



**Sustainable Food Trust**  
*A global voice for sustainable food and health*

# MAXIMUM GROWTH: WHATEVER THE COST

*Use of growth-promoting antibiotics and beta-agonists in US meat production:  
implications under a US/UK trade deal.*



November 2020



# MAXIMUM GROWTH: WHATEVER THE COST

<b>EXECUTIVE SUMMARY</b>	<b>4</b>
The Antibiotics in Question	4
Past use of these antibiotics in the UK	4
Approved uses of the 'growth promoting' antibiotics in the US	5
Beta-agonists	6
Typical use in the US	6
Implications for UK consumers and farmers	6
<b>CONCLUSIONS</b>	<b>7</b>
The fundamental problem	7
The role of regulators in the US	7
How the UK can help the US to resolve these issues	7
<b>CHAPTER 1 – INTRODUCTION</b>	<b>8</b>
The purpose and structure of this report	8
The antibiotics of concern	8
Reasons to be concerned	9
Antibiotic resistance and the contribution of farm animal antibiotics	11
The use of beta-agonists in livestock production	11
Potential issues for UK livestock producers	12
Trade talks	12
Typical use in the US	13
US farm animal welfare	13
<b>CHAPTER 2 – INDIVIDUAL ANTIBIOTICS OF CONCERN</b>	<b>15</b>
Avilamycin – Marketed as Intepriety for poultry and Kavault for pigs by Elanco Animal Health.	15
Bacitracin	16
Bambermycin – Marketed as Flavomycin and Gainpro 10 by Huvepharma	18
Carbadox – Marketed as Mecadox in the US by Phibro Animal Health	18
Chortetracycline - marketed in the US as Aureomycin 50 and Aureomycin 100	19
Monensin - marketed as Rumensin 90 by Elanco US Inc, and as Monovet 90 by Alpharma; Lasal- ocid, marketed as Bovatec by Zoetis Inc.. and Laidlomycin, marketed as Cattlyst by Zoetis Inc.	21
Tylosin – Marketed as Tylan by Elanco US Inc.	23
Virginiamycin (Brand name Stafac)	24
<b>CHAPTER 3 – BETA-AGONISTS</b>	<b>26</b>
History of Beta-agonists in the UK	26
Health concerns	26
Illegal use	27
<b>APPENDIX 1 – THE EXTENT TO WHICH US REGULATORS HAVE ACTED MORE PROMPTLY AND DECISIVELY IN RELATION TO ONE OF THE MOST URGENT ANTIBIOTIC-RESIST- ANCE ISSUES</b>	<b>28</b>
Fluoroquinolones	28
<b>APPENDIX 2 – WAS THERE ANYTHING IMPROPER ABOUT THE WITHDRAWAL OF EV- ERNINOMICIN FROM PHASE III TRIALS?</b>	<b>30</b>

# EXECUTIVE SUMMARY

This report concludes that under a future trade deal with the US or any other country, simply banning hormone-treated beef and chlorine-washed chicken will not be enough to ensure the safety of UK consumers from imported meat.

Intensive livestock businesses in the US routinely use three different types of stimulants to maximise growth rates in livestock: antibiotics formerly licensed as growth-promoters in the UK, a beta-agonist and, as is more widely known, hormones in beef cattle production. Each of these poses potential, though difficult to quantify, risks to consumers. Regulators in the UK and wider EU have protected consumers from these products by not allowing their use in livestock farming, or in a few cases not allowing them to be used in the same way that they are used in the US. This report focuses on the antibiotics and the beta-agonist: why they are used and the risks this use poses.

The fact that antibiotic growth promoters continue to be used in the US, when it was widely understood this ended in 2017, comes down to differing interpretations of what constitutes a medically important antibiotic, plus different approaches to risk. The drugs considered in this report are not classified as critically important in human medicine. Nevertheless, there are serious food safety issues associated with each of them, some immediate, others where action is needed now to prevent problems in the future.

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## THE ANTIBIOTICS IN QUESTION

Ten growth promoting antibiotics are used in total, none of which are any longer permitted in the UK to promote growth. Five of them have been banned in the UK for all purposes and one has never been licensed here. Two of the remaining four antibiotics (chlortetracycline and tylosin) are routinely added to livestock feed in the US at growth promoting levels on a continuous daily basis, to suppress diseases of intensification. Such use would be illegal in the UK, even though these antibiotics are licensed for other uses. In relation to tylosin in pigs and poultry (but not cattle) UK and US permitted uses are broadly similar. Such long-term mass medication at sub-therapeutic doses is widely recognised to be far more likely to result in

antibiotic resistance, than short courses of treatment at higher doses.

Both of the remaining two antibiotics (monensin and lasalocid) are permitted for parasite control in chickens in the UK but are not permitted in beef cattle for any purpose, let alone growth promotion as they are in the US. Some of these antibiotics now require a veterinary feed directive (a prescription from a vet) while others are still available 'over the counter'.

One of the antibiotics can also be added to the feed of dairy cows, specifically to increase milk production, while another can be added to the feed of laying hens, to increase egg production (see sections on monensin and bacitracin in Chapter 2)

In one case (that of carbadox) the principal concern is not antibiotic resistance but the drug's carcinogenic properties and the potential for residues in pig meat. The FDA has been facing strong opposition from the industry for four years over its attempts to ban this antibiotic in pig production, (see section on carbadox in Chapter 2).

On average 5.4 times more antibiotics are used per kilo of meat produced in the US than in the UK. For beef and turkey meat, 8-9 times more is used. UK livestock farmers have halved total use in recent years and aim to reduce use further especially in pig and dairy farming.

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## PAST USE OF THESE ANTIBIOTICS IN THE UK

Nine of these antibiotics were previously licensed as growth promoters in the UK, but all such use had been ended here by 2006 as part of attempts to reduce the problem of antibiotic resistance. The tenth, laidlomycin, has never been licensed in the UK (see Table, opposite).

## APPROVED USES OF THE 'GROWTH PROMOTING' ANTIBIOTICS IN THE US

**Table 1 Antibiotics currently used routinely in US livestock production for prolonged periods at growth promoting rates, either to increase growth or control diseases of intensification**

Antibiotic	Species	Official reasons for use in the US	Growth promoting use in UK banned
Avilamycin	Pigs and Poultry	Control diseases of intensification	2006
Bacitracin	Cattle, Pigs & Poultry & Egg-Laying Hens	Growth promotion in pigs and poultry. Control diseases of intensification in cattle. Increased egg production	1999
Bambermycin	Cattle	Growth promotion	2006
Carbadox	Pigs	Control of diseases of intensification	1999
Chlortetracycline	Cattle	Growth promotion in cattle <sup>1</sup> . Control of liver abscesses in cattle due to high energy feeds. Treatment and control of disease in pigs and turkeys	1970
Laidlomycin*	Cattle	Growth promotion	*Never approved in UK
Lasalosid	Cattle up to about 9 months of age	Growth promotion	In the UK, only licensed in poultry as a coccidiostat
Monensin	Adult Beef Cattle, Suckler & Dairy Cows	Growth promotion & increased milk production	Banned as growth promoter in 2006. Still permitted as a poultry coccidiostat and a bolus in dairy cows.
Tylosin		Treatment and control of shipping fever (BRV) in cattle	1999
Virginiamycin	Cattle, Pigs and Poultry	Diseases of intensification including liver abscesses in feedlot cattle	1999

<sup>1</sup> The data sheet and product label for Aureomycin 50 (an antibiotic containing chlortetracycline) available on the official Dailymed website and on the website of at least one veterinary drug supplier, indicates that Aureomycin 50 can still be used to improve weight gain and feed conversion in beef cattle. The data sheet and product label are a single pdf that was updated in June this year (2020). It is unclear whether this is intended or an oversight. However, a related product, Aureomycin 100 can also be used continuously for disease control at the same growth promoting rate of just 70 mg/kg body weight

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## BETA-AGONISTS

When used in livestock feed, beta-agonists act as non-hormone growth promoters that also make animals leaner. The beta-agonist, ractopamine is widely used in beef cattle, pork and turkey production in the US. The use of beta-agonists in livestock production is banned in the UK, EU, Russia and China, due to concerns about the possible impact on human health of residues in meat. There are also persistent concerns about their effect on animal welfare (see section on animal welfare in Chapter 1 and Chapter 3 on beta-agonists).

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## TYPICAL USE IN THE US

It is typical for feedlot cattle in the US to be:

- implanted with five pellets under the skin, consisting of two hormones and the antibiotic tylosin to reduce the risk of infection. This can also be given to suckling calves,
- given a second hormone growth promoter in feed, if only one is implanted,
- given the non-hormone growth promoter, ractopamine in feed,
- given two other antibiotics in feed (one to suppress disease, one to stimulate growth)

The hormone pellets are slow release so last for several months, but the four feed additives will often be added to cattle feed every day from weaning until slaughter, with the exception of ractopamine which should be withdrawn three days before slaughter to reduce residues in meat. That's a total of five separate growth simulants in an individual animal. Hormones can only be used in cattle. Antibiotics are also used to promote growth in pigs and poultry. In addition to cattle, ractopamine is also used in pigs and turkey production, but not is not licensed for broiler chickens.

Animals showing actual signs of disease can also be treated with therapeutic antibiotics, as in other countries. The high use of therapeutic antibiotics in the US is also a cause for concern,

but not the subject of this report.

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## IMPLICATIONS FOR UK CONSUMERS AND FARMERS

Making the animals grow faster can increase profit margins considerably. An underlying concern of this report is that if meat or other products produced with all or any of these drugs is allowed to be imported into the UK, as part of a trade deal post-Brexit, consumers will be put at risk from consuming the meat, while UK livestock farmers will be put at a major commercial disadvantage and may go out of business.

There are human health concerns about meat produced with each of the products covered in this report. Some of these are immediate, others are more long-term and relate to the potential compromising of antibiotics that have been identified as having the potential to treat hospital superbugs, cure cancer and even, in one case, treat COVID-19. These issues are detailed in Chapter 2, in the health implication sections under each individual antibiotic and, in relation to beta-agonists, in Chapter 3.

In addition, there are also animal welfare and complex environmental and biodiversity issues associated with the types of intensive livestock production that the routine use of these drugs makes possible. Those are addressed in Chapter 1.

Of these ten antibiotics, the seven licensed for growth promotion are: bacitracin, bambarmycin, carbadox, chlortetracycline (see footnote to Table 1), monensin, lasalocid and laidlomycin. Bacitracin is also licensed to increase egg production and monensin to increase milk production. The other three - avilamycin, tylosin and virginiamycin - were for many years permitted for growth promotion in the UK as well as the US. Tylosin is also permitted for therapeutic use in the US and UK. In the US, avilamycin and virginiamycin are now licensed for long-term disease control. While tylosin is widely used in veterinary medicine at full therapeutic rates in the US and UK, it also permitted for continuous use at growth promoting rates in cattle and pigs to suppress disease in the US.



# CONCLUSIONS

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## THE FUNDAMENTAL PROBLEM

There are two fundamental drivers of the high use of antibiotics and other growth stimulants in the US. The first can be traced to cut-price competition between supermarkets and other multiple-retailers, and the extent to which this results in lower profit margins for livestock production companies and large-scale farmers. This encourages producers to use any technical aid at their disposal in order to compete profitably. Once one company adopts a new product or approach that increases margins, all those selling to mainstream outlets are forced to do the same in order to survive financially.

The second, is that diseases of intensification are a major problem in all types of intensive livestock production, but these seem to be even more significant in the US than in the UK, because drug-based solutions have largely been used instead of system-based solutions. The root causes are stress from early weaning; very long distance transport; the large numbers of animals kept together in generally over-crowded confinement; the often unhygienic living conditions; the lack of opportunity to display natural behavioural instincts; extreme weather conditions and unnatural diets, very high in energy or protein and low in fibre.

This is compounded by the centralisation and concentration of the US livestock feeding and slaughtering sectors in the hands of a small number of very large companies, often located vast distances from where the livestock originate. Young cattle raised on grass on small, traditional farms, often weaned abruptly on the day they head to feedlots, can then be transported for more than 24 hours, leaving them stressed and highly prone to bovine respiratory virus (shipping fever). As a result, they are often put straight onto antibiotics when they arrive at a feedlot. Similarly, the unnatural early weaning of pigs makes them vulnerable to *E. coli* and other infections, like swine dysentery, setting them on a path of continuous antibiotic dependency for life.

High energy diets for cattle based on corn (maize) help to maximise daily weight gain but cause rumen acidosis, which then results in liver abscesses. In pigs and poultry, high protein and high grain diets encourage necrotic enteritis,

a severe intestinal disease caused by bacteria which can rapidly lead to death. So much money and expertise has been invested in these systems that the possibility of making radical changes in order to prevent such diseases naturally seems out of the question to those involved. As such, managers seek technical fixes and keep the animals on antibiotics all the time. The entire industry and their political representatives then oppose any move to reduce the range of products upon which they have come to rely.

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## THE ROLE OF REGULATORS IN THE US

It is clear that the Food and Drug Administration (FDA) in the US has been doing what it can to reduce the threats to human health from the use of antibiotics in livestock production. It agreed a voluntary ban with the livestock industry in 2017 on the use of almost all medical antibiotics for growth promotion. It has also required veterinary oversight for the use of some antibiotics that had previously been allowed over the counter without a veterinary feed directive (prescription). Under what we can only assume to be pressure from the industry it has, however, allowed the continuing use of the antibiotics detailed in this report, in ways that would not be permitted in the UK. That partly relates to the fact that we recognise the precautionary principle in the UK and are prepared to take action in advance of a problem that can reasonably be anticipated, based on the available evidence. In the US, the evidence base needs to be much stronger and entirely conclusive before such action is taken.

