DgF as the main digestible energy source, either *ad libitum* or at 75% of *ad libitum*, from weaning (at 32-36 d) to 63-64 d of age. Across their experiment, they observed that over 90% of the mortalities were caused by digestive disorders, but that the different experimental sites (four different sites; two with a low incidence and two with a high incidence of digestive disorders) showed large differences in sanitary status (see also section **4.2.3 Sanitary factors**). Therefore, they grouped sites with low or high incidence of digestive disorders and examined these two categories separately. They observed no differences in morbidity or mortality between the diets and feeding levels for the sites with good sanitary conditions. However, for the sites with poor sanitary conditions, feed restriction was linked to a lower mortality, but not morbidity, during the restriction period and, consequently, across the whole fattening period. No differences in mortality or morbidity were observed between the two diets, which was suggested to be due to the relatively moderate variations and high values of the DgF to starch ratios that were used. However, an interaction was observed between diet and intake level for morbidity across the restriction period, with the lowest morbidity for the feed-restricted animals fed with the starch-based diet. In terms of growth, a trend was observed for an interaction between feeding level and diet, where the reduced growth from feed restriction was greater for rabbits fed with the DgF-based diet than with the starch-based diet. Gidenne & Feugier (2009) applied different levels of feed restriction (*ad libitum* and 80%, 70% or 60% of *ad libitum*) and observed that for the restricted rabbits, the mean retention time of particles and liquids was increased, the VFA concentration was higher and thus the caecal pH was lower. Together, these changes might result in a reduced pathogen proliferation (De Blas et al., 2012). This contrasts with the earlier mentioned idea that a shorter retention time would be beneficial for the digestive health in rabbits (Gidenne et al., 2010a), as has also been observed in practice, with a higher fibre supply being linked to a shorter rate of passage of particles and liquids (Gidenne (1994) in Gidenne et al. (2009a)). This was also noted by Gidenne et al. (2009a), who concluded that the results from Gidenne & Feugier (2009) indicate that the digesta transit does not play a key role in digestive health.

Overall, it appears that a feed restriction can positively impact mortality from gastrointestinal disease, as also indicated in **Figure 4.6**, where the reported mortality levels of several feed restriction studies are shown. Looking at this figure, there appears to be a positive effect of feed restriction at all levels of mortality, but especially at higher levels of mortality (i.e., for the lines positioned higher on the y-axis). However, it must be noted that not all studies observed positive effects of feed restriction on mortality in rabbits (e.g., Martignon et al. (2021) where mortality was relatively low in general and it was reported that the sanitary conditions were good).

Timing-based strategies

Besides direct feed restriction in terms of amount, there are also timing-based feeding strategies. For example, Romero et al. (2010) examined the effects of a reduced feed access of 8h per day, from 09:30 to 17:30 each day, in growing rabbits. They compared two treatments, one where rabbits were fed *ad libitum* from weaning to slaughter and one where rabbits had limited feed access for the first two weeks after weaning, after which they were also fed *ad libitum*. They performed two trials, with no difference in mortality in the first trial where mortality was generally low (1.0%), but with a difference in mortality in the second trial where mortality was generally higher (16.0%). This higher mortality in the second trial was potentially linked to the lower sanitary status (see also section **4.2.3 Sanitary factors**). In the second trial, a mortality of 22.9% was observed for the *ad libitum* fed rabbits, during the first two weeks after weaning. In the restricted rabbits this was 4.2% (see also **Figure 4.7**). During this same period the morbidity also differed, with 33.3% and 8.3% for the *ad libitum* and restricted rabbits, respectively. From two weeks after weaning until slaughter, the morbidity and mortality rates of the two groups did not differ. It is important to note, however, that Romero et al. (2010) observed that their time restriction also resulted in a quantitative feed restriction, as the restricted rabbits showed a feed consumption of about 85.9% of the *ad libitum* fed rabbits. They posed that the reduced mortality in feed-restricted rabbits may be explained by a decrease in the flow of nutrients reaching the caecum, and a subsequent lower proliferation of pathogenic bacteria. However, not all studies note an effect of time restriction on quantitative feed intake, yet observe positive effects of feeding time restriction on (gut) health. Wang et al. (2021) studied whether night-restricted feeding could contribute to improved gut health. They divided rabbits across two groups, one with daytime feeding (access throughout the day, with feeding at 06.00) and one with night-restricted feeding (feed access from 19.00 to 06.00). Both groups received the same amount of feed and throughout the full trial there was no significant

difference in feed intake between the two groups. They observed that the daytime fed rabbits, that had feed available all day, mainly ate during the daytime. Furthermore, they observed differences between the two groups in terms of microflora structure, with the daytime fed rabbits showing significantly enriched potentially conditioned pathogenic bacteria, among other things. In terms of mortality, they reported significant odds ratios ranging from 2.36 to 3.28 for daytime fed versus night-restricted fed rabbits. In terms of the odds of diarrhoea, they observed significant ratios ranging from 1.87 to 2.07 for daytime fed versus night-restricted fed rabbits. Overall, Wang et al. (2021) hypothesize, based on their results, that night-restricted feeding 1) significantly changed the microbiome structure and optimized its composition, 2) linked to this, promoted diurnal rhythm changes in beneficial gut microorganisms and the production of beneficial metabolites, and 3) strengthened the diurnal rhythm of intestinal clock(-control) genes, partially benefitting promoted intestinal barrier function and integrity. In another study, Birolo et al. (2021) examined the effects of different feed restriction programmes and refeeding systems on, among other things, morbidity and mortality. From weaning, these rabbits received one of five feeding regimes: 1) *ad libitum* feeding throughout the trial, 2) daylight access to feed followed by fast refeeding until *ad libitum*, 3) night access to feed and fast refeeding until *ad libitum*, 4) night access to feed and slow refeeding until *ad libitum*, and 5) night access to feed and very slow refeeding until 12-hour access to feed until slaughter. The access to the feeders was varied, to achieve a reduced feed intake of all restricted groups from 80% to 70% in the first week of the trial, followed again by an increase from 70% to 80%. For all restricted rabbits, the feeding time therefore decreased from 14 to 9 hours per day, from 28 to 34 days old, followed by a week of 8 h/day feed access (35-42 days old). From 43 days old onwards, refeeding started, with a rate of +4 h/day until 24 h/day (fast refeeding), +1 then +2 h/day until 24 h/day (slow refeeding), or +0.5 h/day until 12 h/day (very slow refeeding). It must be noted that from 28 to 53 days of age, the feed was supplemented with an antibiotic and therefore the observations from this period are not representative of the effects of the different feeding regimes. However, from 54 days of age onwards, a fattening diet without antibiotic supplementation was provided. No health problems were recorded during the first four weeks of the trial, but in the last two weeks a severe enteric disease (ERE-like) was observed. Across the whole trial, the morbidity and mortality did not differ between the different feeding programmes, but the mortality due to digestive disorders was lower in the *ad libitum* group compared to all the feed restricted groups together. The authors however note that this result needs to be confirmed with a larger number of animals.

