Review on Antimicrobial Resistance
Tackling drug-resistant infections globally

ANTIMICROBIALS IN AGRICULTURE AND THE ENVIRONMENT: REDUCING UNNECESSARY USE AND WASTE

THE REVIEW ON ANTIMICROBIAL RESISTANCE

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EXECUTIVE SUMMARY

The precise quantity of antimicrobials used in food production globally is difficult to estimate, but the evidence suggests that it is at least as great as the amount used by humans. Indeed in some parts of the world antimicrobial use is far greater in animals than in humans; in the US, for instance, more than 70 percent of medically important antibiotics are used in animals.

The relative use in agriculture, without better policies, is likely to grow even more due to the rise of economic growth, wealth, and with these, food consumption of the emerging world. Consumption of antimicrobials by animals to produce meat products, in the BRICS countries (the major emerging economies of Brazil, Russia, India, China and South Africa) alone, for example, is set to double between 2010 and 2030.

Just as there is a clear correlation between rising levels of human use of antibiotics and growing resistance, as we showed in our recent paper *Rapid Diagnostics: Stopping Unnecessary Use of Antibiotics,* the same is essentially true in agriculture. Higher use of antibiotics drives increased drug resistance, as bacteria are exposed more often to the antibiotics used to treat them. This is also true for other medicines, such as antifungals.

The risks associated with the high use of antimicrobials are threefold. Firstly, it presents the risk that drug-resistant strains are passed on through direct contact between humans and animals (notably farmers). Secondly, these drug-resistant strains have the potential to be passed onto humans more generally through the food chain, i.e. when consumers prepare or eat the meat itself. Finally, there is a further indirect threat to human health as result of animal excretion. Both resistant bacteria, as well as significant volumes of antibiotics consumed, are then excreted by animals (with most of the active ingredient unmetabolised). This both releases resistant bacteria into the environment as well as causing the environment to be tainted with antibiotics, providing further opportunities for exposure to bacteria and creating additional selective pressure that leads to the development of drug resistance.

As in humans, the proper therapeutic[1] use of antibiotics in animals is essential for treating infection. It offers considerable benefits, both in terms of animal welfare and food production, though excessive and inappropriate use of antibiotics is undoubtedly a problem in many areas.

Much of the use of antibiotics in animals is not therapeutic however. Instead, significant volumes are used either prophylactically amongst healthy animals, to stop the development of an infection within a flock or herd, or simply for growth promotion, to speed up the pace at which animals gain weight. Both uses are particularly prevalent in intensive agriculture, where animals are kept in confined conditions.

Although there is growing evidence to suggest that the use of antibiotics for growth promotion may only provide modest benefits to farmers in high-income countries – typically less than five percent – some argue that the impact of stopping their use for this purpose would be significant, particularly in lower-income settings, and unjustified without clearer evidence of the extent of the threat to human health.

There is no doubt though that prolonged exposure to antibiotics creates ideal conditions for the cultivation of drug resistance; and there is evidence to show that this can increase the localised prevalence of antibiotic-resistant bacteria very significantly. In addition to assessing individual case studies, the Review has undertaken a literature review of 280 published, peer-reviewed research articles that address the issue of antibiotic use in agriculture. The outcomes of this literature review are discussed in more detail in this paper but of 139 academic studies the Review found, only seven (five percent) argued that there was not a link between antibiotic consumption in animals and resistance in humans, while 100 (72 percent) found evidence of a link. This suggests that antibiotic use in animals is a factor in promoting resistance in humans and provides enough justification for policy makers to aim to reduce global use in food production to a more optimal level.

As well as the volume used, the types of antibiotics that are used in food production must also be considered. Some last-resort antibiotics for humans are being used extensively in animals, with no replacements as of yet on the way. This problem was highlighted by a recent Chinese finding of a bacterial gene conferring resistance to colistin, a last-resort antibiotic for treating multidrug-resistant infections caused by Gram-negative bacteria in humans, but which is also used extensively in livestock in some countries, including in Europe. This gene is particularly worrying as it can transfer easily from bacteria to bacteria, meaning it could spread quickly. The study also found this gene in 20 percent of the animals tested in the area and one percent of the people in the area, strongly indicating that the selection of this resistance was due to the use of colistin in animals and that this was capable of transferring to humans. This has brought home the huge threat posed by the use of important human antibiotics in agriculture.

1. In this paper the term 'therapeutic use' is used to describe treating an animal that already has an infection. Use to prevent an infection, is not covered by this term, and is referred to as 'prophylactic use'.

As well as the risks created from humans and animals excreting antimicrobials into the environment, there is particular concern over the way that antimicrobials are manufactured, where pollution during the production phase can exacerbate this problem. During the manufacture of antimicrobials, destined for human or veterinary use, untreated waste products containing high levels of end products or active ingredients may be discharged into water courses. Some experts argue that this process is a particular risk for resistance because the concentrations of antimicrobials found in such scenarios can be many thousands, or even millions, of times higher than at sewage sites, for example. It only takes one occasion, in one setting, for resistance to emerge, and then we can only try to limit its spread. Therefore reducing 'hotspots' where the risk is greatest is very important.

This paper proposes three broad interventions to take bold global action to substantially reduce the use of antibiotics in agriculture and the quantities being dispersed into the environment:

1. A global target to reduce antibiotic use in food production to an agreed level per kilogram of livestock and fish, along with restrictions on the use of antibiotics important for humans.

a. We need to reduce global levels of antibiotic use in agriculture, to an agreed limit for each country, but it should be for individual countries to decide how best to achieve this goal - a global target would make this possible. We believe an ambitious but achievable target for reducing antibiotic use in agriculture is needed, to reduce use over the next 10 years. There are countries that have advanced farming systems with very low levels of antibiotic use, particularly in Scandinavia. Denmark has combined low use with being one of the largest exporters of pork in the world. Reducing levels of use to that of Denmark for example, an average of less than 50 milligram (mg) of antibiotics used a year per kilogram (kg) of livestock in the country, may be a good starting point for such a target. We think this would be feasible without harming the health of animals or the long-term productivity of farmers. This is based on our understanding of academic literature and case studies. The exact level of a target would, however, need to be discussed and tested by experts. Low and middle-income countries may need more time to achieve such a target, while many of these countries may already be below the threshold.

b. As well as reducing the quantity of use, the types of antibiotics used are also important. Currently many antibiotics that are important for humans are used in animals. We believe that countries need to come together and agree to restrict, or even ban, the use of antibiotics in animals that are important for humans.

2. The rapid development of minimum standards to reduce antimicrobial manufacturing waste released into the environment. This needs to be viewed as a straightforward issue of industrial pollution, and it is the responsibility of all actors in the supply chain to ensure that industrial waste is treated properly as a matter of good manufacturing practice. The risk of drug resistance must urgently become a key environmental consideration for all pharmaceutical companies, healthcare buyers and regulatory agencies everywhere. Failing to do this does most harm to the health of populations living near the manufacturing sites who are exposed to polluted water, and are in a way are paying the price of cheap antibiotics for the rest of the world. But in the long-term, we know that resistance spreads and these strains will in time likely become a global problem.

3. Improved surveillance to monitor these problems, and progress against global targets. There remain too many knowledge gaps regarding patterns of antimicrobial use in agriculture and release during manufacturing, and what this means for resistance and, ultimately, human health. This needs to change if meaningful progress is to be made.

As with the human health aspects of AMR, these are complex issues that require concerted, coordinated action at an international level. Drug-resistant infections know no borders and do not respect barriers between industry, regulators and buyers, or between animals, humans and their wider environment. There are encouraging signs of some governments adopting a broad 'one health' approach to tackling the issue of resistance, but it is an approach that needs to be replicated by others.

We believe that success can only be achieved by considering a full range of interventions:

- In agriculture, these should take into account the key drivers of the real or perceived need for antibiotics, whether for use as therapy, prophylaxis (prevention), or growth promotion. Interventions will no doubt include improvements in infection control, better animal husbandry practices, greater use of vaccines and the adoption of diagnostic devices to ensure better-targeted and more appropriate veterinary prescribing. In manufacturing, these should take into account the potential to prevent waste as well as to treat it.

- This paper, though not prescriptive as to how countries should act, will focus primarily on the roles that fiscal measures (that is, taxation and subsidies) and regulation could play in reducing the risks associated with agricultural use of antimicrobials and environmental contamination.

INTRODUCTION

In this latest paper published by the independent Review on Antimicrobial Resistance (AMR), we consider the impact of antibiotic use in animals, particularly the agricultural sector, as well as the release of antimicrobials and resistant bacteria into the environment from animal use, human use and manufacturing plants.

2015 has been a good year for positive policy statements about the misuse of antimicrobials in agriculture from the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE).

This paper sets out how the world could take action, to build on such positive statements, reducing unnecessary use of antimicrobials in agriculture and their release into the environment. First, it shows the extent of global use of antibiotics and antifungals in food production, and the ways in which antibiotics in animal and human waste pass into the wider environment. Second, it examines the risk this antimicrobial use and waste poses to human health. Third, it discusses the economic benefits of using antibiotics in agriculture, and the costs of changing practices. Fourth, it looks at the problems in the manufacturing process of antimicrobials, and how waste products are dealt with. Fifth, it proposes policy interventions to reduce antimicrobial use in agriculture and improve manufacturing practices for antimicrobials. Finally, it examines options that could be pursued to implement these policies.

The work of the Review

The Review on AMR was commissioned by the British Prime Minister, and is hosted by the Wellcome Trust. It is tasked with recommending, by the summer of 2016, a comprehensive package of actions to tackle AMR globally. In the meantime, we are publishing a series of papers looking at individual aspects of the wider AMR problem[2].

Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations was published in December 2014, and set out the findings of economic modelling work to quantify the global human and economic burden of an unchecked rise in drug resistance between now and 2050. We estimated that unless effective action is taken, drug-resistant strains of tuberculosis (TB), malaria, HIV and certain bacterial infections could by 2050 be claiming 10 million lives each year. This would come at an economic cost of 100 trillion USD wiped off global GDP over the next 35 years.

Our second paper, T*ackling a Global Health Crisis: Initial Steps* was published in February 2015, showing the extent to which research on tackling AMR has been neglected over several decades and setting out five areas for immediate action to slow the rise of drug resistance. This included the establishment of a 2 billion USD Global Innovation Fund for AMR; steps to reverse the 'brain drain' that is undermining research efforts in microbiology and other relevant fields of research; and a greater focus on research into combination therapies, and other means of making existing antibiotics last longer.

In May 2015, *Securing New Drugs for Future Generations* examined the problems of antibiotic development and outlined our initial proposals for bold action by governments around the world to stimulate and incentivise the development of much-needed new antibiotics. This identified key gaps in the antibiotics pipeline, and called for a global system of antibiotic market entry rewards, offering lump-sum payments to successful developers of antibiotics that meet a defined clinical need. This package of action – designed to support a pipeline of 15 new antibiotics over a decade – was costed at between 16 billion and 37 billion USD over ten years.

In October 2015, *Rapid Diagnostics: Stopping the Unnecessary Use of Antibiotics* examined the extent of unnecessary use of antibiotics and how the world can combat this with rapid diagnostics. We proposed three interventions to encourage innovation and uptake of diagnostics for bacterial infections: firstly, Diagnostic Market Stimulus pots to provide payments for successful products that are purchased. Secondly, access for diagnostic developers to bid for funds from a Global Innovation Fund, and thirdly, support to build the economic evidence for rapid diagnostics.

After publishing this paper on antibiotic use in agriculture and the environment, we will publish further papers between now and the spring of 2016, exploring alternatives to conventional antibiotics, and the role of sanitation and infection prevention and control measures in reducing the global burden of drug resistance.

2. All the publications of the Review on AMR are available on the website: http://amr-review.org/

1.

THE SCALE OF ANTIMICROBIAL USE IN GLOBAL FOOD PRODUCTION IS VERY LARGE

For the purposes of considering antimicrobial use in food production, we have looked at the use of antibiotics and antifungals in the following areas: livestock production (beef, swine and poultry); fish farming; and crop growing. In addition to use in food producing animals, antibiotics are also given to pets, and this issue is discussed in Appendix G.

Livestock production

Estimates of total annual global antibiotic consumption in agriculture vary considerably, due to poor surveillance and data collection in many countries, ranging from around 63,000 tonnes[3] to over 240,000 tonnes[4]. However it is clear by any measure that use is widespread, on a scale at least equivalent to use in humans, and is projected to increase. Van Boeckel et al. (2015) estimate that global consumption of antibiotics in agriculture will increase by 67 percent from 2010 to 2030, and consumption of antibiotics amongst the BRICS will increase by 99 percent in that same time period.

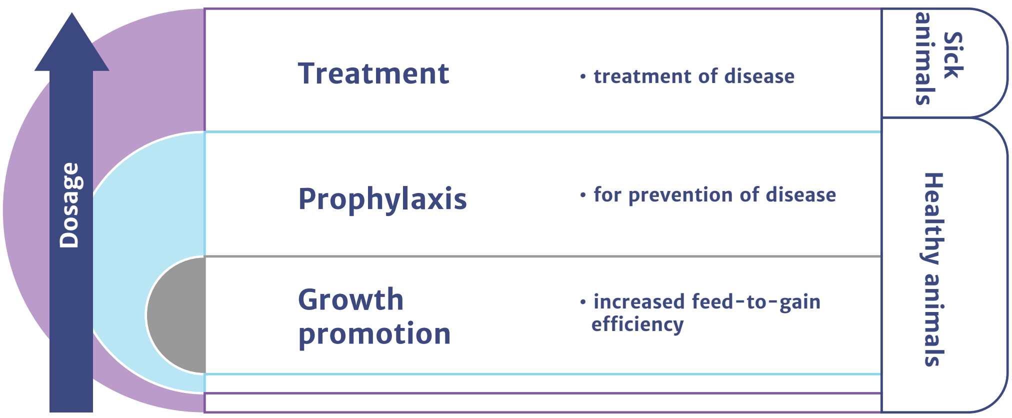
The proportion of antibiotics used in livestock compared with humans is also very surprising to many not well versed in this issue. More than 70 percent of the antibiotics deemed medically important for human health by the FDA sold in the United States (and over 50 percent in most countries in the world) are used in livestock[5].

With this quantity of antibiotic use in the food chain, it deserves very close attention from anyone concerned with rising antibiotic resistance.

Why do we use such large quantities of antibiotics in our livestock? These antibiotics are used for different purposes, some to protect or improve the health of the animals, and others to stimulate quicker growth and maximize profits. Figure 1 illustrates the three main uses of antibiotics in livestock.