It should, however, be acknowledged that on a few critical issues, where the evidence of risk to consumers is very strong, the FDA has to its credit, acted more quickly and decisively than UK or EU regulators (see Appendix I for one example).

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## HOW THE UK CAN HELP THE US TO RESOLVE THESE ISSUES

The US livestock industry is driven by profit motives. Change will only come when enough countries refuse to import meat produced with growth promoters of any kind.

# CHAPTER 1 – INTRODUCTION

## THE PURPOSE AND STRUCTURE OF THIS REPORT

The use of hormones in US beef production to promote growth in beef cattle has been widely publicised within the context of a UK/US free trade deal<sup>1</sup>. With a view to the possible importation of US beef, pork, chicken and turkey meat into the UK post-Brexit, this report considers the potential issues for UK consumers and farmers associated with the use in US livestock production of ten antibiotics, once permitted as growth promoters in the UK, but prohibited for this purpose here.

It also looks at the issues associated with one non-hormone growth promoter, the beta-agonist ractopamine, widely used in cattle, pig and turkey feed in the US, which is also not permitted in the UK, or the wider EU, Russia or China due to food safety concerns.

Under current UK import standards, meat produced in ways not permitted in the UK can still be imported providing it meets minimum WTO standards<sup>2</sup>. This has not been a significant issue in the past because most of our imported beef has come from Ireland and other EU countries<sup>3</sup>. All imported pig meat has come from Denmark, The Netherlands and Germany<sup>4</sup>, all operating to the same standards as the UK. In the case of non-EU imported chicken, which mostly comes from Brazil and Thailand, the European Commission has managed to ensure that production practices relating to exports

to the EU are in line within those in the UK and wider EU<sup>5</sup>. More recently, the EU has restated its total commitment to a ban on the use of antibiotics for growth promotion and from January 2022 will be introducing an additional ban on the preventative use of antimicrobials in groups of animals. These requirements will also have to be met by all countries exporting meat to the EU<sup>6</sup>.

Official figures clearly show that based on the weight of active ingredients, the overall use of antibiotics in US meat and dairy production is far higher than in the UK. Analysis of US and UK government data by the Alliance to Save Our Antibiotics found that overall, US farmers use 5.4 times more antibiotics per kilo of meat produced than UK farmers, with use in beef cattle and turkeys 8-9 times higher<sup>7,8</sup>, a picture confirmed by a separate independent analysis of the data within the US<sup>9</sup>. In contrast, UK livestock farmers have reduced antibiotic use by 50% in recent years<sup>10</sup> and also set ambitious targets for further reduction in pig and dairy farming in particular<sup>11</sup>.

## THE ANTIBIOTICS OF CONCERN

It is important to make clear that this report does not consider all the antibiotics used in animal agriculture or even the most serious threats to public health associated with the development of antibiotic resistance due to the use of antibiotics in livestock production. Instead it looks solely at the antibiotics formerly

1 Millstone, E and Lang, T (2018) Hormone-treated beef: Should Britain accept it after Brexit? Food Research Collaboration. Available at: <https://foodresearch.org.uk/publications/hormone-treated-beef-should-britain-accept-it-after-brexit/>

2 Young, R (2020) Personal (oral) Communication with Dr Liam Fox, MP.

3 AHDB (2019) The UK cattle yearbook. Available at: [https://projectblue.blob.core.windows.net/media/Default/Imported Publication Docs/CattleYearbook2019\\_190718\\_WEB\\_FINAL.pdf](https://projectblue.blob.core.windows.net/media/Default/Imported%20Publication%20Docs/CattleYearbook2019_190718_WEB_FINAL.pdf)

4 BMPA (undated) Pigmeat, accessed 21 November 2020. Available at: <https://britishmeatindustry.org/industry/imports-exports/pigmeat/>

5 European Commission (undated) EU import conditions for poultry and poultry products, accessed 20 November 2020. Available at: [https://ec.europa.eu/food/safety/international\\_affairs/trade/poultry\\_en](https://ec.europa.eu/food/safety/international_affairs/trade/poultry_en)

6 EUR-LEX (2019) Authorisation, import and manufacture of veterinary medicines, 27 February. Accessed 20 November 2020. Available at: <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:4381220>

7 Alliance to Save Our Antibiotics (2020a) US livestock receive more than five times as many antibiotics as British livestock. Available at: <http://www.saveourantibiotics.org/news/press-release/us-livestock-receive-more-than-five-times-as-many-antibiotics-as-british-livestock/>

8 Poultry World (2020) US/UK antibiotic use in poultry examined, 5 June. Available at: <https://www.poultryworld.net/Health/Articles/2020/6/USUK-antibiotic-use-in-poultry-examined-593547E/>

9 Wallinga, D (2020) Big Beef, Its Antibiotic Habit, and Protecting Our Future. Available at: <https://www.nrdc.org/experts/david-wallinga-md/big-beef-its-antibiotics-habit-and-protecting-our-future>

10 ASOA (2020b) New European rules on farm antibiotic use, September. Available at: <https://www.saveourantibiotics.org/media/1842/2022-changes-to-european-law-farm-antibiotics.pdf>

11 Calvert, A (2020) New targets for antibiotic use aim to build on past successes, Farmers Guardian, 20 November, p6.





### Introducing Kavault (avilamycin)

Reduce the incidence and overall severity of diarrhea in the presence of pathogenic *E. coli* in groups of weaned pigs. Kavault is an easy, cost-effective way to deliver more thriving pigs out of the nursery.



Former UK antibiotic growth promoter Avilamycin, is now licensed to prevent disease in the US, but being advertised with imagery the industry associates with growth promotion

classified as growth promoters in the UK, which can still be used in the US, either specifically to promote growth or continuously similarly low doses for prolonged periods, in order to suppress diseases of intensification. This is in order to demonstrate that such use poses a range of threats to public health that are generally overlooked in the US.

All these antibiotics are added to livestock feed or occasionally water in the US at low levels on a continuous daily basis – a practice which completely ended in the UK on 1 January 2006. In most cases this is for the rest of the animal's life, but with one of these antibiotics, avilamycin, treatment is limited to 21 days in chickens and 42 days in pigs. The antibiotics are used either to increase growth rates, or to suppress diseases of intensification, in ways very similar, and often identical, to their previous growth promoting use in the UK.

In the case of two diseases in feedlot cattle, shipping fever and liver abscesses, which are responsible for much of the use of antibiotics to control or suppress diseases, it is not that the diseases are not real. The issue is that both problems could be resolved in natural ways without continuous daily antibiotics if producers did not feel the commercial pressure to maximise growth through unnatural feeding, long distance transport and other practices which put the animals under stress.

Of the nine former UK growth promoting antibiotics that can be used legally in the US at growth promoting rates (or very close to them) and one additional growth promoter that was never licensed here, five are not permitted in the

UK for any purpose. Of the other five, the ways they are used in the US and in some cases the species in which they are permitted, would not be allowed in the UK.

This continuing use of antibiotics with known growth promoting properties is a surprise because there was a voluntary agreement between the FDA and the livestock industry in 2017 to stop using antibiotics for growth promotion in US livestock<sup>12 13</sup>.

The practice is justified, however, at a regulatory level in the US by the qualification that 'medically important' antibiotics are no longer used in this way. None of these antibiotics is classified as 'critically important' in human medicine. As this report will show, however, there is considerable scope for disagreement with the assumption that the antibiotics used for growth promotion and continuous disease control in the US are not medically important (see under each antibiotic in Chapter 2).

## REASONS TO BE CONCERNED

Of the ten antibiotics in total, one of them, bacitracin, is already used in human medicine. Three others, chlortetracycline, tylosin and virginiamycin, are closely related to medically important antibiotics. The FDA has been trying to ban another, carbadox and the other five have all been identified as important antibiotics. These can cause spread, or may cause or spread, resistance to other more medically important antibiotics and/or that could be developed for use in human medicine to cure infections caused by hospital superbugs and, in one case, kill cancer cells and even COVID-19 (see section on monensin in Chapter 2).

Of the other five antibiotics permitted in the US only two are licensed in the UK for any purpose. One of these, lasalocid, used in feedlot beef cattle in the US, is permitted for parasite control in poultry in the UK but not for use in cattle. Another, monensin, used in US beef and also dairy farming in the US, to increase growth and milk production, respectively, is permitted only as a slow release bolus in UK dairy farming for cows and heifers on high energy diets. The issues are explored in detail under each antibiotic but briefly summarised in Table 2 (see next page).

<sup>12</sup> McKenna, M (2017) After Years of Debate, the FDA Finally Curtails Antibiotic Use in Livestock, Newsweek 13 January. Available at: <https://www.newsweek.com/after-years-debate-fda-curtails-antibiotic-use-livestock-542428>

<sup>13</sup> CDC, Food and Food Animals. Available at <https://www.cdc.gov/drugresistance/food.html>

**Table 2 Summary of Reasons to be concerned about the use of each antibiotic**

Antibiotic	Permitted in the UK?	Summary of concerns
Avilamycin	No	Initial indications that it could increase multi-drug resistance in enterococcal infections
Bacitracin	No	Can cause colistin resistance and therefore resistance to medical drug of last resort, polymyxin B. Also been found to be effective against clostridium difficile so should not be used as a growth promoter or in agriculture at all
Bambermycin	No	One of the components of bambermycin has a unique form of action and has been identified as a potential new antibiotic for use in human medicine
Carbadox	No	This antibiotic is known to be carcinogenic. The FDA in the US is trying to ban it because they say recent evidence shows that residues in pork can persist longer than previously realised. The industry is resisting this, however.
Chlortetracycline	Yes, but not in cattle, as in the US, and not for Continuous daily use as in US	Chlortetracycline is a tetracycline antibiotic. Their widespread use in livestock production has created a vast reservoir of tetracycline-resistant bacteria. Some of the newer semi-synthetic tetracyclines, e.g minocycline and tigecycline, which are very important in human medicine, have been designed to resist cross-resistance with tetracyclines. However, scientists predict this will eventually crumble due to the development of mutations. As such, reserving the use of tetracyclines in veterinary medicine for treatment and ending their continuous daily prophylactic use and any use for growth promotion, would appear to be prudent.
Laidlomycin	No	These three antibiotics are all members of the ionophore family. Until recently they have only been considered for use in livestock production because they are relatively toxic. However, several studies have now identified them as important antibiotics that could be developed for human medicine. One group of scientists has said they, 'show a high degree of promise for the potential control of drug-resistant bacterial and parasitic infection'. Monensin also has anti-cancer and anti-virus action and has even been suggested as a possible treatment for COVID-19. Because the ionophores are relatively toxic they create a significant welfare problem. Accidental over-dosing in cattle feed results in internal organ damage, distress and painful deaths every year.
Lasalosid	Yes, in poultry	
Monensin	Yes, in poultry and as a bolus in some dairy cows	
Tylosin	Yes. In pigs and cattle, but not in cattle feed as in the US, or prolonged sub-therapeutic use as in the US	Tylosin was banned for growth promotion in the UK because it is a macrolide antibiotic and members of the same family are the only antibiotics that can be used to treat invasive campylobacter infections in children. It's continuous daily use in US cattle production is a particular concern because beef is a major source of a campylobacter infections in the US.
Virginiamycin	No	Cross-resistant to drug of last resort, Synercid. This is not currently used in the US but is recommended by the NHS in the UK for complicated skin infections.

For more detail on each antibiotic see Chapter 2

For clarification, pig, poultry producers and calf-rearers in the UK can also use chlortetracycline and tylosin preventatively but they cannot be added to cattle feed. The EU is planning to end this preventative use of antibiotics from 2022, except exceptionally in individual animals. The UK Government has recognised the need to reduce the use of antibiotics in healthy animals just in case they become ill, but has not yet committed to match the EU in this respect<sup>14</sup>.

## ANTIBIOTIC RESISTANCE AND THE CONTRIBUTION OF FARM ANIMAL ANTIBIOTICS

Overall it is generally believed that the use of antibiotics in human medicine is the major cause of antibiotic resistance, but for certain infections, farm animals appear to be a significant source. In 2013 the Center for Science in the Public Interest (CSPI) in the US drew attention to data from a CDC report which found that 22% of antibiotic resistant illnesses were linked to foodborne pathogens<sup>15</sup>. Antibiotic resistance is a growing problem worldwide. As a result, the number of people affected by and dying from untreatable infections continues to increase. In 2019 the Centers for Disease Control and Prevention (CDC) in the US reported that 2.8 million antibiotic resistant infections now occur in the US every year and 35,000 people die (up from 23,000 in 2013)<sup>16</sup>. At the same time the number of antibiotics that hospital doctors can completely rely on to save lives decreases.

While two major classes of antibiotics, the cephalosporins and the fluoroquinolones were created synthetically, most antibiotics have been developed from natural substances with antibiotic properties, and it is proving particularly difficult to find suitable new, natural antibiotic substances from which to create safe and effective new antibiotics<sup>17</sup>. It can cost in excess of US \$1.5 billion to develop a new antibiotic, but while one new antibiotic<sup>18</sup> class is showing some promise, no new major class of antibiotics have yet become available to treat gram-negative



Engain 9, The beta-agonist ractopamine used in pig feed.

infections, since the fluoroquinolones were developed in the 1960s.

