Looking beyond antibiotics

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TIME TO VACCINATE

MSD Animal Health

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Content

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Introduction

Antimicrobial resistance (AMR) is one of the most urgent problems of our generation. It is already the cause of 700,000 human deaths every year and this figure is projected to rise to 10 million each year by 2050 if the problem is left unresolved. That's more deaths than are currently caused by cancer (O'Neill, 2016).

Antibiotics are used across agricultural industries, but increasingly pressure is being applied to reduce reliance on these vital medicines, to maintain an effective treatment portfolio for generations to come. The industry is doing this without compromising animal health or welfare and by using a selection of management practices which focus on disease prevention strategies as an alternative to antimicrobial use.

These include high standards of biosecurity to protect farms from incoming disease; good management, husbandry and hygiene practices to curtail the spread of infection within the farm; and high standards of animal welfare to promote general health and a strong immune response.

Key among the preventive measures is vaccination – the process by which the animal gains immunity or resistance to a particular infection. Vaccination has always played a role in modern livestock farming in helping to control infectious disease. By preventing or reducing those infections, vaccination also has the scope to help reduce the need for antimicrobial use.

Through their focus on disease prevention strategies, UK livestock producers have already demonstrated the degree to which they can reduce on-farm antimicrobial use. In October 2017, Defra reported that sales of antibiotics for use in animals in the UK had fallen to their lowest level since records began, exceeding a government target two years ahead of schedule (VMD, 2017).

But further ambitious targets have now been set for every major livestock sector with the aim of continuing this reduction (RUMA, 2017).

The responsible use of antibiotics

The agricultural industry is always going to need medicines for health and welfare, and antibiotics are always going to play an effective role. Their responsible use across all livestock sectors needs to be prioritised so they are only used appropriately when required, using as little as possible but as much as necessary.

Vaccine programmes should be implemented when possible to protect against preventable diseases; reliance should not be on antibiotics to treat the conditions after they occur. However, there will always be occasions when individual animals are subjected to treatable conditions and need effective treatment to protect animal health and welfare.

Vaccines should be administered whenever possible, but when antibiotics are used, due to necessity, vets and producers must use them responsibly in line with animal health plans.

Ultimately, emphasis should be placed on controlling infectious diseases through proactive and robust prevention programmes, in which vaccines play a crucial role and if antibiotics are required, they must be used responsibly.

John FitzGerald, says vaccines have, from the 1960s, made a major contribution to improving farm animal health, welfare and productivity.

"Vaccines are vital components in preventing a wide variety of diseases and a key tool in reducing antibiotic use.

"Vaccination mimics infection and so it provides immunity without the animals succumbing to the disease. Thus, the animal becomes resistant to the disease before it becomes infected and so, if the animal is exposed to the infection at a later date, it will usually not show any signs, or only minor signs, of illness. This results in animals being healthier and also requiring less antibiotic treatment – beneficial to the animal, the farmer and the consumer."

John FitzGerald, Secretary General of the Responsible Use of Medicines in Agriculture (RUMA) Alliance

Professor Nigel Gibbens, the UK's Chief Veterinary Officer, has urged the industry not to rest on its laurels but to continue to ensure antibiotics are used responsibly so they remain effective for future generations. He says: "We need to make progress on diagnostics, vaccines and management practices and better understand and mitigate risks from the environment. Science has an important role to play."

The role and success of vaccination is well understood and has been extensively demonstrated in the field of human medicine. The immunisation vaccination provides has been described by the World Health Organisation (WHO) as, arguably, the single most cost-effective preventive health intervention. WHO has also identified the role of vaccination in limiting the spread of antimicrobial resistance.

Antimicrobials and antibiotics

The difference between the terms antimicrobial and antibiotic is simple. Antimicrobial is an umbrella term used to describe a drug designed to kill or slow the spread of a range of microorganisms. These could be bacteria, viruses, protozoa or fungi. An antibiotic is a type of antimicrobial, designed specifically to target bacteria.

Polio, which has been all but eliminated around the world, is perhaps the most well-known example of a vaccination success in human health. In agriculture too, there have been numerous sector-specific successes, one of which was recently seen in the campaign against *Salmonella* in the poultry industry, which began in the late 1980s and whose breakthrough came with the widespread vaccination of hens. This was driven by the British Egg Industry Council Lion Code of Practice which set out standards for flock biosecurity and bacteriological testing and stated flocks must be vaccinated against *Salmonella enteritidis* (Cogan and Humphrey, 2003). So successful has the campaign been that *Salmonella* infection in the human population has plummeted, from a peak in England and Wales of 33,000 in 1997 (Cogan and Humphrey, 2003) to 8,558 in 2015 (Public Health England, 2016).

This significant success was followed by revised advice from the Food Standards Agency in 2017 that children, pregnant women and the elderly could now safely eat raw or lightly cooked eggs produced under the British Lion Code of Practice. The industry has also seen a significant reduction in antibiotic use in the poultry sector, by 44% between 2012 and 2015 (British Poultry Council, 2016).

Aquaculture is a sector which has embraced positive disease prevention, and as a result has seen major reductions in antibiotic usage. The Norwegian salmon industry saw a dramatic decline in antibiotic use to control vibriosis and furunculosis following the introduction of a combination vaccine. Today, that industry's antibiotic use is virtually nil, while salmon production has soared, from 15,000m tonnes in the 1990s to around 50,000m tonnes today (Kibenge et al., 2012).

What is antimicrobial resistance?