The most controversial of these uses is growth promotion, because it does not serve to maintain the health of the livestock. As with any antibiotic use, this increases the chances that resistant bacteria will develop. Not long after antibiotics were first used widely in human medicine it was discovered that they had the effect of promoting more rapid growth when given to farm animals at low levels, helping them reach their full market weight more quickly. However, there is evidence to suggest that use of antibiotics at low or 'sub-therapeutic' levels fosters the development of resistant bacteria[6]; one recent study showed that sub-therapeutic use of antibiotics in agriculture resulted in huge increases in the number of antibiotic resistance genes, relative to an antibiotic-free site in a similar region[7]. This clearly raises concerns from a human health perspective and indeed many countries have already banned the use of antibiotics for these purposes, with the notable EU ban in 2006, and the US recently moving towards a voluntary re-labelling of antibiotics to reduce their use as growth promoters.

Figure 1. Current uses of antibiotics in livestock



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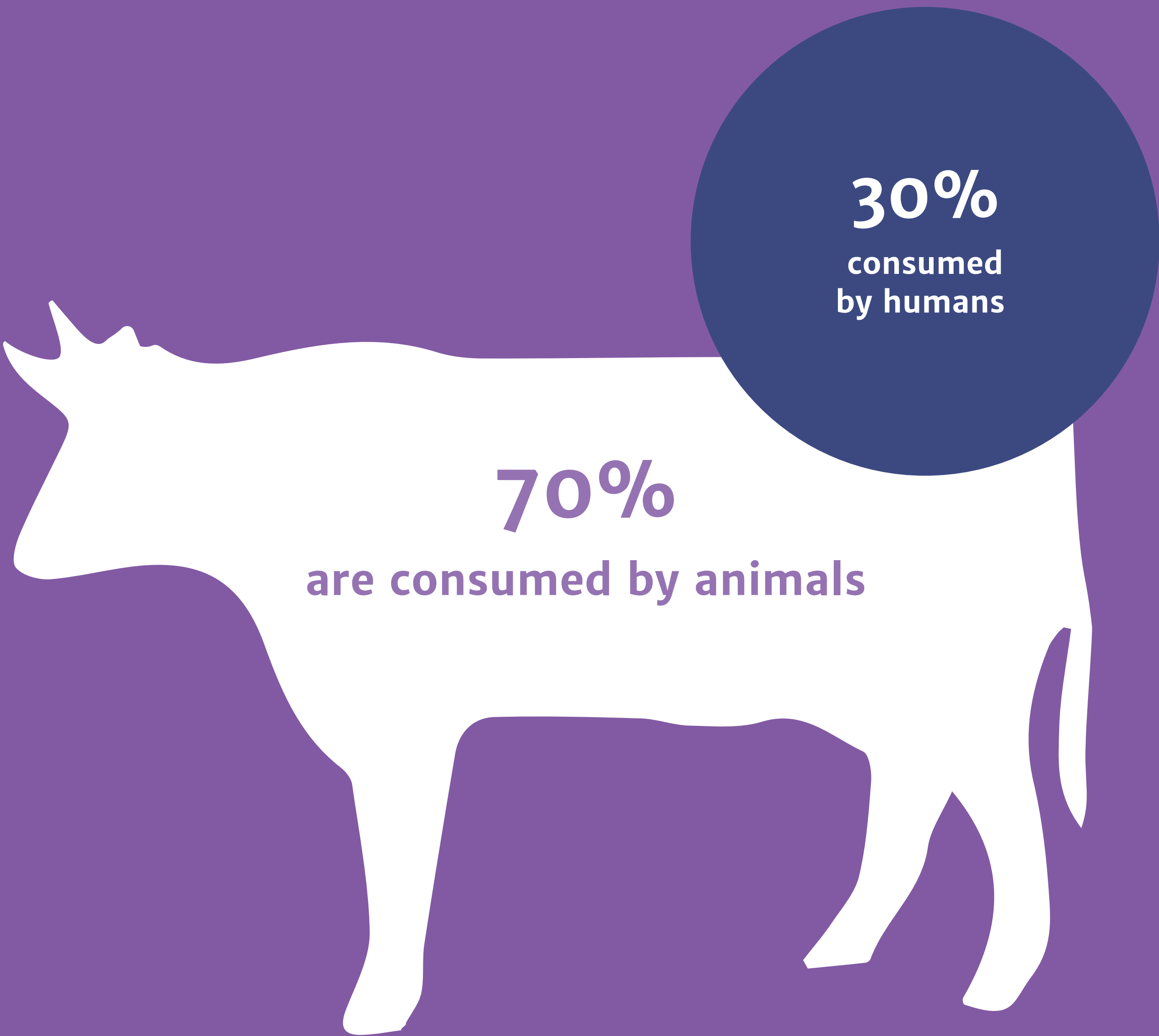
4. Delia G, Review of Evidence on Antimicrobial Resistance and Animal Agriculture in Developing Countries, Evidence on Demand, International Livestock Research Institute, 2015, DOI: http://dx.doi.org/10.12774/eod_cr.june2015.graced.
5. Animal consumption figure of 8,893,103kg from FDA, 2012. Human consumption of 3,379,226kg in 2012 based on calculations by IMS Health. The figures are rounded from 72.5% used in animals and 27.5% used in humans.
6. Allen, HK, Antibiotic Resistance Gene Discovery in Food-Producing Animals. *Current Opinion in Microbiology*, 2014, 19 (0) 25–29, doi:10.1016/j.mib.2014.06.001.
7. Zhu et al, Diverse and Abundant Antibiotic Resistance Genes in Chinese Swine Farms. PNAS, 2013 110(9): 3435–40. doi:10.1073/pnas.1222743110.

ANIMALS IN THE USA CONSUME MORE THAN TWICE AS MANY MEDICALLY IMPORTANT ANTIBIOTICS AS HUMANS



Source: Animal consumption figure of 8,893,103kg from FDA, 2012. Human consumption of 3,379,226kg in 2012 based on calculations by IMS Health.
The figures are rounded from 72.5% used in animals and 27.5% used in humans.

Aquaculture

In aquaculture, antibiotic doses can be higher proportionately than those in livestock. Not only can residues of antibiotics remain in fish products, but the antibiotics used in fish feed can remain in the aquatic environment for an extensive period of time, through excretion, exerting selective pressure and spreading rapidly through water systems. Indeed, some suggest 70-80 percent of antibiotics given to fish are excreted into water[8,9].

There are regulatory controls around maximum residue levels in place in some regions already, for example Europe. Indeed, countries with relatively strict rules for antibiotic use in agriculture generally have similarly strict rules for aquaculture – where they cannot be used for growth promotion in land-based agriculture, they cannot be used for that purpose in aquaculture either[10].

Use of antibiotics in aquaculture and its impact on the environment is a growing concern amongst scientists, yet quantifying the amount of use and how much is being disseminated into the environment is very difficult. As with the use of antibiotics in food production more generally, there is a need for better data.

Norwegian salmon – how antibiotic use can be reduced

Use of antimicrobials in aquaculture in Norway fell by 99 percent between 1987 and 2013, despite the industry's output growing more than 20 fold over that time[11]. This reflects:

- The increased availability and use of effective vaccines.
- Better farm hygiene and selection of better farm sites, with good water exchange. European fish farms generally use area-based management and have a high focus on biosecurity (i.e. not letting fish in or out of farms – infections are therefore less likely to spread from wild to farmed fish and vice versa). There are also fish health inspectorates in Europe (under the Fish Health Directive), who sign off on biosecurity.
- Stricter regulatory oversight. From 1989, it became mandatory to submit copies of prescriptions issued to farmed fish to the Norwegian Government Fish Inspection and Quality Control Service, and – from 2004 – to the Norwegian Food Safety Authority.

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Crops

It is estimated that the amount of antibiotics used for crops is relatively low in comparison to the quantities used in livestock, with estimates ranging from 0.2 to 0.4 percent of total agricultural antibiotic consumption[12]. For this reason direct use of antibiotics on crops is probably not a priority area to find major reductions, but should not be ignored.

However, fungal diseases tend to pose much larger threats to crops and therefore fungicides are used in significant quantities. They are commonly used on cereals and grapes in particular, but also used in many other areas, such as in tulip production.

The number of patients relying on antifungals to stay alive has increased over the last two decades, as advances in modern medicine have allowed many more patients with weakened immune systems to survive. This increased use in humans alongside the use of fungicides in agriculture has meant that resistance is becoming an increasing problem[13].

Fungal infections contribute to the deaths of almost three quarters of a million people each year[14]. While many fungicides appear not to pose a threat to humans through resistance, azole-based fungicides do. Azole-based therapies are the most important class of oral drugs we have to fight the infections caused by the fungus *Aspergillus*. An increase in azole-resistant infections is likely to worsen what is already a significant human health impact[15].

Azole use varies hugely between different parts of the world: nearly 50 percent of the total acreage of European cereal and grapevine production is treated at least once a year, compared with less than five percent in the US[16]. The differences are substantial, and while the reasons may not be fully understood, they are in part due to Europe's wetter climate, smaller farm sizes, and different soil. What is increasingly clear is that there is a strong link between countries where azole-based fungicides are used and the incidence of antifungal resistance. The Netherlands, for example, uses a large amount of fungicides in their tulip production. The standard practice is to dip every tulip bulb in fungicide before it is planted. The Netherlands also has one of the highest rates of antifungal resistance for azoles in strains of *Aspergillus fumigatus*, which is now approaching seven percent[17].

Our proposals for fungicide use

World food production relies heavily on fungicides and this would make a full ban on their use very difficult. However, we believe that new classes of clinical antifungals that are developed in the future should be banned from use in food production. There might also be scope to ban certain azoles from use in non-food crop production, such as tulip production, now. Going forward, there needs to be greater surveillance of antifungal resistance, more research into alternatives to fungicides, and consideration as to how to minimise resistance developing from their use. The latter could include research into reducing their persistence in the environment, and build on established evidence into which fungicides build up less resistance than others[18], in order to move away from those that are the worst for resistance.

Finally, as previously discussed, fungicide use differs hugely between different regions, with the US using about a tenth as much as Europe. Greater research is needed to understand why Europe uses a comparatively large amount of fungicides, and to see if lessons can be learnt from use in the US.

"We believe that new classes of clinical antifungals that are developed in the future should be banned from use in food production. There might also be scope to ban certain azoles from use in non-food crop production, such as tulip production, now."

Antiparasitics

Because of the similarities between antiparasitics and other types of antimicrobials used in agriculture, we do not focus heavily on them in this paper, but many of the solutions we have put forward could be applied to this important area too. In particular we recognise that resistance to antiparasitics for certain zoonotic parasites has become a major problem[19, 20]. Like fungicides, antiparasitics play an important role in agriculture, and would be difficult to replace. We thus need to invest in more research to develop agricultural practices that limit the build-up of resistance to human drugs, as well as stopping new drugs for humans being used in agriculture.

Available at: http://www.gaffi.org/wp-content/uploads/GAFFI_Road_Map__interactive-final0415.pdf.

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Use in food production passes through to the environment through animal waste

According to an Food and Drug Administration (FDA) Report, 2011[21], 93 percent of medically-important antibiotics were administered via feed or water in agriculture in the US. Scientific studies also suggest that 75-90 percent of tested antibiotics are excreted from animals un-metabolised[22] and enter sewage systems and water sources.

Therefore, animal waste not only contains resistant bacteria, but also antibiotics that could then foster the emergence of resistance in bacteria beyond those in an animal's gut – including bacteria that may pose a greater risk to humans. This manure from farm animals is often used on crops as a fertiliser, which has been shown to create resistance[23].

Reducing unnecessary use of antibiotics in livestock should help tackle this problem at the source, but creating rules to reduce the use of manure from animals that have been treated with antibiotics is another policy that countries could consider to reduce the risk of resistance problems in the environment. Given that farmers frequently sell their animals' manure, this could create an additional incentive to lower antibiotic use. Clearly a number of issues would need to be worked through to design and implement such a change, including the time period which animals would need to have been free of antibiotics before their manure could be used, and a safe alternative way to dispose of waste from animals that had received antibiotics.

Once in the environment, it is difficult to predict how quickly antimicrobials will degrade, whether they come from animal use, human use or manufacturing, as they are very diverse chemically. Some degrade easily, while others bind to organic matter and can persist in their active states for long periods of time. This adds to the need for further study of this issue.

Human waste is also a problem

As with the use of antibiotics in animals, most of the antibiotics consumed by humans are excreted and therefore pass into the environment[24]. Inappropriate human disposal of antibiotics, for instance by flushing them down the toilet, plays a role in this[25]. Public awareness of the problems this can cause is necessary to help to change this behaviour.

In countries with less developed sanitation infrastructure, there is a higher risk that waste will not be treated, and sometimes be closer to communities, thus increasing the risks of exposure, the carriage of resistant bacteria by otherwise healthy people, and the rate of drug-resistant community-acquired infections. It is in these settings that there is an additional concern about antibiotics and resistant bacteria passing into the environment as sewage treatment systems are often not fully functional or do not use appropriate technologies[26].

The problem is particularly acute in the waste of patients in hospital settings[27], who are far more likely to be on antibiotics than someone in the general population, meaning the antibiotic concentrations are often much higher. Multiple studies have found significant concentrations of antibiotics in hospital effluent in different countries such as Germany[28] and India[29], among others, suggesting that this is a problem that affects most, if not all, countries. If resources are limited it may make sense to target waste from hospitals that are likely to have higher levels of antibiotics and resistant bacteria.

Even in countries with advanced sewage systems there are studies that have shown the presence of antibiotics downstream of sewage treatment plants, which might act as hotspots for resistance development[30], with antibiotics from human, animal and manufacturing use converging. This is usually due to the fact that even these countries do not have advanced systems in place to treat this water to ensure that any traces of antibiotics are removed. This is primarily due to the cost that such a change in infrastructure would entail, as treatments to remove some, if not all, antibiotics and resistant bacteria are advanced and therefore could be very expensive.

However, reducing unnecessary use of antibiotics will clearly help to counteract this problem at the source. Our paper published in October 2015, entitled *Rapid Diagnostics: Stopping the Unnecessary Use of Antibiotics*, discussed how we need to incentivise the innovation and uptake of diagnostics to reduce the unnecessary human use of antibiotics.

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IS THIS A PROBLEM FOR HUMAN HEALTH?

What does the existing literature say?

