A Nuffield Farming Scholarships Trust Report

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The Power of the Microbiome to Produce Happy, Healthy Pigs

Heidi Natasha Hall

May 2021

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A Nuffield (UK) Farming Scholarships Trust Report

Date of report: May 2021

"Leading positive change in agriculture. Inspiring passion and potential in people."

Title	The Power of the Microbiome to Produce Happy, Healthy Pigs
Scholar	Heidi Natasha Hall Bsc Hons
Sponsor	The John Oldacre Foundation
Objectives of Study Tour	To understand each of the factors affecting gut health and the link this has with animal performance. This would include veterinary interaction, nutrition, genetics, animal husbandry and management on the unit. I wanted to understand the relationships between these co-factors and what people believed were the most important.
Countries Visited	America, Canada, Denmark, Hungary, Portugal and Vienna as well as visits in the UK and information gained from South Korea and China following travels there in November 2018 and Jan 2019.
Messages	• We need to have a holistic view and approach to raising animals for food. • All factors influence gut health and therefore animal performance to a varying degree and the priority or order of their importance can be different depending upon the site or simply the viewpoint of those involved. • Gut health is affected by all interacting forces on the animal through stress and this is central to managing animals; to ensure good productivity, health and welfare. • The sow should be our focus for intervention as she directly and indirectly affects the progeny health and performance.

1 Executive Summary/Abstract

With the ever-increasing pressure to reduce antimicrobials and the looming crisis of antimicrobial resistance, pig producers must review their unit in a holistic manner with gut health at its centre. Gut health has been linked to both general health and lifetime performance. Harnessing the power of the microbiome, the population of bacteria which reside in the gut, is the key to sustainable pig production. Macro factors affecting gut health and the microbiome such as management, genetics, health and nutrition are rarely discussed in partnership due to the difficulties in assessing these jointly in a scientific manner. This review looks to evaluate the strategies implemented in major pig producing countries to understand how we can best manage pigs to ensure they are both happy and healthy.

Here we discuss the differences and similarities in pig producers in different regions and suggests possible links between these factors and how we may be able to produce pigs with less requirement for antibiotics, which in turn could help to reduce the risk of antimicrobial resistance. Pigs produced without antibiotics are generally managed in a more holistic manner and focus is given to ensuring the breeding herd is also of high health. As medication use is known to increase the risk of AMR and this is passed on and retained for the lifetime of the animal. Minimising medication use and so reducing the risk of AMR in the breeding herd will help us to limit AMR in the production herd.

2 Contents

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3 Introduction

I may be considered by some to be a farming outsider, I have no history of farming in my family and in my early life lived in a heavily urban part of West Yorkshire, Leeds. However, I have always had a deep respect and interest in animals, from a very young age I wanted to be a vet and work to help improve the lives of animals around me.

As with many childhood dreams, mine was re-shaped following a number of events, A few veterinary practice work experiences and the realisation that my grades were not straight A's. So, I reassessed my objectives and chose to attend Leeds University and studied Zoology; encompassing animal metabolism, nutrition and physiology. I realised that I could work with some of the most numerous animals in the world, those raised to feed the human population. I would dedicate my career to improving their health, welfare and performance, by becoming an animal nutritionist.

I took my next steps with AB Agri ltd. on their Commercial Nutrition Graduate Scheme, here I cut my teeth in understanding the farming industry, the challenges of livestock production and how we can look to feed for a better future for animals and humans. Now 8 years later I work for Anpario plc. a UK based additives company focussed on solutions for animal production, globally. My day to day role is varied, I manage all pig trials and help develop new products to answer current issues in pig production. I also interact with our regional offices, distributers and customers to share trial or product information and gather their thoughts on current challenges. I was introduced to the Nuffield scholarship first at AB Agri by Michelle Sprent and again at Anpario by Helen Houghton (MCVS), Helen helped me and Anpario see what a great opportunity this could be for my personal and career development. Over the next 6 months I started to evaluate the industry I worked in and looked for issues which I couldn't answer in my current role. Ones which were multifactorial and needed a combined approach. I have been looking at Gut Health in my work as it is something we try to harness to improve animal production. It is still an ambiguous term and I wanted to better understand its meaning and how to measure/affect it. We are also consistently reviewing animal health and looking for alternative solutions to medication. The role of gut health in managing animal health is increasingly understood. My aim is to better manage gut health to help reduce the risk of antimicrobial resistance (AMR). All industries are reviewing antibiotic use and consistently challenging ourselves to reduce levels used in animal production. I felt a project reviewing gut health and the link between AMR would be extremely interesting and how nutrition, management, veterinary interaction and genetics affected this relationship is something I am not able to investigate in my current role. Hence my project, I hope it gives you food for thought.

In my personal life, I met my husband, Mike, before University and he has supported me throughout my studies, career progression and Nuffield scholarship. This past year Mike has been building our home, while we live in a static caravan with 2 cats (Cleo and Boo) and our dog (Yogi). Mike has also helped look after my two horses (Rocco and Tom) while I have travelled the world for my Nuffield project. I hope by the time this report is published to have moved into our new house and to be ready for the arrival of our first child who is due in August 2020. We may yet be able to reset the animal/human balance in the household.