## THE USE OF BETA-AGONISTS IN LIVESTOCK PRODUCTION

The report also considers the implications relating to the beta-agonist ractopamine which is neither an antibiotic nor a hormone. This is widely used as a feed additive in US beef, pork and turkey production. In cattle it is used for up to 42 days before slaughter, in pigs for about two months before slaughter and in turkeys for the last 7-14 days before slaughter. When added to livestock feed, beta-agonists stimulate muscle growth at the expense of fat deposition. With health professionals advising that consumers should only eat lean meat, beta-agonists have been used in the US for the last thirty years to increase profits by ensuring that slaughter animals grow as quickly, and are as lean, as possible. There is a separate debate to be had about whether the advice from health professionals to avoid animal fats because they contain a high proportion of saturated fat is sound, but this is outside the scope of this report. The more relevant aspect is that regulators in the UK, EU, China and Russia have all banned the use of beta-agonists in livestock

<sup>14</sup> ASOA (2020) New European rules on farm antibiotic use. Available at: <https://www.saveourantibiotics.org/media/1842/2022-changes-to-european-law-farm-antibiotics.pdf>

<sup>15</sup> CSPI (2013) CDC Report on Antibiotic Resistance Doesn't Deliver Action Steps to Address Food Safety, Says CSPI, 16 September. Available at: <https://www.cspinet.org/new/201309161.html>

<sup>16</sup> CDC (2019) Biggest Threats and Data, accessed 20 November 2020. Available at: <https://www.cdc.gov/drugresistance/biggest-threats.html>

<sup>17</sup> Imai, Y, Meyer, KJ, Iinishi, A et al. (2019) A new antibiotic selectively kills Gram-negative pathogens, Nature 575: 459-483. Abstract available at: <https://pubmed.ncbi.nlm.nih.gov/31747680/>

<sup>18</sup> Rex, JH (2020) What Does An Antibiotic Cost To Develop? Available at: <https://amr.solutions/2020/03/06/what-does-an-antibiotic-cost-to-develop-what-is-it-worth-how-to-afford-it/>

production in their own countries, due to concern about possible detrimental impacts on heart and cardio-vascular health, from residues of the drug in meat and offal. Chapter 3 looks at the issues associated with beta-agonists.

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## POTENTIAL ISSUES FOR UK LIVESTOCK PRODUCERS

The UK currently imports 26% of its beef and 60% of its pork, but most of this currently comes from other EU countries which also have total bans on the use of antibiotics for growth promotion. Ireland is the main beef exporter to the UK and Denmark, The Netherlands, Germany and Poland in relation to pork. This makes the UK a very attractive market for the US. Imported chicken comes from the EU, Brazil and Thailand but exporters have to meet EU production standards. The value of beef, pork and poultry exports from the US in 2017 exceeded \$18 billion and US trade negotiators have made it clear that they want to export meat to the UK as part of any trade deal that might be agreed.

UK beef producers already operate on extremely low margins. According to Defra, lowland grazing livestock producers in England made an average profit of just £15,500 p.a. between 2014-17 with 94% of this coming from direct payments<sup>19</sup>. This inevitably creates concern that the coming changes in support systems for agriculture being introduced from 2021 will reduce the average income of grazing livestock producers further. Former NFU chief economist, Sean Ricard, has predicted that the combination of support payment changes and a no-deal Brexit could put half of all UK farmers out of business by the mid-2020s<sup>20</sup> even without negative impacts from a trade deal.

UK beef and lamb production has declined by 25% and 27% respectively since the mid-1980s and additional price pressure due to cheap imports of beef could force even more UK producers out of businesses. Those that survive are likely to do so by becoming larger in scale

and more intensive in nature, emulating US production methods as much as they can. There is then likely to come a point at which they demand to be able to use the same practices and products that are permitted in the US.

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## TRADE TALKS

In recent months significant attention has been given to the continuing use of hormone growth promoters in US beef production due to the prospects of a free-trade deal between the UK and the US following Brexit.

As a result of the US Presidential election, the likely timetable and outcome of such an agreement is even less clear than it was. The UK Government, nevertheless, remains very keen to agree a trade deal with the US. At the same time, the US Government is known to want US meat to be allowed into the UK, as part of any deal. Incoming president Joe Biden is also likely to support the US intensive meat industry. In 2017 he said, 'We are not going to sign anything the chicken farmers of Delaware don't like'<sup>21</sup>.

Earlier this year Farmers Weekly reported that US Agriculture Secretary, Sonny Perdue, insists that all food produced in the US complies with food safety standards and is entirely safe. He also made clear that being able to export beef to the UK is a key objective for the US in any trade deal with the UK<sup>22</sup>. While the change of administration may slow down the progress of a trade deal, it seems unlikely that these fundamental US positions will change due to the change of administration.

Since US politicians maintain that all the products they permit in US food production are entirely safe, they present UK (and EU) concerns over the importation of American food products as protectionism. Perdue told Farming Today on BBC Radio 4, 'If [UK] farmers are constrained by things other than food safety, by protectionism and other things, my suggestion would be for the leaders of the UK to unshackle them, to let

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19 Defra (2018) Defra Evidence and Analysis Paper No.7, p36. Available at: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/740670/agri-bill-evidence-paper.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/740670/agri-bill-evidence-paper.pdf)

20 Rickard, S (undated) No Deal: the Door to the Decimation of UK Farming. Available at: [https://d3n8a8pro7vhmx.cloudfront.net/in/pages/19999/attachments/original/1565772927/PV\\_NoDeal\\_SeanRickard\\_13Aug19\\_FINAL.pdf?1565772927](https://d3n8a8pro7vhmx.cloudfront.net/in/pages/19999/attachments/original/1565772927/PV_NoDeal_SeanRickard_13Aug19_FINAL.pdf?1565772927)

21 Merrick, R (2017) Brexit: Chlorine-soaked chicken will be on sale in UK if US gets its own way in a trade deal, Nick Clegg warns, The Independent. Available at: <https://www.independent.co.uk/news/uk/politics/brexit-latest-news-chemical-chicken-hlorine-soaked-uk-us-trade-deal-nick-clegg-lib-dem-warns-donald-trump-joe-biden-a7529706.html>

22 Clarke, P (2020) Chlorinated chicken and hormone beef still on the table says US, Farmers Weekly. Available at: <https://www.fwi.co.uk/news/eu-referendum/chlorinated-chicken-and-hormone-beef-still-on-table-says-us>





A Five Rivers feedlot in Colorado which can hold 98,000 cattle.

them compete on that level playing field.’<sup>23</sup>

## TYPICAL USE IN THE US

In the US, it is quite common for US feedlot cattle to have one and sometimes two different hormones implanted under the skin along with an antibiotic, usually tylosin, to reduce the risk of infection and to have two antibiotics (one specifically for growth promotion, the other for disease control), plus a beta-agonist and sometimes a further hormone that can be added to their feed on a regular daily basis. At the same time, they are given very high energy diet largely based on corn (maize). This results in maximum daily weight gain weight and therefore brings considerable commercial advantages for producers. Perdue’s comments add to concerns that if beef produced with all or any of these products is allowed into the UK,



Stocking densities for chickens are higher in the US than the UK

the UK Government will eventually be forced to allow UK cattle farmers to use such products too, since they will not otherwise be able to complete commercially.

With pigs and poultry, the main issue, apart from over-crowding and unhygienic conditions, is the use of very high protein diets, heavily based on soya meal, which tend to encourage a disease known as necrotic enteritis which can result in high mortality and therefore be costly for producers if not prevented.

## US FARM ANIMAL WELFARE

US federal legislation on animal welfare is generally lacking. Stocking densities for broiler chickens are higher in the US than the UK, though not significantly higher than permitted under certain circumstances in the EU, from where we import chicken. In the US there is a voluntary National Chicken Council code, which it is said most producers follow, but these are generally lower than those of the UK/EU and only cover a few aspects. In contrast, in the UK and EU there is detailed legislation relating to all aspects of animal welfare. Individual US states can set their own legislation but three of the largest US chicken producing states, Alabama, Arkansas and Georgia do not have any relevant legislation. In the UK/EU chicken litter must be cleaned out and replaced with fresh, dry litter, and the buildings thoroughly disinfected between batches of chickens. In the US there

<sup>23</sup> Sonny Perdue (2020) Interview with Charlotte Smith broadcast on Radio 4. Farming Today This Week, Radio 4, 23 May.





A cattle truck in Oregon: Farm animals can be transported for 28 hours in the US

are no such requirements<sup>24</sup>.

In the UK/EU maximum journey times are 12 hours (with the exception of recently hatched chicks) and there are detailed requirements relating to animal welfare during transit, which do not exist in the US. In the US, journey times are supposed to be limited to 28-hours, after which animals should be unloaded, fed and watered. However, there are no requirements relating to the welfare of animals during transport and it is claimed there is little enforcement of journey times and there exist loopholes that can be exploited. According to the American Society for the Prevention of Cruelty to Animals (ASPCA) just twelve US states have gone further than federal legislation and banned certain forms of confinement<sup>25</sup>, but illnesses and injuries are often left unnoticed or untreated, overcrowding is commonplace, animals can be treated roughly and medical procedures are undertaken without anaesthetics<sup>26</sup>.

There is clear evidence that long journeys for beef cattle travelling from farms to feedlots can increase the incidence of disease and need for antibiotic medication. Apart from the obvious

lack of ability to graze pasture, feedlot cattle can also suffer from extremes of heat, dust, cold, wet and muddy weather, which can occur at different times of the year. There is also the welfare issue that significant numbers of cattle become seriously unwell after accidental overdosing with any of the three ionophore antibiotic growth promoters. There are reports most years of cattle dying in extreme pain and distress as a result (see section on monensin in chapter 2). In 2013, Zilmax (zilpaterol) marketed, by Merck and Co was voluntarily withdrawn after Tyson Foods said they would no longer buy treated cattle because many were arriving at slaughterhouses lame and distressed. In relation to ractopamine use in pig production there is a label warning that it, 'may increase the number of injured and/or fatigued pigs during marketing<sup>27</sup>'. There is no easy way to find information on the effects, if any, of ractopamine on cattle welfare.

<sup>24</sup> ADAS (2016) Comparison of the Regulatory Framework and Key Practices in the Poultry Meat Supply Chain in the EU and USA, Association of Poultry Processors and Poultry Trade in the EU Countries. Available at: <https://www.britishpoultry.org.uk/identity-cms/wp-content/uploads/2018/05/2016-ADAS-EU-US-comparison.pdf>

<sup>25</sup> ASPCA, Farm Animal Confinement Bans by State. Available at <https://www.asPCA.org/animal-protection/public-policy/farm-animal-confinement-bans>. Accessed 25 July 2020.

<sup>26</sup> ASPCA, Farm Animal Welfare, Farm Animals Need Our Help. Available at <https://www.asPCA.org/animal-cruelty/farm-animal-welfare>. Accessed 25 July 2020.

<sup>27</sup> Paylean 45 – ractopamine hydrochloride granule, Elanco US Inc. Product label information available via the Dailymed website. Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ef0786ec-7a7e-4033-a031-fc8a75e94cff>

## CHAPTER 2 – INDIVIDUAL ANTIBIOTICS OF CONCERN

### AVILAMYCIN – MARKETING AS INTEPRITY FOR POULTRY AND KAVALT FOR PIGS BY ELANCO ANIMAL HEALTH.

Avilamycin is not used in human medicine. It was permitted as an antibiotic growth promoter, Maxus G100 marketed by Elanco, in pigs and chickens in the UK and wider EU until 2006.

#### USE IN THE US

In 2016, Elanco Animal health gained approval to introduce avilamycin in the US as Intepriety to reduce deaths from necrotic enteritis in broiler chickens<sup>28</sup> and as Kavault to reduce the severity of E.coli infections in pigs<sup>29</sup>. Both these conditions could be addressed by management changes: lower protein diets in chickens and later weaning in pigs. Despite the claims of ‘new’ this is the same product that was banned in the UK. However, whereas Maxus G100 was available over the counter without a prescription and could be fed continuously at very low levels, use of Intepriety requires a veterinary feed directive (a prescription from a vet) and in chickens use is limited to 21 days. Use of Kavault is also initially recommended for 21 days but can be extended to 42 days by the vet if

deemed necessary. The dosage rates for this prophylactic use are also slightly higher than the growth promoting rates used in the UK and the EU until 2006.

By 2020 approval had been gained in the US for its use in poultry in combination with the ionophore antibiotics narasin (as Monteban and Maxiban) and monensin (as Coban)<sup>30</sup>, most probably resulting in increased usage.

#### WHY UK CONSUMERS SHOULD BE CONCERNED ABOUT EATING PORK OR CHICKEN PRODUCED WITH AVILAMYCIN

Like most things about antibiotic resistance, this is a complex issue with no simple answer. A closely related antibiotic, everninomicin (brand name Ziracin) was under development by Schering-Plough for treating MRSA, VRE and other highly resistant gram-positive infections such as penicillin-resistant streptococci. Initial results were very positive and it was found to be even more effective than vancomycin. However, Phase III trials were stopped in 2000. Schering-Plough said only that ‘the balance between efficacy and efficiency did not justify further development’. This has left a number of questions unanswered (see Appendix II).