With human use of antibiotics it is widely accepted that there is a correlation between use and resistance, as discussed in our paper on rapid diagnostics[31]. Countries or areas that use more antibiotics, often have higher rates of resistant bacteria, meaning infections are harder to treat. It is also evident that use of antibiotics in animals is correlated with the development of resistant bacteria, as in human use of antibiotics[32].

The link between the use of antibiotics in animals and resistant infections in humans, however, is more contentious and normally focuses on the likelihood that resistant bacteria in animals, created by the selection pressures of antibiotic use, will be transferred to humans. This transfer could potentially happen through direct contact with an animal, from consumption of undercooked or unpasteurised animal products, or via the spread of resistant bacteria into environmental reservoirs, which may then transmit resistance genes to human bacteria, or come into contact with humans directly[33].

It is sometimes suggested that the current evidence is not strong enough to take policy steps now to reduce antibiotic use in agriculture. While we definitely would benefit from more data, generated by better surveillance systems, our research has indicated that the evidence is already compelling.

As part of our analysis, we have undertaken a literature review using a sample of 280 published, peer-reviewed research articles that address the issue of antibiotic use in agriculture. The outcomes of this literature review support the proposal that antibiotic use in animals is a factor in promoting resistance in humans.

We found 280 papers, via the National Center for Biotechnology Information's (NCBI) PubMed database with the search terms "drug resistance, microbial" AND "agriculture". We believe these papers should be representative of the wider literature. Of the 280 papers we looked at, 88 (31 percent) were deemed not to be applicable. Of the remaining 192 papers, 114 (59 percent) openly stated or contained evidence to suggest that antibiotic use in agriculture increases the number of resistant infections in humans. Only 15 (eight percent) argued that there was no link between antibiotic use and resistance. The other 63 did not take a clear stance. Further to this, the majority of studies opposing a reduction of agricultural antimicrobial use were authored by people affiliated to either governments or industry, in contrast to the majority of studies that were affiliated to universities. Of the 139 academic studies the Review found, only seven (five percent) argued that there was no link between antibiotic consumption in animals and resistance in humans, while 100 (72 percent) found evidence of a link. The methodology and further details from this study are detailed in Appendix C, and a list of all the papers and how they were classified is available on our website: www.amr-review.org.

In light of this information, we believe that there is sufficient evidence showing that the world needs to start curtailing the quantities of antimicrobials used in agriculture now. Where gaps in the evidence remain, they should be filled. But given all that we know already, it does not make sense to delay action further: the burden of proof should be for those who oppose curtailing the use of antimicrobials in food production to explain why, not the other way around.

> *"Of the 139 academic studies the Review found, only seven (five percent) argued that there was no link between antibiotic consumption in animals and resistance in humans, while 100 (72 percent) found evidence of a link."*

Human and animal antimicrobials often overlap

Humans and animals are often affected by similar, or even the same, pathogens. Therefore it stands to reason that many of the antimicrobials used to treat these infectious diseases are similar. Indeed many antimicrobials that are used in animals and in aquaculture, are important for human use. Some of these are used in animals for growth promotion, as well as therapeutically to treat sick animals, including tetracyclines and macrolides.

Of the 41 antimicrobials that were authorised for sale in animals, and sold in the US in 2012, 31 are currently deemed by the FDA to be important for human health[34]. This means that only 10, or about a quarter of the agents listed, have no direct overlap with antimicrobials that are used in humans. Half of these 10 antimicrobials are ionophores, which are not used to treat animals that are already sick. Four of the five remaining antimicrobials are classified by Marshall and Levy (2011) to be

disinfectants into wastewater by hospitals in relation to other sources—a review. Chemosphere, 2001, 45, 957–69..

29. Diwan V, Tamhankar AJ, Khandal RK, et.al., Antibiotics and antibiotic-resistant bacteria in waters associated with a hospital in Ujjain, India. *BMC Public Health, 2010*, .10:414, doi:10.1186/1471-2458-10-414.

30. Michael I, Rizzo L, McArdell CS, et.al. Urban wastewater treatment plants as hotspots for the release of antibiotics in the environment: A review. *Water Research*, 2013, 47, 957-995.

31. Review on Antimicrobial Resistance, Rapid Diagnostics: Stopping Unnecessary Use of Antibiotics. 2015.

32. Khachatourians GG, Agricultural use of antibiotics and the evolution and transfer of antibiotic-resistant bacteria. *Canadian Medical Journal Association*, 1998,159:1129-36.

33. Rushton, J., J. Pinto Ferreira and K. D. Stärk, Antimicrobial Resistance: The Use of Antimicrobials in the Livestock Sector. *OECD Food, Agriculture and Fisheries Papers*, 2014, No. 68, OECD Publishing. http://dx.doi.org/10.1787/5jxvl3dwk3f0-en.

34. FDA, 2012 Summary report on Antimicrobials sold or distributed for use in Food-producing animals .FDA, 2012 Summary.

similar enough to drugs used in humans to still cause cross-resistance[35]. This highlights the lack of antimicrobials that we have to treat animals without posing a threat to human health.

One of the main reasons for the crossover in use is that the market for human antimicrobials is much larger than for animal antimicrobials, so most of the innovation at present comes for drugs for humans. Therefore, antimicrobials for animals are often found by adapting molecules that work in humans. These then go through a similar trial process to human antimicrobial trials, however these are far less expensive as it is cheaper and easier to run tests on animals than on humans.

Having totally separate research and development strands for animals and humans is neither sensible nor feasible. If a highly useful antimicrobial is found through animal research, the desire will often be to use it in humans. However on occasions when a new antimicrobial is not viable for use in humans, because of biological or economic reasons, it still might play an important role in animal health.

Therefore we would like to see drug companies maintain their animal units, collaborating with research on the human side, when conducting their research on animal antimicrobials. In particular, we have already called for antimicrobial libraries to be re-opened to check for old drugs that might now be useful[36]. This process should also consider antimicrobials that might work in animals but not in humans. Antimicrobials that are ruled out in the future on efficacy or safety grounds for humans, should be tested to see if they could be used therapeutically in animals.

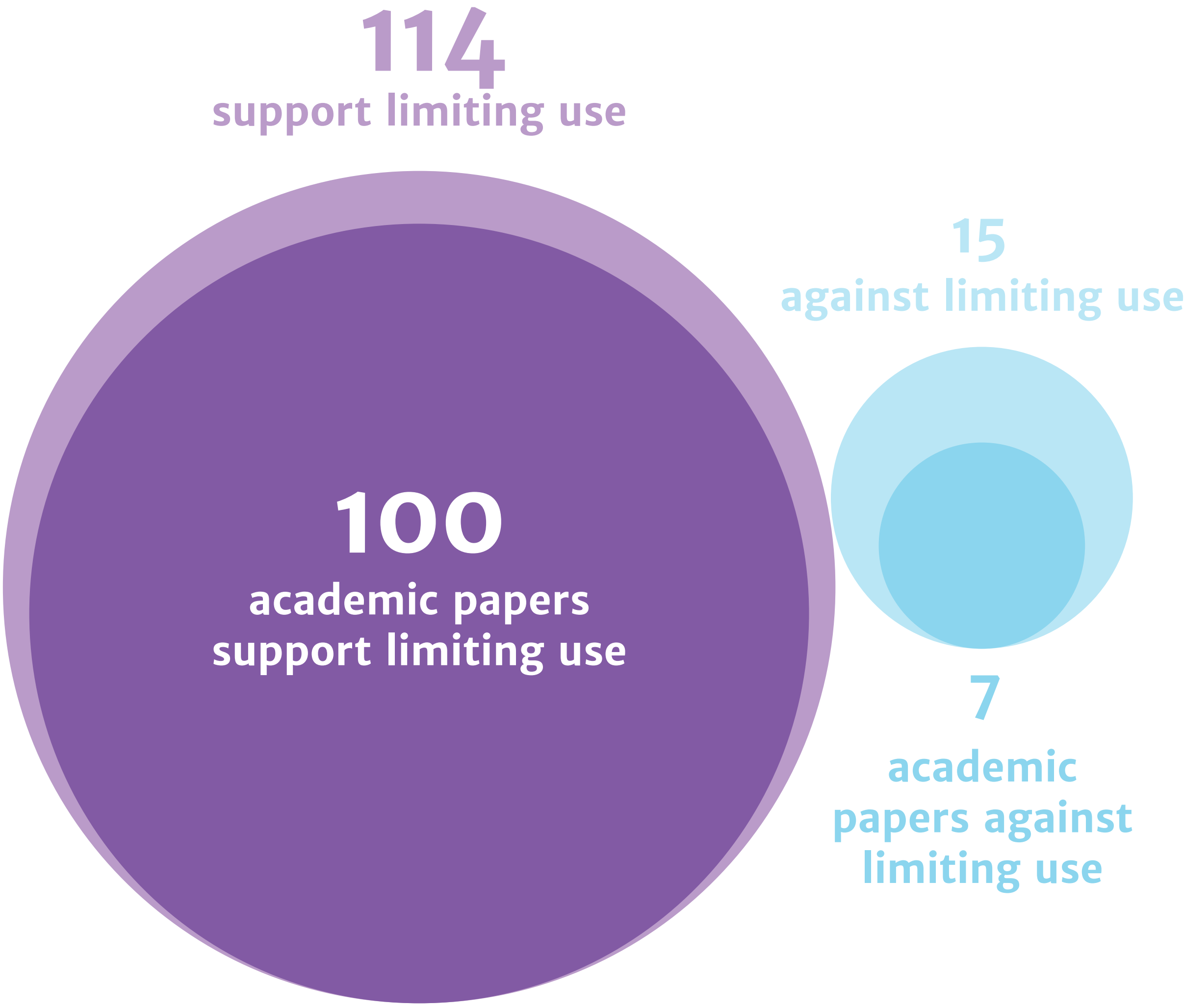
Some of this research is already underway, but more could usefully be done. If the market is not there to incentivise this investment, then lump sum payments could be considered, perhaps similar to the suggestions in our paper on human antibiotics[37]. Reducing the crossover of antimicrobials used by both humans and animals could play an important role in reducing the burden of disease on humans, reducing the risk of cross-resistance.

35. Marshall, BM, Levy SB, Food animals and antimicrobials: impacts on human health. Clinical Microbiology Reviews, 2011, 24:718–733.

36. Review on Antimicrobial Resistance, Securing New Drugs for Future Generations - the pipeline of antibiotics. 2015.

37. Review on Antimicrobial Resistance, Securing New Drugs for Future Generations -the pipeline of antibiotics. 2015.

MOST PUBLISHED PAPERS PROVIDE EVIDENCE TO SUPPORT LIMITING USE OF ANTIBIOTICS IN AGRICULTURE



Based on a representative sample using the 280 papers from the NCBI's PubMed database found with the search terms "drug resistance, microbial" AND "agriculture", 88 of which were deemed not to be applicable as they did not address antibiotic use in agriculture. Papers were categorised as 'supportive', if they provided evidence to support limiting antibiotics in agriculture, 'against', if they provided evidence that we should not be concerned with limiting antibiotics in agriculture and 'neutral', if they did not explicitly take a stance. There were 63 papers that were categorised as neutral. Of the papers classified as neutral, 36 were written by academics. Academic papers are defined as those that were written by academics.

Source: Review's own analysis.

Resistance to colistin – a last-resort antibiotic for humans

A recent example of how use of antibiotics in animals has created major human health risks is provided by the November 2015 study in China by Liu et al[38]. This study found new evidence of a link between animal use of antibiotics and resistance found in humans. Colistin is our last defence against multi-resistant bacteria, especially those resistant to carbapenem antibiotics. The potential damaging effect that the drug can have on patients' kidneys, means that it is only used where doctors have no better options. However, the global AMR crisis means that doctors are increasingly forced to use colistin even though they would prefer not to.

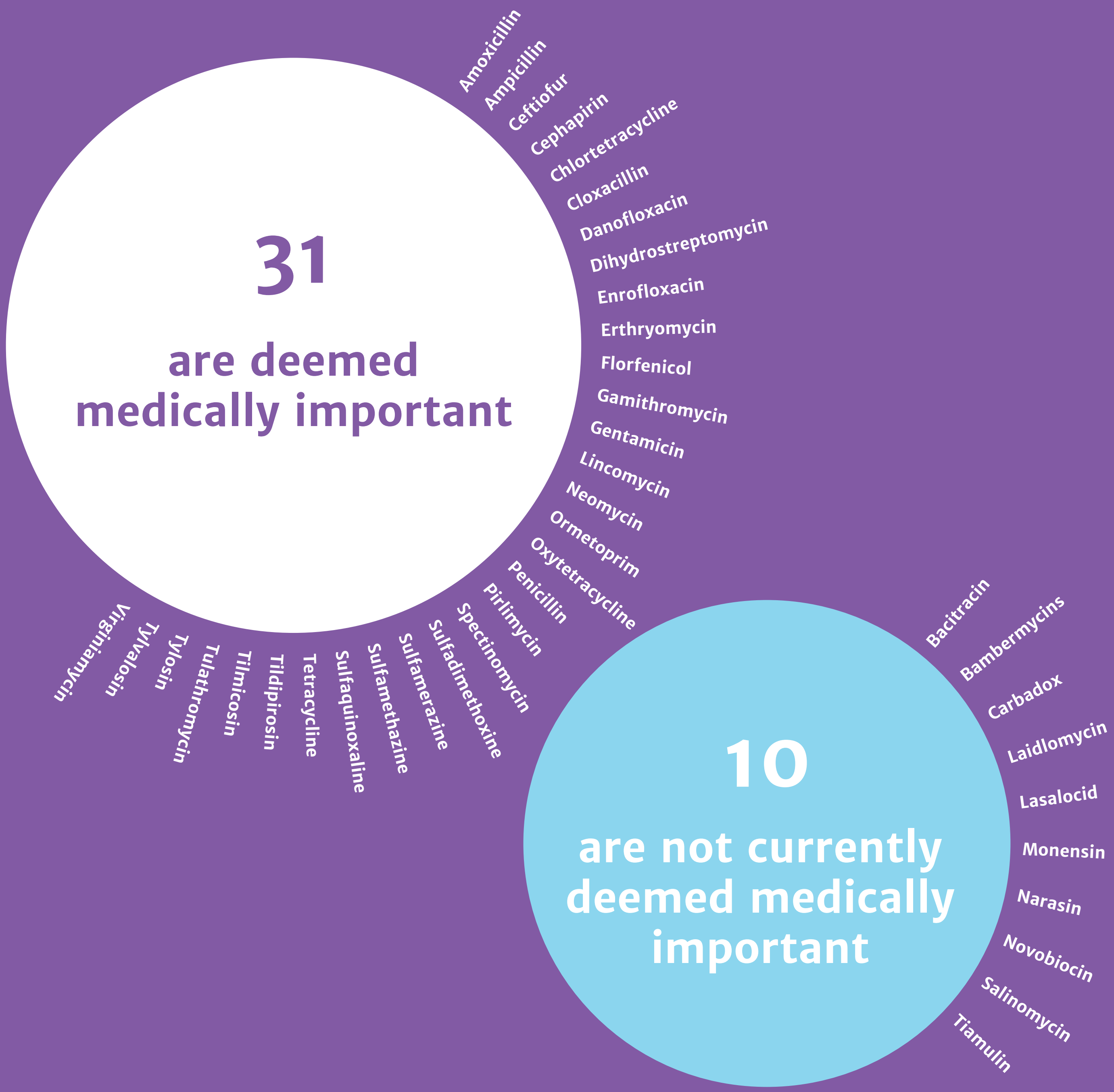
Unfortunately bacteria resistant to colistin are not new. Indeed, in some countries they are a widespread and ever-increasing problem, but their colistin resistance is not usually transferable between strains. Liu and colleagues examined areas in China where colistin is routinely given to pigs and they found colistin-resistant *E. coli* in more than 20 percent of animals and in 15 percent of raw meat samples. Those rates of resistance are bad enough, but what made this report far more disturbing was that these bacteria all had colistin resistance that could easily be transferred between different bacteria, something that had never been reported before. Furthermore, they also found that about one percent of hospital patients sampled were infected by *E. coli* or *Klebsiella* bacteria that had the same piece of DNA, making them resistant to colistin too.

