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Antimicrobial Resistance

THE USE OF ANTIMICROBIALS IN THE LIVESTOCK SECTOR

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Abstract

ANTIMICROBIAL RESISTANCE:
THE USE OF ANTIMICROBIALS IN THE LIVESTOCK SECTOR

by

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The use of antimicrobials in livestock production provides a basis for improving animal health and productivity. This in turn contributes to food security, food safety, animal welfare, protection of livelihoods and animal resources. However, there is increasing concern about levels of antimicrobial resistance in bacteria isolated from human, animal, food and environmental samples and how this relates to use of antimicrobials in livestock production. The report examines antimicrobial usage in livestock and its impact on public health and the food economy. Policy issues and knowledge gaps to manage antimicrobial use and the risk of antimicrobial resistance are identified and discussed.

Keywords: Animal health, animal productivity, antibiotics, antimicrobials, growth promoters.

Table of contents

Abbreviations

AGDP	Agricultural Gross Domestic Product
AGPs	Antimicrobial growth promoters
AMR	Antimicrobial Resistance
CIPARS	Canadian Integrated Program for Antimicrobial Resistance Surveillance
DANMAP	Danish Integrated Antimicrobial Resistance Monitoring and Research Programme
DCDA	Defined Course Dose Animal
DDD	Defined Daily Dose
DDDA	Defined Daily Dose Animal
ECDC	European Centre for Disease Prevention and Control
EFSA	European Food Safety Agency
EMA	European Medicines Agency
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
FDA	Food and Drug Administration
MDR	Medical Device Reporting
MRSA	Methicillin-resistant Staphylococcus aureus
NARMS	National Antimicrobial Monitoring System
OIE	World Organisation for Animal Health
PBPs	Penicillin-binding Proteins
PCU	Population Correction Unit
SPS	Sanitary and Phytosanitary
US	United States
VRE	Vancomycin-resistant *Enterococci*
WHO	World Health Organization
WTO	World Trade Organization

Note: Consumption of antimicrobial agents is equivalent to antimicrobials sold, prescribed or used amounts of antimicrobials.

Executive Summary

The use of antimicrobials in livestock production[1] provides a basis for improving animal health and productivity. This in turn contributes to food security, food safety, animal welfare, protection of livelihoods and animal resources. However, there is increasing concern about levels of antimicrobial resistance in bacteria isolated from human, animal, food and environmental samples and how this relates to use of antimicrobials in livestock production. The report examines antimicrobial usage in livestock and its impact on public health and the food economy. Policy issues and knowledge gaps to manage antimicrobial use and the risk of antimicrobial resistance are identified and discussed.

Antimicrobials are used in livestock production to treat sick animals, protect healthy animals in contact with sick ones and during periods of transport or similar stresses. They are also used as growth promoters in some countries and production systems in the absence of clinical disease, which is controversial and has led to a number of countries limiting or banning antimicrobials used in this way. Evidence from policy changes on antimicrobial use in livestock suggest that livestock productivity is not impaired if the limiting or banning of antimicrobials can be combined with improved management, reduced stress, use of modified genetics and investment in disease prevention measures. However, data on growth response to limiting antimicrobials as growth promoters are not easily available and this has impeded an international consensus. The absence of data around this area also impedes any conclusions on links with antimicrobial growth promoters and resistance emergence.

Livestock production uses a range of antimicrobial types (classes) and there is overlap with those used in human medicine. This creates a complex picture when examining the ecological link between antimicrobial use and bacteria and resistance genes that circulate in livestock, humans and the environment. Available data do not allow the quantification of the contribution of the use of antimicrobials in livestock to the development of resistance in humans. For example, veterinary sales data provide insufficient resolution and there is a lack of harmonisation of data on antimicrobial sales and use across species. There are insufficient data to develop global maps of antimicrobial resistance in livestock and humans, and this lack of data impedes accurate comparisons between humans, livestock species, industries, countries or regions.

Significant knowledge gaps remain in areas such as the economic contributions of antimicrobials through their reduction in livestock disease burdens and their estimated impacts on hunger and poverty alleviation. The role of the environment in the ecology of antimicrobial resistance also requires research. A priority has to be the establishment of data required and the data collection procedures following internationally agreed standards regarding animals (OIE[2]) and food (*Codex Alimentarius*[3]), to allow these complex issues to be

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[1] This covers all terrestrial food animal species.

[2] The OIE is the WTO reference organisation for standards relating to animal health and zoonoses (http://www.oie.int)

fully comparable and understood. This could be the basis of initial global policies on antimicrobial use in livestock and a building block to protect the "global public good" of antimicrobials.

1. Introduction

Antimicrobials are compounds that have an impact on microorganisms be they bactaeria, viruses, fungi or protozoa. Their actions can either inhibit growth of the microoganisms or kill them. Antimicrobials have been part of the human existence since the 1940s, allowing us to achieve extraordinary improvements in both human and veterinary medicine. Being an essential tool to fight infectious diseases, besides saving human and animal lives, they also indirectly contribute to food security, food safety, protection of livelihoods and animal resources and poverty alleviation by improving animal health and productivity. It is well documented that livestock production dominates the use of the world's land surface and that livestock produce around 30% of the agricultural gross domestic product (AGDP) in the developing world and about 40% of global AGDP (Pagel et al., 2012). By supplying meat, milk, eggs and offal, livestock currently account for approximately 13% of worldwide calorie consumption and 30% of protein consumption (Steinfeld et al., 2006), and this is expected to increase in the future.

Unfortunately the efficacy of antimicrobial use in human and livestock health is being threatened (Elhani, 2011), by high resistance rates and treatment failures owing to resistance in some bacteria isolated from humans, animals, food and environmental samples (Finley et al., 2013). Multiple reports related to human health have shown the increased costs and mortality rates associated with resistance (IDS, 2010; Tansarli et al., 2013; Kim et al., 2001; McEwen, 2006; WHO, 2012 4; World Economic Forum. Global risks 2013). The World Health Organization (WHO) has shown a growing awareness of antimicrobial resistance (AMR) as a global threat leading to it being a focus of the World Health Day on 2011 and major publications (WHO, 2012). In addition, from a public and animal health perspective, the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE) and the WHO recognised the need to speak with one voice and take collective action through a coordinated approach, the "One Health" concept, with shared responsibilities to tackle antimicrobial resistance worldwide.

It is recognised that resistance is a natural and ancient phenomenon (D'Costa et al., 2011), but with growing concern that the current global levels of resistance in humans are, in part, due to the use of antimicrobials in animals. The general topic of AMR has been gaining increased attention, from very different sectors such as the food industry, pharmaceutical industry, media, governments, policy makers, and consumers.

Defining boundaries between the use of antimicrobials in humans and its use in animals with the impact of this use on the occurrence of resistance in humans is extremely difficult, if not impossible. Any use of antimicrobials in animals can ultimately affect humans, and vice versa (Edwards et al., 2012; Gulberg et al., 2011). Resistance bacteria/genes carried by commensal bacteria in food-producing animals can reach people, mainly directly via the food chain (Aarestrup et al., 2008), by consumption of inadequately cooked food, handling of raw food or by cross contamination with other foods. Resistant bacteria can also spread through the environment (e.g. via contaminated water) or through direct animal contact on farms.

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3. *Codex alimentarius* produces international food standards, guidelines and codes of practice contribute to the safety, quality and fairness of this international food trade (http://www.codexalimentarius.org)

There are 27 different antimicrobial classes used for the treatment or as growth promoters in animals (Table 1) most of which are also used in humans, but there are nine exclusively used in animals (Pagel et al., 2012). It is important to note that not all the antimicrobial classes listed in Table 1 are approved for use in all countries, or for the same indication, species or dose in the countries in which they are approved. In the livestock sector, antimicrobials can be used for:

- Therapeutic purposes (treatment of sick animals).
- Prophylaxis (when antimicrobials are administered to a herd or flock of animals at risk of a disease outbreak).
- Methaphylaxis (when antimicrobials are administered to clinically healthy animals belonging to the same flock or pen of animals with clinical signs).

Many organisations including the Food and Drug Administration (FDA), American Veterinary Medical Association (AVMA) and *Codex Alimentarius* define disease prevention (prophylaxis) and disease control (metaphylaxis) as therapeutic uses. Thus, treatment, metaphylaxis and prophylaxis is described by many as therapeutic.