At face value this might suggest that avilamycin is the one former growth promoting antibiotic that can be fed to healthy pigs and chickens as a preventative measure for fairly long periods without a threat to human health. It needs to be noted, however, that avilamycin has only been approved for use in the US for four years, and by last year US scientists had already found two examples of avilamycin-resistant enterococci, one in retail chicken, the other from a live chicken<sup>31</sup>. The scientists said they tested samples of chicken because, ‘Since these



28 Feedstuffs.com (2016) Elanco introduces Intepriety (avilamycin) for poultry. Available at: <https://www.feedstuffs.com/story-elanco-introduces-intepriety-avilamycin-poultry-122-141580>

29 Feedstuffs.com (2016) Elanco develops new avilamycin antibiotic for swine. Available at: <https://www.feedstuffs.com/story-elanco-develops-new-avilamycin-antibiotic-swine-45-136886>

30 WattPoultry.com (2020) Animal-only Intepriety now available, 30 March. Available at: <https://www.feedstuffs.com/story-elanco-introduces-intepriety-avilamycin-poultry-122-141580>

31 Zhao, S, Li, C, Mukherjee, S, Hsu, CH, Singh, R, Gilbert, J and McDermott, P (2019) Complete Genome Sequences of Two Avilamycin-Resistant Enterococcus faecium Strains Isolated from Chicken in the United States, Microbiology Resource Announcements 8 Nov. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6872881/>

approvals [i.e. the approvals for Intepirity and Kavault] represent the first uses of avilamycin in the United States, there are no data available to assess the potential impact of avilamycin on the emergence of antimicrobial resistance among pathogens from food-producing animals.’

This is a serious concern because in both cases the enterococci were multi-drug resistant, not simply resistant to avilamycin. The one in retail chicken was resistant to nine important antibiotics, the one from the live chicken to five medically important antibiotics<sup>32</sup>. In relation to the retail chicken, the enterococci were resistant to the medically important macrolide erythromycin as well as the veterinary macrolide tylosin.

This is particularly significant because in 2018, as part of a license variation, Elanco told the FDA that ‘Resistance to avilamycin does not select for cross-resistance to macrolides, and to date there are no reports of plasmid-mediated resistance to avilamycin that could result in the co-selection of resistance to other medically important antimicrobials in the United States.’<sup>33</sup> If that was true at the time it would seem that it is no longer the case. As such Elanco’s assurances were based not so much on evidence, as on the absence of data. So far no one appears to have checked pork and pigs for resistant enterococci in the US.

These findings should not really come as a surprise. As early as 1999 in Denmark, where avilamycin had been used for many years, scientists found that 69% of samples of the main enterococcus strain to acquire transferable resistance, *E. Faecium*, were resistant to avilamycin<sup>34</sup>, so it seems likely that with time, resistance to avilamycin in enterococci in the US will increase. In 2004, scientists in New Zealand also found that avilamycin was maintaining vancomycin-resistant enterococci in poultry after the use of the related antibiotic, avoparcin in poultry production had ended<sup>35</sup>. A similar phenomenon had also been found with

pigs found in Denmark.

Wisely, avoparcin (effectively, vancomycin marketed for use as a growth promoter) was never permitted in US livestock production, so there is no major reservoir of vancomycin-resistant enterococci (VRE) in US farm animals. However, given the widespread use of vancomycin in US hospitals and the fact that in 2019 there were 54,500 cases of VRE and 5,400 deaths in the US<sup>36</sup>, extreme caution is surely needed? Sewage from hospitals and even the community will inevitably contain VRE and this could find its way into the farm animal population via wildlife or sewage spread on farmland. With the ability of enterococci to become resistant to multiple antibiotics so easily, it suggests that the widespread use of avilamycin in US pig and poultry production could with time become an additional source of VRE and perhaps other highly drug-resistant infections in people.

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## BACITRACIN

In human medicine bacitracin is used, sometimes in combination with other antibiotics, in ointments for infected skin, nose and eye conditions. In the past it was also available for intramuscular injection, but the FDA asked all the companies marketing it in this way to withdraw their products voluntarily because such use could cause significant side effects.

The use of bacitracin in livestock production was banned in the UK and other EU countries in 1999.

## USE IN US LIVESTOCK PRODUCTION

The US has taken a fundamentally different approach to bacitracin in livestock production from the UK. The use of bacitracin is not included in the Food and Drug Administration’s Center for Veterinary Medicine’s list of medically important antibiotics for human health<sup>37</sup> but it is

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32 Ibid.

33 Elanco (2018) Freedom of Information Summary, Supplemental New Animal Drug Application NADA 141-439 Intepirity. Available at: <https://webcache.googleusercontent.com/search?q=cache:wcjgwgrwW8IJ:https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/3950+&cd=1&hl=en&ct=clnk&gl=uk&client=firefox-b-d>

34 Wegener, H C, Aarestrup, FM, Borgø Jensen, L, Hammerum, Am and Bager, F (1999), Use of Antimicrobial Growth Promoters in Food Animals and Enterococcus faecium Resistance to Therapeutic Antimicrobial Drugs in Europe, Emerging Infectious Diseases 5. Available at: [https://wwwnc.cdc.gov/eid/article/5/3/99-0303\\_article](https://wwwnc.cdc.gov/eid/article/5/3/99-0303_article)

35 Manson, J, Smith, JMB and Cook, GM (2004) Persistence of Vancomycin-Resistant Enterococci in New Zealand Broilers after Discontinuation of Avoparcin Use, Applied Environmental Microbiology 70: 5764-5768

36 CDC (2019) Antibiotic Resistance Threats in the United States. Available at: <https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf>

37 FDA Guidance for Industry No.152. Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their





Bacitracin was banned in the UK in 1999

marketed for growth promotion in pigs and poultry and disease control in cattle as an over-the-counter feed additive which does not even require any veterinary involvement when used to reduce disease in cattle.

It is currently marketed for use in livestock feed as BMD 30, 50 and 60 by Zoetis. It is used to increase egg production and feed efficiency during the first seven months of egg-laying, and as a growth promoter in pigs of all ages, including pregnant sows; broiler and replacement chickens; turkeys; pheasants; and quail. In feedlot cattle it is no longer marketed as a growth promoter, but is promoted as a treatment to reduce 'the number of liver condemnations.' It can be administered in cattle feed either at a high dosage level for five days or at a low dosage level continuously.

To be consistent with current US regulations one would expect such use to require the authorisation of a veterinarian. There appears to be no withdrawal period, meaning that eggs can be collected, and animals slaughtered, while receiving bacitracin in feed. Residues are not an issue with bacitracin, but withdrawal periods can also allow time for resistance levels in bacteria to decline somewhat. There is also no prohibition of off-label use, except in California<sup>38</sup> which essentially means that intensive livestock companies can use it in any way they wish. When off-label use (known as extra-label use in the US) is not restricted, vets are free to prescribe antibiotics in ways other than those for which it is approved. With over the counter antibiotics that do not require a veterinary feed directive from a

vet it is not clear whether end user is also free to vary the recommended dosage themselves. It's notable that Zoetis calls it an antibacterial rather than an antibiotic. Whether this is what allows them to avoid veterinary oversight for a product with recognised antibiotic properties is not clear.

## WHY WE SHOULD BE CONCERNED ABOUT IMPORTING MEAT PRODUCED WITH BACITRACIN INTO THE UK

Recently researchers have discovered that bacitracin can cause colistin resistance, even in the absence of colistin. USA, Chinese and Japanese scientists working together, have discovered that its use in livestock production may be resulting in the development MCR-1, the gene which can add colistin resistance to bacteria that are already resistant to multiple antibiotics. Colistin is not used in US livestock production at the present time, yet the researchers found this resistant gene in E.coli in US pigs. A similar worrying development has been found in poultry in Romania.

Bacitracin was banned for farm use in the UK in 1999 due to growing concerns about the rise of antibiotic resistance and the difficulty of finding new, effective and non-toxic antibiotics to replace those that are becoming ineffective. Although there was little or no use in human medicine at the time, it was known that bacitracin could kill MRSA, for example in nasal infections, and there was concern that Staphylococcus aureus could eventually develop resistance to the few existing antibiotics effective against such infections. So, the basic concern was to prevent a reservoir of bacitracin-resistant bacteria developing in food animals due to their potential spread to humans.

## EMERGING NEW CONCERNS

The antibiotic Colistin (polymyxin E) is closely related to and cross-resistant with polymyxin B, an antibiotic of last resort for a range of multiple antibiotic-resistant infections caused by Gram-negative bacteria such as E.coli, Klebsiella pneumoniae and multi-drug resistant gonorrhoea. It was widely used in livestock production in some countries, but once the link was discovered in 2016 between the use of colistin on farms and polymyxin B resistance in

Microbiological Effects on Bacteria of Human Health Concern. Food and Drug Administration, Center for Veterinary Medicine, October 23, 2003. Available at <https://www.fda.gov/media/69949/download>

38 BMD 50 Bacitracin Methylene Disalicylate Type A Medicated Feed Article Antibacterial, Zoetis Inc, accessed 14 November 2020. Available at: [https://www.zoetisus.com/contact/pages/product\\_information/msds\\_pi/pi/BMD\\_50.pdf](https://www.zoetisus.com/contact/pages/product_information/msds_pi/pi/BMD_50.pdf)

hospitals, China immediately banned all farm use, and most countries have either now banned colistin or severely limited its use in animals. It is now clear that bacitracin use also needs to be ended on farms to protect the efficacy of polymyxin.

Even more recently, German scientists have discovered that bacitracin has both the potential to kill the hospital superbug *Clostridium difficile* and to neutralise its toxic effects<sup>39</sup>.

## HISTORICAL NOTE ON BACITRACIN

Bacitracin is a mixture of several antibiotics, all members of a large family. It was first isolated in 1945 at the University of Columbia College of Physicians and Surgeons, and it is worth mentioning the circumstances because they show how, as with penicillin and a number of other important medical breakthroughs, its discovery owes more to luck and an observant scientist than to a systematic attempt to develop a new antibiotic. While treating a young woman with an infected leg injury, the bacteriologist noticed that something was killing the bacteria in one part of the wound. The antibiotic substance was isolated and developed commercially, gaining FDA approval in 1948<sup>40</sup>. At one level this helps to illustrate why it is proving difficult for drug companies to develop new antibiotics to order, they usually also need a certain amount of luck.

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## BAMBERMYCIN – MARKETING AS FLAVOMYCIN AND GAINPRO 10 BY HUVEPHARMA

Until 2006, Bambermycin, as Flavomycin 80 was permitted as growth promoter in the UK for adult cattle, calves, pigs, chickens, laying hens, turkeys and rabbits.

### CURRENT USE IN THE US

Bambermycin, marketed as Flavomycin, is licensed in the US as an antibiotic growth promoter in broiler chickens, pigs and turkeys.

As Gainpro 10, it is available as an over-the-counter antibiotic without veterinary oversight to increase weight gain and feed efficiency in both feedlot and grazing cattle including suckler cows. A 28-week study in 1991 found that its inclusion in feed increased daily weight gain by up to 15.2%<sup>41</sup>.

## WHY UK CONSUMERS SHOULD BE CONCERNED ABOUT IMPORTED MEAT PRODUCED WITH BAMBERMYCIN

Bambermycin is not used in human medicine and has long been considered unsuitable for use as a medical antibiotic. However, it is made up of four different antibiotics all members of a large family of antibiotics, the Moenomycins which themselves are members of an even larger family, the phosphoglycolipids. One of the components of bambermycin, moenomycin A has a unique form of action and has been identified as having potential to be developed as an important new antibiotic for use in human medicine<sup>42</sup>. As such it would seem that the UK/EU ban on the use of bambermycin in 2006 was prudent and is likely to have prevented a reservoir of bambermycin-resistant bacteria developing in food animals in the UK.

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## CARBADOX – MARKETING AS MECADOX IN THE US BY PHIBRO ANIMAL HEALTH

Carbadox is a toxic and carcinogenic antibiotic that is not used in human medicine. It was previously licensed as an antibiotic growth promoter in the UK/EU, but banned along with a related antibiotic, olaquinox, in 1999. The ban was justified in Europe in relation to the risk to those who manufactured carbadox and those who incorporated it into pig feed.

### USE IN THE US

Carbadox is currently used in pig feed in the US to promote growth and control swine dysentery

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39 Zhu, Z, Schnell, L, Müller, B, Müller, M, Papatheodorou, P and Barth, H (2019) The Antibiotic Bacitracin Protects Human Intestinal Epithelial Cells and Stem Cell-Derived Intestinal Organoids from *Clostridium difficile* Toxin TcdB, Stem Cells International ID 4149762, available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6701344/pdf/SCI2019-4149762.pdf>

40 Bacitracin, Wikipedia, accessed 14 November 2020.

41 De Schrijver, R, Fremaut, D and Claes, B (1991) Flavomycin effects on performance of beef bulls and nutrient digestibility in wethers, Dtsch Tierarztl Wochenschr, 98: 47-50

42 Ostash, B, Saghatelian, A and Walker, S (2007) A streamlined metabolic pathway for the biosynthesis of moenomycin A, Chemistry and Biology, 14: 257-67. Available at: <https://pubmed.ncbi.nlm.nih.gov/17379141/>



and several other diseases of intensification.

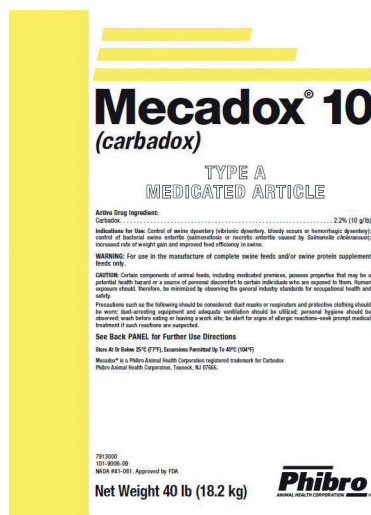
## WHY THE UK CONSUMERS SHOULD BE CONCERNED ABOUT IMPORTED PORK PRODUCED WITH CARBADOX

Pig farmers are required to withdraw feed containing carbadox 42 days before slaughter due to concern about residues of carbadox in pork. But with only a tiny proportion of pork sampled there is always the risk that withdrawal periods have not been strictly observed. As has been shown in the UK with another toxic antibiotic, lasalocid<sup>43</sup>, batches of non-medicated feed produced after a batch of medicated feed can still contain substantial levels of the relevant drug or drugs, because it is difficult and often impractical to clean all the elevators, augers and other components of the mill thoroughly between feed batches. This might possibly account for the fact that one out of 587 dairy cows slaughtered for meat in February 2016 tested positive for carbadox at high enough levels to report even though carbadox is not used in cattle feed<sup>44</sup>.

