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Reducing UK Antibiotic Use in Animals

Antibiotics are widely used to treat infectious disease in animals and humans. A recent government review of antimicrobial resistance (AMR) recommended reducing antibiotic use in agriculture. This POSTnote discusses the current use of antibiotics in animals and the options available for reducing that use.

Overview

- Concerns over the spread of antimicrobial resistance has led to a move to reduce unnecessary antibiotic use in animals and humans worldwide.
- Antibiotic use in agriculture varies from one sector (poultry, dairy, etc.) to another and depends on the prevalence of endemic disease. Use has been declining, but more progress is needed to meet targets for 2020.
- Approaches to reducing antibiotic use include better animal husbandry, improving housing, herd/flock health management, vaccination and disease eradication.
- Enacting change involves managing interactions with vets and clients (farmers or pet owners), and knowledge exchange.

Background

Antibiotics are used to support animal health and welfare, in both companion animals (pets) and livestock. The 2016 O'Neill review,[1] part of the Government's 5-year AMR strategy, recommended reducing antibiotic use in agriculture. Agriculture accounted for 33%, and companion animals 8%, of total UK antibiotic sales in 2016.[2,3] This includes the use of some Critically Important Antibiotics (CIAs. Box 1). Every antibiotic dose risks generating drug-resistant bacteria, so minimising unnecessary antibiotic use in humans and animals can prevent the development of Antibiotic Resistance (ABR).[4,5] ABR and AMR are often used interchangeably but refer to different things.[6] Antimicrobials refer to all chemicals (including heavy metals) and drugs that can kill microorganisms (bacteria, fungi, parasites and viruses). Antibiotics are a subset of antimicrobial drugs that kill or inhibit the growth of bacteria.

ABR occurs when bacteria undergo genetic changes that protect them from antibiotics.[7] These changes can evolve over time or can be acquired from other bacteria.[8] ABR has happened naturally in the environment for millennia,[9] but the inappropriate clinical use of antibiotics can accelerate this process.[10] Clinically significant ABR is reached when a particular antibiotic can no longer effectively treat a bacterial infection.[7] While ABR is increasing in human medicine, treatment failure is relatively rare in veterinary practice.[2,11] However there is concern over the potential of transfer of ABR from bacteria that infect animals to bacteria that infect humans (pathogens). This will be explored in a forthcoming POSTnote. The following sections outline trends in antibiotic use, use in different agricultural sectors and use in companion animals.

Current Antibiotic Use

In the past, antibiotics were routinely added to animal feed as growth promoters,[12] however, this practice was banned in the EU in 2006.[13] There has been a general downward trend in antibiotic use in the EU, with a decrease of 8.3% between 2005 and 2009[14], continuing with a 12% reduction from 2011 to 2014.[15] In comparison there was a 22% decline in use in the UK from 2011 to 2014.[15]

In response to the O'Neill report, the Responsible Use of Medicines in Agriculture (RUMA) Alliance set up a Targets Task Force of vets and farmers, to work with industry and government, to set UK sector-specific antibiotic targets up to 2020.[16] It has also published health and husbandry guidelines on how to achieve them, while noting that some antibiotic use will continue to be necessary to treat the underlying endemic disease common to all sectors.[1,16] Total UK antibiotic use in agricultural animals dropped by 27% between 2014 and 2016 to 45 mg of antibiotic per kg of livestock (mg/kg),[2] exceeding the Government target of 50mg/kg by 2018. UK human antibiotic use by comparison was 129 mg/kg in 2014.[17] UK agricultural use of CIAs (Box 1) has also fallen to a record low of 1.5% of total sales compared to the EU average of 9.1%.[2,15] Overall UK

Box 1: Antibiotic use in Agriculture
Critically Important Antibiotics
The European Medicines Agency (EMA) has identified a number of Critically Important Antibiotics (CIAs) that it considers to be vital in maintaining human health.[18] These include fluoroquinolones, 3rd and 4th generation cephalosporins and colistin. The Veterinary Medicines Directorate (VMD) has recommended that CIAs are only used in animals after diagnostic tests indicate that their use is necessary.[19,20,21] The European Parliament voted in 2016 to restrict or ban veterinary use of CIAs, and to tighten rules on feed containing antibiotics, however this is still in the process of being ratified.[7]