4 Background

While antimicrobial resistance (AMR) is not a new challenge it has been attracting more attention in recent years due to increasing fear that there is a link between antimicrobial use and the presence of AMR (O'Neill, 2014). Therefore, UK pig production along with livestock production globally must act responsibly with the aim of reducing antimicrobial use (AMU). There is a wealth of evidence that supports the link between gut health and general health (Miniello *et al.*, 2017; Toribio-Mateas, 2018; Aluthge *et al.*, 2019).

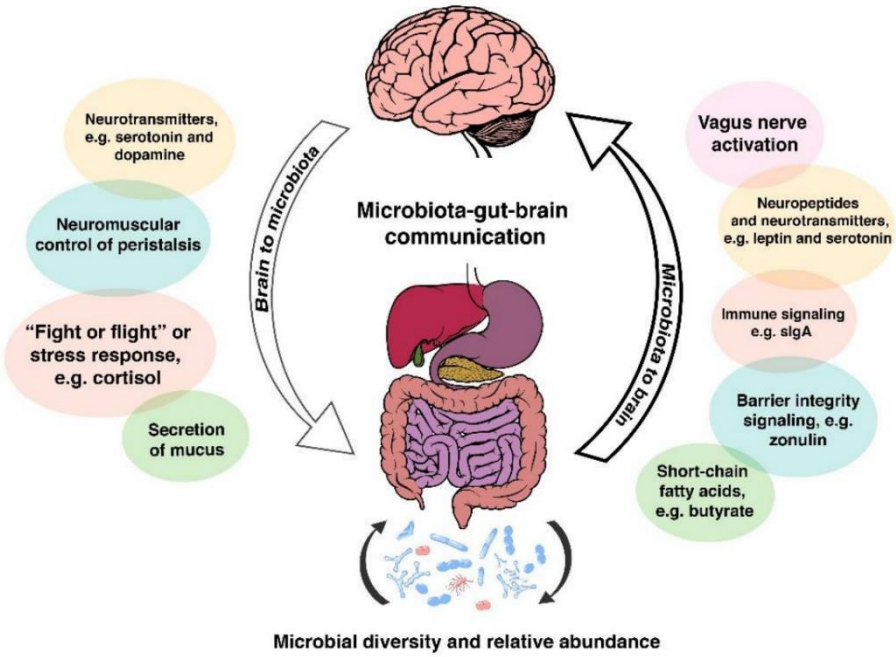
4.1 Antimicrobials and Bacterial resistance

Global livestock production is under increasing pressure to reduce the use and potential misuse of antimicrobials (AM) in the hope of mitigating the threat of antimicrobial resistance (AMR), and while this is not a new concept (Wise *et al.*, 1998), it has recently received further interest through the World Health Organisation's (WHO) 'one health' initiative (Iskandar *et al.*, 2020). AMR is a natural evolutionary trait of bacteria, whereby AMU adds selective pressure to the bacterial population and over time resistance to the compound used can arise (Samore and Lipsitch, 2002). This can then be transferred to other bacteria in the animal gut or environment and so AMR can spread to other livestock, other animals and humans who are in contact with the animal or the resistant bacteria; furthermore, AMU increases the risk of AMR (Samore and Lipsitch, 2002; Looft *et al.*, 2012). In the last decade reports have suggested AMR to be the biggest threat to human health by 2050 with over 10 million human deaths attributable (O'Neill, 2014). Since the 2014 report there has been renewed interest in potential alternative strategies for managing animal health and thereby reducing reliance on AM (Vanrolleghem *et al.*, 2019; Raasch *et al.*, 2020).

4.2 Gut Health and Antimicrobial Use

Gut health has struggled to be effectively described and is still considered an ambiguous term with multiple descriptions available (Pluske, Turpin and Kim, 2018). Generally, good gut health is considered the presence of a well diverse microbiota along the gastrointestinal tract that confers many benefits including; improved feed digestion and bacterial production of vitamins such as vitamin B12 (LeBlanc *et al.*, 2013; Miniello *et al.*, 2017). The notion is that an increased level of bacterial diversity of the microbiome can help to manage any unwanted, potentially pathogenic bacteria without the need for medication (Miniello *et al.*, 2017; Toribio-Mateas, 2018). A beneficial state of 'eubiosis' is synonymous with lower levels of gut inflammation which is mediated by the microbiota (Etienne-Mesmin, Chassaing and Gewirtz, 2017; Roager and Licht, 2018). Short chain fatty acid production can even play a role in gut homeostasis but it is not clear as to whether the increased production of butyrate in the gut is a direct or indirect benefit of good gut health (Hamer *et al.*, 2008; Leonel and Alvarez-Leite, 2012; Clarke *et al.*, 2014; Bedford and Gong, 2018), as such it is potentially a marker for gut health but not enough is known about individual differences between pigs for us to set a minimum required level as a performance indicator. Analysis and minimum detection limits of SCFA may also hamper its use as a performance metric.