The most plausible explanation for the wide occurrence of this newly discovered resistance gene in animals and meat is that bacteria with it have been selected by farmers giving colistin to their animals. It seems clear that this use in agriculture has led to humans getting infections caused by resistant bacteria. We need to take urgent steps to make sure that the use of antibiotics in animals that are important for human use, are restricted and where necessary banned.

38. Liu Y, Wang Y, Walsh TR, et al., 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*, 2015, Published Online, In Press Corrected Proof, doi: 10.1016/S1473-3099(15)00424-7.

MOST ANTIBIOTICS USED IN ANIMALS ARE MEDICALLY IMPORTANT FOR HUMANS

Of the 41 antibiotics* that are approved for used in food producing animals by the FDA, 31 are categorised as being medically important for human use.



Source: FDA, 2012 Summary report on Antimicrobials sold or distributed for use in Food-producing animals.

* Includes ionophores

Review on Antimicrobial Resistance

3.

WHAT IS THE ECONOMIC BENEFIT OF USING ANTIBIOTICS FOR FOOD PRODUCTION?

The scientific debate around the impact of antibiotic use in animals and the extent of its impact on human health is likely to continue for some time as we develop more advanced ways of tracing the origins of resistant bacteria. However, we think there is a case for action now, particularly in relation to antibiotics that are not used to treat animals when they are sick. This is on the basis that there is a threat to human health, even if more evidence is needed to quantify that threat precisely.

The counter argument to this is the increased financial cost that could be placed on food producers through restricting use, which could ultimately mean higher meat prices for consumers.

However, there is growing evidence to suggest that antibiotics used as growth promoters do not have as much economic benefit as previously thought[39], particularly in countries with advanced farming techniques. This undermines the economic arguments in favour of using antibiotics for growth promotion: that the farmer will suffer productivity losses if he or she does not use growth promoters. Recently published papers suggest that the benefit from a growth perspective of using antibiotics sub-therapeutically in animals has declined over time, due to the changing microbial composition of animals fed antibiotics[40]. They also tend to be most effective when the conditions the animals are kept in are poor[41], with low standards for infection control and cramped conditions. General improvements in these standards seem to have reduced the effectiveness of antibiotics as growth promoters. Studies in the US, Denmark and Sweden, after the 2000s, showed that growth promoters had less effect than they had done in earlier decades on the growth rate, and feed efficiency of animals. The impact after the 2000s was typically less than five percent[42]. Further work is needed in this area, particularly looking at the economic impact on low and middle-income countries that may experience a bigger impact from a reduction in antibiotic use.

There is also a long-term risk to food production from overusing antibiotics in livestock in the form of rising resistance amongst animals, leading to higher mortality and morbidity, just as we have discussed for humans in previous papers. This could pose challenges to global food security as well as farmers' profits. In the case of severe untreatable infections, farmers may be faced with the loss of entire flocks or herds.

When assessing this problem globally there is a huge variance in how countries address it. However there are case studies that show it is possible to significantly reduce use, without a damaging economic impact. Two countries that have made large strides in reducing antibiotic use in their livestock sectors in recent years, while retaining their commercial competitiveness, are the Netherlands and Denmark, as discussed below.

> *"There is growing evidence to suggest that antibiotics used as growth promoters do not have as much economic benefit as previously thought"*

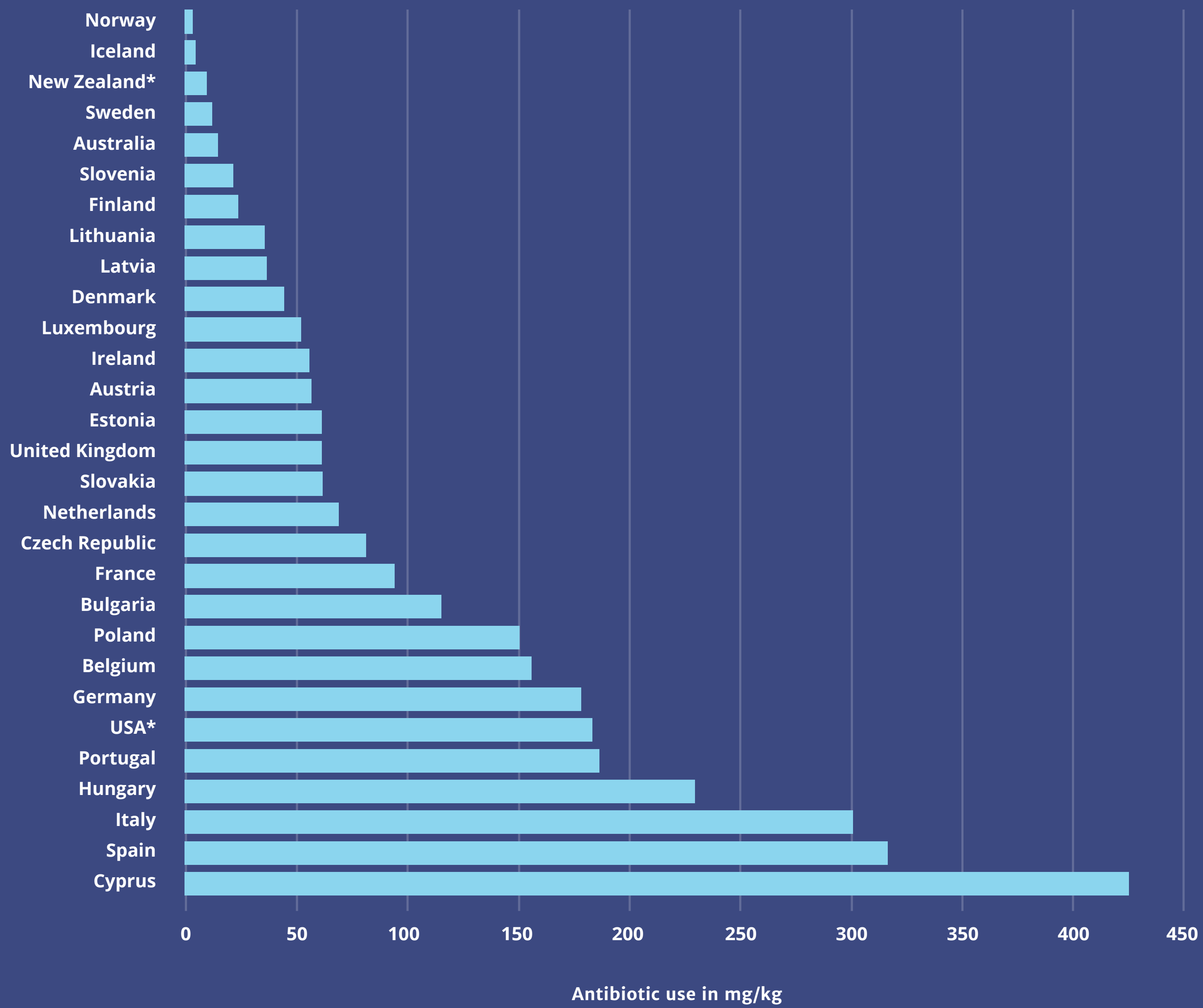
39. Graham J, Boland J, Silbergeld E, Growth Promoting Antibiotics in Food Animal Production:An Economic Analysis. *Public Health Reports*, 2007 122 (1), 79-87.

40. Laxminarayan, R., Van Boeckel T, Teillant A, The Economic Costs of Withdrawing Antimicrobial Growth Promoters from the Livestock Sector. OECD Food, Agriculture and Fisheries Papers, 2015, No. 78, OECD Publishing. http://dx.doi.org/10.1787/5js64kst5wvl-en.

41. *Ibid.*

42. Laxminarayan R, Van Boeckel, Teillant A, Global antimicrobial use in the livestock sector. OECD, 2015, Working Party on Agricultural Policies and Markets, Trade and Agriculture Directorate, Committee for Agriculture, TAD/CA/APM/WP(2014)34/FINAL.

ANTIBIOTIC USE IN AGRICULTURE VARIES GREATLY BY COUNTRY



Source: European Medicines Agency (2011) and the national governments of the US, Australia and New Zealand.

* Animal biomass estimated based on number of animals.

NB: All figures are given in milligram (mg) purchased for every kilogram (kg) of livestock biomass and do not include ionophores and oligosaccharides.

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Two case studies for lowering antibiotic use in agriculture

Denmark

In 1995, Denmark began to pursue policies to regulate antimicrobial usage in livestock. They banned antibiotic growth promoters (AGPs) from pig production in a series of steps; avoparcin in 1995, virginiamycin in 1998, and a comprehensive ban on all AGPs in 2000. In 1995, they also established DANMAP, a surveillance system to monitor antibiotic resistance in humans and farm animals.

Between 1992 and 2008, Danish swine production increased by 47 percent, showing that swine production continued to thrive following the ban[43]. However, the number of operating Danish farms decreased, indicating that farms either consolidated or closed – experts suggest that only the farms with good farm management techniques in place were able to remain profitable after the ban.

During the same period, antimicrobial use in swine decreased by 51 percent[44] on a like for like basis, from 100.4 to 48.9 mg/kg meat. Although therapeutic use initially increased as there were more disease outbreaks (possibly due to the loss of prophylactic benefits from antibiotics being used as growth promoters), overall use of a type of macrolide (a critically important class of antibiotics for humans) decreased.

Between 1995 and 2008, antimicrobial use in poultry decreased 90 percent in absolute terms, from 5,000 kg to 500 kg[45]. The 500 kg used was solely for therapy, and poultry production has slightly increased over this time period. Rates of vancomycin-resistant *E. faecium* in chickens and pigs declined.

What makes Denmark such an interesting example is that today it is one of the largest exporters of pork in the world, exporting around 85 percent of the pork it produces[46]. 70 percent of the pork produced is exported to other EU countries, with around 15 percent exported to countries outside the EU. Of the non-EU countries, China, Japan and Russia are among the largest importers of Danish pork[47]. This highlights that it is possible to have low antibiotic use and be commercially competitive in a wide range of markets. However, there were up-front costs for Danish farmers as they moved to new farming practices less reliant on antimicrobials.

The Netherlands

Similar to Denmark, in 1999 Dutch officials established MARAN, a system for monitoring antibiotic resistance in food pathogens, animal pathogens, and indicator organisms. However, The Netherlands did not ban growth promoters until 2006, when the EU-wide ban occurred. Dutch sales data indicate that therapeutic drug usage increased to levels that kept total antibiotic use static after the termination of growth promoters in 2006, indicating a possible ambiguity between 'therapeutic' and 'non-therapeutic' use[48]. The Dutch case study indicates a need for interventions beyond simply banning types of use of antibiotics, as rates of zoonotic disease increased on farms throughout the country.

However, in 2009, the government intervened, mandating a 50 percent reduction in total antibiotic usage by 2012 through defined daily dosages and transparency in prescriptions[49]. From 2007 to 2012, antibiotic sales to Dutch livestock farms decreased 56 percent without any reduction in production or profits[50]. Dutch farmers have shifted their focus from using antibiotics to optimising the living conditions of livestock[51]. The Dutch experience shows that it is possible to reduce antibiotic use in a short time period and still maintain production.

43. Cogliani C, Goossens H, Greko C, Restricting antimicrobial use in food animals: Lessons from Europe. *Microbe*, 2011, 6(6), 274- 279.

44. *Ibid.*

45. *Ibid.*

46. Danish Agricultural and Food Council, ' *Danish Pig Meat Industry*, Availablefrom:http://www.agricultureandfood.dk/Danish_Agriculture_and_Food/Danish_pig_meat_industry.aspx, [Accessed 16th November 2015]

47. *Ibid.*

48. Cogliani C, Goossens H, Greko C, Restricting antimicrobial use in food animals: Lessons from Europe,' *Microbe*, 2011, 6(6), 274- 279.

49. *Ibid.*

50. McKenna, M, 'The Abstinence Method: Dutch farmers just say no to antibiotics for livestock,' Article in *Modern Farmer* June 17, 2014, Available at: http://modernfarmer.com/2014/06/abstinence-method/ [Accessed on 17th November 2015].

51. *Ibid.*

52. Sum of Us, Changing Markets and Profundo, Bad Medicine: How the pharmaceutical industry is contributing to the global rise of antibiotic-resistant superbugs, 2015, Available at: https://s3.amazonaws.com/s3.sumofus.org/images/BAD_MEDICINE_final_report.pdf, Accessed on: 16th November 2015.

53. Larsson DGJ, de Pedro C, Paxéus N, Effluent from drug manufactures contains

4.

