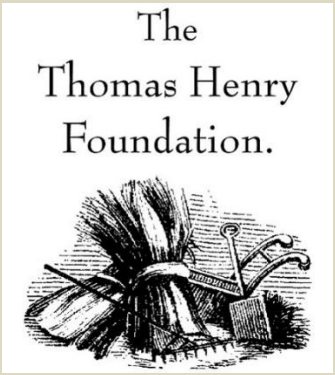
A Nuffield Farming Scholarships Trust Report

Award sponsored by

The Thomas Henry Foundation



Feeding for Health – Combating Antimicrobial Resistance

Mark Little

May 2021

NUFFIELD UK

NUFFIELD FARMING SCHOLARSHIPS TRUST (UK)

Awarding life changing Scholarships that unlock individual potential and broaden horizons through study and travel overseas, with a view to developing farming and agricultural industries.

"Leading positive change in agriculture"

"Nuffield Farming" study awards give a unique opportunity to stand back from your day-to-day occupation and to research a subject of interest to you. Academic qualifications are not essential, but you will need to persuade the Selection Committee that you have the qualities to make the best use of an opportunity that is given to only a few – approximately 20 each year.

Scholarships are open to those who work in farming, food, horticulture, rural and associated industries or are in a position to influence these industries. You must be a resident in the UK. Applicants must be aged between 22 and 45 years (the upper age limit is 45 on 31st July in the year of application). There is no requirement for academic qualifications, but applicants will already be well established in their career and demonstrate a passion for the industry they work in and be three years post tertiary education. Scholarships are not awarded to anyone in full-time education or to further research projects.

Full details of the Nuffield Farming Scholarships can be seen on the Trust's website: www.nuffieldscholar.org. Application forms can be downloaded but only online submission is accepted.

Closing date for completed applications is the 31st July each year.

ISBN: 978-1-912059-44-7

Published by The Nuffield Farming Scholarships Trust
Southill Farm, Staple Fitzpaine, Taunton, TA3 5SH
Tel: 01460 234012
Email: director@nuffieldscholar.org
www.nuffieldscholar.org

A Nuffield (UK) Farming Scholarships Trust Report

Date of report: May 2021

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

Title	Feeding for health - combating antimicrobial resistance
Scholar	Mark Little
Sponsor	The Thomas Henry Foundation
Objectives of Study Tour	The objective of my study tour is to find out more about nutritional solutions to increase cattle health. Ensuring animal health will reduce antibiotic usage because a healthy animal does not need antibiotics.
Countries Visited	France, Norway, The Netherlands, The USA, UK, Spain and Switzerland
Messages	We should not concentrate on nutritional solutions to simply replace antibiotics, many increase cattle immunity and health and therefore make them less likely to need antibiotics. Probiotics, prebiotics, essential oils, plant extracts, plant fibres, bacteriophages and using the quorum sensing theory have potential positive effects on cattle health however, none of these are a 'silver bullet' solution. Many of the nutritional solutions are not as effective nor as cost effective compared to antibiotics. This means that it is difficult to secure the investment needed to improve, refine and optimise their function in cattle. Animal health is an interconnected relationship between genetics, farm management, vaccination and nutrition and a holistic view must be taken to pick the area to make the most difference on-farm. I feel positive for the future as there are many different companies working on nutritional solutions to improve animal health. We are not there just yet, but the momentum of work is increasing, and solutions will come.

Executive Summary

Antibiotic resistance occurs when bacteria are no longer susceptible to an antibiotic that would normally have an activity against them and is a significant health concern for humans and animals. As healthy animals do not need antibiotic treatment, keeping them healthy is an important strategy to prevent the development of antibiotic resistance. The aim of this work was to define the practical role of nutritional management and products on farm and document those which have a health benefit. Visits were made to farms, companies and universities in the USA, The Netherlands, Norway, England, France, The Netherlands, Switzerland and Spain, examining practical nutritional practices to support cattle health and decrease the use of antibiotics, and experience how farmers have developed their farm business using these solutions. Bacteriophages and some essential oils have an antibacterial activity, but have limitations compared to antibiotics. Probiotics, prebiotics, essential oils, plant extracts, plant fibres, and quorum sensing increase cattle immunity and health, thereby helping cattle resist a bacterial challenge that would normally cause disease. However, many of the nutritional products are not as effective as antibiotics, while being more expensive and needing further investment to improve their activity. When placing these products on farm, it is important to consider genetics, farm management, vaccination, and nutrition to pick the best solution to make the largest difference. There is a growing consumer interest in the health and welfare of food producing animals and these products may be in increasing demand in the future.

Contents

DISCLAIMER

The opinions expressed in this report are my own and not necessarily those of the Nuffield Farming Scholarships Trust, or of my sponsor, or of any other sponsoring body.

Please note that the content of this report is up to date and believed to be correct as at the date shown on the front cover

CONTACT DETAILS

Mark Little
40 Laverys Bridge Road
Moira
Craigavon
County Armagh
Northern Ireland
BT67 0PQ

Tel: (+44) 7977471517

Email: markwlittle@me.com

Nuffield Farming Scholars are available to speak to NFU Branches, Agricultural Discussion Groups and similar organisations

Published by The Nuffield Farming Scholarships Trust
Southill Farmhouse, Staple Fitzpaine, Taunton TA3 5SH
Tel : 01460 234012
email : director@nuffieldscholar.org
www.nuffieldscholar.org

Personal Introduction

I grew up on a 100-cow, dairy and suckler cattle farm in County Fermanagh, Northern Ireland, where my father and brother continue to farm. I graduated as a veterinary surgeon from University College Dublin in 2002 and worked in mixed practice in Northern Ireland. At the start of my career, the majority of my workload was emergency work. However, as I really enjoyed building a working relationship with farmers and improving their farm profitability, this developed over the course my career to routine farm visits including dairy herd health and disease prevention work.

During these routine farm visits, I would often arrange joint visits with the cattle nutritionist so we could work together to achieve a better outcome for farmers. This fueled my interest in animal nutrition and after 10 years in practice, I gave up this work to concentrate on a PhD researching dairy cow nutrition and immunology.

Since completing that in 2017, I have been working as Technical Manager for Trouw Nutrition Ireland where I manage a team that provides veterinary and nutritional support to feed mills and farmers in Northern Ireland and the Republic of Ireland.

I live in Moira, County Armagh with my wife, Joleen, who is a small animal veterinary surgeon and a wonderful mother to our two young girls, Tilly and Daisy.

Background to my Study

Antibiotics are substances that control bacterial activity, either by inhibiting their growth, termed bacteriostatic, or killing them altogether, termed bactericidal (Walsh, 2003). Due to their antibacterial function, antibiotics are used in human medicine to treat and prevent infections and diseases that have a bacterial aetiology. Although difficult to quantify due to other advances in medicine, antibiotics have contributed to an increase in average human life expectancy, up to 29.2 years as in the example of the US between 1900 and 1999 (CDC, 1999).

Antibiotics are also used in livestock production to treat and prevent disease, ensuring the health and welfare of animals, while also controlling zoonotic diseases and ensuring safe food for humans. An additional use of antibiotics are as growth promoters, when low subtherapeutic doses are continually supplemented in animal feed to enhance health and improve feed conversion efficiency and growth rates. Although this growth promotion effect of antibiotics was documented as far back as 1953 (Jukes and Williams, 1953), the exact mechanism of action is still unclear. Some suggestions include a modification of intestinal flora which decrease pathogenic bacteria, while others suggest it is due to a decrease in the loss of the feed nutritive value due to microbial fermentation (Corpet, 2000). Despite these theories, it is notable that the effect of antibiotic growth promotion is more noticeable in animals housed in unhygienic environments (Prescott and Baggot, 1993), which suggests antibiotics mitigate the losses due to disease build up during poor management. The practice of using antibiotic growth promoters in animals, was banned by the European Union in 2006, and the United States in 2017, due to the concern that this practice may lead to the development of antibiotic resistance and that the resistant bacteria could transfer to humans (Hughes and Heritage, 2004, Martin et al., 2015).