It is now acknowledged that there is a major link between gut health and general health (Aluthge *et al.*, 2019). An animal which is routinely ill and requiring medication is not likely to have a balanced microbiota and there are studies linking AMU to a higher risk of future pathogen challenge in the intestine (Croswell *et al.*, 2009; Starke *et al.*, 2014). This may be due to the way in which broad spectrum AM work. By affecting a large population of bacteria within the gut there is more likely to be empty niches following treatment, where neutral or beneficial bacteria have also been affected by the AM treatment. This then leads to further dysbiosis as opportunistic bacteria proliferate faster which has subsequent negative connotations on later animal health and performance (Croswell *et al.*, 2009; Guevarra *et al.*, 2019). Management, genetics and nutrition all have links to gut health as stress through cortisol production has major implications on the gut and the bacterial population (Nowland *et al.*, 2019), with specific bacterial populations such as the genus *Bacteroides* being shown to be negatively affected by social disruption in the study by Bailey *et al.* (2011). Recent studies have further elucidated this microbiota-gut-brain axis as highlighted in Figure 1 (Toribio-



Mateas, 2018). Intensive pig production must take account of these factors when attempting to reduce reliance on medication. Supporting good gut health and reducing the likelihood of an imbalance in gut microbiota could help to reduce the likelihood of pathogen challenge following times of high stress such as weaning (Moeser, Pohl and Rajput, 2017; Guevarra *et al.*, 2019).

Figure 1. Simplified schematic of the interactions between the gut and brain (Source: Toribio-Mateas, 2018)

4.3 Weaning and Antimicrobial Resistance

Weaning is the most stressful point in a commercial pigs life (Lallès *et al.*, 2007; Moeser, Pohl and Rajput, 2017), therefore managing this situation well can benefit the gut microbiome (Guevarra *et al.*, 2019) and lifetime animal performance. Not coincidentally, weaning is also the focus for many nutritional and AM interventions. Traditionally high levels of zinc, commonly in the form of zinc oxide, is fed to help manage gram-negative bacteria in the hind gut and reduce the likelihood of post-weaning diarrhoea (PWD) (Poulsen, 1995; Slade *et al.*, 2011; Weber, 2017). PWD is common in

pig production but recently it has been suggested that up to 50% of PWD is not linked to bacterial issues and this 'low-pathogen diarrhoea' is potentially due to nutritional challenges such as antigens from feed materials (Pedersen *et al.*, 2015; Weber *et al.*, 2015; Weber, 2017). This would suggest that the use of AM; zinc or antibiotics, at weaning could be displaced with improved nutritional support at this time. When protein is poorly digested in the small intestine it flows through to the caeca, this leads to an imbalance in the microbial population in the lower gut which impedes normal gut function (Weber, 2017). Cases of bacterial PWD can lead to dehydration, wasting and increased mortality (White, 2017) and so medical intervention is necessary. However, in the cases of 'low pathogen diarrhoea', AM use may not have much benefit and could lead to AMR. There is also increasing evidence that zinc use can increase the risk of AMR (Fairbrother, Nadeau and Gyles, 2005; Yazdankhah, Rudi and Bernhoft, 2014) and has since been banned at pharmaceutical levels in swine diets from June 2022. As AMR is not able to be removed from a system once it has developed, we are only able to reduce AMR if we focus on reducing it at each point in the pig's life. As weaning is one of the most common points for medication use it should also be a focus for AMR reduction (Munk *et al.*, 2018).

4.4 Maternal Transfer

The sow is not commercially viewed as a large factor in piglet health and performance post-weaning. However the initial bacterial seeding of the gut and early nutrition is set by the sow, so her influence is potentially being overlooked (Katouli *et al.*, 1997; Thompson, Wang and Holmes, 2008; Mulder *et al.*, 2009). By concentrating on piglet health at or immediately after weaning we are ignoring the maternal influence in gestation and through lactation (Nowland *et al.*, 2019). Sow nutrition, management and the use of natural interventions could have an impact on the early health of piglets. This then in turn would affect post-weaning piglet performance and later health post-weaning (Thompson, Wang and Holmes, 2008; Fix *et al.*, 2010; Nowland *et al.*, 2019). As AMR has the potential to be transferred from the sow to her piglets before weaning (Pollock *et al.*, 2020) sow health should be a focus for us to help ensure piglets are robust in time for weaning and to help reduce AMR in the pig production cycle. Through the transfer of maternal antibodies there is also potential for us to manipulate innate immunity to the benefit of the progeny and protect piglets from known pathogens on the unit (Boulinier and Staszewski, 2008). The feeding of natural AM alternatives to sows to help improve sow performance, immunity or gut health could also benefit piglet performance post weaning through maternal transfer (Leonard *et al.*, 2011; Tan *et al.*, 2015; Hall, Wilkinson and Le Bon, 2021).