The FDA has been trying to ban the use of carbadox in the US since 2016<sup>45</sup>. In July this year it set out its reasons. First pointing out that

carbadox has been found to be carcinogenic in laboratory animals, the agency explains that under normal conditions it would not be allowed to approve an animal drug that is carcinogenic. But to this it adds that there is an exemption where this can be done if it causes no harm to the animals and 'no residues of the drug will be found by an approved regulatory method in any edible tissues of or foods from the animal'. They then state that since the drug was last approved in 1998, 'Subsequent human food safety information demonstrates that carcinogenic carbadox residues persist longer than previously known'<sup>46</sup>.

The FDA is, however, meeting strong opposition from the pig industry. The manufacturing company, Phibro, continues to argue that it is safe. They state that, 'They will continue to defend swine producers'<sup>47</sup> ability to use Mecadox [carbadox] to protect the health and welfare of their animals. Mecadox continues to be available for use by swine producers'. In September the National Pork Producers Council added its voice, with an argument that has been used before in relation to antibiotic growth promoters generally, stating that, 'Removal of carbadox would inevitably increase use of other antibiotics and the likelihood of difficult to control antibiotic resistance'<sup>48</sup>.



Carbadox is carcinogenic and was banned in the UK in 1999

## CHLORTETRACYCLINE - MARKETING IN THE US AS AUREOMYCIN 50 AND AUREOMYCIN 100

Chlortetracycline is a member of the tetracycline family of broad-spectrum antibiotics, several members of which including doxycycline, minocycline and tigecycline are very important in human medicine. Its use for growth promotion in farm animals was banned in the UK in 1970 on the recommendation of the Swann Committee in 1969, due to the death of at least 4 children

43 Young, R and Nunan, C (2004) Too hard to crack? Eggs with drug residues, Soil Association. Available at: [https://www.soilassociation.org/media/4938/policy\\_report\\_2004\\_too\\_hard\\_crack.pdf](https://www.soilassociation.org/media/4938/policy_report_2004_too_hard_crack.pdf)

44 United States National Residue Program Quarterly Report Jan-Mar 2016, p7. Available at: <https://www.fsis.usda.gov/wps/wcm/connect/ad768d8c-f822-4ed5-bcd2-75cd1c45d6d7/Residue-Quarterly-Report-Q2-FY2016.pdf?MOD=AJPERES>

45 Einstein-Curtis, A (2016) FDA looks to ban pig drug carbadox on carcinogenic residue fears, Feed navigator.com. Available at: <https://www.feednavigator.com/Article/2016/04/12/FDA-looks-to-ban-pig-drug-carbadox-on-carcinogenic-residue-fears>

46 FDA (2020) Questions and Answers regarding Carbadox. Available at: <https://www.fda.gov/animal-veterinary/product-safety-information/questions-and-answers-regarding-carbadox>

47 National Hog Farmer (2020a) Phibro reiterates safety of carbadox product, 23 July. Available at: <https://www.fsis.usda.gov/wps/wcm/connect/e890ec75-ec60-43c7-a04e-6cbeb2574a79/Residue-Quarterly-Report-Q4-FY2015.pdf?MOD=AJPERES>

48 National Hog Farmer (2020b) Pork producers oppose FDA proposal to revoke carbadox, 19 September. Available at: <https://www.nationalhogfarmer.com/livestock/pork-producers-oppose-fda-proposal-revoke-carbadox>

from salmonella blood poisoning infections that were resistant to tetracycline. Oxytetracycline (another member of the same family) is widely used in veterinary medicine in the UK and elsewhere, but only to treat specific infections at full therapeutic doses for 1-5 days.

## USE OF CHLORTETRACYCLINE IN THE US

In the US, all chlortetracycline products for farm animals now require a veterinary prescription. In addition, the products are no longer permitted for off-label use. A large number of feed additives containing chlortetracycline are on the market for treating and controlling disease in cattle, pigs and poultry. However, one chlortetracycline product, Aureomycin 50, is still licensed simply for growth promotion in beef cattle feed, dairy replacement heifers, pigs and turkeys. This is particularly surprising since most chlortetracycline products included in the FDA's list of Medically Important Antimicrobial Drugs<sup>49</sup> indicate that such use has been ended. The Zoetis product label information on the Daily Med website, updated in June 2020, clearly states under Indications of Use, 'Growing Cattle (over 400lb): Increase rate of weight gain, improved feed efficiency, and reduction of liver condemnation due to liver abscesses at mg per head per day.'<sup>50</sup> It is unclear whether this is correct information or a mistake. In practice, however, it may make little difference. Another product Aureomycin 100 can be used at the same 70 mg/head per day rate indefinitely to reduce liver abscesses. As well as being incorporated into feed, Aureomycin 50 and 100 can be applied by 'top dressing', a practice long banned in the UK where farmers sprinkle the antibiotic on top of feed. It is known to be difficult to ensure that all animals in a group receive the recommended amounts when using this method.

The use of chlortetracycline in adult cattle feed in the UK has never been permitted. Oral use is permitted in calves for up to 7 days to treat specific infections. In the US Aureomycin is

also permitted in pig and poultry feed to treat various infections, but only for 5-14 days, similar to the UK.

## WHY UK CONSUMERS SHOULD AVOID BEEF, PORK AND TURKEY MEAT PRODUCED WITH AUREOMYCIN 50

A decision was taken in principle by the UK/EU, that due to the rise of antibiotic resistance, using antibiotics simply to increase growth rates should be ended. The EU will also be banning the use of prophylactic (i.e. preventative) medication in healthy farm animals from 2022<sup>51</sup>. Consuming meat produced in this way undermines the basis of that decision and could lead to back-tracking in the UK post-Brexit. From a food safety perspective, the long-term use of chlortetracycline antibiotics at low dosage rates is far more likely to encourage tetracycline resistant bacteria on meat carcasses than the short-term use of tetracycline antibiotics at full therapeutic doses.

Modern, semi-synthetic tetracycline such as, minocycline and closely related, glycylcyclines, like tigecycline, have been engineered to resist tetracycline resistance, which is widespread in bacteria from intensive farm animals, due to past, and in some cases, continuing widespread use of tetracyclines in livestock feed and water<sup>52</sup>. At present that is holding up and tigecycline, for example, is effective in treating highly multi-drug resistant infections in hospitals and therefore saving lives. However, one group of scientists has speculated that tigecycline will eventually acquire cross-resistance with tetracyclines due to the likely development of mutations<sup>53</sup>. They make no recommendations about farm use of tetracyclines, but a similar process has happened with other antibiotics such as the 3rd generation cephalosporins, once marketed to farmers as being immune to the development of resistance. These were known as 'hospital workhorses' little more than a decade ago. Today they can now no longer be relied upon to save lives due to high levels of resistance in *E. coli*. Their use in farming has

49 US FDA (2020) List of Medically Important Antimicrobial Drugs. Available at: <https://www.fda.gov/animal-veterinary/judicious-use-antimicrobials/list-medically-important-antimicrobial-drugs-affected-gfi-213>

50 Zoetis Inc. (2020) Aureomycin 50 Granular A data sheet, Revised June 2020. Dailymed website, accessed 17 November 2020. See product label datasheet. Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0706637a-1062-48ca-be00-4ef4b1dc37db>

51 Johnson, R (2018) EU bans prophylactic use of antibiotics in farming, The Pig Site, 25 October. Available at: <https://www.thepigsite.com/news/2018/10/eu-bans-prophylactic-use-of-antibiotics-in-farming-1>.

52 Chopra, I and Roberts, M (2001) Tetracycline Antibiotics: Mode of Action, Applications, Molecular Biology, and Epidemiology of Bacterial Resistance, *Microbiology and Molecular Biology Reviews*, 65:232-260. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC99026/>

53 Linkevicius, M, Sandegren, L and Anderson, DI (2016) potential of Tetracycline Resistance Proteins to Evolve Tigecycline Resistance, *Antimicrobial Agents and Chemotherapy*, 60:789-796. Available at: <https://aac.asm.org/content/60/2/789>

been drastically cut, and resistance has declined as a result, but the genie may not completely go back in the bottle.

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## MONENSIN - MARKETING AS RUMENSIN 90 BY ELANCO US INC, AND AS MONOVET 90 BY ALPHARMA; LASALOCID, MARKETING AS BOVATEC BY ZOEITIS INC.. AND LAIDLAMYCIN, MARKETING AS CATTLYST BY ZOEITIS INC.

Until 2006 Monensin was permitted as a growth promoting antibiotic in UK cattle production. It is now only permitted, under veterinary prescription, as a slow release bolus in dairy cows in high input systems where the cows can develop acidosis due to the use of very high energy diets. Lasalocid has never been approved in the UK in cattle or as a growth promoter in any species, despite its recognised growth promoting effects. It is, however, permitted as a coccidiostat in broiler chickens and other poultry species. Laidlomycin has never been approved in the UK.

### USE IN THE US

Monensin is permitted in feed as a growth promoter in growing cattle, both at pasture and in feedlots. It is also permitted for improved feed efficiency in suckler cows and to increase milk production in dairy cows. It can also be used to prevent coccidiosis<sup>54</sup>.

Use of the antibiotic lasalocid is approved specifically as a growth promoter for use in calves up to 300 kg in weight, except veal calves. It is not allowed in veal calves because no safe withdrawal period has been established for them. In the early 2000s, in

the UK, the widespread use of lasalocid in poultry, including in pullets being reared for egg production, resulted in about 12% of eggs being contaminated with residues, some at high and potentially harmful levels<sup>55</sup>. It can also be used to control parasites that cause coccidiosis which can be a major problem in intensive livestock production<sup>56</sup>.

Laidlomycin is approved for growth promotion and increased feed efficiency in cattle in the US<sup>57</sup>.

### WHY THE UK SHOULD NOT IMPORT BEEF OR DAIRY PRODUCE PRODUCED WITH MONENSIN, LASALOCID OR LAIDLAMYCIN

Monensin, lasalocid and laidlomycin are members of a large family of antibiotics, the ionophores, some of which have been used to promote growth and control diseases of intensification in intensive livestock production since the early 1970s. Similar issues apply to all three antibiotics.

The ionophores all have relatively high toxicity and have not been used in human medicine as yet. As a result, veterinary drug regulators often exclude them from reports on the use of antibiotics in livestock production. However, none of the ionophores has been permitted in beef production in the UK since 2006, and there are two fundamental reasons why we should not import beef into the UK that has been produced from cattle being fed ionophores. First, there is increasing evidence that ionophores may after all be needed in human medicine<sup>58,59</sup>. They have been extensively studied and are known to have a wide range of very important properties, and so some may prove important in human medicine:

### AS AN ANTIBIOTIC

One component of monensin, monensin A has

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54 Rumensin 90 – monensin granule. Drug label information, accessed 16 November 2020. Available via Dailymed website at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3e6db03e-55d5-4802-b0d2-3bc566e976b2>

55 Young, R and Nunan, C (2004) Too hard to crack? Eggs with drug residues, Soil Association, Bristol. Available at: [https://www.soilassociation.org/media/4938/policy\\_report\\_2004\\_too\\_hard\\_crack.pdf](https://www.soilassociation.org/media/4938/policy_report_2004_too_hard_crack.pdf)

56 Bovatec – lasalocid sodium granule. Drug label information, Dailymed website, accessed 16 November 2020. Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3e6db03e-55d5-4802-b0d2-3bc566e976b2>

57 Cattlyst – laidlomycin propionate potassium granule. Drug label information, Dailymed website, accessed 16 November 2020. Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4625ca45-89eb-48e5-83e7-ee7259c18796>

58 Kevin, DA, Meujo, DAF and Hamann, MT (2009) Polyether ionophores: broad-spectrum and promising biologically active molecules for the control of drug-resistant bacteria and parasites, Expert Opinion on Drug Discovery 4: 109-146. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4896753/>

59 Yoon, M J, Kang, Y J, Kim, IY, Kim, EH, Lee, JA, Lim, JH, Kwon, TK and Choi, KS (2013) Monensin, a polyether ionophore antibiotic, overcomes TRAIL resistance in glioma cells via endoplasmic reticulum stress, DR5 upregulation and c-Flip downregulation, Carcinogenesis 34: 1918-1928. Abstract available at: <https://pubmed.ncbi.nlm.nih.gov/23615398/>

been identified as a potential antibiotic for treating MRSA and other multi-drug resistant infections caused by gram-positive bacteria<sup>60</sup>. It has been identified as a potential treatment for the hospital superbug *Clostridium difficile*<sup>61</sup>. In addition, it has been suggested that the use of ionophores in livestock may already be resulting in resistance to other antibiotics due to co-selection (the ability to encourage bacteria to become or remain cross-resistant with antibiotics that are only distantly related or not related at all), a potentially serious problem that requires further investigation<sup>62</sup>.

## AS AN ANTI-VIRAL DRUG TO TREAT COVID-19

It has also been shown to have anti-viral properties<sup>63</sup>. Recently it has also been suggested by scientists that it could be developed as a drug to treat patients with COVID-19<sup>64</sup>.