Antibiotic resistance occurs when bacteria are no longer susceptible to an antibiotic that would normally have an effective bacteriostatic or bactericidal activity against them (Walsh, 2003). The development of antibiotic resistance can occur as a natural consequence of using antibiotics. This is because in any population of bacteria some will be naturally resistant to antibiotics. Therefore using antibiotics will kill or prevent the multiplication of susceptible bacteria, leaving those with natural antibiotic resistance to survive, selecting for a pure population of antibiotic resistant bacteria (Reygaert, 2018). In addition to natural resistance, antibiotic resistance can be genetically acquired from other bacteria through various mechanisms that include plasmid-mediated transmission of resistant genes (Reygaert, 2018). The misuse and overuse of antibiotics unnecessarily exposes bacteria to antibiotics and accelerates the natural selection process, therefore it is important to use antibiotics only when necessary. In addition, continually exposing bacteria to suboptimal doses of antibiotics, such as growth promoters, allows bacteria to develop mechanisms to survive in the presence of antibiotics and helps in the selection of resistance (Davies and Davies, 2010).

The World Health Organisation (WHO) describes antibiotic resistance is one of the most significant threats to health and food security at present (WHO, 2020). The effects globally on human health could be devastating due to the loss of ability to effectively treat and prevent many common bacterial infections and diseases, resulting in longer duration of sickness and increased numbers of deaths (Michael et al., 2014). It is estimated that antibiotic resistance already contributes to 700,000 deaths annually worldwide, which could rise to 10 million per year by 2050 if there is no action to prevent the development of antibiotic resistance (WHO, 2019b). Similarly, the loss of ability to treat common infections in animals represents a significant health and welfare concern, increasing animal suffering and deaths, along with loss in farm productivity (Bengtsson and Greko, 2014).

Antibiotic resistance in animals is important to human health as there is increasing evidence that the widespread use of antibiotics in agriculture may contribute to the development of resistance to antibiotics used in human medicine (WHO, 2005). There is a concern that bacteria that are resistant to antibiotics could potentially transfer resistance genes between animals, humans and the environment (Landers et al., 2012). Simply, antibiotic resistant bacteria do not respect species barriers and that is why the WHO talks about a holistic and multisector approach, called One Health. This is a call for the human and animal health sectors to work together to try to prevent the development of antibiotic resistance.

In the human health sector, the WHO recommends that health professionals minimize the usage of antibiotics, choose the most appropriate antibiotic (often based on culture and sensitivity) and prescribe the correct dose and duration of treatment (WHO, 2020). In the agriculture sector, the recommendations fall into five focus areas

1. Promote good practice at all steps of food production and processing.

This WHO recommendation ensures that agricultural products do not carry zoonotic diseases and are safe to eat, by reducing the risk of food poisoning. The basis of this is to conduct a hazard analysis and identify critical control points in food manufacturing and processing (Mortlock et al., 1999) as improper procedures have been associated with foodborne disease outbreaks in humans (Panisello et al., 2000).

2. Antibiotics must be under veterinary control

In many countries, antibiotics are supplied without regulation, prescription or even professional advice on usage (Auta et al., 2019, Garcia et al., 2020). For example, a survey of chicken farmers in the Ningxia region in China found that the 59% were able to buy antibiotics without prescriptions and 62.5% did not record their usage (Xu, 2020). This WHO recommendation calls for government regulation to enforce that antibiotics are only available through registered veterinarians so that they correctly identify diseases that are caused by bacteria thereby, preventing antibiotics being used to treat viral or parasitic diseases where they have no effect.

3. Do not use antibiotics for growth promotion or to prevent diseases in healthy animals

As the excessive use of antibiotics (Milanov et al., 2016) and the exposure of bacteria to repeated and prolonged subtherapeutic concentrations of antibiotics (Avguštin, 2012) have been identified as drivers to selection antibiotic resistant gene in animal production. Eliminating both these practices would reduce selection pressure of antibiotic resistant bacteria, including *Salmonella, Escherichia, Campylobacter* and *Enterococcus* genera (Avguštin, 2012).

4. Vaccinate animals to prevent diseases so they remain healthy

Although many diseases, such as bovine respiratory disease may have a viral aetiology, they are frequently complicated by a secondary bacterial infection. Therefore, using vaccines preventatively before risk periods of infectious disease can help reduce the need for antibiotics (Hoelzer et al., 2018). For example, the introduction of circovirus vaccination on a Dutch sow finishing farms demonstrated a decreased antibiotic use from 1.72 animal daily doses/kg/year to 0.56 animal daily doses/kg/year (Raith et al., 2016).

5. Improve biosecurity on farms and improve hygiene and animal welfare to prevent infections.

Instigating a high biosecurity protocol helps to prevent the introduction of disease onto farms, while good hygiene and welfare keeps the disease challenge at lower levels. For example, German pig farms that had higher visitor and staff hygiene regulations and a better cleaning and disinfection procedure had lower antimicrobial usage than those with a poorer visitor and staff hygiene regulations, and poorer cleaning and disinfection procedures (Raasch et al., 2018). Therefore, improving biosecurity and hygiene can support farm practices that help ensure animals stay healthy and a more prudent use of antibiotics.

Examining these widely accepted WHO principles to help prevent the development of antibiotic resistance: -

- The first recommendation is based on food plant and processor hygiene to ensure the production of food that is safe and free from harmful contaminants. Rather than help prevent the development of antibiotic resistance in animals, the recommendation aims to reduce the development of antibiotic resistance in humans by ensuring food does not cause disease, hence reducing the usage of antibiotics in humans.
- Recommendations two and three focus on limiting antibiotic usage so they are used prudently in food production animals. Antibiotics do have a place, but ensuring they are only used when appropriate, reduce unnecessary antibiotic usage and therefore the reduce the risk of antibiotic resistance developing.
- Recommendations four and five focus on keeping animals healthy through increasing vaccination and improving biosecurity and hygiene through good farm management to keep animals healthy.

Keeping animals healthy is an important strategy in the fight against antibiotic resistance as healthy animals do not need antibiotic treatment and the recommendations in the WHO (2020) report quite rightly identify vaccination and management as important methods to achieve this. However, there is no mention of any other strategy to keep animals healthy either in this report or the British Veterinary Association (BVA) policy for veterinarians (BVA, 2019, WHO, 2020). Despite this, the RONAFA review published by the European Medicines Agency (EMA) and European Food Safety Authority (EFSA) highlights the need to consider alternatives to antibiotics to improve animal health (EFSA, 2017). These include nutritional solutions such as improving feed quality and the use of nutritional additives, for example probiotics and prebiotics (EFSA, 2017) and optimizing nutrition to enhance immunity (NRC, 1999). Indeed, in a review by Tang et al. (2017), the potential for non-antibiotic alternates for disease prevention and the need for additional research is stressed. Therefore, there is a need to explore the links between nutrition and health, a statement which is also made in the UK's national action plan to tackle antimicrobial resistance (HMGovernment, 2019)

With nutrition, there have been studies and summaries to explore the links between nutrition and health in humans and animals, but these tend to be in specific contexts. For example, the effects of nutrition including vitamins, trace minerals, amino acids and fatty acids have been reviewed in context to the recent COVID pandemic (Calder, 2020). With production animal nutrition, Sordillo (2016) reviewed the linkages between immunity and disease susceptibility in transition cows, which is a period that dairy cows are known to be faced with a number of hormonal, metabolic and management

challenges leading to increased levels of disease. However, the links between nutrition and health outside specific challenges have been less well explored, with some studies in pigs (Pluske et al., 2018) and poultry (Kogut, 2009), but less evidence in ruminants. Therefore, this needs more investigation, to which this travel scholarship explores the role of functional nutrition in cattle health. Could novel solutions reduce the need to use antimicrobials in food producing animals, particularly ruminants? Could new feed technologies and solutions that show promise in laboratory work have practical applications to increase animal health?

