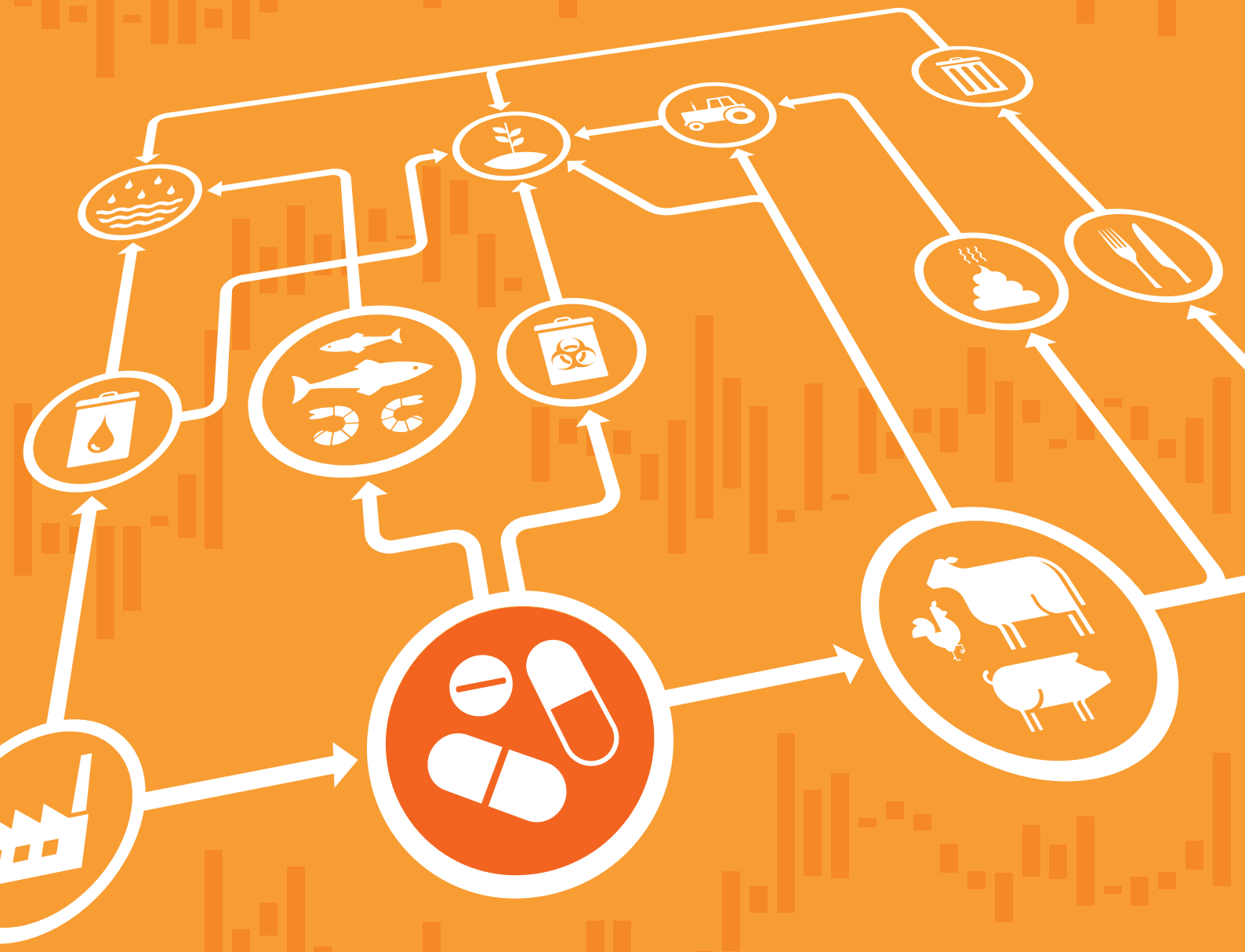
FAIRR
A COLLER INITIATIVE



Feeding resistance

Antimicrobial stewardship in the animal health industry

JULY 2021

Contents

About this report

This thematic report is a first of its kind focused on highlighting the role of the animal health industry and its efforts to reduce and mitigate the growing risk of antimicrobial resistance (AMR). The aim of the report is to encourage an open dialogue between the animal health industry and its stakeholders including institutional investors, policy makers and broader civil society on the need for greater transparency across antimicrobial supply chains and to accelerate efforts to promote responsible use of antimicrobials within animal agriculture worldwide.

FAIRR carried out more than twenty interviews with key stakeholders including investors, sustainability specialists, academics, companies, and civil society. Further, the report draws from a number of sources including academic journals, media, industry government publications, and public disclosures from ten publicly listed animal health companies. These are:

- Dechra Pharmaceuticals PLC (Cheshire, UK)
- Elanco Animal Health Inc. (Indiana, USA)
- Jinhe Biotechnology Co., Ltd. (Liaoning Province, China)
- Merck & Co., Inc. / MSD outside of North America (New Jersey, USA)
- Orion Oyj (Uusimaa, Finland)
- Phibro Animal Health Corporation (New Jersey, USA)
- Vetoquinol S.A. (Lure, France)
- Virbac S.A. (Carros, France)
- Zoetis Inc. (New Jersey, USA)
- Zydus Cadila / Cadila Healthcare Ltd. (Gujarat, India)

Acknowledgments

A special thanks to Dr Emma Berntman of EOS at Federated Hermes for her role in supporting FAIRR in delivering this report.[i]

EOS at Federated Hermes is a leading stewardship services provider working on behalf of pension funds and other large institutional investors, representing assets under advice of US$1.5 trillion as of 31 March 2021. Its engagement activities enable long-term institutional investors to be more active owners of their assets, through dialogue with companies on environmental, social and governance issues. It believes this is essential to build a global financial system that delivers improved long-term returns for investors, as well as better, more sustainable outcomes for society.

Federated Hermes
EOS

FAIRR would like to thank the following individuals who shared their time, expertise and insights during the research process for this report. Their participation does not imply endorsement of this report.

Dr Emma Berntman, Engagement Lead, EOS at Federated Hermes

Dr Juan Carrique-Mas, Veterinary Epidemiologist, Wellcome Trust Intermediate Clinical Fellow – ViParc Project, University of Oxford

Theis Christensen, Business Development Manager, Novozymes

Jacobine Das Gupta, Director Sustainability, Lead Nutrition, DSM

Madlen Davies, Chief global health correspondent, The Bureau of Investigative Journalism

Gerrit Dubois, Responsible Investment Analyst, Degroof Petercam Asset Management

Professor Will Gaze, University of Exeter Medical School

Laura Higham, PhD Student – One Health Joint Programme (AMR), Edinburgh University

Natasha Hurley, Campaign Manager, Changing Markets Foundation

Ridhima Kapur, Head of Sustainability Strategy, Novozymes

Derrick Lewis, Senior Manager, R&D, Novozymes

Catherine McCabe, Senior Associate, Analyst, Responsible Investment

Dominic Moran, Professor of Agricultural and Resource Economics, Edinburgh University

David Nickell, VP Sustainability & Business Development, DSM

Fredric Nyström, Head of Responsible Investment, Öhman

Milena Ognjenovic, Buy-side Equity Analyst, Degroof Petercam Asset Management

Julie Louise Rastad, Marketing Director, Animal Health, Novozymes

Dr Kristen Reyher, Reader in Veterinary Epidemiology and Population Health, Bristol University

Suzi Shingler, Campaign Manager, Alliance to Save our Antibiotics

David Tsoupros, Vice President, Senior Research Analyst, AllianceBernstein

Professor Thomas Van Boeckel, ETH Zürich

Maria Walsh, Director of Global Marketing for Swine, DSM

Andrea Weber, Investment Manager, Verium AG, formerly at Bank J. Safra Sarasin AG

i The views included in this report are those of FAIRR and not necessarily those of EOS at Federated Hermes.

List of abbreviations

AHI	Animal Health Institute
ALPHA	African Livestock Productivity and Health Advancement
AMRIA	AMR Industry Alliance
AMR	Antimicrobial resistance
API	Active pharmaceutical ingredient
ARBs	Antimicrobial resistant bacteria
ARGs	Antimicrobial resistance genes
ASF	Asian Swine Fever
ASOA	Alliance to Save Our Antibiotics
BIRDY	Bacterial Infections and Antimicrobial Drug-Resistant Diseases among Young Children in Low-Income Countries
BPC	British Poultry Council
bTB	Bovine tuberculosis
BVD	Bovine viral diarrhoea
CAFOs	Concentrated Animal Feeding Operations
CDDEP	Centre for Disease Dynamics, Economics & Policy
CIAs	Critically Important Antimicrobials
CMOs	Contract manufacturing organisations
CSU	Colorado State University
CTC	Chlortetracycline
EAGA	East Africa Growth Accelerator
FAO	Food and Agriculture Organisation
FDA	Food and Drug Administration
FD&C Act	Food Drug and Cosmetic Act
FPA	Food producing animals
GMP	Good Manufacturing Practice
HfA	HealthforAnimals
HP-CIA	Highest Priority Critically Important Antimicrobials
LA-MRSA	Livestock Associated Methicillin Resistant Staphylococcus aureus
mcr-1 gene	Mobilised colistin resistance 1 gene
MFAs	Medicated Feed Additives
MIAs	Medically Important Antimicrobials
MRSA	Methicillin Resistant Staphylococcus aureus
NAE	No Antibiotics Ever
NIAA	National Institute for Animal Agriculture
NOAH	National Office for Animal Health
OIE	World Organisation for Animal Health
PNECs	Predicted no-effect concentrations
PRI	Principles for Responsible Investment
PSCI	Pharmaceutical Supply Chain Initiative
R&D	Research & Development
RWA	Raised without antibiotics
VHIA	Veterinary Highly Important Antimicrobial Agents
VMD	Veterinary Medical Directives
VRE	Vancomycin-resistant enterococci
WAAW	World Antimicrobial Awareness Week
WHO	World Health Organisation

Foreword

When we think about transformation in the animal agriculture sector, investors tend to focus on emissions reductions, protein innovation and deforestation. Yet alongside these urgent environmental threats, there are key public health risks at the heart of intensive animal agriculture that are often overlooked.

In the conversation about safe and sustainable food, it's rare that the animal health sector even gets a mention. Yet this industry is much more than a specialised medical niche. It's a $47bn sector that is essential for the prevention, control, diagnosis, and cure of diseases affecting the 70 billion farmed animals on the planet – which eventually end up on our supermarket shelves and restaurant menus.

That means the animal health sector is a touchstone of whether we will be able to rise to one of the biggest health challenges currently facing public health: Antimicrobial resistance (AMR).

> Antibiotic overuse is a pandemic accelerator hidden in plain sight.

Cited by the World Health Organisation (WHO) as one of the top ten global public health threats facing humanity, AMR refers to the emergence of superbugs that are resistant to antibiotics. An AMR crisis threatens to make even routine operations such as a hip or knee replacement life-threatening because we may no longer have effective antibiotics available to treat patients in recovery.

At present, antimicrobial-resistant infections are responsible for an estimated 700,000 deaths each year.[1] The World Bank warns that AMR will induce a possible 11% loss to livestock production in low-income countries by 2050.[2] This isn't a distant concern, it's a pressing challenge.

An estimated 70% of antibiotics are used in farmed animals, so both Pharma and farmer have a responsibility to reduce antibiotics in meat supply chains. But this report shows that the animal health sector is failing to live up to its responsibilities to manage the risks we all face from antibiotic resistance.

Animal health firms sit at one end of a multi-billion-dollar animal protein value chain. AMR cannot be solved without stewardship and cooperation from this industry which manufactures, markets and sells antimicrobial products to protein producers to treat the animals we eat.

FAIRR's wide-reaching analysis of the animal health sector comes at an important moment. The G7's recent commitment to "*curb the silent pandemic of antimicrobial resistance*" will likely help accelerate existing regulatory momentum and scrutiny from both consumers and investors.

Despite this growing pressure, all companies lack a strategic approach to antimicrobial stewardship that covers all elements of their business, including better supply chain transparency, manufacturing standards, responsible use and innovation, and is consistent across markets.

Plus, where some companies are investing in activities to address the issue, these efforts are increasingly being undermined by lobbying activities and marketing practices focused on either maintaining or promoting the use of antimicrobials.

In particular, this report sheds light on the implications of a lack of consistency around the classification and usage of ionophores in food-producing animals. Securing higher regulatory scrutiny and standards on ionophores will be a crucial litmus test for the animal health industry's ability to reduce the use of antibiotics in farm animals. It will also be important for meeting consumer demand for more sustainable meat raised without routine use of antibiotics.

AMR could be the next pandemic we face. As the world recovers from COVID-19, we must ensure that we're doing all we can to avoid the next public health crisis from antimicrobial resistance.

As responsible stewards of capital, investors have an important role to play in safeguarding our food system from pandemic risks. I encourage all investors in the sector to begin meaningful engagement with companies to encourage better stewardship, R&D investment with a focus on alternatives to antibiotics, and call for disclosure of the percentage of revenues that come from antibiotics to promote understanding of sector-wide exposure to risks.

This report, 'Feeding Resistance', is a vital contribution to building the momentum needed to ensure the protection of the animal health sector from damaging practices and increasing regulatory risk. We look forward to the strengthened action and partnerships that result from this important research.

Jeremy Coller
Chair of FAIRR
Chief Investor Officer of Coller Capital

Executive summary

Antimicrobial resistance (AMR) is a systemic global risk to public health and the economy. For animal health companies, antibiotics and other antimicrobials are a volume business and their overuse and misuse in animal agriculture is a significant contributor to this risk, catalysed by manufacturing, marketing and sales practices.

AMR is gaining prominence as a key issue of our time. Last year, the scope of World Antimicrobial Awareness Week (WAAW) was expanded for the first time to include all antimicrobials, not just antibiotics.[3] This year AMR was a key item in the G7 agenda. Health and Finance Ministers have committed to working together to *"curb the silent pandemic of antimicrobial resistance"* by exploring market incentives to bring new antimicrobials to market, improving antimicrobial stewardship, strengthening supply chain resilience, and addressing antimicrobial effluent from manufacturing plants entering the environment.[4] For animal health companies with exposure to antimicrobials, this commitment will likely help to accelerate existing regulatory pressures and stakeholder scrutiny including those from investors, consumers and civil society on their business. This means companies will need to adopt a comprehensive and strategic approach to addressing AMR that is consistent across markets and supports better supply chain transparency, manufacturing standards, stewardship, and innovation.

This report summarises the contribution of animal agriculture to AMR and examines the current practices of the ten largest publicly listed animal health companies who produce antimicrobials across manufacturing, sales and marketing, innovation and R&D, and stewardship. The report also explores some of the key actions the sector must take to future-proof its long-term sustainability.

FAIRR hopes this report will open up the conversation with investors and the sector itself to ask challenging questions, drive greater disclosure and provide scrutiny over the readiness of animal health companies against further restrictions in antimicrobial production and use, and to determine how resilient companies' portfolios are to the changing protein production landscape.

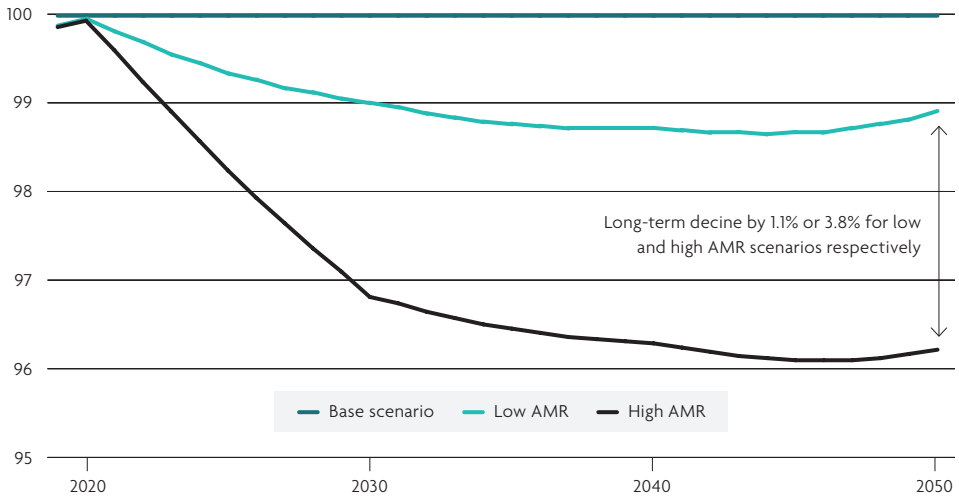
Antimicrobial resistance (AMR) is a growing global health crisis, and a systemic risk that will have long-term, and far-reaching, economic impacts. At present, antimicrobial resistant infections globally are responsible for an estimated 700,000 deaths per annum.[5] These deaths happen where serious infections are resistant to multiple medicines and cannot be effectively treated. The World Health Organisation (WHO) have estimated that AMR has already reached 50% in many major bacteria groups such as *E. coli, K. pneumonia* and *S. aureus* around the world.[6] Many more infections now take longer to treat, are more expensive to treat, or more frequently require hospitalisation due to their severity.

By 2050, the World Bank forecasts an impact to annual global GDP of between 1.1% per annum in a "mild" AMR scenario, to 3.8% in a "high" AMR scenario, by 2050 (see Figure 1). This also includes significant impacts to livestock production and the trade in livestock products – such as a possible 11% loss to livestock production in low-income countries by 2050, which has the potential to adversely impact the future revenues of animal health companies and the livelihoods of these communities.[7] The World Bank has highlighted animal agriculture as a *"critical frontier"* for tackling AMR.[8]

The misuse and overuse of antimicrobials in clinical human settings as a contributor of AMR is well understood and has received a large amount of public attention. It is now well accepted that similar antimicrobial misuse and overuse in animal agriculture also contributes to the global AMR burden.[9,10] Without greater efforts to tackle growing AMR, it is likely it could become the next pandemic.

An estimated 70% of global antimicrobial use by volume occurs in animal agriculture.[11] The routine use of antimicrobials for therapeutic and non-therapeutic purposes has helped facilitate the expansion of modern industrial farming by enhancing growth rates and preventing disease caused by the crowding of animals in tight spaces. However, the effects of growth promotion are diminishing. In the 1980s, antibiotics increased growth in pigs by about 15%, whereas now the effect is only a few percent.[12] As the efficacy of antibiotics as growth promoters continues to decrease, farmers may shift to more effective alternative options, if available. This could have a material impact on companies that continue to derive revenue from the sale of antibiotics for growth promotion.

Figure 1: Forecast losses to global GDP in low impact and high impact AMR scenarios, 100 = no AMR impact



Source: World Bank estimate, March 2017

The animal health sector is highly consolidated and dominated by a small number of large players. Historically, the sector has operated with a high degree of opacity and a low level of external scrutiny, particularly in relation to its contribution to AMR. The distinct lack of transparency and oversight over the production and manufacturing of antimicrobials including the treatment of wastewater discharged into the environment is an increasing risk for animal health companies, whose supply chains are complex involving multiple suppliers across geographies.

Animal health companies operate within the law, but – because these laws vary so widely country-by-country – are frequently able to utilise loopholes in the definition and allowed usage of antimicrobials. This has created an inconsistent approach to sales, marketing and package sizing practices that is helping to further entrench poor practices that contribute to the global AMR burden in markets where regulation and public pressure to curb use is absent. This is especially the case in emerging markets, where the growth in industrial farming is driving higher rates of antibiotics use.

As the significance of the contribution of animal-related antimicrobial use to AMR becomes ever clearer, regulators have started to respond with enhanced scrutiny. At the same time, desire for higher welfare and sustainably sourced meat and dairy products is growing among consumers, alongside a continuing trend towards alternative proteins. These pressures are increasing the risk profile of the intensive animal agriculture sector, and in turn are having an impact on the animal health sector, with animal protein producers looking beyond antimicrobials and towards preventive care and alternative treatment options as its first line of defence for protecting welfare and animal health.

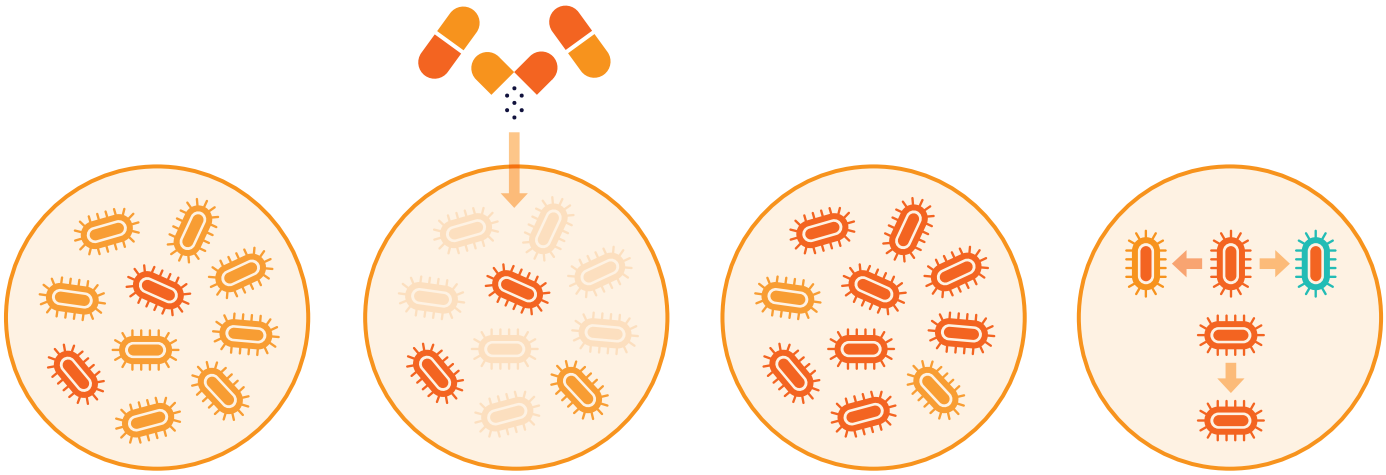
Forward-thinking animal health companies are pre-empting these changes – reducing their exposure to antibiotics, investing in alternative treatment options, and looking to the pet care and companion animals' market. Some are also investing in targeted stewardship activities, for example working with farmers and veterinarians to enable and encourage appropriate use of antibiotics. But a coherent, strategic, business-wide approach is often lacking, with these same companies frequently lobbying against the tightening of regulations around antimicrobials. Some animal health companies have yet to take concrete action to address the growing risk of AMR, exposing themselves to increasing regulatory, supply chain, reputational and market risks.

Investors must therefore pay particular attention to the product portfolio composition of their investee companies to establish their baseline exposure to AMR and consider the consistency of messaging, marketing practices, supply chain transparency, innovation, and stewardship activities.

Antimicrobial resistance in animal agriculture

Antimicrobial resistance is a global threat to human health. The use of antimicrobials – particularly antibiotics – in the farming of livestock is a significant contributor to this threat.

Figure 2. AMR occurs when pathogens such as a bacteria, viruses, fungi or parasites no longer respond to the antimicrobial agents designed to destroy them.



1

Initial population containing mostly susceptible bacteria with few resistant bacteria. Changes to bacteria over time can make them resistant to the antimicrobial agents contained within antibiotics which leads to a natural level of AMR.

2

Antibiotics kill susceptible bacteria and leave behind resistant bacteria, leading to higher levels of AMR than naturally occurs.

3

Resistant bacteria have preferred conditions and grow and dominate the population

4

Those bacteria that survive can then pass on this resistance to other bacteria – either through reproduction (vertical transmission), or cell-to-cell to unrelated bacteria within the same or different bacterial species (horizontal transmission).

Source: UN Environment, Frontier 2017 Report

What is antimicrobial resistance?

Antimicrobial resistance (AMR) presents a global threat to health and development and is cited by the World Health Organisation (WHO) as one of the top ten global public health threats facing humanity.[13]

AMR occurs when pathogens such as a bacteria, viruses, fungi or parasites no longer respond to the antimicrobial agents designed to destroy them (see Figure 2). Competition for survival between bacteria and other pathogens leads to a natural level of AMR, but this is exacerbated by orders of magnitude through excessive use of antimicrobial agents in humans, animals, and plants. Indeed, misuse and overuse of antimicrobials are the main drivers in the development of drug-resistant pathogens.[14]

Antibiotic use in animal agriculture

It is well established that antimicrobial misuse and overuse in clinical human settings is a driver of AMR that is threatening human health.[15] What is less widely known is that similar misuse and overuse in animal agriculture is also a key contributor to the global AMR burden.[16,17,18] While it is not possible to prove without doubt a causal link between specific cases of increased antibiotic use in animals and rising AMR in humans due to epidemiological challenges in proving the transmission routes of antimicrobial resistant bacteria (ARBs), there is a growing body of evidence which supports this link.[19,20]

Currently, an estimated 70% of global antimicrobial use by volume occurs in animal agriculture.[21] These drugs – critical enablers of modern medicine – have been crucial to the expansion of modern industrial farming operations worldwide.

The routine use of antimicrobials – specifically antibiotics – for therapeutic and non-therapeutic purposes helps to mitigate the effects of over-crowing, poor ventilation systems, and limited biosecurity measures leading to greater disease incidence amongst animals. The use of antimicrobials also helps to increase feed efficiency allowing for shorter growing periods and higher rates of production.

Table 1. Types of antibiotic use in animal agriculture.

THERAPEUTIC	NON-THERAPEUTIC[ii]		
Treatment	Prevention		Growth promotion
	Metaphylaxis	Prophylaxis	
Treatment of animals with clinical evidence of infectious disease.	Treatment of a group of animals that have been in close contact with clinically infected animal(s). No clinical evidence of disease; disease likely in incubation phase.	Animals at high risk of infectious disease, but no current disease in animal(s) or wider herd/flock. Common when environmental conditions or changes increase risk of infection, e.g. live transport, close confinement, crowding. Preventative use in practice is very similar to use for growth promotion as the dosage remains comparable, this means preventative use can still have growth promoting effects despite not being named as growth promotion.	Low doses. Stimulates growth and/or increases feed efficiency. May also prevent (primarily enteric) disease due to their intended function as antibiotics to treat disease.
Non-routine	Non-routine	Routine	Routine
✓✓ Judicious use permits treatment	✓ Appropriate tool in judicious use policy	✗ Can be avoided or reduced via improved welfare / biosecurity	✗✗ Not medically necessary

ii FAIRR has followed the categorisation of Tang et al, in a WHO commissioned study. Comparison of different approaches to antibiotic restriction in food-producing animals: stratified results from a systematic review and meta-analysis, 2019. p.3. https://gh.bmj.com/content/4/4/e001710

Transmission of resistant bacteria between animals and humans

Intensive animal farming operations represent reservoirs of ARBs and antimicrobial resistance genes (ARGs) that pose a risk to human health.[22,23] For example, AMR in bacteria such as *E. coli* is prevalent and widespread across livestock operations. Studies commonly find resistance to multiple drugs in their analysis of livestock populations, often in line with the usage patterns of antimicrobials in their respective regions.[24,25] There is a growing body of evidence on the transfer of ARBs and ARGs to human populations – both directly and indirectly.[26]

> A 2015 study in Germany found that 10% of MRSA infections outside of hospitals initiated in livestock, and that 77-86% of humans who work with pigs directly – mainly veterinarians and farmers – carry LA-MRSA.

Direct transmission of ARBs and ARGs from livestock to humans occurs through animal to human contact, usually on farms where workers have frequent direct contact with animals. For example, Livestock Associated Methicillin Resistant *Staphylococcus aureus* (LA-MRSA), which is particularly prevalent in pigs, was identified to have spread to humans via livestock workers, and is only treatable with a small number of antibiotics – similar to the hospital and community spread strains of MRSA.[27] The LA-MRSA strain was first detected in humans in a hospital patient in the UK and is now present across Europe and the rest of the world.[28] The bacteria can cause local skin infections and, in the worst cases, may result in blood stream infection or pneumonia, which can be serious. While transmission from human to human is not as easy for LA-MRSA, it is still possible, and most transmissions occur when livestock workers pass it on to those they live with.

A 2015 study in Germany found that 10% of MRSA infections outside of hospitals initiated in livestock, and that 77-86% of humans who work with pigs directly – mainly veterinarians and farmers – carry LA-MRSA. This reduces significantly for their family members, where the rate is 4-5%.[29] This is of concern, as it indicates the use of antibiotics in animals is a direct health risk for livestock workers, as well as presenting a broader pandemic concern should a more transmissible resistant bacteria evolve.

Figure 2. Transmission routes across the animal agriculture value chain.

Source: Adapted and modified from AMR Industry Alliance, Making Antibiotics Responsibly, pg. 7.

Direct transmission of ARBs and ARGs from animals to humans can also occur through the consumption of meat.[30] For example, in Phnom Penh, Cambodia, the Institut Pasteur tested pregnant women as part of the Bacterial Infections and Antimicrobial Drug-Resistant Diseases among Young Children in Low-Income Countries (BIRDY) programme, found pan-resistance to antibiotics (i.e., resistance to multiple classes of antibiotics) in 70% of women. This was significantly higher than in the Ile-de-France region of France where only 5-6% of people tested were found to have resistance to multiple classes of antibiotics. This was attributed to high incidence of resistant *E. coli* bacteria in meat and fish in Cambodia. Further, resistance to chloramphenicol was found, an antibiotic that has not been used in human medicine in Cambodia for the last 20 years, but related antibiotics florfenicol and thiamphenicol are regularly used in food animals in the country.[31] Although it is scientifically difficult to accurately pinpoint how ARBs and ARGs arise in humans, it is thought in this case that resistance has been conferred via local meat markets.

There are many more routes beyond the food chain by which antimicrobial agents used in animal agriculture, and the resulting resistant bacteria and genes, contaminate the environment and indirectly come into contact with humans.[32,33,34,35] Although the route of transmission is unclear, many – if not most – of these indirect transmission routes relate to the production and use of antibiotics. These routes include:

- **Inefficient metabolism of orally administered antibiotics**, such as those added to animal feed or to water – this varies across species, with an estimated 30-90% of ingested doses excreted unmodified or partially digested.[36,37,38,39,40]
- **Animal excreta and the application of manure or compost to fields** – these activities contribute active antimicrobials to the environment, as well as resistance genes and resistant bacteria.[41,42,43,44,45]
- **Wastewater from feedlots** – antibiotics and ARGs in feedlot groundwater have been found at higher than natural concentrations in the groundwater of surrounding environments, suggesting wastewater from feedlots is increasing the prevalence of ARGs in the surrounding area.[46,47]
- **Wastewater from pharmaceutical production** – there are multiple studies reporting the link between manufacturing effluent containing high concentration of antibiotics residues and increased levels of resistance in these locations.[48,49,50,51,52]

Antibiotics as a pollutant

Antibiotics are recognised as pollutants that can impact the microbial populations in soil, water, sediments, plants and animals.[53,54] At least two thirds of the world's waterways contain unsafe levels of antibiotics, using the concentrations set by the AMR Industry Alliance (AMRIA) which are the industry standard,[55] with concentrations varying by location. For example, the Danube in Austria has been found to have four times the safe levels of antibiotics, while in Bangladesh concentration levels have been found at 300 times safe levels.[56,iii] The study surveyed 91 rivers globally finding that nearly 2/3 contained antibiotics.

Studies emphasise the significant environmental concerns posed by the spread of resistant bacteria in soil and aquatic ecosystems as a result of manure or compost application.[57,58,59,60] Antimicrobials directly affect plant growth and development, for example by delaying seed germination and shortening primary root length.[61] Resistant bacteria can also enter and colonise plant tissues, modifying the population of endophytic – i.e. bacteria that live within – plants and posing a further threat to human health.[62]

iii Safe levels' refers to the AMR Industry Alliance established levels which range from 20-32,000 ng/l.

Current use of veterinary antibiotics is not critical to animal production, but could pose a critical risk to human health

Some antibiotics given to animals can be categorised as veterinary only, meaning they are exclusively for animal use. Others are shared-class in which case the same drug may be used in both animals and humans. Resistance to medically important antibiotics (MIAs) used to maintain human health, including shared-class antibiotics, is of primary concern. In some cases, however, an antibiotic may start as veterinary only and later become shared-class – for example, see the colistin case study on page 16. The poorly regulated use of veterinary-only antibiotics poses a health risk for humans.

Ionophores (including monesin, lasalocid, salinomycin, narasin, maduramicin and semduramicin), the second most commonly used class of antimicrobial in agriculture, are a case in point.[63] They are primarily used to prevent the parasitic disease coccidiosis, but also possess antibacterial properties which helps to prevent disease and improve feed efficiency.[64] This has led to their widespread use as growth promotors[65] and prophylactics. For example, salinomycin and monensin, are applied as feed

additives in the production of pigs and cattle respectively to improve feed efficiency and to prevent and treat disease.[66]

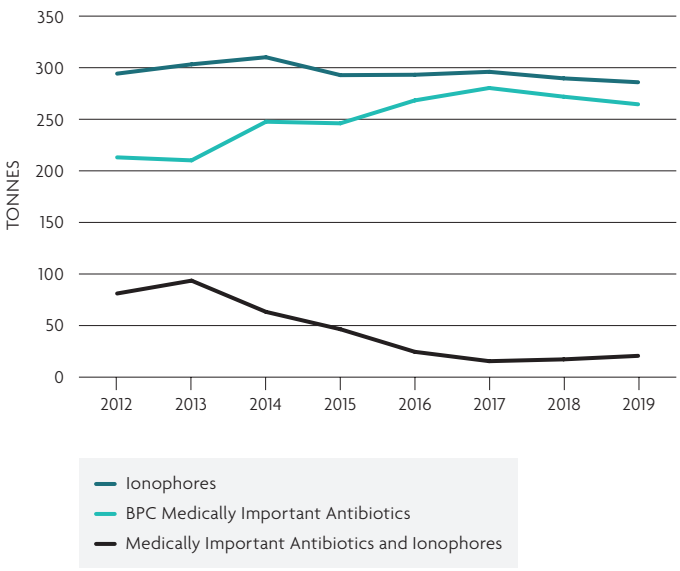
Although ionophores do demonstrate a degree of antibacterial activity, they are not widely considered to be antibiotics.[67] This has resulted in a lack of consistency in how different jurisdictions classify and permit the use of ionophores. Several governments specifically exclude ionophores from antibiotic use regulations; others do not (see table 2).[68] Such inconsistency has created loopholes whereby the routine use of ionophores remains widely prevalent. Ionophores are routinely added to the feed of most intensively farmed chickens in the EU for coccidiosis control and are used for growth promotion in countries where regulation allows[69] – such as the US.[iv] Growth promotion in cattle is understood to be due to alterations in the gut microbiome, which causes changes to ruminal fermentation and consequently results in increased feed efficiency.[70] Between 2012 and 2017, the use of MIAs in UK poultry farming decreased from 82 to 14 tonnes annually.[71] In contrast the use of ionophores within the British poultry industry increased by 33%, ostensibly to tackle and prevent coccidiosis, but with the side effect of also promoting growth – something which MIAs would have done prior to new regulation preventing their use for prophylaxis in the EU.[72]

iv Coccidiosis, caused by protozoa of the genus Eimera, is the most widespread parasitic disease in poultry, as well as affecting other species such as cattle and pigs. It is most common in intensive farming systems and results in severe damage to the intestines, consequently inhibiting nutrient absorption and growth.

Table 2. The definition of ionophores varies by jurisdiction

Jurisdiction	Classification
World Organisation for Animal Health (OIE).[73]	Class Ionophores as Veterinary Highly Important Antimicrobial Agents (VHIA)
United States Food and Drug Administration (FDA)	Classifies ionophores as antibiotics and permits their use for growth promotion.
EU legislation	Ionophores are classed as animal-only antimicrobials rather than antibiotics and no veterinary prescription is required for their use, though their use as growth promoters is banned. Thus, in the EU, 'raised without antibiotics' (RWA), may mean ionophores were used.

Figure 3. There has been a reduction in the use of MIAs across British poultry farming. However, this reduction has been offset by the increase in ionophore use, indicating limited change in husbandry practices between 2012-2019.



Source: Figures from the British Poultry Council (BPC) and the Alliance to Save our Antibiotics (ASOA)

"The UK's increased use of ionophores is a concerning trend, as it seems to be rising at the same rate that the use of other antibiotics is decreasing, almost in a perfect mirrored curve in the opposite direction. Ionophores do have a role to play in antimicrobial resistance, and they're being used at much higher levels than ever before, who knows what kind of unforeseen risk could be lurking behind what seems like a new industry-wide reliance on a particular type of medicine?"