Antimicrobials are also used for growth promotion. The goal of the use of antimicrobials as growth promoters is to decrease the time and total feed consumption needed to grow an animal to market weight. However, the exact mechanism by which this effect is achieved has never been fully clarified (Pagel et al., 2012). The European Union (EU) and the United States (US) currently have different policies regarding this issue: In the EU, the marketing authorisation for all antimicrobial growth promoters was withdrawn on 1 January 2006 as a response to increasing concerns on resistance and reduced efficacy. In the US, growth promoters can still be legally used. However, recent initiatives indicate a change of policy in the future. For example, *Guidance for Industry #213*, finalised in December 2013, recommends sponsors remove their indications for production uses of antimicrobials that are also used in human medicine and recommends that all therapeutic uses of those same antimicrobials be under veterinary oversight.[4]

In this report our main goal is to provide a structured synthesis of the available literature, in an attempt to answer the questions: What are the main risks and benefits that derive from the use of antimicrobials in livestock? Are there alternatives to the use of antimicrobials? Which policies can be more useful to protect human and animal health, and at the same time allow space for the sustainability of the agricultural industry? What are the main current knowledge/research gaps in this area?

In order to address these questions, we start by looking at the extent of antimicrobial consumption, both for treatment and as growth promoters, in livestock. We then later analyse its economic and health impact. In the last sections, we look at different policy options.

2. Antimicrobial use and antimicrobial resistance

Antimicrobials are widely used in human and animal medicine. The way they are used in livestock is related to the production systems in which the animals are kept and the health problems they encounter. The quantity and type of antimicrobial used depends on the species, production system and microorganisms in the environment. In addition the overall access to the antimicrobials and the knowledge of their use are important with the latter provided mainly by the veterinarian to the livestock keeper. The strategies and the extent of

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[4] www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf

consumption will be described in the first two parts of this section. This is followed by a discussion of resistance – what it is and how it is thought to develop.

Practices of antimicrobial use

Antimicrobials are "naturally occurring, semi-synthetic or synthetic substances that exhibit antimicrobial activity (killing or inhibition of growth of microorganisms) at concentrations attainable *in vivo.*" Anthelmintic and substances classed as disinfectants or antiseptics are excluded from this definition (from OIE Animal Health Code).

The overall intention of the use of antimicrobials as growth promoters is to improve the production performance of livestock. When used for a therapeutic purpose, antimicrobials participate to safeguard animal welfare through significantly decreasing the risk of death of animals and reducing the severity and time they are sick. The use of antimicrobials as growth promoters can also improve their ability to utilise feed. Antimicrobials have therefore become an important component of the way livestock are raised and have contributed to allowing the use of more productive animals and the production of larger quantities of food for human consumption (Castanon, 2007). The increased livestock productivity has allowed animal-derived foods to become cheaper and more widely available to all consumer groups.

The range of antimicrobials used in livestock is limited with only certain types licensed for use in certain species and production systems. In some countries there are restrictions on the classes of antimicrobials used in livestock and therefore not all the classes listed in Table 1 are available in all countries.

Antimicrobial veterinary medicine products are commonly used for the treatment of infectious diseases caused by bacteria, i.e. therapeutic use. Bacteria are the oldest form of life, the most numerous and the most diverse, being ubiquitous in every living being and environment compartment (cited in Oliver et al., 2011). Animal exposure to bacteria is therefore normal and frequent with all mammals carrying a substantial and diverse micro-flora on their skin and in their guts – the microbiome. Some bacteria are pathogenic and the use of antimicrobials is to control and manage these pathogenic bacteria in order to decrease morbidity and mortality in livestock raised. Data on the value of these interventions in terms of food production and increased utility from companion animals are not readily available making a cost-benefit analysis of antimicrobial in animals difficult.

The effect of the use of an antimicrobial in an animal is multidimensional. The explanation of the biological and pharmacological mechanisms that occur after an antimicrobial is administered is beyond the scope of this paper. However, it is important to highlight that antimicrobials will affect the pathogenic agents and have a general impact on the microbiome (Acar et al., 2012; Cotter et al., 2012). In fact, public health and food safety concerns derive from the unintended effects of antimicrobials in these commensal bacteria normally resident in the gastro intestinal tracts of food animals (Looft et al., 2012).

Additionally, the continued use of a single antimicrobial may lead to resistance to multiple structurally unrelated antimicrobials, which is covered in more detail below in the section antimicrobial resistance.

Table 1. Antimicrobial classification and use for treatment and as AGPs in livestock

Antimicrobial class	**Major intensive systems**				**Minor extensive systems**		**Other**			
	Avian	**Bovine**	**Pig**	**Fish**	**Goats**	**Sheep**	**Bee**	**Rabbit**	**Camelids**	**Equine**
Aminocyclitol	☐	☐	☐	☐	☐	☐		☐		☐
Aminoglycoside	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Bicyclomycin	☐	☐	☐	☐						
Cephalosporin										
- Cephalosporin 1st G		☐	☐		☐	☐				☐
- Cephalosporin 2nd G		☐								
- Cephalosporin 3rd G	☐	☐	☐		☐	☐		☐		☐
- Cephalosporin 4th G		☐	☐		☐	☐		☐		☐
Coumarin		☐		☐	☐	☐				
Diaminopyrimidine	☐	☐	☐		☐	☐		☐		☐
Fusidane		☐								☐
Glycophospholipid	☐	☐	☐							
Glycopeptide	☐		☐							
Kirromycin			☐							
Lincosamide	☐	☐	☐	☐	☐	☐	☐			
Macrolide	☐	☐	☐	☐	☐	☐	☐	☐		☐
Nitrofuran	☐	☐	☐							
Orthosomycin	☐							☐		
Penicillin	☐	☐	☐	☐	☐	☐		☐	☐	☐
Phenicol	☐	☐	☐	☐	☐	☐		☐		☐
Phosphonic acid	☐	☐	☐	☐						
Pleuromutilin	☐		☐		☐	☐		☐		
Polypeptide	☐	☐	☐		☐	☐		☐		☐
Quinolone										
- Quinolone 1G	☐	☐	☐	☐	☐	☐		☐		☐
- Quinolone 2G (Fluoroquinolone)	☐	☐	☐	☐	☐	☐		☐		☐
Quinoxaline			☐							
Rifamycin		☐	☐		☐	☐		☐		☐
Streptogramin	☐	☐	☐			☐				
Sulfonamide	☐	☐	☐	☐	☐	☐		☐		☐
- Sulfonamide + diaminopyrimidine	☐	☐	☐	☐		☐		☐		☐
Tetracycline	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Thiostrepton	☐		☐							

Source: Adapted from Acar JF, Moulin G, Page SW, Pastoret PP. (2012), “Antimicrobial resistance in animal and public health: introduction and classification of antimicrobial agents”, *Revue Scientifique et Technique*, Vol. 31(1):15-21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22849264.

The need for the use of antimicrobials is heavily influenced by husbandry practices and its direct link to animal health. A 2009 UK report found that use of antimicrobials in the intensively farmed pig sector in the UK was 115 times higher than in sheep farming, where grazing was the common production method (VMD, 2009). In the United States, 16% of all lactating dairy cows receive antimicrobial therapy for clinical mastitis each year; 15% of beef calves that enter feedlots receive antimicrobials for the treatment of respiratory clinical problems, and 10% of apparently healthy calves receive the same dose of antimicrobials as a prophylactic or metaphylactic measure. Approximately 42% of beef calves in feedlots are fed tylosin (a veterinary macrolide drug), to prevent liver abscesses that have negative impact on growth and 88% of fattening pigs are treated with growth promoters in their feed (tetracyclines and tylosin) (Landers et al, 2012).

In dairy cattle, it has become common at the end of a period of lactation for the farmer, under the supervision of their veterinarian, to use antimicrobial infusions into the udder. This treatment is often not for a specific infection, rather it is to reduce the risk of future infections while the cow is dry. This is commonly termed a prophylactic dose of antimicrobials. While it has been commonly assumed that this is effective in preventing and controlling future mastitis, it is now being questioned and alternative practices are being employed. The types of antimicrobials commonly used for this prophylactic treatment are penicillins and cephalosporins directly targeted at the udder. Antimicrobials can also be used therapeutically in dairy cattle when there are udder or uterus infections that may occur when the animal is milking (during lactation), or when calves suffer pneumonia or diarrhoea. Most treatments in dairy systems are therefore usually individual, just like in horses or companion animals. In contrast, animals in poultry and swine industries are managed in groups, and the antimicrobial treatments they receive are usually at herd or flock level. It is rare that an individual animal would be treated, because these species and specific group of animals are normally given antimicrobials at a given time. Extensively reared animals such as sheep and goats generally receive less antimicrobials.