This report discusses findings from farm and university visits to The USA, Norway, England, The Netherlands, France, Switzerland and Spain, detailing examples of good and poor practice, new nutritional technologies that have potential to support cattle health, how management and nutrition could be intrinsically linked and how farmers develop their farm business based around the story of high health.

It is hoped that the outcome of this project will result in practical solutions that improve animal health and welfare, making a difference for famers and food producers. The aim is to increase animal health, reduce antibiotic usage, and increase food animal welfare, all resulting in safer, high quality food and increased consumer confidence in UK animal products.

My study Tour

The initial data gathering stage took place from November 2018 until March 2019 to collate a database of potential contacts detailing their name, organization or association, and country. This involved internet searches limited to universities, commercial nutrition companies and farm businesses using the keywords animal nutrition, dietary management, animal health and antibiotic resistance. In addition, during the Nuffield Farming Scholarship Trust Conference in November 2018 and the Contemporary Scholars Conference in March 2019, attendees were asked if they had farming and nutritional contacts who are working in the study area.

To make the 10-week travel scholarship achievable while being as productive as possible, the list of potential contacts were refined and reduced to the countries with the most contacts and technologies deemed to be novel and promising, resulting in a list of eight countries. Then there was a second data gathering stage on the selected countries to build on the list of potential contacts. This involved internet searches using a wider set of keywords, animal nutrition, feeding, feeding management, diet, dietary management, animal health, prevent disease, antibiotic resistance, antimicrobial resistance, AMR, cattle, cows, calves, pigs and poultry. The contacts searched were also widened to include research organisations, universities, government organisations, international animal nutrition companies, local animal feed suppliers, food processors and manufacturers, and farm businesses.

From this larger list of potential contacts, an initial email was sent outlining the purpose of the Nuffield Farming Scholarship, the study topic being investigated, how this relates to their area of interest and then the aim to meet up in-person and discuss the topic. If no response was received, this was followed up by two more emails and one phone call.

This resulted in a list of people interested in discussing their work and the visits were conducted during a time that best suited the most people. Visits were made to universities, government organisations, international animal nutrition companies, local feed suppliers, biotechnology companies and farm businesses. The date of travel and country visited is described in Table 1. The COVID-19 pandemic in March 2020 mean that travels to Switzerland and Spain were cancelled and these interviews took place by video conferencing.

Table 1: Date and country visited during the study

Date	**Country**
May and June 2019	The USA (Texas, Kentucky, Tennessee and Pennsylvania)
August 2019	The Netherlands
September 2019	Norway
October 2019	England
October 2019	France
February 2020	The Netherlands
March 2020	Switzerland
April 2020	Spain

During the travel scholarship, detailed interviews were conducted with participants. There were no set questions as this may have guided answers and stilted the flow of conversation. In addition,

it was deemed important to capture the passion and drive of the interviewees. Therefore, open questions were asked such as

- How important is antibiotic resistance to you and your work?
- Who is the driving force behind this work? (to differentiate between government, consumer or personal drive)
- What nutritional products/management changes are you working on to help reduce the use of antibiotics
- Are they fully developed and how successful are they?
- How do you see these solutions that show promise in laboratory work having practical applications to increase animal health?
- How do you see your solution being used in the ruminant sector?
- How do you implement your unique product or management technique?
- What is the market demand for you product/service?
- What is the national and local consumer interest in antibiotic resistance and your solutions?
- How much of a value do you think farmers and consumers place on your solutions?

The role of nutrition in animal health

Antibiotic use in beef feedlot production in Texas

The scholarship started in the USA with a visit to the Wrangler Feedyard, a commercial research station for Cactus Feeders in Texas who finish 1.2 million cattle per year. Although the use of antibiotics as growth promoters have been banned in the USA in 2017, they are still used in large quantities in feedlot beef production as confirmed by visits Cactus feeders and Texas A&M university. Most of the beef production in the USA use what is termed the 'big three' feed additives, which are: -

1. Beta agonists, used to increase feed efficiency. This is an increase in the rate of weight gain without any additional feed intake (Johnson et al., 2014). Beta agonists are banned from use in food producing animals in the European Union by EC Directive 96/22/EC, as the maximum safety residue level for human consumption is not known (Woodward, 2009).
2. Monensin (Rumensin®), a monovalent carboxylic polyether ionophore antibiotic used to increase weight gain and improve feed efficiency through changes the rumen bacterial population towards those that favour the production of propionate, a more efficient source of energy for cattle, compared to the other volatile fatty acids, acetate and butyrate (Schelling, 1984, Abrar et al., 2015).
3. Tylosin antibiotic (Tylan®), an in-feed antibiotic used to reduce the incidence and severity of liver abscesses (Nagaraja and Chengappa, 1998).

Figure 1: Hormones, ionophones and antibiotics are supplied and used in large quantities in the Texas feedlot industry. Photo: Author's own.

During the visit, the need to use antibiotics to reduce liver abscesses was questioned, particularly considering that the main cause of liver abscesses is rumen acidosis due to a high starch/low fibre diet (Nagaraja and Lechtenberg, 2007). Wrangler feedlot have conducted an internal study (no reference available), comparing a standard diet which includes Tylosin antibiotic with a higher fibre/lower starch diet. Although there was no control, there was no difference in the incidence of liver abscesses between treatments. However, cattle on the high fibre/lower starch treatment grew slower and took longer to reach slaughter weight, with a mean loss in income of $28 per head compared to the treatment using Tylosin. As Cactus Feeders finish 1.2 million cattle per year, the use of in-feed Tylosin returns $33.6 million and is considered an essential additive throughout the entire six-month finishing period.

When Wrangler feedlot were asked for an opinion on using two different in-feed antibiotics continuously in finishing cattle, it was responded with the strong view that other countries, such as Thailand and China, use more antibiotics in food producing animals therefore, this practice was not considered bad. They also had the view that as Monensin is not used in human medicine, using it presents a lower risk to the development of antibiotic resistance in humans. This is not correct as antibiotic resistance can be transferred between bacteria of different species by a variety of mechanisms (Reygaert, 2018).

Figure 2: Antibiotics, including those expired, are available for anyone to purchase without a prescription. Photo: Author's own.

During a visit to a Texan agricultural shop, the low cost and convenience of antibiotics was demonstrated as systemic and intramammary antibiotics were freely available for purchase without a prescription. This included Critically Important Antibiotics (CIA) as defined by the World Health Organisation (WHO, 2019a), as they are essential in the treatment of human diseases and therefore it is vitally important to maintain their efficacy. The risk of antibiotic resistance developing in CIA would be disastrous for human health. In addition, there was a clearance table for antibiotics near or past the expiry date. These antibiotics may have a reduced activity meaning if used, they deliver a

suboptimal dose to cattle (Verma and Samanta, 2016). As exposing bacteria to a low concentration of antibiotics has been identified as one of the major drivers of antibiotic resistance (Hughes and Heritage, 2004), it is worrying that this route of selling antibiotics could drive antibiotic resistance.

Although the trip started with poor examples of antibiotic stewardship, it is important to document the reality of beef production in Texas. Further studies could explore the reasons why farmers in different parts of the world use antibiotics in production animals. For example, if antibiotics were a higher priced, would this deter farmers in the USA from using them?

