INDEPENDENT REVIEW ON ANTI-MICROBIAL RESISTANCE (AMR)

REGULATION-INNOVATION INTERACTIONS IN THE DEVELOPMENT OF VETERINARY ANTIMICROBIAL DRUGS AND DIAGNOSTICS

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SUPPLEMENTARY REPORT 3

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14 December 2014

Content

Summary 3
1. Background on Veterinary Drug and Diagnostic Use 5
1.1 Antimicrobial use in animals 5
1.2 Notifiable Diseases 8
1.3 Limited Use of Microbiological Diagnostics outside of Notifiable Diseases 8
2. Policy Context: Growing Concerns over Antimicrobial Use in Animals 9
2.1 Policy in the EU 9
2.2 Examples of National Activity 10
2.3 Overview of UK Activity 12
2.4 European Commission Proposals for the Regulation of Veterinary Medicinal Products 13
2.5 Policy in the US 13
3. Impact of EU and US Regulation and Policy Environments on Veterinary Drug Innovation 14
4.15 Impact of EU and US Regulation and Policy Environments on Veterinary Diagnostic Innovation 15
5 17Other Potential Barriers to Drug and Diagnostic Innovation 17
6. Alternatives to Antimicrobial Drugs 17
7. Concluding Remarks and Recommendations 18
References 19

Summary

The current policy environment is casting what may be a complete blight on work to develop innovative antibiotics for use in animals. Our sense is that commercial drug companies can see no investment case to spend the money necessary to bring novel animal antibiotics to market, when the nature of the market into which the drugs will emerge is so uncertain. The problem is not the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) regulations that apply today. Rather, it is the reasonable commercial expectation that more regulatory or policy instruments will emerge that will limit, or even ban, the use of novel animal drugs. Such an environment already exists in some countries. For example, new policies in the Netherlands halved overall livestock antibiotic use between 2008 and 2012, and effectively removed some drug classes from the livestock market (Ministry of Economic Affairs, 2014).

With a range of national and EU-level initiatives, antimicrobial consumption intensity[1] in EU livestock fell by around 15% between 2010 and 2012 (ESVAC Project, 2014), yet France, Germany, Italy, and Spain all still consume livestock antimicrobials at higher level of intensity than the Netherlands and many countries have not reduced consumption at all. Furthermore, there are very large and apparently idiosyncratic differences in the intensity and pattern of national veterinary antimicrobial consumption. Therefore, it seems entirely reasonable for veterinary drug companies to believe that the commercial market for antimicrobial drugs could shrink substantially for a long time to come.

Consider the following scenario. In 5 years' time, governments may be making large lump-sum payments to drug companies for novel human drugs, and may be implementing stringent stewardship programmes to limit the use of such drugs in human health systems. These actions will likely make it politically difficult to allow the widespread use of these novel drugs, or their close analogues, in cows, pigs, sheep, and chickens. Furthermore, there will be little reason to develop attractive candidates for the small[2] and less profitable animal market rather than a human market that is made attractive by government incentives.

The likely reduction in the use of antimicrobial drugs in veterinary medicine (in the EU and US at least) has implications for animal welfare and for the economics of food production. It increases the importance of rapid and cheap animal diagnostics, of the discovery and development of new vaccines, of improvements in animal genetics, and of good animal husbandry practices and agricultural biosecurity.

The situation with innovation in diagnostics is more complex. Drug stewardship pressures are likely to rise, and bacterial susceptibility testing before antibiotic use will become more common (following a pattern already seen in the Netherlands and some other countries). These factors will increase demand for diagnostic tools and services. Furthermore, for many routine bacterial infections, the regulatory barriers for animal diagnostics are low or even non-existent at an EU level. On the other hand, veterinary diagnostics markets are small and very fragmented. National regulation varies. Customers tend to be price sensitive. Decisions to diagnose and treat livestock – the major segment of the market – are generally made by farmers on an economic basis. Furthermore, the "notifiable disease" system, where government agencies have sole responsibility for monitoring, diagnosing, and responding to a set of serious infectious diseases, skews the diagnostics market. While the notifiable diseases are agreed at a supra-national level, the precise way they are diagnosed is not. Thus there are national differences in the regulation and use of diagnostics for notifiable diseases and this increases cost and complexity for the commercial sector (EMVD, 2012).

We recommend policy initiatives to try to harmonize veterinary diagnostic regulation at an EU level, as has been the case for human diagnostics since 1998. We also recommend funding from research councils to bridge various gaps in expertise. For example, there seems to be little cross-

[1] mg of drug per unit of livestock biomass per year.

[2] The veterinary market in Europe is only around 2.5% of the size of the human market.

talk between geneticists and veterinarians. In a world of constrained antimicrobial use, animal breeding / genetics may become an important factor to reduce infection. There may be other similar gaps. The prevention and management of infection in animals in an environment of constrained antibiotic use becomes less of a veterinary prescribing problem and more a broader problem to integrate drugs, diagnosis, vaccination, breeding, biosecurity, and husbandry.

Note that this report is US and EU-centric. It may be that the regional concerns we discuss, and the corresponding policy responses, are not priorities in, for example, India, China, or Brazil.

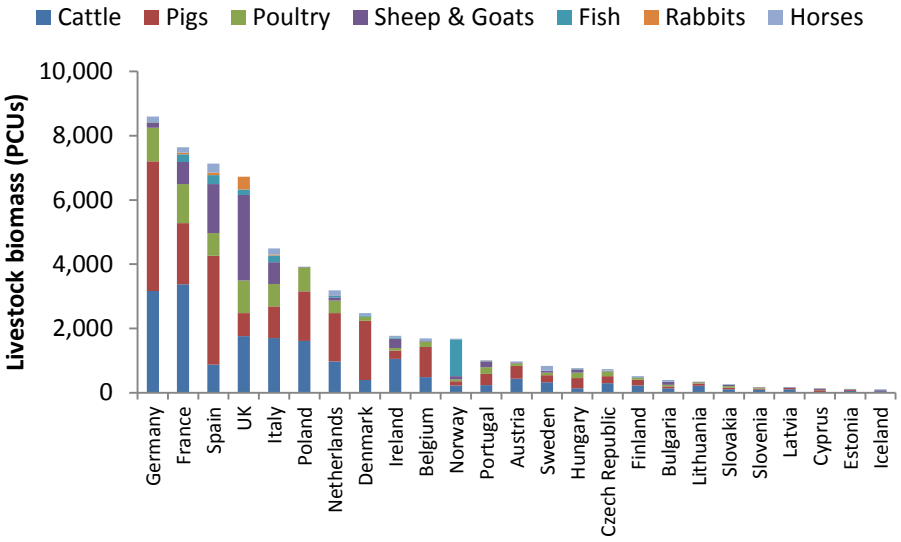
1. Background on Veterinary Drug and Diagnostic Use

The material in this report is based on a survey of the academic, policy, and regulatory literature, and on interviews and email correspondence with 9 experts from the fields of academic and applied veterinary medicine, veterinary pharmaceuticals, and veterinary diagnostics. The experts came from both public sector and private sector bodies.

1.1 Antimicrobial use in animals

Antimicrobials (AMs) have long been used in the US and Europe to treat animal infections, to prevent animal disease (i.e., prophylaxis and metaphylaxis[3]), and to promote animal growth[4]. The quantities and types of antimicrobials used in animals depend on biomass, animal husbandly practices, local prescribing habits, and species-specific pathology. Figure 1 provides a quantitative view of livestock biomass in Europe. Companion animals (e.g., dogs, cats) form only a very small proportion of the total biomass and are not included in the graph (ESVAC Project, 2013).