Prophylaxis and Metaphylaxis
Prophylaxis is when antibiotics are used for disease prevention. Routine prophylaxis is being phased out.[16] However if a disease spreads quickly (such as respiratory illness), a vet can make a clinical judgement to treat all of the animals in a pen (metaphylaxis).[20,22],[23] For safety and practicality, 29% of antibiotics are administered in water and 44% in feed.[2,24] The EU will ban routine prophylaxis, but has stated that prophylaxis and metaphylaxis may be used " where the risk of bacterial infection or disease is high" and "consequences are likely to be severe".[25,26]

Withdrawal Periods
For meat, eggs or milk to be sold in the EU, the animal has to undergo a 'withdrawal period' allowing antibiotics (and other drugs) to be processed and excreted, before animal produce can enter the food chain. Food has to comply with Maximum [antibiotic] Residue Limit (MRLs), set by the EMA.[27] These MRLs are considered to be safe for human consumption and below a concentration that inhibits bacteria. This is audited by the VMD and animal produce containing residues above the MRL are discarded and an investigation instigated.[28]

agricultural use of antibiotics was 58% below the EU average (135.5mg/kg) in 2015.[15] This is in part due to the high ratio of sheep and cattle (which tend to have low antibiotic use) raised in the UK compared to pigs (which currently rely on higher antibiotic use).[29,30,31,32]

The Pig Sector
While the pig sector is the highest user of antibiotics in UK agriculture, overall usage has reduced by 50% (263 to 131mg/kg) since 2015,[2,33] , with a target of 99mg/kg[16] by 2020, and a 90% reduction in CIA use.[34] Much of this sector is intensive (Box 2), with 70—75% of pigs reared indoors.[35,36,] For example, a sow produces around 11 piglets per litter, 2—3 times a year without breaks for immune system or physical recovery. [37,38] [39,]The nature of pig production means that large numbers of young pigs are kept together resulting in higher risk of infection.[37] The pig industry suffers from several endemic diseases, [40,41] including respiratory, diarrheal, lameness and mastitis (teat infection) disease.[16] An example of this is post-weaning diarrhoea, which can be controlled using zinc oxide, rather than antibiotics. However zinc oxide will be prohibited in the EU from 2022.[42,43,44]

The Poultry Meat Sector
The poultry sector was a high user of antibiotics. However, the British Poultry Council's Antibiotic Stewardship scheme[45] has encouraged responsible use by driving down routine prophylactic antibiotic and CIAs (Box 1) use since 2011,[46] although fluoroquinolones may be used as a last resort.[45] This saw an 82% reduction in antibiotic use by 2017 (from 47mg/kg in 2011 to 10mg/kg in 2017 in chickens).[45] As an integrated sector, coordinating change, driving best practice and knowledge exchange has been easier to enact than on smaller, individually owned, farms.

The Cattle and Sheep Sectors
The dairy sector has intermediate antibiotic usage averaging 26mg/kg.[16] Milk production has increased from ~1,500 litres per cow per year in the 1800s, to 7,557 litres in 2017.[47,48,49] This high productivity increases the risk of mastitis, costing the dairy industry £300m a year.[50,51,52] An annual break in milking for 2 months is standard in all dairy cows, when antibiotics have traditionally been routinely administered (routine prophylaxis) to the udder to prevent mastitis.[51] This practice is being reduced with the increased use of non-antibiotic teat sealants to keep out infection.[53] Most dairy cows are kept inside for part of the year, yet 8% of farms keep cows permanently housed, which increases milk yield but has been linked to foot infection, mastitis, increased aggression.[54,55,56] Sheep and beef cattle are thought to have low antibiotic usage at ~11mg/kg (although surveillance is poor).[16] Most are reared in extensive systems (Box 2)[20] and these sectors are mainly made up of smaller farm holdings. Intensification is not possible as these animals only produce 1—2 offspring per year, allowing recovery time between breeding cycles.[57,58,59] Most disease, and highest vet contact time, occurs during birthing and weaning.[16,58]