4.5 Feeding for Gut Health

Dietary manipulation of weaning pigs to offset the challenges of weaning is of current interest and diet formulations are increasingly important to help manage the bacterial balance in the gut at weaning. Diets formulated to have restricted crude protein (CP) levels following weaning, as low as 17% CP compared to traditional diets of over 20%, have been found to be beneficial (Nyachoti *et al.*, 2006; Heo *et al.*, 2008; Bhandari *et al.*, 2010), especially in times of health challenge. This helps to reduce the likelihood of undigested protein entering the lower gut and so could help to manage the risk of PWD (Cooper *et al.*, 2001). Secondly, diets formulated to have a minimum level of fibre, and more specifically to have set inert and fermentable fibre levels, can have benefits on gut health (Jha and Berrocoso, 2016). Combined studies are scarce, but lower protein and increased fermentable carbohydrate diets as tested in Bikker *et al.* (2007) did not show a benefit, this may be due to the

short trial duration as microbial changes may have longer-term effects which would only have been seen in the lifetime performance of the pigs. These dietary changes could help to reduce the stress on the piglets naïve digestive system, as weaning has a direct detrimental effect on the gut microbiome, therefore weaning stress is a major factor in lifetime health and performance (Ramayo-Caldas *et al.*, 2016; Aluthge *et al.*, 2019). Feeding for health may in future be a key requirement of diet formulation, this would also make inclusions of more expensive 'functional' feed ingredients easier, and costs should be evaluated against lifetime performance and health (medication use) rather than short-term benefits, such as weight gain. The literature supports this notion (Choct, 2009; Yang, Iji and Choct, 2009) but more work is needed to understand the nutritional requirements of animals under challenge and to combine this with microbial analysis to assess the changes within the microbiome.

Considering these elements, to better understand the factors affecting gut health, I visited industry professionals and researchers in different countries and professions in order to obtain a varied outlook on the use of medication in the swine production sector. This study reviews the macro factors, such as nutrition, management and veterinary interaction, which affect gut health and aims to evaluate the benefits of different approaches undertaken by producers in various countries to help reduce AMU in the hope of limiting AMR. Reproduction

5 Methods

The countries visited were chosen based on pig production and export volumes as well as antimicrobial use, these were the USA, China, South Korea, Denmark, the Netherlands, Portugal and Canada. I visited producers, researchers, nutritionists, geneticists, and veterinarians and discussed with them their views on the biggest factors which affect gut health, how these interact and how we may be able to leverage these relationships to better support the pig. See Appendix 1 for example questions.

Table 1. highlights my visits in each of the countries, the questions were designed to understand whether an interviewee felt gut health was important and then to understand what they may affect this, whether they felt they could affect medication use and if they thought this was necessary in relation to AMR. Specifics on how they would look to reduce medication use was not necessarily given but the reasons behind choices or how producers differed from others was sought. My aim was not only to understand how the individual managed gut health but how they measured this or how important they felt this was to the general health and performance of the herd.

Table 1. Countries and people, visited.

Country	Month, year	Visits	Objectives
Netherlands	November 18	Beneficial Microbes Conference	Conference highlighting the most recent research into gut health and processes following which major changes can be seen
Korea /China	Dec 2018/Jan 2019	Local feed and livestock producers as well	Individual meetings and seminars held on gut and joint health for pig and poultry.

		as global integrators.	
USA	May 2019	ISU, Nuffield post CSC tour	Iowa Pork board presentation, meeting with Dr John Patience (ISU) to understand his views on Pig production and NAE* production in Iowa/US.
UK/ Ireland	April- June 2019	JSR, ABN, TEAGASC, RVC/UCPH	Virtual meetings/ meetings and calls to discuss various aspects of pig production. With renowned nutritionists, geneticists and technical specialists.
USA	May- June 2019	ISU, KSU, Food and Health centre (Nebraska UNI) Smithfield, Iowa Select, USDA MARC, Pipestone, Devenish etc	Following the cancellation of World Pork Expo (ASFv) meetings were organised to catch up with many of the companies which would have attended. Kansas state and Iowa state university meetings also held with Nutritionists, Geneticists and microbiologists. Commercial companies including Pipestone, Smithfield and Iowa Select meetings were also held to understand commercial perspective on gut health and NAE* production.
Portugal	Sept 2019	UTAD (University of Tras os Montes e Alto Douro) ICBAS (Oporto University)	Discussions held with researchers and consultants to understand how they would best manage pigs for better health and feed manufacturers to assess perceptions of gut health and whether it is a focus for them.
Canada	October 2019	Alberta, Saskatoon, Prairie swine centre, Magowan's feed, NAE pig producer	Discussions with researchers and feed consultants looking to understand how research is targeted and why. Discussions with producers producing animals with very few or no antibiotics as standard.
Denmark	May 2019, Nov 2019	Zinc Summit (SEGES), University of Copenhagen, DTI, DTU, farm visit	Meetings to discuss vet and nutritional interaction on farm, AMR and zinc removal strategies.

*NAE; No antibiotics ever

6 Results

Some of the largest pig producing regions were visited such as the US and China. Focus was found in the main to be based on production capacity and efficiency. Health in pig dense regions in these countries was, in general, preventative and looked to ensure pig diseases did not spread from pig units to their neighbours. In this way antimicrobial usage (AMU) is generally higher as applications

tend to be in feed or water to all animals rather than individual pigs. Gut health, in these regions, was less of a focus and in some cases was not deemed important, especially for sows. Interestingly, gut health was commonly discussed by commercial companies rather than researchers or producers and so was seen to be a marketing tool rather than a tangible asset to pig production. In contrast many researchers felt gut health was ambiguous and were more focused on management, health, and AMU. There were individuals such as the Nebraska Food and Health Center who are solely focused on gut health and through the use of animal models for human research are able to share this data with the pig production industry.