In beef cattle and also pigs, it is also common to use antimicrobials prophylactically. Producers can anticipate certain periods of increased stress (e.g. movement/long trips of animals), where the probability of the development of clinical infections is increased. To help reduce the risk of clinical infections, animals can be treated with antimicrobials before the development of clinical signs. There are also situations where some of the animals in a herd show clinical signs of disease, but not all. In these situations all animals – healthy and sick – are given antimicrobials in order to manage the problem. This metaphylactic use of antimicrobials is common in systems where animals are managed in groups.

There are also situations where a sick animal requires treatment, which cannot be achieved with drugs licensed for that species. In this situation, another substance may be used *“off-label”* or “*extra-label”*, depending of the regulatory system in a given country, which indicates the use of a substance in an animal species or for an indication for which this substance is not licensed. As it is still important to treat these animals for animal welfare purposes, the “cascade” approach has been developed. This approach allows veterinarians to alleviate animal suffering by using clinical judgment to prescribe a medicine if no veterinary authorised medicine exists. The veterinarian starts with a product that is licensed for another animal species or another indication in the same species. If such a product is not available, they may consider using a substance authorised for human use, though in Europe additional hurdles exist for food-producing animals. The use of antimicrobials in countries with strict licensing and application procedures ensures that there is control on the range of antimicrobials used in livestock.

The most controversial use of antimicrobials is their use as growth promoters. The potential growth promoter effect of antimicrobials was discovered in the 1940s, when it was observed that when healthy animals were fed dried mycelia of *Streptomyces aureofaciens* containing chlortetracycline residues their growth improved (Castanon, 2007). The same approach was advocated in the mid-1950s, as researchers found that small, sub-therapeutic quantities of antimicrobials used as feed additive decreased the time and total feed needed to grow an animal to market weight (Marshall, B.M. et al.,2011).

The exact mechanism by which the antimicrobials promote greater efficiency of feed use and hence growth has never been fully clarified (Pagel et al., 2012), reflecting the complexity of the impact of antimicrobials on the microbiome and the interaction of this population with the animal. Since the level of gut absorption of some of the antimicrobials used as growth promoters is reduced, the actual mechanism of action must be at the gut level (Dibner et al., 2005). These can include: direct effect on the microflora leading to decreased competition for nutrients, reduction in microbial metabolites that depress growth and a reduction in opportunistic pathogens and subclinical infections ((Dibner et al., 2005). Some of the more recent theories point to a non-antimicrobial but anti-inflammatory effect in the gut (Niewold, 2007), modulation of gut immune responses (Costa et al., 2011) or subtle changes in population composition of the gut microbiome (Danzeisen et al., 2011). It is important to note that there will be differences between ruminant and non-ruminant animals due to their different intestinal physiology, but antimicrobials for growth promotion are more commonly used in pig and poultry systems that are monogastrics.

Data on the faster growth generated by increasing consumption of antimicrobials for growth promotion have been published and provide a convincing argument for use in pigs and poultry, particularly during the early stages of life (Thomke, 1998) and potentially under poor hygiene conditions (SOU, 1997). The differences in growth rates between animals consuming or not consuming antimicrobial growth promoters (AGPs) have been less easy to identify in more recent production systems where hygiene conditions will have changed due to improvements in housing, feed and water. There is evidence that in some systems there is little value of AGPs in livestock production, and the use of AGPs in poultry units in the US actually reduces profit margins (Graham, 2007).

Given that there is a link between antimicrobial use and antimicrobial resistance, the use of antimicrobials for growth promotion is controversial (Landers et al., 2011). This has led to the precautionary banning of their use in some countries, but this is currently not a globally accepted policy. According to a recent OIE survey 51% of 152 participant countries have completely banned growth promoters, 19% have partially banned their use and 30% have no ban.[5] Within the countries with bans the reductions in antimicrobial use is often not straightforward and with any change in management requires some adjustments.

Extent of antimicrobial consumption in animals

In order to assess the risks related to non-human consumption of antimicrobials, data on the extent of consumption are an important piece of information. However, the availability of livestock consumption data varies greatly at global level. Data on monetary value of the antimicrobials need to be treated with caution as the cost of antimicrobials differs across the world, in part owing to taxation policies for antimicrobials, and is not applicable for assessing risks. Therefore, any inference drawn on the consumption of antimicrobials through the sale value of antimicrobials cannot be made.

In 2011, Vetnosis, a research and consulting firm specialising in global animal health and veterinary medicine, reported that the total global animal health market was equivalent to

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[5] http://www.oie.int/eng/A_AMR2013/Presentations/S2_4_FrançoisDiaz.pdf.

USD 22 billion, with just over a quarter (26%) being medicinal feed additives.[6] Of the feed additive market nearly a half (47%) was in Northern America and a third (32%) in Europe (Vetnosis, 2013).[7] These figures for both markets are difficult to interpret for reasons explained in the previous paragraph and also because they include additives to control parasites known as coccidia. For Europe this would be the entire figure as antimicrobials are banned as AGPs.

Asia and Pacific region has relatively sparse data on antimicrobial use despite it having over half the world's pig population and a very high proportion of its poultry and the majority of the ducks. Many of these animals are reared in intensive or semi-intensive systems, with high population densities and the use of concentrate feed systems. Otte et al. (2012) estimated that the region has nearly half of the global antimicrobial market, with total 2011 sales in the region of about USD 1.8 billion. The use of antimicrobials in this instance is different from the commercial value as the total global sales are USD 22 billion. This demonstrates the differences and problems between monetary value and physical quantity of production.

Owing to the differences in the structure of the drug distribution systems, the monitoring schemes for antimicrobial consumption can be very different between countries. This key source of information to assess animal exposure and therefore public health risk is currently inadequately recorded and represents a key obstacle to risk assessment. The OIE made a recent survey on the proportion of OIE Member Countries that have an official system for collecting quantitative data on consumption and only 42 of the 154 participating countries have such a system in place.

Even at the European level, there are significant differences between countries, as emphasised in a recent report published by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC, 2011). For example France has monitored antimicrobial use since 1999 and the UK produces an annual report on the use of antimicrobials since 1999 (ESVAC, 2011). Since 1996, the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) reports annually not only on consumption but also on the occurrence of antimicrobial resistance in zoonotic, indicator and pathogenic bacteria from animals, food and humans in Denmark. Sweden (SWEDRES-SVARM) and Norway (Norm-Norm-Vet) have similar systems. The Swedish system involves the collaboration of the Swedish Institute for Communicable Disease Control and the National Veterinary Institute. The report fully integrates antimicrobial use in humans, animals and food and discusses resistance in a holistic perspective. Information is also available from New Zealand (Pagel et al., 2011), the US (NARMS) (Pagel et al., 2011) Canada (CIPARS) and Japan (Hosei et al., 2013). However, only very limited information is available from most of the developing countries, with Kenya being a notable exception where both the total amounts and the classes of antimicrobials are monitored (Mitema et al, 2001).

There are a number of ways in which antimicrobial consumption can be recorded: In the simplest terms, it is possible to estimate consumption through the sales value or quantity of antimicrobials sold. The source of data can be import data or sales data from pharmaceutical companies, pharmacies, feed mills or veterinarians. The value of sales is not a useful measure from a biological point of view, because it does not provide information on the quantities actually consumed. However, these data are important for economic

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[6] Medicinal feed additives refers to more than just antimicrobials, evidenced by the fact that the products are sold in the EU where antimicrobial feed additives are no longer allowed.

[7] Note this includes coccidiostats and histomonstats that are not part of the antimicrobials that this study is focused on.

assessments and in discussions on the value of the use of antimicrobials in livestock production.