Companion Animals
Pets live longer than farm animals and receive more complicated and costly healthcare including surgery and repeated antibiotic treatments. [60] While there are no comparable antibiotic usage figures for this sector, EU studies show that CIAs are two to three times more likely to be prescribed to cats, than to pigs, cattle or dogs.[61] A UK study found that one in four cats and dogs receive antibiotics in a consultation, and CIAs make up 39% of cat and 5.4% of dog antibiotic prescriptions respectively.[62] Surgical prophylaxis (where antibiotics are given in advance of surgery to reduce the chance of infection) is being phased out in both human and veterinary medicine.[63,64,65,66] Pets have more contact with humans than livestock, which may increase risk of resistant bacteria transmission.[67]

Options for Reducing Antibiotic Use
The following sections outline approaches to reducing antibiotic use in animals. These include better animal husbandry, housing and herd/flock health planning, as well as making better use of vaccines and using them in disease eradication. Other approaches include "antibiotic free" food labelling, changing prescribing habits, training for vets and farm workers, and further research.

Animal Husbandry
Animal husbandry is the practice of managing and breeding livestock. Good stock keeping is crucial for animal health and welfare,[20,31] and includes the animals' environment, thermal comfort, stocking density, nutrition and disease monitoring.[16,68] Areas for reducing antibiotic use include:

Box 2: Intensive and Extensive Farming Systems
Intensive farming is driven by consumer/retail pressure for affordable and plentiful food, and can increase the risk of disease. Extensive systems include outdoor ("on pasture"), free-range and organic, and claim (based on limited data) to use fewer antibiotics.[20,30,69]

- Intensive systems are indoor-housed with larger herd sizes and stocking densities (the amount of animals in a space). This can increase risk of disease[70,71] due to closely shared environments and less ventilation, which increase disease transmission, and often requires metaphylaxis treatment.[20,72] Overcrowding can also cause thermal discomfort and increase animal stress. However the UK has regulations in place for maximum stocking densities.[73] The high productivity (fast growth) common in intensive systems, can place higher stress on the animals, and lower immunity.[58,74,75,76]
- Intensive farming allows more control over the system and animal environment. This means that changes are easier to enact, and farmer and vets may have more contact time with animals for disease monitoring.[77,78,79] Significant reductions achieved in the UK poultry sector show that it is possible to keep disease rates low in intensive systems with good management. Extensive systems have less control and contact time, so self-limiting illnesses may run their course before being identified.[58] This means that antibiotics may be less likely to be used, but this can also present a welfare challenge due to unidentified illness.[78]
- Extensive systems tend to have more natural "enrichment"[80] providing the opportunity for increased welfare and health, but these systems need to be managed well to achieve this.[58,59,77]

- **Biosecurity** – practicing good hygiene principles to prevent disease spread, on a farm or between farms.[68,81,82,83] These include hand washing, disinfection and protective clothing, as well as quarantine measures for new animals.
- **Enrichment and welfare** – welfare refers to the physical and mental well-being of animals. Lower well-being causes stress, which compromises the immune system[84] and can lead to damaging behaviours such as tail biting in pigs,[20,85,86,87] and feather pecking in poultry.[88] Adding enrichment to the animals' environment can support animal well-being by allowing them to perform natural behaviours.[89,90] For example, straw or peat allows pigs to practice foraging behaviours that helps reduce tail biting.[87,91,92] Enrichment has also been found to improve pig immune response to porcine reproductive and respiratory syndrome virus (PRRSV).[93] A recent Government consultation suggested welfare as an area for investment of 'public money for public goods'.[94]
- **Colostrum and weaning** – colostrum, the milk produced by mammals immediately after birth, is concentrated with nutrients and immune boosting antibodies.[95] Animals fed this have lower disease rates for the rest of their lives. Weaning too young can contribute to increased stress, post-weaning diarrhoea and lower immunity.[58,96,97,98,99] The UK mandatory weaning age for pigs is 21-28 days. Studies suggest that those weaned at 28 days have lower endocrine stress and PRRSV incidence than those weaned at 21 days.[100,101,102,103,104,105,106] No advantage is seen with post-42 day weaning.[107]
- **Mixing animals** – mixing of different ages and groups should be avoided,[20,68] as it causes stress by disrupting animal social ties and can introduce new diseases.[108,109]