Figure 1. Relative Livestock Biomass by Species in the EU in 2011 (Expressed in "PCUs")



***Legend**. Livestock biomass is from the 2013 ESVAC report which summarises EU veterinary antibiotic use to 2011* (ESVAC Project, 2013)*. The unit shown on the vertical axis is the "PCU" or Population Corrected Unit, which is a measure of biomass rather than a measure of animal numbers.*

Given the fact that agricultural animal biomass substantially exceeds human biomass in both the EU and United States, the proportion of antibiotic tonnage[5] used in animals is relatively large, even though average consumption per unit of live biomass is often lower in livestock than in humans (Moulin, et al., 2008) (Kummerer, 2003). The ratios will vary country by country, but our estimates suggest that human antimicrobial consumption, per Kg of live biomass, is roughly 2x to 3x times

[3] Therapeutic use in animals typically involves high doses for short periods of time on individual animals. Metaphylatic use typically involves treating a group of animals once an index case has been identified and where epidemiology suggests the group is likely to be or become infected. Treatment is over the incubation period of the disease. Prophylactic use typically involves antibiotics administered to groups of animals in feed or water during vulnerable periods. An example would be when pigs are weaned and mixed into new groups.

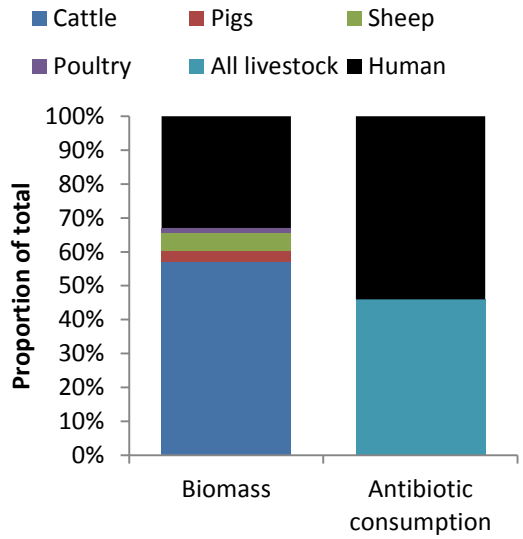
[4] Although use for growth promotion was banned in the EU in 2006, and will have been phased out in the US by 2016.

[5] It is both interesting that surveys such as ESVAC (ESVAC Project, 2014) and UK-VARSS (UK-VARSS, 2013) have to rely on crude weight measures for the quantity of antibiotic that is consumed. This suggests that surveillance is still very crude. In most areas of pharmacology, potencies of drugs vary by many orders of magnitude. Thus a kilogram of drug A in indication X is not equivalent to a kilogram of drug B in indication Y. The same is almost certainly true of veterinary antimicrobials, both in terms of their therapeutic effects on animals and in terms of the evolutionary selection pressures that they exert on microbes.

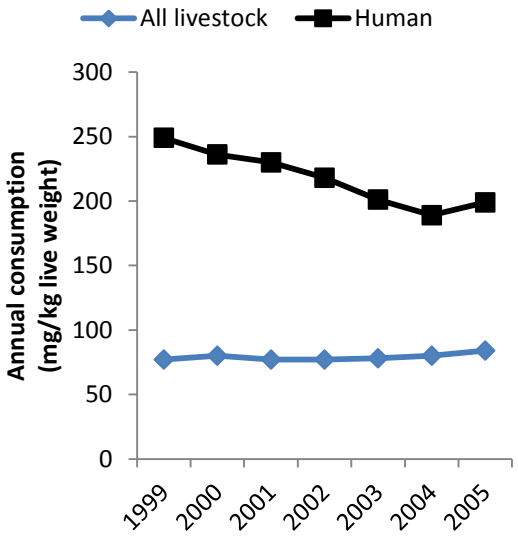
higher than livestock consumption[6] in both the US and UK. Published work suggests a similar ratio in France (Moulin, et al., 2008).

Figure 2. Illustrative Biomass and Antimicrobial Consumptions – Livestock vs, Humans

Relative live biomass and antibiotic consumption – UK example



Antibiotic consumption per kg of live biomass – French example



Legend. *The left hand graph shows UK livestock and human biomass, and our estimates of relative antibiotic consumption. The figure is based on data from (Kummerer, 2003) (Moulin, et al., 2008) and (UK-VARSS, 2013). The right hand figure shows French antibiotic consumption for livestock and humans. Consumption is shown on the basis of mg/Kg live weight per year. It is based on data in (Moulin, et al., 2008).*

Table 1 summarises major antibiotic uses within the major livestock species. Note that it is difficult to get quantitative data on antimicrobial use at the species or disease level, because most antibiotics that are approved for veterinary use can be prescribed to a variety of different species for a variety of different infections (ESVAC Project, 2013) (ESVAC Project, 2014) (De Briyne et al., 2014). However, in general, extensively farmed sheep and goats are treated to a much lesser extent that more intensively farmed pigs, poultry, and cattle.

Table 1. Major Veterinary Uses of Antimicrobials

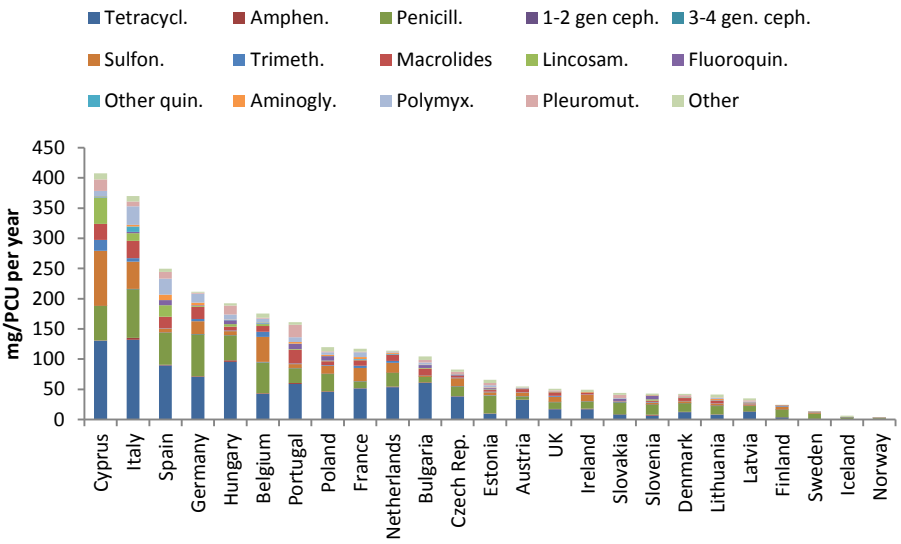
Cattle	Pigs	Sheep	Poultry	Other animals
Mastitis (treatment and prophylaxis) Respiratory disease Diarrhoea	Respiratory disease Diarrhoea Prophylaxis at weaning	Skin diseases including wounds and abscesses Locomotion (e.g., foot infections)	Respiratory diseases Diarrhoea	Skin diseases including wounds and abscesses Respiratory diseases Urinary tract infections

Legend*. Based on a large survey of EU Vets published by De Briyne et al, (2014).*

[6] For example, based on figures from Kummerer (Kummerer, 2003), we estimate that in 2000 in the US, livestock consumed around 125mg/Kg of antibiotics per year, while US humans consumed around 250mg/Kg of antibiotics per year. Of course, this is a crude comparison as the potency of different antibiotics varies substantially, and the pattern of antibiotic usage is different in livestock and humans.