Quantity sold is a crude measure, which provides some information on the sale of antimicrobials, but it does not provide sufficient information to examine the relevance of the use of a specific substance in livestock. Further information is needed on the class of antimicrobials used, as effective doses can vary greatly between classes (and even within classes), the species and production systems that are applied to and the number of livestock involved. The ideal measure is the amount of antimicrobials used per unit of livestock produced, e.g. meat, milk, eggs or fibre (ESVAC, 2011; see below). An important observation is that, irrespective of the data collection point, the amount of active substance is highly relevant as antimicrobials are dosed in mg/kg, and the amounts sold or used are in mg, kg or tonnes of active substance. From these quantity estimates other measures can be derived.

Antimicrobials cover a range of classes (Table 1) and not all are used in livestock. The ones that are used in livestock are priced differently, and the frequency of the use of the different classes will reflect the process of restrictions, the awareness of the people involved in using the antimicrobial and the price differences. This may well have an impact on the emergence of antimicrobial resistance as discussed below.

The comparison of country data should be done with great care (ESVAC, 2011). Recently Bondt et al. (2013) attempted to compare antimicrobial exposure based on sales data from Denmark and the Netherlands, and concluded that simple country comparisons, based on total sales figures, carry the risk of serious misinterpretations. Grave et al. (2010) compared the sales of veterinary antibacterial agents in ten European countries and found that 48% of the sales of veterinary antibacterial agents were for tetracyclines. They reported a wide variation in the usage between countries from 18 to 188 mg of antibacterial drug sold/kg of biomass of slaughtered food animal. Their conclusion was that the difference could not be explained solely by animal species demographics, and that data on animal husbandry practices, pharmaceutical drugs availability in the market and veterinary prescription habits would help to provide a better explanation.

The recent ESVAC report attempts to address these shortcomings by standardising the process through using a denominator that looks at livestock population and meat production – population correction unit (PCU[8]). Nearly three quarters of the antimicrobials for livestock are consumed in Germany (21.6%), Spain (21.1%), Italy (19.8%) and France (10.6%), with the highest consumers for mg/PCU being Cyprus (407.6 mg/PCU), Italy (369.7 mg/PCU) and Spain (249.2 mg/PCU). The figures ESVAC produce indicate the reliance on certain classes of antimicrobials for livestock and also that much of the application is mainly through premixes, oral powder and solutions (Figure 1). This point is of relevance when thinking of how antimicrobials are applied.

Similar reports, but not comparable with EU work, have been published for the US[41] and New Zealand.[9] The US report was compiled by the FDA as part of The Animal Drug User Fee Act (ADUFA), which requires antimicrobial drug sponsors to annually report the amount of antimicrobial active ingredient in the drugs they sold or distributed for use in food-producing animals. The report does not summarise the data in mg/kg of meat and eggs produced. It is important to note that the US figures include the ionophore class of antimicrobials which accounts for almost 30% of quantity of antimicrobials used in the United States. The European reports does not include ionophores, which are used to control parasites

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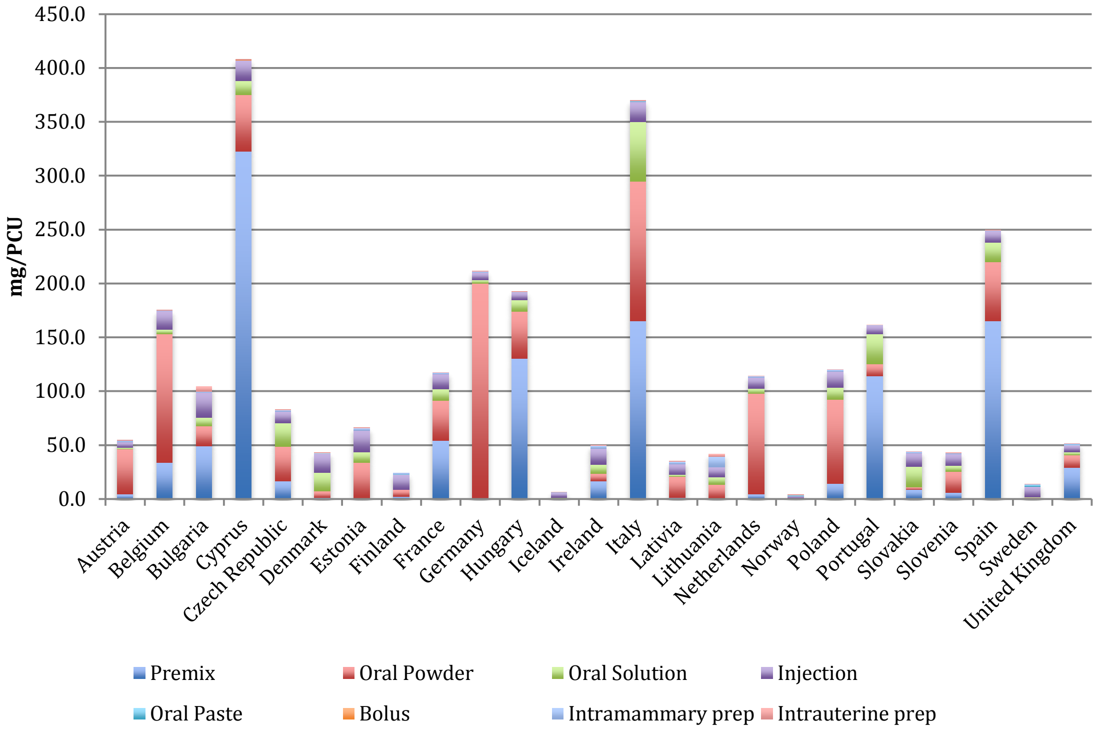
[8] PCU is the estimated weight of livestock and slaughtered animals. It is a proxy for the animal biomass at risk of being treated with antimicrobial agents.

[9] Antibiotics Sales Analysis: 2009-2011, http://www.mpi.govt.nz/Default.aspx?Tabld=126&id=2121.

and are not included in the EU data. This demonstrates the difficulties with cross regional and country comparisons. No information was found for Asia and the Pacific, Latin America or Africa.

Figure 1. Estimated antimicrobial use to produce 1Kg of meat in 25 European countries in 2011



PCU = population correction unit.

1. Note by Turkey:

The information in this document with reference to “Cyprus” relates to the southern part of the Island. There is no single authority representing both Turkish and Greek Cypriot people on the Island. Turkey recognises the Turkish Republic of Northern Cyprus (TRNC). Until a lasting and equitable solution is found within the context of the United Nations, Turkey shall preserve its position concerning the “Cyprus issue.”

2. Note by all the European Union Member States of the OECD and the European Union:

The Republic of Cyprus is recognised by all members of the United Nations with the exception of Turkey. The information in this document relates to the area under the effective control of the Government of the Republic of Cyprus.

Source: ESVAC (2013), Vetnosis. Medicinal Feed Additives. Available at: http://www.vetnosis.com/index.php?p=content&id=55.

To facilitate data comparison, the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC), after consultation with its members, suggested the use of two standardised units of measurement. However, the global use of these concepts is not fully accepted and applied.

A prerequisite for the use of these measurement units is that data can be collected by species. The proposed units are:

- Defined Daily Dose Animal (DDDA): an adaptation of the defined daily dose (DDD) used in human medicine, “the assumed average maintenance dose per day for a drug used for its main indications in adults”.[10]
- Defined Course Dose Animal (DCDA): is the technical unit of measurement usually based on recommendations as described in summary of product characteristics and in some cases on information from experiments or scientific literature.

Note that agreed doses between countries can differ and this can affect the usefulness of this metric.

However, the global use of these concepts is not fully accepted and applied. For example, France has developed an indicator of exposure called the Animal Level of Exposure to Antimicrobials (ALEA). This estimates the level of exposure by dividing the weight of animals treated with the weight of the population potentially consuming antimicrobials (ANSE, 2010).

In order to compare the use of antimicrobials between humans and animals, caution needs to be exercised. There are major differences in antimicrobial consumption in livestock and humans (Table 2). As shown in Figure 1, the main route of administration for antimicrobials in livestock is through premixes, oral powder and solutions, indicating that these applications are done at herd or flock level rather than individual animal level. Two issues arise from such applications, the dosing cannot be guaranteed to be optimum for each animal, and many animals are likely not to be clinically sick at point of the treatment.