Probiotics and Prebiotics

In contrast to the strong view of Texan farmers that their production methods are best way to produce food, farmers in Pennsylvania have the understanding that they are producing food for consumers and therefore should meet their demands. This is because Pennsylvania dairy farmers supply milk into the large population centres of New York, Washington, and Philadelphia where consumers have concerns for the environment, health of cattle and the usage of antibiotics on farm. Therefore, along with management changes such as misting sprays to keep cattle cool during the hot summers, they also consider nutrition as an important tool to keep cattle healthy

In Pennsylvania farms, yeasts are one of the common in-feed additives included in dairy cattle diets as a probiotic. Several companies produce an active dry yeast, which is a process to preserve whole yeast cells through drying, so when used in-feed they reactivate as live yeast. Yeasts alter the ruminal microbial population, thereby changing the volatile fatty acids produced (Putnam et al., 1997) with a metanalyses showing an increase in milk yields and constituents (Poppy et al., 2012). Despite the widespread usage of yeast in dairy farms, the effects on health have been less proven, with studies mainly focused on maintaining milk yields during periods of heat stress (Moallem et al., 2009) and maintaining rumen pH (Chung et al., 2011).

Figure 3: Heat stress is common in Pennsylvania and yeast products have helped with a reduction in heat stress associated mastitis. Photo: Author's own.

Pennsylvania dairy farms also routinely use the polysaccharide prebiotics α-glucans and β-glucans, which are derived from dried components of yeast cell wall. These have been shown to interact with immune cells and bind bacteria to prevent them attaching in the gastrointestinal tract (Kogan and

Kocher, 2007) with some improvements in the markers of mammary health (Ząbek et al., 2013). While on a tour of farms in Pennsylvania with a farm nutritionist, there were many practical examples of farms using yeast cell wall products to reduce the incidence of subclinical mastitis associated with heat stress.

The visit to Pennsylvania demonstrated some practical nutritional solutions to prevent disease however, farmers completely trust the nutritionist to formulate diets and include additives and there were examples where the farmer did not understand the reason why additives were included in the herd ration.

Bees, Honey, Pollen and Propolis

To investigate if nutritional solutions to support human health have potential applications in cattle, a visit was made to a French Nuffield scholar studying insect farming in the West of France.

Unsurprisingly, the main product produced from bees is honey. Honey is widely known for its health benefits as it contains antibacterial substances therefore, is regularly used to assist wound healing, particularly in horses (Bischofberger et al., 2013, Carnwath et al., 2014). However, much of the health properties of honey are due to pollen. Bees get covered in pollen as they collect nectar from plants and use it as a source of amino acids and vitamins. Different pollen has different activities and honey from bees that pollinate the Manuka bush, also known as the New Zealand tea tree bush, has been shown to have a greater antimicrobial activity and an immune modulating effect (Dart et al., 2015).

Propolis is often referred to as bee glue as it is created from resins and tree saps, which bees mix along with their saliva and use it to seal cracks in the hive. Propolis is made into ointments that can be used on wounds due to the natural antibacterial properties.

The bee's ability to self-medicate the hive was talked about during the visit. As a beehive can be a humid environment, if there is a bacterial infection outbreak in a hive, bees visit flowers whose pollen has antibacterial properties to bring back to the hive. If there is a fungal outbreak, they will bring back pollen from flowers with an antifungal activity. Therefore, future studies could explore the activity of different pollens.

Although honey, pollen and propolis have health benefits, the application in animal feed is limited as the quantity produced is small and the human market demands a higher price than the animal market.

Figure 4: Visiting the beehives in France. Photo: Author's own.

Essential oils

The study trip continued with the French company Phytosynthese. Following reports from small French farmers that cattle eating certain plants and herbs were healthier, Phytosynthese was founded in 1996 with an aim to develop and produce essential oils and plant extracts and to replace antibiotics. Essential oils are volatile compounds obtained from aromatic plants, with different activities such an antioxidant, prooxidant and cytotoxic effects (Bakkali et al., 2008, Amorati et al., 2013).

Phytosynthese initially investigate the activity of new products with bacterial inhibition studies. Once this is proven, they conduct their own research to ensure the plant compounds are safe for animals to consume and then carry out animal trials to confirm the health benefits, detail the active ingredient and confirm the mode of action. Rather than single ingredients, they focus on combinations of plant extracts and essential oils that work together in synergism, such as grape, chestnut, rosemary, turmeric, citrus and cinnamon.

An important part of the manufacturing process is encapsulation, where they coat the final product to:

- Preserve the active ingredients, because some ingredients are volatile
- Increase the palatability and acceptance in the feed because some of the essential oils have a very potent smell
- Obtain a suitable sized particle that mixes well in the feed which enables them to get to the site of action in the cattle. This is particularly important to bypass the rumen in cattle

Similar to the previous examples with yeast cell walls, essential oils are used in France to alleviate heat stress in cattle and the associated high somatic cell count in milk. During visits to the Giraud and Marendon family farms, they attribute a low milk somatic cell count over the last two years to the inclusion of an in-feed product that through internal Phytosynthese studies have anti-inflammatory, antioxidant, and immune modulating properties. This has reduced the somatic cell count enough to enable them to produce milk in the bonus quality band during summer, a feat unheard with neighbouring farmers at that time of year.

A relatively new focus for Phytosynthese is the promotion of animal health and welfare, a very important concept to the French consumers. A visit to the supermarket demonstrated this with shelves containing high welfare meat with the quality assurance marks ‘Label Rouge,’ and ‘Blue Blanc Coeur’, giving French farmers some differentiation within a crowded world market.

Figure 5: The promotion of high welfare food in France, on street billboards and at the Sommet De L'Elevage agriculture show. Photo: Author's own.

Therefore, Phytosynthese have been developing essential oils with anti-inflammatory and antioxidant functions to increase cattle health and welfare. These include

- An essential oil with antioxidant properties.
- Propolis from bees to modulate the immune function. Although this is a relatively high price as discussed previously, the internal studies conducted by Phytosynthese reinforce the work carried out by Slanzon et al. (2019) to reduce the incidence of calf diarrhoea and antibiotic usage.

The Curat herd of pedigree Charlois cows in central France use this combination to modulate the immune system and reduce the severity of pneumonia in calves. However, rather than selling beef to the meat processor and the supermarket route, they supply and deliver a weekly meat package to customers who work in Paris office blocks. These customers are extremely keen to know details about their food, such as where it comes from, the breed of cattle, did they have any disease and is it natural and sustainable. Food is important and although essential, it is not just a fuel, it is to be appreciated, enjoyed and is an important part of everyday routine, hence the reason why French people spend a long time at lunch and dinner. They care deeply about animal welfare and want to know the cattle have lived a happy and healthy life. The Phytosynthese products are an important part of the nutritional solutions in improving herd health and the natural and sustainable story that many French consumers' demand.

Figure 6: Patrick Curat and his successful 'Happy Farm' business supplying meat direct to Paris consumers. Photo: Author's own.

In addition to the study trip to France, both Wrangler feedlot and Texas A&M research station have conducted unpublished research on essential oils. Texas A&M concluded that essential oils do have an effect to increase cattle health, but not as large an effect as the standard 'big three' feed additives. Wrangler feedlot confirmed that essential oils do make a difference, but they have less of an economic return when compared to the antibiotics.

Plant fibres

Phytaxis are a Swiss company who have been exploring the use of plant fibres to improve animal health and reduce antibiotic usage. The idea to develop a cattle health product came from the human studies that show dietary fibres, such as inulin and oligofructoses, stimulate the immune system (Anderson et al., 2009). The first animal trials that Phytaxis carried out using in-feed plant fibres produced some undesirable effects on the carcass fat quality. However, the process was refined and Phytaxis have developed a patented process to extract polyphenols and a pure bioactive polymer from structural fibre components (cellulose, hemicellulose or lignin) of two specific plants.