Antimicrobial resistance (AMR) is the ability of microorganisms to survive or grow in the presence of an antimicrobial agent which is usually sufficient to inhibit or kill that species of microorganism. This resistance comes about because microorganisms – like all living creatures – can adapt to their environment over generations. Those which develop an adaptation which allows them to resist an antimicrobial drug, are those which survive. These go on to multiply, passing their resistant traits on to the next generation and eventually creating a resistant population. Although this is a natural phenomenon, there is evidence that inappropriate and excessive use of antimicrobials speeds the rate at which resistance develops.

The development of AMR lies behind the international drive to cut antimicrobial use. If the medical and veterinary professions can reduce the need for the use of antimicrobials, they will prolong the efficacy of these drugs and retain their life-saving properties for the benefit of all.

Antibiotic use in fish in relation to Norwegian salmon production

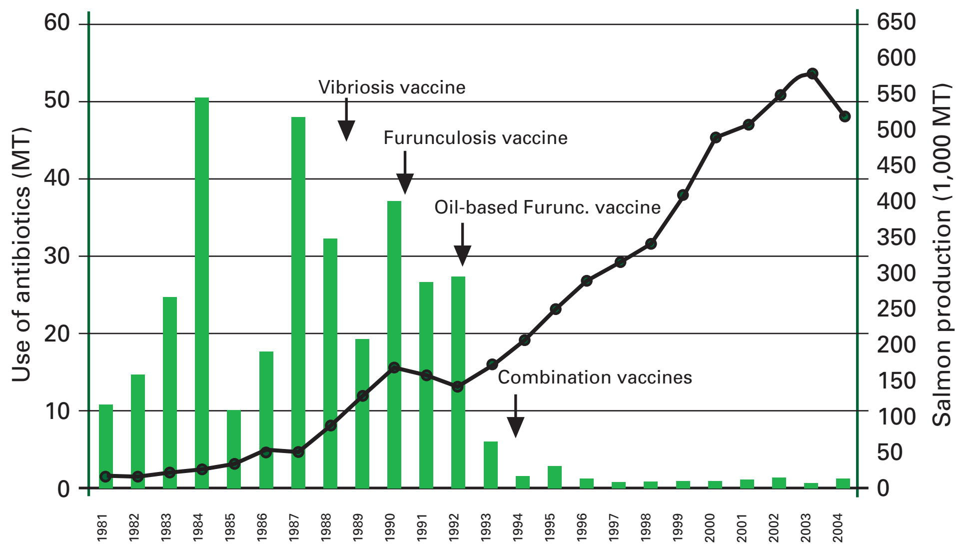

Fig. 1. Antibiotic use in fish (green bars) in relation to Norwegian salmon production (black line), 1981–2004. Note the dramatic drop in antibiotic use following the introduction of oil-based vaccines in 1992. These vaccines offered high protection against vibriosis caused by *Listonella (Vibrio) anguillarum* and furunculosis caused by *Aeromonas salmonicida* (Håstein et al., 2005).

Source: Kibenge et al., 2012

Similarly, the pig industry – which has been blighted by porcine reproductive and respiratory syndrome (PRRS) with its high economic cost to the industry – has now found effective methods of eliminating the PRRS virus using a vaccination plan together with high levels of on-farm hygiene and biosecurity (Rathkjen and Dall, 2017).

These and other farming success stories have demonstrated that vaccination can significantly reduce the need for antimicrobial use when used as part of an improved management strategy, while creating healthy stock and driving forward efficiencies of production. It is quite possible for these win-win situations to be replicated across the agriculture industry, and a range of new technologies can help further speed this process along its way.

These include innovations such as multivalent vaccines which immunise against up to 10 different pathogens with one injection; nasal vaccine sprays, which closely mirror the route of real-world infection and protect against respiratory disease; and needle-free vaccination such as the IDAL system, which uses a high-pressure stream of fluid to vaccinate pigs in the dermis. These technologies can not only improve the efficiency and efficacy of vaccination, they can enhance animal welfare while raising standards in product quality and animal performance. Some are already widely used across commercial farms and they have the scope to facilitate the uptake of vaccination in the years ahead.

This publication seeks to explore the potential of vaccination to control or prevent infection across a range of key livestock diseases and as a result, to produce healthier stock, to improve efficiency and productivity, and reduce the need for antimicrobial use in the agriculture sector.

How can vaccination and immunisation help with AMR?

When an animal or human is vaccinated it gains immunity or resistance to a particular infection. By reducing the incidence and spread of that infection, immunisation (through vaccination) will inevitably lead to a reduction in the need for antimicrobials, which are generally used to treat infection after it has occurred.

"Vaccines can help limit the spread of antibiotic resistance. The global increase in disease caused by drug-resistant bacteria, due to overuse and misuse of antibiotics, is a major public health concern.

"Vaccinating humans and animals is a very effective way to stop them from getting infected and thereby preventing the need for antibiotics. Making better use of existing vaccines and developing new vaccines are important ways to tackle antibiotic resistance and reduce preventable illness and deaths."

World Health Organisation (WHO), 2017

Beef and dairy

An introduction to the UK beef and dairy sectors

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Ruminants are unique in their ability to use by-products of food processing and fibrous feedstuffs which are not digestible by humans to produce very high-quality protein. Milk, beef and veal make a huge contribution to feeding the global human population.

> *“Milk, beef and veal make a huge contribution to feeding the global human population.”*

All those involved in the livestock industry, including vets and farmers, are responsible for the health, welfare and productivity of food-producing animals, the quality and safety of the food they produce and protecting the environment. As such, we are integral to the concept of ‘One Health’ which encompasses animal health, human health and environmental health.