## AS A CANCER TREATMENT

The ionophore salinomycin, previously marketed in the UK as the growth promoter, Salocin in pig production and currently used in intensive poultry systems in the US to control parasites, has recently been used in a successful pre-clinical trial to treat cancer of the eye<sup>65</sup>. It has also shown promising results against pre-clinical colorectal cancer cells<sup>66</sup>. Monensin has also been shown to inhibit various types of cancer cells,

including those causing pancreatic cancer<sup>67</sup>. Lasalocid A has also been shown to have similar anti-cancer properties<sup>68</sup>.

## ANIMAL WELFARE CONCERNS

The second reason is that there are significant animal welfare issues associated with the use of ionophores in livestock production. Due to their high toxicity, accidental overdosing which can and does occur for several different reasons, has long caused serious suffering and often death in a significant number of cattle<sup>69</sup>. This can be particularly acute when animals are also treated with or come into contact with certain other antibiotics at the same time<sup>70</sup>. The Vet Group in the US gives a warning of the toxicity of lasalocid in cattle. It says, 'Lasalocid toxicity has been a regular cause of death over the years'. It lists the signs of lasalocid toxicity as: depression, scouring (diarrhoea), weakness, rapid breathing, high temperature, recumbency, an absent look known as 'star gazing', and sudden death. Their website article includes a distressing photograph of several calves that died from lasalocid toxicity and at least one that had not died when the photograph was taken. They also say that even animals that survive the initial poisoning can later develop all the same symptoms and others, such as weight loss, swellings, congestive heart failure and sudden death. They say that in calves the normal dose is 1 mg per kg body weight but that just 3-5 times

60 Lowicki, D and Huczynski, A (2013) Structure and Properties of Monensin A and Its Derivatives: Summary of the Achievements, Biomed Research International. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3586448/>

61 Tam, J, Beilhartz, GL et al. (2015) Small molecule Inhibitors of *Clostridium difficile* Toxin B-Induced Cellular Damage, Chemistry and Biology, 22:175-185. Available at: [https://www.cell.com/ccbio/pdfExtended/S1074-5521\(14\)00458-X](https://www.cell.com/ccbio/pdfExtended/S1074-5521(14)00458-X)

62 Wong, A (2019) Unknown Risk on the Farm: Does Agricultural use of Ionophores Contribute to the Burden of Antimicrobial Resistance? mSphere. Available at: <https://msphere.asm.org/content/msph/4/5/e00433-19.full.pdf>

63 Lowicki, L and Huczynski, A (2013) Structure and Antimicrobial Properties of Monensin A and Its Derivatives: Summary of the Achievements, Biomed Research International. Available at: [https://www.researchgate.net/publication/236062171\\_Structure\\_and\\_Antimicrobial\\_Properties\\_of\\_Monensin\\_A\\_and\\_Its\\_Derivatives\\_Summary\\_of\\_the\\_Achievements](https://www.researchgate.net/publication/236062171_Structure_and_Antimicrobial_Properties_of_Monensin_A_and_Its_Derivatives_Summary_of_the_Achievements)

64 Sandulu, A (2020) Coronavirus: Scientists could repurpose drugs to treat infection, Medical News Today. Available at: <https://www.medicalnewstoday.com/articles/coronavirus-existing-drugs-could-be-repurposed-to-treat-infection>

65 Zhou, J, Liu, S, Wang, Y, Dai, W, Zou, H, Wang, S, Zhang, J and Pan, J (2019) Salinomycin effectively eliminates cancer stem-like cells and obviates hepatic metastasis in uveal melanoma, Molecular Cancer, 18, 159 (2019). <https://doi.org/10.1186/s12943-019-1068-1>. Available at: Salinomycin effectively eliminates cancer stem-like cells and obviates hepatic metastasis in uveal melanoma. Mol Cancer 18, 159 (2019). <https://doi.org/10.1186/s12943-019-1068-1>

66 Klose, J et al. (201) Salinomycin: Anti-tumor activity in a pre-clinical colorectal cancer model, Plus One. Available at: <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0211916>

67 Wang, W, Wu, X and He, T-C et al. (2018) Monensin inhibits cell proliferation and tumor growth of chemo-resistant pancreatic cells by targeting the EGFR signaling pathway, Nature Scientific Reports 8. Available at: <https://www.nature.com/articles/s41598-018-36214-5> - citeas

68 Yoon, M J, Kang, Y J, Kim, IY, Kim, EH, Lee, JA, Lim, JH, Kwon, TK and Choi, KS (2013) Monensin, a polyether ionophore antibiotic, overcomes TRAIL resistance in glioma cells via endoplasmic reticulum stress, DR5 upregulation and c-Flip downregulation, Carcinogenesis 34: 1918-1928. Abstract available at: <https://pubmed.ncbi.nlm.nih.gov/23615398/>

69 The Ohio State University, Ohio BEEF Cattle Letter, 'Be aware when Feeding Ionophores to Cattle – an Overdose May prove Deadly', accessed 16 November 2020. Available at: <https://u.osu.edu/beef/2018/01/31/be-aware-when-feeding-ionophores-to-cattle-an-overdose-may-prove-deadly/>

70 Basaraba, RJ, Oehme, MW et al. (1999) Toxicosis in Cattle from Concurrent Feeding of Monensin and Dried Distiller's Grains Contaminated with Macrolide Antibiotics. Abstract available at: <https://journals.sagepub.com/doi/abs/10.1177/10406387990100113>



this dose can cause these symptoms<sup>71</sup>.

Similar symptoms and warnings in relation to monensin are listed by Ohio State University. A 2015 report from dairyherd.com (no longer available online) reports that 233 calves died on one farm from an accidental overdose with monensin. In a recently removed article on the Drover's website (a copy of which was saved) it is pointed out that ionophore poisoning can also occur even when the correct dose is given when certain other antibiotics are being used at the same time or when heavy rain dissolves 'salt forms of minerals which, if leached from the mineral feeders, can increase the concentration of ionophore remaining<sup>72</sup>.

## TYLOSIN – MARKETING AS TYLAN BY ELANCO US INC.

Until 1999, tylosin was licensed for growth promotion in pigs in the UK. It remains available for the treatment of disease in cattle, pigs and poultry

### USE OF TYLOSIN IN THE US

Tylan 40 is just one of a very large number of antimicrobial products containing tylosin that are on the market in the US. While tylosin products are no longer permitted for growth promotion in the US, Tylan 40 is permitted for continuous use in beef cattle feed at just 8-10 grams per ton. While tylosin was never approved for use in cattle feed in the UK, the dosage rate is similar to the previous growth promoting rate of tylosin feed additive for pigs in the UK of 10-40g per tonne. Tylan 40 can also be fed to pigs at 100g per ton for 3 weeks followed by 40g

per ton until slaughter<sup>73</sup>. Such use requires a veterinary feed directive to control disease, but is essentially the same as using it as a growth promoter.

## WHY UK CONSUMERS SHOULD AVOID BEEF IN PARTICULAR PRODUCED WITH ROUTINE LOW-LEVEL USE OF TYLOSIN

Tylosin was banned in the UK and EU due to the fact that it is a macrolide antibiotic. Macrolides are important in both human and veterinary medicine. For example, the macrolide erythromycin is the drug of choice for people who are allergic to penicillin. The direct concern is that campylobacter has become common on some US feedlots<sup>74,75</sup>. The current extent of campylobacter on beef in the US is not clear, however, campylobacter from could also pass from feedlots to human via water<sup>76</sup> a transmission route that is recognised. Pigs are also a source, but a minor one<sup>77</sup>. Macrolide antibiotics are one of the two main classes of antibiotics available to treat invasive campylobacter infections when they occur and the only ones suitable for children. Erythromycin and its close relative, azithromycin are the drugs of choice<sup>78</sup>. The fluoroquinolone ciprofloxacin can also be used, but only in adults. As a result, the concern is acquired macrolide resistance in campylobacter due to the use of tylosin in cattle feed.

As long ago as 2007, representative of Elanco who market tylosin products, acknowledged that the sub-therapeutic use of tylosin in chickens (the most significant source of campylobacter food poisoning) results in macrolide resistance in campylobacter, whereas its short-term use at a full therapeutic dose

71 The Vet Group (2020), Lasalocid (Bovatec) toxicity: be aware, and prepare! 29 June, accessed 16 November 2020. Available at: <https://www.thevetgroup.com.au/lasalocid-bovatec-toxicity-be-aware-and-prepare/>

72 Arnold, M (2018) Be Aware When Feeding Cattle Ionophores: An Overdose May Prove Deadly, Drovers. No longer available on the Drovers, website but can be accessed at: <https://u.osu.edu/beef/2018/01/31/be-aware-when-feeding-ionophores-to-cattle-an-overdose-may-prove-deadly/>

73 Elanco (2020) Tylan 40 Type A Medicated Feed Article. Revised July 2020. Available via the Dailymed website: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2134d14f-3d1a-4564-9944-a47d594f031d>

74 Besser, TE, LeJeune, JT, Rice, DH, Berg, J, Stiborn, RP, Kaya, K, Bae, W and Hancock, DH (2005) Increasing Prevalence of Campylobacter jejuni in Feedlot Cattle through the feeding period, Applied and Environmental Microbiology, 71:5752-5758. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1265937/>

75 Hannon, SJ, Allen, B, Waldner, C, Russell, ML, Potter, A, Babiuk, LA and Townsend, HGC (2009) Prevalence and risk factor investigation of Campylobacter species in beef cattle feces from seven large commercial feedlots in Alberta, Canada, Canadian Journal of Veterinary Research 73:275-282. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2757708/>

76 Besser, TE, LeJeune, JT, Rice, DH, Berg, J, Stiborn, RP, Kaya, K, Bae, W and Hancock, DH (2005) Increasing Prevalence of Campylobacter jejuni in Feedlot Cattle through the feeding period, Applied and Environmental Microbiology, 71:5752-5758. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1265937/>

77 Harvey, RB (2015) Campylobacter in the Pork Food Chain, Pork Information Gateway. Available at: <https://porkgateway.org/wp-content/uploads/2015/07/campylobacter-in-the-pork-food-chain1.pdf>

78 CDC (2019) Campylobacter (Campylobacteriosis). Available at: <https://www.cdc.gov/campylobacter/campy-antibiotic-resistance.html>



does not<sup>79</sup>. This is significant but in relation to poultry there is little major difference in the use of tylosin between the US and UK at present. There is an interesting historical note here. The Swann Committee which published its report in 1969 recommended that the use of tylosin for growth promotion should be ended, along with similar use of tetracyclines and penicillin. The Government initially agreed to this, but representatives of Elanco argued strongly against the need for this<sup>80</sup>, and eventually the Department of Health and Social Security accepted their arguments and the ban was not introduced. It would then take until 1999 until its use as an antibiotic growth promoter was finally banned in the UK.

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## VIRGINIAMYCIN (BRAND NAME STAFAC)

Virginiamycin is a streptogramin antibiotic. It is not used in human medicine, but the closely related drug Synercid, which is a combination of two antibiotics both closely related to virginiamycin, can be given intravenously and used to treat patients with highly drug-resistant strains of MRSA and a hospital superbug known as VRE (vancomycin-resistant enterococci) which have failed to respond to other antibiotics.

All food animal use of virginiamycin was banned in the UK in 1999 and in 2014, after a long campaign by the Soil Association, its use in horse feed was also banned<sup>81</sup>.

## USE IN US LIVESTOCK PRODUCTION

In the US, virginiamycin is permitted in the feed of cattle, pigs and poultry, both to treat infections and to control (i.e. reduce the incidence of) the diseases of intensification: liver abscesses in cattle, swine dysentery in pigs and necrotic enteritis in poultry. A veterinary prescription is now needed, but the antibiotic can also be fed continuously at low levels similar to those previously licensed for growth

promotion in the UK. In feedlot cattle, for example, it can be fed continuously at between 85-240 mg per head per day<sup>82</sup>. The lowest approved dose is therefore just over double the highest dose previously permitted in the UK for growth promotion of 40 mg<sup>83</sup>. However, as with bacitracin, off-label use is only prohibited in California. As such there is nothing to stop a veterinary surgeon prescribing it at a lower dose. In pigs it can be included at a rate of just 25g per ton for continuous feeding. This is within the same range of 10-40g per tonne previously permitted in the UK just for growth promotion. Similarly, the US approved rate of just 20g of virginiamycin per ton to control necrotic enteritis in poultry is within the same range as the past growth promotion range of 10-40g per tonne. However, as with bacitracin, there is no restriction of off-label use, except in California.

## WHY WE SHOULD BE CONCERNED ABOUT IMPORTING MEAT PRODUCED WITH VIRGINIAMYCIN INTO THE UK

The principal concern with the widespread use of virginiamycin is the development of virginiamycin-resistant enterococci, which could render the antibiotic Synercid ineffective for the treatment of vancomycin-resistant enterococci (VRE). Enterococci are gut bacteria in humans and animals. They rarely cause infections in animals, but can cause urinary tract and other infections in humans and contaminate wounds through faecal contamination and cause blood poisoning if the initial infection fails to respond to antibiotics. Antibiotic resistance and death rates in enterococci is very high (see under avilamycin, above).

Synercid is a combination of two antibiotics, both closely related to virginiamycin. Scientists list it as one of just four remaining antibiotics they can use to treat VRE. They say, 'The emergence of multidrug resistance in enterococci is worrisome and of global concern<sup>84</sup>.