MANUFACTURING AND DISPOSING OF ANTIMICROBIAL WASTE IRRESPONSIBLY

As well as the problems with antimicrobial use in food production, and how resistant bacteria might be able to transfer to humans and the environment, there is also a problem at the source. The active pharmaceutical ingredients (APIs) for antibiotics need to be manufactured in such a way that contamination, by the APIs, of the waste produced during their manufacture is kept to a minimum. There is growing evidence, however, to show that currently this is not always the case. APIs are the biologically-active ingredients in a pharmaceutical drug. In the case of antimicrobials, after the APIs are manufactured they are often sold to pharmaceutical companies, who produce the final product.

Most API manufacturing takes place in China and India, for a lower cost than, for example, making similar products in Europe. The APIs produced are sold to pharmaceutical companies who make end products to sell to consumers around the world[52]. We all therefore benefit from the low cost of production of APIs, which is partly facilitated by the fact that manufacturing standards, and thus the cost to comply with them, are low. However, the burden of this low cost production - manufacturing waste being released near the relevant plant that contains very elevated levels of APIs - is borne by the local community. This is a supply chain problem that pharmaceutical companies and their suppliers need to solve together.

An important study by Swedish researchers in 2007[53] examined a wastewater treatment plant in India that received effluent from 90 bulk API manufacturers. It revealed that shocking levels of pharmaceutical active ingredients were being discharged into a nearby river. It also showed that the concentration of ciprofloxacin, a commonly used antibiotic, exceeded levels toxic to some bacteria by 1000-fold. To put this in perspective, this means that waste water or effluent in some areas where APIs are released via manufacturing waste have a far higher concentration of antibiotics than you would expect to find in the blood of a patient taking the drug[54].

Recent studies have shown that environments polluted with waste from antibiotic manufacturing could be important reservoirs of antibiotic resistance[55, 56]. A study in China[57] showed that levels of oxytetracycline, a common antibiotic, from a manufacturing facility that supposedly treated its waste, were still considerable. These are just a few examples from many studies that have been done all over the world.

One of the reasons for these poor practices is that there are currently no, or very few, standards for API discharge anywhere in the world; either for municipal waste treatment plants or for the manufacturing companies[58]. This lack of standards is in part due to the scientific challenges of establishing the level of threat the issue poses to human health. There have been recent efforts to identify the concentrations at which resistance might emerge, which could be used to develop drug-specific limits for waste water[59]. There need to be concerted efforts to develop these and other standards into enforceable regulations and this debate, while necessary, should not prevent a basic minimum standard being introduced now.

“*Waste water or effluent in some areas where APIs are released via manufacturing waste have a far higher concentration of antibiotics than you would expect to find in the blood of a patient taking the drug*”

extremely high levels of pharmaceuticals. *Journal of Hazardous Materials*, 2007, 148, 751–755, doi:10.1016/j.jhazmat.2007.07.008.

54. Larsson, DGJ, Pollution from drug manufacturing: review and perspectives. *Philosophical Transactions of the Royal Society B*, 2014, 369: 20130571 http://dx.doi.org/10.1098/rstb.2013.0571.

55. Bengtsson-Palme J, Boulund F, Fick J, et.al., Shotgun metagenomics reveals a wide array of antibiotic resistance genes and mobile elements in a polluted lake in India. *Frontiers in Microbiology*, 2014, 5:648, http://dx.doi.org/10.3389/fmicb.2014.00648.

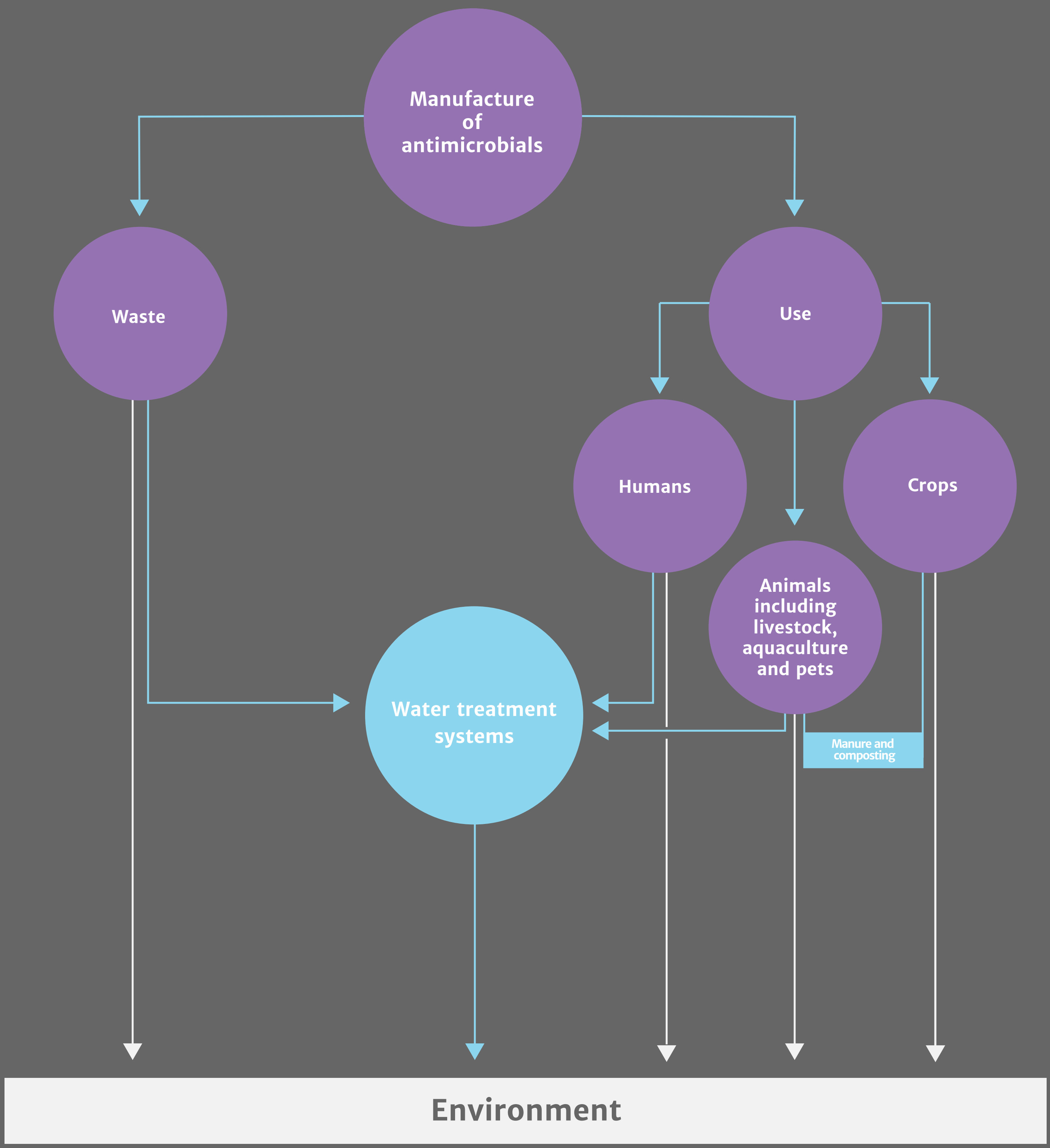
56. Flach CF, Johnnin A, Nilsson I, Isolation of novel IncA/C and IncN flouruquinolone resistance plasmids from an antibiotic-polluted lake. *Journal of Antimicrobial Chemotherapy*, 2015, 70(10), 2709-17.

57. Li D, Yang M, Hu j et.al. Determination and fate of oxytetracycline and related compounds in oxytetracycline production wastewater and receiving river. *Environmental Toxicology and Chemistry*, 2008, 27: 80-86.

58. Agerstrand M, Berg C, Björlenius B et al, Improving Environmental Risk Assessment of Human Pharmaceuticals. *Environmental Science*, 2015, 49, 5336-5345, DOI: 10.1021/acs.est.5b00302.

59. Bengtsson-Palme J, Larsson DGJ. Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. *Environment International*,2015,86:140-149, doi:10.1016/j.envint.2015.10.015.

HOW ANTIMICROBIALS REACH THE ENVIRONMENT



Review on Antimicrobial Resistance

5.

THREE PROPOSALS TO REDUCE ANTIBIOTIC USE IN FOOD PRODUCTION AND IMPROVE ANTIMICROBIAL MANUFACTURING WASTE MANAGEMENT

1.

We need a global target to reduce antibiotic use in food production to an agreed level per kilogram of livestock and fish, along with restrictions on the use of antibiotics important for human health.

We have outlined the research that is available and believe this is compelling enough to warrant a significant reduction in antibiotic use, both by overall quantity and by antibiotics that are important for human health.

a. Quantity of use.

We think the best way to reduce overall antibiotic use is to establish targets or limits for antibiotic use in agriculture and aquaculture,to an agreed limit for each country, whilst allowing individual countries to work out the best way to meet their goals. An ambitious, but achievable, and appropriately enforced target could secure a global reduction in use, while allowing individual countries flexibility to decide how to reach those reductions. We think this would be more effective than a ban on growth promotion because, whilst welcome, it is very difficult to define and enforce by type of use, and might well lead to either individuals or systems redefining use that is growth-promoting as prophylactic, or even therapeutic. We also believe that the world needs to go further than just preventing use as growth promotion, in order to reduce the risk that antimicrobial resistance poses.

We therefore recommend that governments, experts, and international bodies come together – from the fields of human as well as animal health – to set an ambitious but achievable target for countries to reach. Below we set out initial thoughts for the level of such a target to lower use over the next 10 years. We look forward to feedback and discussions from interested stakeholders and experts before our final report in spring 2016, on the level at which a target should be set and how long should be given to implement this.

Denmark has shown that a very productive farming industry can be sustained alongside relatively low levels of antibiotic use. If a target were set at a level that Denmark has shown to be achievable, while being one of the largest pork exporters in the world, it would be somewhere in the order of 50mg of antibiotics/kg[60] of livestock or fish. We believe that real progress needs to be made in the short-term on this issue and therefore any target that is set should not be more than 10 years away for high-income countries. The most logical way to reduce use significantly would be to make the targets legally binding, with individual targets for specific countries, however it might be more difficult to gain a political consensus to achieve this.

While these proposals may appear radical, The Netherlands reduced its consumption by 56 percent in three years, so that it is now only slightly above a threshold of 50mg of antibiotics/kg, without bearing large economic costs. Antibiotic use in many low and middle-income countries is lower than this, primarily because their farming systems have not yet become reliant on antibiotic use. For those who do use more than our proposed target, we realise that changing farming practices might take more time, as resources are likely to be more scarce and the transitional costs higher. These countries should also have the aim of reducing antibiotic use to under the target level, however greater flexibility over the time to achieve this target might be necessary.

In practice this means that the EU would need to reduce its antibiotic consumption by around two-thirds, from its current average of 146.7 mg/kg, and would require reductions in consumption for 18 of the 26 EU countries we have data for, including the UK. This may sound like a large reduction, but there are many high-income countries that have very productive agricultural sectors that are either under or close to this target,

60. Ideally measured in a way that is similar to the European Surveillance of Veterinary Antimicrobial Consumption, who take account of animals imported or exported for fattening or slaughtering in their estimates.

such as Sweden, Ireland, Norway, Denmark, The Netherlands and New Zealand. Indeed, we have analysed the productivity of livestock production, assessing the comparative amount of animals in a country against the value of animal produce using data provided by the US Department of Agriculture (USDA). This analysis showed no reduction in productivity for countries that used smaller quantities of antibiotics. Between 1992 and 2012, Denmark reduced its antibiotic consumption more than any other country in Europe, but it had the second highest growth rate in agricultural productivity, with this increasing by 65 percent, against the European average of just 25 percent in the same period. It therefore seems clear that a reduction in antibiotic use need not lead to a less productive agricultural sector. High-income countries that need to reduce antibiotic use in agriculture should consider, and learn lessons from, the many other countries that have achieved this while maintaining productivity.

Our proposal also comes at a time when many major retailers in the US are moving towards lower levels of antibiotic use in their products. Under a new directive, the US federal government requires its agency to take antibiotic use and AMR into account when choosing meat suppliers. If this federal commitment were extended more widely, this could go some way to meeting such a target.

b. Type of antibiotics used.

We have indicated that there is a significant crossover between the antibiotics used in animals and humans, and that this can impact on the ability of the same or similar antibiotics to work effectively in humans. A recent, high-profile example of this was the resistance of bacteria to colistin in pigs and humans in China, which we have discussed earlier in the paper.

There are clear questions over the ethics and prudency of this use. Agricultural use has the potential to encourage the emergence of drug resistance that can transfer to the human population, severely undermining the efficacy of products that may be one of a few – or the only – options for use against difficult-to-treat infections.

It is encouraging that there have been steps towards identifying those antibiotics that are most ‘critical’ to human health, and prioritising the reduction of their use in agriculture (or outright withdrawal from it) above other products where the implications of rising resistance are less severe for human medicine. For instance, the European Medicines Agency (EMA) recently published an updated draft strategy for veterinary antimicrobial use[61], which sets out the need to restrict significantly the animal usage of products critical to human health, to those instances where no alternative exists for the treatment of a given condition or animal.

However, progress in this field has sometimes been hampered by a lack of consistency in the definition of antibiotics critical to human use. The WHO, for instance, has established its own categorisation of antibiotics critical to human use[62], which focuses on the conditions treated by particular products and the range of alternatives available. However, the recent EMA strategy is based on separate advice from its own Antimicrobial Advice Ad Hoc Expert Group (AMEG)[63], which adopts an alternative methodology based on a wider assessment of the risk of transmission of resistance from animals to humans. The FDA, in turn, has its own methodology.

It is not our role to question the validity or robustness of any individual process or report on this issue. However, we believe the next step should be to agree a harmonised global approach towards identifying those antimicrobials of greatest importance to human health, for which the risks from animal usage are highest. Given the consistency of the sentiment and rationale underpinning the approaches already taken, we believe this should happen within the next year, and should form the basis of restricting, and where necessary, banning antimicrobials that are important for human health.

This approach needs to be dynamic enough for any new antibiotics for human use to be added, and potentially allow for antibiotics to be removed if they are deemed no longer to be important for human health.

61. Committee for Medicinal Products for Veterinary Use (CVMP). CVMP strategy on antimicrobials 2016-2020 (draft). European Medicines Agency, 2015

62. World Health Organization. Critically Important antimicrobials for human use 3rd revision. Geneva, 2011.

63. European Medicines Agency, Answers to the requests for scientific advice on the impact on public health and animal health of the use of antibiotics in animals. 2014.

A PLAN TO REDUCE DRUG RESISTANCE FROM FOOD AND PHARMACEUTICAL PRODUCTION

2.