There is perhaps no area where the ‘One Health’ approach is more relevant than in the global fight against the development of antimicrobial resistance. Although the cattle industries are relatively modest users of antibiotics on a UK, EU or global scale when compared to human health, they nevertheless need to use medicines responsibly. In the most part this means using as little as possible and only using antibiotics when they are required to treat disease. Furthermore, it means avoiding the use of medicines critical to human health.

The most effective way to reduce antibiotic use in cattle is to prevent disease through animal breeding, good hygiene, optimising nutrition, improving animal accommodation and all aspects of animal husbandry through herd health planning and vaccination. That is the proactive management of a herd for health, welfare and productivity. Healthy animals don’t require treatment.

"Healthy animals don't require treatment."

However, even though vaccines are available for many common diseases including neonatal diarrhoea, bovine respiratory disease (BRD), mastitis, bovine viral diarrhoea (BVD), bovine herpes virus 1 (BoHV-1/IBR), clostridial and other diseases around the world, the majority of cattle go unvaccinated. Not all vaccines will be effective 100% of the time; these diseases are complex and in some cases hard to control. However, we should not be repeatedly treating sick cattle year after year with antibiotics without using every tool we have at our disposal to prevent disease, including vaccination.

Needing to treat cattle with antibiotics is costly in financial terms as well as wasteful of resources. Sick animals, even if they don't die, grow slower, need more feed, and have less productive lives than healthy animals. Veterinary medicines are costly, but investment in disease prevention through vaccination is likely to have a far more positive cost-benefit than the reactive use of antibiotics to treat pre-existing disease.

Even now, many antibiotics are given to cattle which do not need them, when other preventive or therapeutic approaches would be more appropriate. This results in cost to the farmer, productivity losses and an increased risk of antibiotic resistance developing on farms. We need antibiotics when animals are sick, but we must do all we can to preserve their effectiveness by using them as little as possible.

"We need antibiotics when animals are sick, but we must do all we can to preserve their effectiveness by using them as little as possible."

Some in the industry call for more vaccines to be developed, but we could do so much more with the ones we already have if we used them appropriately in all herds. Cattle producers should work with their vets to ensure they are using vaccines appropriate for their herds, are storing them correctly and administering them in the correct way, at the correct times and to the correct cattle.

"Cattle producers should work with their vets to ensure they are using vaccines appropriate for their herds."

Professor David C Barrett

Cattle disease examples

BVD

Bovine viral diarrhoea (BVD) is a highly contagious disease of cattle which suppresses the animal's immune system and increases its susceptibility to other disease. Much of the damage BVD causes to the beef and dairy cattle industries is through secondary infection. Classic effects of either primary or secondary infection include infertility, abortions, calf scour and pneumonia. Some of the secondary effects are typically treated with antibiotics, particularly in calves.

The between-herd prevalence of active BVD infection in the UK is estimated to be 20% (ADAS, 2015) and the cost of the disease to the UK cattle (beef and dairy) industry is around £40 million/year (Bennett and Ijpelaar, 2003). The mean cost per cow per year is £46.50, a cost mostly attributed to fertility losses (Yarnall and Thrusfield, 2017). However, studies on which this estimate is based are probably vastly underestimating the financial cost of secondary infections due to immune suppression (Yarnall and Thrusfield, 2017).

A control strategy for BVD revolves, primarily, around preventing the birth of persistently infected (PI) calves, which result when the dam is infected with BVD in the first 120 days of gestation. A PI calf remains infected throughout its life and constantly sheds the virus, serving as a permanent source of infection for other animals. Vaccination of female, adult breeding stock to protect them from viral infection during pregnancy is the central pillar of BVD control, alongside testing, identifying and removing PI animals from herds. Vaccination also reduces the incidence of infertility associated with BVD infection, and reduces adverse clinical effects seen in acutely infected youngstock, such as a rise in temperature, reduced immune cell counts, and subsequent virus shedding (Guazzetti et al., 2004; Newcomer et al., 2015; Valla et al., 2008). However, in the UK, vaccination is only currently undertaken in 27% of eligible stock (MSD, 2017).

BVD control and eradication strategies are centred around surveillance, vaccination and identification and removal of PIs. This approach is high on the UK agricultural sector's agenda, with national eradication schemes already adopted in Scotland and Northern Ireland, and other schemes being rolled out in England and Wales. Further research is required to quantify antimicrobial use in animals that require treatment of secondary diseases as a consequence of immune suppression due to BVD virus infection.

BRD/pneumonia

Bovine respiratory disease (BRD) is a complex of diseases often referred to as pneumonia. It is the biggest cause of death in calves from weaning to 10 months (Statham, 2013), and is caused by a range of pathogens, including viruses and bacteria. These infective agents invade the respiratory tract and can quickly result in permanent damage to the lungs. Death can result within as little as 24 to 36 hours of clinical signs appearing, and surviving animals can suffer a growth check which could impact their productivity for life.

Around half of all cattle herds are thought to be affected with BRD and within those herds, the prevalence of the disease is estimated at 28% for dairy and 52% for beef (ADAS, 2015). The high prevalence is backed up by abattoir data which notes lung damage as the cause of 23.3% of problems found in calves at post-mortem inspection in abattoirs (Watson et al., 2011). Lung damage is associated with both slower growth and lower carcase grades (Williams and Green, 2007).