The extract has multiple properties with internal trial work demonstrating polyphenol activity such as: -

1. Antioxidant ability. In the plant, polyphenols and sugars are bound together to form dietary fibre, which limits their biological activity. When the bonds are separated, polyphenols are liberated to exert their antioxidant activity as described in the review by Gessner et al. (2017)
2. Anti-inflammatory effect on the immune system, as discussed by (Gessner et al., 2017).

3. An improvement in intestinal health, either by improving the intestinal barrier integrity (Sandoval-Ramírez et al., 2020) or through modulation of the gut microbiota ,which has been demonstrated in humans (Cardona et al., 2013).
4. An ability to bind to mycotoxins in animal feed (Galvano et al., 2001).

The in-feed products made by Phytaxis are particularly targeted towards increasing young animals' defences against harmful microorganisms, meaning that a bacterial challenge which would normally result in disease are too low to be harmful. As this has an impact on the immune system, it is hoped that there may be benefits not only with intestinal disease, but also other diseases such as pneumonia.

However, a reoccurring theme is that compared to antibiotics, these products are not as effective, yet more expensive, while also needing further future investment to improve and refine their function.

Quorum Sensing

A meeting with academics from Utrecht University in The Netherlands brought on the discussion of quorum sensing. As discussed in the review by Kalia (2013), bacteria produce small molecules, which communicate with other bacteria. When the numbers of signalling molecules are low, this communicates that bacteria numbers are low and they could be defeated by the animal's defences therefore, bacteria remain dormant to evade detection. When the number of signalling molecules are higher, then the population of bacteria is larger. Once they reach a critical threshold, these signalling molecules activate bacteria to change their function, come out of their dormant stage and switch on various behaviours such as the production of biofilm to defend against the immune function.

Some companies, use this knowledge to produce natural plant substances to interfere with the signalling molecules therefore, tricking the bacteria into thinking they are on their own and remain in a dormant phase' as described in the review by LaSarre and Federle (2013). Many of these companies base their activity on garlic, clove and cinnamon to help prevent the bacteria from producing a biofilm protective layer, leaving them susceptible to attack from the immune function.

Although a relatively new company, AHV has been having good on-farm success in The Netherlands and Ireland.

Bacteriophages

Researchers in Barcelona, Nottingham and Loughborough universities are prominent in conducting research with in-feed bacteriophage applications for animals. Bacteriophages are highly specialised viruses that target and kill bacteria and are found abundantly and naturally occurring in the environment (Ackermann, 2003).

De Paepe et al. (2014) describe the way bacteria work, to summarize they: -

- attach to bacteria
- inject their genetic code (DNA) into the bacteria
- this hijacks the internal workings of the bacteria
- the bacteria becomes a factory to produce new bacteriophages

- the bacteriophages replicate in the cell
- numbers of new bacteriophages increase so much they rupture the bacteria and are released into the surroundings
- the cycle continues with bacteriophages targeting new bacteria

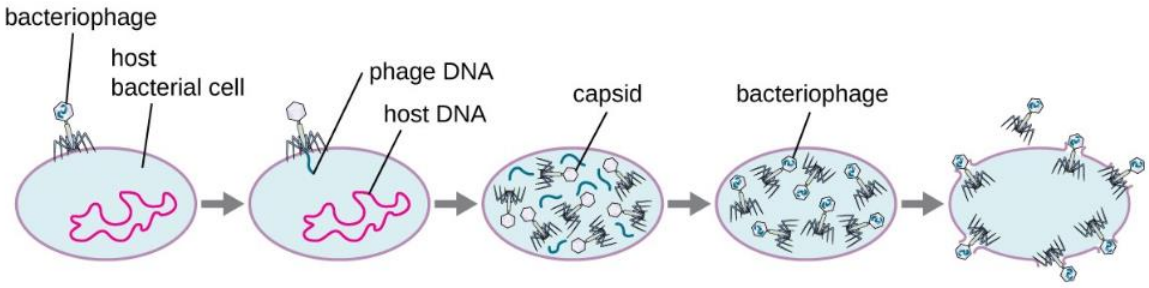


Figure 7: The mechanism through which bacteriophages kill bacteria. Source: OpenStax Microbiology

Bacteriophages operate in a targeted way toward specific bacterial species, leaving others untouched. It was explained that this is important as it means there are no side effects. However, this specific target can limit bacteriophage applications due to differences in regional strain variation of bacteria. For example, a bacteriophage that has activity against a UK strain of Salmonella has been shown not to have activity against a strain from Thailand, due to different surface receptors.

In animal research, bacteriophages have been applied to septicaemia in chickens and colostrum deprived calves. This presents another difficulty as unlike antibiotics which can be delivered in-feed, bacteriophages can be more difficult to get to the site of infection. Research has involved encapsulating bacteriophages to enable them to survive the acid stomach for intestinal infections, infusing into the blood for septicaemia, infusing into the mammary gland for mastitis and delivered via an aerosol for pneumonia.

However, just as bacteria develop resistance to antibiotics, they can develop resistance to bacteriophages, termed phage resistant mutants. Future work to address this is ongoing, such as examining bacteriophages with new targets for example, the sex papillae of bacteria which renders them unable to reproduce or against the toxin producing parts of bacteria making them harmless.

However, research has been difficult to fund as bacteriophage designs are easily reproduced and the technology can be quickly adopted, meaning the research and development investment has limited return. Additionally, the reoccurring paradigm with novel nutritional solutions is true for bacteriophages. They offer great potential as an alternative to the use of antibiotics, but the cost of research to develop them, produce them and deliver them to the site of infection does not have the return in investment compared to the cost effectiveness of antibiotics.

Nutritional management

The Norwegian University of Life Sciences are conducting research in keeping the cow and calf together for 6 weeks after calving. Although removing the calf at birth is best for calf health as it has been shown to reduce incidence and severity of scour (Abuelo et al., 2019), this practice can be

controversial with consumers. Therefore, the 'SmartCare' study is examining the provision of separate cow and calf resting areas while restricting cow-calf contact to feeding times, on the health of the cow and calf. This is a novel example of how nutritional management can potentially have benefits for calf health.