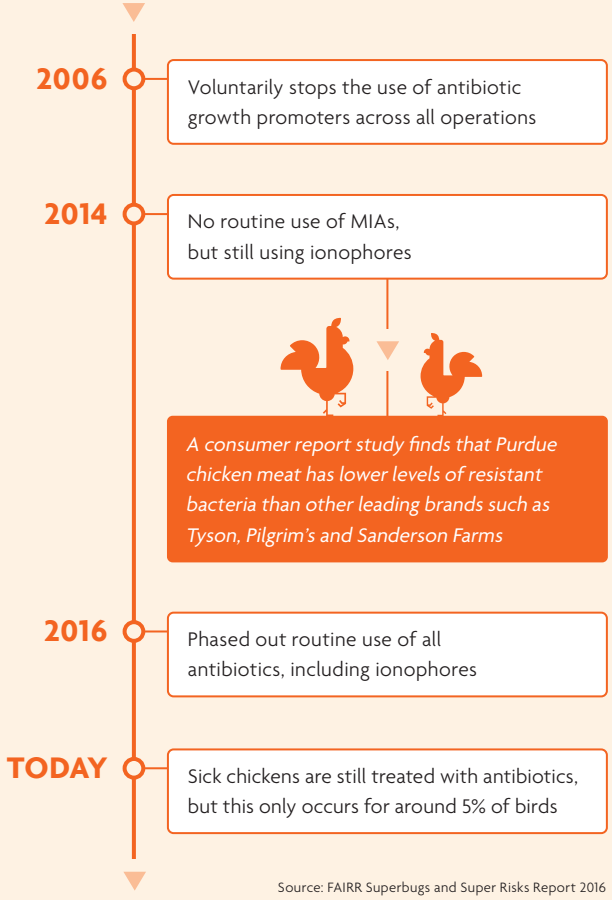
Suzi Shingler
Campaign Manager, Alliance to Save our Antibiotics

Widespread use of ionophores in food producing animals is problematic for three key reasons:

- **Potential for use in human medicine.** There is evidence ionophores could be important in human medicine against widely resistant bacteria. Currently, ionophores are considered too toxic to be used in human medicine and are therefore not classified as MIAs, but several studies indicate their future potential– or that of closely related antibiotics – to be developed as effective treatments for *Clostridium (C.) difficile*, a bacteria that can often be fatal for humans.[74] Very few antibiotics are currently available to treat *C. difficile* and it follows that, using the precautionary principle, ionophores should be administered responsibly to reduce the risk of AMR in this bacteria.
- **Contribution to AMR.** Even without a role in human health, there is evidence that use of ionophores in intensive animal farming can contribute to the global public health crisis of AMR more widely, including increasing resistance to MIAs.[75] For example, ionophores may increase the incidence of poultry *vancomycin-resistant enterococci* (VRE), which can cause severe infections in humans. Following evidence that VRE had been present at Norwegian poultry facilities for several decades the industry decided to phase out the use of ionophores, reducing consumption by 99.5% from 2016-2018.[76] Recent testing showed no presence of VRE – supporting the association between ionophores and its onset.[77]
- **Environmental toxicity.** In addition to AMR concerns, the toxicity of ionophores raises concerns about residues in food and the environment – impacting humans, wildlife, soil and aquatic organisms.[78,79,80,81,82] The specific impacts are not well understood due to a lack of research, but it is known that under incorrect dosing, ionophore poisoning can occur in animals. However, more frequently it occurs in non-target species and can result in death. Horses are particularly susceptible to ionophore toxicity, being 20 times more sensitive than cattle and 200 times more sensitive than poultry to monensin on a mg/kg basis. In 2012 there was a recall of horse feed contaminated with monensin in the US from Western Feed following reports that some horses had died.[83,84] There is currently no remedy to ionophore poisoning and therefore prevention is vital.[85]

CASE STUDY

Ionophores are not critical for poultry production: the case of Perdue Farms



Source: FAIRR Superbugs and Super Risks Report 2016

Perdue Farms has become a leading fresh poultry brand in the US putting commercial pressure on its competitors to take action. Tyson and Pilgrim's have now set goals for reducing their antibiotic use. Tyson has been the world's largest No Antibiotics Ever (NAE) poultry producer since June 2017. According to the National Chicken Council, about half of the US chicken industry has eliminated the use of human antibiotics, and that percentage is expected to keep growing.

For the producers of veterinary drugs i.e., animal health companies, the lack of regulatory scrutiny on ionophore use has had a favourable impact on revenue. In fact, Elanco, one of the largest animal health companies has seen an increase in absolute revenue derived from the sale of ionophores since 2018. In 2020, 85% of Elanco's revenue from animal-only antimicrobials resulted from the sale of ionophores.[86] Further the company has explicitly stated in its 2020 10K report that *"ionophores are a special class of animal-only antimicrobials, and because of their animal-only designation, mode of action and spectrum of activity, their use has not to date been impacted by regulations or changing market demand in many international markets."* The company acknowledges that any *"changes in the market acceptance or regulatory treatment of ionophores"* that restricts their use will have material financial impacts on the animal health sector, and on the company's own revenue.

CASE STUDY

Colistin – veterinary antibiotics can become important to human health

Polymixin E, commonly referred to as colistin, is an antimicrobial agent that was first discovered in 1949.[87] Its use in human medicine began in the 1950s but never became widespread due to potential toxicity to kidney and nervous system functions.[88,89] From the 1970s onwards, it was replaced by less aggressive drugs.[90]

As it dropped out of favour in human medicine, use of colistin gained traction in animal agriculture.[91,92,93] In 2015, prior to being banned for use as a growth promoter, sales of colistin sulfate premix were estimated to be $71.5mn in China.[94] In 2018, despite being banned for use as a growth promoter, the polymyxin class of antimicrobials including colistin was the seventh[95] most used antibiotics class in food-producing animals in the EU[96] It is typically used as a group treatment, administered orally to treat and prevent gastrointestinal infections across most terrestrial livestock and poultry species.[97]

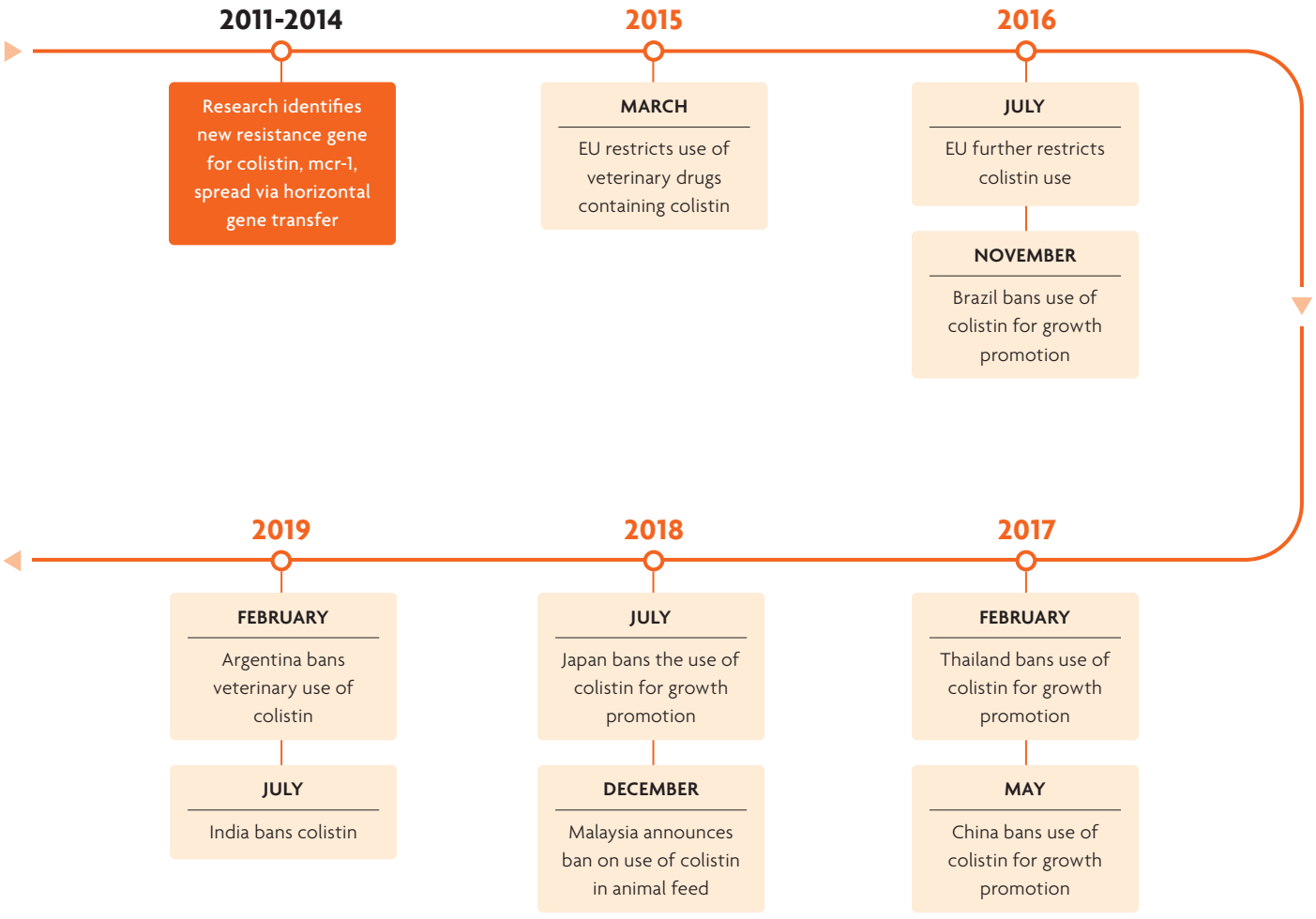
Until the 2010s, there was little to no concern about overuse or the rise of resistance: the drug was not considered medically important for humans, and resistance to colistin was also believed to be rare.[98] Resistance was understood to develop through vertical gene transfer only – that is, reproduction – limiting the spread of resistant genes.[99,100] New scientific evidence between 2011 and 2014, however, showed that transfer of a resistance gene named *mcr-1* was possible between unrelated organisms, and identified the *mcr-1* gene in a range of bacteria species from multiple samples.[101,102,103] Similar studies verified the presence of resistance gene *mcr-1* across human clinical, food, animal and natural environment settings – and across continents.[104,105]

Given extremely limited use in human medicine, it is highly probable that *mcr-1* – and its recent presence in human samples – emerged as a result of use in animals.[106,107,108] Indeed, a WHO-commissioned study noted that colistin provides *"an illustrative example of the emergence, selection and widespread dissemination of a resistance gene as a consequence of antimicrobial use in food animals, and subsequent transfer of bacteria harbouring that resistant gene to humans."*[109]

Due to the development of multi-drug resistance against other antimicrobials, colistin has emerged as a last-resort treatment option for life threatening infections in human medicine.[110,111,112] But as a result of colistin use in food animals, a resistance gene for this drug is already widespread.[113,114,115]

The discovery of widespread *mcr-1* colistin resistance sounded the alarm globally, and many jurisdictions have since responded by restricting or banning its use in animal agriculture.[116] The cautionary example of colistin also demonstrates that the distinction between animal-only and shared-class antibiotics is not set in stone. For a time, colistin was an animal-only antibiotic. The unrestricted use of antibiotics currently considered animal-only not only jeopardises their long term efficacy in veterinary medicine and risks the spread of resistance to other shared-class antibiotics – it also risks the future of drugs that may become directly important to human medicine.[117,118] Animal health companies, as the producers of these drugs, have a role to play in promoting responsible antimicrobial use to protect the long-term efficacy of these drugs in humans and animals.[119,120,121,122]

Figure 4. Timeline of countries responding to colistin resistance crisis*



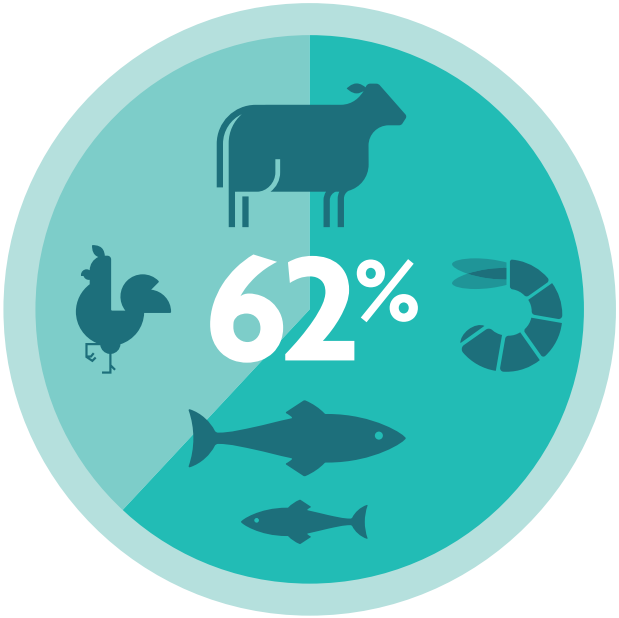
* This a non-exhaustive list of countries. The purpose of this timeline is to highlight country response to the colistin resistance crisis.

Source: FAIRR 2021

The investor case for engagement

The animal health sector is a consolidated industry with enormous influence. Farm animal health is big business and represents approximately 62% of the global $47.1 billion market.[123] Antimicrobials are an established element of leading companies' revenues that is facing increasing headwinds from regulation and changing consumer demand. Nonetheless, animal health companies are looking towards emerging markets as the next frontier of growth given the intensification of farm animal production is driving demand for antimicrobials.

Total animal health market value: **$47.1 billion**,[124] and farm animal health estimated to represent **62%** of this total market.[125]



Top ten publicly listed companies had a total revenue of **$18.2 billion** in 2020 and make up **40%** of the global animal health market.

The animal health sector landscape

FAIRR analysed publicly available data from ten of the largest publicly listed animal health companies with direct exposure to antimicrobials – those that manufacture and sell antimicrobials for farm animals. These are: Dechra, Elanco, Jinhe, Merck & Co., Orion, Phibro, Vetoquinol, Virbac, Zoetis and Zydus Cadila.[v]

Given the role of antimicrobials in helping to maintain farm animal health across today's prevalent industrial system of production, these drugs represent a well-established part of company portfolios. FAIRR found that sales of antibiotics represent approximately 24%[vi] of the total animal health market, and between 7-43% of individual companies' total revenue. These figures are likely to be higher if expanded to include all antimicrobials, however, this level of disclosure is not available in the public domain.

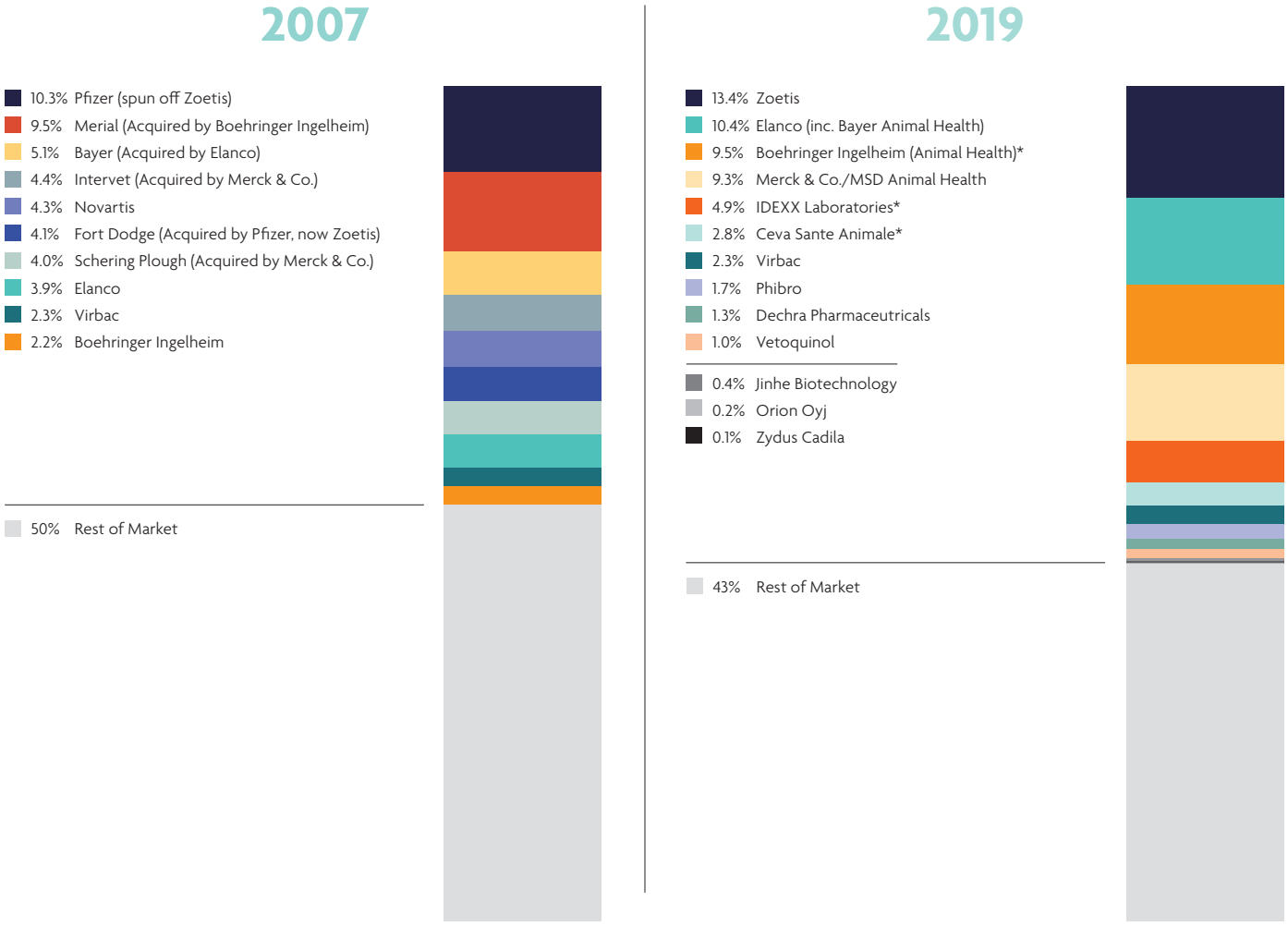
Leading animal health companies account for a large proportion of the global animal health market

The animal health market has undergone a large amount of consolidation over the past 10-15 years, with significant M&A activity taking place. Table 3 shows how the animal health landscape has shifted from 2007 to now, with the larger companies significantly increasing their share of the market.

v Companies have been selected based on five criteria: whether they are a publicly listed company, size of market share, exposure to antibiotics, manufacturing capacity (i.e. do they manufacture their own products?) and availability of detailed public disclosure. Covetrus and IDEXX laboratories were excluded as Covetrus remains primarily a distributor and IDEXX has no exposure to antibiotics.

vi Calculated by FAIRR using revenue derived from antibiotics/antimicrobials (as disclosed) for five leading animal health companies (the only companies that disclose this level of detail) representing a third of the global animal health market between 2015-2020. The figure was calculated using weighted averages with the weighting factor of market share of each company. The formula used to calculate the weighted average for each year was $\bar{x} = \frac{\sum_{i=1}^{n} w_i x_i}{\sum_{i=1}^{n} w_i}$ where w = market share, x = revenue from antimicrobials/antibiotics and n = total number of companies. The final figure was calculated using a simple average of the weighted average for each year. These companies provide a good proxy for the whole market as they represent a similar split between companion animal and food producing animal segments.

Figure 5. Summary of consolidation for the top ten animal health companies (public and private) between 2007–2019



*Companies are not included in FAIRR analysis. Boehringer Ingelheim and Ceva Sante Animale are private companies, IDEXX Laboratories is a publicly listed diagnostics company and does not manufacture antibiotics. .

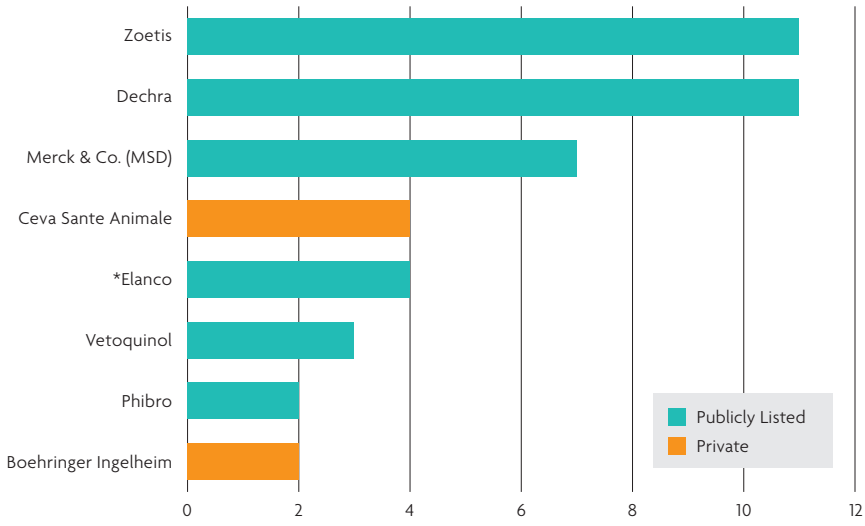
Source: Virbac's 2019 Half Year Presentation and Dechra's 2020 Annual Report

Figure 6. Number of acquisitions since 2015 to date

Note: This list is non-exhaustive. It summarises acquisitions of whole companies and does not include acquisitions of product ranges or brands.

Zydus, Orion, Jinhe and Virbac are not included in the chart as they have not acquired any whole companies since 2015.

*Elanco spun off from Eli Lilly in 2018. Note that one acquisition prior to 2018 is included here and was completed by Eli Lilly who acquired Novartis Animal Health in 2015 for $5.4 billion. Novartis continues to be a part of Elanco. This greatly increased Eli Lilly's product portfolio, strengthened its geographic representation and increased its manufacturing and R&D capabilities. Most importantly, this strengthened Elanco's position within animal health



Source: FAIRR 2021

Emerging markets as the next frontier of growth given expansion in industrial animal farming is driving higher rates of antibiotic use

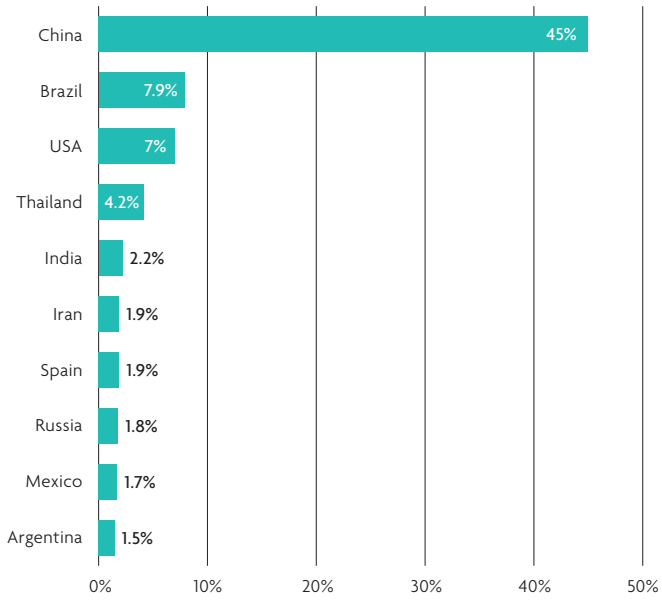
US and European animal health companies are looking to emerging markets as growth drivers for their business, with six of eight animal health companies naming emerging markets as key growth areas in their public reporting, specifically Brazil, India and China. These countries are already the largest consumers of antibiotics for animal agriculture in the world (see Figure 4) and will remain so.[126] Between 2017 and 2030 it is expected Brazil's consumption will increase 11.8%, China's 7.3% and India's 7% – with global usage increasing 11.5%.[127] These projections are due to expected increases in animal production in emerging markets. The OECD estimates that between 2020 and 2029 global meat consumption will increase by 12% with most of this growth driven by emerging markets as high income countries' consumption per capita is expected to level off.[128] Up to a third of the increase in antimicrobial usage in emerging markets is estimated to be attributable to a shift to large-scale intensive farming operations where antimicrobials are routinely used.[129]

- **Zoetis** expects further expansion beyond the US, "*most notably China*", which already contributes 4% of its revenue.[130]
- **Elanco** reports "*new strength in emerging economies*", illustrated with its mission to repopulate China's swine herd.[131]
- **Vetoquinol** aims to "*benefit from the strong growth expected in Asia*". It already has presence in China – where it has recently acquired a 'Good Selling Practice' license required for distributing veterinary pharmaceuticals –and India. In 2019, it also acquired Clarion Biociencas, a veterinary drug manufacturer based in Brazil – expanding its footprint in the world's third largest animal health market.[132]
- **Virbac** states that it is expanding internationally and expects an annual growth rate of 5% for the foreseeable future in emerging markets such as India.[133]
- **Dechra** acquired Brazilian livestock pharmaceutical producer Venco in 2018 which has a presence in multiple South American countries.[134]
- **Phibro** states that it has "*established direct presence in many important emerging markets*" and that its global footprint reaches "*key high growth regions*". These regions are defined as "*countries where the livestock production growth rate is expected to be higher than the average*" and includes Brazil, China, India, and Russia amongst others.[135]

Whilst animal health companies do not explicitly point to the sale of antimicrobials as a growth category within emerging markets, they remain a core part of farming practices in these countries and growth promotion and routine prophylactic use is widespread. Regulation is not yet sufficient to adequately address the issue, which is further exacerbated by poor biosecurity and high levels of infectious diseases, lax manufacturing, and procurement systems, limited economic capacity to invest in new infrastructure, and few trained veterinarians. Further, deficits in awareness and knowledge of AMR and the proper handling and storage of antimicrobials has a knock-on effect on quality, safety and effectiveness of the antimicrobials being produced and used,[137] leading to a greater potential for AMR.[138]

The projected increase in antibiotic use in emerging markets is a key cause for concern given the social and economic impacts of increased AMR. Animal health companies, as the producers and marketers of these drugs have a key role to play in influencing usage.

Figure 7. Emerging markets have the largest share of global antimicrobial consumption in animal agriculture with China well ahead of all other countries.

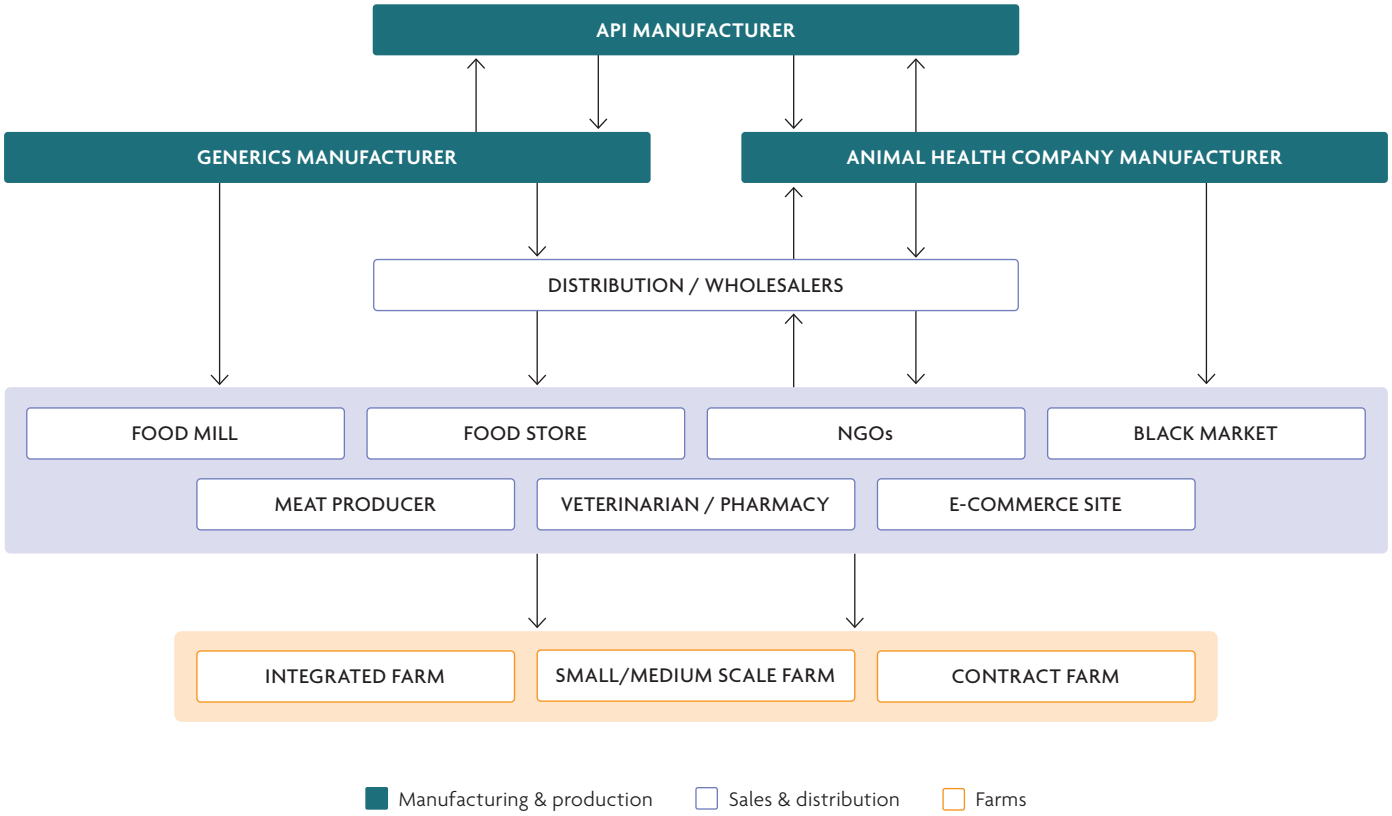


Source: Chart taken from Tiseo, K. et al. 2020[136]

Antimicrobial manufacturing and production as a contributor to AMR

Antimicrobial supply chains, particularly within the animal health industry, receive little external oversight. There is a distinct lack of transparency that starts at the factory level and affects all elements of the value chain – including distribution, sales, and on-farm use.

Figure 8. The animal health pharmaceutical supply chain from production to on farm usage is complex



Source: FAIRR 2021

Poor manufacturing practices increase supply chain risk for animal health companies

Active pharmaceutical ingredient (API) production for antibiotics is an important contributor to the elevated presence of antibiotic residues in the environment.[139] Untreated wastewater from API production processes releases these residues into the environment around factories, increasing the risk of antimicrobial resistance developing. These resistant genes can then spread to humans and animals through soils and waterways.[140]

Current manufacturing practices set few or no restrictions on concentrations of antimicrobials discharged in waste streams, and common waste treatment methods are not designed to remove antimicrobial residues from manufacturing effluent. In fact, traditional pharmaceutical treatment methods can activate antimicrobial sludges and increase their potency during processes meant to neutralise active ingredients.[141]

The World Health Organization's (WHO) Good Manufacturing Practice (GMP) certification – the global standard for manufacturers of pharmaceuticals – does not currently cover antibiotic discharge specifically, and the WHO has acknowledged the challenge its incorporation into on-site inspections would involve.[142] GMP enforcement agents are undertrained and already stretched for time during site inspections, which have a maximum length of two to five days depending on the site.[143] This means that GMP inspections, intended to ensure appropriate manufacturing practices are being used, do not adequately address antimicrobials being discharged into the environment or the practices that allow for this.[144]

Despite a lack of antimicrobial coverage, companies producing antibiotics have still previously been sanctioned for failing to meet GMP standards relating to wider manufacturing practices. Poor management is endemic in the industry and extends beyond the disposal of antimicrobial sludge. Cases of infringement are frequent, and the FDA has historically banned imports of all antibiotics and drugs for humans and animals from certain manufacturing sites where GMP standards have not been met.[145] In 2015 alone, the US FDA issued 80 Chinese production sites with a Form 483 for violating manufacturing regulation in relation to the safety of the manufacturing process. One case included all imports to the US from a Zhejiang Hisun site in Taizhou, China being banned – affecting Pfizer (who spun off Zoetis in 2013) and Merck & Co.[146] It appears that Zoetis is currently being supplied by Zhejiang Hisun (see Figure 6),[147] despite the manufacturing site's notable infractions of GMP.[148] Notably, Zhejiang province is an area of high antimicrobial resistance and antibiotic production.

CASE STUDY

Financial implications of poor manufacturing oversight

Dechra has eight manufacturing sites across the world and in recent years has been using acquisitions to expand its manufacturing capabilities. In 2020 it acquired Ampharmco, an American pharmaceutical company, giving it access to an FDA-approved facility in the US, and it is currently upgrading a manufacturing site in Brazil.[149]

The company has a goal to increase in-house manufacturing capability from 50% to 75% over the next three to five years. This is in response to previous past quality issues as well as increasing scrutiny from the US Food and Drug Administration (FDA) on smaller US-based manufacturers.[150]

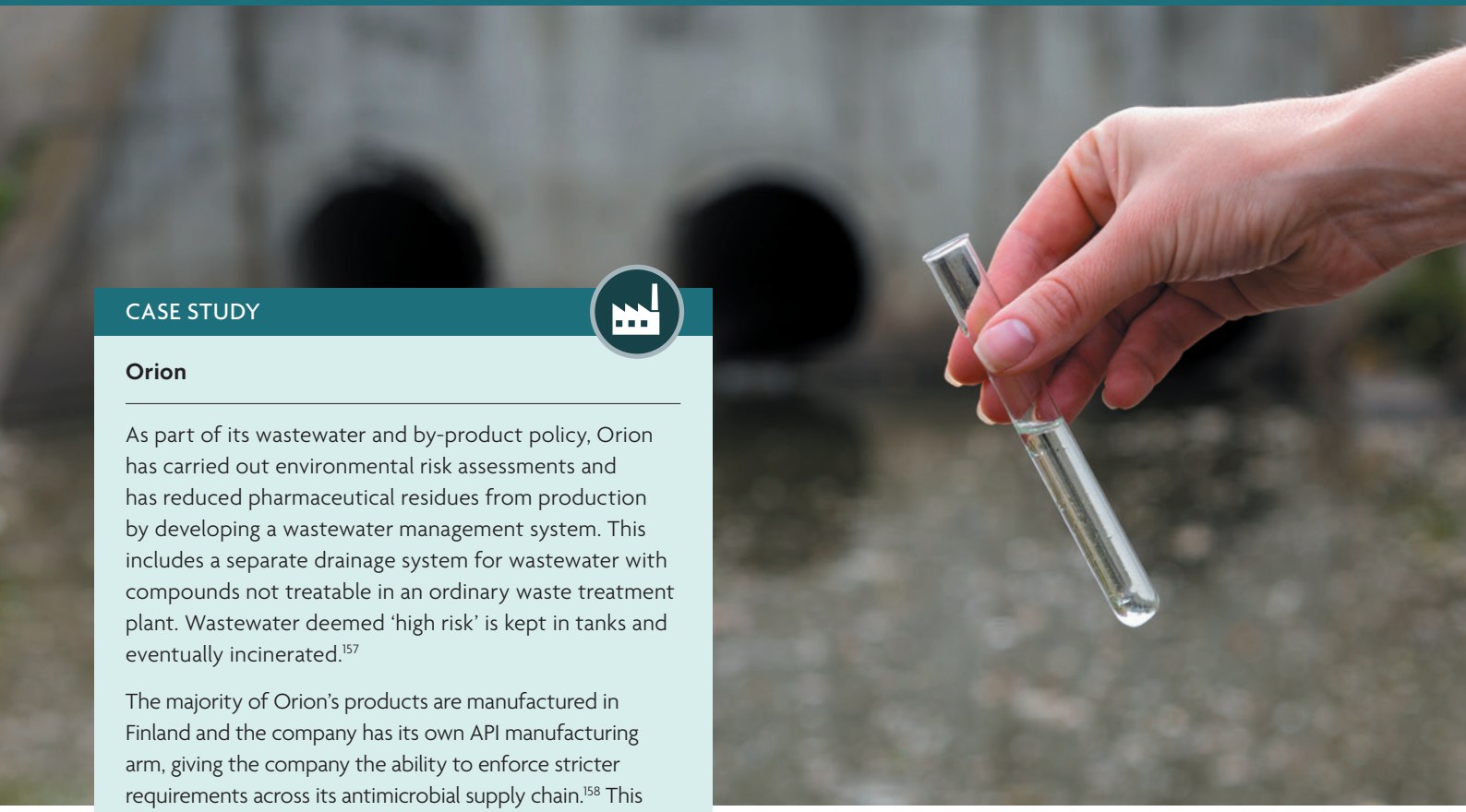
Dechra has recently faced financial consequences associated with supply chain disruptions after one of its contract manufacturing organisations (CMOs), Altere, got shut down by the FDA in FY2019-20. Approximately $14 million of revenue ran through this CMO and the company had to do a product recall which caused a loss of $1.4 million.[151] Another CMO in India was also shut down by the FDA, leading to temporary production suspension of two products.[152]

Dechra currently sources *"nearly all"* of its antibiotics from China.[153] This is a concern in light of reports by Changing Markets and others highlighting environmental pollution from active pharmaceutical producers in the region.[154]

Although Dechra has some independent processes in place to deal with contaminated water in addition to normal waste, and to treat water prior to release in accordance with GMP requirements; it is unclear whether this includes antibiotic waste and whether these processes extend to its CMOs.

Animal health companies do not tend to disclose their API and generic suppliers and there is limited discussion in public reporting around how animal health companies work with suppliers to address antibiotics discharge in wastewater. Zoetis, Merck, Elanco, Vetoquinol and Orion are involved in the Pharmaceutical Supply Chain Initiative (PSCI), which looks to address responsible business practices in supply chains – including setting a framework for managing the release of pharmaceuticals into the environment.[155] Except for Orion, which has taken steps to enhance its efforts through the development of a wastewater and by-product policy (see Case Study on page 24), it is not yet clear how the rest of the companies are addressing antibiotics discharge in their supply chains.

> The G7's 2021 Health Minister's meeting communique specifically calls for the need to address the release of antimicrobials into the environment via manufacturing and other methods and the risk this poses for AMR. They urged the WHO to "accelerate the adoption of changes to relevant Good Manufacturing Practice (GMP) guidance sections applicable to waste and wastewater from antimicrobial production and for industry to take these standards into account as part of their Environmental, Social and Corporate Governance responsibilities."[156]



CASE STUDY

Orion

As part of its wastewater and by-product policy, Orion has carried out environmental risk assessments and has reduced pharmaceutical residues from production by developing a wastewater management system. This includes a separate drainage system for wastewater with compounds not treatable in an ordinary waste treatment plant. Wastewater deemed 'high risk' is kept in tanks and eventually incinerated.[157]

The majority of Orion's products are manufactured in Finland and the company has its own API manufacturing arm, giving the company the ability to enforce stricter requirements across its antimicrobial supply chain.[158] This includes a set of standards for suppliers, and a code that requires materials to be purchased only from responsible suppliers. Pharmaceuticals in the environment is one element considered in the procurement process, which appears to go beyond what most other companies are doing.[159]

It is also important to note that Orion derives most of its revenue from human pharmaceuticals,[160] where the focus on antimicrobial waste and industry engagement to develop solutions for reducing the environmental impacts associated with broader pharmaceutical effluents has been greater than in the animal health sector.