The cost of the disease to the industry is estimated at £50 to £80 million (Barrett, 2000; Johnson, 1999), or between £30 and £500 per affected calf (ADAS, 2013; Andrews, 2000; Scott, 2017; Statham, 2013). The wide variation in these figures is a result of the difficulties associated with obtaining absolute prevalence figures both between and within herds in the UK, and also the complexities associated with quantifying the effects of infection during an outbreak. The impact on mortality resulting from an outbreak is estimated as 1.62% (ADAS, 2015), but long-term morbidity (reduction in liveweight gain and effects on long-term productivity) is more difficult to quantify from the literature.

Antibiotics are commonly used for the treatment of BRD, and anecdotally, a substantial proportion is used for this purpose on farms in the UK. This is driven, in part, by frequent repeat treatment for recurring cases and blanket treatment of whole groups, despite the lack of evidence to support this approach (Scott, 2017).

There is scope to reduce the need for antibiotic use through better disease prevention, which, for such a multifactorial disease, should be based on improving biosecurity, husbandry and environment, and providing protection through vaccination. Since only 17% of eligible animals are currently vaccinated (MSD, 2017), there is an opportunity to significantly improve protection across the whole national herd. With a wide range of vaccines available, protection can be tailored to the individual farm based on the rearing system and pathogens present.

A field study conducted in the Netherlands sought to quantify the link between effective vaccination and therapeutic antibiotic use. It showed that controlling respiratory disease through the vaccination of young calves led to a reduction in daily doses of antibiotic by 14.5% on 40 veal farms (Vahl et al., 2014).

Neonatal scour

Diarrhoea or scour in the new-born calf is widespread in the farming industry and under reported. A survey of over 1,000 farmers conducted in 2010 suggested over 70% of farms had experienced deaths in calves due to scour (Intervet, 2010). Recent estimates suggest diarrhoea causes the death of 1-2% of calves born in the UK (ADAS, 2015). Surviving animals experience reduced growth rates as a result of damage to the gut, and reduced food conversion efficiency (ADAS, 2015). With well over half the UK's dairy and beef units affected (ADAS, 2015), neonatal scour costs the cattle industry around £11 million a year, or £58 for every animal affected (Bennett and Ijpelaar, 2003).

Once an outbreak has occurred, treatment should be focused on electrolyte and fluid therapy to replace lost fluids. As the main causes of scour are non-bacterial, treatment with antibiotics is often inappropriate – yet they are commonly used. Historically, antimicrobials could be included in ready-mixed milk powders to feed calves on a unit as a method of disease prevention. This strategy was banned by the Veterinary Medicines Directorate (VMD) in 2012 and should no longer be practised. In addition, unlicensed use of oral antibiotics to treat scour can upset the balance of the calf's natural gut microflora.

Calf scour is best controlled by preventive vaccination of breeding cows and improved management practices, with particular attention paid to the environment, hygiene and diet. Plenty of colostrum should be fed as it contains high levels of antibodies which are vital to fight infection in very young calves. By vaccinating the cow, prior to calving, against the key pathogens known to cause nearly half of scour cases – rotavirus, coronavirus and *E. coli* – immunity is passed through the colostrum to the calf, which is then better able to fight disease early in life (AHDB, 2017).

This improved immunity in the calf to prevent disease occurrence could be expected to reduce the need for antibiotic use, although quantifying this reduction requires further research. However, only 13% of eligible animals are currently protected by vaccination (MSD, 2017).

IBR

Infectious bovine rhinotracheitis (IBR) is a respiratory disorder caused by bovine herpesvirus type 1 (BoHV-1), but this virus also causes a range of other problems to varying degrees, including poor fertility (Graham, 2013; Nettleton and Russell, 2017). Infected dairy cows also exhibit a drop in milk production while calves infected with BoHV-1 can go on to develop fatal secondary bacterial respiratory infection (Nettleton and Russell, 2017). The effects of BoHV-1 are particularly damaging in a naïve herd suffering exposure to the virus for the first time. The virus also establishes a lifelong latent infection in individuals which can be reactivated, and continues to spread at times of stress (Nettleton and Russell, 2017). Infection can be a barrier to international trade in livestock and semen, particularly to countries which have eradicated the disease or categorised it as notifiable.

In the UK, BoHV-1 is estimated to be present in over 70% of herds (Nettleton and Russell, 2017) and costs the industry up to £36 million (Bennett and Ijpelaar, 2003; CHAWG, 2014;). Even subclinical infection is estimated to cost £200 per year per dairy cow in lost income due to milk loss (Stratham et al., 2015).

However, control measures, including BoHV-1 marker vaccines, are effective and eradication is possible over a period of time (Nettleton and Russell, 2017). But currently only 22% of eligible cattle are vaccinated against the disease (MSD, 2017) and many more would need to be enrolled to achieve this aspiration. As well as reducing the clinical disease and its spread (Nettleton and Russell, 2017), vaccination has been shown to improve fertility, increase milk production and reduce culling (Raaperi et al., 2015). Research is needed to establish the extent to which antibiotic use could be reduced through the control of BoHV-1, particularly with respect to its involvement in respiratory disease.

Mastitis

Mastitis is one of the most significant and complex diseases affecting dairy cows and has a high financial and welfare cost. Caused by mammary infection from a wide range of pathogens, its average incidence on UK dairy farms is 47 to 65 cases per 100 cows per year (Down et al., 2016). It occurs in its clinical form in 65% of herds (ADAS, 2015), although it exists in every dairy herd to some extent. The annual cost to the UK industry is £200 to £300 million (Bennett et al., 1999; Green, not dated; Hillerton and Berry, 2005) while the total cost of a severe case is calculated at £435.80 per affected cow (Kossaibati and Esslemont, 2000). Milk production can drop by over 400kg per lactation for a clinical case (ADAS, 2015).