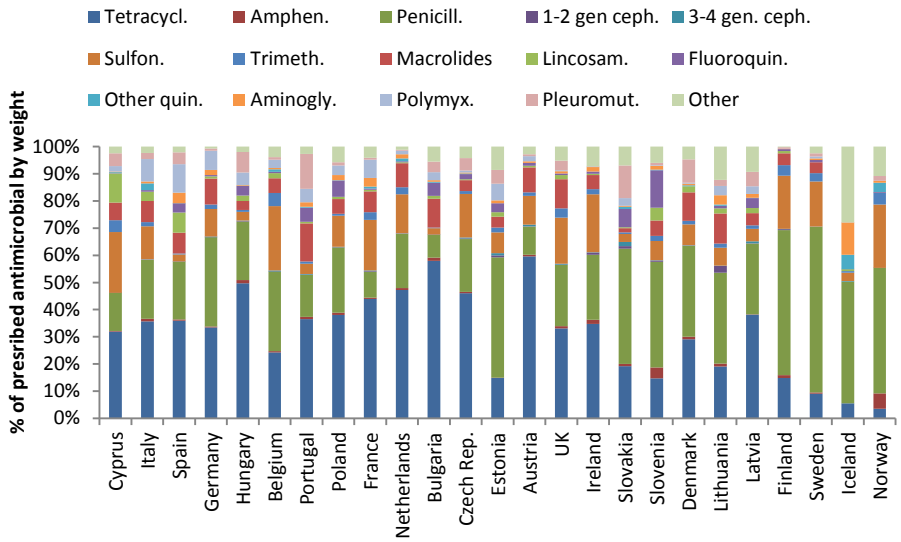
There are very large national differences in veterinary antimicrobial use between different European countries (Figures 3 & 4, below). If the ESVAC data are to be believed (ESVAC Project, 2013; ESVAC Project, 2014), consumption in terms of mg/PCU per year varies by more than 100 fold between high-use countries (e.g., Cyprus, Italy, Spain) and low use countries (e.g., Sweden, Iceland, and Norway). The pattern of usage also varies substantially, with different countries favouring different drugs. Both the quantity and the pattern of consumption appear to reflect idiosyncratic national differences in prescribing habits and not simply differences in the local livestock population or its pathology (ESVAC Project, 2014; De Briyne et al., 2014).

Figure 3. Variation in Intensity of Veterinary Antibiotic Use across the EU (2011 Data)



***Legend**. Data are from the ESVAC Project (2013). The vertical axis shows the mg of active antimicrobial ingredient prescribed per unit of livestock biomass (PCU) per year.*

Figure 4. Variation in Pattern of Veterinary Antibiotic Use across the EU (2011 Data)

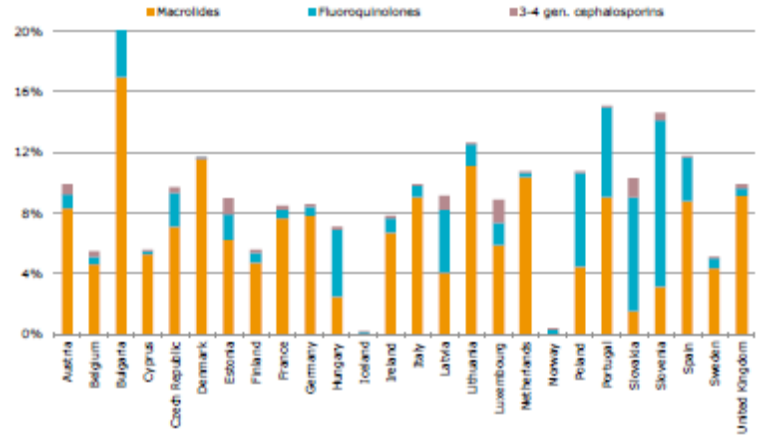


***Legend**. Data are from The ESVAC Project (2013). The vertical axis shows the percentage, by mass, of active antimicrobial ingredient prescribed in 2011.*

Unsurprisingly perhaps, the variation in national prescribing patterns extends to the subset of antimicrobial agents that the WHO defines as most important for human health, the so-called Critically Important Antibiotics, or CIAs. The WHO's "highest priority" CIAs include the 3rd and 4th

generation cephalosporins, macrolides, and fluoroquinolones. It is the veterinary use of CIAs that causes the highest level of policy concern in some countries (see, for example: Ministry of Economic Affairs, 2014). In Bulgaria, CIAs constitute nearly 20% of all antimicrobials prescribed to animals. In Norway, on the other hand, CIAs are hardly used at all in the veterinary setting.

Figure 5. Variation in the Use of the WHO's Critically Important Antimicrobials (CIAs)



***Legend**. Data are from The ESVAC Project (2014). The vertical axis shows sales of WHO Critically Important Antimicrobials (CIAs) as a percentage of total national antimicrobial sales, by mass of active ingredient. Note that total national antimicrobial sales also vary substantially between countries (Figure 3). CIAs are antibiotics that are defined by the WHO as having the greatest importance in human medicine.*

1.2 Notifiable Diseases

It is worth pointing out that much serious infectious disease in animals is managed by culling and not by medical treatment of any kind. The EU, for example, has a list of "notifiable diseases[7]". These are animal diseases that pose a serious economic[8] risk or sometimes a welfare risk to animals (e.g., foot and mouth disease, brucellosis), and/or which pose a threat to human health (e.g., bovine tuberculosis, avian influenza). Many notifiable diseases are viral rather than bacterial in origin.

Neither vets nor farmers have the option of treating these diseases. Rather, there is a legal obligation to report any suspected occurrence to a government agency. In the case of the UK, vets or farmers must notify the Animal and Plant Health Agency (APHA). APHA vets will then investigate the suspected disease, will take samples for testing, will oversee diagnostic testing in centralized reference laboratories, will restrict access to the farm, and may restrict access around the farm. If the disease is confirmed, some (e.g., tuberculosis) or all (e.g., avian influenza, foot and mouth disease) animals on the farm – and perhaps at adjacent farms - will be culled.

Notifiable disease testing is the responsibility of national agencies and this has a major impact on the market for veterinary diagnostic tests, as we discuss later.