Overall, the physiological mechanisms behind the observation of the restriction in feeding or feeding time resulting in mostly positive effects on gastrointestinal health remain uncertain (Gidenne et al., 2012) and more research in this area is required. In all cases, however, there might be interactions between diet or feeding strategy and management practices, such as sanitary conditions.

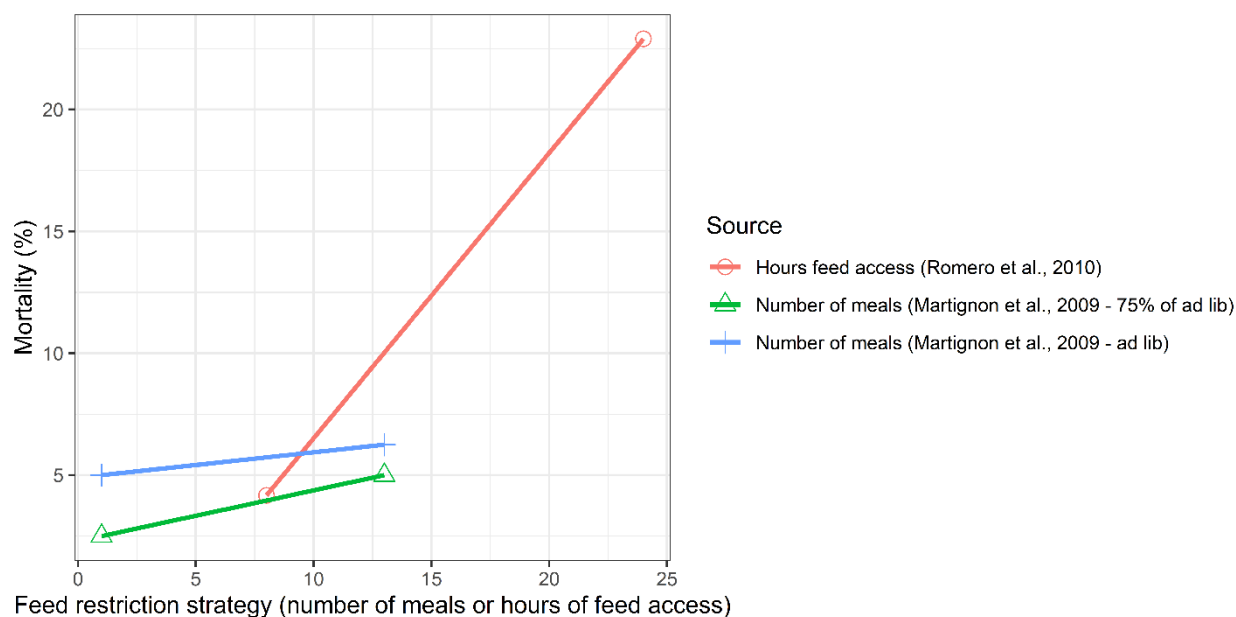


Figure 4.7 Visualisation of the relationship between timing-based feed restriction and mortality after weaning. Based on Martignon et al. (2009) across the restriction period and Romero et al. (2010) across the restriction period.

4.2 Management

Stress events during rearing, handling, age and weight of the animals at weaning, and environmental conditions may predispose rabbits to digestive disorders and enteropathies (Tazzoli, 2012). Consequently, several management factors may contribute to a reduced or increased disease or mortality prevalence. These include doe productivity and weaning related factors, environmental or housing related factors, and sanitary status related factors and are discussed in more detail below. It is important to note that many studies only recorded general mortality, and not the underlying causes. Therefore, the results are not directly translatable to digestive disease and should be interpreted with caution.

4.2.1 Doe productivity and weaning related factors

Different doe productivity and weaning related factors may play a role in the occurrence of digestive disorders, including weaning age, doe fertility and productivity, and transfer of young rabbits.

4.2.1.1 Weaning age

Stress caused by separation from the mother is a main cause of increased susceptibility to digestive diseases (Tazzoli, 2012). Several studies examined the effect of weaning age on rabbit performance, but the results are inconsistent. El-Sabroun & Aggag (2017) examined the effects of weaning age on productive performance, with weaning ages of 23, 28 and 33 d of age. The rabbits were housed in cages, with *ad libitum* access to pelleted feed, and were moved to other cages at weaning. The mortality rate (causes not recorded) of the rabbits was recorded across the period of 23-63 d of age, and it was observed that the mortality was higher for the rabbits weaned at 23 d than for the rabbits weaned at 28 or 33 d (3.9% versus 1.3% and 1.1%, respectively). This suggests that later weaning may be beneficial. It must be noted that in the Netherlands weaning commonly occurs around 35 d of age, so relatively late in comparison with these discussed studies. Other studies report negative effects of later weaning. For example, Bouquin et al. (2009) performed a retrospective case-control study to examine farm characteristics and rearing management practices after weaning that are potentially linked to ERE. They observed that the risk of ERE expression was increased when rabbits were weaned after 35 days, instead of earlier. Bouquin et al. (2009) mention that this might be due to earlier weaning resulting in a better body condition in the does, heavier litters with better immunity and lower pre-weaning mortality. Furthermore, they hypothesised that early weaning reduces the transfer of pathogens and noted that earlier weaning implies earlier specific nutrition of young rabbits around weaning time and earlier adaptation to solid feed. Indeed, Paës et al. (2019) studied the effects of a solid substrate gel, provided inside the nest from 3 to 18 days of age, on microbiota implantation and colonization, and observed that increased feed consumption early in life appeared to promote the development of microorganisms that are adapted to plant degradation. They concluded that this could prepare rabbits for the weaning transition. In practice, kits have access to the mother's feed starting from approximately 16 to 18 days old, as they can then leave the nest (Gidenne & Fortun-Lamothe, 2002; Paës et al., 2019). Interestingly, it has been observed that when suckling rabbits start to eat solid food, they preferentially eat from the same feeder as the doe, instead of from a feeder specifically for the kits, suggesting that the first solid food ingestion is influenced by initiation or imitation of the mother (Fortun-Lamothe & Gidenne (2003) in Gidenne et al. (2010b)). Yet, as the nutritional requirements of the kits and the doe differ, with high-fibre low-starch diets required for kits and energy-rich diets for the doe, it would be beneficial for practice to separate the feed for the kits and for the doe (Gidenne & Fortun-Lamothe, 2002). Alternatively, Gidenne & Fortun-Lamothe (2002) suggest that the stress from the sudden change in diet around weaning could potentially be reduced through progressive weaning: leaving out some suckling bouts, such as on day 16, 18, 20 and 22, before final weaning, for example. Bouquin et al. (2009) also reported that an increased ERE expression was linked to a high mortality rate before weaning. They suggest that this early mortality could be due to initial disease expression, but note that it could also be due to poor maintenance conditions or poor health status of the does. In the following sections, several of these related explanatory factors are discussed in more detail, but overall it appears that different management factors may interact and therefore one needs to look at the complete picture to determine the effect of management factors in more detail.