We need minimum standards to improve waste management in antimicrobial production

We need to improve standards of waste management to avoid scenarios where very high concentrations of antibiotics or APIs are released into the environment. There are different ways that this might be achieved. Our preferred route would be to have a minimum regulatory standard. However, while this is established, we believe there is a case for other participants in the supply chain to act now, improving transparency and standards for how antibiotic waste is treated.

Regulation: Any pharmaceutical, or indeed chemical product, undergoes a risk assessment to judge its safety in the environment and whether this is a threat to human and environmental health. However, there are currently no risk assessments undertaken for APIs or antibiotics that consider the impact that they could have on resistance in the environment.

There is not an existing body of empirical data about the concentrations of APIs and antibiotics in water courses and the impact of these on resistance. Such a body could be complex and time-consuming to generate, but that does not mean risk assessments should not be done, nor does it mean that targets should not be set. We instead propose that minimum standards for manufacturing of APIs and antibiotics be set based on the best available thinking in this area. These standards could then evolve and be refined as the evidence base and understanding continue to grow.

A good starting point for such standards might be a recent study[64], which proposed maximum limits for concentrations of common antibiotics in water. It assumes that the level at which these antibiotics have no effect on the environment is 10 percent of this maximum limit and proposes that this 10 percent level could be considered a reasonable limit for the concentration it is acceptable to find in a particular body of water.

Further discussion is needed as to how best to set these targets, and we welcome the views of experts in advance of our final report, but once agreed upon, they could be enshrined in relevant regulation, ideally as part of a broader framework for which there is a degree of international harmonisation. For example, this could readily use existing regulatory frameworks such as the Good Manufacturing Practice (GMP) guidelines that deal with medicinal products in Europe or national regulations that deal with hazardous waste. Details of both are provided in Appendices E and F.

We think it is important that regulation for a minimum standard is brought in swiftly, but recognise that manufacturers will need a period of time to change their processes, without causing significant disruptions in the supply of antimicrobials.

The supply chain driving change: Major buyers of generic antibiotics could factor appropriate management of environmental considerations, including the amount of APIs and antibiotics that the company or their suppliers generate as waste, into their procurement decisions. An alternative approach would be to integrate these considerations into reimbursement appraisals for generics, a process currently driven predominantly by price. In either case, effective reporting and oversight of the company's waste management and that of their suppliers would be key, something that is already a feature (and a challenge) in many industries, including food and clothing production. However, we note that many buyers – whether governments or private actors - have other near term priorities, that could push these sorts of considerations down the priority list.

Alternatively, a wider group of stakeholders could engage with companies and encourage or demand change. Such stakeholders could include the community itself, non-profits with aligned goals or long-term shareholders. Clearly, a situation where the buyer group and this wider stakeholder group come together would be even more powerful, as was the case, for example, with the development of the Roundtable for Sustainable Palm Oil. This was led by Unilever (a major global buyer) and the World Wildlife Fund for Nature (a key NGO stakeholder) and propelled by a rising awareness and desire for action on climate change amongst consumers. It has and continues to drive the palm oil industry, which is concentrated in two key countries (Malaysia and Indonesia), towards more sustainable practices, delivering both climate change and biodiversity benefits. In the case of AMR, though public awareness is rising, the fact that consumers do not make purchase decisions directly for antimicrobials but are rather guided by healthcare professionals may limit their engagement and suggest that buyers or NGOs, shareholders, civil society would need to lead the charge.

It is true that some companies have already made efforts to improve their environmental management through risk assessment frameworks. However, these do not currently consider the risks associated with rising resistance[65]. Rising awareness of the issue and a desire to protect their long-term licenses to operate within local communities (particularly if coupled with the above stakeholder engagement) may lead them to make some progress before legislative intervention.

64. Bengtsson-Palme J, Larsson DGJ. Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. *Environment International*,2015,86:140-149, doi:10.1016/j.envint.2015.10.015.

65. Murray-Smith RJ, Coombe VT, Grönlund MH, et.al., Managing emissions of Active Pharmaceutical Ingredients from Manufacturing facilities: An Environmental Quality Standard Approach. Integrated *Environmental Assessment and Management*, 2011, 8 (2), 320-330.

3.

Radically improve the surveillance of antibiotic use in agriculture and antimicrobial manufacturing waste

We need to radically improve the surveillance of antibiotic use in agriculture and the impact this and manufacturing have on resistant bacteria in animals, humans and the environment. The welcome announcement by the UK Government of 265 million GBP for the Fleming Fund to help improve surveillance in low and middle-income countries will help to achieve this goal. However, further international action is needed.

Not only will improved surveillance give us more information about where the biggest problems lie, both in unnecessary use and resistance, it will also help to inform and enforce global targets for reducing antibiotic use in food production, to ensure that any commitments made are being achieved. On the manufacturing side it will also help inform and improve the level at which a minimum standard is set.

As well as helping to achieve the two proposals we mention, surveillance of resistant bacteria in animals and the environment, along with the impact on the health of patients, needs to be more coordinated in order to improve our process of tracking the causes of resistant infections.

"Not only will improved surveillance give us more information about where the biggest problems lie, both in unnecessary use and resistance, it will also help to inform and enforce global targets for reducing antibiotic use in food production"

6.

HOW POLICIES TO LOWER USE COULD BE IMPLEMENTED

The economic case for interventions to lower unnecessary use:

When individuals take an action that has an external effect on third parties, economists label these effects as 'externalities'. Carrying and spreading infectious diseases, particularly pathogens that are resistant to common treatments, has large negative externalities, whilst actions that reduce the infection rate in society, such as vaccines, have positive externalities[66]. Every country aims to increase the number of positive externalities and reduce the number of negative externalities that take place. Externalities create suboptimal outcomes because often an individual's incentives will not align with those of society at large. This means that while an individual might make a decision that is best for them, it may not be ideal for society.

Within the realm of agriculture and the environment, there are negative externalities when farmers use antibiotics and fungicides, which have the potential to increase resistance rates in society, whilst positive externalities occur when farmers take steps that stop infections spreading. Some actions have both positive and negative externalities, such as treating a sick animal with antibiotics before the infection spreads. In this situation, there is the potential of increasing resistance because of the antibiotics the animal receives, but there is also likely to be a reduction in the number of animals that become sick, and this creates a positive externality that is likely to far outweigh the negative externalities of using the antibiotics[67,68]. Conversely, if the animal is not sick, the negative externalities may well outweigh the positive externalities. The case is even simpler on the manufacturing side, where releasing large amounts of active antibiotic ingredient into a lake represents an example of industrial pollution, creating a clear negative externality.

How could countries lower their levels of use in agriculture?

Many countries have become very good at controlling externalities. A wide range of policies from smoking bans to waste controls have been created to control the pollution of water, land, air and even noise; these principles go back to the 19th century and beyond, and are not controversial. At the same time states encourage education, vaccination and recycling, which all have positive externalities. The two most common ways of dealing with externalities are either regulation or changing the cost of the action, so that decision makers internalise the costs and benefits to society. This is normally achieved by a tax on negative externalities and subsidies for positive ones[69].

From a standard economic perspective, governments and international bodies can (i) implement regulation to reduce antibiotic use, (ii) tax use or (iii) subsidise the cost of implementing infection control measures or alternatives. Each of these has merits and downsides, which we discuss in Appendix A, and a comprehensive policy intervention may include all three. We feel that there is a need to reduce the quantity of antimicrobials used in agriculture, however for a variety of political, economic and cultural reasons a policy that works well in one country may not work well in another. For this reason we believe that there should be international targets for reducing use, but that individual countries should decide how to meet these targets.

Alternative approaches to reducing antibiotic use in agriculture to meet a global target:

As well as creating the right economic conditions for incentivising change, there are a number of interventions that policy makers, the farming industry and governments should examine in order to reduce their antibiotic consumption.

Vaccines

Vaccines can protect animals against bacterial infections, reducing the need for prophylactic and therapeutic use of antibiotics. Bacteria do not develop resistance to vaccines in the same way they do to antibiotics, but they can still evolve to evade vaccines. For this reason some vaccines may require regular 'updates' to make sure they continue to offer adequate levels of protection against circulating strains.

Some studies suggest that antibiotic consumption could be roughly halved if farm animals were properly vaccinated, which could make a significant impact on resistance. Going forward, the better vaccines we have the greater this reduction could be[70].

66. Chen F, Toxvaerd F, The economics of vaccination. *Journal of Theoretical Biology*, 363, 105-117.
67. Hollis A, Ahmed Z, Preserving Antibiotics, Rationally, *New England Journal of Medicine*, 2013, 369, 2474-2476.
68. Plumer, B, The Case for an Antibiotics Tax, Article in Washington Post, January 13, 2014, Available at: https://www.washingtonpost.com/news/wonk/wp/2014/01/13/the-case-for-an-antibiotics-tax/, [Last accessed on 30th November 2015].
69. North DC, Thomas RP, The Rise of the Western World: A New Economic History. Cambridge University press, 1999, first ed. 1973.
70. Bak H, Rathkjen PH, Reduced Use of Antimicrobials after Vaccination of Pigs Against Porcine Proliferative Enteropathy in a Danish SPF Herd. Acta VeterinariaScandinavica 2009, 51(1).
71. Allen H K, Levine UY, Looft T, Bandrick M Casey TA, Treatment, Promotion, Commotion: Antibiotic Alternatives in Food-Producing Animals. *Trends in Microbiology*, 2013, 21(3), 114-119.
72. Cheng G, Hao H, Xie S, Wang X, Dai M, Huang L Yuan Z, Antibiotic Alternatives:

While the current standard of vaccines is generally considered to be high, there are some areas where the science exists but has not been commercialised because there is not the incentive to do so[71]. Furthermore, high prices are reportedly an important impediment to mass vaccination of poultry, for example[72]. Even where the price of intravenous vaccines and the cost to administer these might be affordable for large animals, for small animals and fish the overall cost may be too high, and ones that can be administered via feed or bath mechanisms, for a lower per animal cost, may be needed.

Regulation and taxation of antibiotics would strengthen the economics of vaccines, as farmers would be pushed to seek alternatives to their current practices. This would make the market stronger and increase investment into new vaccines that match farmers' needs. However there may be a case for greater intervention, where the cost of creating new vaccines is too high, because of the wide benefits that vaccines create. We will be assessing the vaccines market for humans and animals in more detail in a paper early next year. This will include a market assessment and consideration of the current interventions that support the development of vaccines for humans, such as the advanced market commitment provided by Gavi (the Vaccine Alliance), to purchase pneumococcal vaccines. There could be a case for having a similar commitment on the animal side – whilst recognising that the distribution of public and private benefits will often be different in vaccines designed for food-producing animals from those for human use – and we will consider this, along with the possibility of vaccines having access to a global innovation fund and other interventions in our paper next year.

More information on our proposals on vaccines so far is available in Appendix D.

Diagnostics

The arguments in favour of rapid diagnostic devices for farm animals are in many ways similar to those for humans, which we laid out in an earlier paper[73]. Rapid, cheap and easy to use diagnostics will allow farmers to know very quickly when their animals become ill, and allow them to separate those animals, potentially preventing the spread of an infection and reducing the need to use antibiotics in many animals. Diagnostics will also reduce the need for prophylactic use, since farmers would be able to test their animals regularly to see if they have a bacterial infection, rather than undertaking prophylactic use, just in case. Diagnostics that can test susceptibility would be even more useful because they would allow vets or farmers to give the antibiotic that is most likely to cure the animal and least likely to cause resistance in humans, thus allowing us to protect antibiotics critical for human use.

Similarly to vaccines, regulation and taxation of antibiotics would strengthen the market in this area. The human diagnostic market is almost inevitably going to be better at creating diagnostics than the animal market, and the case for intervention there is stronger. Therefore it seems sensible for human-based innovation to lead here, but policy-makers should take steps to make sure that where possible technology is adapted to work in animals too.

Public awareness

Public awareness and education can also play an important role, especially where consumers have a clear choice between the products that they purchase and consume. Responding to consumer pressure from activist groups, several companies, including fast food chains, wholesale producers and food retailers, have imposed voluntary guidelines and targets to reduce the use of antibiotics in their supply chains[74]. Overall, sales of 'antibiotic-free' chicken in the US rose by 34 percent in 2013[75]. This increase seems to be driven largely by consumer demand influencing private companies – 86 percent of consumers want 'antibiotic-free' meat at their local grocery store and more than 60 percent would be willing to pay more for it[76].

These changes made by individual companies might be among the most practical short-term shifts to reduce use, at least in agriculture. To support this effort, requirements to ensure that labelling makes reference to antibiotic use would improve consumer knowledge and help enable consumers to make a more informed choice. This might not simply be a case of having products labelled as 'antibiotic-free'. Indeed this might provide incentives for farmers to withhold antibiotic treatment when an animal might need it, for fear of the economic cost of not being able to sell the meat. It may well be better to have a 'responsible use of antibiotics' label, or something similar.

As well as labelling changes, a global public awareness campaign on AMR, such as the Review has already called for, could include a strand focussed on antibiotic use in agriculture and the environment. One of the challenges for such a campaign would be to create long-term behaviour change by consumers, but if it could be achieved it has the potential to provide excellent value for money.

The Substitution of Antibiotics in Animal Husbandry? *Frontiers in Microbiology*, 2014, 5(217).

73. Review on Antimicrobial Resistance, Rapid Diagnostics: Stopping Unnecessary Use of Antibiotics. 2015.

74. See Consumer Reports report (full citation below) on prevalence of antibiotic-free meat in 123 major US supermarkets and the National Defence Research Council's case study (.NDRC, Case study Going mainstream: Meat and poultry raised without routine antibiotics use, 2015, Available at: http://www.nrdc.org/food/files/antibiotic-free-meats-CS.pdf .

75. Wall Street Journal, Meat companies go antibiotics-free as more consumers demand it, November 2013,[Online] Available at: http://www.wsj.com/articles/meat-companies-go-antibiotics-free-as-more-consumers-demand-it-1415071802.

76. Consumer Reports, Meat on drugs: the overuse of antibiotics in food animals & what supermarkets and consumers can do to stop it,' Consumer Reports, 2012, Available at: https://www.consumerreports.org/content/dam/cro/news_articles/health/CR%20Meat%20On%20Drugs%20Report%2006-12.pdf.