It has been estimated that globally more antimicrobials are used to treat healthy animals than unhealthy humans (WHO, 2012), with global antimicrobial use outside of human medical care being around 100 000 tonnes per year. At country level the situation can be quite different and great caution needs to be applied due to the differences in how data are collected in human and animal health plus the vastly different biomasses of the humans and animals. So, for example, in 2009 some estimates have been made that in the US, of the antimicrobials sold for both humans and animals, almost 80% were reserved for livestock and poultry (Edwards et al., 2012). In 2012, Denmark (DANMAP, 2012) used 103 tonnes of antibiotics in animals and 50 tonnes in humans, reflecting that this country has a large livestock population relative to the human population. Interpretation of antimicrobial use in humans and animals should recognise that for every person in the world there are two to three times the numbers of animals when measured in biomass terms. For true comparisons the use per population correction unit between humans and animals would be needed. For example SWEDRES-SVARM reported in 2012 that for Sweden there was a use of 65 tonnes in humans and 12 tonnes in animals. When corrected for the biomass of respective populations, this corresponds to 104mg/kg for humans versus 15 mg/kg to animals. The relatively low use in animals is related to investments in animal health systems that reduce the need for antibiotics in animals.

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[10] Page 13 of ESVAC (2013) Revised ESVAC reflection paper on collecting data on consumption of antimicrobial agents per animal species, on technical units of measurement and indicators for reporting consumption of antimicrobial agents in animals http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/12/WC500136456.pdf.

Table 2. Differences in strategies and context of antimicrobial use in animals and humans

Livestock use	Human use
Differences in patient characteristics	
Populations often treated through feed or water	Individuals treated
Many different monogastric and polygastric species	Only one gastrointestinal type
Majority of animals are young	Full spectrum of ages, neonate to geriatric
Doses rates for oral herd or flock treatment dependent on food or water intake	Oral dose usually based on age (less frequently on bodyweight)
Range of bodyweights can be large across different species	Limited range of weights
Differences in diagnostic context	
Diagnosis supported by disease behaviour in population	Diagnosis based on individual features
Chronic comorbidities rare	Chronic comorbidity common in older humans
Diagnostic pathway may involve post-mortem investigation	Post-mortem investigation avoided
Differences in treatment context	
Cost of treatment is an important consideration	Cost less important
Withholding/withdrawal periods must be observed	No withholding period
For injection, long-acting injections preferred for a majority of species but not all	Short-acting injections or oral preparations are normal practice
Parenteral injections administered to sites that can be trimmed at slaughter	Parenteral injections administered to sites with least pain or reactivity
Prevention (metaphylaxsis) of infection most important factor	Treatment of infection usual practice

Source: Adapted from Pagel SW, Gautier P. Use of antimicrobial agents in livestock. Rev Sci Tech. 2012;31(1):145-88. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22849274.

Antimicrobial resistance development

The development of antimicrobial resistance is a natural phenomenon that occurs as a consequence of any use of antimicrobials, but maybe exacerbated when misuse occurs. Resistance is a complex issue with recent research indicating that resistance can develop even in an antimicrobial-free environment (Rodriguez-Verdugo et al., 2013). This section discusses what occurs when resistance develops and provides data demonstrating a relationship between use of antimicrobials in livestock and the emergence of resistance. A later section will explore in more detail the environmental impact of the use of antimicrobials in livestock.

Bacteria have developed several different mechanisms that allow them to be resistant against different antimicrobials, an essential “weapon” for survival. In fact this is a natural, ancient phenomenon. Bhullar et al. (2012) found resistant bacteria to different commercially available antimicrobials, in a cave that had been isolated for over four million years. Another research group has shown that 30 000 year-old DNA samples already contained genes encoding for resistance against β-lactam, tetracycline and glycopeptides (D'Costa et al, 2011).

The general mechanisms of resistance can include, for example, production of β-lactamases, efflux pumps, or mutations that alter the expression and/or function of porins and Penicillin-Binding Proteins (PBPs) (Papp-Wallace, 2011). The genes that code these resistance mechanisms are frequently transferred horizontally between different bacteria, one of the major mechanisms of resistance spread, though this does not apply to all resistance mechanisms.

The continued use of a single antimicrobial can lead to resistance to multiple structurally unrelated antimicrobials. When the genes coding for this resistance are located on the same plasmids and transposons (Summers, 2002), which are mobile genetic elements that can be transmitted between bacteria of the same or different species. This amplifies the negative impact by causing so-called co-resistance. Co-resistance refers to the tolerance of a bacterium to therapeutic concentrations of more than one class of antimicrobials. The generally accepted concept of multi-drug resistance (MDR) is co-resistance to three or more classes of antimicrobial drugs. Co-resistance may also result in co-selection or co-amplification of the resistant bacteria: If a bacteria is resistant to antimicrobials A and B, using antimicrobial A can also co- select for increased resistance to antimicrobial B. Such co-selection may occur in the presence of sub- therapeutic levels of antimicrobials. As an illustration of these phenomena, the use of ceftiofur in cattle both co-selected and co-amplified a non-type-specific *E.coli*, co-resistant to tetracycline as well as other classes of drugs (Alali et al., 2009). It should be noted that high levels of antimicrobial use leads to a high selection pressure for resistance and therefore sustained practices in the application of antimicrobials increases the likelihood of the development of resistance.

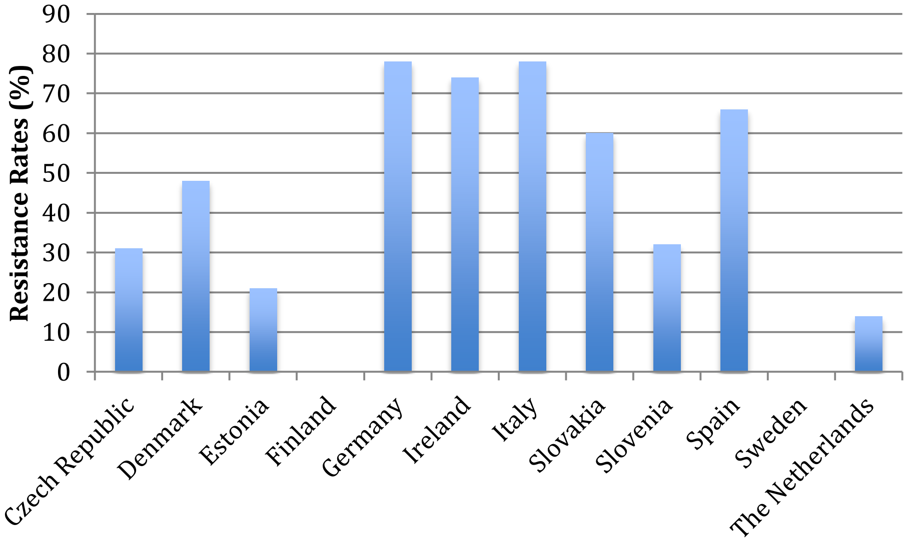
It is generally accepted that humans can be exposed/acquire resistance genes (or bacteria) from animals, either by direct contact or by the consumption of food. Considering the complexity of global food production, following the track of resistance genes or bacteria in food systems is challenging. In 1986, Hummel et al. (1986) tracked the spread of nourseothricin (a streptogramin antimicrobial), used solely for growth promotion in pigs. Before the use of this antimicrobial as a growth promoter, resistance was very uncommon. However, after only two years, resistance was detected in the *E.coli* of pigs, people in direct contact with animals and also reported in people in the region attending hospital. The proportion of *E.coli* strains with resistance was highest in the pigs (33% of strains identified) and lowest in the hospital cases with urinary tract infections (1% of strains identified). By comparison no resistance was detected in any animal or human tested in regions not using noursethricin (Dibneret al., 2005).

Data from Europe indicate that the pattern of resistance across countries and their livestock population varies. In the major pig producing areas of Germany, Spain, Denmark and Italy, *Salmonella spp* bacteria were found to have a high level of resistance to tetracyclines. *Salmonella* bacteria were found to have a moderate rate of resistance in the Netherlands (Figure 2). It is important to recognise that how resistance is monitored and reported varies across countries and regions, and for comparisons in the future there need to be recognised guidelines.

Similar data are presented for Asian countries from poultry systems with a wider range of antimicrobials in Table 3 and this uses *Salmonella* as the exemplar organism. It is questionable if *Salmonella* bacteria is an appropriate species to track for changes in resistance and *E.coli* would be a more appropriate choice (Chantziaras et al., 2014).