The link between antimicrobial production and AMR hotspots

China and India, both global leaders in the manufacturing of APIs and antibiotics for clinical and veterinary use, have been designated as AMR hotspots – meaning high levels of ARBs have been found.[161]

What is most worrying is the speed at which resistance is increasing. A recent study led by Thomas Van Boeckel at ETH Zurich, and the Center for Disease Dynamics, Economics & Policy (CDDEP) found central India to be a new hotspot for AMR, also found that antibiotic resistance has nearly *tripled* in less than a decade from 2008 to 2018 in low- and middle-income countries.[162] Increased resistance to antimicrobials in animals will have economic consequences for farmers as illness in animals will be harder to treat and this will likely be passed on to consumers through increased food prices – this could affect the ability for low- and middle-income countries to feed growing populations.[163]

It is estimated that patients with antibiotic resistant infections in China cost the country $77 billion in 2017 alone.[164] Common food-borne pathogens in the country such as *E.coli, Campylobacter spp., Salmonella and Staphylococcus aureus* show high levels of AMR as a result of the use of antimicrobials in food producing animals, and are key contributors to antibiotic resistant infections in humans.[165]

India supplies around 20% of the world's generics drugs, including those sold by the largest animal health companies. Meanwhile, China produces approximately 50% of the world's APIs, of which 90% are exported to India to make generic and branded products.[166] Leading animal health companies such as Zoetis and Dechra purchase APIs to produce their own branded antibiotics as well as some of their branded generic drugs – i.e. those that are out of patent – from generics manufacturers in China and India.[167,168]

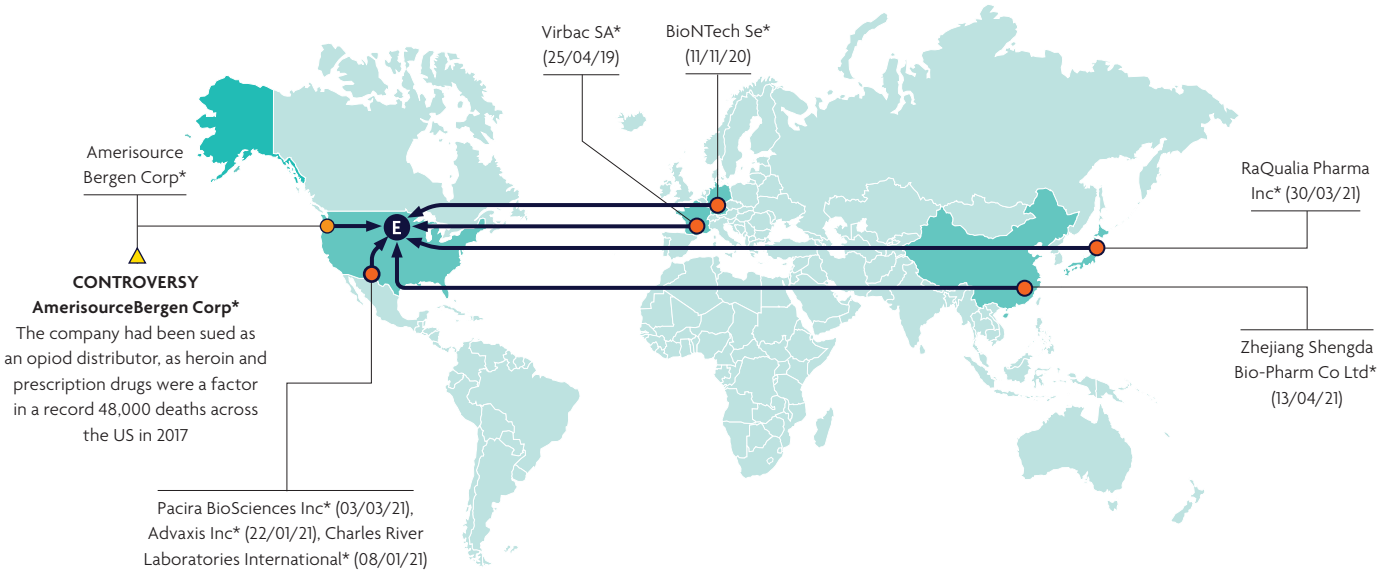
A 2016 study in Hyderabad – the centre of antimicrobial production in India – found that antibiotic concentrations in the Musi river, which flows through the city centre, were 1,000 times greater than the usual concentrations found in rivers in European countries such as Germany or the UK.[169] A further study of the Kazipally Lake in 2014, which is located on the edge of Patancheru in India and known as a site used for the dumping of pharmaceutical waste, identified resistance genes across every major class of antibiotics.[170] The communities that live in these local areas rely on the rivers and lakes for drinking water for themselves and their livestock, and fish the waters.

In 2020, in response to the growing spread of antibiotic resistant bacteria, the Indian government introduced a first of its kind regulation to limit antibiotic residues found in effluent for 121 different antibiotics.[171]

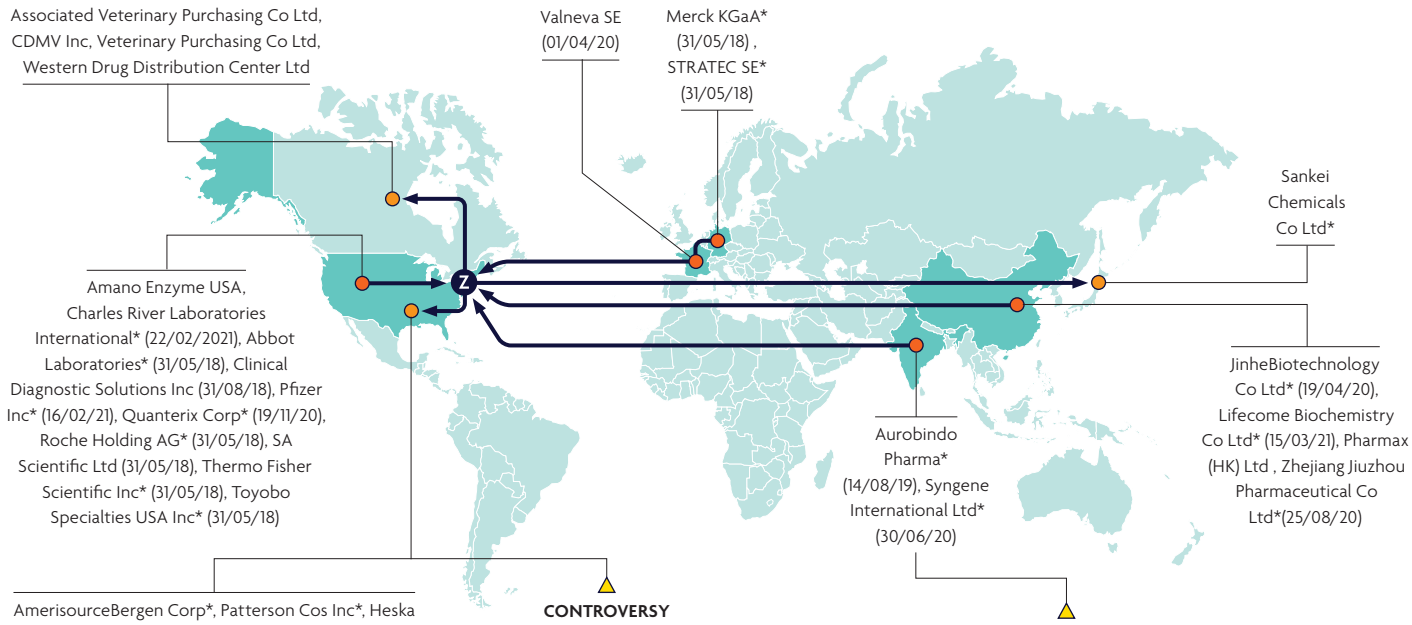
Figure 9. FAIRR has partially mapped the supply chains of the two largest animal health companies: Zoetis and Elanco

Animal Health Company · Suppliers · Customers

ELANCO SUPPLY CHAIN MAP



ZOETIS SUPPLY CHAIN MAP



**Companies that are publicly listed. Customers and suppliers included here are not exhuasative but include the publicly available data and illustrate the complexity of the supply chain. Sources: Bloomberg, US Customs Import Data from Port Examiner, Truevalue Labs. Date listed is the last known date of engagement.*

CASE STUDY

Aurobindo

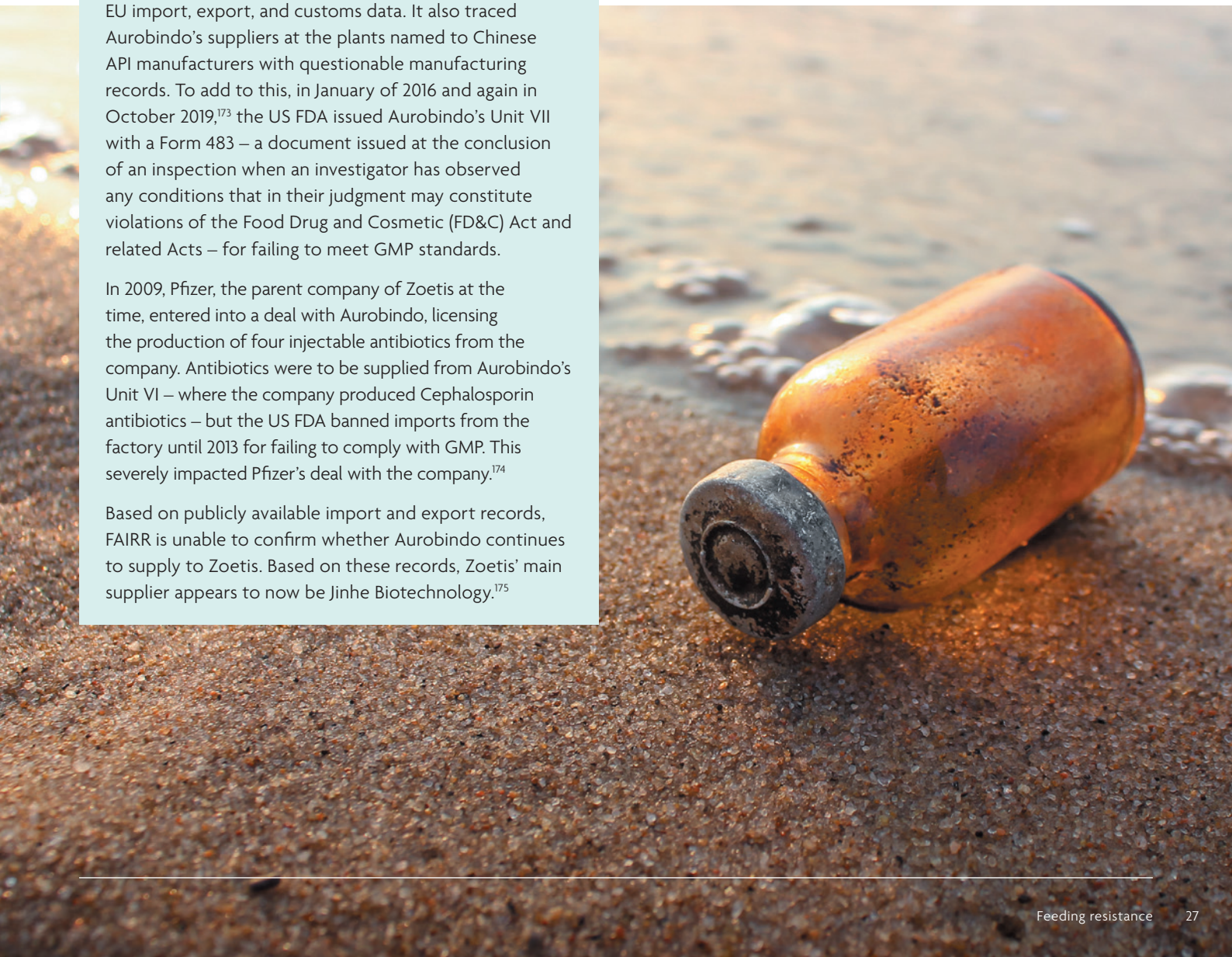
Aurobindo is one of India's largest generics manufacturers and have previously supplied to Zoetis. Over the last decade, Aurobindo has faced a number of serious allegations including the dumping of pharmaceutical discharge and a failure to meet GMP standards.

A 2016 investigation, conducted by Changing Markets, found worrying levels of resistance to key antibiotics around Aurobindo's factories near Hyderabad. At its Unit VII site, total resistance to three major classes of antibiotics was found – cephalosporins, carbapanems, and fluoroquinolones.[172] The report linked Zoetis to the purchase of two antibiotics, Ceftiofur and Amoxicillin, from Aurobindo Unit VII site using Indian, US and EU import, export, and customs data. It also traced Aurobindo's suppliers at the plants named to Chinese API manufacturers with questionable manufacturing records. To add to this, in January of 2016 and again in October 2019,[173] the US FDA issued Aurobindo's Unit VII with a Form 483 – a document issued at the conclusion of an inspection when an investigator has observed any conditions that in their judgment may constitute violations of the Food Drug and Cosmetic (FD&C) Act and related Acts – for failing to meet GMP standards.

In 2009, Pfizer, the parent company of Zoetis at the time, entered into a deal with Aurobindo, licensing the production of four injectable antibiotics from the company. Antibiotics were to be supplied from Aurobindo's Unit VI – where the company produced Cephalosporin antibiotics – but the US FDA banned imports from the factory until 2013 for failing to comply with GMP. This severely impacted Pfizer's deal with the company.[174]

Based on publicly available import and export records, FAIRR is unable to confirm whether Aurobindo continues to supply to Zoetis. Based on these records, Zoetis' main supplier appears to now be Jinhe Biotechnology.[175]

Increased resistance to antimicrobials in animals will have economic consequences for farmers as illness in animals will be harder to treat and this will likely be passed on to consumers through increased food prices – this could affect the ability for low- and middle-income countries to feed growing populations.



CASE STUDY

Reducing antimicrobial residues in pharmaceutical effluent – learning from the human pharmaceutical sector

There is a need for minimum standards for manufacturing antimicrobials in order to reduce the negative impacts associated with effluents containing antimicrobials entering the environment.[176] This is already happening on the human pharma side with the Antimicrobial Resistance Industry Alliance (AMRIA) – set up by 13 leading companies that account for a third of the global supply of antibiotics.[177] Merck & Co., and its animal health subsidiary, are members of the alliance.[178]

The AMRIA is creating a framework for companies to control their antimicrobial waste and ensure responsible and safe disposal. The framework includes risk-based targets for predicted no-effect concentrations (PNECs) for wastewater, in order to tackle the issue of antimicrobial concentrations and resulting AMR within the environments surrounding manufacturing sites.[179] Within 4-7 years, companies committing to the framework are expected to:

- Work with independent technical experts to develop risk based PNECs for antimicrobials and good practice methods to reduce environmental impact (which has been achieved).
- Establish a common framework for managing antimicrobials discharge which builds on the Pharmaceutical Supply Chain Initiative (PSCI) – of the ten animal health companies assessed in this report, only five were identified as being full or partial members and these are Elanco, Merck & Co., Orion, Zoetis (not full member) and Vetoquinol (not full member).[180]
- Work with stakeholders to develop a practical mechanism to transparently demonstrate that supply chains meet standards.
- Review manufacturing and supply chains to assess good practice for releasing antimicrobials into the environment.

This framework could also be utilised by animal health companies to ensure an aligned approach towards effective, lower impact manufacturing which explicitly addresses antimicrobial effluents in wastewater.

Issues with product quality

Manufacturing practices that lead to poor product quality can also contribute to increased resistance levels. For example, studies show that certain antibiotics produced by some generics manufacturers in India and China contain differing levels of APIs to those shown on the ingredient labels.[181,182] A study of poultry producers in the Mekong Delta of Vietnam found that of the antibiotics tested less than a third contained all active antimicrobial ingredients within 10% of what was stated on the label.[183] The variation between actual and reported ingredient strength has led to animals not receiving the minimum dose necessary to treat their illness, increasing the likelihood of resistance in certain bacteria developing.[184]

The current opaqueness of the antimicrobial supply chain and the concentration of manufacturing within India and China have raised concern. Concern centres around manufacturing practices and the issue of AMR in the environment, product quality and accessibility of drugs. The G7 Health Ministers' 2021 communique called for a risk-based approach which acknowledges the need for greater transparency and better mapping of the antimicrobial supply chain and to strengthen supply chain resilience by building a geographically diverse and better regulated system.[185] This will allow stakeholders to better understand which manufacturers are producing which drugs and for pharmaceutical companies to be able to see which of their suppliers are committing bad practices. There are also calls to put in place measures that will assure product quality and drug availability.[186]

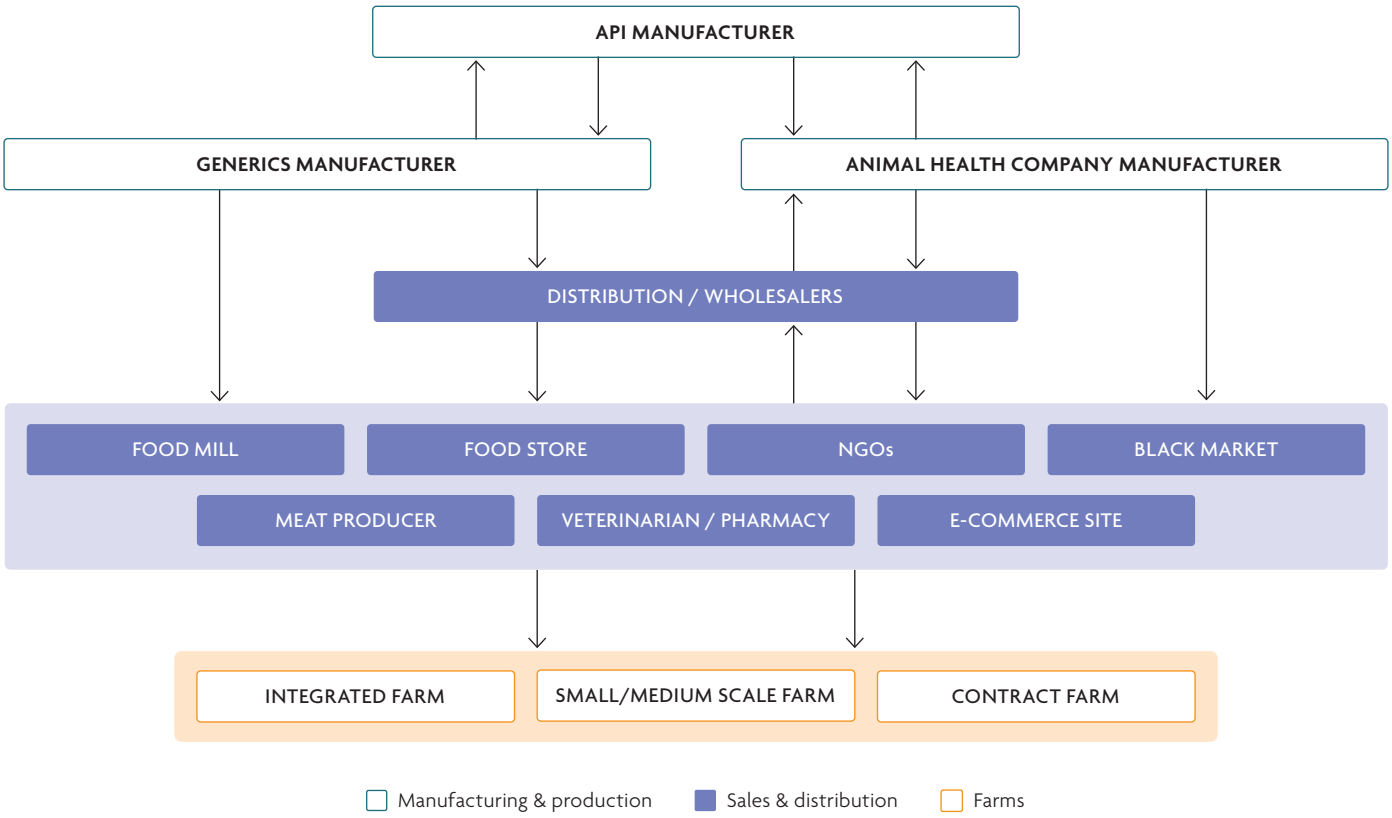
Engagement questions for investors

- Has the company mapped out its supply chain and carried out a risk analysis to identify high-risk vs low-risk suppliers?
- Does the company have environmental risk management strategies in relation to wastewater and other effluent from antimicrobials manufacturing?
- What standards does the company apply to third party suppliers across markets?
- Does the company have mechanisms in place to ensure third party suppliers are effectively treating antimicrobial waste and reducing pharmaceutical discharge into the environment?
- How is the company working with its suppliers and broader stakeholders to raise manufacturing standards, including the reduction of antimicrobial residues from manufacturing effluent and ensuring product quality?

Sales, marketing and regulating use

Animal agriculture accounts for an estimated 70% of total global antimicrobial use.[187] Current marketing and packaging of these drugs, particularly in emerging markets, do little to change the ingrained behaviour of routine antimicrobial use for growth promotion or prophylaxis.

Figure 10. The animal health pharmaceutical supply chain from production to on farm usage is complex



Source: FAIRR 2021

Sales, marketing and package sizing practices contribute to growing AMR

Animal health companies continue to sell shared-class antibiotics for use in livestock. In the US, 65% of antibiotics considered important, in some cases critically, to human health – such as penicillin and tetracycline – are sold for use in livestock.[188] Using shared-class antibiotics in animal production directly impacts the effectiveness of these drugs for use in humans, with clear evidence that resistance to these drugs developed in animals can spread to humans through the consumption of meat, direct contact with animals, or via the environment.[189]

The biggest concern is that these shared-class antibiotics are being used routinely for non-therapeutic purposes such as growth promotion and prophylaxis, and the long duration and lower dosages of use increases the chance of resistant bacteria developing.[190] In the US, Switzerland and the EU the use of shared-class antibiotics for these purposes is restricted. But in emerging markets, non-therapeutic usage is more common as there is less regulation, and enforcement of regulation, where it exists, is weaker. Use for prophylaxis can account for as much as 84% of total antibiotic use in animal agriculture in areas such as the Mekong Delta region of Vietnam,[191] while in China, use for growth promotion accounted for an estimated 53% of total usage of antibiotics in food producing animals in 2018.[192]

By labelling products for growth promotion and prophylaxis, animal health companies are directly influencing how farmers administer antibiotics to their animals. Farmers in emerging markets often lack access to veterinarians, and their only guide to uses, dosage, method of application, and expiry date is on the product label.[193,194]

> Zydus Cadila sells a product called Winmyco, which contains a highest-priority critically important antibiotic for human health (as categorised by WHO), in 25kg bags, labelled for use as a growth promoter. This antibiotic is severely restricted for use in humans, yet is being promoted for everyday use for non-medical purposes in animals.[195]

Table 5 highlights a selection of shared-class antibiotics from Zydus Cadila and Jinhe Biotechnology, based in India and China respectively, that are labelled for growth promotion and/or sold in large quantities – practices that promote unnecessary and excessive use. It is important for the animal health sector to reduce pack sizes, which reduces the amount of unused or expired medicines and makes it less likely the drug will be released into the environment. In addition, clear labelling helps to ensure users know how to properly dispose or return unused products to manufacturers. Orion, a Finnish animal and human health pharmaceutical manufacturer, is an example of a company that takes the size of packages and the shelf life of products into consideration.[196]

Table 3. Table showing selection of antibiotics sold by Jinhe Biotechnology and Zydus Cadila.

Jinhe Biotechnology		
Product Name	**Largest Package Size Available**	**Antibiotic**
Explosive Chlortetracycline – 10% chlortetracycline premix	△ 25kg	Chlortetracycline
Explosive Chlortetracycline – 25% chlortetracycline premix	△ 10x 1kg	Chlortetracycline
Powder Series – 32.5% neomycin sulfate soluble powder	1 kg	Neomycin
Powder Series – 10% Amoxicillin soluble powder	1kg	Amoxicillin
Powder Series – 45% Tiamulin Fumarate Soluble Powder	1 kg	Tiamulin*
Microcapsule Series – Microencapsulated 20% Tilmicosin Premix	1 kg	Tilmicosin

Zydus Cadila		
Product Name	**Largest Package Size Available**	**Antibiotic**
Chloran	△ 25kg	Chlortetracycline
Winmyco – Premix	△ 25kg	Tylosin
NE – FIX	△ 5kg	Enramycin
Floxlevo	5L	Levofloxacin
Enrodac – 10	5L	Enrofloxacin
Frankolin	△ 1kg	Tiamulin*

△ Sold for growth promotion
Contains Highest Priority Critically Important Antimicrobials (HP-CIAs)
Contains Critically Important Antimicrobials (CIAs)
Contains Highly Important Antimicrobials (HIAs)

*Is classed as important to human health by the WHO as it is part of a class of antimicrobials known as pleuromutilins. However, at present it is only used in animals.

Source: The data is based on a review of products sold on individual company websites in 2021: https://zydusahl.com/ and http://www.jinhe.com.cn/?PG=PRODS.

The lack of global marketing policies has allowed animal health companies to market products differently and in a way that helps to further entrench poor practices that contribute to the global AMR burden in markets where regulation and public pressure to curb antibiotics use is absent. For example, Zoetis has publicly supported stronger antibiotic regulation in the US, but in India, the Bureau for Investigative Journalism (TBIJ) found that Zoetis had been actively promoting the sale of antibiotics such as Tylosin for growth promotion.[197] Tylosin is a highest priority critically important antibiotic for humans – the highest categorisation possible – and its use in animals for growth promotion has been banned in Europe due to resistance fears.[198] Other companies have also been found to be selling Tylosin for use as a growth promoter, including Zydus Cadila as noted in the table on page 32.

Zoetis responded by removing claims to growth promotion on antibiotics products on its Indian website in 2019 and later committed to removing these claims from its products globally by 1st January 2020.[199]

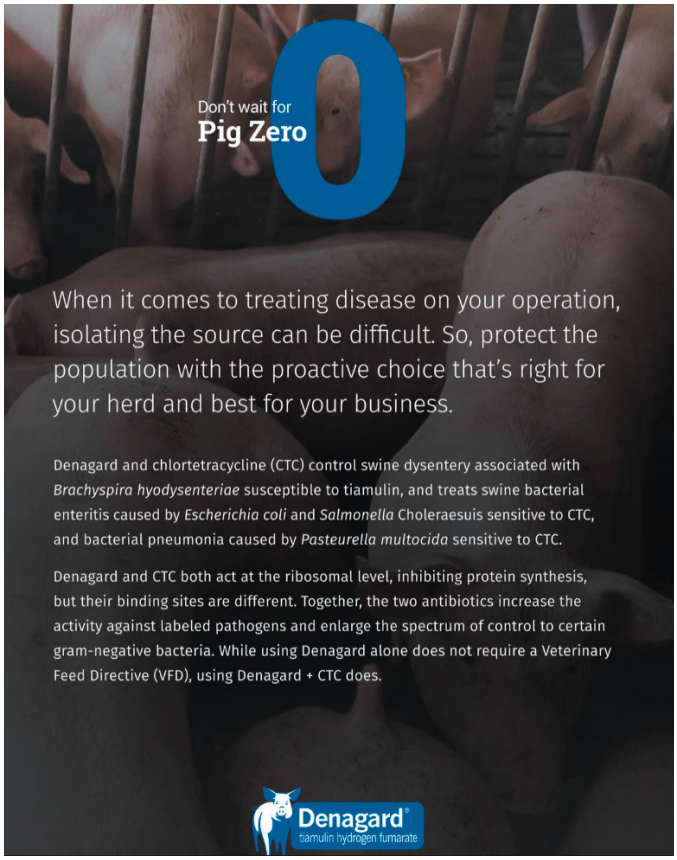
However, despite these claims, FAIRR analysis found online evidence of Zoetis advertising medicated feed products as growth promoters and/or for routine prophylactic use. For example, Linco-Spectin, which contains lincomycin (classified by the WHO as a MIA for humans) is sold in 20kg bags and according to the company's Ecuador website, the product can be used to promote growth and feed efficiency as well as to prevent and control respiratory infections in pigs.[200] In contrast, the same product is advertised on the Colombia website for routine preventative use only and is sold in pre-packed doses of 4.5g.[201]

Another prominent example is Elanco, which said it stopped advertising MIAs as growth promoters in 2016, even in countries where it is still legal.[202] However, the company was found to be promoting the use of antibiotics for prophylaxis, and also advertising growth promotion as a positive side effect of prophylactic use. In 2019, Elanco ran a campaign with the phrase 'Pig Zero' which encouraged farmers to use antibiotics in every pig in the herd, rather than treating only sick animals – going against the advice of the WHO.[203] The company distributed brochures and posters to farmers with messages such as "*singling him out is never this easy*" and "*don't wait for pig zero.*"[204]

The company used this campaign to promote its Denagard product which contains Tiamulin, an antibiotic considered by the WHO as important to human medicine despite only being used in veterinary medicine. Denagard is one of Elanco's top-selling products accounting for over 1% of revenue in 2020.[205] In the same campaign, Elanco also promoted combining Denagard with chlortetracycline (CTC), a MIA, given the potential weight-gain benefits of treating pigs with this mix. These antibiotics are not allowed to be sold for growth promotion in the US, but their use for prophylaxis still has growth promoting side effects. This highlights the difficulty of enforcing restrictions on the use of MIAs for growth promotion, as the drugs are technically being sold for prophylaxis.[206] After the New York Times published a detailed article in 2019, Elanco responded by removing all brochures and posters associated with this campaign. However, the company continues to sell Denagard for the 'control' of disease and does not include an upper time limit (i.e., use for a maximum of 20 days) for the recommended use period.[207]

Figure 11. Screenshot taken from Zoetis website, 28 June, 2021

Figure 9: Pig Zero Advertisement promoting the prophylactic use of Denagard in combination with chlortetracycline, taken from the September 2018 issue of Farm Journal's Pork Magazine.[208]



A complex and opaque supply chain that is increasing the risk profile of the animal health sector

Antimicrobials are predominantly sold through intermediaries, including veterinarians, feed stores, and pharmacies. These intermediaries tend to purchase the drugs via national distributors such as Covetrus, but in some cases animal health companies will also sell directly to veterinarians and pharmacies. Animal health companies therefore have an important role to play in promoting (ir)responsible use of antimicrobials.

Distributors and local vendors are generally not disclosed by animal health companies unless they account for a significant proportion of a company's revenue. This makes it difficult to track and control who is selling products and how they are being marketed and sold. Distributors have been known to stockpile in advance of regulatory changes that would prevent the sale of certain antimicrobials. For example, Phibro noted it saw a jump in revenue at the end of 2019 in its Medicated Feed Additives (MFAs) category in China, which it attributed to distributors in the region stockpiling (and potentially selling) the company's *virginiamycin* product prior to regulatory changes in early 2020 which prohibited labelling MFAs for growth promotion.[209]

This contributes to the issue of antibiotic sales that exist outside of regulation, such as purchases from the black market, feed vendors selling products without prescription and without full knowledge of their uses, and purchases from friends and family. These issues are most prevalent in emerging economies. A study of small- and medium-sized chicken farms in Ningxia, China found that 75% of respondents still use antibiotics that have been banned by the government.[210] Similarly, in Northeast Ethiopia it was found that around 20% of antibiotics were accessed via illegal sources.[211] They have been able to purchase these without prescriptions and keep no records about their usage.[212]

Governments are changing regulation on antibiotics use for growth promotion and prophylaxis

Governments around the world are introducing regulation to restrict the sale of antibiotics, with a particular focus on labelling. Initial bans have focused on growth promotion, but these vary in their coverage.

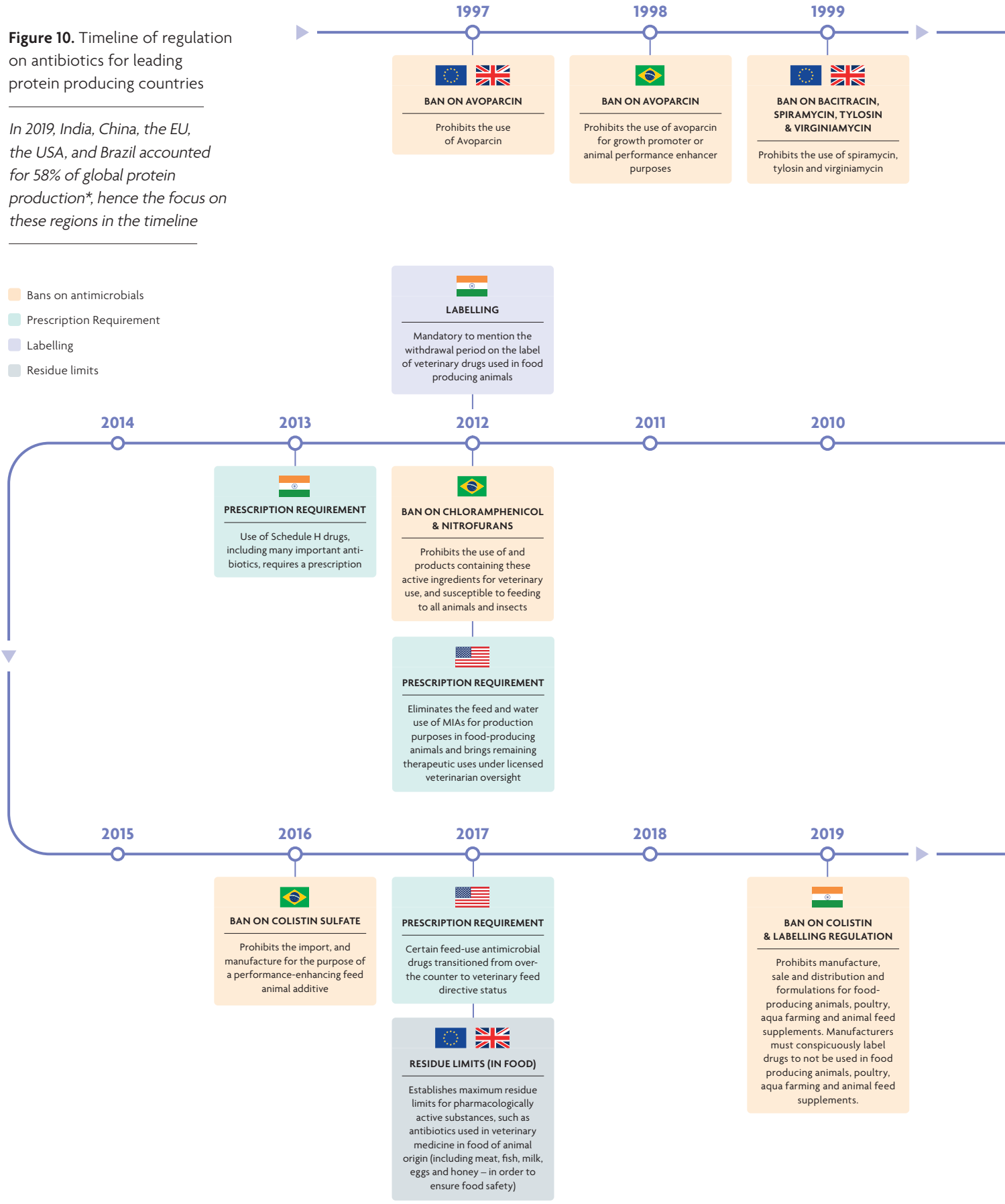
The EU, US, Brazil and China, amongst others, have introduced regulation that prohibits using either shared-class or all antibiotics for growth promotion. In the EU and US the regulation successfully resulted in a reduction in antibiotic used and increased awareness of the need for antimicrobial stewardship, following an initial plateau. In 2017, reported antibiotic use in humans (in mg per kg) was greater than reported use in food producing animals (in mg per kg) for the first time since reporting began.[213]

The EU has also announced that it will be banning the use and labelling of antibiotics for prophylaxis from 2022.[214] This legislation includes new powers to allow the European Parliament to completely exclude certain last-resort antibiotics used in human medicine from being used in farming.[215] This is an important step as there is often very little difference between the dosage used for growth promotion and prophylaxis – meaning the restriction of use for growth promotion may have little impact on the volume of use.