Apart from the timing of weaning, also the removal of maternal milk itself may negatively affect digestive health or resilience. Rebollar et al. (2009) examined the effects of parity order (see section **4.2.1.2 Doe**

fertility and productivity) and two different types of reproductive management on, among other things, rabbit mortality. They examined an intensive (artificial insemination on day 4 *postpartum* and weaning at 25 d of lactation) and a semi-intensive (artificial insemination on day 11 *postpartum* and weaning at 35 d of lactation) reproductive rhythm. They observed no differences in mortality rate for the periods of 21-25 d and 35-60 d of age, but a higher mortality rate for the intensive than for the semi-intensive reproductive rhythm across the period of 25-35 d and clinical signs of diarrhoea were observed in the mortalities. During this period, the rabbits of the intensive reproductive rhythm were already weaned, whereas the rabbits of the semi-intensive reproductive rhythm were not. Gallois et al. (2007) studied weaned and suckling rabbits and examined their response to an infection with enteropathogenic *E. coli* (**EPEC**). At 28 d of age, weaned (at 21 d) and suckling (weaned at 35 d) rabbits were experimentally inoculated with EPEC and the infection progress was monitored. The does, and the kits, were confirmed to not have been exposed to this strain before, to exclude humoral passive protection from doe to kit through milk. It was observed that suckling can temporarily reduce mortality, as the weaned rabbits showed mortalities earlier, starting from 4 d after infection compared to after 8 d for suckling rabbits and reaching 50% mortality at 36 d of age compared to at 45 d of age for the suckling rabbits. However, the total mortality percentage was not observed to be significantly different between the two groups. A similar pattern was seen for morbidity. Moreover, Gallois et al. (2007) observed that suckling temporarily limits faecal *E. coli* excretion, as at 31, 36 and 38 d of age the weaned rabbits excreted more pathogenic *E. coli* than the suckling rabbits, but this difference was no longer present from 42 d of age onwards. The observation that the young rabbits were protected from disease to some extent when they were suckling, but were no longer protected after weaning took place, suggests that milk plays a protective role against EPEC. This protective effect may have several hypothesised origins: 1) some milk components might exert an antimicrobial effect, stopping or reducing bacterial growth (in line with the observed reduced *E. coli* excretion), 2) milk might limit bacterial adhesion to enterocytes, protecting against diarrhoea, and 3) some milk substances might interfere with the mechanisms that lead to diarrhoea, apart from bacterial colonization (Gallois et al., 2007). In terms of bacterial adhesion to enterocytes, Gallois et al. (2007) indeed observed that there was a reduction in the level of adhesion of EPEC bacteria to the ileal epithelium in the suckling rabbits compared to in the weaned rabbits. Overall, this study shows a positive role of maternal milk for digestive health in young rabbits.

4.2.1.2 Doe fertility and productivity

Huneau-Salaün et al. (2015) examined the relationship between husbandry factors, as well as health conditions, and French rabbit farm productivity. They obtained data from 95 farms and observed that mortality during fattening (of unreported causes) was negatively (favourably) correlated to fertility (i.e., number of parturitions divided by the number of artificial inseminations or mating bouts). Rebollar et al. (2009) examined, in addition to the earlier-discussed reproductive management types (intensive, with artificial insemination on day 4 *postpartum* and weaning at 25 d of lactation, and semi-intensive, with artificial insemination on day 11 *postpartum* and weaning at 35 d of lactation), the effects of parity order on mortality during fattening. They observed that, across the period from 25 to 35 d of age, the mortality rate of the kits was lower for the first parity than for later parities (3.3% versus 12.7-15.6%). Moreover, they observed an interaction with the earlier-mentioned reproductive management types across the period from 25 to 35 d of age: kits from second and later parities showed a higher mortality when they came from the group with the intensive reproductive management.

4.2.1.3 Transfer of young rabbits

In addition to the earlier-discussed role of weaning age, Bouquin et al. (2009) observed that the risk of ERE was increased if young, weaned rabbits were transferred to a different room for fattening instead of the does being transferred and the young rabbits remaining in the room in which they were born. Bouquin et al. (2009) suggest that not transferring the young rabbits may minimize stress that would otherwise potentially arise through manipulation as well as temperature and hygrometry differences between rooms. Another potential explanation for this finding is that mixing animals of different ages in the fattening room is avoided through not transferring the young rabbits. In the Netherlands, a large proportion of rabbit farms use park housing, where transfer of young rabbits is common (Rommers et al., 2017).

Overall, the effects of doe productivity and weaning management on rabbit health are somewhat inconclusive and there appears to be limited empirical work on these factors. Likely, different management-related factors

interact, and therefore more research is needed to examine the role of weaning management and doe productivity in the development of a healthy, resilient gastrointestinal tract.