Similar data are presented for Asian countries from poultry systems with a wider range of antimicrobials in Table 3 and this uses *Salmonella* as the exemplar organism. It is questionable if *Salmonella* bacteria are an appropriate species to track for changes in resistance and *E.coli* would be a more appropriate choice (Chantziaris et al, 2014).

Figure 2. Tetracycline resistance in *Salmonella* spp from pigs in Europe*



* Based on 2010 MIC data.

Note: Sweden and Finland do not have *Salmonella*.

Source: EFSA, ECDC. The European Union Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2010. EFSA J. 2012;10(3):2598. doi:10.2903/j.efsa.2012.2598.

Table 3. Percentage of *Salmonella* spp. isolated from poultry and resistant against antimicrobial substance classes in the Asia-Pacific region

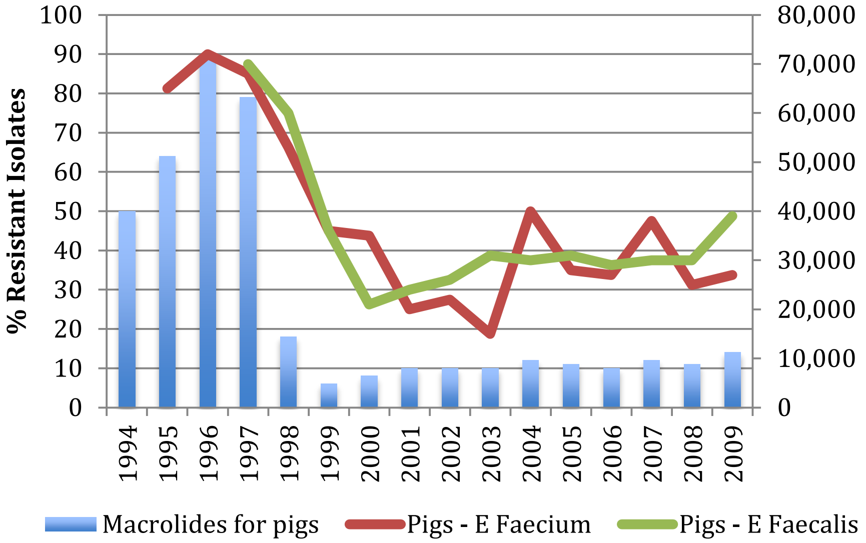
Country	Number of isolates	Percentage of isolates that are resistant against this substance class				
		AMP	CIP	CHL	GENT	TET
Bangladesh	12	75	0	0	0	50
Cambodia	152	17	3	6	1	21
Malaysia (live)	38	Nd	Nd	3	Nd	14
Malaysia (meat)	11	55	9	46	40	55
Sri Lanka	?	7	Nd	0	0	7
Thailand	211	49	1	28	12	59
Viet Nam (M)	50	20	0	22	2	32
Viet Nam (S)	36	17	3	19	3	33

AMP = Ampicillin; CIP = Ciprofloxacin; CHL = Chloramphenicol; GENT = Gentamicin; TET = Tetracycline;
For Viet Nam : M = Medium Size Farm; S = Small Farms.

Source: Otte M., Pfeiffer DU, Wagenaar J. Antimicrobial use in livestock production and antimicrobial resistance in the Asia-Pacific region. Bangkok; 2012:4. Available at: http://cdn.aphca.org/dmdocuments/RBR_1210_APHCA AMR.pdf.

To provide more detail of the relationship between antimicrobial resistance and antimicrobial use, Figure 3 shows the relationship between a change in use of macrolides in pigs and a reduction in resistance.

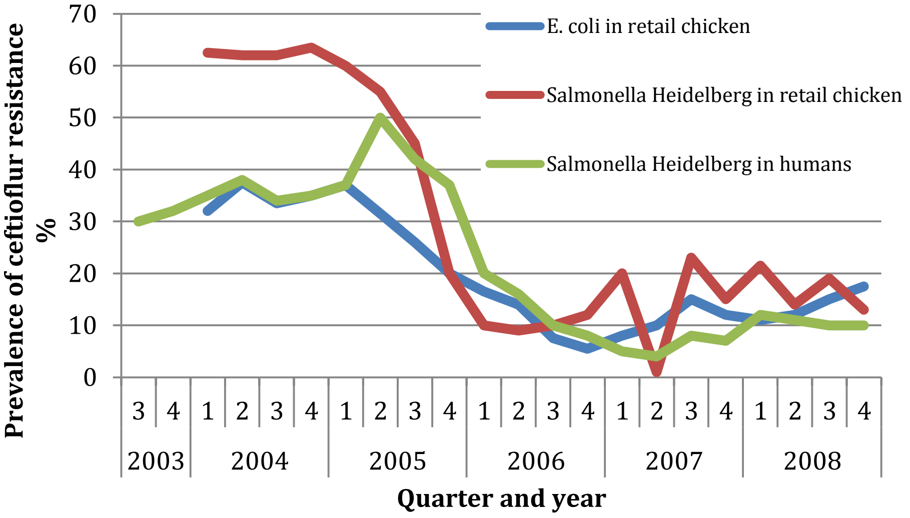
Figure 3. Trend in occurrence of resistance to erythromycin among *Enterococcus faecium* and *Enterococcus faecalis* from pigs and the consumption of macrolides for pigs, Denmark, 1994-2009



Source: Adapted from DANMAP 2009.

Even more interesting was the change in cetiofur resistance in Canadian chicken products and humans with the withdrawal of the use of this antibiotic in the first quarter of 2005 (Figure 4).

Figure 4. Prevalence of ceftiofur resistance[1] among retail chicken *Escherichia coli*, and retail chicken and human clinical *Salmonella* enterica serovar Heidelberg isolates during 2003-2008 in Québec, Canada



[1] Moving average of the current quarter and the previous two quarters.

Source: Dutil L, Irwin R, Finley R, et al. (2010), “Ceftiofur resistance in *Salmonella* enterica serovar Heidelberg from chicken meat and humans, Canada”, *Emerging Infectious Diseases*, Vol. 16(1):48-54. doi:10.3201/eid1601.090729.

Further detail on the complex relationship between antimicrobial use and resistance has been provided by the extraordinary progress made in the past 10-20 years in the use of molecular epidemiology tools. Table 4 presents a brief summary of more specific studies that demonstrate links between use of antimicrobials in livestock and the emergence of resistance.

Table 4. Ecological associations between antimicrobial use in food animals and resistant bacteria in humans

Study question	Results	Author, year, country
Is there a relation between the use of fluoroquiolones and the development of resistance to quinolone in *Campylobacter* subspecies?	Quinolone resistance increased from 0% to 11% in human stool and from 0% to 14% in poultry products between 1982 and 1989, during which time veterinary and human use of fluoroquinolones increased substantially	Endtz et al., 1991, Netherlands[1]
Does the introduction of quinolone use in food animals lead to the emergence of resistance in *Campylobacter jejuni* and *Campylobacter coli*?	Antimicrobial-resistant infections in humans emerged rapidly following the use of quinolone in food animals	Engberg et al., 2001, multiple countries[2]
What is the prevalence of fluoroqinolone resistance in *Campylobacter jejuni* isolates?	Very small prevalence (2%) of resistance to ciprofloxacin in human *Campylobacter jejuni isolates (Use of fluoroquinolones in food animals is not legal in Australia)*	Unicomb et al., 2006, Australia[3]
Source of resistance in *Salmonella* in humans and animals	Few links between resistance *Salmonella* in humans and cattle in Scotland based on molecular epidemiology tools. No information on the other species or on imported food sources	Mather et al. (2013)[4]
Comparison of antimicrobial resistance in pigs, poultry, cattle with antimicrobial use	Very strong correlation between antimicrobial use and antimicrobial resistance in all species	Chantziaras et al. 2014[5]

Notes:

1. Endtz HP, Ruijs GJ, van Klingeren B, Jansen WH, van der Reyden T, Mouton RP (1991), “Quinolone resistance in campylobacter isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine”, *The Journal of Antimicrobial Chemotherapy*, Vol. 27(2):199-208. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2055811 . Accessed 5 May 2014.

2. Engberg J, Aarestrup FM, Taylor DE, Gerner-Smidt P, Nachamkin I (2001), “Quinolone and macrolide resistance in Campylobacter jejuni and C. coli: resistance mechanisms and trends in human isolates”, *Emerging Infectious Diseases Journal*, Vol. 7(1):24-34. doi:10.3201/eid0701.700024.