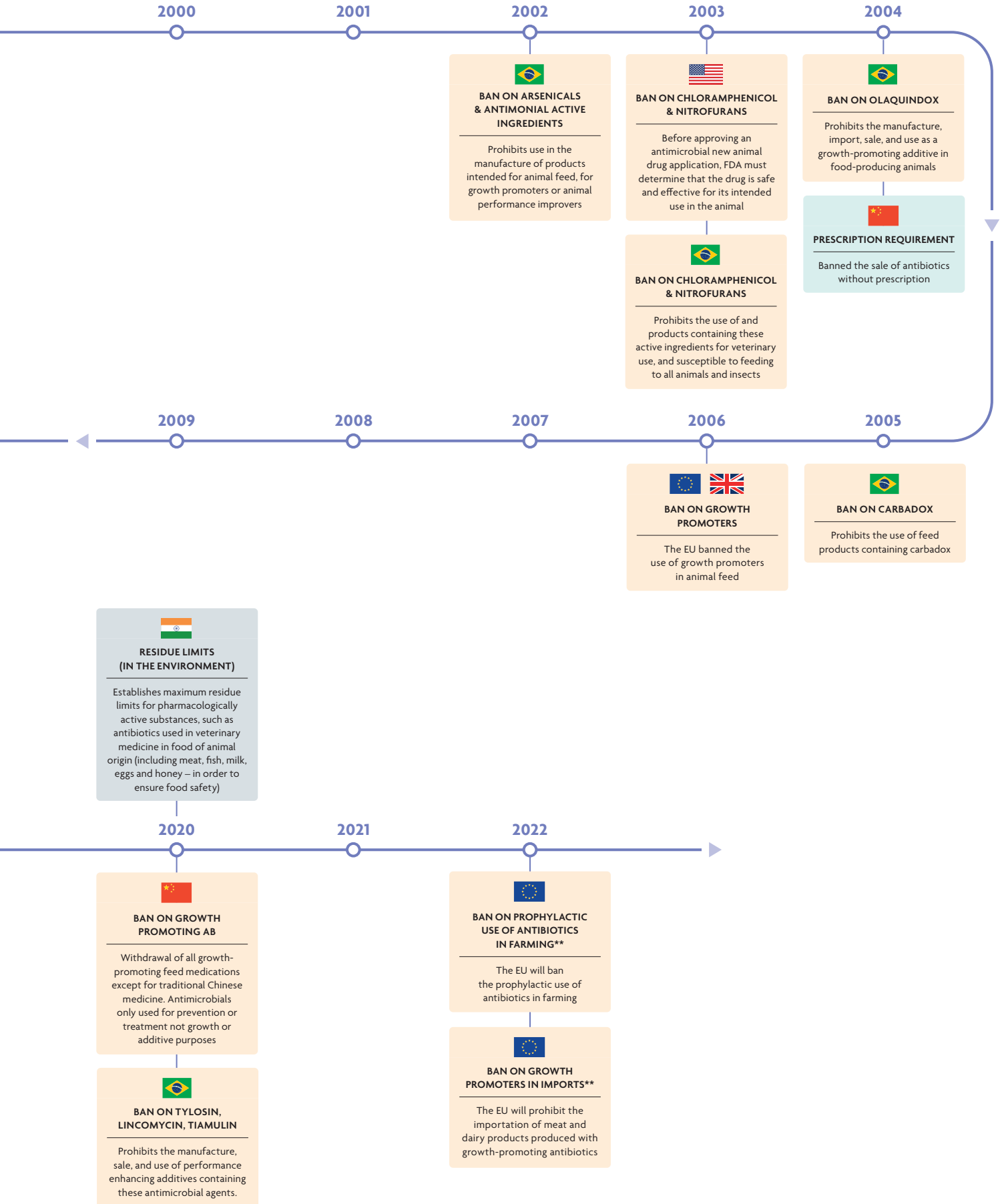
In the US, for example, regulation restricting the use of antibiotics for growth promotion resulted in more than 80 products labelled for growth promotion being taken off the market, but 31 remaining for sale, with growth promotion simply removed from the label and still available for prophylaxis.[216]

Figure 10. Timeline of regulation on antibiotics for leading protein producing countries

In 2019, India, China, the EU, the USA, and Brazil accounted for 58% of global protein production, hence the focus on these regions in the timeline*



*Statistic based on OECD-FAO Agriculture Outlook 2020-2029 database including meats (beef and veal, pigmeat, poultry meat, sheepmeat, dairy, and fish)



**It is unclear whether the UK will adopt these regulations post-Brexit

Similarly, following the European ban on the use of antibiotics for growth promotion in feed, antibiotics continued to be used for prevention, with very similar dosages as before.[217]

Alongside regulation on the usage of antibiotics for growth promotion[vii] and prophylaxis, there has been a shift towards requiring prescriptions. These regulations – termed veterinary medical directives (VMD) – have been introduced in Denmark, India, Switzerland, the EU and the US on certain antibiotics, mostly for those deemed as clinically important or 'last resort' and usually only provided for treatment or metaphylaxis only. In particular e-prescriptions have proven to be effective at driving down sales of MIAs.

However, it is important that regulation restricting the use of one antibiotic does not lead to an increased use of another antibiotic where unintended consequences may occur. For example, data seen by the Bureau of Investigative Journalism, the Guardian and Vet record shows that as a result of the phasing out of colistin, and upcoming bans across the EU and UK on the use of zinc oxide – a commonly used alternative to colistin, the use of aminoglycosides on UK pig farms to treat post-weaning diarrhoea in pigs more than doubled between 2015 and 2019.[218]This is problematic as aminoglycosides are deemed to be CIAs by the WHO, and are a class of drugs that includes gentamicin, which is used in human medicine to treat serious bacterial infections such as meningitis.[219] In response to these findings, the ASOA has said improved pig welfare, including less intensive conditions, improved husbandry and banning the "*stressful*" practice of taking piglets away from sows at an early age, could help achieve the reductions in antibiotic usage required.[220]

Changing regulations have caught out companies unprepared for the transition. For example, US-based Phibro, was impacted by a quick transition in regulation in China.[221] Under announcement no. 194 of the Ministry of Agriculture and Rural Affairs, from the 1st January 2020 the production, import, sale and use of all growth promoting MFAs became illegal. From July 2020, the same applies to commercial feed containing growth promoting MFAs too.[222] As Phibro had been labelling its MFAs as growth promoters, all of which contain virginiamycin – a MIA, it has been blocked from selling them in China since the beginning of 2020. The company already sells products containing virginiamycin for therapeutic purposes in other countries, and has submitted the products for reapproval under therapeutic claims. They will be back in the market once the product is reapproved, but it is likely to be around a year before this happens, partly due to delays caused by the COVID-19 pandemic and African Swine Fever (ASF). The introduction of this new regulation in China means that farmers will need a prescription and the involvement of a vet to use a drug they could previously use freely, and Phibro have stated that this could negatively impact sales.

vii Use of antimicrobials for growth promotion does not require a prescription.

CASE STUDY

Financial implications for animal health companies associated with the introduction of e-prescriptions regulations

Animal health companies are increasingly at risk from new regulation focused on curbing antimicrobial use in farm animals. For example, In 2018, Virbac derived approximately 12.2% of revenue from the sale of antibiotics for food producing animals (excluding aquaculture). However, following the introduction of mandatory e-prescriptions which made it harder to purchase antibiotics for food producing animals in Spain (as at 1st January 2019), and when purchasing veterinary medicines and medicated feed in Italy (as at 1st September 2018); Virbac reported revenue decreases within its pig and poultry antibiotics segment of 9.1% in 2019. In contrast, sales for other products including vaccines and supplements for pig and poultry increased by 6.6% during the same period.[223]

Beyond regulation: growing consumer awareness and civil society pressure

Four of the ten animal health companies examined in this report (Zoetis, Elanco, Phibro and Dechra) list growing consumer awareness of the association between animal antibiotic use and AMR in humans as a material risk to their business. Specifically, the companies cite evolving consumer views of animal rights, nutrition and health-related concerns, as well as the increased uptake of plant-based products as risks in their public reporting. The rapidly changing regulatory environment focused on curbing antibiotic use and mitigating the climate impacts of current production systems are also key concerns for animal health companies that derive sales from farm animal production.

Consumer awareness of AMR and other health-related concerns are leading to increasing demand for meat products labelled as 'organic' and 'raised without antibiotics' (RWA) or without hormones.[224] A 2019 Food Marketing Institute report revealed that in the US production claims on meat and poultry products, such as grass-fed and hormone- and antibiotic-free, pushed sales up 4.8% and that 52% of shoppers would like more

products to be free from antibiotics and hormones.[225] Similarly, a 2018 Consumer Reports survey also in the US showed that nearly 60% of respondents said they would be more likely to dine at a restaurant that serves meat RWA, with an equal number willing to pay more for hamburgers from animals RWA.[226] While consumer demand for RWA is present, it is important to note that if an animal is sick, it should be treated, and in some cases this will require the use of antibiotics.

Further, driven by concerns over animal rights, nutrition and the environment more consumers are shifting to flexitarian, vegetarian and vegan diets. In 2020, flexitarians, or people restricting the number of animal-based products they consume, made up 42% of consumers globally.[227] Vegetarians and vegans made up 5% and 4% of consumers globally respectively.[228] Demand has only been amplified by the recent COVID-19 pandemic, which has highlighted the association between meat consumption (human and animal interaction) and the transmission of dangerous pathogens.[229] In 2020, the US plant-based retail market grew 27% (almost two times greater than the whole US food retail market),[230] compared to 18% in 2019.[231] Growth in plant-based proteins is echoed around the world in Europe,[232] the UK,[233] and Australia.[234] In China, the plant-based market is expected to reach $14.5 billion by 2025,[235] with recent demand intensified by concerns over health and food safety as a result of Covid-19 and African Swine Fever (ASF).[236,237]

Investors are also putting pressure on portfolio companies including those in the food and pharmaceutical sectors to address the growing risk of AMR. The Investor Action on Antimicrobial Resistance (AMR), a coalition between the Access to Medicine Foundation, the FAIRR Initiative, the Principles for Responsible Investment (PRI), the UK Government Department of Health and Social Care and fourteen global institutional investors representing over $11 trillion in combined assets have publicly committed to adopt an 'AMR lens' when making investment decisions and engaging with investee companies and policy makers.[viii,238]

Global food companies across the value chain are responding by strengthening their policies and commitments on antibiotics use and expanding their protein offerings to include plant-based options. For example, McDonald's, one of the world's largest buyers of beef, committed to establish reduction targets for MIAs for its global beef supply chain, and to publicly report on its progress. This commitment is in addition to its efforts to

viii "Applying this "lens" entails the development and application of standards to assess antimi-crobial resistance-related risks and impacts and accountability measures to ensure that that these investments do mitigate– and do not worsen–the emergence, prevalence and impact of antimicrobial resistance." IACG, April 2019.

prohibit the use of HP-CIAs in its poultry supply chain.[239] The company also introduced the McPlant, a plant-based burger, in partnership with Beyond Meat in 2021.[240]

Retailers are also asking their animal protein suppliers to exhibit better antibiotic stewardship. A 2020 report by the Alliance to Save Our Antibiotics (ASOA) showed that by 2019 seven UK retailers adopted bans or partial bans on suppliers that use antibiotics routinely to prevent disease.[241] The report also showed that consumers want more transparency with a large majority of respondents (87%) saying that supermarkets should publish the antibiotic use data they possess.[242]

The ASOA has put pressure on the UK government to match the EU ban on imported meat treated with antibiotics for growth promotion and to also match the incoming ban on routine preventative use of antibiotics in domestic livestock production.[243,244] In the US, the Natural Resources Defence Council (NRDC) has called for a reduction in the use of MIAs in food animal production, specifically by 50% by the end of 2023, relative to a 2009 baseline.[245] This follows last year's FDA data showing a rise in sales of MIAs for the use in food producing animals in 2019.[246]

As consumer awareness on antimicrobial resistance continues to grow alongside regulation to curb use in farm animal production; companies that rely on the routine mass medication of farm animal with antibiotics, both as a means to increase feed efficiency and to reduce mortality rates will be at risk. Forward looking animal health companies with exposure to the sector will need to pre-empt changes that could limit their market access and erode consumer trust in their brands and sector. This means:

- Employing a consistent sales and marketing approach across operating markets in line with the strictest regulation i.e., if operating in the EU then a company should adopt these standards across all its relevant markets;
- Removing growth promotions and routine prophylaxis claims from MIAs with a long-term view to remove such claims from all antimicrobials to protect the efficacy and ensure the promotion of responsible use and protect the efficacy of these drugs; and
- Selling antimicrobials in smaller packaging sizes to reduce waste and promote controlled use.

Engagement questions for investors

- Has the company got policies and practices in place addressing labelling and packaging of antibiotics that aim to lead to reductions in overuse and misuse?
- Does the company sell any antimicrobials marketed as growth promoters and/ or prophylactics? Are these important to human medicine?
- Does the company have policies in place to ensure appropriate and consistent promotional strategies are being pursued across the company?
- Does the company have consistent sales and marketing materials across geographies?
- Does the company have policies/requirements on how distributors and intermediaries market/ distribute their products? Are they tracking sales practices? Do these policies prohibit non-essential uses?

Alternatives to antimicrobials

Evolving external pressures are increasing the focus on alternatives to antibiotics, with companies investing in diagnostic tools, preventative measures, and novel treatments. Many of these alternatives show positive outcomes or have promise but require further development and widening of use in order to make it cost-effective for the animal agriculture industry to use.

The animal health landscape is shifting. Changing consumption patterns and increasing consumer awareness of the links between antibiotic use in food producing animals and human health are having a visible impact on demand within the animal protein sector. Increasing regulatory action – to prohibit the use of antibiotics for growth promotion and address the routine use of shared-class antibiotics for prophylaxis – is putting further pressure on protein producers to invest and transform their approach to farming and fuelling the need for alternatives to antibiotics.

This has a direct impact on animal health companies who are already recognising the commercial opportunities associated with alternatives to antibiotics. The R&D pipeline for alternatives appears to be strong, with companies developing traditional alternatives such as vaccines as well as a range of potential novel options, although the latter are not yet widely available and still require extra testing and development to understand their effectiveness. Patents for new alternatives, particularly treatment options, could be extremely valuable in the long-term, as alternatives become the preferred option for farmers worldwide.[247]

What are the alternatives to antibiotics?[ix]

Although there is currently no silver bullet or direct replacement for antibiotics, there are a growing number of alternative options – such as vaccines, probiotics, prebiotics, immunotherapeutics, and in-feed enzymes – that help reduce disease incidence. These options promote better animal health, particularly when used in conjunction with improved animal husbandry and biosecurity measures that further reduce the need for antibiotics in the first place. Broadly, alternatives to antibiotics fit into three categories: diagnostic tools, preventative methods, and novel treatment options (see full summary of alternatives in table on page 48).

Multiple different alternatives are needed over the lifetime of an animal, and the timing of use is important. For example, vaccines must be administered well before infection, while bacteriophages (see page 48) are used around the time of infection. There are symbiotic relationships between alternatives – for example, use of probiotics has been shown to increase the efficacy of vaccines.[248] Further, time, cost, knowledge, attitudes, availability, accuracy, and usability all impact on the effectiveness of alternatives.[249] To influence greater uptake, policymakers, companies, veterinarians and farmers need to find ways to change existing practices and research needs to be done to find the most effective uses and combinations of alternatives.

In particular there needs to be more research done to assess the cost-effectiveness of using alternatives rather than antibiotics in commercial and non-commercial farm settings where real-world husbandry and other factors impact efficacy. This is difficult due to the complexity of systems and the fact that the use of alternatives requires a change in farming practices rather than a simple product change. The main case study available is that of Denmark, one of the world's largest exporters of pork,[250] who began phasing out the use of growth promoters in pig farming in 1999 by improving biosecurity and husbandry practices and using alternatives to antibiotics.[251] The most crucial aspect of this ban is that it had little to no effect on productivity. Between 1992 and 2008, use of antibiotics per kg dropped by 50%, while productivity increased as the number of pigs per sow increased.[252] However, the reduction has added average 1.6 days to the growth time of pigs,[253] and the total additional cost per pig, measured in 2003, was estimated around $1.09 or just over a 1% increase (taking into account productivity increases and some costs of modifying production systems).[254]

> Ten of the largest animal health companies[x] have committed to invest $10 billion collectively in alternatives by 2025, with the aim to develop 100 new vaccines, 20 new diagnostic tools, 20 nutritional enhancement tools, and 30 other products that will help to reduce the need for antimicrobials.[255]

ix We do not consider pharmaceuticals that are technically classed as antimicrobials such as anticoccidials, antibacterials and antiparicitisides or heavy metals such as copper in this section as these have the potential to confer AMR and due to their potential adverse effects on humans and the environment. We have highlighted only the alternatives to antibiotics that are not seen as dangerous for humans and the environment and that do not have the potential to contribute to the global AMR burden.

x Boehringer Ingelheim, Ceva Sante Animale, Elanco Animal Health, IDEXX Laboratories, Merck & Co., Phibro Animal Health Corporation, Vetoquinol, Virbac, Zenoaq and Zoetis.

Novozymes Case Study: Improving gut health for better performance

Animals in commercial broiler production face a great deal of environmental stress, which can cause inflammation in the gastrointestinal tract. This leads to a higher risk of disease, lower feed conversion and lower weight gain. In response, farmers in the US and European began using antibiotic growth promoters (AGPs) – to prevent disease and improve overall flock health and productivity.

This was the pattern of production for several decades until 2006, when the EU Commission banned the use of AGPs due to concerns around growing anti-microbial resistance. Many key markets like the US and China are slowly moving in this direction as well.

But the question remains – how can farmers maintain the health, welfare and productivity of their flocks in an intensive farming environment? Apart from making changes to husbandry practices and improving biosecurity and health management, experts point to the use of functional feed ingredients as a key lever here.

Since 2001, Novozymes has partnered with DSM Nutritional Products to form the Feed Enzymes Alliance. Together, these two pioneering science companies have delivered transformational innovation for the feed industry for two decades. Novozymes develops and produces enzymes for animal health and nutrition, whereas DSM brings them to market.

In 2018, the Feed Alliance launched Balancius®, the first and only broiler ingredient designed to improve gut functionality. Balancius is a microbial muramidase enzyme which breaks down dead bacterial cell debris and improves the microflora in the gut. This restores balance in inflammatory responses, which leads to a healthy gut and increased efficiency.

Balancius® is used by some of the biggest and most progressive poultry companies in the U.S. Based on 3 complex-wide trials, Balancius® has been shown to:

i. improve nutrient digestibility and absorption and overall gut functionality,

ii. contribute to more sustainable poultry production by improving feed conversation ratio by 3%,

iii. better animal welfare by keeping litter drier, and

iv. better quality by improving breast meat yield and uniformity.

When all these benefits were factored in, integrators estimated that the return on investment was >3:1.

COVID-19 did not impact our business significantly and sales stayed consistent. In fact, COVID-19 has strengthened the value proposition for products like Balancius®. To safeguard public, it is vital that we improve global antibiotic stewardship by safeguarding the efficacy of existing antimicrobials and investing in innovation that allows for the continued reduction of antibiotic use in agriculture.

Regulatory authorities will play a key role in driving this agenda. While much progress has been made on encouraging responsible antibiotic use, current regulations are slowing down innovation and adoption of new solutions by the industry. Within the current setup, feed additive manufacturers can say very little about the specific benefits these products have, unless the products are registered as drugs. This is confusing for customers who struggle to differentiate between what is 'snake oil' and what is effective.

The regulatory pathway for the next generation of solutions is even more complicated. To bring more solutions like Balancius® that can benefit both animals and the farmer to the market, we need to adopt a 'One Health' approach and improve our regulatory systems.

Balancius product from Novozymes-DSM partnership

novozymes | DSM Balancius™

Diagnostics

Despite rising concerns over AMR, antimicrobials are necessary in the treatment of sick animals, and avoiding treatment could impact the welfare of animals. When treating sick animals, it is important to identify the most effective and prudent medication. The ability to diagnose illnesses as viral or bacterial before treatment is crucial for ensuring correct medication is given and that antimicrobials are use in a judicious way. Diagnostics can also be used to monitor the condition of animals on farms and identify illness before outbreaks occur, enabling treatment with fewer drugs across a smaller herd population.

Rapid point-of-care diagnostics are increasingly available and can be used by farmers to make more accurate decisions about appropriate treatment. Diagnostics for dairy cows and cattle are well-used, particularly for bovine tuberculosis (bTB) and bovine viral diarrhoea (BVD) due to their widespread nature. Where the value of the herd is lower, however – for examples for poultry and pigs – farmers may be less inclined to use diagnostic tools.[256]

Diagnostics are not currently common practice for most veterinarians when prescribing antimicrobials to farmers. Most veterinarians still rely on their clinical knowledge and experience to diagnose illness in farm animals.[257] This is because diagnostics have historically taken hours or days to deliver results and there have been questions around the accuracy of some rapid tests.[258] This is changing as animal companies invest more in diagnostics development.

Despite the potential for return on investment in the long run, initial costs can be a barrier to the uptake of diagnostics for many farmers. Antibiotics are still an efficient, effective, and relatively low-cost option. This is especially the case in emerging markets such as China (which consumes half of the world's antimicrobials), where veterinarians tend to lack access to diagnostic tools, especially those for use on farm.[259]

Zoetis is investing in diagnostics and expanding this segment of its business. In 2019, for example, it acquired several small diagnostics companies to increase its R&D and laboratory capacity – including Abaxis, which produces VetScan® diagnostic instruments and rapid tests. These diagnostic tools can be used on farm at point-of-care, saving time for farmers.[260]

Diagnostic tests are a good example of a very effective alternative that can help reduce the need for antibiotics, but that – at least for now – are often deemed too expensive and not quick enough by farmers. The barriers of cost, reliability, and accuracy – particularly in developed markets – appear to be more perceived than proven, so there is a need to shift perceptions and knowledge on the value of diagnostics. There is, however, also a need for better diagnostic tools that are simple and faster to use to encourage farmers to adopt these tools. This requires social, governance (including regulatory) and technical innovation,[261] alongside engagement with veterinarians, regulators, diagnostic developers, and farmers.

Prevention

In addition to diagnostic monitoring, preventative methods include vaccines, improved feed and nutrition and improved animal husbandry, biosecurity, and welfare. Many preventative methods such as probiotics and in-feed enzymes double as growth promoters, with effects often indistinguishable from those of antibiotics.[262] Indeed, in commercial settings growth promotion and disease prevention are hard to separate – when illness is reduced, productivity increases, as healthier animals are able to more efficiently digest feed.[263] To further incentivise the uptake of alternatives, cost-effectiveness studies that show that not only are alternatives as effective as antibiotics but also similarly priced are important.[264]

Vaccines: Vaccines can treat a wide range of viruses, bacteria, funguses, and parasites in animals.[265] They help develop herd immunity and can in some cases eradicate endemic diseases, offering the possibility of large economic savings. A good example of endemic disease control through vaccination is the UK's tackling of Rinderpest in cattle in 2011.[266] In the US, current estimates suggest over 70% of operations vaccinate piglets against Mycoplasma pneumonia and nearly 60% of beef calf operations vaccinate against clostridial diseases caused by *C. chavoei*.[267] As awareness and regulation of AMR grows this is likely to increase.

HealthforAnimals (HfA), the industry alliance of animal health companies, includes vaccination as a key pillar to reducing AMR. Within its roadmap there are a number of relevant targets, including increasing the number of vaccines available, creating new vaccines, and improving access to vaccines through veterinarians in low- and middle-income countries.[268]

Although there are some concerns regarding the impact of vaccines on productivity, there are also studies demonstrating the growth promoting effects on animals.[269] Cost and availability remain as key issues limiting further uptake – both geographically and by disease. Vaccine costs vary greatly depending on the technology it uses, the disease(s) it prevents, intended species, who produces it and where it is being sold. More broadly, there is a distinct lack of formal economic analysis to understand the cost-effectiveness of vaccines at the farm-level. Further, vaccines are only available for certain diseases and access to these are often limited, especially in lower and middle-income countries.[270]

In the US and Europe, vaccine use is relatively well-established when compared to the rest of the world, but more needs to be done globally to facilitate greater vaccine adoption including educating farmers on use and by providing greater availability of quality vaccines.[271]

US-based Merck & Co. is one of the leaders in vaccines production, making more than 90 billion doses a year.[272] The company has developed the IDAL 3G – a device that aims to make it quicker and easier to administer vaccines at accurate doses, so more animals can be vaccinated effectively.[273] It is also engaging farmers directly to generate demand and increase vaccine uptake. For example, its 'Time to Vaccinate' initiative, targets European farmers directly and emphasises the importance of vaccines in preventative care.[274]

Nutrition and feed improvements: Malnutrition leads to weakened immune systems among flocks and herds, which in turn increases the risk of disease within animal populations. There are several different products and approaches that can be used to improve animal health via nutritional means. These include fortified feed, enzymes, probiotics, and prebiotics, which reduce the risk of disease by improving gut microbiomes. This aids digestion and improves feed efficiency.[275] Efficacy varies by species, age of herd or flock, and factors such as weather or feed type and more research is needed to fully understand these interrelations.

Probiotics have been shown to be particularly effective compared to other nutritional products in maintaining animal health. One study demonstrated probiotics can be effective in controlling the clinical symptoms associated with coccidiosis – indeed probiotics proved to be just as effective as ionophores in this case.[276] 20% of dairy farms in the US now use probiotics to prevent disease and improve the productivity of their dairy calves. For feedlots with over 1,000 cattle this increases to 25%.[277]

Prebiotics efficacy, by comparison, has been less consistent, with effectiveness dependent on external factors such as animal species, age, health, housing and other management aspects. Prebiotics are used commercially in chicken and turkey and appear to be less effective in pigs and cattle, but studies have been limited.[278]

Phibro produces Magni-Phi®, a natural feed additive that works by improving intestinal health and optimising nutrient absorption. The product is made from quillaja extract and yucca powder, which have natural medicinal properties. It helps prevent pathogens in poultry and is specifically marketed for poultry produced without antibiotics.[279]

Elanco has also ventured into the nutritional space and in 2016 established its nutritional health division, which develops products including enzymes, probiotics, and prebiotics. This includes Correlink™, an in-feed probiotic for use in poultry.[280]

Nutritional products are mostly limited to use in poultry. Larger animals such as cows and pigs have more complex gut microbiomes, which makes the development of products more difficult and has so far limited product availability.[281] This a key space for innovation given the demand for these products will only increase as demand for antibiotics decrease.

Biosecurity and animal welfare improvements: Evidence has shown that there is a link between improved animal welfare, biosecurity, and reductions in antimicrobial usage.[282] The OIE defines animal welfare as "*the physical and mental state of an animal in relation to the conditions in which it lives and dies.*"[283] Good animal welfare has been shown to improve productivity and reduce animals' stress levels which helps to maintain well-functioning immune systems, so animals are less likely to become ill.[284] Biosecurity can be understood as a set of management practices which are used to prevent pathogens entering a farm, spreading within farms and between farms.[285] This can include ensuring no contact between herds, ensuring clean water supplies, and disinfecting farm machinery and equipment.[286] Improved biosecurity measures have shown reductions in antimicrobial use in both broiler (30% reduction)[287] and pig (47% reduction)[288] farms across Europe.

Further, effective use of alternatives is enabled through a comprehensive approach to farm management which tackles the root causes of disease incidence on farm – poor animal immune systems, high prevalence and easy spread of diseases.[289]

In recognition of the benefit that animal welfare and biosecurity improvements can have in driving down antimicrobial usage, HealthforAnimals (HfA) has committed to training farmers and other key stakeholders on good biosecurity and to increase funding for research in this area. They are also working to improve consumer understanding around antibiotic use and animal welfare emphasising that antibiotics are critical to animal welfare, and that it should not be a case of 'no antibiotics ever', but 'only antibiotics when necessary'.[290]

In low- and middle- income countries, higher AMR rates have been linked to poorer biosecurity, as well as other factors such as less nutritious feed, and less rigorous regulation of veterinary drugs.[291] In Nigeria, poor biosecurity is widespread, increasing mortality rates and impacting farmers livelihoods. This has led to veterinarians recommending prophylactic use of antibiotics as a last resort, despite the known risks of AMR.[292] Use of antimicrobials and poor biosecurity are closely linked, and a first step to reducing the reliance on antimicrobials would be to improve farm biosecurity. However, for many farmers, particularly smallholders, improving biosecurity is an inaccessible option as it requires structural changes to farms, changing stocking density and other measures that require large injections of capital.[293] These investments can be cost-effective over time as animals require fewer drugs and productivity can increase as animals get ill less frequently, but many farmers lack access to savings or loans that could facilitate these investments.

Novel treatment options: Novel options such as bacteriophages (or 'phages') offer a more direct alternative to antibiotics for the treatment of disease. Phages are viruses that have the ability to kill bacteria. They are prevalent in all terrestrial and aquatic environments, helping to control bacterial populations. In fact, they are the most abundant biological forms in the biosphere.[294]

Phages are a promising but underdeveloped and under-researched treatment option. They have many advantages, including being non-toxic, specific to one bacterial species, effective against multi-drug resistance, and self-replicating.[295] They are also environmentally friendly. A recent study on the use of phages in shrimp aquaculture found that not only did they address *Vibrio* infections, but also led to better growth, survival rates and production rates. The cost of using phages, however, is high compared to probiotics, in-feed enzymes and antibiotics, and overall cost savings are minimal.[296] Further, there remains concern over the stability of phages in different environments and the specific conditions in which they can be effective.[297]

Other novel treatment options include Virbac's novel solution to treat disease using a new technology based on plant extracts (boldo and meadowsweet). It promotes the natural secretion of antimicrobial peptides and keratinocytes to battle bacterial infections. The product is currently under-development and targets dogs only. However, it looks promising, with evidence it could tackle resistant bacteria.[298]

Zoetis' agreement with Colorado State University (CSU) will enable the company to explore the livestock immune system and target new immunotherapies, which could reduce the reliance on antibiotics in food-producing animals. The initial focus is on the biotherapeutics for cattle, but this could be expanded to pigs and poultry.[299]

Alternatives to antibiotics are a necessary and growing area of focus, with many animal health companies committing to significant investment in the development of viable options. Those that are not will likely face increased financial pressures in the medium to long-term as the animal protein sector looks beyond antibiotics and towards preventive care and alternative treatment options as its first line of defence for protecting welfare and animal health.

Mileutis Case Study: Bio-pharmaceuticals and Immunomodulators innovation

Mileutis is a Bio-pharmaceutical company based in Israel south of Tel Aviv near the Weizmann Institute of Science focused on the discovery, development, and commercialization of novel biologically sourced, antibiotic free, safe, and residue-free therapies. Mileutis' mission is the development of Bio-pharmaceutical products to create a healthier world where antibiotics, and hormones are largely replaced with residue free and safe Human and Animal Healthcare products to significantly reduce the global threat of Anti-Microbial Resistance (AMR) from the overuse of antibiotics.

Mileutis technology portfolio includes 5 granted patents in the US, and 62 granted patents worldwide.

Mileutis, with its safe, and residue free small milk derived protein based (peptides) products designed to improve both animal and human health while reducing antibiotic use, is proud to be a part of the solution to addressing AMR. AMR is largely caused by the overuse of antimicrobial medicines with 70% coming from the animal healthcare sector.

Mileutis' initial focus is on the Dairy Industry segment of the Animal Healthcare market, in which its leading products can reduce up to 90% of currently administered antibiotic treatments to dairy cows. Dairy farmers lack a safe and effective way to manage Mastitis which is the #1 problem facing the Dairy industry affecting over 30% of cows worldwide. It is an infectious disease resulting in inflammation in the mammary gland of the cow. This is the primary cause of milk production loss and overuse of antibiotics to try and treat or prevent the disease, often unsuccessfully, resulting in economic losses exceeding $30 billion globally per year.

Today, there are no FDA-approved, non-antibiotic, non-genetically modified (GMO), intramammary treatments for the management of mastitis. Mileutis is solving this problem with its Next Generation biologically sourced, safe, and residual free Bio-pharmaceuticals, Imilac™, administered at the beginning of the Dry-Off period and Milac™, administered during lactation. These natural and innovative novel treatments act through an immune-modulatory effect enabling the management of infectious and chronic diseases without the use of antibiotics revolutionizing the way veterinarians treat and manage mastitis. The European Medicines Agency (EMA) published a positive opinion on the safety of Mileutis products by confirming that no Maximum Residue Level (MRL) evaluation is required for Mileutis' technology.

Mileutis Founders, Jose and David Iscovich

> "Mileutis is taking the lead in combatting AMR."

In addition to addressing the global challenge of AMR, Mileutis' products have many benefits for the farmers, consumers, the environment, and the dairy cows themselves. Consumers will receive a product free of antimicrobials and hormones; the farmer benefits from advanced technology that increases milk production per cow for added revenues, while reducing wasted milk, nutrient input and waste output per unit for cost savings; and the cow's wellbeing is improved by a faster dry off (involution) period and a more efficacious treatment of mastitis in severe cases. The product is easy to use for the farmers and has a clear safety profile. With increased output per cow, fewer cows will be needed to produce the same amount of milk. Benefits to the environment include reduced GHG (Greenhouse Gas) emissions and increased availability of arable land for food and other crops as less land will be needed for grazing.

The company is preparing for the final regulatory track and launch of its leading line of products in selected markets.

Mileutis

DSM Case Study: China

The animal agriculture industry in many parts of the world is continuing to evolve their production practices in light of the growing body of data linking Antimicrobial Resistance (AMR) to antibiotic usage. In more recent years, legislation banning the use of antimicrobials as growth promoters in large markets such as China and monitoring of total antibiotic usage on farm and the upcoming ban of therapeutic Zinc Oxide use in feed in Europe are accelerating this change. As a consequence, the demand for alternative solutions to support the health and welfare of animals without compromising productivity has also risen.

At DSM, we recognise the changing needs of the animal industry and work closely with our customers on their journey to continue to safeguard the health, productivity and welfare of their animals in this new Antibiotic Growth Promotors (AGP)-free era. The launch of our strategic initiative, We Make It Possible in 2020, reflects our commitment to helping make animal protein more sustainable and to be a change agent in addressing the biggest sustainability concerns in animal agriculture of which tackling AMR is a key platform.

Given that AMR reduction has long been a strategic direction of DSM, this has facilitated the creation of an extensive portfolio of eubiotic solutions including organic acids, phytogenics, probiotics and novel gut health enzymes which allow us to better address the specific needs of our customers and help them in the transition to this new reality.

One such solution that has been pivotal in supporting our swine customers maintain the health and productivity of their animals is our VevoVitall®. This well proven solution has become the cornerstone of nutritional health strategies for post-weaned pigs in many parts of Europe in the last decade. In the last year, since the ban of AGPs in China, the Chinese swine market has also recognized the unique attributes of this highly effective solution which has been reflected in very fast adoption of this technology in this market. VevoVitall® improves the growth performance of post-weaned pigs on average by 10% by reducing intestinal pH and modulating the intestinal microbiome and delivers a minimum of a 3:1 return on investment making it an attractive solution to the removal of AGPs. VevoVitall® also reduces ammonia emissions by up to 17% which further improves the growing conditions for the pigs as well as reducing these nitrogenous emissions to the environment.

VevoVitall® is also the backbone of another more specific new solution we have recently brought to the Chinese market called VevoWin®. VevoWin® has been developed to help mitigate the risk of viral transmission through feed which is a genuine biosecurity risk in the spread of African Swine Fever (ASF) in China. The VevoWin® technology has been shown to dramatically reduce the viral load of ASF and other swine relevant viruses in contaminated feed and is an effective way to protect pigs from ASF infection from feed. VevoVitall® and VevoWin® are a few of our offerings that lessen the need for AGPs and support sustainable pig production.

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

Table 5. Summary highlighting some of the available alternatives to antibiotics and their potential uses

Alternative type	Mechanism of Action[300]	Growth Promotion	Disease Prevention	Disease Treatment	Targets specific infection	Timing of administration[301]	Species effectiveness	Price
Vaccines	Primes host immune response	?	✓	✗	✓	Applied before infection	All species	$$$$$
Diagnostic Tools	Diagnose the cause of animal's illness, can help to prevent spread of disease	✗	✓	✗	✓	Continuous (monitoring), after infection (diagnosis)	All species	$$$$$
In-feed Enzymes	Help animals digest plant materials	✓	✓	✗	✗	Continuous use	All except ruminants	$$$$$
Prebiotics	Improves gut health	✓	✓	✗	✗	Continuous use	All except mature ruminants	$$$$$
Probiotics	Improves gut health	✓	✓	✗	✗	Continuous use	All species	$$$$$
Organic Acids	Targets bacteria	✓	✓	✗	✗	Continuous use	All species	$$$$$
Biosecurity	Prevents disease occurrence and spread	✓	✓	✗	✗	Continuous use	All species	$$$$$
Good Animal Husbandry	Prevents disease occurrence and spread	✓	✓	✗	✗	Continuous use	All species	$$$$$

Source: FAIRR 2021 and Pew Charitable Trusts 2017

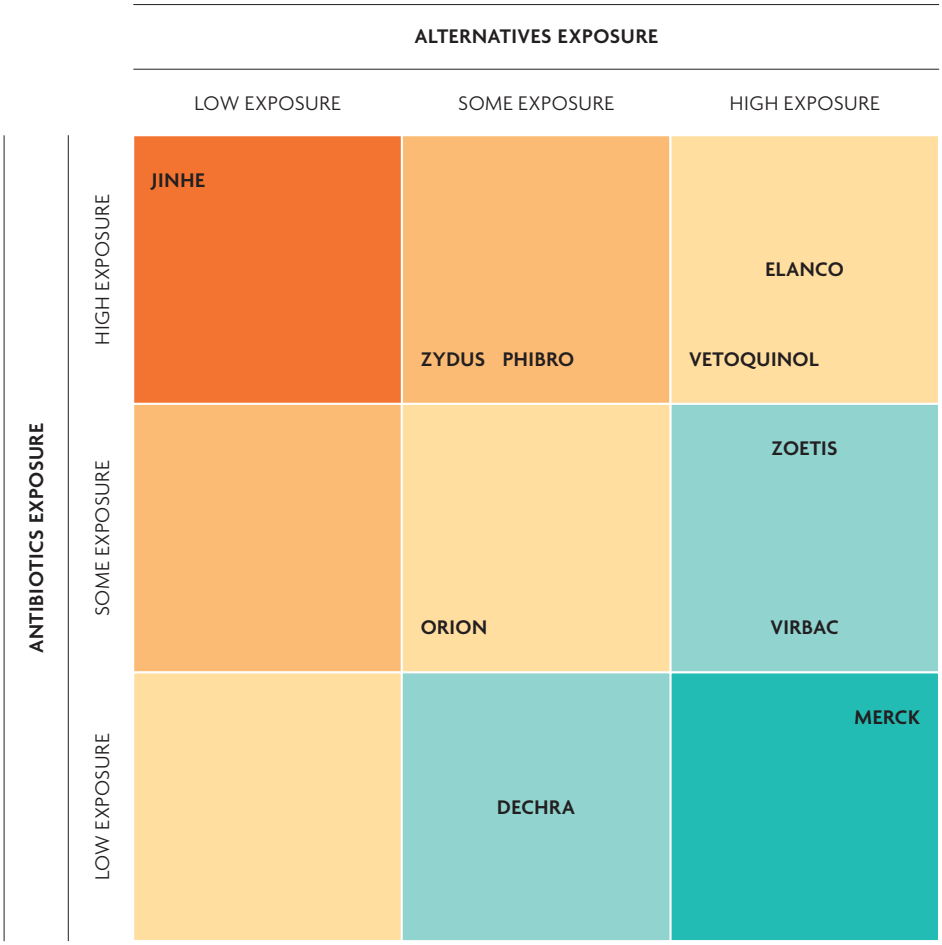
Engagement questions for investors

- What actions are the company taking to increase the number of alternatives available for farmers?
- What percentage of R&D spend is dedicated to developing alternatives to antibiotics?
- Does the company have a coherent strategy to increase development and uptake of alternatives, including farmer education and training?
- Is the company developing any novel alternatives to antibiotics e.g., bacteriophages?
- How is the company working to better understand the cost implications of shifting to alternatives to antibiotics? (i.e., conducting cost-effectiveness studies of new products)

Assessing portfolio exposure to antibiotics

As the risk profile of the animal agriculture sector increases, there is a declining focus on food producing animals, including antibiotics, at least for some of the larger players. These companies are looking towards innovation and diversification as key elements for building resilient portfolios. This includes investing in alternatives to antibiotics to support high-quality animal proteins with better welfare as well as shifting to the lower risk and higher growth pet care and companion animals market.