However, Synercid is not currently

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79 Belanger, AE and Shrylock, TR (2007) Macrolide-resistant *Campylobacter*: the meat of the matter, *Journal of Antimicrobial Chemotherapy*, 60: 715-723. Available at: <https://academic.oup.com/jac/article/60/4/715/713932>

80 Mackinnon, JD (1981) The Use of Tylosin in Feed and Therapy – A Review, in *Ten years On From Swann*, pp51-70, proceedings of a symposium, The Association of Veterinarians in Industry, London

81 *Veterinary Record* (2012) VMD to phase out importation of virginiamycin for veterinary use. Available at: <https://veterinaryrecord.bmj.com/content/171/2/35.2>

82 V-MAX 50 virginiamycin power, listing on Dailymed website, see drug label info, accessed 12 November 2020. Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=de8f877b-06fe-41bc-a409-d4e5546cb5da>

83 Mounsey, MD (Ed) (1996/7) *Handbook of Medicinal Feed Additives*, HGM Publications, pp. 183-

84 Ahmed, M and Baptiste, KE (2017) Vancomycin-Resistant Enterococci: A Review of Antimicrobial Resistance Mechanisms and Perspectives of Human and Animal Health, *Microbial Drug Resistance*. Abstract available at: <https://pubmed.ncbi.nlm.nih.gov/29058560/>

recommended for the treatment of VRE in the US or the UK. The NHS recommends it only for the treatment of ‘complicated skin and skin structure infections caused by *Staphylococcus aureus* and *Streptococcus pyogenes*’<sup>85</sup>. While a study in 2000 found that it cured or improved the condition of 19 out of 23 patients with VRE<sup>86</sup> in another study the antibiotic linezolid cured a case of VRE that had not been cured by Synercid<sup>87</sup>. At present Linezolid is the only antibiotic recommended for the treatment of VRE in the US. Despite its use being restricted to very specific cases, Linezolid resistance is, nevertheless, increasing worldwide and one study reports that it failed to cure two out of four cases in a US hospital in 2017. In such cases, it seems that a small number of other antibiotics, including Daptomycin and Tigecycline are still preferred to Synercid<sup>88</sup>. Yet cases of resistance to all these antibiotics also occur<sup>89</sup>.

On this basis it could be argued that the continuing use of virginiamycin in livestock production poses only a small threat to human health. However, enterococci have a remarkable ability to develop resistance to antibiotics very quickly and enterococcal resistance to all major classes of antibiotics occurs not infrequently<sup>90</sup>. Evidence is emerging to show that a number of unrelated antibiotics are also able to promote or maintain VRE in the absence of vancomycin or its related antibiotics. A lab-based study in 2017 found that while only one of five strains of *E. faecium* (one of the two main causes of VRE) developed resistance to Synercid after low concentration exposure to virginiamycin, some mutants also developed resistance to three other antibiotics: tylosin, nitrofurantoin and kanamycin<sup>91</sup>. As such, the prudent approach would be to end the use of virginiamycin in the US on the same precautionary basis it was ended in food animals in the UK and wider EU in

1999.

Vancomycin resistance is complex and there are many different types of ‘Van’ genes involved. Scientists say, ‘VanA-VRE are more commonly associated with poultry than other food animals (e.g. cattle and pigs), with some geographic differences. On the other hand, Van C and VanN-VRE phenotypes have been detected frequently from farm and companion animals as well as meat products destined for human consumption (i.e. chicken, pigs, cow and horse). They also add, ‘The role of animals and food products in the human VRE population dynamics needs to be further defined. While many aspects of VRE are well known to human and public health, both veterinary and agricultural awareness of these ongoing issues is sparse’<sup>92</sup>.

In general, the drugs of last resort have more serious side effects than more commonly prescribed antibiotics. The most likely reason these antibiotics are still effective is because they have not been widely used for this reason. As such, if the importation of beef, pork or poultry from the US brought virginiamycin-resistant enterococci to the UK, this could eventually render Synercid ineffective.

85 NHS RxList, Synercid, accessed 16 November 2020. Available at: <https://www.rxlist.com/synercid-drug.htm> - description

86 Winston, DJ, Emmanouilides, C, Kroeber, A, Hindler, J, Bruckner, DA, Territ, MC and Busuttill, RW (2000) Quinupristin/Dalfopristin Therapy for Infections Due to Vancomycin-Resistant *Enterococcus faecium*, *Clinical Infectious Diseases* 30:790-797. Available at: <https://academic.oup.com/cid/article/30/5/790/321336>

87 McNeil, SA, Clark, NM, Chanrasekar, PH and Kauffman, CA (2000) Successful Treatment of Vancomycin-Resistant *Enterococcus faecium* Bacteremia with Linezolid after Failure of Treatment with Synercid (Quinupristin/Dalfopristin), *Clinical Infectious Diseases* 30:403-4. Available at: <https://academic.oup.com/cid/article/30/2/403/382939>

88 Abbo, L et al. (2019) Linezolid- and Vancomycin-resistant *Enterococcus faecium* in Solid Organ Transplant Recipients: Infection Control and Antimicrobial Stewardship Using Whole Genome Sequencing, *Clinical Infectious Diseases*, 69: 259-265.

89 García-Solache, M and Rice, LB (2019) The *Enterococcus*: a Mode of Adaptability to its Environment, *Clinical Microbiology Reviews* 32, Issue 2 e00058-18. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6431128/pdf/CMR.00058-18.pdf>

90 Ibid.

91 Ge, B et al. (2017) Effects of low concentrations of erythromycin, penicillin, and virginiamycin on bacterial resistance development in vitro, *Nature Scientific Reports*, DOI:10.1038/s41598-017-09593-4. Available at: <https://www.nature.com/articles/s41598-017-09593-4>

92 Ahmed, Mo and Baptiste, KE (2017) Vancomycin-Resistant *Enterococci*: A Review of Antimicrobial Resistance Mechanisms and Perspectives of Human and Animal Health, *Microbial Drug Resistance*, DOI: 10.1089/mdr.2017.0147. Abstract available at: <https://pubmed.ncbi.nlm.nih.gov/29058560/>

## CHAPTER 3 – BETA-AGONISTS

While the use of hormone growth promoters in the US has been widely publicised, the use of beta-agonists in US beef production has received little publicity in the UK. Beta-agonists are non-hormonal drugs that relax the muscles of airways and make for easier breathing. They have long been used in human medicine for specific medical reasons. However, they also have the effect of increasing the production of lean meat and feed efficiency in cattle and pigs during the latter stages of feeding before slaughter. Until 2013 two beta-agonists were widely used in US beef production. At the present time only one is legally available though there is some evidence of occasional illegal use with a third beta-agonist, clenbuterol, though that problem is not confined to the US.

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### HISTORY OF BETA-AGONISTS IN THE UK

In 1989, shortly after hormone growth promoters were banned in the UK and the EU, efforts were made by certain pharmaceutical companies to get beta-agonists licensed as an alternative. Two presentations at the Association of Veterinarians in Industry symposium in London in December that year, one by Dr Vernon Fowler from the North of Scotland College of Agriculture the other from Dr Paul Allen from the National Food Centre in Dublin, promoted them as problem-free replacements to hormones<sup>93</sup>. The licensing attempts were unsuccessful in the UK, and a wider EU Council Directive in 1996 prohibited the 'placing on the market of beta-agonists for administering to animals, the flesh and products which are intended for human consumption'<sup>94</sup>.

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### HEALTH CONCERNS

At the time, the health concerns to justify the ban were based more on illegal use and general lack of data about the effect of residues on

humans, than on specific evidence of harm. In a mirror image of that approach, the Food and Drug Administration in the US approved the use of the beta-agonist ractopamine in pig production without conducting any tests itself<sup>95</sup>. In 2006 JECFA (the Joint FAO/WHO Expert Committee on Food Additives) confirmed its provisional previous Acceptable Daily Intake levels (ADIs) per person and Maximum Residue Levels (MRLs) per item of food for Ractopamine, allowing meat produced with it to be marketed under WTO rules. Although the EFSA (European Food Safety Authority) panel commissioned no new studies, the members looked more widely at the available research<sup>96</sup> and were concerned by the widely varying results between different studies. The only study in humans found increased heart rates at all three higher dosage rates. With only six participants and one man having to be withdrawn from the study due to adverse cardiac effects, EFSA decided that there were too many weaknesses in the data to set an ADI and MRLs for ractopamine. As a result, it could not be licensed in the EU. The highest levels of drug residues are generally found in liver and kidney. JECFA had set MRLs for ractopamine in pork of 150 micrograms/kg for liver and 200 for kidney. China banned imports of all meat produced with beta-agonists, in part because the Chinese are particularly fond of offal<sup>97</sup>.

Russian regulators have taken a similar position. A review by Russian scientists (in translation) reports the position they presented to the relevant FAO/WHO body, the Codex Alimentarius Commission 'The acceptable ractopamine daily intake [as agreed by JECFA] is insufficiently validated and cannot be used for the determination of maximum permitted levels of ractopamine in meat and meat by-products (offal).' They also state that, 'By taking into account the levels of animal products consumption in Russian Federation [it] will lead to unacceptable human health risk level that will promote increasing heart diseases and life

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93 The Association of Veterinarians in Industry (1989) Animal Health in a Safer Environment, Proceedings of a Symposium, London.

94 EU Council Directive 96/22/EC (1996 of 29 April. Available at: <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31996L0022&from=EN>

95 Centner, T. J., Alvey, J.C and Stelzl, A.M. (2014) Beta agonists in livestock feed: Status, health concerns and international trade, *Journal of Animal Science*: 92:4234-4240. Abstract available at: <https://pubmed.ncbi.nlm.nih.gov/25057027/>

96 Bories, GP, Brantom, J, et al. Safety evaluation of ractopamine: EFSA panel on additives and products or substances used in animal feed (FEEDAP) EFSA J. 1041-52. Available at: <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2009.1041>

97 Centner, T. J., Alvey, J.C and Stelzl, A.M. (2014) Beta agonists in livestock feed: Status, health concerns and international trade, *Journal of Animal Science*: 92:4234-4240.

Ractopamine is banned in the UK, EU, Russia and China

expectancy reduction. In this connection Russia states against of acceptance of maximum permitted levels of ractopamine in food'. A point to note here is that MRLs (the safe residue level in any particular food) are calculated from the ADI (the estimated safe daily intake of a chemical) based on assumptions about how much of each food an average person consumes. If someone were to consume twice or three times as much as an average person in one day they could exceed the ADI.

Optaflexx (ractopamine), marketed by Elanco Animal Health is currently in use in the US (and also available as Paylean for use in pigs and turkeys) but Zilmax (zilpaterol) marketed by Merck and Co was withdrawn in 2013 after Tyson Foods said they would no longer buy treated animals because many were arriving at slaughterhouses lame and distressed.

Merck then withdrew their product which had been in use in the US since 2006 and was also licensed in 14 countries. In 2015, after undertaking further trials they said 'The results from the observations and additional studies all reaffirm Zilmax's safety and conclude that it has no negative impact on the well-being of cattle'<sup>98</sup>. However, despite requests from cattlemen and positive statements about the drug, it does not appear to be back on the market five years later. Attempts to check this via US farm drug suppliers brought up messages saying, 'information not available outside the US' and, 'We have purged all EU sources from our website'.

According to Penn State Extension, the use of Zilmax increased profit by \$3-4 per animals<sup>99</sup>. In steers it is claimed to increase carcase weight by up to 20 lbs. Heifers in a trial in 2004/5 treated with Optaflexx as well as a hormone

growth promoter and two antibiotics for 35 days before slaughter had average carcase weights 11 pounds higher than heifers fed the same diet without Optaflexx. However, the Optaflexx feed additive cost \$0.26 a day and the treated animals were only fractionally more profitable overall<sup>100</sup>.

These very small financial gains from using such products seem almost insignificant until we remember that some feedlots hold 50,000 cattle at a time and typically have 2.5 crops of cattle through each feedlot annually. As such even a extra \$1-4 per beast would bring in an extra \$125,000 to \$500,000 profit annually.

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## ILLEGAL USE

A third beta-agonist, clenbuterol (commonly known as 'angel dust') is occasionally discovered to have been used illegally in beef production, but that problem is not unique to the US. One of the most recent cases was reported in Ireland in 2016<sup>101</sup>. The use of clenbuterol is also illegal in the US and China. It was banned in Mexico in 2000, but illegal use was said to be continuing in 2014 in Central Mexico. In addition, it is available in many countries under veterinary prescription for use in horses. It seems that supplies are available on the black market and some illegal use also continues in the US and China<sup>102</sup>. It is also a banned performance enhancing drug in athletics, but athletes have tested positive for clenbuterol after eating beef containing residues of it<sup>103</sup>.

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98 Merck Animal Health (2015) About Zilmax. Available at: <http://www.zilmax.com/about-zilmax.aspx>

99 Penn State University Extension (2017) Use of Beta-Agonists in Cattle Feed. Available at: <https://extension.psu.edu/use-of-beta-agonists-in-cattle-feed>

100 Griffin, W. A. et al. (2006) Effects of Optaflexx Fed in Combination with MGA on Feedlot Heifer Performance', 2006 Nebraska Beef Report. Available at: <https://core.ac.uk/download/pdf/188122841.pdf>

101 Case, P (2016) Probe into 'angel dust' found in cattle, Farmers Weekly. Available at: <https://www.fwi.co.uk/news/probe-angel-dust-found-cattle>

102 Drovers (2011) Clenbuterol still a problem: Available at: <https://www.drovers.com/article/clenbuterol-still-problem>

103 USDA (2019) Clenbuterol and Meat Consumption. Available at: <https://www.usda.org/spirit-of-sport/clenbuterol-and-meat-contamination/>

# APPENDIX 1 – THE EXTENT TO WHICH US REGULATORS HAVE ACTED MORE PROMPTLY AND DECISIVELY IN RELATION TO ONE OF THE MOST URGENT ANTIBIOTIC-RESISTANCE ISSUES

While US regulators have not stopped all use of antibiotics for growth promotion, they have acted more quickly and decisively than UK regulators in relation to one of the most immediate threats to human health, linked to the use of antibiotics in livestock production.