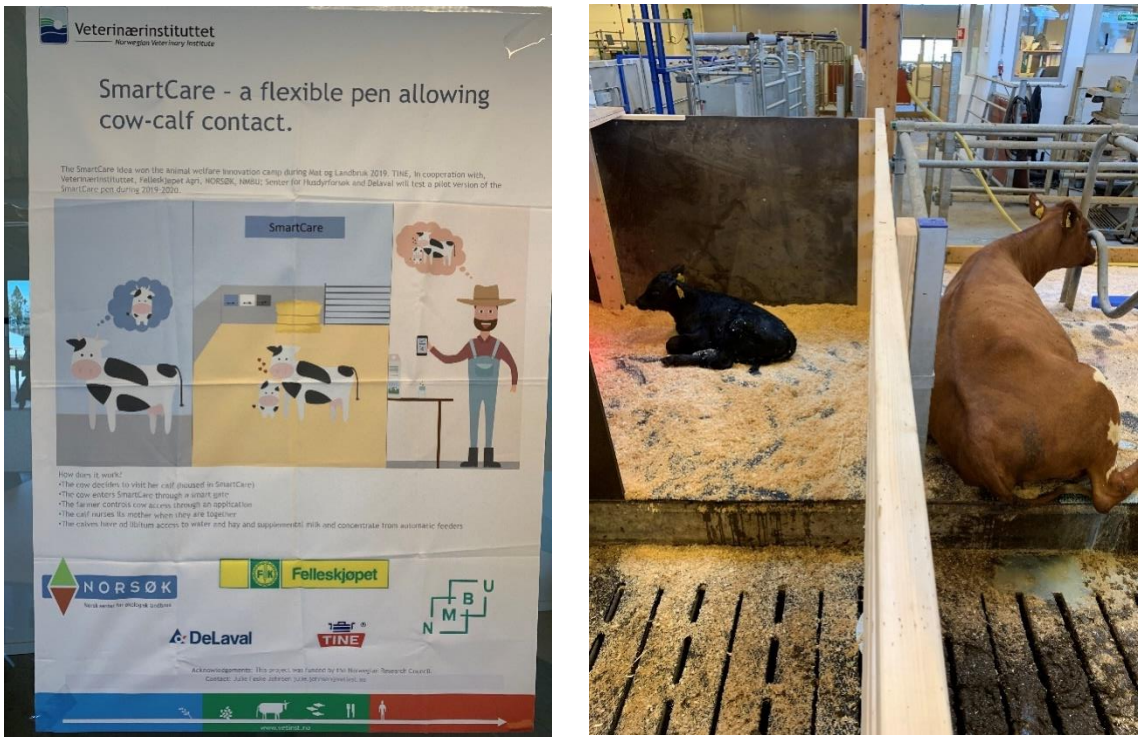


Figure 8: Smartcare, a project investigating cow-calf contact for the first 6 weeks after calving, recognising consumer feelings on calf welfare. Photo: Author's own.

When visiting veal farms in The Netherlands with a veterinarian, there were good examples of the effects of nutritional management on calf heath. Ensuring the milk replacer powder is mixed at the correct concentration and temperature, and excellent hygiene of the mixing plant and feed buckets have been practically shown to be important. In addition, keeping calf feeding time consistent at 12-hour intervals has practically lowered stress and disease in calves. This has been demonstrated during daylight saving time change in spring and autumn, as compared to a sudden change in calf feeding time, changing it by 15 minutes per day over four days reduces the incidence of pneumonia.

These examples are good to demonstrate that in addition to novel solutions, nutritional management can bring benefits to herd health. While visiting the veal farms with the veterinarian and talking to lecturers from Utrecht University, the interconnected relationship between genetics, farm management, medicines and nutrition was discussed. Each of these have an important role to play and to improve herd health is it essential to consider all areas.

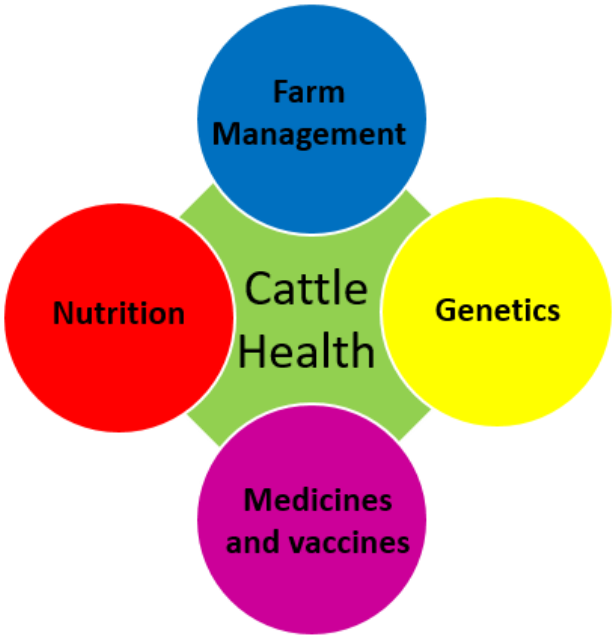


Figure 9: Animal health is an interconnected relationship between genetics, farm management, medicines and nutrition. Author's own.

Conclusions and Recommendations

Antibiotic resistance is a serious threat to human and animal health therefore, it is imperative to explore all solutions to halt its development. This Nuffield Farming Scholarship study trip explored the role of nutritional management and solutions, and their potential to keep cattle healthy to reduce the usage of antibiotics.

There are no nutritional additives that can directly replace antibiotics with regards antibacterial activity. Essential oils have an antibacterial action, but they are not as effective as antibiotics. In addition, bacteriophages need more research and development to improve their activity and enable them to be delivered to the site of infection.

Many of the in-feed nutritional solutions increase cattle immunity and health, thereby helping cattle resist a bacterial challenge that would normally cause disease. Probiotics, prebiotics, essential oils, plant extracts, plant fibres, and quorum sensing have been shown to have positive effects on cattle health however, none of these are a 'silver bullet' solution. It was also found that many of these are not as effective at keeping cattle healthy as when antibiotics are used in this way, while being more expensive than antibiotics and needing investment to improve their activity.

However, it is important to consider cattle health as an interconnected relationship between genetics, farm management, vaccination and nutrition and to take a holistic view to choose the area to make the most difference on-farm. For example, if farm management such as ventilation is poor, no nutritional management or solution will solve the problem and hence will be considered to have failed.

For farmers, this study has demonstrated the successful use of nutritional products to increase herd health and reduce disease. These products should not be considered as a replacement for antibiotics and a good nutritionist can help with recommendations on how to place them to achieve the best on-farm results. Although this is an investment in the herd, there is growing consumer interest in purchasing food products that are from high health herds.

For the nutritionists and veterinary surgeons, there are many potential nutritional solutions however, they do not replace good management. If these products are used on the correct farm and at the correct time, particularly on farms already good at herd management, they can result in herd health benefits. As farmers trust veterinary surgeons and nutritionists to make decisions, it is important to give constructive holistic advice.

For researchers, it is important to continue to improve nutritional solutions to increase cattle health. Antibiotics may not always be so cost effective and the future may really need your work.

After my study tour

This study tour and report has fuelled my interest in further developing nutritional solutions in animal health and welfare in the UK. What struck me most in my report conclusions was the relationship between genetics, farm management, medicines and nutrition and I am passionate in continuing to explore how best to drive this forward to find practical solutions for farmers. Therefore, rather than the end of a project, this is only beginning.

At the start of this journey, one of my aspirations was to further link the veterinary and nutrition industries. With this, I am exploring a new role combining veterinary medicines and nutritional management to completely focus on preventative health. This will be a consultant type role ensuring that farmers benefit from the most appropriate and practical advice for their herd health.

I have endeavoured to share my findings with as many people as possible. During the North of Ireland Veterinary Association (NIVA) February meeting, I arranged for the four 2019 Nuffield scholar veterinary surgeons to present their findings. This was a great opportunity to promote the Nuffield Scholarship, communicating how this is open to veterinary surgeons, which resulted in many probing questions for the scholars. In addition, I have arranged a further NIVA meeting for November 2021 on the Smartcare project in Norway, to make sure veterinary surgeons are updated with the latest and ground-breaking research that I encountered during my travels.

Acknowledgement and thanks

Sincere thanks to my generous sponsor, The Thomas Henry Foundation for making this fantastic opportunity possible.

It's been a real honour and privilege to be part of the Nuffield Farming family and thanks to the Nuffield Farming Scholarships Trust, especially Mike Vacher and Helen Woolley for their hard work and leadership. A special thanks for Wyn Owen for enabling me to be in the first Aberystwyth intake resulting in my Nuffield report gaining university accreditation. I really appreciate the opportunity and thank you for your guidance and support throughout.

I feel extremely lucky to have made lifelong friends in the 2019 Nuffield Scholar group and I am honoured to have shared this journey with you.

Throughout my travels, I have met people who have specially set aside time out of their busy schedules to talk to me about their work and passion with animal health. I can't thank you enough for sharing your insights which has developed my interest, shaped my views, and kindled my interest for the future. Also, many thanks indeed to Garth Boyd in Trouw Nutrition for always seeing the bigger picture and supporting me through this.