In contrast, in countries such as Canada, the Netherlands and Denmark, and to some extent, Portugal and the UK gut health was discussed as a research focus and pig health was seen to be directly affected by poor gut health. Sow nutrition was also seen to be more important due to the link between sow and piglet health through maternal transfer.

6.1 Antibiotic Free Systems

In the US there are a large number of producers who run No Antibiotic Ever (NAE) or Raised Without Antibiotic (RWA) systems as either all or part of their production. If they are an NAE producer, they target ~85% of their production to conform to NAE and the other 15% will require therapeutic medication. Therapeutic medication includes both prophylactic (to prevent infection) and metaphylactic use (to prevent the spread of infection). In the US and China bans on the use of antibiotics such as Tylan have recently been implemented whereas in Europe, Canada, and South Korea these have been banned for several years. Zinc and some other pharmaceutical products such as Carbadox are not classed as antibiotics and so are permissible for use in NAE systems in the US. However, while I was there the use of Carbadox was under question by the FDA and so weaning was a particularly challenging time for producers.

In Canada, I visited a couple of producers who were following the NAE system and management practices were geared to help ensure sows and pigs had a strong immune system. This included feedback to gilts from older sows and the use of saliva ropes. Vaccination protocols were key, they were targeted to the unit and needed to be in place before a unit could look to remove antibiotics. In Europe, UK, Portugal, and Denmark vaccine programmes were also considered the cornerstone of healthy production and vets in all regions felt they needed to be reviewed yearly for best protection of the unit. Producers were recommended to investigate what diseases were the current issue on their unit and vaccinate accordingly.

In the US and in China there are a number of global exporters who enforce strict guidelines for medication use on their producers. These producers are generally more focused on gut health and typically have a multidisciplinary team around them who help them with the management of the unit. Health is an issue, in China and South Korea in particular, environmental pressures and hygiene are key challenges, as such, ABF systems are very rarely seen in these countries.

In Europe, UK, Portugal, the Netherlands, and Denmark medication is under stricter government control and in general animals do not receive medication in feed or water any longer. However, in Portugal many interviewees suggested medication was easy to obtain and not always through the proper routes. This may be a case in all countries but from my discussions seemed to be a particular

problem in the US, China, and Portugal/Spain. While ABF systems are not common, in general, medication use is lower.

6.2 Antimicrobial Resistance

Interestingly, the term antimicrobial resistance (AMR), while recognized by most, was not acknowledged to be an issue in all regions. When in China there was an understanding that the government would soon be banning in-feed and water medication due to the risk of AMR. However, many producers were preparing other means of securing AB for use to ensure they did not see a performance breakdown. In the US, while 'raised without antibiotics' (RWA) or 'no antibiotic ever' (NAE) systems have been growing in popularity over the last 10 years (Singer *et al.*, 2019), many producers and some researchers felt that AMR was not linked with AMU as few papers had proven the link. On the contrary, they felt it was natural and should be expected and not feared. Therefore, processes and management did not need to change. Confusingly, many research funding opportunities were secured through links to AMR and its risk to human health, therefore, there seems to be a disconnect between funding bodies and researchers in some cases.

In contrast, Denmark was perhaps the most focused, as a region on the whole, on monitoring and reducing AMU to help reduce AMR. Researchers at DTU, who I visited, were working on monitoring AMR across different farms and countries. Others were looking at the links within a farm and how we can best support animals to reduce the need for medication. This resonates with the efforts in the Netherlands and to an extent in the UK. In particular, I spoke with one researcher and consultant in Ireland who has been working for a number of years with producers to reduce AMU on their unit. He believed, in the long run, lifetime performance benefits and less time spent medicating and reporting AMU resulted in better profit for the unit. Another contact who worked between Denmark and the UK was part of an EU funded project reviewing strategies to reduce AM use. The primary driver for this funding and many other projects is AMR. Also, a consultant based in Portugal but who works globally set his business up on management principles to reduce AMU. He spoke about the need to manage the parent stock better through improved nutrition, gut health, and immunity to reduce stressors, this would then lead to healthier progeny. The costs, they argued, can be outweighed as we should see less mortality and better herd performance in the long run (3-5 years) and as we have fewer parent animals, we are able to concentrate efforts and funding on more valuable stock.

6.3 Genetics

While aggressive behaviour is not a selected trait, good body condition and feed efficiency are. This can lead to differences in feeding behaviour as was mentioned by several interviewees. Pig breeds can be grouped into snackers or meal eaters. Genetic traits would need to be managed differently to ensure stress was not increased, for instance, if all animals wanted to feed at the same time (meal eaters) this should be made possible. Gut health may also be affected by these behaviors but to what degree we do not fully understand, for one, potential pathogens residing in the lower gut may find it easier to migrate up into the small intestine during periods of starvation.