4.2.2 Environmental and housing factors

Different environmental and housing-related factors may play a role in the occurrence of digestive disorders, including the climate conditions, group size and composition, stocking density (space allowance), housing type and floor type.

4.2.2.1 Climate conditions

Several studies mention a potential role of climate conditions in the occurrence of digestive disease. For example, Lebas et al. (1997) mention that, when the temperature is low and humidity is close to the saturation point, water may condense on less insulated walls. This may result in more penetrating cold, as water is a good heat conductor, and subsequently in more heat loss in the rabbits and often digestive (and respiratory) disorders follow (Lebas et al., 1997). The ventilation rate, or air speed, may also play a role. When there is an imbalance between the air flow and temperature, with an air speed too high for a certain temperature, a cold draught will arise, which might be linked to intestinal blockage (Morrisse (1981) in Lebas et al. (1997)). Furthermore, Kylie et al. (2017) report an increased prevalence of enteritis during the winter months in a study on Ontario meat rabbit farms. They hypothesize that this might be linked to difficulties with providing adequate barn ventilation while at the same time maintaining suitable ambient temperatures, and, consequently, the ventilation might be lower than ideal. This reduced ventilation, in combination with irregular cleaning and disinfection of cages, may subsequently result in higher ammonia levels and reduced immunity (Kylie et al., 2017). On the other hand, too high temperatures or a too high temperature-humidity index (**THI**) may also result in (general) health troubles. For example, postweaning mortality (of non-specified cause) was higher in the season with the highest THI in a study conducted in Nigeria (Asemota et al., 2017).

4.2.2.2 Group size and composition

Szendrő & Dalle Zotte (2011) reviewed the effects of different housing conditions on the performance and behaviour of meat rabbits and discussed, among other things, the group size in which rabbits were kept. They concluded that it appears that general mortality is not strongly linked to group size. For example, Princz et al. (2009) examined different housing systems, that also differed in group sizes (2 versus 13 rabbits per group; with the same stocking density). Although the housing type itself may have impacted the results, they observed no differences in mortality between the two group sizes. However, other studies do observe a difference in mortality between rabbits housed in different group sizes. In a meta-analysis by Sommerville et al. (2017) it was observed that, regardless of enrichment provisioning and at a given space allowance, general mortality did increase with group size, yet especially so when no enrichments were provided. However, they noted that this was potentially strongly linked to space allowance (see section **4.2.2.3 Stocking density (space allowance)** below). To summarize, the evidence tends to point towards an increased mortality with increasing group sizes, which potentially is linked to an increased infection pressure (as for example suggested by Szendrő et al. (2010)). Also the composition of the group may affect the occurrence of digestive disease, as Bouquin et al. (2009) observed a trend for a higher ERE expression being linked to cohabitation of rabbits of different ages in the same fattening room.

4.2.2.3 Stocking density (space allowance)

Szendrő & Dalle Zotte (2011) reported, in their review, that there is no clear relationship between stocking density (i.e., space allowance) and mortality. In accordance with this, Fétiveau et al. (2021) observed no effect of stocking density on mortality rate, when they studied two housing systems (see section **4.2.2.4 Housing type**) and two densities, of 17 and 9 rabbits/m² respectively. However, Sommerville et al. (2017) observed in their meta-analysis that, although space allowance did not affect general mortality in the absence of enrichment objects, mortality increased with space allowance when enrichment objects were provided. They suggested that this was linked to the nature and number of environmental enrichments, as increased space allowance may have resulted in increased interaction with enrichments. Given that it can be difficult to ensure adequate hygiene of the enrichments, and given that there may be competition for the enrichments, this might result in higher mortality rates (Sommerville et al., 2017). It appears that observed mortality or disease differences for different stocking densities may be related to other, confounding effects.

To give another example, Bouquin et al. (2009) observed, in addition to other, earlier-discussed factors, that the risk of ERE expression after weaning was higher if the volume of the fattening room exceeded 0.14 m³/kg, indicating a lower rabbit density is linked to a higher ERE expression. According to Bouquin et al. (2009), this observation suggests that ERE affected farms may have difficulties with managing atmospheric and ventilation conditions (see earlier section **4.2.2.1 Climate conditions**). They discuss that many rabbits farms (in France) have expanded from small-scale units to intensive production systems and that in some cases the buildings have only been restructured without much attention for the environmental conditions.

4.2.2.4 Housing type

The type of housing system may also affect the occurrence of disease or mortality. For example, Rauterberg et al. (2019) compared a common housing system (i.e., small groups in cages with wire-mesh floor, an elevated platform, a box and one gnawing stick) to a new housing system (i.e., large groups, slatted plastic floor, elevated platforms with partly solid floor, boxes and different enrichment materials). They observed no differences in diarrhoea occurrence between the two housing systems, but did observe a higher mortality rate (no causes of death noted) for the new housing system across the period from weaning to slaughter. They noted that the mortalities rates were high for both systems, and therefore a general health problem may have played a role, but the larger groups (see also section **4.2.2.2 Group size and composition**) and lack of hygiene in the new system may have increased the mortality rate even further through an increased infection pressure. As no differences in disease occurrence were observed, only mortality differences, it might be that animals in a cleaner environment are more likely to recover from disease (Rauterberg et al., 2019). Dal Bosco et al. (2002) examined rabbits reared in cages, wire-netted pens or straw-bedded pens. They observed that the mortality rate was lowest in cages. They hypothesised that the higher mortality for the rabbits in pens was linked to an increased infection pressure due to the larger group size. For other types of housing or enrichment, no differences in mortality may be observed. For example, Fétique et al. (2021) observed no statistically significant difference in mortality between rabbits with or without access to an outdoor area. Postollec et al. (2008) studied three housing systems: 1) large pens with a platform (60 rabbits/pen), 2) small pens with a platform (10 rabbits/pen), and 3) conventional standard cages without a platform (6 rabbits/cage). All housing systems had a stocking density of 15 rabbits/m². They observed a low general mortality rate (0.7%) in their study, and subsequently no differences between the housing systems.