Global action on CFCs

The world has been successful at coming together to tackle similar environmental and public good challenges to the ones this paper highlights, which we believe we can learn lessons from. Chlorofluorocarbons (CFCs) are organic compounds that until the early 1970s appeared to be a crucial part of many appliances ranging from fridges, to deodorants, to aeroplanes and fire extinguishers. In the 1970s, it was discovered that there was an increasing amount of CFCs in the environment and that this was doing serious damage to the Earth's ozone layer. Increasingly robust evidence showed that the ozone layer was getting thinner, and this was linked to CFC production, so that by the early 1980s the scientific questions were considered to have been settled.

Despite this, many in the CFC industry continued to argue that the evidence did not warrant action, possibly because they experienced large financial benefits from preventing change. CFC producers spent large sums in the 1980s to lobby the public and government, similar to campaigns that have taken place in the tobacco industry and around fossil fuels. The head of the world's largest CFC producer wrote to the US Congress in 1988 stating that "At the moment, scientific evidence does not point to the need for dramatic CFC emission reductions[77]."

Despite the efforts of industry, many countries began to bring in regulation limiting their domestic use and production of CFCs. Similarly to antimicrobial resistance, CFCs affected all countries, not just those generating emissions. To combat this, the Montreal Protocol was created, where signatories agreed to strict targets, which were imposed across the world to reduce emissions to about 5 percent of the 1980 levels, with sanctions for those who broke them. Funding was given to help low and middle-income countries adapt to the new rules and they were given less strict time deadlines. In 1990, this was extended to an agreement that high-income countries would eliminate all CFC use by 2000 and low and middle-income countries would do so by 2010.

Every country in the UN has now ratified the Montreal protocol, and virtually no new CFCs are produced in the world today. This system worked because the public widely supported greater efforts to stop CFCs and put pressure on politicians, who were then willing to enact radical new rules. These new rules then helped to encourage industry to find innovative ways stop using CFCs. The threat of sanctions as well as funding ensured that all countries were willing to abide by the rules. While there were transition costs to the reduction of CFCs, these were not nearly as significant as originally expected, and innovation in industry allowed for an orderly transition away from CFCs. While this process was not perfect, and we would like to see lower and middle-income countries take a leading role in tackling this problem, the Montreal protocol has interesting parallels for how AMR could be tackled in agriculture[78].

Appendix F has further information on how the global problem of hazardous waste disposal has been dealt with in recent decades, and how we can draw lessons from this in tackling the problem of manufacturing waste from antibiotics.

77. Benedick, R E., Ozone Diplomacy: New Directions in Safeguarding the Planet. Cambridge, Mass: Harvard University Press, 1998.

78. DeSombre, ER, The Experience of the Montreal Protocol: Particularly Remarkable, and Remarkably Particular. *UCLA Journal of Environmental Law and Policy*, 2000, 19(1).

7.

NEXT STEPS

This paper proposes that we need to reduce the unnecessary use of antibiotics in animals and improve waste management practices during antimicrobial manufacturing. However, while this is a very important part of the picture, if the world is truly to tackle AMR, there are further issues that we also need to consider.

Going forward we will provide analysis and recommendations in areas including:

- Preventing and limiting the spread of infections. Prevention removes the need for therapeutic treatment, thereby reducing the need for antimicrobials to be used. The ways we can improve this range from washing our hands better, to improving global health infrastructure and surveillance systems, to track and act on the spread of resistant infections.

- Alternatives to antibiotics. Although antibiotics have become the dominant treatment for bacterial infections and will continue to play a key role, there are other opportunities to tackle bacterial infections that we will explore, including the role of vaccines, phage and other alternatives therapies that could replace or accompany antibiotics.

Moving towards action

It is generally accepted that AMR is one of the biggest threats facing mankind, and the imperative for action is growing at both an individual and a global political level. We need progress on both of these fronts in order to tackle this threat, and this cannot be limited to action on human use. This must include progress on the use of antimicrobials in food production, which accounts for more than half of global use. It must also include action to ensure that manufacturing practices are improved and the quantities of APIs reaching the environment through waste are reduced.

In May, the World Health Organisation (WHO) released its Global Action Plan for AMR, with one of its main objectives being to "optimize the use of antimicrobial medicines in human and animal health". In particular, the WHO announced that "more widespread recognition of antimicrobial medicines as a public good is needed in order to strengthen regulation of their distribution, quality and use," and to regulate "inappropriate or unregulated use of antimicrobial agents in agriculture." At the same time the UN's Food and Agriculture Organization (FAO) has called on members to "take urgent action at regional, national and local levels to mitigate risks posed by inappropriate antimicrobial usage and antimicrobial resistance in food, agriculture and the environment." And the World Organisation for Animal Health (OIE) recommended that we need to "continue to develop and update standards and guidelines related to antimicrobial resistance and the prudent use of antimicrobial agents including updating regularly the OIE List of Antimicrobial Agents of Veterinary Importance." That these three bodies took the step of agreeing specific recommendations on the challenge of rising drug resistance, with all their member countries signed up, is testament to the urgency and high stakes at play.

These are difficult problems, and action will inevitably mean short-term economic costs, but the economic cost of inaction, which could mean a cumulative hit to the world economy of 100 trillion USD by 2050, dwarves these costs. This is not to mention the many millions of lives that will be lost if we do not curb resistance or find long-term solutions to producing, using and disposing of antimicrobials.

We have already called for action at the G20 and UN General Assembly, to agree specific recommendations for action, and are pleased to see the international progress that is being made. The recent communiqués from the German G7 presidency and Turkish G20 presidency both highlighted this, naming AMR as one of the main health threats we face, and asking the 2016 G20 to continue to work towards solutions. Agreement at this level is essential, and we hope that 2016 will be the year when specific actions are agreed, and implementation begins.

"We have already called for action at the G20 and UN General Assembly, to agree specific recommendations for action, and are pleased to see the international progress that is being made"

APPENDIX A:

ECONOMIC POLICY INTERVENTIONS

Regulation

Regulation has been one of the main ways in which countries have tried to reduce their antibiotic use in agriculture.

The Scandinavian countries were ahead of the curve in banning antibiotics for use as growth promoters. However it is difficult to judge the extent to which their reduction in use was due to regulation and how much of it was linked to the greater public awareness that accompanied their changes. In 2006 the EU banned all antibiotics used as growth promoters and required veterinary prescriptions for antibiotics used in food animals, though allowing member states to grant exemptions in some cases. The success of the ban varied greatly between European nations, with some Northern European countries going beyond the ban and setting targets for use, such as in The Netherlands, whilst in many other countries antibiotic use remained very similar in level to before the ban. In the US, the FDA recently negotiated voluntary regulations where antibiotics would not be used as growth promoters. However there is a question as to how effective this will be, with the Pew Charitable Trusts finding 66 antibiotics still allowed for sale at dosages low enough for growth promotion, 29 of which were classified by the FDA as critically important for human medicine[79].

This shows the main problem with narrowly-defined regulation. It is very difficult for governments and international bodies to observe what type of use a farmer is undertaking, or even the amount of antibiotics they are using. Checking this requires some sort of oversight, which countries like Denmark have invested heavily in, but other European states have mostly ignored. The reason we have proposed that countries have limits on the amount of use rather than the type of use, is because this is far easier to observe and measure, though it still relies on far greater data collection, collation and analysis than most of the world has at the moment, which is why we propose to combine a target with a radical improvement in surveillance. There are simpler regulations that countries could bring in to reduce demand for antibiotics, such as creating clearer standards of when antibiotics are necessary, incentivising farmers to improve animal hygiene and use vaccines more regularly, and delinking vet payments and profits from prescribing antibiotics.

Taxing antimicrobials

As previously discussed, every time a farmer uses antimicrobials a cost is created for the whole of society, regardless of whether the use of an antimicrobial is justified or not. The theory behind taxing antimicrobial use is that by forcing farmers to pay an additional cost for every antimicrobial they use, they will then take into account the costs that their action has on society at large. The tax would thus be set at a rate that is roughly equal to the societal cost of the antimicrobials used. By aligning the farmers' incentives with those of society more broadly, this policy would aim to make them act in the way that is best for everybody.

For example, regulation that attempts to lower prophylactic use of antimicrobials would run the risk of interfering with some prophylactic use that is useful for society. If five animals in a much larger herd became sick with a bacterial infection, it would be likely that some of the other animals would become sick too. By quickly treating the rest of the herd with comparatively low dosages of antimicrobials, most of those animals might escape disease, and the herd as a whole could use significantly less antimicrobials. While regulation could achieve this aim too, there are observational difficulties, meaning the state may struggle to tell whether a farmer is using antimicrobials reasonably, which could cause treatment delays, costing both the farmers and the regulators, time and money.

The second benefit of a taxation system is that it would encourage farmers to use alternatives to antimicrobials, such as improved husbandry, vaccines and diagnostics, as the antimicrobials would be more expensive to use.

In order to implement such a system the demand curve for antimicrobials needs to be better understood. A tax should be set that discourages growth promotion, and unnecessary prophylactic use, but that does not stop farmers from adequately treating their sick animals. In absolute terms this cost might be low, particularly if the aim is just to discourage growth promotion. However, because antimicrobials are relatively cheap, the tax might need to be high relative to the cost of the product.

The calculation of the levels at which drugs would be taxed should also look to discourage antimicrobials that are most likely to cause resistance in humans. Antimicrobials that are more likely to increase resistance, especially in regard to drugs used in humans should be taxed more heavily, and most antibiotics used in agriculture are also used in humans (this is indicated by our infographic: *Many antimicrobials used in animals are important for humans*).

The biggest implementation worry for this approach is that farmers might be able to circumvent the tax by buying

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79. Policy Brief, Gaps in FDA's antibiotics policy, The Pew Charitable Trusts, November 2014.

counterfeit or black-market drugs. As the paper we published in November 2015[80] showed, counterfeit drugs being sold to humans is a problem, and a tax on the agricultural side would risk increasing that problem for agriculture. For this reason, we recommend that any tax is levied at the earliest possible point, such as when the products leaves the factory, so that the number of entities that need to be taxed are reduced. While the risk of people circumventing this system would still exist, governments are often better at raising taxes than regulating, because the former is profitable while the latter costs money. The cost of circumventing any system created by governments would also cost money and thus drive up the price of antimicrobials, which would reduce their use.

Such an intervention might be more difficult for manufacturing practices and how waste is dealt with, as it would be hard to record exactly how much waste each factory produces. The options of regulation and subsidies might be better suited to dealing with this issue.

Subsidies to support alternatives

There are a number of interventions that can be taken to reduce the amount of antimicrobials needed in agriculture, such as improving infection control, using different herds or crop types, vaccines, diagnostics, surveillance, and behavioural change. All of these actions could also be incentivised by either regulation, or a tax on antimicrobial use, encouraging farmers to reduce use and find alternatives. However, in many of these areas an additional intervention may help farmers more quickly and easily move away from antibiotic use, in a way that is beneficial for everyone.

From an economic point of view it makes sense to subsidise actions that are not in an individual's interest to take, but are beneficial to society as a whole. The rationale is that society should pay a small amount of money to farmers, so that they can change their farming practices, and reduce the chances of people becoming ill with resistant infections. This principle does not only have to work within states. For example, one of the reasons for success in the reduction of CFCs was that high-income countries helped emerging economies move away from CFCs, because they recognised it was in their interest to do so.

Some governments may also want to protect smaller farmers. When Denmark banned antibiotic use for growth promotion in finishing pigs in 1998 it saw a very small economic cost. In the fifteen years since 2000, when all antibiotics for growth promotion were banned, the country's pig industry has become increasingly productive. However, there were large switching costs for farmers. Often farms had to construct new buildings to house their pigs in a way that reduced the spread of infection, as well as invest in more resilient breeds of pigs. These switching costs led to large numbers of smaller pig farms either being consolidated into bigger farms or going out of business. In order to limit this effect on farmers and ease the transition, subsidies could be provided to transition to lower antibiotic use, or farmers could be given access to support loans. Given that productivity rates should remain comparable after the transition, this could potentially be a one-off payment. Further extensive research is needed into the potential transitional costs for different countries and livestock types across the world, to quantify the size of subsidies that would be needed.

Within drug manufacturing, giving subsidies to help develop better processes and potentially buy new equipment that reduces the level of APIs in manufacturing waste, which in turn reduces the build-up of resistance in the local environment, is again in everybody's interest. People in higher-income countries have long benefited from low prices of drugs produced in a environmentally unsound way in lower-income countries. Indeed the pollution that is caused has an especially large impact on those living locally, but has grave consequences for everyone, as resistance travels. We now need to work with those countries and industries to reduce this pollution. Sharing technology and providing subsidies or loans to support transition may make sense.

80. Review on Antimicrobial Resistance, Safe, secure and controlled; managing the supply chain of antimicrobials, 2015.

APPENDIX B:

IONOPHORES AND THEIR USE IN FOOD PRODUCTION

Ionophores can be used as feed additives to stimulate growth, and prophylactically to prevent a parasitic infection, known as coccidiosis, in cattle and poultry[81]. Several governments and companies specifically exclude ionophores from antibiotic use regulations[82], based on their apparently distinct mechanism of action; others do not. Europe, for example, has banned ionophores for growth promotion[83], though these are still available to use to treat parasitic infections (as anti-coccidiostats).

Ionophores work by puncturing the cell membrane of bacteria, which rapidly results in the death of the microbe. There is a debate about whether this is fundamentally different to the way most antibiotics work. Though there are studies that suggest that resistance or tolerance to ionophores can develop, there are others that suggest that ionophore use is unlikely to lead to resistance in people as this resistance or tolerance tends to develop more slowly, and may well be a reversible change - one that disappears once the drug is removed. This suggests that this type of resistance may not be able to spread to other microbes[84,85].

We have not made assumptions on whether ionophores should be included in a global target to reduce antibiotic use in agriculture. This is something that international policy makers would need to agree when the target is set. It is clear to us, however, that more research is needed to ensure that ionophores, and other widely used antimicrobials, are not contributing to resistance problems.

81. National Office of Animal Health, Anticoccidials May 2010, Available at:http://www.noah.co.uk/issues/briefingdoc/13-anticoccidials.htm.

82. Duax WL, Griffin JF, Langs DA, Smith GD, Grochulski P, Pletnev V, Ivanov V., Molecular structure and mechanisms of action of cyclic and linear ion transport antibiotics. *Biopolymers*. 1996, 40(1), 141-55.

83. European Commission, 2006, Ban on antibiotics as growth promoters in animal feed enters into effect, IP/05/1687, Brussels.