Animal Housing
In some sectors animals are housed in facilities that have been adapted for farming rather than purpose built.[110,111] New housing designs are better for managing disease, with better ventilation, stock management, and sophisticated water systems that allow targeted antibiotic metaphylaxis and addition of supplements to improve health.[30,83] A remaining design challenge is that hard flooring in housing is linked to foot infection in cows and pigs.[54,112] This can be mitigated by use of soft surfaces such as sand[113] or straw, although the latter has variable effects on disease.[91,114] It is possible to retro-fit ventilation systems,[111] or install balcony systems[115] to reduce stocking densities (Box 2). Danish government investment in new housing for pig farms has helped to reduce antibiotic use (to 42 mg/kg)[116] and increase productivity.[117] However, financial insecurity may be a barrier to improving farm infrastructure, with 20% of UK farms experiencing a loss in 2017.[55,118,119,120,121]

Herd health planning
The Red Tractor assurance scheme requires farmers to draw up a Herd Health Plan and review it regularly with a vet (annually in poultry, sheep, beef and dairy farms, and quarterly in pig farms).[79] Vets advise on disease prevention and predict the type and number of disease outbreaks. They often pre-emptively prescribe antibiotics, vaccines or other medicines, based on the farm's disease history (where data is available) which, for practical and economic reasons, the farmer will administer.[24] Under EU regulations, antibiotics can only be obtained following prescription by a vet.[122]

Vaccines
Vaccines are a valuable tool in preventing and reducing illness (PN433, PN581, see Box 3) and antibiotic use. For example, a study in the Netherlands on 40 farms, showed that bovine respiratory disease vaccination in young calves reduced antibiotic use by 14.5%.[123] However effective vaccines are not available for all agricultural diseases.[124] Viral vaccines are particularly important, as viruses often present similar symptoms (such as respiratory disease) to bacterial infection, which could lead to erroneous antibiotic use.[125] Viruses can also affect the immune system leading to secondary bacterial infections.[124] For example PRRSV infects 31% of UK pigs and was estimated to cost the industry £47m in 2013.[82,126,127,128,129] While there is a PRRSV vaccine available its efficacy has been questioned, due to the high genetic variability of the virus, and its persistence on vaccinated farms.[130,131,132,133,134]

Disease Eradication
It is sometimes possible to eradicate a disease on an individual farm or country-wide basis.[68,124] The devolved administrations in Scotland, Wales and Northern Ireland support a programme to use vaccination, biosecurity and culling to eradicate bovine viral diarrhoea (BVD),[135,136] a disease estimated to cost the UK £61m a year.[135,137] In England, BVD is the target of a voluntary industry-led programme using similar measures.[137] PRRSV is another candidate for such programmes with successful eradication occurring in countries such as Sweden.[138,139,140]

Box 3: Future Research and Innovation – Antibiotic Alternatives
New approaches for reducing antibiotic use in animals include the use of new vaccines, genome editing, bacteriophage and probiotics to prevent or control animal disease.[70,141] The development of cheap, effective, "point-of-care" diagnostics, and sensors for early disease detection and management, are also a high priority.[1,142,143]

- Vaccines – the most modern vaccines are known as 'conjugate' vaccines and are too expensive for animal use.[144] A cheaper way of making conjugate vaccines has been developed[145,146] which will target endemic bacteria for the animal market.[147] Other new technologies help to speed up vaccine development, to tackle fast mutating viruses such as PRRSV.[148,149] Notifiable diseases are infectious disease of national importance that are important to animal or human health.[150] Vaccine research on notifiable diseases is supported by Defra, but endemic disease vaccines would be more likely to reduce routine antibiotic use.[66,151]
- Genome editing – new genome editing technology (PN541), makes it possible to provide specific disease protection. For instance, it has been used to derive PRRSV-resistant pigs that are undergoing trials.[152,153,154] The European Court of Justice recently ruled that current GM regulations apply to genome edited products.[155]
- Bacteriophages – phages are viruses that infect and kill bacteria, but are harmless to humans and animals. [156,157] In the USA phages are used in the food industry, to kill *Salmonella*, *E. coli* and MRSA.[156,158] Proof of concept and safety have been shown elsewhere but commercial use is not permitted in the EU.[159,160]
- Probiotics – these are bacterial cultures associated with gut health (PN574). They are being evaluated as an aid to reduce infections, with some success in poultry feed,[161,] and surface sanitation,[162] but more conclusive research is needed.[68,163] Probiotics are thought to work in several ways including immune modulation, manipulating other bacteria, or by "exclusion theory", where beneficial[164] bacteria outcompete harmful bacteria.[161]