## FLUOROQUINOLONES

In 1997, the US Food and Drug Administration (FDA) prohibited the extra-label use of fluoroquinolones and in 2005 they completely withdrew approval for this class of antibiotics in poultry production<sup>104</sup>. Extral-label use (off-label use in the UK) allows veterinary surgeons the discretion to use antibiotics in ways other than those that are approved, if no other licensed antibiotic is available for a specific condition. In the UK, US and elsewhere, specialist poultry vets were prescribing the fluoroquinolone enrofloxacin, marketed as Baytil, Enroxil and other brands, for use in the drinking water of day-old chicks as a preventative measure against possible *E. coli* and other infections.

After initial lobbying from the Soil Association, and more recently from the Alliance to Save Our Antibiotics<sup>105</sup>, the UK poultry industry reluctantly agreed not to use fluoroquinolones in healthy birds to prevent diseases developing. The package leaflet for Baytril 10% oral solution, for example, now states, 'Do not use for prophylaxis'. However, UK regulators still approve the use of fluoroquinolones for the treatment of infections in chickens and turkeys<sup>106</sup>, whereas the FDA does not allow this.

The UK regulator, the Veterinary Medicines

Directorate (VMD), acknowledges that, 'Use of the product deviating from the instructions given in the SPC [summary of product characteristics] may increase the prevalence of bacteria resistant to the fluoroquinolones and may decrease the effectiveness of treatment with other quinolones due to the potential for cross resistance. Since enrofloxacin was first authorised for use in poultry, there has been widespread reduction in susceptibility [i.e. increased resistance] of *E. coli* to fluoroquinolones and emergence of resistant organisms.'<sup>107</sup>

Fluoroquinolones have been one of the two main classes of antibiotics that can be used to treat invasive campylobacter infections in humans. Most people who get campylobacter infections recover naturally, but in a small proportion of cases the infection can be much more serious and require antibiotics. Chickens are the biggest source of campylobacter food poisoning, with about half of all retail chickens in the UK being contaminated<sup>108</sup>. As a result, the spread of fluoroquinolone-resistant campylobacter from chickens to humans is a serious concern.

The development of the fluoroquinolones from the late 1970s onwards was a major breakthrough in antibiotic treatments. The parent compound was simply discovered as an impurity during the manufacture of quinine for the treatment of malaria. This antibiotic, nalidixic acid, has since been modified synthetically to create a large family of broad-spectrum antibiotics<sup>109</sup> with the ability to penetrate parts of the body and therefore treat infections, which many other antibiotics are unable to reach, even

104 CIDRAP (2005) FDA to ban enrofloxacin in poultry. Available at: <https://www.cidrap.umn.edu/news-perspective/2005/07/fda-ban-enrofloxacin-use-poultry>

105 ASOA (2016) Why the use of fluoroquinolones antibiotics in poultry should be banned. Available at: <https://www.saveourantibiotics.org/media/1495/why-the-use-of-fluoroquinolone-antibiotics-in-poultry-must-be-banned-alliance-to-save-our-antibiotics-july-2016.pdf>

106 VMD (2018) Enroxil (enrofloxacin) 100 mg/ml oral solution for chickens and turkeys. Available via the Veterinary Medicines Product Database: <https://www.vmd.defra.gov.uk/productinformationdatabase/>

107 VMD (2018) Summary of Product Characteristics Enroxil 100 mg/ml oral solution for chickens and turkeys. Available at: [https://webcache.googleusercontent.com/search?q=cache:JkzOivhWhtYJ:https://www.vmd.defra.gov.uk/productinformationdatabase/SPC\\_Documents/SPC\\_493794.DOCX+cd=2&hl=en&ct=clnk&gl=uk&client=safari](https://webcache.googleusercontent.com/search?q=cache:JkzOivhWhtYJ:https://www.vmd.defra.gov.uk/productinformationdatabase/SPC_Documents/SPC_493794.DOCX+cd=2&hl=en&ct=clnk&gl=uk&client=safari)

108 NHS (2020) Why you should never wash raw chicken. Available at: <https://www.nhs.uk/live-well/eat-well/never-wash-raw-chicken/>

109 Andersson, MT and MacGowan, AP (2003) Development of the quinolones, *Journal of Antimicrobial Chemotherapy* 51, Suppl. SI, 1-11.



when they would otherwise be effective<sup>110</sup>. They have become progressively more important over the years as new members of the family have been developed with additional features. Despite their diversity, however, antibiotic resistance to fluoroquinolones is increasing rapidly and while cross-resistance does not currently exist between all fluoroquinolones, this is increasing step by step<sup>111,112</sup>.

Developing new antibiotics that will cure infections caused by bacteria belonging to one half of the bacterial kingdom, known as Gram-negative bacteria, is proving to be more difficult than with the other half, the Gram-positive bacteria. This is because Gram-negative bacteria have a tougher outer wall making it harder for antibiotics to penetrate. One new antibiotic substance, darobactin, is under consideration as a potential antibiotic to treat infections caused by Gram-negative bacteria<sup>113</sup>, but no new class of antibiotics of the same importance as the fluoroquinolones has been successfully developed and introduced in almost fifty years.

Due to their extensive use in both farm animals and human medicine, the fluoroquinolones are already becoming less effective and reliable against campylobacter<sup>114</sup> tuberculosis, salmonella, gonorrhoea and many other similar infections that have acquired multiple antibiotic resistance. Antibiotic resistance from chicken is also a major source of antibiotic resistance in *E. coli* infections, such as urinary tract infections<sup>115</sup>, where the fluoroquinolone Cipro (ciprofloxacin) is an important antibiotic for treating infections.

As such, it has to be in the interests of society as a whole to limit the use of fluoroquinolones, in both human and veterinary medicine, as far as possible.

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110 Oliphant, CM and Green, GM (2002) Quinolones: A Comprehensive Review, *American Family Physician* 65: 455-465. Available at: <https://www.aafp.org/afp/2002/0201/p455.html>

111 Andersson, MT and MacGowan, AP (2003) Development of the quinolones, *Journal of Antimicrobial Chemotherapy* 51, Suppl. SI, 1-11.

112 Dalhoff, A (2012) Emergence and Spread of Antimicrobial-Resistant Pathogens in an Era of Globalization, *interdisciplinary Perspectives on Infectious Diseases*. Available at: <https://www.hindawi.com/journals/ipid/2012/976273/>

113 Imai, Y, Meyer, KJ et al. (2019) A new antibiotic selectively kills Gram-negative pathogens, *Nature* 576: 459-464, Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7188312/>

114 Sproston, EL, Wimalaratna, HML and Sheppard, SK (2018) Trends in fluoroquinolone resistance in *Campylobacter*, *Microbial Genomics* 4 (8) August. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6159550/>

115 Nunan, C and Young, R (2012) *E. coli* superbugs on farms and food, *Soil Association*. Available at: <http://sustainablefoodtrust.org/wp-content/uploads/2013/04/E.Coli-Superbugs-single-pages.pdf>

## APPENDIX 2 – WAS THERE ANYTHING IMPROPER ABOUT THE WITHDRAWAL OF EVERNINOMICIN FROM PHASE III TRIALS?

In October 2000, a scientist from the Pasteur Institute in Paris suggested in a published letter, that the use of avilamycin should be ended because it was cross-resistant with everninomicin<sup>116</sup> (the House of Commons Agriculture Committee in the UK had been widely criticised for a similar recommendation in 1998 which was to end all use of antibiotics for growth promotion). In response, Dr Thomas Shrylock from Elanco argued that there was incomplete cross-resistance, but not full cross resistance. He then pointed out that the question was by then no longer relevant anyway, because Schering-Plough had withdrawn everninomicin (Ziracin) from trials<sup>117</sup>.

Dr Shrylock from Elanco and Aimee Belanger from Elanco's parent company, Eli Lilly, then set out their case that Schering-Plough did not withdraw everninomicin from trials and further development because the use of avilamycin was already compromising its effectiveness<sup>118</sup>.

Some years later a Danish scientist published research which seems to confirm the claims of Belanger and Shrylock. Both avilamycin-sensitive and avilamycin-resistant strains were checked to see if they were resistant to everninomicin. The conclusion: 'Complete agreement between decreased susceptibility to avilamycin and everninomicin was found'. That sounds as if the strains were not completely resistant to everninomicin. However, the fact that avilamycin reduced the effectiveness of everninomicin would surely have been enough to have ended the continuing routine use of avilamycin in pig and poultry feed for growth promotion in the EU, if everninomicin had continued from phase III trials into medical use, as was widely

anticipated? Avilamycin eventually lost its license in the EU anyway at the beginning of 2006. But when the everninomicin trials were suspended it was not clear that would happen.

Reduced susceptibility to antibiotics can lead to full resistance. One early documented example is that penicillin remained entirely effective against *Streptococcus pneumoniae* (a cause of pneumonia, meningitis and the serious ear infection, otitis media) until 1960, when intermediate resistance was first observed. Fully resistant strains were seen from the mid-1970s and by the late 1990s, 40% of cases in the US were fully resistant<sup>119</sup>.

It is clear that there were some issues with the development of everninomicin. A trial with healthy volunteers found kidney and liver issues in some patients, and it was unclear whether these related solely to everninomicin or partially to some of its breakdown products, which had not been fully identified at the time. However, the researchers pointed out that vancomycin is actually toxic to the kidneys. They therefore, concluded, 'This agent [everninomicin (Ziracin)] is safer than vancomycin or teicoplanin in patients with reduced renal [kidney] function, but consideration should be given to the possibility of formation of urate stones and subsequent renal impairment.'<sup>120</sup> At a conference in 1997 Schering-Plough had stated that while other antibiotics from the same family as everninomicin cause kidney damage that could not be reversed, everninomicin did not. But they also reported that it had a negative effect on the liver in the case of 10% of patients<sup>121</sup>.

Another aspect is that at the time, rather more replacement antibiotics for vancomycin

116 Courvalin, P (2000) Will Avilamycin Convert Ziracin to Zerocine?, *Emerging Infectious Diseases* 6 Number 5, October. Available at: [https://wwwnc.cdc.gov/eid/article/6/5/00-0521\\_article](https://wwwnc.cdc.gov/eid/article/6/5/00-0521_article)

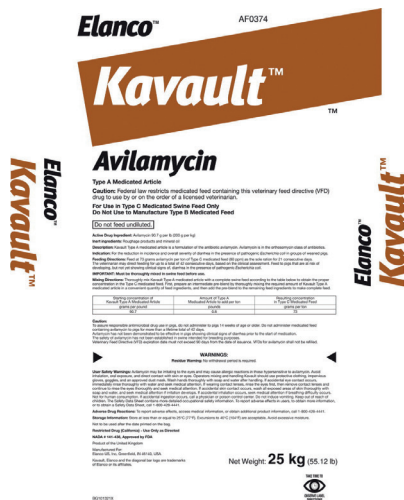
117 Shrylock, T (2001) Will Avilamycin Convert Ziracin to Zerocine? *Emerging Infectious Diseases* 7 Number 3, June. Available at: [https://wwwnc.cdc.gov/eid/article/7/3/01-7336\\_article](https://wwwnc.cdc.gov/eid/article/7/3/01-7336_article)

118 Belanger, AE and Shrylock, TR (2005) Avilamycin did not play a role in the discontinuation of evernimicin as a clinical drug candidate *JMS Letters, Journal of Mass Spectrometry* 40: 1109

119 Young, R, Cowe, A, Nunan, C, Harvey, J and Mason, L (1999) The Use and Misuse of Antibiotics in UK Agriculture, Part II, Antibiotic Resistance and Human Health, Appendix VII, Soil Association, Bristol. Available at: [https://www.soilassociation.org/media/4947/policy\\_report\\_1999\\_use\\_misuse\\_antibiotics.pdf](https://www.soilassociation.org/media/4947/policy_report_1999_use_misuse_antibiotics.pdf)

120 Nagashima, S., Niwa, M., Nishiki, K., Hosoya, T., Hishida, A., & Uematsu, T. (2004). Effects of SCH27899 (Ziracin), an oligosaccharide everninomicin antibiotic, on urate kinetics in humans. *European Journal of Clinical Pharmacology*, 60(4). doi:10.1007/s00228-004-0755-y

121 The Pharmaletter 2000 S-P discontinues Ziracin development after risk:benefit review. Available at: <https://www.thepharmaletter.com/article/s-p-discontinues-ziracin-development-after-risk-benefit-review>



Avilamycin but was banned in the UK in 2006

came onto the market than most people had expected, including Linezolid, Daptomycin and Synercid. In addition, vancomycin has remained more effective against MRSA and enterococci than many people feared. Elanco had a profitable farm antibiotic in avilamycin that needed no further development. Schering-Plough had a potentially life-saving antibiotic for human medicine that needed more investment and might only result in modest sales in the immediate and even medium-term future. Without the emergence of whistle-blower, we will probably never know the truth, but it is difficult to avoid the suspicion that we haven't been told the full story and that maybe there was some sort of a deal between Elanco and Schering-Plough? Almost all antibiotics of last resort cause problems. The reason they are still effective today is because most of them have been little used in the past due to their toxicity or other serious side-effects. From a lay-person's perspective, one would assume that the build-up of urate and the development of kidney stones or gout (issues identified in the study in Japan) could have been counted through increased intake of bland fluids.



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