4.2.2.5 Floor type

Different studies report effects of floor type on the observed mortality or morbidity rate of rabbits. For example, as mentioned earlier, Dal Bosco et al. (2002) examined rabbits reared on a wire net floor or on straw litter. They compared the wire-netted and straw-bedded pens to conventional cages and observed that the mortality rate was lowest in cages, but also that the mortality was higher in the straw-bedded pens than in the wire-netted pens. They hypothesised that this higher mortality in straw-bedded pens was linked to more contact with excreta, which could have increased contamination rates. Matics et al. (2018) studied rabbits in enriched cages (8 rabbits/cage, 15 rabbits/m² floor space, wire-mesh floors, equipped with footpads, and elevated plastic-mesh platforms) or enriched pens (65 rabbits/pen, 15 rabbits/m² floor space, plastic-mesh floors and plastic-mesh elevated platforms). They observed that, across the fattening period, the penned rabbits had a higher mortality rate than the caged rabbits. Matics et al. (2018) suggested that this might have been due to the rabbits preferring to stay underneath the platforms, resulting in high local densities. Many rabbits may defecate and urinate there, soiling the plastic-mesh floor, potentially resulting in increased infection rates. The cages, on the other hand, had wire-mesh floors, resulting in lower contamination risk (Matics et al., 2018).

Overall, it can be difficult to disentangle the effects of the different environmental and housing factors that might play a role in rabbit health. There are indications that mortality increases with increasing group sizes, which is potentially linked to increased infection pressure. However, it is highly likely that there are interactions with housing type (as well as the rabbits' behaviour in the different housing types), climatic conditions (temperature, humidity), and sanitary conditions (see next section).

4.2.3 Sanitary factors (biosecurity)

In addition to doe productivity and weaning-related and environment- or housing-related factors, sanitary factors (i.e., biosecurity) may also play a large role in preventing the occurrence of digestive disease. For example, the incidence of ERE mortality can be reduced through improvement of hygiene and breeding management (Licois et al., 2006). There appears to be a relationship between the environment, *C. perfringens* proliferation and the incidence of ERE (see **Figure 4.8**), and De Blas et al. (2012) suggest that the accumulation of spores and vegetative cells of *C. perfringens* in the environment might explain the difference in ERE incidence among rabbit farms. However, even though good sanitary conditions are of importance for reducing ERE incidence, a study in Canada has indicated that only few biosecurity measures are routinely implemented and the awareness level of biosecurity practices is poor in most cases (Kylie et al., 2017).

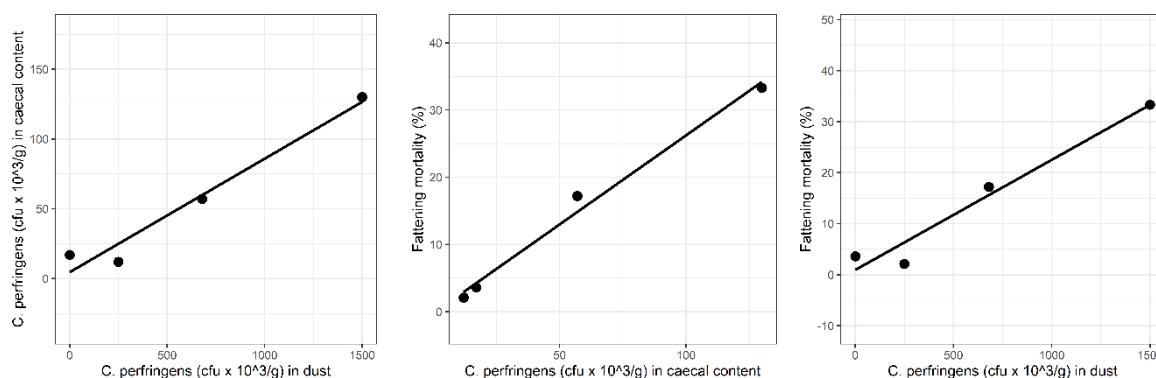


Figure 4.8 Relationships between the concentration of vegetative cells of *C. perfringens* in dust or caecal contents and fattening mortality. Based on data from De Blas et al. (2007, in De Blas et al. 2012).

4.2.3.1 All-in all-out management

A major leverage point would be the introduction of all-in all-out management, a production strategy in which all rabbits are moved into and out of facilities or production phases at the same time (National Farm Animal Care Council, 2018). This has for example been noted in the proposed Welfare Quality protocol for rabbits, where all-in all-out management is mentioned as one of the approaches for achieving absence of disease in rabbits (de Jong et al., 2011). In line with this, Maertens & De Groote (1992) observed in a study on a different topic (that is, yeast supplementation) that the mortality was much lower for the batch of rabbits housed in an all-in all-out unit than for their littermates from the same batch in a continuously occupied unit (1.7% versus 12.1%, respectively). Moreover, the earlier-discussed trend for a higher ERE expression being linked to cohabitation of rabbits of different ages in the same fattening room that was observed by Bouquin et al. (2009) was hypothesised to indicate that ERE expression may be reduced through all-in all-out management, instead of having animals present at all times that can serve as hosts for pathogenic agents (Bouquin et al., 2009).

4.2.3.2 Sanitary status

Garrido et al. (2009) studied whether disinfection of the farm contributed to reduced general mortality in rabbits during two consecutive reproductive cycles. They compared a farm that was spray-disinfected by spraying a disinfectant (containing 15% gluteraldehyde, 10% didecilmethyl ammonium chloride, 10% cipermetrine and 100% solvents and excipients, and active against Gram-positive and Gram-negative bacteria, viruses, spores, fungi and micoplasmas) before the trial and after the first fattening period to a farm that was only disinfected before the trial but not after the first fattening period. They observed that the rabbits housed at the farm with no disinfection between fattening periods showed a higher mortality. More specifically, they observed an interaction between farm and period, with a similar mortality in the first fattening period and a higher mortality for the rabbits housed at the farm with no disinfection between fattening periods in the second fattening period. This highlights that adequate disinfection may contribute to a reduced general mortality in rabbits. The sanitary status strongly links to housing rabbits individually or in groups (as also discussed earlier). Bennegadi et al. (2001) studied the impact of sanitary status, as well as a fibre deficient diet (discussed earlier, see section **4.1.1.1 Fibre**), on non-specific enteropathy from weaning (28 d) to slaughter (70 d). They examined SPF and conventional rabbits in individual cages ('experiment 1'),

and for the conventional rabbits both individual and collective breeding cages ('experiment 2'). In the conventional animals of experiment 1 the diarrhoea appeared to last longer than for the SPF rabbits. In the comparison between conventional and SPF rabbits (experiment 1), no difference in mortality was observed, but a lower morbidity and health risk index were observed for the SPF rabbits. Combining the data on conventional rabbits from experiment 1 and 2, it was observed that the mortality was higher in the collective cages compared to individual cages. Contrastingly, the morbidity was higher in the individual cages compared to the collective cages. The health risk index did not differ between the individual and collective cages. Interactions between sanitary status and the earlier-discussed diets were only observed for growth parameters and are not discussed here.