1.3 Limited Use of Microbiological Diagnostics outside of Notifiable Diseases

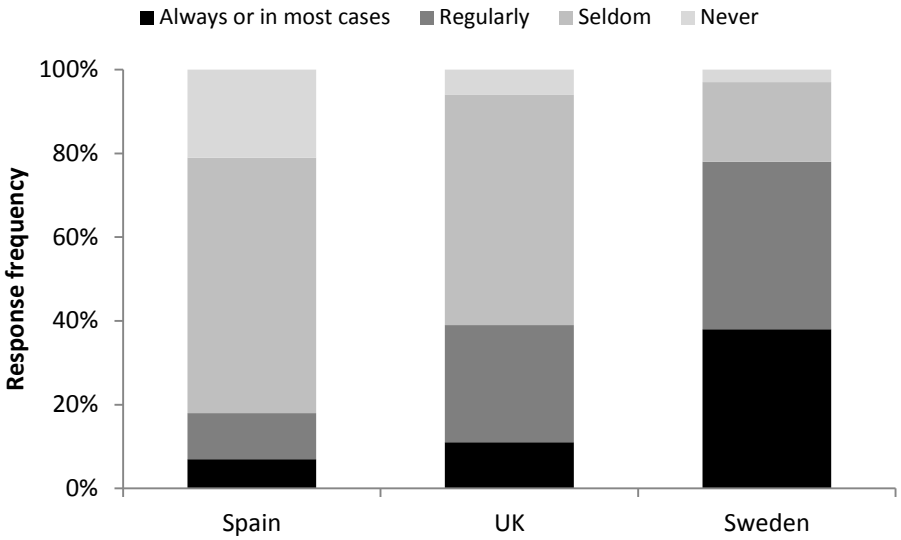
Most human antimicrobial prescribing is initially "empiric", with the drug generally selected on the basis of the clinical syndrome, and microbiology performed in potentially serious cases and/or in the event of failure of the initial antibiotic choice (Livermore & Wain, 2013). A similar empiric approach dominates in the case of veterinary prescribing, but perhaps with an additional economic overlay (De Briyne et al., 2013). In most cases, susceptibility testing occurs only as a consequence of initial antibiotic treatment failure. As with antimicrobial drug use, there appear to be major

[7]For the UK notifiable disease list and guidance see: https://www.gov.uk/government/collections/notifiable-diseases-in-animals

[8]Effective treatments or prophylaxis exists for some notifiable diseases, but it not used for commercial reasons. Most European countries used to vaccinate animals against foot and mouth disease, for example.

national differences in susceptibility testing (Figure 6, based on figures from De Briyne et al., 2013), with some of the variation driven by national AMR policies (Ministry of Economic Affairs, 2014).

Figure 6. How Often Do Vets Perform Susceptibility Testing Before Prescribing an Antibiotic?



Legend. *Based on from Table 6 of De Briyne et al., 2013. The graph shows the frequency of responses to questions on antimicrobial susceptibility testing in Spain, the UK, and Sweden. Given the nature of the De Briyne et al., 2013 study, it would be wrong to give too much weight to the precise figures.*

2. Policy Context: Growing Concerns over Antimicrobial Use in Animals

Policy consensus has emerged, first in Europe and in more recently in the US, that the use of antimicrobials in animals can promote the evolution of resistant strains and increase the frequency of resistance genes and that this can pose a risk to human health[9]. There is much less consensus on the magnitude of the risk[10]. For a good review of the evolution of evidence and thinking on this point, spanning the period from 1969 to 2012, see guidance published in 2012 by the FDA (FDA, 2012). There is now policy pressure on both sides of the Atlantic to reduce the use of antimicrobials in livestock production.

2.1 Policy in the EU

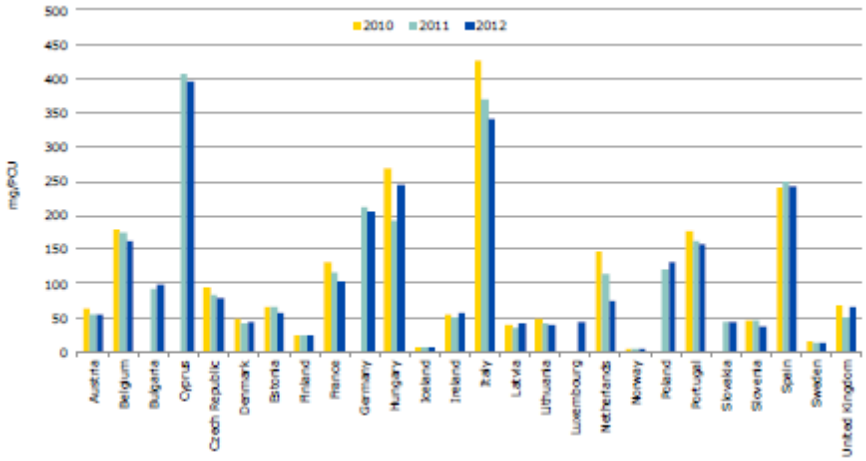
The current situation in the EU reflects a generally higher level of concern over antibiotic use than has historically existed in the US. At an EU level, the use of antimicrobials as growth promoters in animal feed was banned at the start of 2006. The EMA has monitored veterinary antimicrobial use since 2010 via the European Surveillance of Veterinary Antimicrobial Consumption project (ESVAC Project, 2013) (ESVAC Project, 2014) (European Medicines Agency, 2011). There is a range of

[9] In principle, resistant organisms or resistance genes can move from animals to humans in several ways. First, there can be transfer via food that is produced from animals that harbour resistant bacteria. Second, resistant bacteria from animals can enter the soil and/or water courses. However, processes in soil and water are currently relatively poorly understood (e.g. Jechalke et al. 2014, Gaw et al. 2014). Third, there can be transfer via direct contact between humans and animals. There is some evidence of transmission of methicillin-resistant Staphylococcus aureus (MRSA) from animals to humans as well as from humans to animals by direct contact (Catry et al. 2010). MRSA has been found in in dairy cows, pigs and veal calves as well as horses and small companion animals (such as cats and dogs). If a human infects an animal, this may produce a reservoir of infection that may in turn be transmitted to other humans.

[10] While there is consensus on the ***existence*** of a risk to human health, there is much less consensus on the magnitude of the risk and on the degree to which the risk can be mitigated by changing antibiotic use in animals. Witness for example a recent 'head to head' argument in the BMJ between a physician and a veterinarian (Wallinga & Burch, 2013).

initiatives, some at the EU level, and others managed nationally, to assess and track the AMR problem and to reduce antimicrobial use (European Medicines Agency, 2014) (De Briyne et al., 2013). The European Commission is also introducing new regulations for veterinary medicinal products, which may limit the use in animals of drugs that might promote the evolution of resistance to human medicines.

Figure 5. 15% Reduction in Antimicrobial Use Per Unit Livestock Biomass in Europe from 2010 to 2014



***Legend**. Data are from The ESVAC Project (2014). The graph shows antimicrobial consumption (mg/PCU) across the EU member states in 2010, 2011, and 2012. Average consumption has declined by around 15% from 2010 to 2012. Consumption fell by nearly 50% in the Netherlands.*

2.2 Examples of National Activity

Several national efforts appear to have had a major impact on antimicrobial drug use. We outline two of them here, and then make some brief comments on the UK. The first example comes from the Netherlands. The second example comes from Denmark.

Starting in 2008, the Dutch implemented a policy that aimed to reduce antimicrobial drug use in food producing animals (Ministry of Economic Affairs, 2014). An explicit motivation for the programme appears to have been the contrast between antimicrobial use in the Dutch human health system (Dutch hospitals are characterized by low levels of antimicrobial resistance and strict control of prescribing) and what appeared to be relatively liberal antimicrobial use in agriculture. Furthermore, there were concerns over the transfer of resistant bacterial strains from animals to humans.

The Dutch programme involved benchmarking antibiotic use by vet and by herd, herd health plans with nominated vets and periodic herd visits, and specific targets for reduced use of antimicrobial drugs. Then in 2011, the *"human healthcare risks became pivotal for Dutch antibiotics policy in livestock production"* (Ministry of Economic Affairs, 2014) and specific drug restrictions were introduced.