There were discussions in the UK and the US on genetic traits for health. With some Genetic companies testing for resilience and even resistance of breeds to key diseases such as PRRS and PED. This has been coined by some as breeding for robustness and may happen somewhat naturally in closed herds as the animals selected for best performance do so under the challenges present on

that unit. Resistance may be a preference by the veterinary profession as by definition resilience could include silent carriers of a disease. However, for pig dense regions this may be beneficial as a low level of virus is likely to be present on a unit through air transfer. Therefore, resilience may help a unit maintain performance levels, but the herd would be likely to test positive for the disease. Resistance may be best but harder to achieve as the animal would not be carrying the disease so must have developed or acquired a natural immunity.

6.4 Nutrition

Nutrition is interlinked with all areas we have discussed but in specific terms only the Netherlands seemed particularly invested in nutrition for health over performance. Having removed zinc, due to environmental and AMR concerns, from weaner diets several years ago they spoke about the need to balance protein and fibre, as well as ensuring fibre is optimized by balancing the inert and fermentable portions. Denmark, the UK, Canada and then Portugal would closely follow with diet quality being a focus for all feed manufacturers as well as consistency of raw materials and in general a higher value is attained for finished feed when compared to Asia and the US.

In Canada, I saw a focus on nutritional research with dietary recommendations being investigated for sick animals. However, these studies do not currently convey to changes in commercially produced feed and many diets are high in protein and lack functional fibre in North America. In China and South Korea diets are largely hand or floor mixed and so one of the biggest issues is consistency as each batch is likely to differ in macro nutrients as well as ingredients used. Fluctuations in crude protein levels or major changes in dietary ingredients are likely to reduce voluntary intakes and lead to animal weight variability within the herd. The gut microbiome would be more challenged as nutrients needed to support the bacterial population may be consistently changing. Therefore, we may see shifts in bacterial population leading to gut inflammation and secondary negative effects on the immune system.

Early nutrition (pre-weaning) is not consistently followed in any region but is considered important in the UK, Netherlands, Denmark, and Canada. Some producers provide creep feed while others simply ensure piglets are in contact with a clean, dry environment with enrichment such as bedding materials which will be consumed and therefore add to the development of the microbiome. Pea starch is commonly used as a piglet drying powder in many regions including the US, Canada, and Europe. The main aim of this is to ensure a piglet is dry to reduce the risk of chilling after birth but there are other benefits following ingestion of the product which would not be the same if an inorganic or mineral product were used (Figure 2).

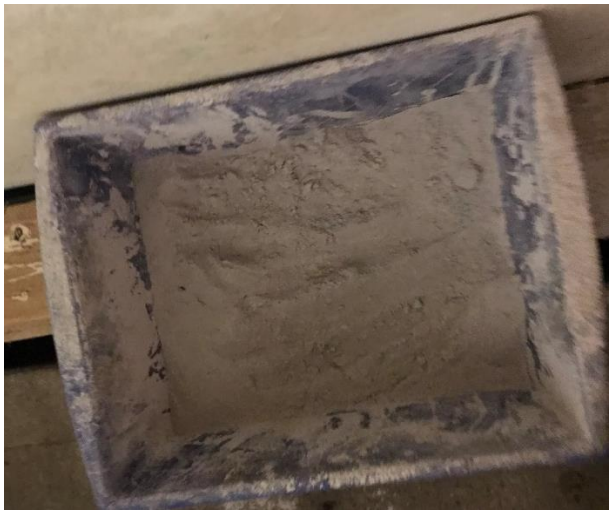


Figure 2. Pea starch powder used for drying newborn piglets. (Source: anonymous, permission granted to Author)

6.5 Management

Management is a focus in most pig producing countries, some still use sow crates (US, China, South Korea) for others these have been banned or are in the process of being phased out due to consumer/retailer demands (UK, Portugal, Netherlands, Denmark, and Canada). However, sow stalls are generally used in all regions for a short space of time, usually between service and pregnancy confirmation (around 30- 40 days of gestation). This helps to manage sow condition through individual feeding and lowers the risk of stress due to bullying during the most critical time for abortion. While sow stalls themselves have little bearing on gut health; stress levels, feed intake and frequency and sow mobility do. Figure 3 shows a typical sow stall set-up in Canada which is mirrored in many countries.

Figure 3. Typical Sow stall room design. (Source: anonymous, permission granted to Author)

7 Discussion

Many interviewees felt several factors co-affect gut health namely nutrition, management and the immune system. With our understanding of the gut-microbiome-brain axis this is logical as these three macro factors affect levels of stress on the animal which means cortisol levels are influenced. Interestingly in the literature, many studies only evaluate gut health following a dietary intervention or application of a commercial additive. This may be due to the inherent difficulties of evaluating management changes but this is potentially an area we must focus on to improve our understanding of how the gut microbiome is altered on farm following health and management changes and thus how we need to produce pigs for best lifetime performance.

This review sits apart from most as it evaluates the perspectives of the people working with swine and evaluates the affect macro factors have on gut health, animal health and so medication use. This may be considered hearsay, due to the nature of this study, no samples were taken, or performance results analysed to prove or disprove the hypothesis. But this gives us valuable insight into new research opportunities and highlights possible links which may have been overlooked.