To my family and friends, I simply could not have done this scholarship without your support. The largest thanks go to my wife Joleen for your never-ending support and kids Tilly and Daisy for the warmest welcomes on the returns from my travels.

References

ABRAR, A., TSUKAHARA, T., KONDO, M., BAN-TOKUDA, T., CHAO, W. & MATSUI, H. 2015. Effect of monensin withdrawal on rumen fermentation, methanogenesis and microbial populations in cattle. *Animal Science Journal,* 86**,** 849-854.

ABUELO, A., HAVRLANT, P., WOOD, N. & HERNANDEZ-JOVER, M. 2019. An investigation of dairy calf management practices, colostrum quality, failure of transfer of passive immunity, and occurrence of enteropathogens among Australian dairy farms. *Journal of Dairy Science,* 102**,** 8352-8366.

ACKERMANN, H. W. 2003. Bacteriophage observations and evolution. *Research in Microbiology,* 154**,** 245-251.

AMORATI, R., FOTI, M. C. & VALGIMIGLI, L. 2013. Antioxidant Activity of Essential Oils. *Journal of Agricultural and Food Chemistry,* 61**,** 10835-10847.

ANDERSON, J. W., BAIRD, P., DAVIS JR, R. H., FERRERI, S., KNUDTSON, M., KORAYM, A., WATERS, V. & WILLIAMS, C. L. 2009. Health benefits of dietary fiber. *Nutrition Reviews,* 67**,** 188-205.

AUTA, A., HADI, M. A., OGA, E., ADEWUYI, E. O., ABDU-AGUYE, S. N., ADELOYE, D., STRICKLAND-HODGE, B. & MORGAN, D. J. 2019. Global access to antibiotics without prescription in community pharmacies: A systematic review and meta-analysis. *J Infect,* 78**,** 8-18.

AVGUŠTIN, J. 2012. Animal production systems as a selective environment for antibiotic resistance genes. *Acta agriculturae Slovenica,* 100.

BAKKALI, F., AVERBECK, S., AVERBECK, D. & IDAOMAR, M. 2008. Biological effects of essential oils – A review. *Food and Chemical Toxicology,* 46**,** 446-475.

BENGTSSON, B. & GREKO, C. 2014. Antibiotic resistance—consequences for animal health, welfare, and food production. *Upsala journal of medical sciences,* 119.

BISCHOFBERGER, A. S., DART, C. M., PERKINS, N. R., KELLY, A., JEFFCOTT, L. & DART, A. J. 2013. The Effect of Short- and Long-Term Treatment with Manuka Honey on Second Intention Healing of Contaminated and Noncontaminated Wounds on the Distal Aspect of the Forelimbs in Horses. *Veterinary Surgery,* 42**,** 154-160.

BVA 2019. BVA position on the responsible use of antimicrobials in food producing animals. https://www.bva.co.uk/take-action/our-policies/responsible-use-of-antimicrobials/ [Accessed on 04 September 2020].

CALDER, P. C. 2020. Nutrition, immunity and COVID-19. *BMJ Nutrition, Prevention & Health,* 3**,** 74-92.

CARDONA, F., ANDRÉS-LACUEVA, C., TULIPANI, S., TINAHONES, F. J. & QUEIPO-ORTUÑO, M. I. 2013. Benefits of polyphenols on gut microbiota and implications in human health. *The Journal of Nutritional Biochemistry,* 24**,** 1415-1422.

CARNWATH, R., GRAHAM, E. M., REYNOLDS, K. & POLLOCK, P. J. 2014. The antimicrobial activity of honey against common equine wound bacterial isolates. *The Veterinary Journal,* 199**,** 110-114.

CDC 1999. Achievements in Public Health, 1990-1999: Control of Infectious Diseases. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm4829a1.htm [Accessed on 22 August 2020].

CHUNG, Y. H., WALKER, N. D., MCGINN, S. M. & BEAUCHEMIN, K. A. 2011. Differing effects of 2 active dried yeast (Saccharomyces cerevisiae) strains on ruminal acidosis and methane production in nonlactating dairy cows. *Journal of Dairy Science,* 94**,** 2431-2439.

CORPET, D. 2000. Mechanism of antimicrobial growth promoters used in animal feed. *Comptes Rendus de l' Academie d' Agriculture de France,* 85.

DART, A. J., BISCHOFBERGER, A. S., DART, C. M. & JEFFCOTT, L. B. 2015. A review of research into second intention equine wound healing using manuka honey: Current recommendations and future applications. *Equine Veterinary Education,* 27**,** 658-664.

DAVIES, J. & DAVIES, D. 2010. Origins and evolution of antibiotic resistance. *Microbiology and molecular biology reviews : MMBR,* 74**,** 417-433.
DE PAEPE, M., LECLERC, M., TINSLEY, C. & PETIT, M.-A. 2014. Bacteriophages: an underestimated role in human and animal health? *Frontiers in Cellular and Infection Microbiology,* 4.
EFSA, E. A. 2017. EMA and EFSA Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety (RONAFA). *EFSA Journal,* 15**,** e04666.
GALVANO, F., A., P., RITIENI, A. & GALVANO, G. 2001. Dietary Strategies to Counteract the Effects of Mycotoxins: A Review. *Journal of Food Protection,* 64**,** 120-131.
GARCIA, J. F., DIEZ, M. J., SAHAGUN, A. M., DIEZ, R., SIERRA, M., GARCIA, J. J. & FERNANDEZ, M. N. 2020. The Online Sale of Antibiotics for Veterinary Use. *Animals,* 10**,** 503.
GESSNER, D. K., RINGSEIS, R. & EDER, K. 2017. Potential of plant polyphenols to combat oxidative stress and inflammatory processes in farm animals. *J Anim Physiol Anim Nutr (Berl),* 101**,** 605-628.
HMGOVERNMENT 2019. Tackling Antimicrobial Resistance 2019 - 2024. https://www.gov.uk/government/publications/uk-5-year-action-plan-for-antimicrobial-resistance-2019-to-2024 [Accessed 04 September 2020].
HOELZER, K., BIELKE, L., BLAKE, D., COX, E., CUTTING, S., DEVRIENDT, B., ERLACHER-VINDEL, E., GOOSSENS, E., KARACA, K., LEMIERE, S., METZNER, M., RAICEK, M., SURIÑACH, M., WONG, N., GAY, C. & IMMERSEEL, F. 2018. Vaccines as alternatives to antibiotics for food producing animals. Part 1: Challenges and needs. *Veterinary Research,* 49**,** 64.
HUGHES, P. & HERITAGE, J. 2004. Antibiotic growth-promoters in food animals. *FAO Animal Production and Health Paper.* Rome, Italy: Food and Agriculture Organization of the United Nations.
JOHNSON, B. J., SMITH, S. B. & CHUNG, K. Y. 2014. Historical Overview of the Effect of β-Adrenergic Agonists on Beef Cattle Production. *Asian-Australasian journal of animal sciences,* 27**,** 757-766.
JUKES, T. H. & WILLIAMS, W. L. 1953. Nutritional effects of antibiotics. *Pharmacological Reviews,* 5**,** 381.
KALIA, V. C. 2013. Quorum sensing inhibitors: An overview. *Biotechnology Advances,* 31**,** 224-245.
KOGAN, G. & KOCHER, A. 2007. Role of yeast cell wall polysaccharides in pig nutrition and health protection. *Livestock Science,* 109**,** 161-165.
KOGUT, M. H. 2009. Impact of nutrition on the innate immune response to infection in poultry1 1Papers from the Informal Nutrition Symposium, "Modulating Immunity: The Role of Nutrition, Disease, Genetics, and Epigenetics," were presented at the Poultry Science Association 97th Annual Meeting in Niagara Falls, Ontario, Canada, on July 20, 2008. *Journal of Applied Poultry Research,* 18**,** 111-124.
LANDERS, T. F., COHEN, B., WITTUM, T. E. & LARSON, E. L. 2012. A review of antibiotic use in food animals: perspective, policy, and potential. *Public health reports (Washington, D.C. : 1974),* 127**,** 4-22.
LASARRE, B. & FEDERLE, M. J. 2013. Exploiting Quorum Sensing To Confuse Bacterial Pathogens. *Microbiology and Molecular Biology Reviews,* 77**,** 73.
MARTIN, M. J., THOTTATHIL, S. E. & NEWMAN, T. B. 2015. Antibiotics Overuse in Animal Agriculture: A Call to Action for Health Care Providers. *American journal of public health,* 105**,** 2409-2410.
MICHAEL, C. A., DOMINEY-HOWES, D. & LABBATE, M. 2014. The antimicrobial resistance crisis: causes, consequences, and management. *Frontiers in public health,* 2**,** 145-145.
MILANOV, D., LJUBOJEVIĆ, D., CABARKAPA, I. & ALEKSIC, N. 2016. Impact of antibiotics used as growth promoters on bacterial resistance. *Food and Feed Research,* 43**,** 83-92.
MOALLEM, U., LEHRER, H., LIVSHITZ, L., ZACHUT, M. & YAKOBY, S. 2009. The effects of live yeast supplementation to dairy cows during the hot season on production, feed efficiency, and digestibility. *Journal of Dairy Science,* 92**,** 343-351.