Given how effective the Dutch have been in reducing antimicrobial use, it is worth listing the actions in some detail. According to the Ministry of Economic Affairs (2014), the Responsible Use policy was as follows:

- *"ESBLs* [Extended spectrum beta lactamases]*, not LA-MRSA* [livestock-associated methicillin-resistant Staph. aureus]*, constitute the major resistance problem; policy should focus on containment of ESBL-related risks;*
- *Veterinary use of third and fourth generation cephalosporins in particular should therefore be substantially reduced;* [These drugs are among the WHO's "highest priority" Critically Important Antimicrobials (CIAs), for human health]

- *Systematic use of beta-lactam antibiotics, fluoroquinolones and aminoglycosides in livestock should be banned;* [Fluoroquinolones and aminoglycosides are among the WHO's "highest priority" CIAs]
- *The veterinary use of colistin (and a number of other antibiotics) should be phased out in order to keep it as a last-resort antibiotic for human health care;* [Colistin is one of the WHO's CIAs]
- *Off-label use should be limited to exceptional cases, as was originally intended;*
- ***New antibiotics should be reserved for human health care purposes.*** [our emphasis]
- *Policy measures based on these recommendations are:*
    - *Preventive use* [of antibiotics] *was prohibited by adaptation of the label texts;*
    - *A number of guidelines for veterinary use of antibiotics are being drafted by the KNMvD* [Royal Dutch Society for Veterinary Medicine]*, e.g. a general guideline for responsible use of antibiotics in livestock and specific guidelines for drying off dairy cows, for veal calves during the start-up period, for streptococcus infections in pigs and for the start-up phase of broilers;*
    - *Medication guidelines have been adapted in line with the recommendations:*
        - *Antibiotics that do not cause resistance became first choice, no specific ESBL/AmpC risk antibiotics (and colistin) became second choice,* ***critically important antibiotics for human health care became third choice and a number of last-resort antibiotics were entirely excluded from veterinary use*** .[Our emphasis]
        - *The use of second choice antibiotics has to be substantiated by the sensitivity of the pathogen or by other means. Third choice antibiotics are only to be used on an individual basis and after a sensitivity test for alternatives.*
    - *A legal basis was created for mandatory sensitivity testing before using third choice antibiotics."*

The net effect of the Dutch policy on antimicrobial use appears to have been spectacular. Dutch consumption of antimicrobials in food producing animals has fallen by ~50% since 2009 (Figure 5 and Figure 6). There have been large declines in the use of antibiotics in all major livestock segments, including pigs, poultry, and veal and dairy cattle (Ministry of Economic Affairs, 2014). Dutch agriculture has gone from being a relatively high user of antimicrobials to being somewhere towards the middle of the European pack (compare Figure 3 based on data from 2011 with Figure 6).

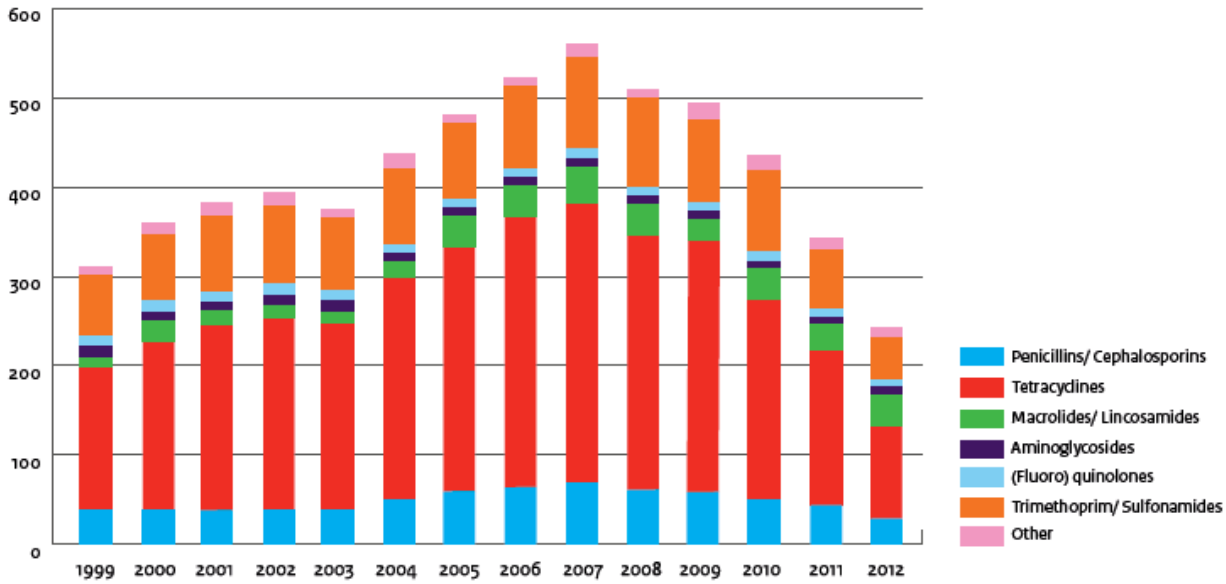
The Danish example concerns pig production (Alban et al., 2013) (Aarestrup, 2010). The initiative grew from domestic concerns over the levels of antibiotic use in intensive pig production. Note, however, that pigs are a major component of Danish livestock production, and that overall Danish veterinary antimicrobial use appears to have been relatively low by EU standards (see Figures 1 and 3, above). Thus, if ESVAC Project (2013) data are to be believed, Denmark was starting with a relatively low level of antibiotic use in pigs.

Denmark introduced in 2010 a voluntary ban on the use of cephalosporins (some of which are among the WHO's Critically Important Antimicrobials), and a "yellow card" scheme that tracks antibiotic use and imposes restrictions on farmers whose pigs consume twice the national average level of antibiotic. The scheme also warned farmers who were close to the limit.

From the introduction of the scheme in 2010 until the end of 2011, antibiotic use in pigs fell by around 25% (Alban et al., 2013). Vaccine use increased. There was some evidence of an increased rate of certain bacterial infections during meat inspections. However, the net effect of the changes on animal health appeared to be small.

The Dutch and Danish examples show that it is possible for national policies to have a large impact on antibiotic use. Furthermore, the bulk of EU livestock resides in member states that appear to have consumption levels that are substantially higher than those in the Netherlands or Denmark (Figure 1 and Figure 3).

Figure 6. Sales of Veterinary Antimcrobials in the Netherlands (Ministry of Economic Affairs, 2014)



***Legend**. This is Figure 4 from: (Ministry of Economic Affairs, 2014). The consumption measure (vertical axis) is tonnes of active antimicrobial ingredient per year. Note that a ban on the use of antibiotics as growth promoters was introduced across the EU in 2006. Policies to reduce antimicrobial use were introduced in 2008.*

2.3 Overview of UK Activity

Various initiatives are under way in the UK with the intention of reducing antimicrobial use in livestock and companion animals. To give a few examples:

- The British Veterinary Association has publicly aligned itself with delivery of the 'UK Five Year Antimicrobial Resistance Strategy'.
- Levy bodies, such as BPEX (pigs), have started discussions on how to reduce antimicrobial usage, although the degree to which these activities have penetrated industry practice is not clear.
- There is work underway to understand prescription practices and usage by vets and farmers with a view to bringing about more discriminating (and less) use of antimicrobials[11]. This includes work published by UK-VARSS (2013). Defra is funding research at Liverpool University, on antimicrobial prescribing practices in the pig industry but this is not yet published. Methods to achieve more discriminating use will likely include industry-agreed treatment algorithms (e.g., step-therapy and/or decision trees). There will likely be more focus on treating individuals rather than groups (for example in mastitis control in dairy cows).