3. Unicomb LE, Ferguson J, Stafford RJ, et al. (2006), « Low-level fluoroquinolone resistance among Campylobacter jejuni isolates in Australia”, *Clinical Infectious Diseases*, Vol. 42(10):1368-74. doi:10.1086/503426.

4. Mather AE, Reid SWJ, Maskell DJ, et al. (2013), “Distinguishable epidemics of multidrug-resistant *Salmonella* Typhimurium DT104 in different hosts”, *Science*, Vol. 341(6153):1514-7. doi:10.1126/science.1240578.

5. Chantziaras I, Boyen F, Callens B, Dewulf J. (2014), “Correlation between veterinary antimicrobial use and antimicrobial resistance in food-producing animals: a report on seven countries”, *The Journal of Antimicrobial Chemotherapy*, Vol. 69(3):827-34. doi:10.1093/jac/dkt443.

Source: Adapted and updated from Landers TF, Cohen B, Wittum TE, Larson EL (2012), “A review of antibiotic use in food animals: perspective, policy, and potential”, *Public Health Rep.* Vol. 127(1), pp:4-22. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3234384&tool=pmcentrez&rendertype=abstract.

The discussion above documents how the emergence of antimicrobial resistance can be related to antimicrobial use, yet it does not include all elements of the impacts of a change in antimicrobial use. One of the gaps that we identify is the lack of synthesis of available data on specific resistance in bacteria found in animal species at a global level. Such analyses are relatively common in relation to use of antimicrobials in humans. For example, the percentage of bloodstream infections showing multi-drug resistance is systematically collected at EU level and regularly published by ECDC.[11]

It is possible to find some illustrations for animals, for example, the spatial distribution of tetracycline resistance among *Salmonella spp*. from pigs. There is a process starting to become more standardised in veterinary medicine but not for all parts of the world. As antimicrobial resistance is a trans-boundary issue, it would be relevant to obtain the global picture. Ideally these illustrations should try to match three different sources of data: antimicrobial use in all species in including humans, resistant bacteria in food with typing to ensure that it distinguishes the source of resistance and resistance in bacteria isolated from humans. This way, a much better evaluation of the relationships between "use and resistance", and "use and efficiency" could facilitate formal risk assessments.

3. Economic and public health consequences: Risks and benefits of antimicrobial use in livestock

The benefits of the use of antimicrobials are clear – livestock that are sick can be made healthy and productive again, and healthy livestock's performance can be enhanced if low levels of antimicrobials are used in their feed. On the negative side, regular use of antimicrobials would appear to be associated with the emergence of resistance, and this resistance limits the usefulness of antimicrobials in both animal and human medicine. There is a trade off on the use of antimicrobials in livestock and some would argue that this is becoming more critical, yet to assess this trade off requires much stronger datasets on antimicrobial use in livestock, resistance gene changes and transmission dynamics into humans.

A possible benefit from the use of antimicrobials in livestock is through food safety. Some studies demonstrated that animals that have evidence of previous infection at slaughter have a higher incidence of carcass contamination with food safety pathogens such as *Campylobacter* and *Salmonella* (Cox, 2005; Hurd et al., 2005; Russel, 2003). Thus, the prophylactic and metaphylactic uses of antimicrobials may provide a public health benefit. There is no accessible research showing the impact of slaughter and processing plant food safety control procedures and the use of antimicrobial spray washes on antibiotic resistant bacteria. The US has extensive data on the beneficial impact of these processing procedures on reducing spoilage and pathogenic bacteria counts on meat products. However, there is a need for more scientific data showing potential control of antibiotic resistant bacteria on meat products with the application of specific food safety controls and antimicrobial spray washes. There are alternatives to the use of antibiotics to reduce bacterial contamination on carcass (such as hot water decontamination) and judgements on the best methods to reduce such contamination needs to be informed by risk assessments and cost effectiveness analysis ((Baptista et al, 2010).

This section will examine the importance of livestock production and the evolution of the production systems we rely on for livestock products. This will provide information on the likelihood of such systems generating more or less risk regarding the emergence of antimicrobial resistance. The risks associated with resistance will then be covered and summarised.

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[11] http://ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/about_programme.aspx.

Importance of livestock production

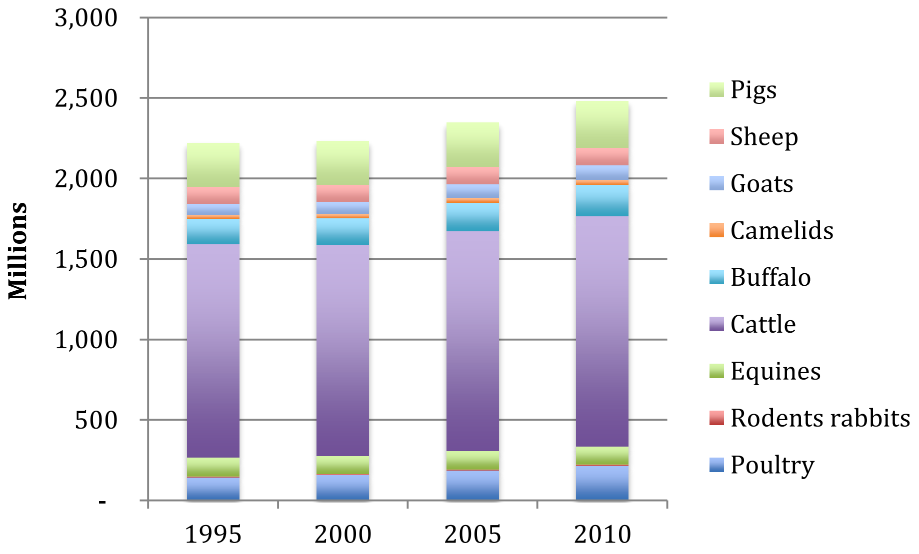
The world population was estimated to be approximately 7.16 billion people in 2013 and is predicted to rise to 8.3 billion in 2030, and over 9 billion in 2050. In addition, this population is urbanising at an accelerating pace. In general, urban populations are richer than rural ones, and they demand more meat relative to other food products.

The response to the greater demand for livestock products has been:

- A general increase in the global livestock populations.
- Intensification of livestock production systems with a reliance on diets of concentrated feeds, indoor housing and use of specialist breeds with greater output per animal.
- Greater densities of livestock populations clustered in areas with access to transport and processing systems.
- Greater complexity of the livestock food systems in terms of feed supply, slaughter, processing and retailing. Many of the food systems are global, for example feed for chickens in Europe can be grown in South America. The breast meat from these birds may then be consumed in Europe, the wings in Africa and the feet in Asia.

It is estimated that in 1995 there were 2.22 billion livestock units[12] globally, and that by 2010 this has grown to 2.48 billion. Whilst cattle continue to be the major livestock species in terms of biomass and value, the most rapid growth in livestock populations has come from poultry and pigs (Figure 5).

Figure 5. Global terrestrial livestock population in millions of livestock units



Source: Data FAOSTAT, 2013; authors' analysis.

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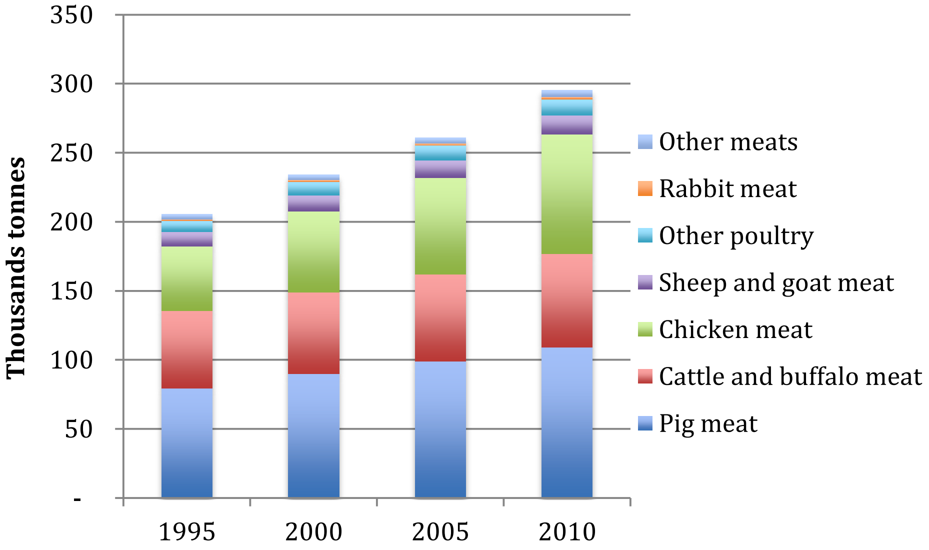
[12] A livestock unit is equivalent to 500 kg live weight and is a means to allow comparisons between different species.