7.1 Management on Gut Health

Most if not all of management practices affect the level of stress the animal is under, which is why good management helps to ensure high welfare. We know that stress has a direct effect on gut health and so an indirect effect on general health through changes in the microbiome (Menneson *et*

al., 2019). Effectively measuring cortisol levels, a key marker of stress, would help us to understand the level of stress but there are inherent challenges with this. individual variation and level of novelty to a practice or process (stimulus) would cause variation in the reading. Also, the way in which cortisol is measured through either salvia or blood do not give a clear picture, more recently hair cortisol is being used for monitoring chronic stress levels (Menneson *et al.*, 2019). However, changes in stress levels over time may be more informative. Stress is known to cause changes in the gut microbiome (Kelly *et al.*, 2015; Toribio-Mateas, 2018) and so lowering stress levels at key timepoints (farrowing and weaning) may help us to ensure the bacterial population is not unnecessarily or irreparably affected. The interviewees which were linked to NAE or ABF systems put great importance on management and the welfare of their livestock. However, in some cases stress was unavoidable and therefore processes were in place to help pigs deal with and recover from stress quicker. In Canada, Denmark and the Netherlands piglets are commonly moved, either at weaning or around 30kg, long distances to finishing farms in either the US, Spain, Italy or Germany. This can mean travel times over 24 hours and restricted feed or water, in the case of Canada and the US. Producers I spoke with felt that this is best managed by ensuring piglets that have arrived at their destination are held in a dark room for a short period before giving access to feed and water. This may help reduce fighting or stress due to new littermates and surroundings and could help to lower cortisol levels before food is consumed. Some also chose to feed the same diet in both locations to help reduce microbiome changes but for other this was not possible. Medication needs are likely to be increased following long distance moves as immune challenges are bound to be different between the two locations, vaccination programmes should take this into consideration.

7.2 Nutrition on Gut Health

7.2.1 Fibre

In Canada, the UK, and the Netherlands there was greater importance seen in fibre content and type in the diet. This may be due to the nutritional systems in place in these countries as many other regions visited follow the US research and nutritional information. In the US, fibre does not really feature as an important dietary nutrient in either piglet or sow diets. However, I believe fibre is the single most important nutrient affecting the gut microbiota (Molist, van Oostrum, J.F. Pérez, *et al.*, 2014; Agyekum and Nyachoti, 2017; Aluthge *et al.*, 2019), but 'fibre' is an ambiguous term encompassing many different components and a better understanding may be gained if we did not discuss 'fibre' but rather fermentable and inert types of fibre. As fermentable fibre is a prebiotic this could be a cost-effective way of supporting good gut health. However, due to the volume of space taken up in the diet there is generally a short-term performance reduction when fibre levels are increased, especially in young animals (Agyekum and Nyachoti, 2017). In general, we may need to investigate further to understand the ratio of fermentable and inert fibre for each life stage and then formulate to this (Molist, van Oostrum, J. F. Pérez, *et al.*, 2014). Unfortunately, there is little published on the balance of fermentable and inert fibre needed to ensure good gut health but it can be seen that inert fibre is beneficial in managing unwanted pathogens such as *E. coli* and helping to support the production of SCFA such as Butyrate (Molist *et al.*, 2010; Molist, van Oostrum, J.F. Pérez, *et al.*, 2014). When the zinc ban comes into effect, we may see more issues in piglets due to unfavourable fibre ratios in the diet. Certainly, those countries with reduced zinc levels were managing this through optimising fibre types to some degree.

7.2.2 Protein

Residual levels of protein which enter the lower gut act as a nitrogen source for bacteria which reside there. Along with fermentable fibre, which acts as an energy source, the bacteria can make use of these to proliferate. An unfavourable gut microbiome is known to arise from a high degree of undigested protein entering the lower gut (Heo *et al.*, 2008). These proteolytic bacteria are potential pathogens such as *Clostridia* and *E. coli.* Protein digestibility and quality are also important to ensure a minimised loss of protein from the upper gut. As well as lost nutrients from animal growth there is also the likelihood of gut inflammation if unwanted pathogens proliferate. This then triggers 'leaky gut' syndrome and results in further nutrient loss and the possibility of pathogens entering the blood stream (Moeser, Pohl and Rajput, 2017).

7.2.3 Additives

Additives such as essential oils and organic acids are common in weaning diets and have gained popularity in diets as alternatives to antibiotics (Kim *et al.*, 2005; Liao and Nyachoti, 2017; Woźniakowska, Kozera and Karpiesiuk, 2017; Nguyen, Seok and Kim, 2020)l. However, no additive should be used in place of good management practices, effective nutrition or vaccination programmes (Raasch *et al.*, 2020). Products are less commonly seen in sow diets; this is likely to be due to the lower margin on sow feed, but in integrated systems even less value was attributed to breeder pig diets. I believe this can be harmful to the lifetime performance of the sow and her progeny. We know beneficial changes in the sow microbiome can have benefits on her piglets and this can be seen past weaning (Hall, Wilkinson and Le Bon, 2021). Discussions with consultants in Ireland and Portugal supported this notion with improved herd productivity and profitability being seen following improvements made to breeding herd health and reduced medication use.