4.3 Animal effects

4.3.1 Genetic variability

Different studies suggest that there could be genetic variability in resistance to enteropathies in rabbits. We here discuss three examples.

Garreau et al. (2008) examined the heritability of a "disease score" for digestive disorders, and distinguished between rabbits dead or alive with no indication of digestive disorders and rabbits dead or alive with a comment indicating the presence of a digestive disorder. They observed a heritability for this disease score of 0.08 ± 0.02 . This same disease score was used by Garreau et al. (2012) to divergently select rabbits for resistance to enteropathies, based on routine observational data of signs of enteropathy, resulting in a group selected for sensitivity (**S**) and a group selected for resistance (**R**). These divergently selected rabbits were experimentally infected with an enteropathogenic *E. coli* 0103 strain and their responses were compared. No differences were observed between the two lines after one generation of selection, in terms of mortality, growth, relative caecum weight, appendix weight and pH of the caecal digesta (Garreau et al., 2012). However, the cumulative mortality was higher in S animals at days 11, 12, and 13 when only the 50% of rabbits with the highest estimated breeding value for the enteropathy score were included and the R animals when only the 50% of rabbits with the lowest estimated breeding value for the enteropathy score were included (Garreau et al., 2012). This suggests that there was a low genetic response to divergent selection, potentially due to a low heritability of resistance to enteropathies and only a single generation of selection, and the additional selection step increased the selection intensity (Garreau et al., 2012). Overall, the results suggest that, if a high selection intensity is implemented, there may be improved resistance to an artificial *E. coli* 0103 infection (Garreau et al., 2012).

Gunia et al. (2015) studied the heritability of different visually-assessed, binary-scored disease traits, including the following (groups of) digestive traits: 1) diarrhoea, that is, morbidity or mortality from diarrhoea, 2) various digestive syndromes, that is, morbidity or mortality from bloated abdomen and various digestive syndromes, excluding diarrhoea, 3) a composite trait of all digestive syndromes, that is, morbidity or mortality from diarrhoea or various digestive syndromes, and 4) digestive mortality, where an animal died of a digestive cause before the end of their test. These four (groups of) traits were all shown to have a significant genetic component and showed heritability values that were significantly different from zero (albeit low; Gunia et al., 2015): 1) for diarrhoea, a heritability estimate of 0.018 (SE 0.003) was reported, 2) for the group of various digestive syndromes, a heritability estimate of 0.011 (SE 0.002) was reported, 3) for the composite trait of all digestive syndromes a heritability estimate of 0.034 (SE 0.003) was given, and 4) the heritability of digestive mortality was estimated to be 0.041 (SE 0.004). Moreover, Gunia et al. (2015) estimated the genetic correlations among these four traits. The genetic correlations were all high and positive, and ranged from 0.71 (SE 0.06) for various digestive mortalities versus digestive mortality to 0.99 (SE 0.01) for diarrhoea versus digestive mortality. This suggests that there is a common genetic determinism for these traits. The phenotypic correlations were lower but still positive, except for the correlation between diarrhoea and various digestive disorders, which was negative (-0.14 (SE 0.00)). In addition, correlations with production traits were examined. The genetic correlations between digestive disease and production traits were mostly favourable. For example, there were negative correlations between the four (groups of) digestive traits and carcass yield. Therefore, there appears to be no trade-off between gut health and production in the selection process (Gunia et al., 2015). However, Gunia et al. (2015) note

that the diagnosis of diseases was made through visual appraisal and therefore the sensitivity and specificity may have been somewhat reduced. In addition to the exposure to the disease potentially being incomplete, this may have resulted in imperfect phenotypes and subsequent underestimated heritabilities (Gunia et al., 2015). Moreover, this study was performed in nucleus herds, where disease occurrence is likely lower than at the commercial level. Consequently, the estimated heritabilities might not be the same for a commercial environment and Gunia et al. (2015) noted that more research was needed to examine the genetic by environment effect in more detail. Indeed, Gunia et al. (2018) examined the heritability of resistance to, among other things, digestive disease (diarrhoea, bloated abdomen, and any form of digestive symptoms) in selection (nucleus farm) and challenging (sib-testing farms) environments. They observed heritabilities of 0.07 ± 0.02 for the selection environment and 0.11 ± 0.03 for the challenging environment for the resistance to digestive disease. This indicates that selection for digestive disease resistance may be feasible. In line with this, Gunia et al. (2022) performed a selection experiment to examine whether breeding for general disease resistance in rabbits is feasible. They used a binary trait as the selection criterion, i.e., healthy versus morbid, sick or dead, and observed a low heritability of 0.035 ± 0.009 . Moreover, they observed a genetic progress of 1.5 genetic standard deviation after four generations of selection. This suggests that breeding for general disease resistance is possible. Of the diseased animals, the majority showed digestive symptoms, which again suggests that breeding for resistance to digestive disease may be feasible.

García-Quirós et al. (2014) studied three different genetic rabbit lines, one of which was a robust line. This robust line was founded for reproductive longevity criteria through selection of females from commercial farms with a minimum of 25 parturitions with more than 7.5 kits born alive per parity, and then selection for litter size at weaning for seven generations. This line was mentioned to be characterized by a great robustness (García-Quirós et al., 2014). The other two lines were founded for litter size at birth and selected for litter size at weaning during seventeen generations or founded and selected during 25 generations for average daily gain from week four to nine of life, respectively. One aspect they monitored was the mortality by digestive disorders and it was reported that the animals from the robust line showed a lower mortality and morbidity than the other two lines (García-Quirós et al., 2014). The robust line may have conferred positive attributes to their offspring and the young rabbits may have had a better ability to tackle digestive disorders (García-Quirós et al., 2014). Therefore, it appears that the use of such lines may have potential as a way to improve general farm health and reduce the use of antibiotics (García-Quirós et al., 2014).