84. Simjee S, Heffron A, Pridmore A, Shyrock TR, Reversible monensin adaptation in *Enterococcus faecium, Enteroccus faecalis* and *Clostridium perfringens of cattle origin:* potential impact on food safety. *Journal of Antimicrobial Chemotherapy*, 2012, 67(10): 2388-2395, doi:10.1093/jac/dks236.

85. Houlihan AJ, Russell JB, The susceptibility of ionophore-resistant *Clostridium aminophilum F* to other antibiotics," *Journal of Antimicrobial Chemotherapy*, 2003, 52, 623-628.

APPENDIX C:

METHODOLOGY OF OUR LITERATURE REVIEW

A Boolean search was undertaken of the PubMed database[86] (US National Library of Medicine, National Institutes of Health), by searching for the terms "drug resistance, microbial" AND "agriculture". When undertaken in July 2015, this returned 280 unique records. Although not necessarily an exhaustive selection of all papers of relevance to this field, this search strategy was used to provide a representative sample of the papers available.

Each paper was categorised according to whether or not it provided evidence to support a ban on antibiotics in agriculture – for example, evidence that antibiotic usage in agriculture negatively impacted human health. Each paper was categorised as for, against or neutral. Several of the papers returned from this search did not address antibiotic usage in agriculture, and these papers were labelled not applicable.

For each paper, the author affiliation was noted and categorised into one of three author affiliation[87] categories: **academia** (typically universities, university hospitals, and other academic institutions), **government** (national and state departments of agriculture and health), and **industry** (pharmaceutical, animal health, and other private companies). If this information was not apparent from the PubMed abstract page, the information was obtained from the actual paper itself. If author affiliation still was not apparent from the paper (as was the case with a small handful of articles dating before 1970) the author's name was searched on Google to determine affiliation. For four papers that had a stance, the author's affiliation could not be ascertained, so these were classed as not applicable.

Article classification	
Y	"yes" - provides evidence to support limiting antibiotics in agriculture
N	"no" - provides evidence that we should **NOT** be concerned with limiting antibiotics in agriculture
X	"neutral" - acknowledges the problem of antibiotic use in agriculture, but does not explicitly defend a stance
NA	"not applicable" - does not address antibiotic usage in agriculture in the paper

Full breakdown of all the papers examined:

	Academia	Government	Industry	Unclear	Total
IN FAVOUR	100	13	1	0	114
AGAINST	7	6	2	0	15
NEUTRAL	32	30	1	0	63
NOT APPLICABLE	49	20	1	18	88
TOTAL	188	69	5	18	280

86. PubMed comprises more than 25 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full-text content from PubMed Central and publisher web sites. PubMed can be accessed at http://www.ncbi.nlm.nih.gov.

87. If multiple authors with different author affiliations were present, the first author's affiliation was used.

After non-applicable papers were removed, the percentage of each affiliation is in brackets:

	Academia	Government	Industry	Total
IN FAVOUR	100 (72%)	13 (27%)	1 (25%)	114 (59%)
AGAINST	7 (5%)	6 (12%)	2 (50%)	15 (8%)
NEUTRAL	32 (23%)	30 (61%)	1 (25%)	63 (33%)
TOTAL	139 (100%)	49 (100%)	4 (100%)	192 (100%)

A full list of these papers and how they were classed is available on our website: www.amr-review.org.

88. Bak H,Rathkjen PH,Reduced Use of Antimicrobials after Vaccination of Pigs Against Porcine Proliferative Enteropathy in a Danish SPF Herd, *Acta Veterinaria Scandinavica* 2009, 51(1).

APPENDIX D:

VACCINES IN AGRICULTURE

Why are vaccines in agriculture important?

Antibiotic use in agriculture has some very desirable effects, but also some undesirable consequences. However, there is some scope to get the best of both worlds. If an animal is successfully vaccinated against infection, then at least two of the desirable effects of antibiotic use are achieved, without contributing to increased AMR. First, the vaccine in essence performs the same task as prophylactic use of antibiotics. Second, by successfully avoiding infection, a vaccine may help in reducing the need for therapeutic use of antibiotics. Mass immunisation of animal herds can lead to significant decreases in antibiotic use and this has been shown in a Danish experiment on vaccination in pigs[88]. Both Nereem (2006)[89] and Thaker and Bilkei (2006)[90] find similarly encouraging evidence. Bak and Rathkjen (2009)[91] even found evidence that, compared to a non-vaccinated control group, vaccinated pigs gained more weight and thus provided a higher yield. This would suggest that at least in some instances, the use of successful vaccination strategies may even decrease the need to rely on antibiotic use to promote growth.

That increased vaccine uptake must be part of a successful strategy to decrease the reliance on antibiotics has already been identified both in policy circles (see briefing of the Parliamentary Office of Science & Technology, 2013[92]) and by the pharmaceutical industry itself[93].

How big an impact can vaccines have on agriculture?

The impact of increased uptake of vaccines in agriculture could have potentially large effects, as there seems to be strong evidence that immunisation programs are successful at reducing the use of antimicrobials[94]. Innovation in the pharmaceutical industry on new vaccines would enhance such effects.

Bak and Rathkjen (2009) reported that mass vaccination more than halved the use of antibiotics for pigs, and they point to other studies, which suggested that antibiotic use could in some cases be entirely eliminated. However, the exact nature and extent of the effects will depend on the specifics of the different animals, diseases and vaccines, and caution is needed to avoid generalising across the agricultural sector. Furthermore, the total impact will also depend on other issues in addition to mere feasibility, such as the ease of delivery of the vaccines, the cost to farmers and the range of vaccines on offer, now and in the future.

Are vaccines important enough to be a main policy tool?

According to the Parliamentary Office of Science & Technology (2013) and the National Office of animal Health (2013), there currently exist vaccines for most of the main animal diseases (for cattle, sheep, pigs, poultry and fish), with a wide range of delivery options. Still, there is evidence that potentially important vaccines are at advanced stages of development yet not being commercialised[95]. Prevailing vaccine prices are reportedly an important impediment to mass vaccination of, for example, poultry[96].

In order to gauge the feasibility of substituting away from antibiotics and towards a heavier reliance on vaccination, we need to know if the price is reasonable, and if the incentives are currently good enough to create new vaccines.

The overall picture that emerges seems to be this: There is an existing range of vaccines available for many of the main animal diseases and interesting new vaccines in the pipeline. Additionally, advances in biotechnology hold the promise of developing new vaccines (Parliamentary Office of Science & Technology, 2013). However, at the present time, the agricultural sector does not seem to fully make use of the available vaccines, due to a perception that prices are too high (relative to the existing alternatives). In turn, weak uptake may go some way towards explaining why some promising vaccines are not being commercialised. However there is a particular need for non-injectable vaccines for smaller animals, particularly fish, where it is prohibitively expensive to inject individual animals.

Other interventions we have considered might help to tackle these problems. A tax on antibiotics would encourage a switch away from antibiotics and an increase in vaccine uptake. As taxes are imposed on antibiotics, vaccines will become more attractive from the perspective of the farmer, even if no additional subsidies to vaccines are offered. Regulation that banned or seriously limited certain types of antibiotic use should have a similar impact, by making it more difficult for farmers to give antibiotics to their animals they will turn to other ways to achieve the desired effect. As all of society gains from a reduction in antibiotic use, vaccines could also be subsidised in order to make them cheaper and more attractive than antibiotics.

89. Nereem JL, Comparative Finishing Performance of Swine Receiving *Lawsonia intracellularis* Vaccination or Continuous Dietary Antimicrobial Medication, in *Proceedings of the 19th IPVS Congress*. 2006, Volume 1. Edited by Nielsen JP, Jorsal SE. Narayana Press; 2006: 246.

90. Thaker MYC, Bilkei G, 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), *Tierärztl Umsch*, 2006, 61, 372-376.

91. Bak and Rathkjen (2009)

92. The Parliamentary Office of Science and Technology is the UK Parliament's in-house source of independent analysis of public policy issues related to science and technology.

93. Vaccines Europe, Role of Vaccination in Reducing Antimicrobial Resistance, 2013,Available at http://www.vaccineseurope.eu/wp-content/uploads/2013/09/AMR-and-Vaccines-June-2013.pdf, [Accessed on: 18th November 2015].

94. Wilby KJ, Werry D, A Review of the Effect of Immunization Programs on Antimicrobial Utilization, *Vaccine*, 2012, 30(46), 6509-654.

95. Allen HK, Levine UY, Looft T et.al., Treatment, Promotion, Commotion: Antibiotic Alternatives in Food-Producing Animals, *Trends in Microbiology*, 2013, 21(3), 114-119.

96. Cheng G, Hao H, Xie S, et.al., Antibiotic Alternatives: The Substitution of Antibiotics in Animal Husbandry?, *Frontiers in Microbiology*, 2014, 5(217).

These policies could also increase the value of the vaccine market from the perspective of the pharmaceutical industry. Since the demand for vaccines would increase, this would encourage both the commercialisation of promising vaccines at late stages of development but also investment in new vaccines for the future.

There might also be a case for health systems and international bodies to fund the research and development of new vaccines. Creating vaccines for animal use is usually far cheaper than for humans, because of the lower costs of running trials. Early stage research could be funded through the innovation fund we have advocated establishing.

Finally, it should be noted that even in the absence of taxes or restrictions on use, over time some movement towards vaccines should be expected. In particular, as treatment over time becomes less efficient (because of increased resistance), vaccines will become a relatively more attractive option, simply because the option to treat will no longer offer the desired outcomes.

APPENDIX E:

GOOD MANUFACTURING PRACTICES

These directives and guidelines provide the minimum standards that medicinal products have to comply with before they can be sold in Europe[97]. These standards are set at a country or regional level, but are broadly harmonious with each other. They are overseen and enforced by regulatory agencies, for example the FDA in the USA. However, their core focus is to make sure food, drugs and APIs are safe for consumption. They do not deal directly with emissions and the collateral damage which could be caused from antimicrobial waste reaching the environment. Sweden has proposed to the EU health ministry, that the GMP be amended to include environmental criteria to regulate the third-party suppliers of many companies that are outside the EU[98].

97. Pruden A, Larsson DGJ, Amézquita A, et.al., Management options for reducing the release of Antibiotics and Antibiotic Resistance Genes to the Environment. *Environmental Health Perspectives*, 2013, 121:878–885.

98. *Ibid*.

APPENDIX F:

HAZARDOUS WASTE DISPOSAL

There are useful examples that we have examined of international coordination to limit the use, and disposal, of potentially harmful substances in the last 30 years. The Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal, the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade, and the Stockholm Convention on Persistent Organic Pollutants all operate with the shared aim of protecting human health and the environment from the ill-effects of hazardous chemicals and wastes[99]. These three conventions regulate different stages in the life-cycles of hazardous materials.

The Basel Convention was the first to come into effect, in the early 1990s, after much of the world realised that higher-income countries were taking advantage of a lack of regulation and enforcement capacity in low and middle-income countries and were transporting and dumping their waste there due to the increasing regulations and costs of waste disposal in their own countries. These included many hazardous wastes including chemical, radioactive, and municipal solid waste among others. The public outcry over this issue led to the adoption of the Basel Convention, which as of 2015, 183 countries were party to. According to the stipulations of the treaty, export of hazardous material for disposal is allowed only if the agreement regarding the disposal is as stringent as the Basel Convention, and hazardous wastes cannot be exported to countries that banned these imports. The convention promotes environmentally sound waste management practices and calls for the reduction of waste production.

The Rotterdam Convention aims to promote information sharing on imports of hazardous chemicals and came into effect in 2004. The aim of the convention was to allow exchange of information for countries importing and exporting hazardous wastes and to force countries to ensure that their producers comply with these rules.

The Stockholm Convention deals with the use of organic pollutants that are persistent in nature and that are capable of accumulating through the food chain, and are a risk for human health and the environment. The Convention requires that developed countries provide financial resources and measures to mitigate the production of persistent organic pollutants (POPs) and dispose of POPs in an environmentally safe manner.

The adoption of these conventions by most of the countries in the world is a demonstration of how countries have come together in the past to harmonise regulations to limit the production, use and disposal of harmful substances into the environment in an effort to protect both human health and the environment, regardless of location. This is particularly important for AMR, given that many manufacturing processes take place in lower and middle-income countries where regulations are either not in place or not strictly enforced and where the negative effects are more keenly felt, but the benefits of these products are felt the world over.

99. Piery K K, Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal. 1989, Audiovisual Library of International Law, United Nations Environment Program.

APPENDIX G:

USE OF ANTIBIOTICS IN PETS

While the overall quantities of antibiotics used in pets are significantly lower than those consumed by the agricultural sector[100], the closer proximity that most members of the public, especially children, have to pets makes them important from a human health perspective.

Antimicrobial use is common in pets for the treatment of diseases, as well as pre- and post-surgery. Similarly to food animals, antimicrobials that are used in humans are often used for treating pets[101]. These include commonly recognised antibiotics such as penicillins, cephalosporins, macrolides, and tetracyclines among others. A study from Denmark in 2003 showed that for total consumption in the country of cephalosporins in animals, over 50 percent was consumed by pets[102]. However, total antibiotic use in food production is usually far higher than that used in pets.

There are a number of studies that link contact between pets and humans with resistant bacteria transfer, this is not uncommon[103,104]. Indeed this transfer can go both ways - to and from human to pet. Studies have shown that pets, as other family members, can be reservoirs for resistant bacteria, such as Methicillin-resistant S*taphylococcus aureus* (MRSA), and multidrug-resistant Gram-negatives, including *E. coli* and *Salmonella*.

Many of the problems with human use and prescription of antimicrobials apply to pets. Therefore the solutions are more akin to the solutions we have set out in our previous paper on human use of antibiotics and rapid diagnostics. Unnecessary empirical treatment due to lack of antimicrobial susceptibility testing for bacteria that cause animal illnesses is a significant problem[105]. Better rapid diagnostics could help to tackle this, along with improved education for vets and animal owners around the dangers of unnecessary use of antibiotics, and better surveillance capabilities.

100. Lloyd DH, Reservoirs of antimicrobial resistance in pet animals, *Clinical Infectious Disease*, 2007, 45(Supplement 2): S148-S152.doi: 10.1086/519254.
101. Guardabassi L, Schwarz S, Lloyd DH, Pet animals as reservoirs of antimicrobial-resistant bacteria, *Journal of Antimicrobial Chemotherapy*, 2004, 54,321-332.
102. DANMAP, 2003: use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark. Sørborg, Denmark: Danish Zoonoses Center;2004.
103. Guardabassi et.al. 2004.
104. Lloyd, 2007.
105. Gaurdabassi et.al. 2004.

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