Clinical cases require prompt treatment which usually takes the form of antibiotics administered via intra-mammary tubes and/or systemic injections. Some products contain antibiotics considered critically important for human health.

During the 1970s, the National Institute for Research in Dairying released the Five Point Plan for mastitis control which focused primarily on contagious pathogens (passed from cow to cow) and was widely adopted by farmers in the UK. One of the focus points was implementing blanket antibiotic dry cow therapy: instilling antibiotics in the udders of all milking cows at the point of drying off, to cure any existing infection and as an attempt to prevent new infection during the dry period.

The Five Point Plan resulted in significant progress in the control of mastitis in the UK, particularly with respect to contagious pathogens. However, the plan did little to tackle ‘environmental’ pathogens – those which are picked up by the cow from the environment. These are controlled via attention to environmental hygiene, and dry cow antibiotic therapy is not as applicable, as the bacteria involved do not tend to persist in the udder from one lactation to the next. In the early 2000s, internal teat sealants were introduced, which contain no antibiotic, but provide a physical barrier to ascending infection throughout the dry period, preventing new infections during this time.

Today, the UK dairy industry as a whole is moving away from the concept of administering antibiotic to all cows at drying off, and towards ‘selective dry cow therapy’, where cows deemed at low risk of having infection at the point of drying off, are given teat sealant only, and no antibiotic, as routine.

The original Five Point Plan has been superseded in the UK by the AHDB Dairy Mastitis Control Plan, an approach which takes into account all manner of data from an individual farm, including disease infection patterns from somatic cell count data and monthly milk recordings in addition to bacteriology results, to inform a specific action plan for the farm in question.

One vaccination is available which can also play a part in control, depending on pathogens present on the farm; research is ongoing in this area. However, an effective control strategy is all-encompassing and may include almost any aspect of animal husbandry and environment management, ranging from milking routine to the choice of bedding.

Sheep

An introduction to the UK sheep sector

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> *"Lamb is a high-quality premium protein produced extensively on a largely grass-based diet."*

Lamb is a high-quality premium protein produced extensively on a largely grass-based diet. There seems to be a sheep-shaped niche within many of our UK farming systems, whether as part of an arable rotation or high on a hillside within one of our national parks. The sheep farms I enjoy visiting showcase our industry at its best and have the potential to demonstrate good health, wealth and welfare, for both sheep and shepherd.

Within the UK sheep industry, we do not use large quantities of antibiotics, so our usage per head is low. However, the issue for the sheep sector is not necessarily how much antibiotic is used but the way in which they are used on some farms. No one doubts the importance of using antibiotics appropriately in the treatment of clinical disease – whether to treat a ewe unable to stand without pain due to footrot, or to rescue a lamb with pneumonia after a stressful journey, or a wet and windy night. The challenge we have is to prevent these cases occurring in the first place and here, alongside appropriate nutrition, hygiene and attentive shepherding, we have some great tools in the shape of vaccinations.

> *"No one doubts the importance of using antibiotics appropriately in the treatment of clinical disease."*

Vaccination works by boosting immunity and protecting the flock from the threat of disease over a reasonable length of time. In contrast, antibiotics can never be used in this way: they can only ever be considered as short-term sticking plasters. It is always inappropriate to use them habitually to prevent or guard against disease.

Efficiency and a low cost of production are important drivers for successful sheep farming.
It is primarily by controlling these factors that enables a sheep farmer to run a robust business - a business that can thrive in the years when both the price of lamb and the weather are favourable, and survive in the years when they are not.

Veterinary costs are important to consider, although I divide them into 'good' costs and 'bad'. A bad veterinary cost is one that involves disease, deaths, loss of production and a failure to thrive with all the associated costs of treatments, increased handling, poor growth rates and stress for the shepherd. In stark contrast, a good veterinary cost is the investment in robust preventive health planning which promotes good health and welfare for the flock and provides peace of mind for the shepherd.

"A good veterinary cost is the investment in robust preventive health planning which promotes good health and welfare.

"It is essential we maintain access to antibiotics as we will continue to need to use them appropriately when disease strikes."

It is essential that we maintain an access to antibiotics as we will continue to need to use them appropriately when disease strikes. However, it is the responsibility of every one of us, both shepherds and sheep vets, to minimise the risk of disease by maximising flock health. One of the simplest ways to achieve this is by appropriate vaccination against the common threats.

Dr Fiona Lovatt

Sheep disease examples

Lameness (footrot)

Lameness is one of the most serious health and welfare issues in the sheep industry and is an increasingly unacceptable sight to the general public. Severe footrot (SFR) or interdigital dermatitis (ID) are found in 90% of lame sheep (Winter et al., 2015), and both are caused by the bacterium, *Dichelobacter nodosus*.

Sheep or lambs affected by average severity footrot lose 0.5 to 2.5kg in weight (Nieuwhof et al., 2008) with severely infected lame ewes having a body condition score under 2.5 (Wassink et al., 2010) (on a scale of 1-5, where the target score is between 3 and 3.5 for most of the sheep year). The cost of lameness to the British industry is £24 million to £80 million each year (Nieuwhof and Bishop, 2005; Winter and Green, 2017), or £89.80 per affected ewe (ADAS, 2013). This cost is accounted for by indirect costs such as reduced flock performance, extra feed required for thin ewes or slow-growing lambs and labour, in addition to the direct costs of treatment, which largely comprises footbathing and injections of antibiotics. Additionally, use of footbaths containing antibiotics does still occur on farms (off-label and often inappropriately), which can make a large contribution to on-farm antimicrobial use.