Several studies specifically studied genetic variability in resistance to ERE, coccidiosis or a fibre-deficient diet, and are discussed below.

Genetic variability in ERE resistance

Garreau et al. (2006) examined the heritability of resistance to ERE, after inoculating rabbits. They observed a significant sire effect on the diarrhoea index (0-1 classification, with 1 when a rabbit presented at least one diarrhoea symptom during the testing period of 0-33 days after inoculation and 0 otherwise), abnormal growth index (0-1 classification where the growth rate across D0-D12 was considered abnormal when it was inferior to the average growth of its control sibs minus two standard deviations) and resilience index (0-1 classification, with a resilient rabbit being alive at D33 and having a normal growth), but not on mortality (Garreau et al., 2006). Furthermore, they estimated the heritability of these traits and observed a heritability of 0.05 ± 0.05 for mortality, 0.21 ± 0.16 for diarrhoea, 0.38 ± 0.21 for abnormal growth and 0.08 ± 0.07 for resilience (Garreau et al., 2006). De Rochambeau et al. (2006) studied the variability in resistance to inoculation with ERE, inoculation with coccidiosis, and a low-fibre diet, in terms of two binary indexes: 1) "alive" (0-1), that is, rabbits were alive or not on day 32 after weaning, and 2) "tolerant" (0-1), with a tolerant rabbit being an animal that was alive at day 32 with any clinical symptom during the full fattening period. They observed for ERE that there was a significant sire effect for the tolerant index, but not for the alive index. Also correlations between sire rankings for the indexes were examined and the two indexes were correlated ($r_s = 0.60$).

Genetic variability in coccidiosis resistance

De Rochambeau et al. (2006) also studied variability in coccidiosis resistance. Rabbits were inoculated with *E. magna* oocysts the day after weaning and were examined for the earlier mentioned binary indexes (alive

and tolerant). A significant sire effect was observed for both indexes. There was also a correlation between the sire rankings for the index alive and the index tolerant ($r_s = 0.44$).

Genetic variability in low-dietary-fibre resistance

De Rochambeau et al. (2006) also studied variability in resistance to a fibre deficiency in the diet. Rabbits were fed with an *ad libitum* fibre-deficient diet (ADF was 100 g/kg instead of the common 180 g/kg) from weaning to 63 days old and were examined for the earlier mentioned binary indexes (alive and tolerant). A significant sire effect was observed for both indexes, but there was no significant correlation between the sire rankings for the index alive and the index tolerant. However, correlations were observed between the indexes for different digestive stresses: the coccidiosis resistance and low-dietary-fibre resistance showed a correlation of $r_s = 0.44$ for alive and of $r_s = 0.42$ for tolerant. This suggests that coccidiosis resistance and low-dietary-fibre resistance may have a shared resistance mechanism (De Rochambeau et al., 2006).

4.3.2 Maternal or litter effects

Several studies have indicated that there is also a litter effect on mortality during fattening. Around 20% of the variation in mortality rate appears to be explained by litter, as 50% of the losses occurred in 14% of the litters, with 50% of the litters showing no losses at all (De Blas et al. (2007) in De Blas et al. (2012)). Moreover, it appears that the intestinal microbiota within litters was more similar than between litters on the same farm (García et al. (2005) in De Blas et al. (2012)). De Blas et al. (2012) hypothesize that the underlying cause for this could be a transmission of immunity through the placenta or milk, or contamination with a pathogen through the mother or shared environment.

Overall, it appears that there is genetic variability in the resistance to different gastrointestinal problems, including general digestive disorders, ERE resistance, coccidiosis resistance and low-dietary-fibre resistance. However, the heritabilities were generally low. Moreover, there appear to be litter effects. Altogether, this suggests that there might be potential to select for improved gastrointestinal health resilience.

5 Concluding remarks

With this report, we aimed to identify risk factors and good practices in relation to gastrointestinal health in rabbits, as gastrointestinal disease is common in rabbits and is a major reason for treatment with antibiotics. We here provided an overview of the published knowledge on rabbit gastrointestinal health. There are many factors that play a (often interacting) role in the susceptibility to, and risk of, GI disease in rabbits. In terms of feed, mainly high fibre, low crude protein diets, specific feed additives and restricted provisioning appear to have potential for reducing the incidence of GI disease. In terms of management, measures related to improved sanitation or reduced stress show potential for reducing GI disease incidence. Also beneficial genetics can reduce the incidence of GI disease. Overall, through the implementation of a production system that combines several of the highlighted approaches, a more robust rabbit production can potentially be achieved, which will contribute to a reduced use of antibiotics. As has become clear in several of the discussed studies, different approaches may interact and therefore more research into the effects of combining different approaches (i.e., whether the effects are additive) is required. This could shine more light on whether GI disease can be completely avoided without antibiotics, or whether antibiotics interventions may still be necessary, albeit to a lesser degree.