Figure 11. AMR risk exposure for ten publicly-listed animal health companies



Source: FAIRR 2021

Current company exposure to antibiotics and alternatives

Innovation and diversification are key to building resilient portfolios, especially for animal health companies with significant exposure to antibiotics. FAIRR assessed the portfolio composition of ten publicly listed animal health companies to establish their AMR risk exposure. Revenue data from antibiotics where publicly available was used to calculate exposure. However, only four of the ten companies assessed disclose this information in their annual reporting: Elanco, Phibro, Virbac and Zoetis. Dechra's exposure has been approximated given the company discloses revenue from food producing animals (15%), and states that "*over half*" its food producing animal segment revenue comes from antibiotics.[302]

For the other five companies, where there was no available information to indicate their exposure, FAIRR has taken the proportion of products across their portfolios that are deemed as antibiotics for food producing animals (FPAs) using individual company websites, across geographies.

There is currently no standardised approach to disclosing revenue coming from antibiotics, with each company using different classifications. For example, Zoetis discloses revenue for antibacterials[303] whereas Virbac excludes antibiotics from aquaculture from their totals as this is reported within the overall aquaculture segment.[304] Greater, and standardised, disclosure is needed to better assess companies' exposure to antibiotics.

FAIRR then assessed individual company exposure to alternatives including vaccines and diagnostics based on four factors that indicate a clear recognition of the growing risks associated with AMR and increased capital allocation to support innovation for alternatives to antibiotics. The factors considered are:

- Dedicated capital expenditure supporting alternatives portfolio expansion.
- Evidence of new product launches across categories (e.g. vaccines, diagnostics, prebiotics, feed) over the past five years.
- Acquisitions of companies specialising in alternatives.
- Acknowledgement of increasing external market pressures including social and environmental challenges associated with AMR referenced as key risks in public reporting. Further, publicly recognises the need for growth in alternatives.

Merck & Co. operates in both the human and animal pharmaceutical sectors, but is mainly a human health company, with its animal health business accounting for just under 10% of revenues in 2020.[305] The company is the strongest placed when it comes to portfolio composition, followed by Dechra, Virbac and Zoetis. Merck & Co.'s animal health portfolio has the highest exposure to alternatives. The company specialises in vaccines and is in the process of opening five new vaccine production sites in four countries.[306] It is also investing in monitoring technology that can help track animals' health and welfare in real time. Since 2019, Merck & Co. has acquired three companies that specialise in monitoring technology across livestock, fish, and poultry.[307,308,309] The company also has a strong position on AMR and has released a Global Antimicrobial Resistance Action Plan with initiatives, actions and commitments outlined for both the human and animal pharmaceutical businesses.[310] Its high exposure to alternatives is couples with a relatively low proportion of antibiotics within its portfolio.

Dechra has very low exposure to antibiotics, which accounted for around 7.5% of its revenue in 2020.[311] The company performs less well in terms of its exposure to alternatives given its efforts are largely focused on vaccines only. Further, while acknowledging incoming regulation and consumer pressure on antibiotics as concerns, it does not link this to the need to address AMR and in fact states that its antibiotics portfolio is already well-matched to "*current best practice prescribing habits*" (i.e., not at risk of increased regulation given the majority of its products are prescription only).[312] However, the company does not define what best practice means in this context or whether its antibiotics portfolio for food producing animals is as well-matched as its companion animal portfolio.

Virbac has a slightly higher exposure to antibiotics than Dechra, at 11% of its revenue.[313] It also spends a significant proportion of R&D funds on preventative medicines (33% in 2019 or $5 million) and is actively and is actively investing in vaccines and biological products such as probiotics and enzymes.[314] The company's vaccines segment for food producing animals grew 13% between 2018 and 2019.[315] In 2021, Virbac are due to open a new facility in Taiwan to address key issues in food production including mass vaccination, food safety and the emergence of disease.[316] However, it should be noted that the company still states that it expects revenue from antibiotics to grow, and the share of revenue from antibiotics has remained steady over the past 5 years (see Figure 12).[317]

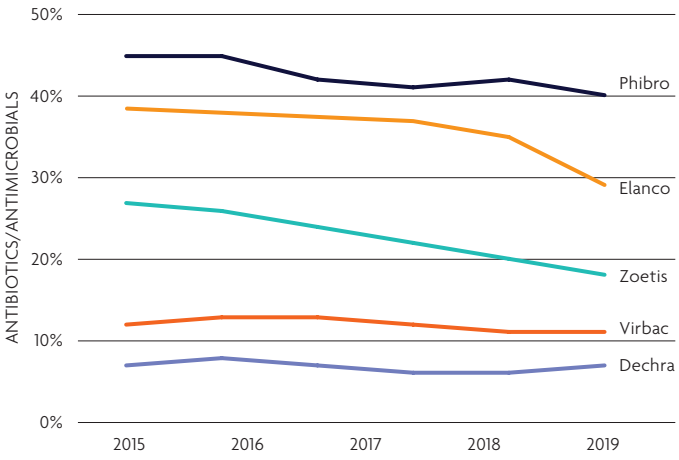
Around 18% of **Zoetis**' total revenue is exposed to antibacterials (which is mostly made up of antibiotics), although this has been decreasing year on year and is down from 20% in 2019 (see Figure 12).[318] The company has been steadily developing its capacity in alternatives, emphasising this as a growth area for the business. In the past five years the company has acquired at least ten alternatives-focused companies, the majority of which focus on diagnostics.[319] Whilst Zoetis does not disclose what percentage of R&D is being spent on alternatives, the company has launched a number of products in the past five years. These include diagnostic ear tags for cows and several vaccines across species including pigs and poultry.[320]

The worst performer of the companies assessed is **Jinhe**. The company mainly sells antibiotics – chlortetracycline, an MIA, is its speciality – and has no disclosure around its R&D pipeline or position on antibiotics. As a Chinese company mainly focused on the domestic market, disclosure is limited across all aspects of the business.

Elanco and **Vetoquinol** hedge their high exposure to antibiotics with high exposure to alternatives. This means they are actively working to diversify their portfolio and reduce the share of antibiotics. Vetoquinol's 2017-2022 strategic plan commits it to investing up to 20% of its R&D pot (which equates to around $6.7 million) into tools that could reduce the need for antibiotics – including the areas of prevention, genetics, vaccines, hygiene, diagnostics and immunostimulants and they have acquired several companies that work in the alternatives space producing diagnostics, vaccines and other products.[321] These include: Farmvet Systems (in 2018), a stake in Plant Advanced Technologies (in 2019), and Brazilian firm Clarion Biociências (in 2019).[322] Further, in 2021, Elanco launched 2 products specifically targeting the growing market for raised without antibiotics (RWA) products in the US, Clinacox, and Zoashield.[323]

Analysing antibiotics revenue for companies over time gives greater insight into how portfolios are changing. For Elanco, Zoetis and Phibro antibiotics as a proportion of revenue have been declining since 2015 (see Figure 12). This is due to a number of factors including intentional portfolio diversification and regulation.

Figure 12. Share of revenue from antibiotics/antimicrobials for key animal health companies from 2015-2020.



Source: FAIRR 2021

Only two companies, Virbac and Dechra for who antibiotics/antimicrobials represent the smallest share of revenue, have not seen a decline in sales of antibiotics/antimicrobials. In fact, Dechra has seen a large increase in sales of antibiotics – which grew 34% from 2019 to 2020. Over half the company's revenue from food producing animals comes from antibiotics (more than 7.5%), and most of these are sold in the EU.[324] Despite increasing regulation, Dechra's antibiotics portfolio has not been negatively impacted as the company states that it follows "*best practices prescribing habits.*"[325] This is in stark contrast to Virbac, which saw a decline in sales following the introduction of e-prescriptions for antibiotics in Italy and Spain, however, this was offset by sales growth in the US and Brazil.[326]

Shifting strategies

Animal health companies recognise the increasing environmental and social risks impacting the animal agriculture sector and are looking elsewhere for growth. Elanco specifically notes the detrimental impact climate change could have on farm animal production and consequentially its own revenue.[327] Phibro,[328] Virbac,[329] Dechra,[330] Vetoquinol,[331] Merck & Co.[332] also discuss the increasing risk of climate change on the sector in their public reporting.

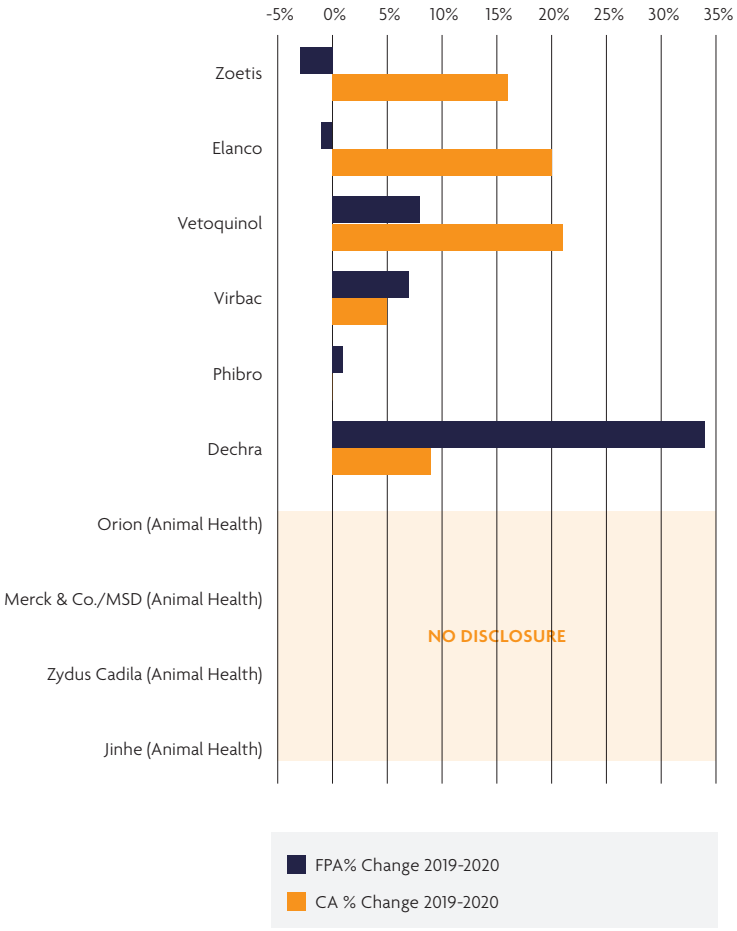
The increase in disease incidence, particularly in relation to African Swine Fever (ASF) in recent years, which decimated pork production in Asia, was felt across the entire supply including the animal health industry. ASF reduced growth in the animal health sector by 1.6% in 2019,[333] and it is still present in China today. Elanco, Zoetis and Phibro have all seen revenues decline, and will likely continue to given there is no known treatment, other than improving on-farm biosecurity measures. Phibro saw revenues drop by $31 million to June 30 2020 as a result of ASF.[334] Elanco is still expecting disruption to its China business as a result of new spikes in ASF, which will effect in sow herd reductions.[335]

COVID-19 has also had a material impact. The closure of the hospitality industry and the shutdown of meat processing facilities due to virus outbreaks, particularly in the US, reduced output capacity. US pork producers saw their output capacity reduce by 50% in early may as around 20% of the industry's workers contracted Covid-19.[336] In Canada, poultry farmers had a reduced output of 12.6%.[337] Elanco estimates that revenue decreased at least $160 million as a result of reduced demand for its products as animal production decreased in the first half of 2020.[338] Dechra,[339] Phibro[340] and Zoetis[341] also discuss the adverse economic impacts in their annual reporting.

Companies are also concerned about reduced demand for animal proteins given increasing public concern on the link between infectious diseases and food animal production. Phibro notes that "*the ongoing economic downturn and quarantines due to Covid-19 could lead to decreased demand for protein, which may lead to end users of our products reducing their herd or flock sizes... demand for protein could be reduced because consumers may associate human health fears related to COVID-19 with animal diseases, food, food production or food animals, whether or not it is scientifically valid.*"[342]

As the risk profile of the animal agriculture sector increases, there is a declining focus on the sector which is being accompanied by a shift towards the pet and companion animal sector, at least for some of the larger players. This is a trend that is reflected in the broader food sector, as more companies, most recently General Mills, expand their petcare businesses.[343]

Figure 13. Revenue change 2019-2020 for FPA and CA segments for the ten animal health companies assessed in the report.



Source: FAIRR 2021

In 2020, the total pet industry in the US market alone surpassed $100 billion, and veterinary care and products represented a third of the market.[344] Fuelled by the pandemic, more people are buying pets and those that are, are spending more on them too with more than 3.2 million pets being bought in the UK alone since March 2020.[345] Four of the ten animal health companies assessed in this report explicitly state that they are looking towards the petcare and companion animal sector for future growth. For Zoetis, the largest animal health company, pet care and companion animals became the dominant segment in 2019 for the first time, surpassing food producing animals.[346]

Dechra and Virbac were the only two companies that saw their food producing animal segment grow faster than their petcare and companion animal segment. Dechra is considered underweight relative to peers in the food producing animal segment, and is actively growing the business through new product development and international expansion to support high-quality animal protein and dairy products. The company notes that the majority of its products are prescription only medicines, including antibiotics, enabling the company to navigate changing regulatory requirements. Virbac also saw strong growth in its food producing animals segment, which it attributes to geographic expansion in the past year.[347]

For integrated animal and human health companies (Orion, Merck & Co., Jinhe and Zydus Cadila) there is a lack of disclosure around their animal health businesses, and they do not publicly report revenue breakdowns by segment. All four companies sell companion animal products, and Merck & Co. in particular is a large brand in the companion animal sector. However, without understanding revenue breakdown it is not possible to understand how exposed companies are to the risks facing the food producing animal segment.

Engagement questions for investors

- Does the company publicly acknowledge the current external market pressures facing antibiotics and the potential impact these could have on company revenue?
- Does the company disclose sales data for antimicrobials, including a breakdown by categorisation i.e. HP-CIAs, MIAs, veterinary-only antibiotics, ionophores, and other antimicrobials?
- If so, what percentage of total sales volumes and revenues come from antimicrobials?
- Can the company disclose sales volumes and revenues in terms of end use?
- What is the company's strategy to diversify its portfolio away from antimicrobials? Is the company thinking about potential targets for this?

Antimicrobial stewardship

Just as risk exposure to antibiotics varies across animal health companies, so does the level of stewardship when it comes to addressing the issue of antimicrobial resistance. Companies have yet to adopt a comprehensive and strategic approach to stewardship that is consistent across markets and supports better supply chain transparency, manufacturing standards, responsible use and innovation. Although many companies are investing in activities to address misuse of antibiotics, these efforts are increasingly being undermined by lobbying activities and marketing approaches focused on maintaining or promoting regular and increased use of antibiotics.

Tackling the issue of antimicrobial resistance requires a comprehensive antimicrobial stewardship approach

Most leading animal health companies have acknowledged their role in addressing AMR and eight out of the ten companies – all except Zydus Cadila and Jinhe Biotechnology – are engaging in stewardship efforts in a variety of ways. Activities typically focus on promoting the use of alternatives such as vaccines to prevent disease incidence and educating stakeholders on the impacts of AMR, as well as what the responsible use of antibiotics looks like.

FAIRR, alongside WHO and other leading bodies on AMR, advocates for a One Health approach to antimicrobial stewardship that encourages multisectoral collaboration and a holistic approach that addresses animals, humans and the environment. For animal health companies, this means greater oversight across its supply chains to assess their impact and ensure that companies' own stewardship efforts are not undermined by actions elsewhere in their business e.g., suppliers. From manufacturing sites and practices to how antibiotics are packaged, labelled, sold and ultimately used – animal health companies need to consider all the ways in which they are, or are not, contributing to AMR. This also necessitates the development and promotion of alternatives to antibiotics and education around their use for farmers. Further, cross-sector collaboration and engagement in public policy efforts through industry organisations, charitable endeavours and government programmes is a key pillar of the One Health approach to ensure positive outcomes for people, animals and the environment.

Figure 14. The One Health Triad

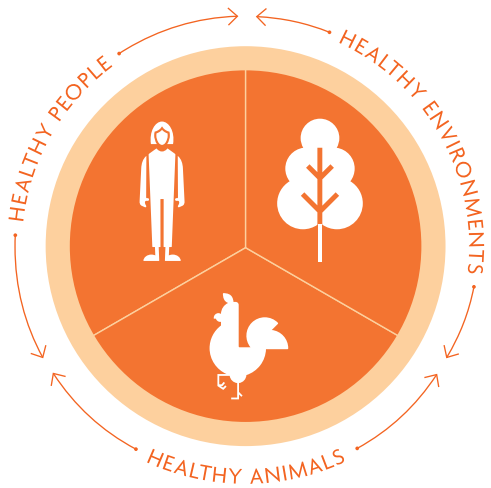


Table 6. The table below outlines the key elements that should be present in a company that has a comprehensive approach to antimicrobial stewardship.

Manufacturing and production	• Discloses who its main suppliers are, including tracing back to API suppliers • Manufacturing policy in place for own operations and third-party suppliers which addresses antimicrobial residues from manufacturing effluent, and uses industry frameworks such as the AMRIA and PSCI to audit suppliers • Specific criteria in its manufacturing policy relating to the quality of antimicrobial products given the increased potential for AMR should products not be of the correct strength
Marketing, sale and use	• Discloses who its distributors are and engages them on the importance of antimicrobial stewardship • Sales incentives are not tied to volumes of antibiotics sold • Consistent marketing and sales approach across all its geographies focused on preventing and reduce the usage of MIAs for growth promotion and prophylaxis • Discloses the proportion of revenue derived from antibiotics and antimicrobials and gives a breakdown based on end use
Alternatives to antibiotics	• Actively developing alternative treatment options and addressing barriers for uptake including cost • Engaging farmers and veterinarians to raise awareness of alternative treatment options across geographies including adoption of biosecurity measures and good animal husbandry practices
Public policy	• Publicly recognises its role in addressing AMR and participates in industry initiatives that are working to address AMR e.g. PSCI, HfA Roadmap, AMRIA • Working to support and drive better tracking and monitoring of antimicrobial usage • Discloses lobbying activities including its position on certain issues/bills, which are in line with the company's strategy to address AMR

Antimicrobial stewardship is not yet fully integrated across businesses

Across leading animal health companies FAIRR consistently found uneven processes of managing the risk of AMR. In general companies lack a strategic approach to antimicrobial stewardship that covers all elements of their businesses. There is no one company spearheading the drive for greater antimicrobial stewardship, unlike the human health side, which according to the Access to Medicine Foundation AMR Benchmark, GSK is playing a leading role. It has the strongest R&D pipeline amongst human health pharmaceutical companies, and has removed all staff incentives linked to increased sales of antibiotics.[348]

Out of ten animal health companies assessed, Merck & Co. discloses more information relative to its peers on its approach to AMR. It has a company-wide policy that details its overarching position on the issue and discusses key actions to date and future plans.[349] This is most likely due to its significant exposure to human health, which has been subject to much greater public scrutiny than animal health operations. Nonetheless, its disclosure around its animal health portfolio remains limited given its only accounts for around 9% of total revenues.[350] For example, it does not provide a breakdown of sales data including antimicrobials sold for food producing animals.

Antimicrobial stewardship activities do not extend to manufacturing

Antimicrobial stewardship begins at the factory. Most leading animal health companies rely on third-party suppliers for their generic products - including antibiotics. Although companies do not disclose who third-party suppliers are and where they are located, most generic suppliers are located in India and China. Some of which have been linked to animal health companies following manufacturing infractions. However, despite this, there remains limited discussion in public disclosures on the need to improve supply chain traceability, transparency and manufacturing standards.

Uneven sales and marketing practices are not addressed as part of stewardship activities

Although animal health companies engage in a range of stewardship activities including educating farmers and veterinarians on the need to reduce antibiotic use, it is unclear whether these activities are leading to a reduction in use. Further, these efforts are often undermined by marketing, labelling and package sizing practices that vary across markets, depending on local regulations and promote growth promotion and/ or routine prophylactic use.

Alternatives are under-researched, and this limits availability and adoption by farmers

Alternatives are critical for reducing antibiotic use. Although there is currently no 'silver bullet', there are a growing number of alternative options that work to reduce the need for antibiotics by preventing disease incidence. At the moment, the key barriers to the uptake of alternatives are availability, accessibility and cost. In particular, cost is an issue. Antibiotics are cheap and farmers know they are effective, whereas alternatives can be more expensive and require higher up-front costs. Further, little research has been done to understand the actual cost-differential between the use of alternatives and a reliance on antibiotics. This is of particular concern in emerging markets where cost is a more significant factor and the use of antibiotics is expected to grow significantly in the next decade to support the intensification of industrial animal farming. Therefore, being able to understand the cost per animal of using alternatives could help to drive greater uptake from farmers in the future.

Engagement in public policy initiatives is limited but has the potential to make a big difference

Public policy is a key area of focus for driving systemic change and improving stewardship across the animal health sector. The sector's efforts are predominantly driven by industry-led initiatives and organisations, individual company stewardship initiatives which usually centre around education, accessibility of veterinarians, veterinary medicines, and infrastructure.

Membership of industry organisations

Membership in one or more industry organisations is a key way that animal health companies work towards addressing AMR. This enables companies to set goals and targets, both at an individual and industry level, and share best practices. HfA, a key industry organisation that includes 6 out of the ten companies assessed in this report, launched the AMR Roadmap to reduce antibiotic use by establishing joint and individual commitments from its members. This is a first of its kind initiative within the sector, and the first progress report is expected sometime in the second half of 2021.

Joint commitments include:[351]

- Invest at least $10 billion in research and development of alternatives.
- Produce tools that reduce the likelihood of human exposure to food borne pathogens such as *Salmonella*, *Campylobacter*, and *E. coli* that are resistant to antibiotics.
- Train over 100,000 veterinarians on the responsible use of medicines, investing over $5 million in veterinary scholarships and grants.
- Conduct at least 50 audits of active ingredient suppliers to ensure they meet standards.
- Provide research grants of at least $1 million.

Although these commitments are a positive step in the right direction, there is no reference to the need to improving transparency in the manufacturing supply chain and address labelling, packaging, or marketing policies to ensure that for example, HP-CIAs, at the minimum, will not be suggested for use as growth promoters or prophylactics across all geographies. How antimicrobials are marketed dictates how they are used, and is therefore an important element of shifting practices to reduce AMR.

Integrated human and animal pharmaceuticals companies, such as Merck & Co. and Boehringer Ingelheim noted (see Table 7) participate in a greater number of industry organisations than their animal health-only counterparts. This is likely driven by the greater scrutiny placed to date on human pharma companies' and their actions to address AMR.

Table 7. Summary of company membership to industry organisations.

Animal Health Company	Pharmaceutical Supply Chain Initiative (PSCI)	HealthforAnimals (HfA)	National Office for Animal Health (NOAH)	Animal Health Europe (AHE)	Animal Health Institute (AHI)	AMR Industry Alliance (AMRIA)
Zoetis	✓	✓	✓	✓	✓	✗
Elanco	✓	✓	✓	✓	✓	✗
Merck & Co. (MSD)	✓	✓	✓	✓	✓	✓
Phibro	✗	✓	✓	✗	✗	✗
Virbac	✗	✓	✓	✗	✗	✗
Vetoquinol	✓	✓	✓	✗	✗	✗
Dechra	✗	✗	✗	✗	✗	✗
Zydus Cadila	✗	✗	✗	✗	✗	✗
Jinhe	✗	✗	✗	✗	✗	✗
Orion	✓	✗	✗	✓	✗	✗
Boehringer Ingelheim*	✓	✓	✓	✓	✓	✓
Ceva Sante Animale*	✗	✓	✓	✓	✓	✗

Note: Zoetis and Vetoquinol are only partial members of the Pharmaceutical Supply Chain Initiative (PSCI).
*Boehringer Ingelheim and Ceva Sante Animale are two of the top 10 biggest animal health companies in the world but are not publicly listed; they have been included for comparative purposes.

Source: FAIRR 2021

Companies are investing in stewardship initiatives, with emerging markets as a key focus area

Changing behaviours is sometimes not as simple as adapting labelling and packaging or introducing stricter manufacturing policies. The distribution and use of antibiotics are complex and vary by geography and farm type. Animal health companies need to go beyond altering their immediate operations to work with veterinarians and farmers to encourage and support a One Health approach.

Animal health companies can, and do, engage in stewardship initiatives that aim to address some of these difficulties. For example, Merck & Co. has partnered with the National Institute for Animal Agriculture (NIAA) to develop a series of videos to educate stakeholders on the challenges faced by producers when trying to reduce antibiotics as well as how to effectively prevent and treat disease while responsibly using antibiotics.[352]

Education of and engagement with farmers and veterinarians is particularly crucial in emerging markets where access to veterinarians and knowledge is limited, and regulation is either absent or not enforced.

Zoetis[353] and Elanco[354] both have stewardship initiatives based in sub-Saharan Africa, which involve training veterinarians, improving awareness of AMR and responsible use of antibiotics as well as educating farmers and stakeholders on good biosecurity and animal husbandry practices. These initiatives are not just focused on stewardship, but also on de-risking emerging markets for companies through early product registrations and brand awareness.

Both companies are also working to reduce the package sizes of products to make them more affordable for farmers who are often smallholders with only one or a few animals.[355, 356] This work shows an understanding from animal health companies that smaller package sizes can help to reduce antibiotic usage, but it is not applied across all operating markets.

Education is another key focus for companies with both Zoetis and Elanco, through its East Africa Growth Accelerator (EAGA) programme,[357] training veterinarians, farmers and other stakeholders on issues such as responsible antibiotic use, the benefits of alternatives, good animal husbandry and biosecurity measures.[358] They both use an approach to train veterinarians and farmers to be able to educate others which leads to a greater scope of impact. Elanco has also partnered with Farm Radio International, to reach 4 million smallholder farmers across Tanzania – working with the farmers to train and assist staff on biosecurity and good animal husbandry measures.[359]

Case study: Zoetis A.L.P.H.A. Initiative

Zoetis' A.L.P.H.A. (African Livestock Productivity and Health Advancement) Initiative – part-funded by the Bill and Melinda Gates Foundation aims to expand the availability of critical veterinary products and services and building critical infrastructure in Nigeria, Ethiopia, Uganda, and Tanzania.

A core part of the initiative involves submitting new products for regulatory approval in the countries Zoetis operates in to improve availability of veterinary medicines. This benefits both the company – since it is able to get products approved in new markets – and the countries, which gain access to more products that can help improve animal health. In total, 84 products (65 vaccine and pharmaceutical, 19 diagnostic) have gained product registrations.[360]

The company is also investing in diagnostics in the region and has opened six diagnostics labs, two each in Nigeria, Tanzania, and Uganda. This helps build veterinary capacity and can reduce antibiotic use by ensuring an animal's illness is bacterial before treatment. Farmers can submit samples digitally through the Labcards App and get results without having to travel.[361]

These examples from Zoetis and Elanco demonstrate the role that animal health companies can play in emerging markets where farmers face particular barriers to access knowledge, veterinarians and animal health products. These initiatives have helped to improve farmers livelihoods whilst embedding practices such as early vaccination to help reduce reliance on antibiotics. However, these initiatives are currently limited geographically, and it is unclear whether the companies have plans to embed this work further into their business and integrate stewardship efforts with standard business practices.

Lobbying activities are helping to undermine efforts to support antimicrobial stewardship

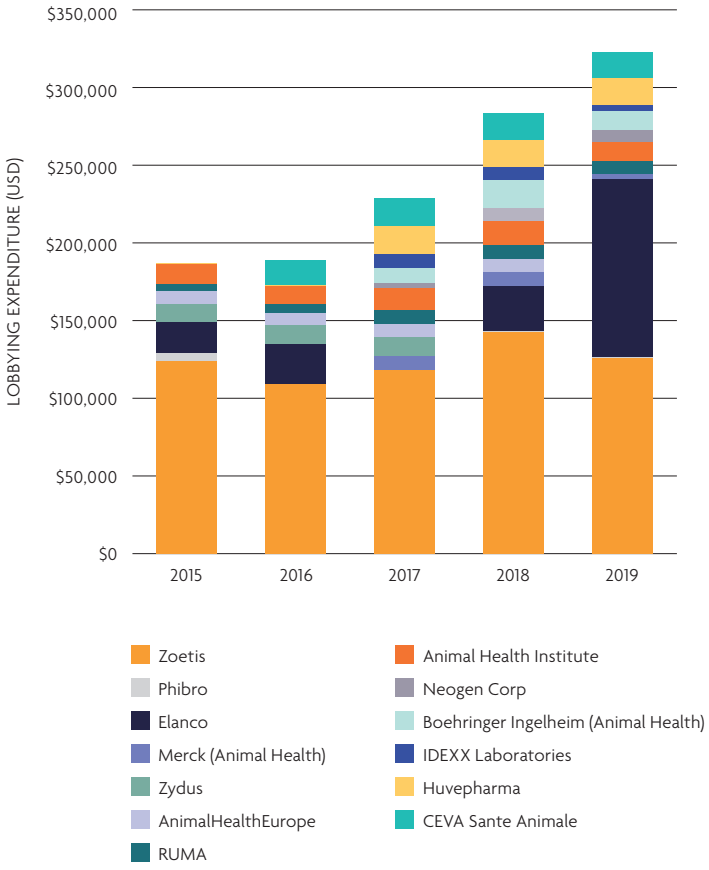
Lobbying efforts by animal health companies directly, and through industry bodies representing them, run contradictory to antimicrobial stewardship efforts. In 2019, animal health companies and organisations spent more than $3.2 million lobbying in the US and EU on issues including tax, trade, antimicrobials, and agriculture.[xi] Despite publicly championing antimicrobial stewardship efforts, leading animal health companies including Elanco, Zoetis and Phibro are devoting resources to lobby on bills aimed at safeguarding antimicrobials for human medicine in order to be able to continue using them in animals.[xii]

There is a lack of transparency on what exactly these lobbying activities support, but relevant bills and issues the companies examined have lobbied on include:

- In Europe: European Council directive 90/167/EEC, which proposes to further regulate medicated feed, a proposal for further regulation on veterinary medicinal products, a bill on action on AMR, as well as regulation on emerging infectious diseases and pharmaceuticals in the environment.
- In the US, antimicrobial use, responsible use of antibiotics in animals and delivering antimicrobial transparency in animals, as well as the H.R.5140 VFD Repeal Act of 2016, which would relax the US rules on veterinary authorisation of antibiotic use.
- Wider agricultural regulation that would have an impact on the uptake of products, including the US Farm Bill and EU Common Agricultural Policy reform, as well as other EU legislation on animal welfare, food safety, the Green New Deal, and Farm to Fork.

If animal health companies are similar to other industries, e.g. oil and gas industry and meat and dairy industry, they will tend to lobby in favour of less stringent regulation. Such efforts are clearly at odds with existing actions focused on for example, improving antimicrobial stewardship in Sub-Saharan Africa. Animal health companies need to also demonstrate how their lobbying aligns with their stewardship efforts on AMR.

Figure 14. Lobbying expenditure of animal health organisations and companies 2015-2019.



Source: FAIRR 2021

Note: information is not assumed to be extensive as companies are generally reluctant to release information around their lobbying activities and spending. Some companies are not directly mentioned but are members of organisations that lobby on their behalf. Information gathered using OpenSecrets.org and LobbyFacts.eu.

xi According to FAIRR data on 15 companies and 3 industry organisations using information from OpenSecrets.org and LobbyFacts.eu. Lobbying expenditure grew from $1,750,000 in 2015 to $3,200,000 in 2019. Note that this figure is not assumed to be extensive as companies are generally reluctant to release information around their lobbying activities and spending.

xii Information on lobbying activities, including specific bills lobbied, accessed online via opensecrets.org (US) and lobbyfacts.eu (EU). Companies are required by law in the US and EU to disclose what bills they have spent money lobbying, but do not have to disclose whether they lobbied for/against said bills.

Little discussion around the future of protein

The changing protein landscape is recognised by the animal health sector as a risk. Concerns around the link between climate change, antimicrobial resistance, zoonotic diseases and intensive animal production have led to increased scrutiny from civil society, consumers and governments alike.

As a result, in recent years animal health companies have begun to link antibiotics and other antimicrobials with the sustainability agenda. Specifically, animal health companies and their industry associations argue that antibiotic use can reduce emissions by improving production efficiency, preventing animals from becoming sick or dying from illness.[362] They also argue that antimicrobials can help to reduce enteric emissions (i.e. methane) from beef and dairy cattle – a current focus area for many protein producers. However, the total climate and broader sustainability impacts resulting from current levels of animal protein production cannot be mitigated through such efficiencies.[363,364]

In its 2020 annual report, Elanco promoted the use of ionophore Rumensin to reduce CO2e emissions from beef and dairy, and to help companies reach Net Zero by 2050. The company states that Rumensin can reduce CO2 emissions by 3.5% and enteric emissions by 5%.[365] Citing sustainability as a reason for the continued non-therapeutic use of ionophores is problematic given the link between the use of ionophores and AMR, alongside other risks.

For animal health companies, tackling AMR means looking holistically across their businesses. This includes ensuring strategies for future economic growth are not reliant upon an increase in the sales of antibiotics or actively working to prevent the introduction of regulation that could restrict sales of antibiotics. Rather than isolated initiatives, which are positive steps forward, animal health companies should look at how every part of their business is impacting AMR and contributing to their antibiotics exposure, taking steps to mitigate this.

Engagement questions for investors

- Does the company recognise their role in addressing AMR?
- Does the company adopt a One Health approach to antimicrobial stewardship which is consistent across the business – segments and geographies?
- Are companies working with/ engaging with broader AMR efforts such as the Davos Declaration and/ or the HfA Industry Roadmap?
- Is the company engaging in stewardship initiatives to educate stakeholders on the need to reduce antimicrobial use and facilitating efforts to do this? Does the company disclose the impact of these stewardship efforts?
- Does the company disclose information on their lobbying activities including what position they have taken on specific bills?

Glossary of Terms

Active pharmaceutical ingredient (API) is "*A substance used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings.*"[366]

Antibiotics refers to chemical substances (for example, penicillin) which are able to inhibit the growth or destroy bacteria and other microorganisms, and which are primarily used in the treatment of infectious diseases.

Antibiotic resistance is a subset of AMR (see antimicrobial resistance) and occurs when bacteria evolve over time to protect themselves from antibiotics and consequently no longer respond to antibiotics that were once able to treat a bacterial infection by that bacterium, making bacterial infections increasingly more difficult and impossible to treat. This antibiotic drug resistance occurs naturally, but the misuse of antibiotics in humans and animals is accelerating the development. It can render many important antibiotics redundant and leads to higher medical costs, increased hospital stays, severe illness and death.[367]

Antimicrobial resistant bacteria (ARBs) are bacteria that have evolved mechanisms to protect themselves from antimicrobials designed to kill or prevent further growth.

Antimicrobial resistance genes (ARGs) are genes found within plasmids which are small pieces of DNA that carry genetic 'instructions' from one bacteria to another. This is one way through which bacteria can confer resistance.

Animal Feeding Operations (AFOs) are agricultural enterprises where animals are kept and raised in confined situations. Animals, feed, manure and urine, dead animals and production operations are confined within a small land area. Rather than the animals grazing, feed is brought to the animals[368].