[11] Some limited data already exists on influences on vets' antimicrobial prescription practices (see, for example, Gibbons et al., 2012, and De Briyne et al., 2013). Important drivers relating to prescribing antibiotics to cattle, identified from a survey of vets in Ireland, included actual or perceived demand by farmers, avoiding a repeat visit, cost of the drug and personal experience of using the drug on specific farms (Gibbons et al., 2012). Further detail is beyond the scope of this document.

2.4 European Commission Proposals for the Regulation of Veterinary Medicinal Products

The European Commission (EC) has prepared draft veterinary medicines regulation, which will likely be voted on by the European Parliament early in 2015, and which should come into force in 2018. While acknowledging some demand for new drugs for animals, the draft regulation and associated documents (e.g., impact assessments, annexes, etc.) tend to emphasize the AMR problem, and the potential risks to humans that follow from use of antimicrobial drugs in animals (European Commission, 2014). For example:

- *"Where relevant, studies shall be submitted providing information on the direct or indirect risks to human health, food safety or animal health of the use of the antimicrobial product in animals,* ***as well as an assessment of the effects of risk mitigation measures proposed by the applicant to limit antimicrobial resistance development****."* (European Commission, 2014) [Our emphasis]
- *The safety documentation shall include an assessment of:(a) the potential toxicity of the veterinary medicinal product and any risk of undesirable effects which may occur under the proposed conditions of use in animals; these shall be evaluated in relation to the severity of the pathological condition concerned; (b) the potential harmful effects to humans of residues of the veterinary medicinal product or active substance in foodstuffs obtained from treated animals and any difficulties these residues may create in the industrial processing of foodstuffs; (c) the potential risks which may result from the exposure of human beings to the veterinary medicinal product at any stage of the lifecycle of the veterinary medicinal product.; (d) the potential risks for the environment resulting from the use of the veterinary medicinal product; (e)* ***the potential risks relating to the development of antimicrobial resistance****.* (European Commission, 2014) [Our emphasis].

The EC also discusses options to make it easier to withdraw animal drugs should concerns arise over drug resistance that might become problematic in humans. For example, the EC's impact assessment complains that *"There are no legal provisions to allow regulators to prohibit or place restrictions on the authorisation for animals of certain classes or groups of antimicrobials that are considered reserved for the treatment of human infections"* and goes on to suggest legislative options to restrict the authorisation and use of veterinary drugs: *"It would allow the competent authorities to decide, based on scientific advice drawn by the EMA, whether or not a) a class of antimicrobials of importance for human health may be authorised for use in animals and b) if it may be authorised, under which specific conditions. This option would provide that a decision could be taken even if a causal relationship between the potential use of veterinary antimicrobials and antimicrobial resistance in humans cannot be fully established at the time of assessment due to incomplete scientific knowledge in the area."* (European Commission, 2014)

We note that current European Medicines Agency's (EMA) strategy paper for veterinary antimicrobials also emphasizes the AMR problem, and the potential concerns that the regulator would have with substantially novel agents: *"Risks related to AMR are to be considered in the benefit/risk assessment and in case these risks are found unacceptably high and cannot be sufficiently mitigated marketing authorisation will not be granted…..* ***Of special concern are molecules that represent totally new modes of action (and thus resistances unrelated to those already evident on the market) and a very strict view will be applied where the molecules in questions are specifically reserved as last resort medicine for use in zoonotic infections in humans.****"* (European Medicines Agency, 2011) [Our emphasis].

2.5 Policy in the US

Until recently, the US has taken a more relaxed view of antimicrobial use in livestock. The FDA has permitted the sale of antimicrobial drugs for treatment of animal disease, for prophylaxis, for metaphylaxis but also to increase feeding efficiency or to promote weight gain; so-called *"production uses"* to adopt the FDA's terminology (FDA, 2012).

Production uses are now being phased out in the US, and will have been eliminated entirely by 2016. For more details of the FDA's new approach, see its web pages on the "Judicious Use of

Antimicrobials[12]". However, and in brief, the FDA is following two principles which will eliminate production use of antimicrobials:

- *"**Principle 1:** The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health.* [i.e., they can be used only for curative, prophylactic, or for metaphylactic treatment]
- ***Principle 2:** The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation."* [Most antibiotic drugs which are administered with feed - the bulk of drugs that are used -have generally been available over the counter, and have not required a veterinary prescription. This will change.]

Since the FDA's guidance in 2012 (FDA, 2012) and 2013 (FDA, 2013), nearly 20 drugs have been voluntarily withdrawn from use for production purposes.

Even prior to the new stringency, the FDA recognized that the evolution of resistance to antimicrobial agents is a function of exposure. The FDA accepted that treating herds or flocks of animals with medically important antibiotics (or their close analogues) was more likely to promote the evolution of resistance than the treatment of small numbers of animals who either had a specific disease or who were at a high risk of catching a disease. However, the prior regulations were cumbersome when it came to limiting the use of established drugs that were already approved for, and being used for, production purposes. Some of these agents have been on the market for more than 30 years.

Not only has the FDA become more restrictive with respect to antibiotics that are used for production purposes, the agency also stresses its scrutiny of potential risks to human health that could arise from resistance that emerges as a consequence of the use of novel antimicrobial drugs in animals (FDA, 2003) (FDA, 2012) (FDA, 2013). So, for example, the FDA has signalled that it will consider the human medical importance of drugs that are being evaluated for new uses in animals. Drugs that are considered risky from a resistance point of view may be approved, but with various restrictions. They will not be available without a veterinary prescription, off-label use may be prohibited, there will be more rigorous post-approval monitoring, and the FDA will likely seek public Advisory Committee review[13].

3. Impact of EU and US Regulation and Policy Environments on Veterinary Drug Innovation

Our interviews suggest that current policy and regulatory environment has had a stifling effect on private sector investment on R&D for new antibiotics for animal use. Our interviewees suggested that there is little or no private sector activity to bring novel antibacterial drugs to the veterinary market:

- [Question] *"Tell us about drug industry investment in new antimicrobials for animal use?*" [Answer:] *"It does not exist."*
- *"The message I am hearing is that no one is investing in novel veterinary antibiotics."*
- *"There may be some minor activity to plug gaps in companies' portfolios (e.g., companies adding generics they don't already carry* [but which are already on the market sold by other companies]*) There may be some discovery work going on for drugs that could, in principle, be*

[12] http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/JudiciousUseofAntimicrobials/

[13] FDA Advisory Committee meetings are commonly held for new drug classes, or where there is some difficult policy issue. The Advisory Committee is composed of external experts. It is briefed by the FDA. It meets in public and hears representations from FDA assessors, from the sponsoring company or companies, and from other interested parties. It then makes non-binding recommendations to the FDA on matters such as approvability and drug labelling. The FDA typically adjudicates in a manner that is consistent with the recommendations of its Advisory Committees.

given to humans or animals or both [in many years' time]. *However, there is very little veterinary development underway* [which could yield new drugs in the next 5 years or so]*."*

- *"The problem is not the regulatory environment today. We understand the current regulations. The problem is that no one knows what is going to happen tomorrow given consumer concerns and political pressure."*
- *"Under some of the current European proposals, the EU may be powered to restrict the use of new or existing antimicrobial drugs, or to remove them from the market entirely. There is also the possibility that new drugs can be rejected on the basis of the risk that human-relevant AMR will emerge. While all this may be understandable, its net effect on private sector R&D investment is dire."*
- *"Some colleagues think that it would be bad for the company's image in the current environment to try to develop and sell novel antibiotics for animals. The marketing people want us to focus instead on non-antibiotic solutions to animal disease problems. That is easier said than done."*
- *"There are proposals to increase the period of data exclusivity for new veterinary antimicrobials to 14 years. I suppose it is possible that this might help, but exclusivity is not very motivating if you can't sell the product."*

Here the veterinary users face an obvious bind. New drugs that are merely close analogues of existing drugs (i.e., the new drugs that are cheapest to bring to market) will often share the same resistance problems as existing drugs. They will also tend to be relatively undifferentiated from very cheap generics. Yet genuinely novel drugs with new kinds of antimicrobial activity are likely to be those that are most jealously guarded for use in humans.