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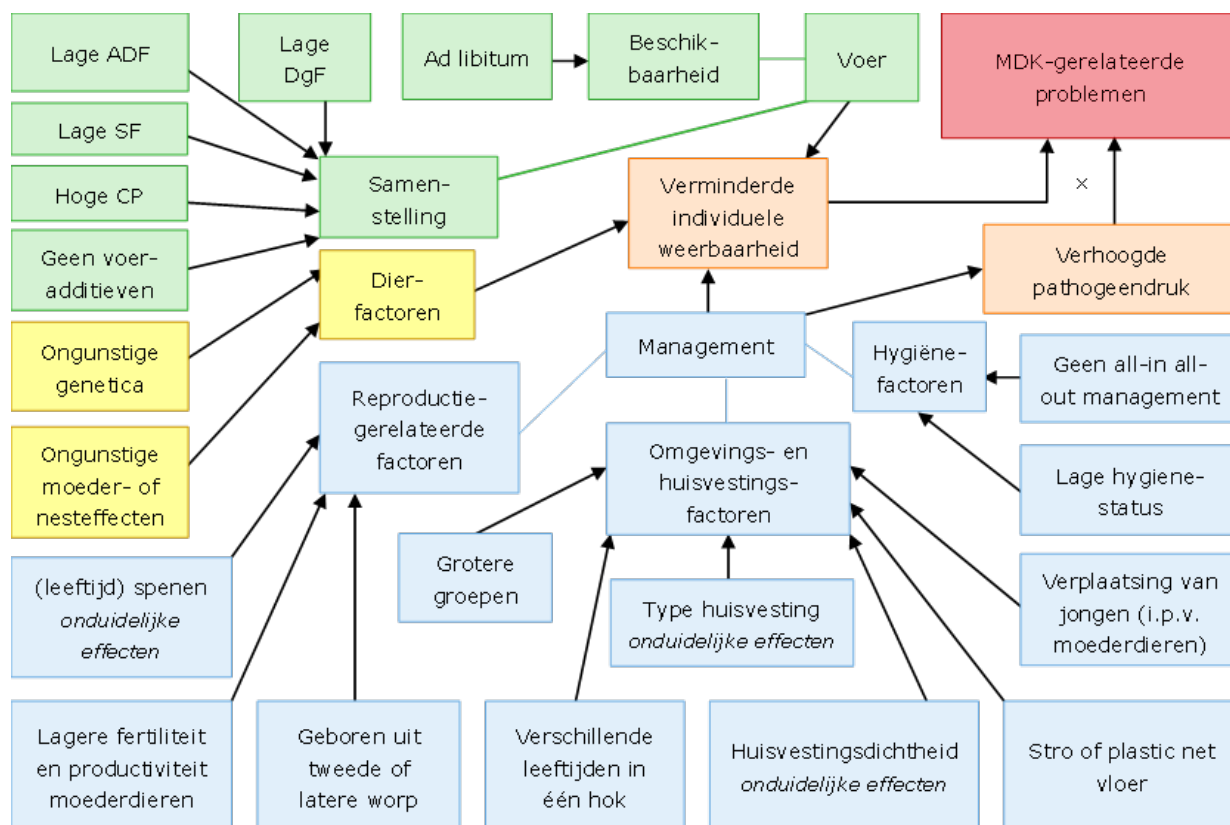
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Appendix 1: Uitgebreide Nederlandstalige samenvatting

Antibiotica worden regelmatig gebruikt om ziektes in productiedieren te behandelen, maar het gebruik hiervan kan negatieve effecten hebben op de gezondheid van dier en mens, bijvoorbeeld door het ontstaan van antibioticaresistente bacteriën of door de ongewenste effecten van antibiotica op de 'goede' bacteriën in het microbioom. Om deze redenen ligt het gebruik van antibiotica onder de loep. De konijnensector heeft in het afgelopen decennium dan ook een antibioticareductie-strategie ingezet, en heeft als ambitie het gebruik van antibiotica verder te reduceren. Uit eerder onderzoek is gebleken dat maagdarmkanaal (MDK)-gerelateerde problemen één van de hoofdaanleidingen zijn voor de inzet van antibiotica in de konijnensector. Zowel 'dikkebuikenziekte' (epizootic rabbit enteropathy) als coccidiose lijken hier een grote rol in te spelen. Het verkrijgen van meer inzicht in welke factoren mogelijk een rol spelen in het ontstaan van (deze en andere) MDK-gerelateerde problemen kan bijdragen aan de ontwikkeling van preventiestrategieën, om latere behandeling met antibiotica zoveel mogelijk te vermijden.

In deze rapportage wordt een overzicht gegeven van het normaal functioneren van het MDK en worden verscheidene interventies voor het voorkómen van MDK-gerelateerde problemen besproken. Hierbij wordt gefocust op drie hoofdcategorieën van preventieve benaderingen: 1) voer, 2) management en 3) dier-gerelateerde factoren. Voor de inhoud is gebruik gemaakt van literatuurstudie, interviews met deskundigen en gesprekken met konijnenhouders.

Uit de rapportage komt naar voren dat het MDK van konijnen gevoelig is voor ontsporing en er zijn dan ook veel factoren die een mogelijke rol spelen in de gevoeligheid voor – en het risico op – MDK-gerelateerde problemen. In het onderstaande figuur is kort samengevat welke voer- (groen), management- (blauw) en dier-gerelateerde (geel) factoren mogelijk invloed hebben op het ontstaan van MDK-gerelateerde problemen.



Overzicht van de risicofactoren die in deze rapportage worden besproken en hun relaties met de incidentie van MDK-gerelateerde problemen.

ofwel via een hogere pathogeendruk ofwel via een verminderde weerbaarheid van het konijn. Voor wat betreft voer kan een verhoogde weerbaarheid van het MDK mogelijk worden bereikt door rantsoenen met veel vezel, weinig ruw eiwit en met bepaalde voeradditieven te voeren, onder een voerbeperkingsstrategie (qua voerhoeveelheid of tijds-toegankelijkheid). Het is hierbij belangrijk om in gedachten te houden dat de effecten van specifieke voercomponenten lastig te achterhalen zijn, omdat het toevoegen van een specifieke component per definitie resulteert in een (relatieve) afname van (een) andere voercomponent(en). Voor wat betreft management, lijken vooral factoren gerelateerd aan stress en hygiëne van belang te zijn. Spenen, omgeving, huisvesting en reiniging zijn belangrijke factoren, waarbij bijvoorbeeld speenleeftijd, groepsgroottes, verschillende typen vloer en schoonmaakstrategieën potentie te bieden voor het reduceren van MDK-gerelateerde problemen. Ofwel: met name hygiënemaatregelen en het verminderen van stress vormen mogelijk goede strategieën om MDK-gerelateerde problemen te voorkomen of verminderen. Voor wat betreft dier-gerelateerde factoren, lijken er mogelijkheden te zijn voor het genetisch selecteren voor een hogere weerbaarheid tegen MDK-gerelateerde problemen.

Alles tezamen genomen lijkt het erop dat er een brede range aan mogelijke benaderingen is om de weerbaarheid tegen MDK-gerelateerde problemen te verhogen en zo het antibioticagebruik in de konijnensector te reduceren. Echter, verschillende benaderingen kunnen mogelijk met elkaar interacteren en het geheel is uiterst complex. Daarom is onderzoek nodig om te kijken naar de effecten van het combineren van verschillende benaderingen, om te bepalen of de effecten additief zijn. Dit kan meer inzicht geven in of MDK-gerelateerde problemen volledig kunnen worden vermeden zonder het gebruik van antibiotica of dat antibiotica-interventies nodig zullen blijven, hoewel mogelijk in mindere mate.

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