Antimicrobial resistance (AMR) occurs when microorganisms (bacteria, viruses, fungi and parasites) evolve mechanisms to protect themselves from antimicrobials drugs that were once able to treat an infection by that microorganism. These resistant microorganisms consequently no longer respond to medicines, making infections increasingly more difficult and impossible to treat. This antimicrobial resistance occurs naturally, but is mainly caused by the overuse of antimicrobials. This drug resistance can render many important medicines redundant and increases the risk of disease spread, severe illness and death.[369]

Antimicrobials refers to drugs that work against a variety of microorganisms (for instance bacteria, viruses, fungi and parasites). An antibiotic drug is an antimicrobial. However, not all antimicrobials are antibiotics.

Antimicrobial Stewardship is a coherent set of actions described by programmes or initiatives which promotes the responsible use of antimicrobials. It is applicable across geographies, from individuals to national and global levels. It is increasingly used under the One Health context, across human health, animal health, and the environment.[·]

Biosecurity is a "*strategic and integrated approach to analysing and managing relevant risks to human, animal and plant life and health and associated risks for the environment. It is based on recognition of the critical linkages between sectors and the potential for hazards to move within and between sectors, with system-wide consequences.*" Biosecurity is an essential element of sustainable agricultural development.[370]

Biotherapeutics are medicinal products where the active ingredient is extracted or produced from a biological source. These drugs are produced during biological processes within cells, rather than being produced synthetically in a laboratory.[371]

Cephalosporins are a class of broad-spectrum β-lactam antibiotics similar in structure and mechanism of action to penicillin. Cephalosporins were originally derived from the fungus *Acremonium* (formally *Cephalosporium*). These are classified by "generations" according to their antimicrobial activity, with successive generations being increasingly active against gram negative organisms and decreasingly so towards gram-positive organisms[372]. 3rd, 4th and 5th generation cephalosporins are classified by the World Health Organisation as Highest Priority Critically Important Antimicrobials (see Highest Priority Critically Important Antimicrobials), whilst the 1st and 2nd generation cephalosporins are classified as Highly Important Antimicrobials (see Highly Important Antimicrobials).[373]

Colistin (also known as polymyxin E) is a polymyxin antibiotic which is increasingly being used as a 'last-line' therapy to treat infections caused by multi-drug resistant Gram-negative bacteria when no other options are available.[374] Colistin is classified by the World Health Organisation under the Highest Priority Critically Important Antimicrobials (see Highest Priority Critically Important Antimicrobials).

Concentrated Animal Feeding Operations (CAFOs) are defined as a large concentrated AFO (see Animal Feeding Operations). These are defined by either one of two criteria. Firstly, when more than 1000 animal units (one animal unit is defined as an animal equivalent of 1000 pounds of live weight and equates to 1000 head of beef cattle, 700 dairy cows, 25000 swine weighing more than 55 pounds, 125,000 broilers chickens or 82,000 laying hens) are kept and raised in confined conditions for more than 45 days per year. Secondly, any size AFO that discharges manure or wastewater into a waterway is defined as a CAFO, regardless of size[375].

Critically important antimicrobials (CIAs) fall within the list of medically important antimicrobials identified and ranked by the World Health Organization according to their importance in human medicine. This term refers to antimicrobials deemed by the WHO as critically important to human medicine.[376]

Eubiotics are a class of feed additive that currently includes prebiotics, probiotics, essential oils and organic acids. These work in a number of ways to support a gut microbiota, digestive health and immune functioning[377].

Factory farming (also known as 'Intensive Farming') refers to the globally adopted farming system that involves crowding large groups of livestock into confined indoor spaces, such as stalls or cages. The USDA defines any farm with more than 1,000 cattle, 2,500 pigs or 125,000 chickens as a CAFO (see Concentrated Feeding Operation) or intensive farming system[378]. In the EU, officials have defined intensive farms as those carrying more than 40,000 chickens or 2,000 pigs[379].

Feed additives (for animal nutrition purposes) are used to improve the quality of feed or to improve an animal's performance and health, by, for example, providing the enhanced digestibility of the feed materials.[380]

Fluoroquinolones are broad-spectrum antibiotics. They are a sub-family of quinolines, classified by the WHO as 'Highest priority critically important antimicrobials' for human medicine in the WHO list of 'Critically important antimicrobials for human medicine'. "*Quinolones are one of the few available therapies for serious Salmonella and E.coli infections. Given the high incidence of human disease due to Salmonella and E. coli, the absolute number of serious cases is substantial.*"[381]

Highest Priority Critically Important Antibiotics (HP-CIAs) are classes of CIAs (see Critically Important Antibiotics) that are the sole, or one of limited available therapies, to treat serious bacterial infections in people.[382]

Industrial farming (see Factory Farming)

Ionophores are a class of antibiotics widely used in intensive poultry farming. At present, ionophores are too toxic to be used in human medicine and so are not currently considered to be medically important.

Medically important antimicrobials (MIAs) refers to the list of antimicrobials the WHO has termed important to human medicine. This term encompasses antibiotics defined as 'critically important', 'highly important' and 'important' to human medicine.[383]

Microbiome refers to the genetic material of all microbes (bacteria, fungi,

One Health is a "*collaborative, multisectoral, and transdisciplinary approach – working at the local, regional, national, and global levels – with the goal of achieving optimal health outcomes recognising the interconnection between people, animals, plants, and their shared environment.*"[384] It is particularly important in areas such as food safety, the control of zoonoses and combating antimicrobial resistance.[385]

Penicillins are classified by WHO as CIA (see Critically Important Antimicrobials)[386].

Phages (see bacteriophages)

Prophylactic or non-therapeutic use is a term used to describe the use of antibiotics to promote growth or to prevent (rather than treat) disease and infection in healthy animals. Such routine use of antibiotics allows livestock to be reared in densely packed and often-unhygienic conditions, contributing to dangerously high levels of AMR.

Raised without antibiotics (RWA) assures consumers that animal products were produced without exposure to antibiotics. The Raised Without Antibiotics (RWA) certification requires that no antibiotics were used in the raising animals and is the only independent certification that covers all animal foods including meat, poultry, seafood, fish, dairy and eggs.[387]

Therapeutic use refers to the use of antibiotics to treat disease that has been diagnosed by a licensed veterinarian. This term refers to the treatment of specific illness, as opposed to non-therapeutic or prophylactic use

FAIRR's questions to HealthforAnimals

FAIRR reached out to HealthforAnimals, as the industry organisation representing animal health companies, to inform the development of this report. Below you can find details of our questions and the organisation's response. The response is also published on its website at https://healthforanimals.org/191-letter-to-fairr.html.

Questions for HealthforAnimals

1. Clear labels on products is an important part of your 2025 commitments. Can you provide more detail on how your members are adapting brochures and packaging to facilitate and improve antibiotics stewardship across geographies?
    a. Have your members removed all reference to the use of antibiotics for growth promotion in product branding across all markets?
    b. How is prophylactic use being addressed in marketing?
    c. Are antibiotics sold with defined doses and durations of use?
2. Do your members have policies / requirements on how distributors and intermediaries' market/distribute their products?
    a. If so, how do companies ensure that these are being followed?
    b. Do companies track how products are sold / their end use?
3. Are sales staff incentives tied to sales volumes of antibiotics?
4. Antibiotics are a volume business – a decrease in usage will ultimately have an impact on revenue. How are you planning for future impact?
    a. How do your members view long-term demand for antibiotics in emerging markets like Brazil, India and China?
    b. Are you considering the impact of shifting demand for animal proteins?
    c. Given investment in R&D is a key part of your 2025 ambitions ($10bn in R&D by 2025) – can you provide an update on how much has been invested to date, key focus areas (vaccines, diagnostics, nutritional enhancements) etc.?
    d. Currently, the cost of alternatives remains high, and access remains an issue for emerging markets. How do you see the shift towards alternatives?
5. Education is a key part of your Roadmap – and it is encouraging to see your members actively supporting a range of initiatives including on-the-ground veterinarian training to improve the responsible use of antibiotics. How are your members reducing the potential conflicts of interest that could arise from training users on antibiotics, which are also the same products sold by the training company?
6. What level of oversight across third-party suppliers of active pharmaceutical ingredients and drug products do your members have?
    a. Do your members have environmental risk management strategies in relation to wastewater and antibiotics manufacturing e.g. discharge limits for antibiotics? If yes, how is compliance being monitored?
    b. We are curious to understand your commitment to "at least 50 audits of active ingredient suppliers to ensure they are meeting appropriate standards"; will you be disclosing information around how you define appropriate standards, and how you decided on the 50 audit target?
    c. How do members actively engage with their third-party suppliers to ensure appropriate manufacturing practices?
7. Can you comment on your position with regards to the use of animal-only antibiotics with respect to the risk of contribution to AMR in animals, the environment and human health?
8. In terms of disclosure around sales data – the Roadmap states that companies will *"share sales data in every market where it is required"* – what does this mean in practice e.g. how will the relevance of markets be determined? Why not share sales data across markets to assist fully with the global One Health approach and surveillance?

HealthforAnimals' Response

Ms. Raven and FAIRR Staff,

Thank you for your recent questions regarding our Members and the animal health sector. HealthforAnimals appreciates the opportunity to answer these questions in order to provide detail on our sector's perspective and actions on antibiotics, antimicrobial resistance and responsible use.

We also believe in open, transparent dialogue on these topics as the best way to build productive conversations that can lead to collaborative solutions. Therefore, we have also posted this letter on our website so others may also view our responses and better understand our perspectives.

Your questions requested our Members insights at each step in the antibiotic lifecycle, from discovery to training to sales. Therefore, we have provided some introductory details then organized information around these steps.

However, answers are tailored to your questions and information at each lifecycle stage should not be viewed as comprehensive. Animal medicines are a complex, innovative area and there is a wide array of topics that can be discussed. We hope this information provides a valuable introduction.

HealthforAnimals Member Overview

HealthforAnimals is the global representative of the 'Animal Health' sector. Our Members provide products that help protect the health of livestock and pets, including vaccines, parasiticides, nutritional supplements, diagnostics, antibiotics and more.

Animal health is highly innovative sector. Emerging technologies such as monoclonal antibodies, herd-specific vaccines, immunotherapy treatments, or A.I.-driven digital technologies demonstrate our sector's ability to deliver cutting-edge innovation into the market and improve the health of animals.

Other companies operate in this sector who are not represented by HealthforAnimals though, including companies focused on specific regional markets and/or generic animal health products. For instance, the hurdles in developing a class of antibiotics (as explained in Discovery), mean older, off-patent products are widely produced and local companies in areas like South Asia can have notable market share.

HealthforAnimals Members believe deeply in proper stewardship of antibiotics as they are a cornerstone of good animal care and the only treatment for a bacterial infection. We cannot afford to lose them. Our companies urge those outside our Membership to ensure they have stewardship and responsible use strategies in place.

Antimicrobial Resistance and One Health

Antimicrobial resistance has been at the top of the global agenda, especially since the United Nations' *Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance*. However, the animal health sector has recognized and worked on this challenge for many years prior.

For instance, the UK Responsible Use of Medicines Alliance (RUMA) was established in 1997 and the European Platform for Responsible Use of Medicines in Animals (EPRUMA) was established in 2005. More recently, Brazil has also formed 'Aliança', a responsible use alliance in the country. Our sector has been active and supportive of these organizations since their inception, and our *Antibiotics Commitment* and *Roadmap to Reducing the Need for Antibiotics* demonstrate how we have worked to bring these same principles to the global level.

We believe these types of activities are why Lord O'Neill described himself as 'positively surprised' by the agricultural sphere in a recent Chatham House review of AMR progress. The fight is certainly not over though, but this early progress coupled with the plans outlined in our *Roadmap* have provided the agricultural sector with strong momentum.

However, even if progress continues to accelerate in agriculture, the challenge of resistance will not be solved. Modelling by the University of Edinburgh found that only addressing antibiotic use in animals, but not people, will have "*little impact on the level of resistance in humans*."

Antimicrobial resistance is fundamentally a 'One Health' challenge that requires action from both human and animal health.

The European Centre for Disease Prevention and Control estimates that *"75% of disease linked to resistant bacteria is due to healthcare-associated infections"* and the European Medicines Agency stated in its 2015-2020 AMR strategy that *"the biggest driver of AMR in people is the use of antimicrobials in humans or human health."* According to the OECD, measures *"as simple as handwashing and more prudent prescriptions"* in human health could reduce future AMR deaths by 75%.

The information provided in this letter demonstrates that our sector is committed to tackling AMR and taking the necessary actions to help stem the tide. However, complementary action is also needed from human health to truly manage this One Health challenge and we hope FAIRR recognizes this when evaluating AMR progress.

Antibiotic Discovery

Medicine discovery is a challenging, expensive and lengthy process. It entails years of research and robust testing that requires a significant investment.

This challenge can be compounded in antibiotics. The WHO has recommended that any new class of antibiotics found to be effective in humans will be considered 'critically important' and recommends these are reserved for human use.

This limits the range of molecules available for animal antibiotic research, which highlights the importance of animal-only antibiotics. These medicines are the only type of new new animal antibiotic class that can be brought to market and therefore are a cornerstone of bacterial disease management and innovation in animal health.

Development

Once a new molecule is discovered, it must be developed into a market-viable product. This includes identifying the necessary information for the product label. All animal medicines, including antibiotics, come with product labels that offer detailed guidance on how to use the medicine appropriately. This can include information such as:

- 'Indications of use': The situations and diseases where the antimicrobial is approved for use.
- Dosage and Administration: Detailed instructions for how to administer the antibiotic effectively. Can include details as specific as quantity, recommended injection location, amount based on animal body weight, etc.
- 'Adverse Reactions': List of possible side effects from a medicine that should be monitored.
- Withdrawal Periods: Amount of time a farmer must wait after administering the antibiotic before slaughter to ensure no 'residues' or trace amounts can be found in the meat or other produce. Withdrawal periods are strictly enforced by authorities.
- Pharmacology: Clinical explanation of how the antibiotic functions, efficacy levels, etc.
- Precautions/Warnings: Cautions for the user (e.g. Not for Human Use) and information on what to do in case of an accident (e.g. accidental human injection).
- Contact: Contact information for the manufacturer to report adverse events or other issues.

Product labels are highly detailed because the objective is to help ensure these medicines are used properly, effectively and responsibly when administered to an animal. The exact contents of labels included in the packaging are legal requirements and the language is established by national regulators.

Assessment

During the authorization process, government regulators assess all animal medicines, including antibiotics, on three aspects – efficacy, safety and quality. Environmental safety is part of this process, which in many regions includes a mandatory environment risk assessment. The assessment conducted for veterinary medicines used in livestock and aquaculture includes predicting environmental concentrations and assessing potential impacts on indicator species in the environment, including effects on beneficial organisms. Animal health companies comply with the stringent legal standards/requirements set by national and international health, animal and environmental regulatory agencies.

Manufacturing

In many cases animal health companies have their own facilities where products are manufactured from start to finish. Products and/or active ingredients for products are also manufactured under contract by other companies. For the animal health sector, this often happens in the same facilities where human health products are manufactured. Third party production facilities must comply with detailed procedures and rules set out in legislation and regulation. Continuous efforts are made to improve emission control at manufacturing facilities. Animal health companies are actively involved in joint initiatives to increase leverage, for example the Pharmaceutical Supply Chain Initiative (PCSI) group of pharmaceutical companies who have joined forces to promote responsible supply chain management and better business conditions across the industry. Many companies have also published their 'Predicted No Effect Concentration' (PNEC) value for antibiotics as part of the AMR industry alliance, which can help with environmental monitoring.

Distribution

Global manufacturing companies – from medicines to any consumer product – rely on a network of distributors to help their goods reach the customer. HealthforAnimals Members have contracts with distributors that help ensure products reach farmers, veterinarians and pet owners.

Companies closely monitor all parts of the supply chain – from active pharmaceutical ingredient (API) producers to distributors to final customers– to ensure medicines are reaching markets and successfully managing any animal health challenges. This is the foundation of any business. If any partners are not meeting

expectations, companies will address it. Not doing so would risk a company's ability to deliver products into a marketplace

Marketing and Sales

Decisions about how a product is marketed are made by individual companies and cannot be addressed by HealthforAnimals. This is outside our purview as marketing coordination by an industry association can raise anti-trust issues.

However, the underlying assumption behind FAIRR's statement that *'antibiotics are a volume business – a decrease in usage will ultimately have an impact on revenue'* is not correct. It overlooks the fact that HealthforAnimals Members offer a full suite of technologies and medicines for the health of animals.

For instance, the European animal health market – the second largest in the world – has experienced a decline in antibiotic sales in recent years, while the overall market continues to grow due to other product categories. This same trend is occurring the U.S., which has seen antibiotics sales fall in recent years while the wider animal health market expands.

A farm that reduces its need for antibiotics often does so through increased adoption of vaccines, nutritional supplements, digital monitoring technologies, rapid diagnostics, etc. HealthforAnimals Members excel at developing these innovations that can improve disease control, which better protects animal health and reduces the need for antibiotics.

It's why sales and/or marketing staff's incentive is to provide the right product for the producer's specific situation. This may be vaccines, nutritional supplements, diagnostics, digital monitoring technologies, parasite control or antibiotics.

A singular focus on antibiotic sales for a company or salesperson would not be a sound business practice. It would ignore the other needs of a farmer and pass up opportunities to provide other tools that can help improve their operation. The producer would likely turn to another company that can help provide much more comprehensive care for their animals.

Antibiotic Use

All antibiotics are sold with defined dosages (See product label information above). This helps ensure an animal receives the amount necessary to tackle the bacterial disease(s) listed under the indication of use. This is an essential piece of information that is required before a medicine can be approved by regulators. One key reason is because using less than the recommended amount of an antibiotic can lead to resistance development.

Duration of use is not included on all products. Strict, defined durations can severely hamper a veterinarian's ability to not only tackle a bacterial disease but manage resistance. That is why in many countries, the regulators have given that judgement call to veterinarians.

For instance, a veterinarian may administer a course of antibiotics to an animal. If the animal is not fully recovered, the veterinarian may recommend continuing the treatment for a few more days. However, if the antibiotic provided a longer duration of use on the label (e.g. 14 days), the veterinarian is required to administer the antibiotic for the complete period. This can lead to unnecessary medicine use.

Providing flexibility in duration of use allows for professionals to evaluate an animal and decide what course of treatment best fits the situation.

This expertise is also essential in deciding exactly *when* an antibiotic should be administered.

Veterinarians are highly skilled animal health professionals. They undergo extensive training and real-world experience that teaches them how disease spreads in an animal, herd, flock or region. This spread is often predictable because of the nature of livestock production.

The animals live in a defined space (i.e. the farm) and are raised on a relatively uniform schedule. For instance, animals will receive vaccines at specific ages and will be raised on a relatively uniform schedule. This efficiency maximizes the natural resources used in raising an animal and leads to a more sustainable operation.

It also leads to predictable times of stress or disease susceptibility for animals, and veterinarians understand when this puts an animal at high-risk of contracting a bacterial disease. This risk puts an entire herd or flock in danger as infections will spread during the incubation period before symptoms are shown.

Therefore, a veterinarian may decide to use a prophylactic antibiotic treatment instead of waiting for animals to suffer an infection and an outbreak to form. They will rely upon epidemiological, diagnostic, and clinical knowledge to inform their decision. This protects the welfare of that animal and those around it.

Veterinarians are a key part of farm animal health plans, including providing oversight on antibiotic use. In some countries this is a legal requirement, in others it is not.

Growth Promotion

Most countries do not allow the use of medically important antibiotics for growth promotion. The European Union ended the use of antibiotic growth promoters in 2006, and major markets like the U.S. and China have also adopted these measures. Animal medicines companies worked proactively with governments in these markets to help implement these regulations and help avoid a negative impact on famer livelihoods or animal welfare.

Today, the World Organization for Animal Health (OIE) states that most countries do not allow antibiotics for growth promotion and the number is falling. Countries where it does still exist are typically those in the global south or 'developing' regions.

The average livestock producer in these markets is a smallholder with 1-2 head of cattle or a small flock of chickens. Livestock provides essential subsistence and nutrition, and these farmers rely on this to avoid hunger and poverty. When certain indications of use for a medicine are phased out, it's essential that these farmers are supported through that transition. Every kilo of milk, meat or eggs that an animal may no longer produce has a direct effect on local food security.

'Alternatives to Antibiotics'

It is important to note that the term 'alternatives to antibiotics' is a misnomer. Antibiotics are currently the *only* way to treat a bacterial infection. There is no alternative. Without antibiotics, animals facing a bacterial disease will suffer and many will die. It's why antibiotics will always be necessary for good health, and systems such as 'Raised Without Antibiotics' can be harmful to welfare.

However, there are products and practices that can reduce the need for antibiotic use. This can include medicines such as vaccines or nutritional supplements, as well as good biosecurity and husbandry.

Farmers recognize the value of tackling bacterial disease early and reducing the need for antibiotic treatments. Adoption of tools and technologies that can facilitate this are on the rise around the world, and HealthforAnimals Members are proud to support this effort.

Responsible Use Training

HealthforAnimals and our Members support robust training on antibiotics because it provides the on-the-ground knowledge necessary to recognize, diagnose and treat the threat of bacterial disease effectively.

Our sector often partners with respected global institutions like the Bill and Melinda Gates Foundation, the World Organization for Animal Health (OIE) and the United Nation's Food and Agriculture Organization (FAO) to provide trainings in regions where veterinary access is a massive challenge. Companies also work with national veterinary authorities to provide this training support.

These partnerships are a testament to our sector's ability to provide clear, competent and neutral trainings that help support responsible use and strengthen veterinary expertise in key regions. These organizations and governments recognize that these trainings offer immense value and are not a 'sales seminar' as FAIRR's questions seem to suggest.

Tracking Sales

Individual national governments determine whether and how they collect and publish sales data. Animal Health companies share this information in countries where this is part of the regulatory regime.

For instance, in the U.S., all companies producing approved antibiotics for use by food producing animals are legally required to report sales data to FDA, and all companies, regardless of product, are required to provide sales data as part of their pharmacovigilance reporting. This data is compiled and published on the FDA site. In the EU, each country collects the data nationally and shares it with the EMA who publishes it annually in the reports from "European Surveillance of Veterinary Antimicrobial Consumption (ESVAC)". The reports are on the EMA site. Data shows that antibiotic sales have trended downwards in both markets in recent years.

In Brazil, the government also formally requests this data annually and industry collects and submits it. In other markets, such as China, Australia, and Canada, the authorities collect data and industry always provides this.

In addition, the OIE collects data at global level from countries and those compilation reports are on their site. The latest version is the "Fourth OIE annual report on the use of antimicrobial agents intended for use in animals". The fact that most countries share data with OIE indicates that most are collecting it – almost always based on input from the companies, and sometimes based on inputs from distributors and veterinarians.

However, sales data is a flawed mechanism for surveillance. If the objective is to manage AMR, then tracking resistance itself provides much more actionable data. For instance, in the United States, the government has operated the 'National Antimicrobial Resistance Monitoring System' (NARMs) since 1996. This public health surveillance system samples bacteria from people, animals and foods to understand if and how bacterial resistance is evolving. It provides valuable, granular insights that allows stakeholders to take targeted action that can better manage resistance.

Sales data can indicate whether disease pressures were especially heavy one year, if outbreaks were lower than expected, types of antibiotics used in response, etc., but it cannot tell us whether bacterial resistance is developing. Only testing for resistance itself can achieve this.

Future Demand

FAIRR asked about changing consumption trends. HealthforAnimals Members recognize that demand for food and protein is quickly evolving. By 2030, our global population is expected to grow to 8.5 billion – nearly 1 billion more than live on our planet today -- and 2 out of 3 people will be in the middle class. This rapid population increase means that even if per capita animal protein consumption were to fall (it is not projected to do so), overall production will still need to rise.

At the moment, FAO and OECD estimate that livestock production will need to increase by 14% by 2029. However, simply increasing the size of current production systems to meet these future needs would require unsustainable increases in natural resources use. We must increase production efficiency and drastically cut food waste from farm to fork.

This must occur in developed regions, but also emerging markets in South America, Asia and Africa. These regions are becoming increasingly sophisticated agricultural producers. In livestock, this often means greater use of technologies like vaccines, nutritional supplements, and rapid diagnostics.

HealthforAnimals Members, as animal health companies with comprehensive portfolios, are committed to providing tools that can facilitate these shifts and ensure sustainable production well into the future.

Looking Ahead

HealthforAnimals Members are committed to being responsible stewards of antibiotics and ensuring these products remain effective well into the future. Our *Roadmap to Reducing the Need for Antibiotics* outlines our strategy and provides many examples of specific actions undertaken. We will also release an interim report in 2021 to demonstrate progress towards our Roadmap Commitments.

However, AMR is not a challenge we can solve alone. We look forward to working with others across the value chain to address this joint challenge.

Sincerely,

Carel du Marchie Sarvaas
Executive Director
HealthforAnimals

Endnotes

1 Interagency Coordination Group on Antimicrobial Resistance (2019) No Time to Wait: Securing the future from drug-resistant infections. Report to the Secretary-General of the United Nations, April 2019. WHO. Available from: https://www.who.int/docs/default-source/documents/no-time-to-wait-securing-the-future-from-drug-resistant-infections-en.pdf?sfvrsn=5b424d7_6#:-:text=The%20true%20magnitude%20of%20antimicrobial,tuberculosis%20(18%2C19).

2 World Bank (2017) Drug-Resistant Infections: A threat to our economic future. Washington, FC: World Bank. Available from: https://documents1.worldbank.org/curated/en/323311493396993758/pdf/final-report.pdf

3 WHO (2020) World Antimicrobial Awareness Week 2020 – Handle with care: United to preserve antimicrobials. Accessed 16/07/2021. Available from: https://www.who.int/news-room/events/detail/2020/11/18/default-calendar/world-antimicrobial-awareness-week-2020

4 Department of Health & Social Care (2021) Policy paper: G7 Health Ministers' Meeting, communique, Oxford, 4 June, 2021. Available from: https://www.gov.uk/government/publications/g7-health-ministers-meeting-june-2021-communique/g7-health-ministers-meeting-communique-oxford-4-june-2021#antimicrobial-resistance

5 O'Neill, J. (2016) Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. London, UK: The Review on Antimicrobial Resistance. Available from: https: //amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf

6 FoodPrint (2020) Antibiotics in Our Food System. Available from: https://foodprint.org/issues/antibiotics-in-our-food-system/

7 World Bank (2017) Drug-Resistant Infections: A Threat to Our Economic Future. Available from: https://documents1.worldbank.org/curated/en/323311493396993758/pdf/final-report.pdf

8 World Bank (2017) Drug-Resistant Infections: A Threat to Our Economic Future. Available from: https://documents1.worldbank.org/curated/en/323311493396993758/pdf/final-report.pdf

9 Magouras, I., et al. (2017) Antimicrobial Usage and -Resistance in Livestock: Where Should We Focus?. Frontiers in veterinary science. 4(148). Available from: https://doi.org/10.3389/fvets.2017.00148

10 Tang, K.L., et al. (2017) Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. The Lancet: Planetary Health. 1(8), E316-E327. Available from: https://doi.org/10.1016/S2542-5196(17)30141-9

11 Van Boeckel, T., et al. (2015) Global trends in antimicrobial use in food animals. Proceedings of the National Academy of Sciences. 112(18), 5649-5654. Available from: https://doi.org/10.1073/pnas.1503141112

12 Schoenmakers, K. (2020) How China is getting its farmers to kick their antibiotics habit. Nature, 586, S60-S62. Available from: doi: https://doi.org/10.1038/d41586-020-02889-y1

13 WHO (2020) Antimicrobial resistance. Available online at: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance [Accessed 14th July 2021].

14 WHO (2020) Antimicrobial resistance. Available online at: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance [Accessed 14th July 2021].

15 WHO (2020) Antimicrobial resistance. Available online at: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance [Accessed 14th July 2021].

16 Magouras, I., et al. (2017) Antimicrobial Usage and -Resistance in Livestock: Where Should We Focus?. Frontiers in veterinary science. 4(148). Available from: https://doi.org/10.3389/fvets.2017.00148

17 Akinbami, O. R., et al. (2018) Prevalence of extended spectrum beta lactamase and plasmid mediated quinolone resistant genes in strains of Klebsiella pneumonia, Morganella morganii, Leclercia adecarboxylata and Citrobacter freundii isolated from poultry in South Western Nigeria. PeerJ. 6:e5053. Available from: https://doi.org/10.7717/peerj.5053].

18 Scott, A. M., et al. (2018) Is antimicrobial administration to food animals a direct threat to human health? A rapid systematic review. International journal of antimicrobial agents. 52(3), 316–323. Available from: https://doi.org/10.1016/j.ijantimicag.2018.04.005

19 Graham, D. W., et al. (2019) Complexities in understanding antimicrobial resistance across domesticated animal, human, and environmental systems. Annals of the New York Academy of Sciences. 1441(1), 17–30. Available from: https://doi.org/10.1111/nyas.14036 [Accessed 14th July 2021].

20 Tang, K.L., et al. (2017) Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. The Lancet: Planetary Health. 1(8), E316-E327. Available from: https://doi.org/10.1016/S2542-5196(17)30141-9

21 Van Boeckel, T., et al. (2015) Global trends in antimicrobial use in food animals. Proceedings of the National Academy of Sciences. 112(18) 5649-5654. Available from: https://doi.org/10.3390/antibiotics9120918

22 Argudín, M.A., et al. (2017) Bacteria from Animals as a Pool of Antimicrobial Resistance Genes. Antibiotics. 6 (2), p.12. Available from: http://dx.doi.org/10.3390/antibiotics6020012

23 Scott, A. M., et al. (2018). Is antimicrobial administration to food animals a direct threat to human health? A rapid systematic review. International journal of antimicrobial agents. 52(3), 316–323. Available from: https://doi.org/10.1016/j.ijantimicag.2018.04.005.

24 Akinbami, O. R., at ayl. (2018) Prevalence of extended spectrum beta lactamase and plasmid mediated quinolone resistant genes in strains of Klebsiella pneumonia, Morganella morganii, Leclercia adecarboxylata and Citrobacter freundii isolated from poultry in South Western Nigeria. PeerJ. 6:e5053. Available from: https://doi.org/10.7717/peerj.5053

25 Scott, A. M., et al. (2018). Is antimicrobial administration to food animals a direct threat to human health? A rapid systematic review. International journal of antimicrobial agents. 52(3), 316–323. Available from: https://doi.org/10.1016/j.ijantimicag.2018.04.005

26 Perez, F. and Bonomo, R. A. (2020). Colistin resistance in China: from outer membrane to One Health. The Lancet. Infectious Diseases, 20 (10), P1106-1108. Available from: https://doi.org/10.1016/S1473-3099(20)30242-5

27 UK Government. LA-MRSA: Information for people who work with livestock. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/479015/LA-MRSA.PDF [Accessed 15 May 2021]

28 Sahibzada, S., et al. (2017) Transmission of highly virulent community-associated MRSA ST93 and livestock-associated MRSA ST398 between humans and pigs in Australia. Scientific Reports. 7(5273). Available from : https://doi.org/10.1038/s41598-017-04789-0

29 Cuny, C., et al. (2015) Livestock-Associated MRSA: The Impact on Humans. Antibiotics. 4, 521-543. Available from: doi:10.3390/antibiotics4040521

30 Florez-Cuadrado, D., et al. (2018) Antimicrobial Resistance in the Food Chain in the European Union. Advances in food and nutrition research. 86, 115–136. Available from: https://doi.org/10.1016/bs.afnr.2018.04.004

31 Institut Pasteur (2019) Food Contamination in Cambodia Contributing to the Burden of Antibiotic Resistance. Available from: https://www.pasteur.fr/en/institut-pasteur/institut-pasteur-throughout-world/news/food-contamination-cambodia-contributing-burden-antibiotic-resistance.

32 Nüesch-Inderbinen, M. and Stephan, R. (2016) Epidemiology of Extended-Spectrum β-Lactamase-Producing Escherichia coli in the Human-Livestock Environment. Current Clinical Microbiology Reports, 3, 1–9 (2016). Available from: https://doi.org/10.1007/s40588-016-0027-5

33 Botelho, R.G., et al. (2015) Veterinary Antibiotics in the Environment, Emerging Pollutants in the Environment - Current and Further Implications. IntechOpen. Available from: https://www.intechopen.com/books/emerging-pollutants-in-the-environment-current-and-further-implications/veterinary-antibiotics-in-the-environment

34 UNEP (2017) Frontiers 2017 Emerging Issues of Environmental Concern. United Nations Environment Programme, Nairobi..

35 Hong, P.-Y., et al. (2013) Environmental and Public Health Implications of Water Reuse: Antibiotics, Antibiotic Resistant Bacteria, and Antibiotic Resistance Genes. Antibiotics. 2(3), 367-299. Available from: https://doi.org/10.3390/antibiotics2030367

36 Kim, K.-R., et al. (2010) Occurrence and Environmental Fate of Veterinary Antibiotics in the Terrestrial Environment. Water, Air, & Soil Pollution. 214, 163-174. Available from: https://link.springer.com/article/10.1007%2Fs11270-010-0412-2

37 National Academy of Sciences (1980) The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds. Available from: https://www.nap.edu/read/21/chapter/1

38 Kümmerer, K. (2009) Antibiotics in the aquatic environment – A review – Part I, Chemosphere, 75 (4), 417-434. Available from: https://doi.org/10.1016/j.chemosphere.2008.11.086

39 Kümmerer, K. (2009) Antibiotics in the aquatic environment – A review – Part 2, Chemosphere. 75(4), 435-441. Available from: https://doi.org/10.1016/j.chemosphere.2008.12.006

40 Du, L. and Liu, W. (2012) Occurrence, fate, and ecotoxicity of antibiotics in agro-ecosystems. A review. Agronomy for Sustainable Development, 32, 309–327. Available from: https://doi.org/10.1007/s13593-011-0062-9

41 Chee-Sanford, J. C. (2009) Fate and Transport of Antibiotic Residues and Antibiotic Resistance Genes following Land Application of Manure Waste. Journal of Environmental Quality, 38 (3), 1086-1108. Available from: https://doi.org/10.2134/jeq2008.0128.