Furthermore, veterinary markets have an unenviable political problem. Let us suppose that governments start to incentivise R&D on novel antimicrobial classes for human use. It would be a brave politician who would pay a major drug company ~$500m for a novel antibiotic that would face extreme stewardship in human populations, and then allow that drug or its close analogues to be prescribed to pigs and chickens. On this general point, the policies that led to a ~50% reduction in antibiotic use in livestock in the Netherlands seem to have been motivated, at least in part, by the perception that efforts to manage AMR in the Dutch health system were not being matched by efforts on Dutch farms (Ministry of Economic Affairs, 2014).

Our limited reading of the materials produced by the trade bodies that represent livestock producers and veterinary medicines companies suggest that their main hope is that future constraints on antimicrobial use are what they would regard as reasonable and moderate (e.g., NOAH, 2014). They are arguing, for example, to retain some veterinary access to WHO Critical Antimicrobial Agents such as 3rd and 4th generation cephalosporins and fluoroquinolones. They do not seem to be asking for, or expecting, much in the way of novel antibiotics.

4. Impact of EU and US Regulation and Policy Environments on Veterinary Diagnostic Innovation

Potential constraints on to future usage appear to be a major disincentive to private sector investment in new veterinary drugs. The situation with veterinary diagnostics that could mitigate the AMR problem is different. In principle, demand ***should*** grow as various policy initiatives push vets and farmers towards more tailored use of antimicrobial drugs[14]. In the Netherlands, for

[14] There is perhaps an intriguing hint on the relationship between diagnostic testing and antimicrobial use if one considers the results of the ESVAC surveys (ESVAC, 2013; ESVAC, 2014) and the surveys published by De Briyne et al.,2013 and De Briyne et al., 2014. Although the quantitative strength of the relationship is weak (with data on diagnostic testing and drug consumption in only a small handful of countries) Sweden appears to have particularly low antimicrobial drug use and particularly high reports of susceptibility testing, while Spain has particularly high levels of antimicrobial use and particularly low reports of susceptibility testing. However, we don't want to over-claim on this point, as the data are sparse and the quantitative relationship is weak.

example, third line antibiotic use now requires prior susceptibility testing (which is also recommended before second line antibiotic use) (Ministry of Economic Affairs, 2014). Furthermore, at an EU level, individual regulatory barriers are low for many diagnostic tests. Tests for non-notifiable diseases have no regulation at the EU level. In the US, companies must gain approval from the US Department of Agriculture (USDA) but the hurdles here are lower than for human diagnostics.

However, our interviewees identified several practical barriers to diagnostic innovation. Many countries have national regulation of veterinary diagnostics, and this varies by country. The standards may not be individually challenging, but they tend to be different to one another.

In Europe, large swathes of diagnostic testing are off-limits for most vets and farmers because they fall within the notifiable disease system. Here, national agencies such as APHA in the UK are monopoly providers of diagnosis. In fact, it can be illegal for commercial manufacturers to sell or use tests for notifiable diseases to vets or farmers. Sometimes the national laboratories use commercial tests, but they often develop their own. Even when they use commercial tests, test regulation and even the test parameters vary country by country (and region by region within countries). Some of this is entirely rational. One wants different thresholds for positive and negative diagnoses depending on the situation in which the test is used[15]. However, the variation adds cost and complexity. Furthermore, the commercial players complain that they sometimes face competition from the public laboratories. These laboratories can have powerful positions in their own national markets, and are also in a position to design, use, and validate their own tests.

The problems, from the perspective of the diagnostics manufacturers, are summarized in a representation from their trade association to EU Directorate General for Health and Consumer Affairs (EMVD, 2012):

- *"The regulatory situation for veterinary diagnostics is confusing for any company aiming to market veterinary diagnostics in Europe as some member states regulate and others do not. Member states that do not regulate* [diagnostics in general, still have] *requirements to implement EU regulations for* [notifiable] *diseases. In addition, markets can be inaccessible due to commercial diagnostic activity of some public reference laboratories that produce "in-house" tests but do not always follow the necessary QA systems…."*
- *In practice,* [even for notifiable diseases], *the EU regulations are interpreted and applied in different manners by the Members States, and the market access for veterinary diagnostics vary from Member State to Member State. In certain Member States (e.g. UK, Italy) the National Reference Laboratories play a key role in the diagnosis of regulated* [i.e., notifiable] *diseases and bear the responsibility of providing diagnostics to regional labs. Typically, this takes place by the provision of "in-house" products or standard operating procedures. Other Member States have adopted a system of verification of manufactured* [i.e., commercial] *products ("batch-to-batch release testing") which leads to a system of batch-to-batch "marketing authorizations" (e.g. Belgium, Netherlands, France). Lastly, in Member States where a registration is obligatory (e.g. Germany, Spain, Romania) batch release is often necessary before products can be commercialized.*
- *"Product registrations in different countries represent a duplication of administrative work without any benefit for public or animal health; they are costly in time and fees: they need to be updated and renewed regularly. In addition, due to the numerous batch releases, manufacturers find themselves in the situation where one single batch of product needs to be tested in different member states before marketing is possible."*

[15] The optimum classification threshold on many tests depends on the frequency of the event that the system is testing for, and on the consequence of false positive or false negative results. To put it in more concrete terms, if one is doing a TB test in cattle in an area where a great many cattle are TB positive, the threshold for calling a result "positive" tends to be low. However, if one is testing in an area where one is fairly sure the cattle are negative, one sets a high threshold to avoid being swamped with false positives.

A recent survey by De Briyne et al. (2013) raised some similar points. It identified problems that follow from a lack of harmonised diagnostic licencing across the EU combined with tests being performed in private and public laboratories, some of which were not specialised in veterinary testing.

5 Other Potential Barriers to Drug and Diagnostic Innovation

Two further barriers to innovation are the relatively modest value of veterinary drug and diagnostic markets, and the price sensitivity farmers who pay for most of the drugs and for diagnostic testing for non-notifiable infections. The decision to treat or diagnose a sick cow, for example, is an economic one. The cost of a diagnostic test must be weighted up against the economic value of the diagnosis. If the first and second line antibiotics are cheap and available, and the diagnostic costs more than the lost milk production, there is little economic incentive to use the diagnostic (in the absence of other incentives). As the interviewees told us:

- *"It depends on how you define markets, but in broad terms, veterinary medicines sold into Europe are worth only about 2% of the value of human medicines sold into Europe."*
- *"When you try to sell any veterinary product, you are generally selling to a highly disparate group of small businesses."*
- *"There is a lot of 'verbal demand' for pen-side testing but less obvious economic demand. Consider the example of mastitis. The old approach was to give the cow an antibiotic (often amoxicillin) and then give the cow a second line drug if it did not get better after the first. When farmers perceive that they have a problem with bugs that are resistant to amoxicillin, they often try to get the vet to prescribe a second line antibiotic first, to avoid the risk of failure with amoxicillin, and the time and production loses that follow from the failed initial treatment. Most countries in the EU (at a national level, but not coordinated across the EU) are making it harder to prescribe the second line antibiotic without doing some kind of bacterial susceptibility testing, of the same kind that would be done for a patient with an infection in a hospital. This requires laboratory testing (either PCR based or conventional microbiology) and is relatively expensive; certainly when compared with the cost of the antibiotics that would have been prescribed. The big problem here is that the farmer has to pay for the testing, and the cost is a major disincentive."*

The De Briyne et al. (2013) survey also pointed towards the cost of testing as a potential barrier to diagnostic use. The survey reported that European vets found that greater use of sensitivity testing would be encouraged by achieving more rapid results at lower cost (De Briyne et al. 2013).