The national prevalence of lameness was recorded in a survey of 809 English sheep farmers as 10.6% in 2004 (Winter et al, 2015). Subsequently, the Farm Animal Welfare Council (FAWC) set a target for the industry to reduce lameness to less than 5% by 2016, and under 2% by 2021. The Five Point Plan was developed by FAI Farms (an independent research organisation dedicated to providing sustainable solutions to challenges encountered in agriculture) and adopted by the wider industry. The plan involved culling, vaccination, quarantine, early treatment and avoidance of exposure to the causative bacteria (through better hygiene, husbandry and management). During the initial on-farm trial of the Five Point Plan, the mean monthly antibiotic treatments per 100 ewes fell from 3.8 to 1.4 within the first year, and was maintained at less than 0.3 treatments per 100 ewes per month in the second and third year of implementation (Clements and Stoye, 2014).

By 2013, a postal survey suggested lameness prevalence in the UK had declined to 4.9% (Winter et al, 2015). When vaccination is used in conjunction with the other four parts of the Five Point Plan, the annual cost of lameness, its treatment and prevention in a flock can decline to just £3.30 per ewe in the flock per year (University of Reading, not dated).

This demonstrates the value of vaccination in raising flock immunity and suggests its continued application as part of the Five Point Plan could lead to further reductions in the need for antibiotic use. However, the uptake of vaccination currently stands at just 16% of eligible animals (MSD, 2017).

Abortion

Around a quarter of all lamb losses are the result of abortion or stillbirth (HCC, 2011). The two main causes are enzootic abortion (EAE) and toxoplasmosis, which account for 52% and 25% of the cases submitted to government laboratories (HCC, 2011), draining £24 million and £12 million from the national flock respectively (Bennett and Ijpelaar, 2003). Vaccines are available to protect against each of these diseases, although the current levels of vaccination, 36% for enzootic abortion and 22% for toxoplasmosis (MSD, 2017), leave the majority of the UK flock exposed to infection.

EAE is caused by the bacterium, *Chlamydophila abortus*, which tends to cause losses in the last weeks of gestation. It is highly contagious, so infected ewes should be isolated and antibiotic treatment is sometimes used to reduce the number of abortions during an outbreak. In addition, there is anecdotal evidence to suggest that in some areas, blanket antibiotic therapy is used for all ewes in advance of lambing to try and prevent outbreaks, against industry advice. However, the benefits of antibiotic control are limited, and because antibiotics don't prevent subsequent infections, in theory, further antibiotic may be required year-on-year to limit abortions (NADIS, not dated (a)). An infected ewe and her lambs will continue to shed *Chlamydophila* at subsequent lambings, adding further to EAE's long-term cost.

Toxoplasmosis is caused by the protozoan parasite, T*oxoplasma gondii*, which is spread in pasture, water and feed contaminated by cat faeces. Untreatable in sheep, it causes stillbirths and weak lambs alongside abortion. A preventive vaccination strategy has the potential to save £85 to £128 for every aborted ewe (NADIS not dated (a); Wright et al., 2014).

Both EAE and toxoplasmosis are zoonotic diseases, presenting risk to human health; in particular, to women during pregnancy (NADIS, not dated (a)).

Clostridial diseases and pasteurellosis

The pathogens responsible for clostridial diseases and pasteurellosis are both present in healthy sheep and the environment, but stress or trigger factors, such as management procedures or nutritional change, can lead to the onset of disease. In either case this is often rapid. Intensive blanket treatment of flocks with antibiotics in the face of outbreaks, although commonly undertaken, is rarely effective and in most cases, the animal is found either dead or dying (HCC, 2007). Deaths usually occur in lambs (but sometimes in ewes) and many cases of early lamb death are caused by inadequate vaccination of ewes against either disease (MSD, not dated).

Clostridial diseases are the most common cause of sudden death in all ages of sheep (Lewis, 1998; MSD, not dated) while around 13% of lamb deaths are attributable to pasteurellosis (AHDB, 2016). There is little published information about the economic value of these losses, but where effective vaccination exists there are few flocks where vaccination would not be financially beneficial and improve animal welfare (NADIS, not dated (b)).

Clostridial bacteria are widespread in soil and occur in small numbers in the gut of healthy sheep, but when they multiply in the animal, they release toxins causing a range of different clostridial diseases (AHDB, 2013). These may affect the digestive tract and internal organs (eg pulpy kidney), damage muscle and circulate in the blood (eg blackleg), or cause nervous damage (eg tetanus).

Similarly, pasteurellosis results from rapid multiplication of the bacteria *Mannheimia haemolytica* (previously *Pasteurella haemolytica*) and *Bibersteinia trehalosi* (previously *Pasteurella trehalosi*), both of which are found in the pharynx and tonsils of healthy stock.

M. haemolytica septicaemia causes sudden death in lambs up to 12 weeks, often as colostral immunity wanes, but also causes fatal pneumonia in older ewes (Lovatt et al., 2014). Systemic pasteurellosis due to *B. trehalosi* typically affects weaned lambs in the autumn and early winter. Very early detection of pasteurellosis gives antibiotic therapy, usually with oxytetracycline, an improved chance of success. However, sheep and lambs can be protected against clostridial diseases and pasteurellosis, through an effective vaccination regime, reducing the demand for blanket antibiotic treatment in the face of outbreaks. Multivalent vaccines – which can protect against different clostridial diseases and pasteurellosis in one product – are considered to be the most practical way of reducing mortality from these infections. By vaccinating the ewe at the appropriate time, she passes on high levels of antibodies to her lambs via colostrum, protecting them for the first weeks of life. Thereafter, young animals need to be started on their own vaccination programme to protect them throughout their lifetime. Veterinary practices widely recommend vaccination as the only option for control of clostridial diseases. This advice, combined with the devastating consequences of the diseases, may account for the high uptake of clostridial vaccines which have a 42% market penetration (MSD, 2017).