7.3 Immunity and Medication use on Gut Health.

Medication use in early life can increase the risk of future AMU and AMR (Croswell *et al.*, 2009; Starke *et al.*, 2014; Munk *et al.*, 2018). Therefore, helping to ensure piglets are weaned with a well-balanced and beneficial microbiome as well as a strong immune system should help to reduce future and lifetime medication need. I would suggest that maternal transfer of immunity and microbiota is the first step which we should manipulate to the benefit of the progeny. Ensuring the sow immune system provides effective innate immunity to the piglets and a microbiome which is well suited to their environment should be a primary focus of breeding herd management. Gut closure in piglets, the point from which they cannot uptake IgG directly across the epithelium, occurs from 24 hours of life and so ensuring good levels of IgG in colostrum and sufficient colostrum uptake is paramount (Rooke and Bland, 2002).

7.4 Antibiotic Free Systems

In the US alone, around 70% of all poultry and 30% of pig production is now following these production methods (personal communication SD 30th April 2019). In general, NAE systems do not give any routine medication to piglets from weaning, a few do not do this from birth, but this is more common in Europe. If treatment is needed, then the pig is segregated physically or by removal of an ear identification tag which denotes it for standard processing at finish. Producers can attain around 80-85% NAE of each batch and this was discussed to be a healthy target as medication, where required, should be given on welfare grounds. Vaccines are permitted, and in fact would be crucial in these systems. Sows are also exempt and there is criticism around medication use in sows during

gestation and lactation to ensure a 'clean' sow and litter for weaning. Some interviewees felt these systems were not sustainable or welfare friendly due to the increased margins available for NAE carcasses, this fits with surveys taken on the veterinary profession in the US (Singer *et al.*, 2019). As the monetary incentive is to produce as many NAE animals as possible in each batch which may lead to animals going untreated. Ultimately there is no scientific evidence that these systems reduce AMU or AMR as this can be passed on from the sow (Munk *et al.*, 2018).

8 Conclusion

This review looked to understand the links between the macro-factors affecting gut health, animal health and ultimately performance. Stress is what links all factors and minimising the level of stress the animal is under is the key to reducing gut inflammation, unnecessary medication use and reducing AMR. We need to routinely measure microbiome changes alongside stress levels in animals, prior to and during research trials, so that we can better understand any performance changes seen. Reducing medication use will become increasingly more difficult especially with increased viral challenge seen in all regions due to new and recurring diseases. In my opinion we should be focussed on ensuring sows are well supported and suited to their breeding environment with regards to nutrition and gut health. We should be targeting medication reduction in the breeding herd, which will be achievable through improving immunity, vaccination protocols and a focus on gut health and by doing so we should see improvements in the performance of their progeny through maternal transfer.

We need to further understand the influence we have on gut health (and it on performance) through effective monitoring on farm and in trials. We can then look to manipulate gut health to favour a microbiome which is best suited to the production system through management of the sow microbiome. This is perhaps the most effective way of ensuring piglets are weaned in a robust state with minimal need for medication and reduced lifetime AMU.

9 Postscript

From the beginning of my Nuffield Scholarship I was keen to accredit my report with Aberystwyth University this extended the writing process but gave me the time to research around the subject and understand more of the science behind some of what we see on farm. I hope to continue with further studies and obtain a Post Graduate Certification. My work has also highlighted some interesting research opportunities I hope to be able o look into.

My travels were extraordinary and even though Covid-19 cut my final trip short it did not hamper me to a great extent. Similarly, African Swine Fever (ASF) was rife and affected my Asian journeys and events which were cancelled in the US and Europe. However, I found travelling on my own both exciting and freeing. I was able to speak to many different researchers and academics about research which was outside my field in a non-commercial manner. My meetings with producers and commercial companies were unbiased and they were far more open than they would have been had we met while I was travelling for work.

While writing my report I fell pregnant with our first child and Ava joined our family while I was carrying out my Aberystwyth studies. Even though this was planned it gave me great training on time management!

I have also been lead editing a book on Insects for Animal feed which is due to be published later in 2021. We have focused on providing an up-to-date reference of this emerging market for Scientists, Nutritionists and Farmers alike.

My role with Anpario has also changed. I took the role of Global Technical Services Manager and I am now responsible for part of the technical team looking after technical queries and product registration. My Nuffield gave me more confidence to seek this position and my travels increased my global knowledge and interpersonal skills with different cultures. Dissemination of my studies will be partly through my work at Anpario where we develop solutions for animal production and gut health.

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12 Appendix

1) How did you come to be in your current role (brief background)?
2) Can you give me a short overview of your day-to-day activities?
3) What do you think are the best two aspects to your countries pig farming and two you are hoping to improve?
4) What is your nutrition/health strategy for Sow, nursery, grower and finisher?
5) What do you think is crucial to be able to produce animals with fewer requirements for antibiotics?
6) What do you define as NAE (no Antibiotics ever)?
7) How many farms/what percentage of the US pork market is NAE?
8) What is the market/ what does the consumer want?
9) Where did this (NAE/RWA) come from/ what were the instigations for the programme?
10) What do you think is the next step for your customers?
11) Where will pig production be in 10 years' time?

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