6. Alternatives to Antimicrobial Drugs

Several of our interviewees expressed concerns over the animal welfare and/or economic implications of substantial restrictions on the use of antimicrobials in animals:

- *"I am personally convinced that there is a need for new antimicrobials for animals. However, the market may not be there given the political environment. We are going to have to rely more on other things. Vaccines should help, but they cannot solve everything.*
- *Some non-antibiotic options for disease control look better from a corporate perspective. There is going to be a gap in the market for things that control disease."*
- *"Of course, you **can** remove antibiotics from agriculture. However, there will be problems with animal welfare and perhaps with food production. People need to remember that there are lots of diseases with no vaccines, and where there is no realistic prospect for a vaccine."*

Similar views have been put forward by various trade associations.

If, as seems likely, tightening of antimicrobial use in veterinary medicine continues, then other methods of infection control become more important. These include:

- **Vaccines**: The global market for veterinary vaccines is already growing at around 4% a year (contrast this with what appears to be a shrinking EU market for veterinary antimicrobial drugs). Most vaccines seek to prevent viral infections and the use of antibacterial vaccines is more limited. Our interviews suggest that veterinary bacterial vaccines available today are somewhat dated and of limited[16] use (e.g., they confer partial resistance to strains of bacteria that may no longer be important). The production of veterinary vaccines is dominated by 4 large companies: MSD, Merial, Zoetis, and Boehringer-Ingelheim.
- **Biosecurity**: Improvements in biosecurity and hygiene practices appear to have been important adjuncts to the reduction of antibiotic use in farms in Denmark and the Netherlands (Alban et al., 2013) (Ministry of Economic Affairs, 2014) and elsewhere (Vergne et al., 2014).
- **Probiotics and other feed additives:** A recent paper by Vergne et al. (2014) considers alternatives to use of antimicrobials in pigs and lists a range of feed additives which may or may not have an effect on pig health. It appears that few have been rigorously evaluated.
- **Genetics**: We have come across relatively little material on the relationship between animal genetics and the AMR problem. However, breeding can be viewed as a good way of managing animal disease (Bishop & Woolliams, 2014). The approach has generally been applied to quantitative traits (e.g., the *degree* of resistance to infection) which result from the combined effects of large numbers of genes. The changes in resistance within a single generation are small, so breeding has to be progressive. Selection pressume must be maintained over many years. Monogenetic traits can be bred into populations much more quickly. There have been attempts to market pigs with E. coli resitance based on a single resistance gene, but our interviews suggest that this has not been a commercial success. There are also various attempts to breed immunologically robust animals. However, their "robustness" may prove to be environment specific, and not general[17].

7. Concluding Remarks and Recommendations

We conclude with some observations and tentative suggestions.

The observations:

- First, the magnitude of the risk to human health from antimicrobial use in animals is contentious, even if there is now consensus on the existence of the risk. It seems likely, however, that in developed countries, the most pressing AMR problem for human health occurs with nosocomial infection, often in severely ill, very elderly, or immunocompromised patients. Thus the most pressing problem is neither resistant bacteria acquired from other humans in the community nor resistant bacteria (or resistance genes) acquired from animals, although these routes of transmission do exist (FDA, 2012). We are not, of course, suggesting that the risk to human health from animal use of antimicrobial drugs does not matter.
- Second, the political focus on the AMR problem in human health systems in the EU and US is real. This scrutiny will likely continue to bring the veterinary use of antimicrobials into

[16] One interviewee pointed towards mycoplasma vaccine used in c 80% of UK pigs. It is a killed bacteria-based vaccine but uses a 1970s strains of the pathogen. It appears to control clinical symptoms but it does not stop pigs from shedding the pathogen, and appropriateness of the strain is now being questioned.

[17] We are aware of work at the Roslin Institute to increase the resistance of chickens to Campylobacter and Salmonella, both of which can cause zoonotic infections in man. We are aware of work on resistance to bovine TB. In aquaculture species (e.g. salmon) selection for resistance to viral diseases such as Infectious Pancreatic Necrosis is being progressed.

the spotlight, almost independent of the actual risk to human health that veterinary use poses. It would be hard to explain to voters why their children should have to jump through diagnostic hoops before getting an antibiotic if the same voters' cats, pigs, and chickens were not required to jump even higher.

- Third, both the desire and ability to manage antimicrobial drug use in animals varies to a huge extent, even within the EU. Some countries appear to use very little drug with considerable caution (e.g., Sweden). Other countries seem much more liberal (e.g., Spain). There has also been a major trans-Atlantic divide, with the EU banning the use of antimicrobials for growth promotion 10 years ahead of the US. We have not had the opportunity to explore antimicrobial use in China, Brazil, India, etc. However, the sense we have is that Europe and the US lie towards the restrictive end of the spectrum.
- Fourth, given the nature of international trade, it seems likely that some production of meat for price-sensitive components of the European and US markets will migrate to countries where concerns over the AMR problem are less pressing, and where veterinary antimicrobial drug use will not meet US or EUs standards. Thus some component of the AMR problem will be exported to countries whose public health systems are less well equipped to deal with it. We note that the global movement of animal products has led to calls for regulation on a worldwide basis (Herrera, 2013).

Our suggestions are narrower in scope than our observations. Given the limited time we have been able to devote to this piece of work, we realize that they may lack novelty, and that there may already be work on these areas.

- The European market for veterinary diagnostics does appear to be unnecessarily complex. It appears difficult and costly for the industry to interact with the national laboratories that are responsible for notifiable disease testing. It can also be costly and duplicative to deal with individual national regulations for diagnostics that are not used in notifiable disease. Might it be possible for the EU to harmonize veterinary diagnostic regulation as it has done for human diagnostics since 1998?
- Our interviewees suggested that there is a high degree of technological overlap between veterinary and human diagnostics, but that there is more limited overlap[18] in terms of the companies that sell into these different markets. Might it be possible to facilitate movement of ideas and people between the veterinary and human diagnostic fields?
- We have also got the sense that there is limited cross-talk between geneticists and veterinarians[19]. Perhaps research councils could support more collaborative work in this area? In fact, there may be a more general point here. The prevention and management of bacterial infection in animals in an environment of constrained antibiotic use becomes less of a conventional prescribing problem and more a broader interdisciplinary problem that must integrate drugs, diagnosis, vaccination, breeding, biosecurity, and husbandry.

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[18] Some firms such as Qiagen, Thermo Fisher, and BioMerieux are involved in both veterinary and human diagnostics.

[19] But see for example, http://www.accelopment.com/en/projects/prohealth

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