MORTLOCK, M. P., PETERS, A. C. & GRIFFITH, C. J. 1999. Food Hygiene and Hazard Analysis Critical Control Point in the United Kingdom Food Industry: Practices, Perceptions, and Attitudes. *Journal of Food Protection,* 62**,** 786-792.

NAGARAJA, T. G. & CHENGAPPA, M. M. 1998. Liver abscesses in feedlot cattle: a review. *Journal of Animal Science,* 76**,** 287-298.

NAGARAJA, T. G. & LECHTENBERG, K. F. 2007. Liver Abscesses in Feedlot Cattle. *Veterinary Clinics of North America: Food Animal Practice,* 23**,** 351-369.

NRC 1999. *National Research Council (US) Committee on Drug Use in Food Animals. The Use of Drugs in Food Animals: Benefits and Risks.,* Washington (DC), National Academies Press (US).

PANISELLO, P., ROONEY, R., QUANTICK, P. & STANWELL-SMITH, R. 2000. Application of foodborne disease outbreak data in the development and maintenance of HACCP systems. *International journal of food microbiology,* 59**,** 221-34.

PLUSKE, J. R., KIM, J. C. & BLACK, J. L. 2018. Manipulating the immune system for pigs to optimise performance. *Animal Production Science,* 58**,** 666-680.

POPPY, G. D., RABIEE, A. R., LEAN, I. J., SANCHEZ, W. K., DORTON, K. L. & MORLEY, P. S. 2012. A meta-analysis of the effects of feeding yeast culture produced by anaerobic fermentation of Saccharomyces cerevisiae on milk production of lactating dairy cows. *Journal of Dairy Science,* 95**,** 6027-6041.

PRESCOTT, J. F. & BAGGOT, J. D. 1993. *Antimicrobial Therapy in Veterinary Medicine*, Iowa State University Press.

PUTNAM, D. E., SCHWAB, C. G., SOCHA, M. T., WHITEHOUSE, N. L., KIERSTEAD, N. A. & GARTHWAITE, B. D. 1997. Effect of yeast culture in the diets of early lactation dairy cows on ruminal fermentation and passage of nitrogen fractions and amino acids to the small intestine. *J Dairy Sci,* 80**,** 374-84.

RAASCH, S., POSTMA, M., DEWULF, J., STÄRK, K. D. C. & GROSSE BEILAGE, E. 2018. Association between antimicrobial usage, biosecurity measures as well as farm performance in German farrow-to-finish farms. *Porcine health management,* 4**,** 30-30.

RAITH, J., TRAUFFLER, M., FIRTH, C. L., LEBL, K., SCHLEICHER, C. & KÖFER, J. 2016. Influence of porcine circovirus type 2 vaccination on the level of antimicrobial consumption on 65 Austrian pig farms. *Veterinary Record,* 178**,** 504-504.

REYGAERT, W. C. 2018. An overview of the antimicrobial resistance mechanisms of bacteria. *AIMS microbiology,* 4**,** 482-501.

SANDOVAL-RAMÍREZ, B. A., CATALÁN, Ú., PEDRET, A., VALLS, R. M., MOTILVA, M. J., RUBIÓ, L. & SOLÀ, R. 2020. Exploring the effects of phenolic compounds to reduce intestinal damage and improve the intestinal barrier integrity: A systematic review of in vivo animal studies. *Clinical Nutrition*.

SCHELLING, G. T. 1984. Monensin Mode of Action in the Rumen. *Journal of Animal Science,* 58**,** 1518-1527.

SLANZON, G. S., TOLEDO, A. F., SILVA, A. P., COELHO, M. G., DA SILVA, M. D., CEZAR, A. M. & BITTAR, C. M. M. 2019. Red propolis as an additive for preweaned dairy calves: Effect on growth performance, health, and selected blood parameters. *Journal of Dairy Science,* 102**,** 8952-8962.

SORDILLO, L. M. 2016. Nutritional strategies to optimize dairy cattle immunity. *Journal of Dairy Science,* 99**,** 4967 - 4982.

TANG, K. L., CAFFREY, N. P., NÓBREGA, D. B., CORK, S. C., RONKSLEY, P. E., BARKEMA, H. W., POLACHEK, A. J., GANSHORN, H., SHARMA, N., KELLNER, J. D. & GHALI, W. A. 2017. Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. *The Lancet Planetary Health,* 1**,** e316-e327.

VERMA, P. & SAMANTA, S. K. 2016. Comparative assessment of antibiotic potency loss with time and its impact on antibiotic resistance. *Comparative Clinical Pathology,* 25**,** 1163-1169.

WALSH, C. 2003. *Antibiotics: actions, origins, resistance,* Washington, American Society for Microbiology (ASM).
WHO 2005. Critically important antibacterial agents for human medicine for risk management strategies of non-human use : report of a WHO working group consultation, 15-18 February 2005, Canberra, Australia.
WHO 2019a. Critically important antimicrobials for human medicine, 6th revision. https://www.who.int/foodsafety/publications/antimicrobials-sixth/en/ [accessed on 14/02/2021}.
WHO 2019b. No Time to Wait: Securing the future from drug-resistant infections. https://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_final_report_EN.pdf?ua=1 [accessed 23/08/202].
WHO 2020. Antibiotic resistance. https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance [accessed 23/08/2020].
WOODWARD, K. N. 2009. Maximum Residue Limits. *Veterinary Pharmacovigilance.*
XU, J. 2020. Antibiotic use in chicken farms in northwestern China. *Antimicrob. Res. Infect. Cont.,* 9.
ZĄBEK, K., MILEWSKI, S., WOJCIK, R. & SIWICKI, A. 2013. Effect of β-1,3/1,6-D-glucan in diet on productivity and humoral and cellular defense mechanisms in sheep. *Acta Veterinaria Brno,* 82**,** 141-146.

978-1-912059-44-7

Published by Nuffield Farming Scholarships Trust
Southill Farm, Staple Fitzpaine, Taunton, TA3 5SH
T: 01460 234012 | E: director@nuffieldscholar.org