Pigs

An introduction to the UK pig sector

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On most pig units, there is a wide range of microorganisms which can cause disease, but generally disease is largely unexpressed in normal conditions. However, a trigger event can cause those infectious agents to proliferate and interact to cause disease. This is seen most acutely with porcine respiratory disease complex (PRDC) which results when a combination of infectious agents are present at a time of stress or challenge. This affects the health of the pig, resulting in reduced performance, increased medication costs, higher mortality and economic loss.

> *"In a relatively short time, we've seen a significant change of emphasis in how we manage these disease challenges on pig units."*

In a relatively short time we've seen a significant change of emphasis in how we manage these disease challenges on pig units. The use of antimicrobials within pig businesses we deal with has reduced significantly as we have switched our focus from treatment to management of disease, or disease potential. In fact, over 15 years the weighting of 75% antimicrobial: 25% biologicals supplied to our farms has reversed to 75% biologicals: 25% antimicrobial.

> *"In fact, over 15 years the weighting of 75% antimicrobial: 25% biologicals supplied to our farms has reversed to 75% biologicals: 25% antimicrobial."*

We now undertake routine and frequent testing of our customer herds by age and stage of production, enabling us to identify not only those pathogens present, but also when in the production cycle we can expect them to express themselves as clinical disease. This allied to rapid progress in vaccine technology and choice has meant we are now able to target and control the 'gateway' pathogens far better.

> *"Rapid progress in vaccine technology and choice has meant we are now able to target and control the 'gateway' pathogens far better."*

By controlling these primary pig pathogens effectively, we see reduced expression of the secondary pathogens for which we historically used antimicrobials.

A number of disease outbreaks we still see are often a result of environmental and management stress factors that allow the secondary pathogens to express themselves as disease in their own right, again requiring antimicrobial intervention. Fortunately, research and development by pharmaceutical companies means biological vaccine solutions are now available for the prevention of these secondary diseases, such as *Actinobacillus pleuropneumoniae* (APP), Glässer's disease (*H. parasuis*) and *Streptococcus suis*. The use of these particular vaccines within the practice is relatively low compared to the 'key' vaccines such as *Mycoplasma hyopneumoniae* or porcine circovirus (PCV2), with penetration rates of 70% and 90% respectively (MSD, 2017). However, they all represent useful tools with growing importance as we look to reduce antimicrobials.

We as a pig industry are charged with a reduction target of 99mg/PCU[1] by 2020 down from the 2015 baseline of 263.5mg/PCU[1], so we must think hard as to how we manage pig units and ultimately, pig health. The prudent withdrawal, or more strategic use, of antimicrobials allows us to test the efficacy and practicality of these useful vaccines. I anticipate usage will rise, which is a positive for the sector in the AMR battle.

> *"We as a pig industry are charged with a reduction target of 99mg/PCU by 2020 down from the 2015 baseline of 263.5mg/PCU."*

Ian Carroll

[1]The mg/PCU is a unit of measurement developed by the European Medicines Agency in 2009 to monitor antibiotic use and sales across Europe, which has also been adopted by the UK in its national reports.

PCU refers to the 'Population Correction Unit' and takes into account the animal population over a year for a country, as well as the estimated weight of each particular animal at the time of treatment with antibiotics. Although it is an estimation it does enable year-on-year comparisons to be made and trends to be seen.

Pig disease examples

Respiratory disease/porcine pleuropneumonia

Respiratory diseases cause major losses in productivity and performance in the pig industry and pleuropneumonia, caused by *Actinobacillus pleuropneumoniae* (APP), is among the most economically damaging. Estimated to reduce returns by, on average, £5.76[2] per pig in an affected herd (Prohealth, 2015), it does so by retarding growth, increasing mortality and through the cost of medication with antibiotics (MSD, 2015; Valks et al., 1996).

APP is air-borne and transmitted largely by nose-to-nose contact. It can rapidly spread within and across pens, and is passed from a sow to her piglets. The bacterium only infects the respiratory tract and can find its way deep into the lungs where it can cause extensive damage. The disease can cause death within as little as three hours from infection, or it can persist as a chronic, subclinical infection, once acute symptoms have subsided.

Treatment is based on antibiotics which, if given in the early phases, helps reduce mortality. However, all known serotypes of APP can be protected against by vaccination, which has been demonstrated to give a significant reduction in the cost of APP medication (Intervet, 2011). Vaccination also reduces mortality while preventing growth-checks and reducing the feed costs associated with APP infection (Rosales et al., 2008; Valks et al., 1996).

Glässer's disease

Glässer's disease is caused by the bacterium, *Haemophilus parasuis*, which is endemic in the majority of pig herds and frequently isolated from the nasal cavities of healthy pigs. However, stress or trigger factors such as early weaning or temperature fluctuations can lead to disease, as can the introduction of a new strain of the bacterium, particularly to a naïve herd.

Although Glässer's itself usually causes disease in weaners, infection of a naïve herd can give rise to clinical signs at any age. *H. parasuis* can also be an important component of porcine respiratory disease complex (PRDC) which occurs at any age from weaning to slaughter.