Consumer Pressure
In the USA there is a growing market for food labelled as "antibiotic free",[165] and an emerging market in the UK.[166] Consumers may associate "antibiotic free" labels with higher welfare. However, in practice, this could encourage poorer welfare actions on farms, whereby ill animals do not receive the antibiotics they need.[167,168] There is concern that such labelling might confuse consumers into erroneously believing that antibiotics are present in food (Box 1).[58,169,170] Most UK retailers require animal produce to be under the Red Tractor assurance scheme, which monitors usage and stipulates responsible antibiotic use guidelines.[79] There have also been proposals to tax antibiotics, or meat products,[1,171,172] to acknowledge the burden of antibiotics on society. It has been suggested that the tax revenue could be used to fund research or provide subsidies for farmers to improve disease control. Raising the price of antibiotics might make other forms of disease control more attractive, and could also discourage unnecessary antibiotic use.[1,31]

Changing Prescription Habits

Research on human behaviours has identified psychological factors that may contribute to antibiotic use. These include viewing antibiotics as "insurance" against disease and death, exacerbated by the lack of rapid diagnostic tests.[31,173,174] Around 60% of vets report that clients expect antibiotics to treat their pets[175,176,177] and similar pressures are seen in farming.[178] This causes concern that if a vet refuses to prescribe unnecessary antibiotics, clients will change to another veterinary practice, or pursue litigation.[31,120,173] In April 2018 the Government launched a "Trust your vet" campaign[179] to support vets in reducing antibiotic use. The British Veterinary Association developed a 7-point plan of responsible prescribing, building on the Royal College of Veterinary Surgeons Code of Conduct that requires that vets use antibiotics responsibly. For pet owners and farmers the death of an animal is an immediate danger compared to the more distant threat of ABR.[176]

The Behavioural Insights Team has been used to change GP prescribing behaviours, informing practitioners of their higher-than-average prescription rates, and a similar approach could be used with farmers and vets.[180] Data for small animal veterinary practices have been made available for benchmarking.[181] This would also be valuable in agriculture, and may lead to peer pressure to drive change.[182,183,184] Another approach is to train vets in motivational interviewing,[185,186] an evidence-based communication method that promotes choice, partnership and client knowledge. Vets given such training have more positive engagement with farmers with less resistance to suggested change.[187] Raising farmers' awareness of vaccines is also a priority. While companion animals have a 78%[188] vaccination rate, eligible livestock animals have lower vaccination rates of between 13-42%.[189] Decisions on vaccine use are made by individual farms taking into account cost and disease history,[190] and the benefit may not be seen when animals remain healthy.[124,] The 'Time to Vaccinate'[191] and #VaccinesWork campaigns aim to raise awareness of vaccine-preventable diseases.

Training
Defra research suggests farmer awareness of AMR is high[179] and that vets have been instrumental in delivering that knowledge.[192] Training in best practice in herd health can help reduce antibiotic use.[84] For example, in a 2009 UK trial to control mastitis, herd health planning led to a reduction in udder infection rates of 15%.[193] Training initiatives include the National Office of Animal Health's Animal Medicines Best Practice Training Programme,[194] and stock-person[195] and milk residue training[196] for farmers is also available. Vets are required to undertake 35 hours of continuous professional development training each year[197] and some courses have a specific focus on ABR. ABR training is not mandatory, and varies between practices.[31]

Research
Initiatives to bring scientists and vets together with farmers can ensure that the full range of skills are used in research and engage farmers with reducing antibiotic use. Examples include Innovative Farmers,[198] Nuffield Farming Scholarships, the Centre for Innovation in Livestock, and the 'Diagnostic Innovation and Livestock' project.[187] However, there is a lack of translational funding between ABR research and industrial commercialisation of innovation (Box 3). Innovate UK is considering ABR as one of its next priorities (Grand Challenges)[199] for UK research funding.

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