42 Bhushan, C., et al. (2017) Antibiotic Resistance in Poultry Environment: Spread of Resistance from Poultry Farm to Agricultural Field. Centre for Science and Environment: New Delhi, India. 36p, Available from: www.cseindia.org

43 Rasschaert, G., et al. (2020) Antibiotic Residues and Antibiotic-Resistant Bacteria in Pig Slurry Used to Fertilize Agricultural Fields. Antibiotics. 9(1), 34. Available from: https://doi.org/10.3390/antibiotics9010034

44 Amador, P., et al. (2019) Prevalence of Antibiotic Resistance Genes in Multidrug-Resistant Enterobacteriaceae on Portuguese Livestock Manure. Antibiotics. 8(1), 23. Available from: https://doi.org/10.3390/antibiotics8010023

45 Ghosh, S. and LaPara, T. (2007) The effects of subtherapeutic antibiotic use in farm animals on the proliferation and persistence of antibiotic resistance among soil bacteria. ISME J. 1, 191-203. Available from: https://www.nature.com/articles/ismej2007311

46 Hong, P.-Y., et al. (2013) Environmental and Public Health Implications of Water Reuse: Antibiotics, Antibiotic Resistant Bacteria, and Antibiotic Resistance Genes. Antibiotics. 2(3), 367-299. Available from: https://doi.org/10.3390/antibiotics20303671

47 Xiaohua, L., et al. (2018) Antibiotic residues in liquid manure from swine feedlot and their effects on nearby groundwater in regions of North China. Environmental science and pollution research international, 25 (12), 11565-11575. Available from: https://pubmed.ncbi.nlm.nih.gov/29427277/

48 Li, J., et al. (2012) Plasmid-Mediated Quinolone Resistance Genes and Antibiotic Residues in Wastewater and Soil Adjacent to Swine Feedlots: Potential Transfer to Agricultural Lands. Environmental Health Perspectives, 120 (8). Available from: https://doi.org/10.1289/ehp.1104776

49 Karkman, A., et al. (2019) Fecal pollution can explain antibiotic resistance gene abundances in anthropogenically impacted environments. Nature Communications. 10(1). Available from: doi:10.1038/s41467-018-07992-3

50 Kristiansson, E., et al. (2011) Pyrosequencing of antibiotic-contaminated river sediments reveals high levels of resistance and gene transfer elements. PLoS One. 6(2). Available from: doi:10.1371/journal.pone.0017038

51 Bielen, A., et al. (2017) Negative environmental impacts of antibiotic-contaminated effluents from pharmaceutical industries. Water Research. 126, 79-87. Available from: doi:10.1016/j. watres.2017.09.019

52 Li, D., et al. (2008) Determination and fate of oxytetracycline and related compounds in oxytetracycline production wastewater and the receiving river. Environ Toxicol Chem. 27(1), 80-86. Available from: doi:10.1897/07-080.1

53 Martinez, J. L. (2009) Environmental pollution by antibiotics and by antibiotic resistance determinants. Environmental Pollution, 157(11), 2893-2902. Available from: https://doi.org/10.1016/j.envpol.2009.05.051

54 Ding, C. and He, J. (2010) Effect of antibiotics in the environment on microbial populations. Applied Microbiology and Biotechnology. 87, 925-941. Available from: https://doi.org/10.1007/s00253-010-2649-5

55 Healthcare in Europe (2019) Global opportunity to tackel antibiotic production waste. Available from: https://healthcare-in-europe.com/en/news/global-opportunity-to-tackle-antibiotic-production-waste.html

56 University of York (2019) Antibiotics found in some of the world's rivers exceed 'safe' levels, global study finds. Available at: https://www.york.ac.uk/news-and-events/news/2019/research/antibiotics-found-in-some-of-worlds-rivers/

57 Bhushan, C., et al. (2017) Antibiotic Resistance in Poultry Environment: Spread of Resistance from Poultry Farm to Agricultural Field. Centre for Science and Environment: New Delhi, India. 36p. Avail-

able from: www.cseindia.org
58 Amador, P., et al. (2019) Prevalence of Antibiotic Resistance Genes in Multidrug-Resistant Enterobacteriaceae on Portuguese Livestock Manure. Antibiotics. 8(1), 23. Available from: https://doi.org/10.3390/antibiotics8010023
59 Ghosh, S. and LaPara, T. (2007) The effects of subtherapeutic antibiotic use in farm animals on the proliferation and persistence of antibiotic resistance among soil bacteria. ISME J. 1, 191-203. Available from: https://www.nature.com/articles/ismej2007311
60 Gao, L., et al., (2015) Application of swine manure on agricultural fields contributes to extended-spectrum β-lactamase-producing Escherichia coli spread in Tai'an, China. Frontiers in Microbiology. 6, 313. Available from: https://doi.org/10.3389/fmicb.2015.00313
61 Cheong, M.S., et al, (2020) Influence of Sulfonamide Contamination Derived from Veterinary Antibiotics on Plant Growth and Development. Antibiotics. 9, 456. Available from: doi:10.3390/antibiotics9080456
62 Kandel, S.L., (2017) Bacterial Endophyte Colonization and Distribution within Plants. Microorganisms. 5(4), 77. Available from: doi: 10.3390/microorganisms5040077
63 FDA (2019) Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals. Available from: https://www.fda.gov/media/144427/download
64 VKM (2015) The risk of development of antimicrobial resistance with the use of coccidiostats in poultry diets. Opinion of the Panel on Animal Feed of the Norwegian Scientific Committee for Food Safety. Available from: https://vkm.no/download/18.2994e95b15cc5450716152d3/1498142579152/0025301628.pdf
65 Wong, A. (2019) Unknown Risk on the Farm: Does Agricultural Use of Ionophores Contribute to the Burden of Antimicrobial Resistance? Journal of Clinical Microbiology. Available from: https://doi.org/10.1128/mSphere.00433-19
66 Dunshea, F. R., et al. (2014) Meat, Animal, Poultry and Fish Production and Management: Antibiotic Growth Promotants. In: Dikeman, M. and Devine, C. (eds) Encyclopedia of Meat Sciences (Second Edition), pp. 172-176. Available from: https://doi.org/10.1016/B978-0-12-384731-7.00018-0.)
67 Review on Antimicrobial Resistance (2015), Antimicrobials in Agriculture and the Environment. Available at: https://ec.europa.eu/health/sites/health/files/antimicrobial_resistance/docs/amr_studies_2015_am-in-agri-and-env.pdf
68 Review on Antimicrobial Resistance (2015), Antimicrobials in Agriculture and the Environment. Available at: https://ec.europa.eu/health/sites/health/files/antimicrobial_resistance/docs/amr_studies_2015_am-in-agri-and-env.pdf
69 The Pig Site (2012) Current Antimicrobial Use and Resistance Issues in the European Union – Reality and Resolution. Available from: https://www.thepigsite.com/articles/current-antimicrobial-use-and-resistance-issues-in-the-european-union-reality-and-resolution [Accessed 15 July 2021]
70 Callaway, T.R., et al. (2003) Ionophores: their use as ruminant growth promotants and impact on food safety. Curr Issues Intest Microbiol. 4(2), 43-51. Available from: https://pubmed.ncbi.nlm.nih.gov/14503688/
71 Alliance to Save Our Antibiotics (2019) Massive use of ionophore antibiotics in poultry production. Available from: https://www.saveourantibiotics.org/news/press-release/massive-use-of-ionophore-antibiotics-in-poultry-production/
72 Alliance to Save Our Antibiotics (2019) Massive use of ionophore antibiotics in poultry production. Available from: https://www.saveourantibiotics.org/news/press-release/massive-use-of-ionophore-antibiotics-in-poultry-production/
73 OIE (2014) OIE List of Antimicrobial Agents of Veterinary Importance and OIE Standards and Activities. Available from: https://www.ema.europa.eu/en/documents/presentation/presentation-world-organisation-animal-health-oie-list-antimicrobial-agents-veterinary-importance_en.pdf
74 Alliance to Save Our Antibiotics (2019) Massive use of ionophore antibiotics in poultry production. Available from: https://www.saveourantibiotics.org/news/press-release/massive-use-of-ionophore-antibiotics-in-poultry-production/
75 VKM. (2015) The risk of development of antimicrobial resistance with the use of coccidiostats in poultry diets. Opinion of the Panel on Animal Feed of the Norwegian Scientific Committee for Food Safety. Available from: https://vkm.no/download/18.2994e95b15cc5450716152d3/1498142579152/0025301628.pdf
76 Alliance to Save Our Antibiotics (2019) "Swan song" for routine antibiotic use, 50 years on? Available from : https://www.saveourantibiotics.org/media/1808/swann-song-for-routine-antibiotic-use.pdf..
77 Alliance to Save Our Antibiotics (2019) "Swan song" for routine antibiotic use, 50 years on? Available from : https://www.saveourantibiotics.org/media/1808/swann-song-for-routine-antibiotic-use.pdf.
78 Bak, S. A. and Björklund, E. (2014) Occurrence of Ionophores in the Danish Environment. Antibiotics. 3(4), 564-571. Available from: https://doi.org/10.3390/antibiotics3040564
79 Hanson, M., et al. (2009) Environmental risk assessment of ionophores. Trends in Analytical Chemistry. 28(5), 534-542. Available from: https://doi.org/10.1016/j.trac.2009.02.015
80 Žižek, S. and Zidar, P. (2013) Toxicity of the ionophore antibiotic lasalocid to soil-dwelling invertebrates: avoidance tests in comparison to classic sublethal tests. Chemosphere. 92(5), 570–575. Available from: https://doi.org/10.1016/j.chemosphere.2013.04.007
81 Zižek, S., et al. (2011) Does monensin in chicken manure from poultry farms pose a threat to soil invertebrates?. Chemosphere, 83(4), 517–523. Available from: https://doi.org/10.1016/j.chemosphere.2010.12.058
82 Žižek, S., et al. (2015). Degradation and dissipation of the veterinary ionophore lasalocid in manure and soil. Chemosphere, 138, 947–951. Available from: https://doi.org/10.1016/j.chemosphere.2014.12.032
83 College of Agriculture, Food and Environment (2012) Ionophore Intoxication in Horses. http://equine.ca.uky.edu/news-story/ionophore-intoxication-horses
84 Reuters (2012) Animal feed recalled, effect on horses feared. Available from: https://www.reuters.com/article/us-recall-horsefeed-idUSTRE8220JG20120303
85 College of Agriculture, Food and Environment (2012) Ionophore Intoxication in Horses. http://equine.ca.uky.edu/news-story/ionophore-intoxication-horses
86 Elanco (2021) 2020 Annual Report. Available from: https://s1.q4cdn.com/466533431/files/doc_financials/2020/ar/2020-Annual-Report_Elanco_vf-00.pdf
87 Wertheim, H., et al. (2013) Global Survey of polymyxin use: A call for international guidelines. Journal of Global Antimicrobial Resistance. 1(3), 131-134. Available from: https://doi.org/10.1016/j.jgar.2013.03.012
88 Catry, B., et al. (2015) Use of colistin-containing products within the European Union and European Economic Area (EU/EEA): development of resistance in animals and possible impact on human and animal health. International Journal of Antimicrobial Agents. 46(3), 297-306. Available from: https://doi.org/10.1016/j.ijantimicag.2015.06.005
89 Lim, L.M., et al. (2012) Resurgence of Colistin: A Review of Resistance, Toxicity, Pharmacodynamics, and Dosing. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 30(12), 1279-1291. Available from: https://doi.org/10.1592/phco.30.12.1279
90 Wertheim, H., et al. (2013) Global Survey of polymyxin use: A call for international guidelines. Journal of Global Antimicrobial Resistance. 1(3), 131-134. Available from: https://doi.org/10.1016/j.jgar.2013.03.012
91 Schoenmakers, K. (2020). How China is getting its farmers to kick their antibiotics habit. Nature, 586, S60-S62. Available from: doi: https://doi.org/10.1038/d41586-020-02889-y
92 Catry, B., et al. (2015) Use of colistin-containing products within the European Union and European Economic Area (EU/EEA): development of resistance in animals and possible impact on human and animal health. International Journal of Antimicrobial Agents. 46(3), 297-306. Available from: https://doi.org/10.1016/j.ijantimicag.2015.06.005
93 Webb, H.E., et al. (2017) Illustrative examples of probable transfer of resistance determinants from food animals to humans: Streptothricins, glycopeptides, and colistin. F1000Research. (6)1805. Available from: https://doi.org/10.12688/f1000research.12777.1
94 Perez, F. and Bonomo, R. A. (2020) Colistin resistance in China: from outer membrane to One Health. The Lancet: Infectious Diseases. 20(10). Available from: https://doi.org/10.1016/S1473-3099(20)30242-5
95 European Medicines Agency (2020) Sales of veterinary antimicrobial agents in 31 European countries in 2018. Available from: https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2018-trends-2010-2018-tenth-esvac-report_en.pdf
96 Kumar, H., et al. (2020) Understanding of Colistin Usage in Food Animals and Available Detection Techniques: A Review. Animals. (10)1892. Available from: doi:10.3390/ani10101892..
97 Catry, B., et al. (2015) Use of colistin-containing products within the European Union and European Economic Area (EU/EEA): development of resistance in animals and possible impact on human and animal health. International Journal of Antimicrobial Agents. 46(3), 297-306. Available from: https://doi.org/10.1016/j.ijantimicag.2015.06.005
98 Webb, H.E., et al. (2017) Illustrative examples of probable transfer of resistance determinants from food animals to humans: Streptothricins, glycopeptides, and colistin. F1000Research. (6)1805. Available from: https://doi.org/10.12688/f1000research.12777.1
99 Cheng, H.-Y., et al. (2010) Molecular characterization of the PhoPQ-PmrD-PmrAB mediated pathway regulating polymyxin B resistance in Klebsiella pneumoniae CG43. J. of Biomed. Sci. 17(60). Available from: https://doi.org/10.1186/1423-0127-17-60
100 Vidovic, N. and Vidovic, S. (2020) Antimicrobial Resistance and Food Animals: Influence of Livestock Environment on the Emergence and Dissemination of Antimicrobial Resistance. Antibiotics. 9(2), 52. Available from: https://doi.org/10.3390/antibiotics9020052
101 Schoenmakers, K. (2020). How China is getting its farmers to kick their antibiotics habit. Nature, 586, S60-S62. Available from: doi: https://doi.org/10.1038/d41586-020-02889-y
102 Liu, Y.-Y., et al. (2016) Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. The Lancet: Infectious Diseases. 16(2). Available from: https://doi.org/10.1016/S1473-3099(15)00424-7
103 Sun, J. et al. (2018) Towards Understanding MCR-like Colistin Resistance. Trends in Microbiology. 26(9), 794-808. Available from: https://doi.org/10.1016/j.tim.2018.02.006
104 Vidovic, N. and Vidovic, S. (2020) Antimicrobial Resistance and Food Animals: Influence of Livestock Environment on the Emergence and Dissemination of Antimicrobial Resistance. Antibiotics. 9(2), 52. Available from: https://doi.org/10.3390/antibiotics9020052
105 Webb, H.E., et al. (2017) Illustrative examples of probable transfer of resistance determinants from food animals to humans: Streptothricins, glycopeptides, and colistin. F1000Research. (6)1805. Available from: https://doi.org/10.12688/f1000research.12777.1
106 Webb, H.E., et al. (2017) Illustrative examples of probable transfer of resistance determinants from food animals to humans: Streptothricins, glycopeptides, and colistin. F1000Research. (6)1805. Available from: https://doi.org/10.12688/f1000research.12777.1
107 Liu, Y.-Y., et al. (2016) Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. The Lancet: Infectious Diseases. 16(2). Available from: https://doi.org/10.1016/S1473-3099(15)00424-7
108 Vidovic, N. and Vidovic, S. (2020) Antimicrobial Resistance and Food Animals: Influence of Livestock Environment on the Emergence and Dissemination of Antimicrobial Resistance. Antibiotics. 9(2), 52. Available from: https://doi.org/10.3390/antibiotics9020052
109 Webb, H.E., et al. (2017) Illustrative examples of probable transfer of resistance determinants from food animals to humans: Streptothricins, glycopeptides, and colistin. F1000Research. (6)1805. Available from: https://doi.org/10.12688/f1000research.12777.1.
110 Wertheim, H., et al. (2013) Global Survey of polymyxin use: A call for international guidelines. Journal of Global Antimicrobial Resistance. 1(3), 131-134. Available from: https://doi.org/10.1016/j.jgar.2013.03.012
111 Vidovic, N. and Vidovic, S. (2020) Antimicrobial Resistance and Food Animals: Influence of Livestock Environment on the Emergence and Dissemination of Antimicrobial Resistance. Antibiotics. 9(2), 52. Available from: https://doi.org/10.3390/antibiotics9020052
112 Catry, B., et al. (2015) Use of colistin-containing products within the European Union and European Economic Area (EU/EEA): development of resistance in animals and possible impact on human and animal health. International Journal of Antimicrobial Agents. 46(3), 297-306. Available from: https://doi.org/10.1016/j.ijantimicag.2015.06.005
113 Liu, Y.-Y., et al. (2016) Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. The Lancet: Infectious Diseases. 16(2). Available from: https://doi.org/10.1016/S1473-3099(15)00424-7
114 Sun, J. et al. (2018) Towards Understanding MCR-like Colistin Resistance. Trends in Microbiology. 26(9), 794-808. Available from: https://doi.org/10.1016/j.tim.2018.02.006
115 Schoenmakers, K. (2020). How China is getting its farmers to kick their antibiotics habit. Nature, 586, S60-S62. Available from: doi: https://doi.org/10.1038/d41586-020-02889-y
116 Schoenmakers, K. (2020). How China is getting its farmers to kick their antibiotics habit. Nature, 586, S60-S62. Available from: doi: https://doi.org/10.1038/d41586-020-02889-y
117 Webb, H.E., et al. (2017) Illustrative examples of probable transfer of resistance determinants from food animals to humans: Streptothricins, glycopeptides, and colistin. F1000Research. (6)1805. Available from: https://doi.org/10.12688/f1000research.12777.1
118 Perez, F. and Bonomo, R. A. (2020) Colistin resistance in China: from outer membrane to One Health. The Lancet: Infectious Diseases. 20(10). Available from: https://doi.org/10.1016/S1473-3099(20)30242-5
119 Collignon, P.C., et al. (2016) World Health Organization Ranking of Antimicrobials According to Their Importance in Human Medicine: A Critical Step for Developing Risk Management Strategies to Control Antimicrobial Resistance From Food Animal Production. Clinical Infectious Diseases. 63(8), 1087-1093. Available at: https://doi.org/10.1093/cid/ciw475
120 Sun, J. et al. (2018) Towards Understanding MCR-like Colistin Resistance. Trends in Microbiology. 26(9), 794-808. Available from: https://doi.org/10.1016/j.tim.2018.02.006
121 Catry, B., et al. (2015) Use of colistin-containing products within the European Union and European

Economic Area (EU/EEA): development of resistance in animals and possible impact on human and animal health. International Journal of Antimicrobial Agents. 46(3), 297-306. Available from: https://doi.org/10.1016/j.ijantimicag.2015.06.005
122 Schoenmakers, K. (2020) How China is getting its farmers to kick their antibiotics habit. Nature. 586, S60-S62. Available from: doi: https://doi.org/10.1038/d41586-020-02889-y
123 Dechra (2020) Annual Report and Accounts for the year ended 30 June 2020. Available from: https://dechra.annualreport2020.com/media/281444/dechra-ar2020.pdf
124 Dechra (2020) Annual Report and Accounts for the year ended 30 June 2020. Available from: https://dechra.annualreport2020.com/media/281444/dechra-ar2020.pdf
125 Dechra (2020) Annual Report and Accounts for the year ended 30 June 2020. Available from: https://dechra.annualreport2020.com/media/281444/dechra-ar2020.pdf
126 Tiseo, K., et al. (2020) Global Trends in Antimicrobial Use in Food Animals from 2017 to 2030. Antibiotics. 9(12), 918. Available from: https://doi.org/10.3390/antibiotics9120918
127 Tiseo, K., et al. (2020) Global Trends in Antimicrobial Use in Food Animals from 2017 to 2030. Antibiotics. 9(12), 918. Available from: https://doi.org/10.3390/antibiotics9120918
128 OECD/FAO (2020) OECD-FAO Agricultural Outlook 2020-2029. FAO, Rome/OECD Publishing, Paris. Available from: https://doi.org/10.1787/1112c23b-en
129 Van Boeckel, T., et al. (2015) Global trends in antimicrobial use in food animals. Proceedings of the National Academy of Sciences. 112(18), 5649-5654. Available from: https://doi.org/10.1073/pnas.1503141112
130 Zoetis (2021) 2020 Annual Report. Available from: https://s1.q4cdn.com/446597350/files/doc_financials/2020/ar/Zoetis-2020-Annual-Report.pdf
131 Elanco (2021) 2020 Annual Report. Available from: https://s1.q4cdn.com/466533431/files/doc_financials/2020/ar/2020-Annual-Report_Elanco_vf-00.pdf
132 Vetoquinol (2021) 2020 Universal Registration Document. Available from: https://www.vetoquinol.com/eng/content/2020-universal-registration-document
133 Virbac (2020) Annual Report 2020. Available from: https://corporate.virbac.com/files/live/sites/virbac-corporate/files/contributed/ra2020/Annual_report_2020.pdf
134 Dechra (2020) Annual Report and Accounts for the year ended 30 June 2020. Available from: https://dechra.annualreport2020.com/media/281444/dechra-ar2020.pdf
135 Phibro (2020) 2020 Form 10-K. Available from: https://d18rn0p25nwr6d.cloudfront.net/CIK-0001069899/d6c560f3-c5ea-4682-8498-a888329aa02a.pdf
136 Tiseo, K., et al. (2020) Global Trends in Antimicrobial Use in Food Animals from 2017 to 2030. Antibiotics. 9(12), 918. Available from: https://doi.org/10.3390/antibiotics9120918
137 Desta, A.H. (2015) Veterinary Drugs Handling, Management and Supply Chain Assessment in Afar Pastoral Region of North East Ethiopia. American Journal of Bioscience and Bioengineering. 3(6), 142-148. Available from: https://doi.org/10.11648/j.bio.20150306.111
138 Carrique-Mas, J. and Rushton, J. (2017) Integrated interventions to tackle antimicrobial usage in animal production systems: the ViParc Project in Vietnam. Frontiers in Microbiology. 8, 1062. Available from: https://dx.doi.org/10.3389%2Ffmicb.2017.01062
139 Changing Markets (2016) Superbugs in the Supply Chain: How pollution from antibiotics factories in India and China is fuelling the global rise of drug-resistant infections. Available from: https://www.mightyearth.org/wp-content/uploads/2016/10/CHANGING-MARKET-SUPERBUGS-IN-THE-SUPPLY-CHAIN-GUARD-FONT-FIN-PRINT.pdf
140 UNEP (2017) Antimicrobial Resistance: Investigating the Environmental Dimension. Frontiers 2017: Emerging Issues of Environmental Concern. UN Environment Program. p.12-20. Available from: https://wedocs.unep.org/bitstream/handle/20.500.11822/22263/Frontiers_2017_CH1_EN.pdf?sequence=1&isAllowed=y
141 WHO (2019) Environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Drug Information. 33(4), 709-712. Available from: https://apps.who.int/iris/handle/10665/330804
142 WHO (2020) Annex 6: Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Technical Report Series. No. 1025. Available from: https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/trs1025/trs1025-annex6.pdf?sfvrsn=c947184b_2
143 WHO (2020) Annex 6: Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Technical Report Series. No. 1025. Available from: https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/trs1025/trs1025-annex6.pdf?sfvrsn=c947184b_2.
144 WHO (2020) Annex 6: Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Technical Report Series. No. 1025. Available from: https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/trs1025/trs1025-annex6.pdf?sfvrsn=c947184b_2
145 Changing Markets (2016) Superbugs in the Supply Chain: How pollution from antibiotics factories in India and China is fuelling the global rise of drug-resistant infections. Available from: https://www.mightyearth.org/wp-content/uploads/2016/10/CHANGING-MARKET-SUPERBUGS-IN-THE-SUPPLY-CHAIN-GUARD-FONT-FIN-PRINT.pdf
146 Changing Markets (2016) Superbugs in the Supply Chain: How pollution from antibiotics factories in India and China is fuelling the global rise of drug-resistant infections. Available from: https://www.mightyearth.org/wp-content/uploads/2016/10/CHANGING-MARKET-SUPERBUGS-IN-THE-SUPPLY-CHAIN-GUARD-FONT-FIN-PRINT.pdf
147 Data from Bloomberg
148 Data collected using import/export records from importgenius.com
149 Dechra (2020) Annual Report and Accounts for the year ended 30 June 2020. Available from: https://dechra.annualreport2020.com/media/281444/dechra-ar2020.pdf
150 Dechra (2020) Results Presentation: Interim results from 1 July to 31 December 2019. Available from: https://webcasting.brrmedia.co.uk/broadcast/5e32dfceb9710760e29249a6
151 Dechra (2020) Results Presentation: Interim results from 1 July to 31 December 2019. Available from: https://webcasting.brrmedia.co.uk/broadcast/5e32dfceb9710760e29249a6l
152 Dechra (2020) Results Presentation: Interim results from 1 July to 31 December 2019. Available from: https://webcasting.brrmedia.co.uk/broadcast/5e32dfceb9710760e29249a6
153 Dechra (2020) Results Presentation: Interim results from 1 July to 31 December 2019. Available from: https://webcasting.brrmedia.co.uk/broadcast/5e32dfceb9710760e29249a6
154 Changing Markets (2016) Superbugs in the Supply Chain: How pollution from antibiotics factories in India and China is fuelling the global rise of drug-resistant infections. Available from: https://www.mightyearth.org/wp-content/uploads/2016/10/CHANGING-MARKET-SUPERBUGS-IN-THE-SUPPLY-CHAIN-GUARD-FONT-FIN-PRINT.pdf
155 Pharmaceutical Supply Chain Initiative. What we do. Available from: https://pscinitiative.org/principles [Accessed 15th July 2020].
156 Department of Health & Social Care (2021) Policy paper: G7 Health Ministers' Meeting, com-munique, Oxford, 4 June, 2021. Available from: https://www.gov.uk/government/publications/g7-health-ministers-meeting-june-2021-communique/g7-health-ministers-meeting-communi-que-oxford-4-june-2021#antimicrobial-resistance
157 Orion (2020) Orion Group Sustainability Report 2019. Available from: https://www.orion.fi/globalassets/documents/orion-group/sustainability/orion_sustainability-report_2019.pdff
158 Orion (2020) Orion Group Sustainability Report 2019. Available from: https://www.orion.fi/globalassets/documents/orion-group/sustainability/orion_sustainability-report_2019.pdf
159 Orion (2020) Corporate Governance Statement 2019. Available from: https://ml-eu.globenewswire.com/Resource/Download/4f800dc9-a7f8-40f3-a0f8-97159901042e
160 Orion (2020) Financial Statement Release 2019. Available from: https://ml-eu.globenewswire.com/Resource/Download/0cabdd96-17f4-4b08-abdc-39aa60b5abda
161 Devraj, R. (2019) India and China top hot spots of antimicrobial resistance in animals. Available from: https://www.scidev.net/global/news/india-and-china-top-hot-spots-of-antimicrobial-resistance-in-animals/
162 The Center for Disease Dynamics, Economics & Policy. Antibiotic Resistance. Available from: https://resistancemap.cddep.org/AntibioticResistance.php [Accessed 15th July 2020]
163 Grace, D. (2015) Review of Evidence on Antimicrobial Resistance and Animal Agriculture in Developing Countries. International Livestock Research Institute. Available from: http://a4nh.cgiar.org/files/2015/06/EoD_Consultancy_June15_Ag_Related_AMR.pdf
164 Zhen, X., et al. (2021) Economic burden of antibiotic resistance in China: a national level estimate for inpatients. Antimicrob Resist Infect Control. 10(5). Available from: https://doi.org/10.1186/s13756-020-00872-w
165 Devraj, R. (2019) India and China top hot spots of antimicrobial resistance in animals. Available from: https://www.scidev.net/global/news/india-and-china-top-hot-spots-of-antimicrobial-resistance-in-animals/
166 Changing Markets (2016) Superbugs in the Supply Chain: How pollution from antibiotics factories in India and China is fuelling the global rise of drug-resistant infections. Available from: https://www.mightyearth.org/wp-content/uploads/2016/10/CHANGING-MARKET-SUPERBUGS-IN-THE-SUPPLY-CHAIN-GUARD-FONT-FIN-PRINT.pdf
167 Changing Markets (2016) Superbugs in the Supply Chain: How pollution from antibiotics factories in India and China is fuelling the global rise of drug-resistant infections. Available from: https://www.mightyearth.org/wp-content/uploads/2016/10/CHANGING-MARKET-SUPERBUGS-IN-THE-SUPPLY-CHAIN-GUARD-FONT-FIN-PRINT.pdf.
168 Dechra (2020) Results Presentation: Interim results from 1 July to 31 December 2019. Available from: https://webcasting.brrmedia.co.uk/broadcast/5e32dfceb9710760e29249a6
169 Changing Markets (2016) Superbugs in the Supply Chain: How pollution from antibiotics factories in India and China is fuelling the global rise of drug-resistant infections. Available from: https://www.mightyearth.org/wp-content/uploads/2016/10/CHANGING-MARKET-SUPERBUGS-IN-THE-SUPPLY-CHAIN-GUARD-FONT-FIN-PRINT.pdf
170 Changing Markets (2016) Superbugs in the Supply Chain: How pollution from antibiotics factories in India and China is fuelling the global rise of drug-resistant infections. Available from: https://www.mightyearth.org/wp-content/uploads/2016/10/CHANGING-MARKET-SUPERBUGS-IN-THE-SUPPLY-CHAIN-GUARD-FONT-FIN-PRINT.pdf.
171 The Gazette of India (2020). Available from: http://moef.gov.in/wp-content/uploads/2020/01/finalization.pdf
172 Changing Markets (2016) Superbugs in the Supply Chain: How pollution from antibiotics factories in India and China is fuelling the global rise of drug-resistant infections. Available from: https://www.mightyearth.org/wp-content/uploads/2016/10/CHANGING-MARKET-SUPERBUGS-IN-THE-SUPPLY-CHAIN-GUARD-FONT-FIN-PRINT.pdf
173 Business Standard (2020) Aurobindo's oral solid formulations unit under USFDA scrutiny. Available from: https://www.business-standard.com/article/companies/aurobindo-s-oral-solid-formulations-unit-under-usfda-scrutiny-120013001064_1.htmll
174 Changing Markets (2016) Superbugs in the Supply Chain: How pollution from antibiotics factories in India and China is fuelling the global rise of drug-resistant infections. Available from: https://www.mightyearth.org/wp-content/uploads/2016/10/CHANGING-MARKET-SUPERBUGS-IN-THE-SUPPLY-CHAIN-GUARD-FONT-FIN-PRINT.pdf
175 ImportGenius (2019) U.S. Customs Records for Zoetis Inc. Available from: https://www.importgenius.com/importers/zoetis-inc
176 Tell, J., et al. (2019) Science-based Targets for Antibiotics in receiving waters from pharmaceutical manufacturing operations. Brief Communication. Integrated Environmental Assessment and Management. 15(3) 312-319. Available from: doi: 10.1002/ieam.4141.
177 AMR Industry Alliance (2019) Making antibiotics responsibly. Available from: https://www.amrindustryalliance.org/wp-content/uploads/2019/11/Making-antibiotics-responsibly_A-common-manufacturing-framework-to-tackle-AMR.pdf
178 AMR Industry Alliance. Our members. Available from: https://www.amrindustryalliance.org/our-members/ [Accessed 15th July 2020]..
179 Tell, J., et al. (2019) Science-based Targets for Antibiotics in receiving waters from pharmaceutical manufacturing operations. Brief Communication. Integrated Environmental Assessment and Management. 15(3) 312-319. Available from: doi: 10.1002/ieam.4141.
180 Pharmaceutical Supply Chain Initiative. About us. Available from: https://pscinitiative.org/membership [Accessed 2 July 2020].
181 Larsson, D.G., et al. (2007) Effluent from drug manufactures contains extremely high levels of pharmaceuticals. Journal of Hazardous Materials. 148 (3) 51-755. Available from: DOI: 10.1016/j.jhazmat.2007.07.008
182 Changing Markets (2016) Superbugs in the Supply Chain: How pollution from antibiotics factories in India and China is fuelling the global rise of drug-resistant infections. Available from: https://www.mightyearth.org/wp-content/uploads/2016/10/CHANGING-MARKET-SUPERBUGS-IN-THE-SUPPLY-CHAIN-GUARD-FONT-FIN-PRINT.pdf
183 Yen, N.T.P., et al. (2019) Labelling and quality of antimicrobial products used in chicken flocks in the Mekong Delta of Vietnam. Veterinary Medicine and Science. 5(4), 512-516. Available from: https://doi.org/10.1002/vms3.189.
184 Yen, N.T.P., et al. (2019) Labelling and quality of antimicrobial products used in chicken flocks in the Mekong Delta of Vietnam. Veterinary Medicine and Science. 5(4), 512-516. Available from: https://doi.org/10.1002/vms3.189.
185 Department of Health & Social Care (2021) Policy paper: G7 Health Ministers' Meeting, communique, Oxford, 4 June, 2021. Available from: https://www.gov.uk/government/publications/g7-health-ministers-meeting-june-2021-communique/g7-health-ministers-meeting-communique-oxford-4-june-2021#antimicrobial-resistance
186 Department of Health & Social Care (2021) Policy paper: G7 Health Ministers' Meeting, com-

munique, Oxford, 4 June, 2021. Available from: https://www.gov.uk/government/publications/g7-health-ministers-meeting-june-2021-communique/g7-health-ministers-meeting-communique-oxford-4-june-2021#antimicrobial-resistance
187 Van Boeckel, T., et al. (2015) Global trends in antimicrobial use in food animals. Proceedings of the National Academy of Sciences. 112(18), 5649-5654. Available from: https://doi.org/10.1073/pnas.1503141112
188 Wallinga, D. (2020) Don't ignore another disease threat. Nature. Available from: https://www.nature.com/articles/d41586-020-02891-4
189 Tang, K.L., et al. (2017) Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. The Lancet: Planetary Health. 1(8), E316-E327. Available from: https://doi.org/10.1016/S2542-5196(17)30141-9
190 The Bureau of Investigative Journalism (2018) Antibiotics in agriculture: the blurred line between growth promotion and disease prevention. Accessed 15 March 2021. Available from: https://www.thebureauinvestigates.com/stories/2018-09-19/growth-promotion-or-disease-prevention-the-loophole-in-us-antibiotic-regulations
191 Carrique-Mas, J., et al. (2013) Antimicrobials usage in chicken production in the Mekong Delta of Vietnam. Zoonoses and Public Health. 62(1), 70-78. Available from: https://doi.org/10.1111/zph.12165
192 Schoenmakers, K. (2020) How China is getting its farmers to kick their antibiotics habit. Nature. 586, S60-S62. Available from: https://doi.org/10.1038/d41586-020-02889-y
193 Carrique-Mas, J., et al. (2013) Antimicrobials usage in chicken production in the Mekong Delta of Vietnam. Zoonoses and Public Health. 62(1), 70-78. Available from: https://doi.org/10.1111/zph.12165
194 Desta, A.H. (2015) Veterinary Drugs Handling, Management and Supply Chain Assessment in Afar Pastoral Region of North East Ethiopia. American Journal of Bioscience and Bioengineering. 3(6), 142-148. Available from: https://doi.org/10.11648/j.bio.20150306.11
195 Zydus AHL. Poultry: non-biologicals. Accessed 15 July 2021. Available from: https://zydusahl.com/domestic/non-biologicals/
196 Orion (2020) Orion Group Sustainability Report 2019. Available from: https://www.orion.fi/globalassets/documents/orion-group/sustainability/orion_sustainability-report_2019.pdf
197 The Bureau of Investigative Journalism (2018) World's biggest animal drugs company sells antibiotics to fatten livestock in India despite superbug risk. Available from: https://www.thebureauinvestigates.com/stories/2018-10-12/worlds-biggest-animal-drugs-company-sells-anti-biotics-to-fatten-livestock-in-india-despite-superbug-risk
198 The Irish Times (1998) EU bans four antibiotic products in animal feed. Accessed 12 February 2021. Available from: https://www.irishtimes.com/news/eu-bans-four-antibiotic-products-in-animal-feed-1.225522
199 The Bureau of Investigative Journalism (2018) World's biggest animal drugs company sells antibiotics to fatten livestock in India despite superbug risk. Available from: https://www.thebureauinvestigates.com/stories/2018-10-12/worlds-biggest-animal-drugs-company-sells-antibiotics-to-fatten-livestock-in-india-despite-superbug-risk
200 Zoetis Ecuador. Linco-Spectin Premix. Available from: https://www.zoetis.com.ec/products/porcinos/linco-spectin.aspx [Accessed 15 July 2021]
201 Zoetis Columbia. Linco-Spectin Premix. Available from: https://www.zoetis.com.co/products/porcicultura/premezclas/linco-spectin-880.aspx [Accessed 15 July 2021]
202 Meat Institute (2016) One Health, One Purpose: Elanco's Antibiotic Stewardship Progress Report. Available from: https://www.meatinstitute.org/index.php?ht=a/GetDocumentAction/i/126628
203 WHO (2017) WHO Guidelines on the use of medically important antimicrobials in food-producing animals. Geneva: World Health Organisation. Available from: https://apps.who.int/iris/bitstream/handle/10665/258970/9789241550130-eng.pdf
204 The New York Times (2019) Warning of 'Pig Zero': One Drugmaker's Push to Sell More Antibiotics. Available from: https://www.nytimes.com/2019/06/07/health/drug-companies-antibiotics-resistance.html
205 Elanco (2021) 2020 Annual Report. Available from: https://s1.q4cdn.com/466533431/files/doc_financials/2020/ar/2020-Annual-Report_Elanco_vf-00.pdf
206 Lo, C. (2019) Herd health: agriculture's role in the global AMR crisis. Pharmaceutical Technology. Available from: https://www.pharmaceutical-technology.com/features/animal-antibiotics/
207 Elanco. Denagard®(tiamulin hydrogen fumarate). Available from: https://www.elanco.us/products-services/swine/denagard#attachments-labels [Accessed 15th July 2021]
208 QWINC. Pig Zero. Available from: http://digitaledition.qwinc.com/publication/?m=40916&i=526473&p=1 [Accessed 15th July 2021]1
209 Phibro (2020) Q4 2020 Earnings Call. Available from: https://s23.q4cdn.com/951333210/files/doc_financials/2020/q4/Phibro-Animal-Health-Corp-Q4-2020-Transcript-08-27-20.pdf
210 Schoenmakers, K. (2020) How China is getting its farmers to kick their antibiotics habit. Nature. 586, S60-S62. Available from: https://doi.org/10.1038/d41586-020-02889-y
211 Desta, A. H. (2015) Veterinary Drugs Handling, Management and Supply Chain Assessment in Afar Pastoral Region of North East Ethiopia. American Journal of Bioscience and Bioengineering. 3(6). 142-148. Available from: https://doi.org/10.11648/j.bio.20150306.11
212 Schoenmakers, K. (2020) How China is getting its farmers to kick their antibiotics habit. Nature. 586, S60-S62. Available from: https://doi.org/10.1038/d41586-020-02889-y
213 European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA) and European Medicines Agency (EMA) (2021) Third joint inter-agency report on integrated analysis of consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals in the EU/EEA, JIACRA III. 2016–2018. Stockholm, Parma, Amsterdam. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/JIACRA-III-Antimicrobial-Consumption-and-Resistance-in-Bacteria-from-Humans-and-Animals.pdf
214 EUR-Lex (2019) 'Council Directive 2019/4/EC on the manufacture, placing on the market and use of medicated feed', amending Regulation (EC) No 183/2005 of the European Parliament and of the Council and repealing Council Directive 90/167/EEC (2019) Official Journal L4, p. 1-23. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32019R0004
215 European Parliament (2018) MEPs back plans to halt spread of drug resistance from animals to humans. Available from: https://www.europarl.europa.eu/news/en/press-room/20181018IPR16526/meps-back-plans-to-halt-spread-of-drug-resistance-from-animals-to-humans
216 The Bureau of Investigative Journalism (2018) Antibiotic use plummets on US farms after ban on using drugs to make livestock grow faster. Available from: https://www.thebureauinvestigates.com/stories/2018-12-19/antibiotic-use-falls-on-us-farms-after-ban-on-using-drugs-to-make-livestock-grow-faster
217 Levy, S. (2014) Reduced antibiotic use in livestock: how Denmark tackled resistance. Environmental health perspectives. 122(6) 160–165. Available from: https://doi.org/10.1289/ehp.122-A160
218 The Guardian (2021) UK pig farms doubled their use of antibiotics vital for humans. Available from: https://www.theguardian.com/environment/2021/jun/17/uk-pig-farms-doubled-their-use-of-antibiotics-vital-for-humans
219 The Guardian (2021) UK pig farms doubled their use of antibiotics vital for humans. Available from: https://www.theguardian.com/environment/2021/jun/17/uk-pig-farms-doubled-their-use-of-antibiotics-vital-for-humans
220 The Guardian (2021) UK pig farms doubled their use of antibiotics vital for humans. Available from: https://www.theguardian.com/environment/2021/jun/17/uk-pig-farms-doubled-their-use-of-antibiotics-vital-for-humans
221 Phibro (2020) Q4 2020 Earnings Call. Available from: https://s23.q4cdn.com/951333210/files/doc_financials/2020/q4/Phibro-Animal-Health-Corp-Q4-2020-Transcript-08-27-20.pdf
222 Phiphar Healthcare Ltd. (2020) The Announcement No. 194 of the Ministry of Agriculture and Rural Affairs of The People's Republic of China. Available from: https://www.phiphar.com/the-announcement-no-194-of-the-ministry-of-agriculture-and-rural-affairs-of-the-peoples-republic-of-china/
223 Virbac (2020) Annual Report 2019. Available from: https://corporate.virbac.com/files/live/sites/virbac-corporate/files/contributed/ra2019/Annual_report_2019.pdf
224 Consumer Reports (2019) Chain Reactive V: How Top Restaurants Rate on Reducing Antibiotic Use in Their Beef Supplies. Available from: https://advocacy.consumerreports.org/wp-content/uploads/2019/10/ChainReaction5beefReportEmbargoed_12sm.pdf
225 Consumer Reports (2019) Chain Reactive V: How Top Restaurants Rate on Reducing Antibiotic Use in Their Beef Supplies. Available from: https://advocacy.consumerreports.org/wp-content/uploads/2019/10/ChainReaction5beefReportEmbargoed_12sm.pdf
226 Consumer Reports (2018) Natural and Antibiotics Labels Survey. Available from: https://advocacy.consumerreports.org/wp-content/uploads/2018/10/2018-Natural-and-Antibiotics-Labels-Survey-Public-Report-1.pdf
227 Euromonitor International (2020) Going Plant-Based: The Rise of Vegan and Vegetarian Food. Available from: https://go.euromonitor.com/rs/805-KOK-719/images/Rise_Vegan_Vegetarian_Food.pdf
228 Euromonitor International (2020) Going Plant-Based: The Rise of Vegan and Vegetarian Food. Available from: https://go.euromonitor.com/rs/805-KOK-719/images/Rise_Vegan_Vegetarian_Food.pdf
229 Food Navigator (2020) Concern over 'next pandemic' spotlights antibiotic use in meat: 'Testing will help restore trust'. Available from: https://www.foodnavigator.com/Article/2020/07/29/Concern-over-next-pandemic-spotlights-antibiotic-use-in-meat-Testing-will-help-restore-trust
230 Good Food Institute (2021) State of the Industry Report: Plant-Based Meat, Eggs, and Dairy. Available from: https://gfi.org/wp-content/uploads/2021/05/COR-SOTIR-Plant-based-meat-eggs-and-dairy-2021-0504-1.pdf
231 Good Food Institute (2019) U.S. State of the Industry Report: Plant-Based Meat, Eggs, and Dairy. Available from: https://gfi.org/wp-content/uploads/2021/01/INN-PBMED-SOTIR-2020-0507.pdf
232 European Commission (2021) Europe's plant-based food industry shows record-level growth. Available from: https://cordis.europa.eu/article/id/429495-europe-s-plant-based-food-industry-shows-record-level-growth
233 The Grocer (2020) Why the future is still plant-based. Available from: https://www.thegrocer.co.uk/promotional-features/why-the-future-is-still-plant-based/650059.article
234 Food Frontier (2021) 2020 State of the Industry: Australia's Plant-Based Meat Sector. Available from: https://www.foodfrontier.org/wp-content/uploads/dlm_uploads/2021/03/Food-Frontier-2020-State-of-the-Industry-2.pdf#gf_2
235 Bloomberg (2021) Beyond Burgers: China's Plant-Based Protein Market Maturing Fast. Available from: https://www.bloomberg.com/news/articles/2021-04-08/beyond-burgers-china-s-plant-based-protein-market-maturing-fast
236 Reuters (2021) Chinese firms bet on plant-based meat as coronavirus fuels healthy eating trend. Available from: https://www.reuters.com/article/us-health-coronavirus-china-plant-based-idUSKBN2660EA
237 The Guardian (2021) China's appetite for meat fades as vegan revolution takes hold. Available from: https://www.theguardian.com/world/2021/mar/09/chinas-appetite-for-meat-fades-as-vegan-revolution-takes-hold
238 Investor Action on Antimicrobial Resistance. Available from: https://amrinvestoraction.org/ [Accessed 15 July 2021]
239 McDonald's (2015) McDonald's Global Vision for Antimicrobial Stewardship in Food. Available from: https://stage-corporate.mcdonalds.com/content/dam/gwscorp/scale-for-good/McDonalds-Global-Vision-for-Antimicrobial-Stewardship-in-Food.pdf
240 Bloomberg (2021) McDonald's quietly rolls out McPlant burger in test markets. Available from: https://www.bloomberg.com/news/articles/2021-02-01/mcdonald-s-quietly-rolls-out-mcplant-burger-in-test-markets
241 Alliance to Save Our Antibiotics (2020) Supermarket Antibiotics Policies Assessment 2020 Report. Available from: https://www.saveourantibiotics.org/media/1826/supermarket-antibiotics-policies-assessment-2020-report.pdf
242 Compassion in World Farming (2020) Waitrose tops latest report on antibiotics. Available from: https://www.compassioninfoodbusiness.com/our-news/2020/01/waitrose-tops-latest-report-on-antibiotics
243 Food Navigator (2020) UK urged to match ban on meat treated with antibiotics. Available from: https://www.foodnavigator.com/Article/2020/12/03/UK-urged-to-match-EU-ban-on-meat-treated-with-antibiotics
244 Alliance to Save Our Antibiotics (2020) Supermarket Antibiotics Policies Assessment 2020 Report. Available from: https://www.saveourantibiotics.org/media/1826/supermarket-antibiotics-policies-assessment-2020-report.pdf
245 NRDC (2020) Livestock Sales of Antibiotics Important to Human Medicine Continue to Rise; Urgent Action is Needed to Address this Public Health Threat. Available from: https://www.nrdc.org/media/2020/201215-11
246 US FDA (2019) Summary Report on Antimicrobials sold or distributed for use in food-producing animals. Available from: https://www.fda.gov/media/144427/download
247 Gould, J. M. (2008) An Overview of Patent Law as Applied to the Field of Veterinary Medicine. AAPS, 10(1) 1-8. Available from: ncbi.nlm.nih.gov/pmc/articles/PMC2751450/
248 The Pew Charitable Trusts (2017) Alternatives to Antibiotics in Animal Agriculture. Available from: https://www.pewtrusts.org/-/media/assets/2017/07/alternatives_to_antibiotics_in_animal_agriculture.pdf
249 The Pew Charitable Trusts (2017) Alternatives to Antibiotics in Animal Agriculture. Available from: https://www.pewtrusts.org/-/media/assets/2017/07/alternatives_to_antibiotics_in_animal_agriculture.pdf
250 Tridge. Global Export of Pork. Available from: https://www.tridge.com/intelligences/fresh-pork-meat/export [Accessed: 10 July]
251 Levy, S. (2014) Reduced Antibiotic Use in Livestock: How Denmark tackled resistance. Environmental health perspectives. 122(6). A160-A165. Available from: doi: 10.1289/ehp.122-A160