The infecting bacteria in Glässer's disease spread to the pigs' lungs, causing inflammation, and, into the bloodstream. They go on to infect the joints and various organs including the brain and in the most acute cases, pigs with severe septicaemia are found dead.

If spotted early enough, and if action is taken rapidly, affected pigs can be treated with antibiotics successfully and recover fully. All pigs in an affected group (not just those showing clinical signs) should be treated (Segalés, not dated).

However, protection against one of the more severe and most frequently isolated strains of *H. parasuis* can be achieved through vaccination which has been demonstrated to be highly effective. Trials showed zero mortality in vaccinated pigs challenged with the bacterium compared with 100% mortality in the unvaccinated control (Bak and Riising, 2002). Other research showed improved immunity to *H. parasuis* through vaccination could be passed from sows to piglets (Cerdà-Cuéllar et al., 2010). Vaccination reduced symptoms and mortality (Finestra et al., 2011; Lopes, 2014) and reduced antimicrobial use in the progeny of vaccinated animals Hagen et al., 2014).

Vaccination only tends to be advised where a problem with *H. parasuis* is anticipated, and is currently undertaken on about 26% of eligible animals, including sows and piglets.

Industry costs relating specifically to Glässer's disease require investigation but PRDC (of which it can be part) has been typically shown to reduce growth by 50g per day (NADIS, not dated (c)) and reduce returns, on average, by £3.78[2] per pig (Prohealth, 2015).

Streptococcus suis

Streptococcus suis is an ever-present bacterium found in the respiratory tract of healthy pigs and reported to be present in carrier animals on almost 100% of pig farms worldwide (Goyette-Desjardins et al., 2014). However, it can cause disease at times of stress, particularly in the presence of other infections and is a significant cause of meningitis and other, generally nervous, disorders. Although it can occur in pigs of any age it is most commonly seen in newly weaned pigs. Usually arising as a secondary infection, it is increasingly found in the presence of respiratory disease. In the absence of treatment, mortality can reach 20% (Gottschalk, not dated).

An extra concern revolves around its zoonotic properties, and although human cases have been sporadic in the past, they are reportedly on the increase and can lead to meningitis and hearing loss (Hughes et al., 2009). In western countries, human mortality from infection is close to 7% but in Asia it can be over 20% (Gottschalk, not dated).

Treatment of pigs involves injection with antibiotics and anti-inflammatories, and antimicrobials are often administered through water or feed. Treating sows with antibiotics before farrowing may reduce pathogen transmission to piglets, although results are controversial (Gottschalk, not dated).

Disease prevention through vaccination can be effective although, due to a lack of industry data on incidence and cost, research is needed to assess its financial value (Busque et al., 1997). However, because antibiotics tend to be administered to whole groups of pigs in response to infection, there is thought to be considerable scope to reduce the need for antibiotic use through immunisation.

[2] Converted from €6.4 at exchange rate of £0.9 = €1

Ileitis

Ileitis comprises a group of conditions involving changes in the small intestine associated with *Lawsonia intracellularis*. This bacterium is present on the majority of farms and exists inside the cells lining the small and large intestines. However, unknown factors trigger disease, which is often associated with heavy faecal contamination. It is characterised by diarrhoea and potentially wasting in growing pigs. Finisher or breeding animals can be affected by inflammation of and bleeding into the terminal part of the small intestine. The disease commonly exists sub-clinically, and – even though diarrhoea is rarely observed in such situations – reductions in daily liveweight gain of 9% to 42%, and reduced feed conversion efficiency of 6% to 37% have been reported (Collins, 2013). However, the economic impact of the sub-clinical condition is difficult to estimate because many producers are unaware it exists in their herds.

In its clinical form, ileitis is estimated by vets to occur in 30% to 56% of herds (Collins, 2013). It is spread through the ingestion of faeces, and rodents may be an important reservoir and vector (Collins, 2013).

Biosecurity and pen hygiene are important components of control. Traditionally, antibiotics have been used for prevention and treatment, sometimes involving continuous medication from about nine weeks until slaughter (Collins, 2013). However, once these antibiotics are removed, the pigs remain susceptible to a later challenge from the pathogen. Furthermore, continuous use of antibiotics may increase the potential for *L. intracellularis* and other bacteria to develop resistance.

Vaccination has been shown to protect pigs from clinical disease and significantly reduce the number of *L. intracellularis* shed in faeces (Collins, 2013), although it is still rarely carried out. In commercial situations where vaccination is practised, the herds often no longer require antibiotic medication, representing important and continuous progress in reducing agriculture's reliance on antibiotics (Collins, 2013).

Conclusion

Antimicrobials have been a cornerstone of modern medicine for much of the past century and in farming, they have played an essential role in improving animal health and welfare for many decades. It is now the task of the whole community – from medical professionals to vets and farmers and from politicians to the general public – to work towards retaining their life-saving properties.

There is no question over the scale of challenge facing the agriculture industry, but there is ample evidence to indicate it is within the sector's grasp. Given the right direction, updated technology and the political will and framework, livestock producers can radically improve on the impressive progress already made.

Immunisation has played a pivotal role in the successes already achieved and – as the farming industry considers new sector-specific targets for antibiotic use – vaccines pave the way for a future beyond antibiotics.

In moving the focus of livestock farming towards disease prevention, vaccines help maintain the benefits antimicrobials have given throughout our lifetimes and play an important part in retaining their life-giving properties for generations to come.

TIME TO VACCINATE

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Time to vaccinate is an initiative from MSD Animal Health to provide information and share experiences about vaccination as a preventive tool for livestock.

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