252 The Pew Charitable Trusts (2010) Avoiding Antibiotic Resistance: Denmark's Ban on Growth Promoting Antibiotics in Food Animals. Available from: https://www.pewtrusts.org/-/media/legacy/uploadedfiles/phg/content_level_pages/issue_briefs/denmarkexperiencepdf.pdf.

253 The Pew Charitable Trusts (2010) Avoiding Antibiotic Resistance: Denmark's Ban on Growth Promoting Antibiotics in Food Animals. Available from: https://www.pewtrusts.org/-/media/legacy/uploadedfiles/phg/content_level_pages/issue_briefs/denmarkexperiencepdf.pdf.

254 The Pew Charitable Trusts (2010) Avoiding Antibiotic Resistance: Denmark's Ban on Growth Promoting Antibiotics in Food Animals. Available from: https://www.pewtrusts.org/-/media/legacy/uploadedfiles/phg/content_level_pages/issue_briefs/denmarkexperiencepdf.pdf

255 Health for Animals (2019) Roadmap to Reducing the Need for Antibiotics. Available from: https://healthforanimals.org/downloads/library/roadmap%20to%20reducing%20the%20need%20for%20antibiotics.pdf

256 Chan, K. et al. (2020) Diagnostics and the challenge of antimicrobial resistance: A survey of UK livestock veterinarians' perceptions and practices. Veterinary Record. 187(12). Available from: https://bvajournals.onlinelibrary.wiley.com/doi/abs/10.1136/vr.105822.

257 Chan, K. et al. (2020) Diagnostics and the challenge of antimicrobial resistance: A survey of UK livestock veterinarians' perceptions and practices. Veterinary Record. 187(12). Available from: https://bvajournals.onlinelibrary.wiley.com/doi/abs/10.1136/vr.105822.

258 The Pew Charitable Trusts (2017) Alternatives to Antibiotics in Animal Agriculture. Available from: https://www.pewtrusts.org/-/media/assets/2017/07/alternatives_to_antibiotics_in_animal_agriculture.pdf

259 Science (2016) China tackles antimicrobial resistance. Available from: https://www.sciencemag.org/news/2016/08/china-tackles-antimicrobial-resistance

260 Zoetis (2020) 2019 Annual Report. Available from: https://s1.q4cdn.com/446597350/files/doc_financials/2020/ar/Zoetis_2019_Annual_Report.pdf

261 Buller, H. et al. (2020) Veterinary Diagnostic Practice and the Use of Rapid Tests in Antimicrobial Stewardship on UK Livestock Farms. Front. Vet. Sci. 7:569545. Available from: doi: 10.3389/fvets.2020.569545

262 The Pew Charitable Trusts (2017) Alternatives to Antibiotics in Animal Agriculture. Available from: https://www.pewtrusts.org/-/media/assets/2017/07/alternatives_to_antibiotics_in_animal_agriculture.pdf

263 The Bureau of Investigative Journalism (2018) Antibiotics in agriculture: the blurred line between growth promotion and disease prevention. Accessed 15 March 2021. Available from: https://www.thebureauinvestigates.com/stories/2018-09-19/growth-promotion-or-disease-prevention-the-loophole-in-us-antibiotic-regulations

264 Kemin. Antibiotic reduction is not a choice anymore. Accessed 15 July 2021. Available from: https://www.kemin.com/eu/en/markets/animal/health/antibiotic-reduction

265 NOAH (2017) Vaccination for animal health: an overview. Available from: https://www.noah.co.uk/briefingdocument/vaccination-animal-health-overview/

266 NOAH (2017) Vaccination for animal health: an overview. Available from: https://www.noah.co.uk/briefingdocument/vaccination-animal-health-overview/

267 The Pew Charitable Trusts (2017) Alternatives to Antibiotics in Animal Agriculture. Available from: https://www.pewtrusts.org/-/media/assets/2017/07/alternatives_to_antibiotics_in_animal_agriculture.pdf

268 HealthforAnimals (2019) Roadmap to Reducing the Need for Antibiotics. Available from: https://healthforanimals.org/downloads/library/roadmap%20to%20reducing%20the%20need%20for%20antibiotics.pdf

269 Thaker, M. and Bilkei, G. (2006) Comparison of the effects of oral vaccination and different dietary antibiotic prophylactic treatment against Lawsonia intracellularis associated losses in a fattening pig production unit with high prevalence of porcine proliferative enteropathy (PPE). Tierarztl Umsch. 61(7) 372–6. Available from: https://docest.com/report-from-the-field.

270 HealthforAnimals (2019) Roadmap to Reducing the Need for Antibiotics. Available from: https://healthforanimals.org/downloads/library/roadmap%20to%20reducing%20the%20need%20for%20antibiotics.pdf

271 HealthforAnimals (2019) Roadmap to Reducing the Need for Antibiotics. Available from: https://healthforanimals.org/downloads/library/roadmap%20to%20reducing%20the%20need%20for%20antibiotics.pdf

272 Merck (2021) Addressing a Global Public Health Threat: Antimicrobial Resistance. Available from: https://www.merck.com/wp-content/uploads/sites/5/2020/08/Global-Antimicrobial-Resistance-Action-Plan.pdf

273 HealthforAnimals (2019) Roadmap to Reducing the Need for Antibiotics. Available from: https://healthforanimals.org/downloads/library/roadmap%20to%20reducing%20the%20need%20for%20antibiotics.pdf

274 MSD Animal Health. Time to Vaccinate. Available from: https://www.timetovaccinate.com/ [Accessed 15th July 2021]

275 HealthforAnimals (2019) Roadmap to Reducing the Need for Antibiotics. Available from: https://healthforanimals.org/downloads/library/roadmap%20to%20reducing%20the%20need%20for%20antibiotics.pdf

276 The Pew Charitable Trusts (2017) Alternatives to Antibiotics in Animal Agriculture. Available from: https://www.pewtrusts.org/-/media/assets/2017/07/alternatives_to_antibiotics_in_animal_agriculture.pdf

277 The Pew Charitable Trusts (2017) Alternatives to Antibiotics in Animal Agriculture. Available from: https://www.pewtrusts.org/-/media/assets/2017/07/alternatives_to_antibiotics_in_animal_agriculture.pdf

278 The Pew Charitable Trusts (2017) Alternatives to Antibiotics in Animal Agriculture. Available from: https://www.pewtrusts.org/-/media/assets/2017/07/alternatives_to_antibiotics_in_animal_agriculture.pdf

279 Magni-Phi® Info Sheet. Available from: https://www.pahc.com/wp-content/uploads/IPPE2020/MP350219GLB-2-Sided-Info-Sheet_no-info-graphics.pdf [Accessed 15 July 2021]

280 Correlink™. Available from: https://www.elanco.com.au/products-services/poultry/products/poultry-correlink [Accessed 15th July 2021]

281 The Pew Charitable Trusts (2017) Alternatives to Antibiotics in Animal Agriculture. Available from: https://www.pewtrusts.org/-/media/assets/2017/07/alternatives_to_antibiotics_in_animal_agriculture.pdf

282 Diana, A. et al. (2020) Effect of welfare standards and biosecurity practices on antimicrobial use in beef cattle. Scientific Reports. 10, 20939. Available from: https://www.nature.com/articles/s41598-020-77838-w

283 OIE (2019) Terrestrial Animal Health Code. Available from: https://www.oie.int/en/what-we-do/standards/codes-and-manuals/terrestrial-code-online-access/?id=169&L=1&htmfile=titre_1.7.htm

284 Diana, A. et al. (2020) Effect of welfare standards and biosecurity practices on antimicrobial use in beef cattle. Scientific Reports. 10. Available from: https://www.nature.com/articles/s41598-020-77838-w

285 Stokstad, M. et al. (2020) Using Biosecurity Measures to Combat Respiratory Disease in Cattle: The Norwegian Control Program for Bovine Respiratory Syncytial Virus and Bovine Coronavirus. Frontiers in Veterinary Science. 167(7). Available from: https://www.frontiersin.org/articles/10.3389/fvets.2020.00167/full

286 UK Government (2012) Guidance: Disease prevenetion for livestock and poultry keepers. Available from: https://www.gov.uk/guidance/disease-prevention-for-livestock-farmers

287 Gelaude, P., et al. (2014) Biocheck.UGent: A quantitative tool to measure biosecurity at broiler farms and the relationship with technical performances and antimicrobial use. Poultry Science. 93(11) 2740-2751. Available from: https://www.sciencedirect.com/science/article/pii/S0032579119385244.

288 Collineau, L., et al. (2017) Profile of pig farms combining high performance and low antimicrobial usage within four European countries. Veterinary Record. 181(24) 657-657. Available from: https://doi.org/10.1136/vr.103988.

289 The Pew Charitable Trusts (2017) Alternatives to Antibiotics in Animal Agriculture. Available from: https://www.pewtrusts.org/-/media/assets/2017/07/alternatives_to_antibiotics_in_animal_agriculture.pdf

290 HealthforAnimals (2019) Roadmap to Reducing the Need for Antibiotics. Available from: https://healthforanimals.org/downloads/library/roadmap%20to%20reducing%20the%20need%20for%20antibiotics.pdf

291 Faunalytics (2020) Antimicrobial Resistance Trends In Low And Middle Income Countries. Available from: https://faunalytics.org/antimicrobial-resistance-trends-in-low-and-middle-income-countries/

292 Adekanye, U., et al. (2020Knowledge, attitudes and practices of veterinarians towards antimicrobial resistance and stewardship in Nigeria. Antibiotics. 9(8). Available from: https://www.mdpi.com/2079-6382/9/8/453

293 Van Boeckel, T. (2019) Global trends in antimicrobial resistance in animals in low- and middle-income countries. Science. 365 (6459). Available from: https://science.sciencemag.org/content/365/6459/eaaw1944

294 Sieiro, C. (2020) A Hundred Years of Bacteriophages: Can Phages Replace Antibiotics in Agriculture and Aquaculture? Antibiotics. 9 (8) Available from: https://pubmed.ncbi.nlm.nih.gov/32784768/.

295 Sieiro, C. (2020) A Hundred Years of Bacteriophages: Can Phages Replace Antibiotics in Agriculture and Aquaculture? Antibiotics. 9 (8) Available from: https://pubmed.ncbi.nlm.nih.gov/32784768/

296 The Fish Site (2020) Study backs the use of bacteriophages in shrimp aquaculture, 7 October. Available from: https://thefishsite.com/articles/study-backs-the-use-of-bacteriophages-in-shrimp-aquaculture

297 The Pew Charitable Trusts (2017) Alternatives to Antibiotics in Animal Agriculture. Available from: https://www.pewtrusts.org/-/media/assets/2017/07/alternatives_to_antibiotics_in_animal_agriculture.pdf

298 HealthforAnimals (2019) Roadmap to Reducing the Need for Antibiotics. Available from: https://healthforanimals.org/downloads/library/roadmap%20to%20reducing%20the%20need%20for%20antibiotics.pdf

299 Zoetis (2020) 2019 Annual Report. Available from: https://s1.q4cdn.com/446597350/files/doc_financials/2020/ar/Zoetis_2019_Annual_Report.pdf

300 The Pew Charitable Trusts (2017) Alternatives to Antibiotics in Animal Agriculture. Available from: https://www.pewtrusts.org/-/media/assets/2017/07/alternatives_to_antibiotics_in_animal_agriculture.pdf

301 The Pew Charitable Trusts (2017) Alternatives to Antibiotics in Animal Agriculture. Available from: https://www.pewtrusts.org/-/media/assets/2017/07/alternatives_to_antibiotics_in_animal_agriculture.pdf

302 Dechra (2021) 2020 Annual Report. Available from: https://dechra.annualreport2020.com/media/281444/dechra-ar2020.pdf

303 Zoetis (2020) 2019 Annual Report. Available from: https://s1.q4cdn.com/446597350/files/doc_financials/2020/ar/Zoetis-2020-Annual-Report.pdf

304 Virbac (2021) 2020 Annual Report: Shaping the future of animal health. Available from: https://corporate.virbac.com/files/live/sites/virbac-corporate/files/contributed/ra2020/Annual_report_2020.pdf

305 Merck & Co. (2021) 2020 Annual Report. Available from: https://d18rn0p25nwr6d.cloudfront.net/CIK-0000064978/4df43d8f-8b85-45da-92ef-7ad82f343c3b.pdf

306 Merck & Co. (2020) Access to health. Available from: https://www.msdresponsibility.com/access-to-health/animal-health/

307 Merck & Co. (2019) MSD Completes Acquisition of Antelliq Corporation to Become Leader in Emerging Digital Technology for Livestock and Companion Animals. Available from: https://www.msd-animal-health.co.uk/2019/04/01/msd-completes-acquisition-of-antelliq-corporation-to-become-leader-in-emerging-digital-technology-for-livestock-and-companion-animals/

308 Merck & Co. (2019) MSD Animal Health completes acquisition of Vaki to further broaden its leadership position in aquaculture to advance fish health and welfare. Available from: https://www.msd-animal-health.com/2019/12/17/msd-animal-health-completes-acquisition-of-vaki-to-further-broaden-its-leadership-position-in-aquaculture-to-advance-fish-health-and-welfare/

309 Merck & Co. (2021) MSD Animal Health compeltes acquisition of poultry sense limited. Available from: https://www.msd-animal-health.co.uk/2021/02/26/msd-animal-health-completes-acquisition-of-poultry-sense-limited/

310 Merck & Co. (2020) Global Antimicrobial Resistance Action Plan. Available from: https://msd20-assets.s3.amazonaws.com/wp-content/uploads/2020/09/15204428/MSD_GAAP_Combined_Digital_One-Pagers_9-15-20.pdf

311 Dechra Pharmaceuticals (2020) 2020 Annual Report: Improving Animal Health and Welfare. Available from: https://dechra.annualreport2020.com/media/281444/dechra-ar2020.pdf

312 Dechra Pharmaceuticals (2020) 2020 Annual Report: Improving Animal Health and Welfare. Available from: https://dechra.annualreport2020.com/media/281444/dechra-ar2020.pdf

313 Virbac (2020) Annual Report 2020. Available from: https://corporate.virbac.com/files/live/sites/virbac-corporate/files/contributed/ra2020/Annual_report_2020.pdf

314 Virbac (2019) Annual Report 2019. Available from: https://corporate.virbac.com/files/live/sites/virbac-corporate/files/contributed/ra2019/Annual_report_2019.pdf

315 Virbac (2019) 2019 Results & Perspectives. Available from: https://corporate.virbac.com/files/live/sites/virbac-corporate/files/contributed/7-Investors/Analysts%20%26%20investors%20presentations/2019/EN/2019_Financials_Strategic_Update_March_2020.pdf

316 Virbac (2019) 2019 Annual Report. Available from: https://corporate.virbac.com/files/live/sites/virbac-corporate/files/contributed/ra2019/Annual_report_2019.pdf

317 Virbac (2020) Annual Report 2020. Available from: https://corporate.virbac.com/files/live/sites/virbac-corporate/files/contributed/ra2020/Annual_report_2020.pdf

318 Zoetis (2021) 2020 Annual Report. Available from: https://s1.q4cdn.com/446597350/files/doc_finan-

cials/2020/ar/Zoetis-2020-Annual-Report.pdf
319 Zoetis (2021) 2020 Annual Report. Available from: https://s1.q4cdn.com/446597350/files/doc_financials/2020/ar/Zoetis-2020-Annual-Report.pdf
320 Zoetis (2021) 2020 Annual Report. Available from: https://s1.q4cdn.com/446597350/files/doc_financials/2020/ar/Zoetis-2020-Annual-Report.pdf
321 HealthforAnimals (2018) Roadmap to reducing the need for antibiotics. Available from: https://healthforanimals.org/downloads/library/roadmap%20to%20reducing%20the%20need%20for%20antibiotics.pdf
322 Vetoquinol (2021) 2020 Universal Registration Document. Available from: https://www.vetoquinol.com/eng/content/2020-universal-registration-document
323 Elanco Animal Health Inc. (2021) Q1 2021 Earnings Call Transcript. Available from: https://www.fool.com/earnings/call-transcripts/2021/05/07/elanco-animal-health-inc-elan-q1-2021-earnings-cal/
324 Dechra Pharmaceuticals (2020) 2020 Annual Report: Improving Animal Health and Welfare. Available from: https://dechra.annualreport2020.com/media/281444/dechra-ar2020.pdf
325 Dechra Pharmaceuticals (2020) 2019 Annual Report: Sustaining Growth Through Expertise. Available from: http://dechra.annualreport2019.com/media/178256/Dechra-Annual-Report-2019.pdf"
326 Virbac (2019) Quarterly financial information. Available from: https://corporate.virbac.com/files/live/sites/virbac-corporate/files/contributed/7-Investors/financial-reports/2019/EN/Virbac_Quarterly%20Financial%20Information_Sept%202019.pdf
327 Elanco (2020) 2019 Annual Report: Building to Lead. Available from: https://s1.q4cdn.com/466533431/files/doc_financials/annual/Elanco_Annual-Report-2019_Letter-and-10k_041020.pdf
328 Phibro (2020) 2019 Form 10-K. Available from: https://d18rn0p25nwr6d.cloudfront.net/CIK-0001069899/d6c560f3-c5ea-4682-8498-a888329aa02a.pdf
329 Vibrac (2021) 2020 Annual Report: Shaping the Future of Animal Health. https://corporate.virbac.com/files/live/sites/virbac-corporate/files/contributed/ra2020/Annual_report_2020.pdf
330 Dechra Pharmaceuticals (2021) 2020 Annual Report: Improving Animal Health and Welfare. Available from: https://dechra.annualreport2020.com/media/281444/dechra-ar2020.pdf
331 Vetoquinol (2021) 2020 Universal Registration Document. Available from: https://www.vetoquinol.com/eng/content/2020-universal-registration-documentf
332 Merck & Co. (2021) 2020 Annual Report. Available from: https://www.annualreports.com/HostedData/AnnualReports/PDF/NYSE_MRK_2020.pdf
333 Zoetis (2021) 2020 Annual Report. Available from: https://s1.q4cdn.com/446597350/files/doc_financials/2020/ar/Zoetis-2020-Annual-Report.pdf
334 Phibro (2020) 2019 Form 10-K. Available from: https://d18rn0p25nwr6d.cloudfront.net/CIK-0001069899/d6c560f3-c5ea-4682-8498-a888329aa02a.pdf
335 Elanco (2021) Q1 2021 Earnings Call Transcript. Available from: https://www.fool.com/earnings/call-transcripts/2021/05/07/elanco-animal-health-inc-elan-q1-2021-earnings-cal/
336 The FAIRR Initiative (2020) An industry infected: Animal agriculture in a post-COVID world. Available from: https://www.fairr.org/article/industry-infected/
337 Financial Post (2020) Chicken farmers to shrink national flock by 12% as coronavirus takes toll on Canada's food supply chain, 16 April. Available from: https://financialpost.com/news/retail-marketing/chicken-farmers-to-shrink-national-flock-by-12-as-coronavirus-takes-toll-on-canadas-food-supply-chain
338 Elanco (2021) 2020 Annual Report: Making Life Better For Animals, Makes Life Better. Available from: https://s1.q4cdn.com/466533431/files/doc_financials/2020/ar/2020-Annual-Report_Elanco_vf-00.pdf
339 Dechra (2020) 2020 Annual Report: Improving Animal Health and Welfare. Available from: https://dechra.annualreport2020.com/media/281444/dechra-ar2020.pdf
340 Phibro (2020) 2019 Form 10-K. Available from: https://d18rn0p25nwr6d.cloudfront.net/CIK-0001069899/d6c560f3-c5ea-4682-8498-a888329aa02a.pdff
341 Zoetis (2021) 2020 Annual Report. Available from: https://s1.q4cdn.com/446597350/files/doc_financials/2020/ar/Zoetis-2020-Annual-Report.pdf
342 Phibro Animal Health Corporation (2020) Form 10-K. Available from: https://d18rn0p25nwr6d.cloudfront.net/CIK-0001069899/d6c560f3-c5ea-4682-8498-a888329aa02a.pdf
343 Food Business News (2021) General Mills to acquire Tyson Foods' pet food business, 14 May. Available from: https://www.foodbusinessnews.net/articles/18616-general-mills-to-acquire-tyson-foods-pet-food-business
344 Pet Food Processing (2021) Pandemic-era pet industry surpasses record-breaking $100 billion in sales, 25 March. Available from: https://www.petfoodprocessing.net/articles/14588-pandemic-era-pet-industry-surpasses-record-breaking-100-billion-in-sales
345 BBC News (2021) Households 'buy 3.2 million pets in lockdown', 12 March. Available from: https://www.bbc.co.uk/news/business-56362987
346 Zoetis (2021) 2020 Annual Report. Available from: https://s1.q4cdn.com/446597350/files/doc_financials/2020/ar/Zoetis-2020-Annual-Report.pdf
347 Virbac (2021) 2020 Annual Report. Available from: https://corporate.virbac.com/files/live/sites/virbac-corporate/files/contributed/ra2020/Annual_report_2020.pdf348 Financial Times (2018) GSK leads drugmakers' fight against superbugs, 23 January. Available from: https://www.ft.com/content/ffa6af22-002f-11e8-9650-9c0ad2d7c5b5
349 Merck & Co. (2021) Addressing a Global Public Health Threat: Antimicrobial Resistance. Available from: https://www.merck.com/wp-content/uploads/sites/5/2020/08/Global-Antimicrobial-Resistance-Action-Plan.pdf
350 Merck & Co. (2020) 2019 Annual Report Form 10-K. Available from: https://annualreport.stocklight.com/NYSE/MRK/20656309.pdf
351 HealthforAnimals (2019) Roadmap to Reducing the Need for Antibiotics. Available from: https://healthforanimals.org/downloads/library/roadmap%20to%20reducing%20the%20need%20for%20antibiotics.pdf
352 Hoard's Dairyman (2018) New antibiotic initiative announced at UN Assembly, and what it means for producers, 27 September. Available from: https://hoards.com/article-24067-new-antibiotic-initiative-announced-at-un-assembly-and-what-it-means-for-producers.html
353 Zoetis (2020) 2019 Annual Report. Available from: https://s1.q4cdn.com/446597350/files/doc_financials/2020/ar/Zoetis_2019_Annual_Report.pdf
354 Elanco (2020) 2019 Annual Report. Available from: https://s1.q4cdn.com/466533431/files/doc_financials/annual/Elanco_Annual-Report-2019_Letter-and-10k_041020.pdf
355 Zoetis (2020) 2019 Annual Report. Available from: https://s1.q4cdn.com/446597350/files/doc_financials/2020/ar/Zoetis_2019_Annual_Report.pdf
356 Zoetis (2020) 2019 Annual Report. Available from: https://s1.q4cdn.com/446597350/files/doc_financials/2020/ar/Zoetis_2019_Annual_Report.pdf
357 Livestock Trend (2020) LabCards: Zoetis Launched Mobile App to ease livestock disease diagnosis, animal sample collection, analysis and profiling for Veterinarians, Animal Health technicians in Nigeria, 1 July. Available from: https://www.livestocktrend.com/2020/07/labcards-zoetis-launched-mobile-app-to.html
358 Zoetis (2020) 2019 Annual Report. Available from: https://s1.q4cdn.com/446597350/files/doc_financials/2020/ar/Zoetis_2019_Annual_Report.pdf
359 Feed Strategy (2018) Elanco Animal Health works to increase food security in East Africa, 17 October. Available from: https://www.feedstrategy.com/africa/elanco-animal-health-works-to-increase-food-security-in-east-africa/]
360 Elanco (2020) 2019 Annual Report. Available from: https://s1.q4cdn.com/466533431/files/doc_financials/annual/Elanco_Annual-Report-2019_Letter-and-10k_041020.pdf
361 Climate Action 100+ (2021) Net-Zero Company Benchmark. Available from : https://www.climateaction100.org/progress/net-zero-company-benchmark/
362 HealthforAnimals (2021) Animal Health, One Health, Nutrition, Livestock, Sustainability, and Growth: Briefing for Food Systems Summit. Available at: https://healthforanimals.org/downloads/library/fss%20briefing%20animal%20health%20all%20languages.pdf
363 IPCC (2014) Climate Change 2014: Mitigation of Climate Change. Contribution of Working Group III to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change [Edenhofer, O., R. Pichs-Madruga, Y. Sokona, E. Farahani, S. Kadner, K. Seyboth, A. Adler, I. Baum, S. Brunner, P. Eickemeier, B. Kriemann, J. Savolainen, S. Schlömer, C. von Stechow, T. Zwickel and J.C. Minx (eds.)]. Cambridge University Press, Cambridge, United Kingdom and New York, NY, USA. Available from: https://www.ipcc.ch/site/assets/uploads/2018/02/ipcc_wg3_ar5_full.pdf
364 Gerber, P.J. et al. (2013) Tackling climate change through livestock – A global assessment of emissions and mitigation opportunities. Food and Agriculture Organization of the United Nations (FAO), Rome. Available from: http://www.fao.org/3/i3437e/i3437e.pdf
365 Elanco (2021) 2020 Annual Report. Available from: https://s1.q4cdn.com/466533431/files/doc_financials/2020/ar/2020-Annual-Report_Elanco_vf-00.pdf
366 WHO (2011) Definition of Active Pharmaceutical Ingredient. Working document QAS/11.426/Rev.1. Available from: https://www.who.int/medicines/areas/quality_safety/quality_assurance/DefinitionAPI-QAS11-426Rev1-08082011.pdf
367 WHO (2020) Fact sheets: Antibiotic resistance. Available from: https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance
368 USFDA (2018) USFDA's Strategy on Antimicrobial Resistance – Questions and Answers. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fdas-strategy-antimicrobial-resistance-questions-and-answers]
369 Mendelson, M., et al. (2017) Antibiotic resistance has a language problem. Nature. 545, 23-25. Available from: https://www.nature.com/articles/545023a
370 International Food Safety Authorities Network (2010) INFOSAN Information Note No. 1/2010 - Biosecurity. Available from: https://www.who.int/foodsafety/fs_management/No_01_Biosecurity_Mar10_en.pdf
371 Johnson, D.E. (2018) Biotherapeutics: Challenges and Opportunities for Predictive Toxicology of Monoclonal Antibodies. International Journal of Molecular Sciences. 19(11): 3685. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6274697/#B1-ijms-19-03685
372 Dorland's Medical Dictionary (2007) Cephalosporin. Elsevier. Available from: https://web.archive.org/web/20090322002521/http://www.mercksource.com/pp/us/cns/cns_hl_dorlands_split.jsp?pg=/ppdocs/us/common/dorlands/dorland/two/000019430.htm
373 WHO (2017) WHO list of Critically Important Antimicrobials for Human Medicine (WHO CIA list). Available from: https://www.who.int/foodsafety/publications/cia2017c.pdff
374 Nation, R.L. and Li, J. (2010) Colistin in the 21st Century. Curr Opin Infect Dis. 22(6), 535–543. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2869076/
375 Natural Resources Conservation Services. Animal Feeding Operations. United States Department of Agriculture. Available from: https://www.nrcs.usda.gov/wps/portal/nrcs/main/national/plantsanimals/livestock/afo/ [Accessed 15 July 2021/
376 WHO (2019) WHO list of Critically Important Antimicrobials (CIA). Available online at: https://www.who.int/foodsafety/areas_work/antimicrobial-resistance/cia/en/
377 The Pew Charitable Trusts (2017) Alternatives to Antibiotics in Animal Agriculture. Available from: https://www.pewtrusts.org/-/media/assets/2017/07/alternatives_to_antibiotics_in_animal_agriculture.pdf.
378 Natural Resources Conservation Services. Animal Feeding Operations. United States Department of Agriculture. Available from: https://www.nrcs.usda.gov/wps/portal/nrcs/main/national/plantsanimals/livestock/afo/ [Accessed 15 July 2021]
379 European Commission (2013) Report from the Commission on the reviews undertaken under Article 30(9) and Article 73 of Directive 2010/75/EU on industrial emissions addressing emissions from intensive livestock rearing and combustion plants. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52013DC0286&from=EN
380 European Commission. Food Safety: Feed additives. Available from: https://ec.europa.eu/food/food/animal-feed/feed-additives_en#:~:text=Feed%20additives%20are%20products%20used,digestibility%20of%20the%20feed%20materials [Accessed 15 July 2021]
381 WHO (2019) WHO list of Critically Important Antimicrobials (CIA). Available online at: https://www.who.int/foodsafety/areas_work/antimicrobial-resistance/cia/en/
382 WHO (2019) WHO list of Critically Important Antimicrobials (CIA). Available from: https://www.who.int/foodsafety/areas_work/antimicrobial-resistance/cia/en/
383 WHO (2013), Critically Important Antimicrobials for Human Medicine, 4th Revision 2013. Available online at: https://apps.who.int/iris/bitstream/handle/10665/251715/9789241511469-eng.pdf?sequence=1
384 CDC. One Health: Basics. Available from: https://www.cdc.gov/onehealth/basics/index.html [Accessed 15 July 2021]
385 WHO. Q&A Detail: One Health. Available from: https://www.who.int/news-room/q-a-detail/one-health [Accessed 15 July 2021]
386 WHO (2019) WHO list of Critically Important Antimicrobials (CIA). Available from: https://www.who.int/foodsafety/areas_work/antimicrobial-resistance/cia/en/
387 NSF. Raised Without Antibiotics Certification. Available from: https://www.nsf.org/testing/food/food-beverage-product-certification/raised-without-anti-biotics-certification#:~:text=The%20RWA%20protocol%20requires%20that,%2C%20fish%2C%20dairy%20and%20eggs. [Accessed 15 July 2021]

CONTACT

Jo Raven
Senior Manager, Research and Engagements at FAIRR
jo.raven@fairr.org

Philippa Thornton
ESG Analyst at FAIRR
philippa.thornton@fairr.org

A special thanks to the following individuals for their contribution to the report:

Kezia St Clere Smithe
Grace Martin
Rhiannon Baldwin

IMPORTANT NOTICE

Established by the Jeremy Coller Foundation, the FAIRR Initiative is a collaborative investor network that raises awareness of the material ESG risks and opportunities caused by intensive animal production. FAIRR helps investors to identify and prioritise these factors through cutting-edge research that investors can then integrate into their investment decision-making and active stewardship processes. FAIRR also runs collaborative investor engagements with global food companies to improve performance on selected ESG issues in intensive animal production.

FAIRR
A COLLER INITIATIVE

$300