Meat production has grown from 205 million tonnes in 1995 to 295 million tonnes in 2010. The most important species are pigs, poultry and cattle, which provide 80% of the meat consumed globally. One of the major changes has been poultry overtaking cattle as a provider for meat in the last ten years (Figure 6). It is acknowledged that aquaculture is also an important protein source.

Figure 6. Global production of terrestrial meat (in c.w.e.) between 1995 and 2010 by species



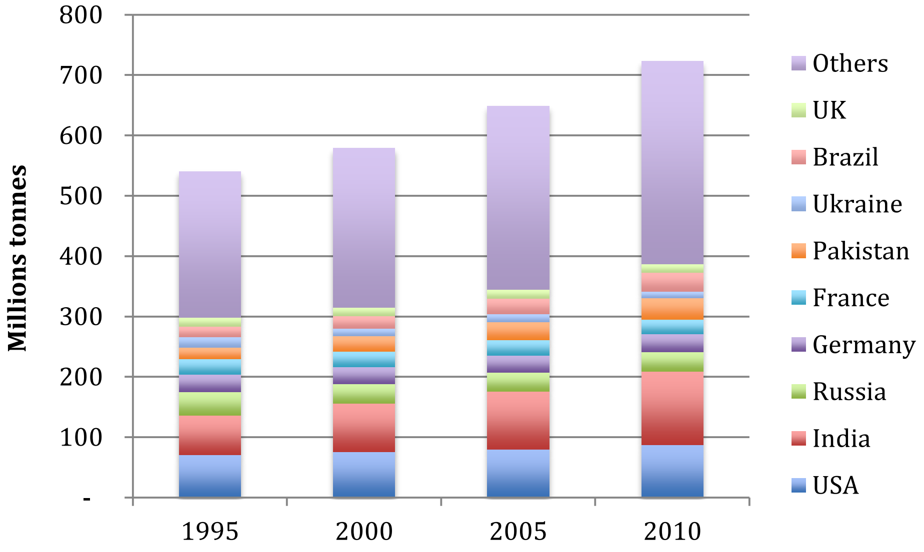
Source: FAOSTAT database, 2013; authors' analysis.

The increased production of meat has not only kept pace with human population growth, it has also allowed a greater level of consumption of meat per person. For example, meat consumption in the developing world has risen from 10 kg per person per year in 1964-66 to 26 kg in 1977-99, and is projected to rise to 37 kg per person per year in 2030. Globally the amount of meat available per person has risen from 35.8 to 41.9 kg per person per year between 1995 and 2010.

In addition to meat production, global milk and egg production have also risen quickly. Milk production is estimated to have risen from 540 million tonnes in 1995 to 723 million tonnes in 2010 (Figure 7). This production is dominated by cattle (83%) and buffalo (13%), and nearly a third of the incremental milk is produced in India and the US (authors analysis based on FAOSTAT data).

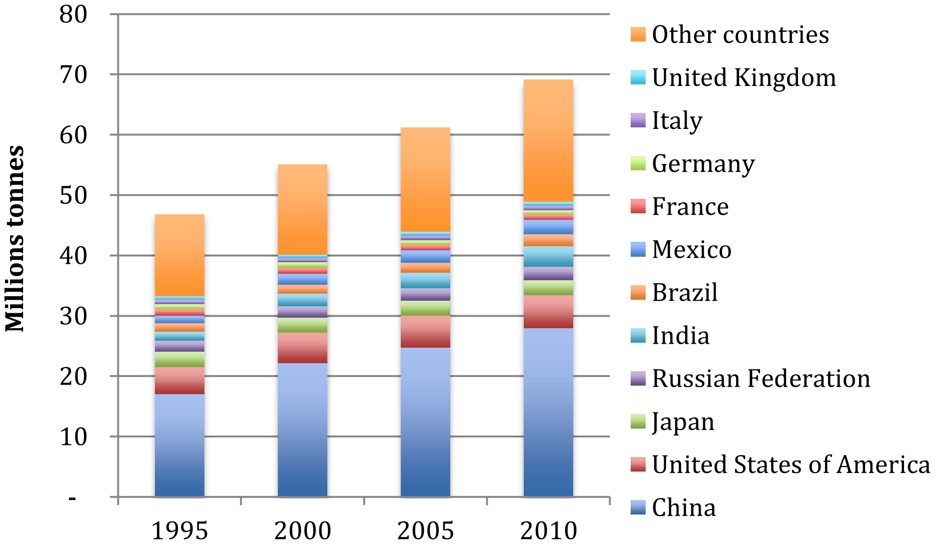
The consumption of milk and dairy products also rose rapidly, from 28 kg per person per year in 1964-66 to 45 kg in 2002. It could further increase to 66 kg per person in 2030 (authors analysis based on FAOSTAT data). Egg production increased from 46 to 69 million tonnes per year between 1995 and 2010 (Figure 8). A large proportion of eggs are produced in China, which has increased its share of global production to just over 40% in 2010 (authors analysis based on FAOSTAT data).

Figure 7. Global milk production by country millions of tonnes



Source: FAOSTAT database, 2013; authors' analysis.

Figure 8. Global egg production by country in millions of tonnes



Source: FAOSTAT database, 2013; authors' analysis.

The availability of proteins from livestock increased over the last twenty years. There has been a switch in terms of the type of protein eaten and also the type of production systems that produce the proteins. The increased production has come through changes in the genetics of the livestock we keep that have been bred to efficiently utilise concentrate feeds, grow quickly, produce high individual quantities of milk or eggs and be able to be kept in confined and very densely populated conditions. It has been conjectured that such conditions may increase the chance of transmission of certain diseases while decreasing the risk of other pathogens between animals and humans (Jones et al., 2013) and change the profile of animal health problems, and the most common is a change in the need to manage intestinal and pulmonary infections in the case of meat animals and udder infections in the case of milk producing animals. Often this is achieved through the use of antimicrobials both as a prophylactic agent in the systems and also as metaphylactic or therapeutic agent. Where animals are managed as groups in intensive systems it is much more likely that farmers and vets will rely on prophylactic and metaphylactic strategies of antimicrobial use. In terms of geographic location there is clustering of species in countries with China being important with regard to pig, poultry and cattle populations and India being important in terms of poultry and cattle populations. Estimates on overall impacts of antimicrobials on the availability of livestock proteins in developing countries vary, with some studies stating this could be as high as 10% and others estimating it to be as little as 2% (Jones et al., 2013). Finally, within countries these systems cluster in specific geographical locations which means their densities are high, and the wastes they produce are concentrated.

The impact of changes in antimicrobials use in our production systems is not well studied. The evidence presented across countries indicates that it is possible to reduce antimicrobial use and retain highly intensive and productive systems of production (Cogliani et al, 2011). The problem with such analysis is that it does not include other resource costs in the production system. These costs include investment in people for managing animals and their overall time, and the investment in animal housing systems that reduce the likelihood of infections and potentially limit the severity and length an animal or a group of animals are sick, costs of alternative disease control strategies and their impact.

Some critical questions remain in this section:

- How much did the use of antimicrobials contribute to the increased accessibility of animal source foods?
- How much did the use of antimicrobials as growth promoters contribute to increased accessibility of animal source foods?

The authors have not come across information on the relation between production systems and antimicrobial use with regard to either improved access or availability of food.

Risks related to antimicrobial resistance spreading from livestock systems

There are three potential routes that antimicrobial resistance could spread from livestock production systems: i) through the food system, ii) direct contact between people and animals and iii) through environmental contamination. As with most public health problems the initial reaction to problems is to focus on the food system to ensure that consumers are not affected. The members of *Codex Alimentarius* have generated guidelines on a structured risk analysis framework that addresses the risks to human health associated with the presence in food of antimicrobial resistance that is linked to the use of antimicrobials in animals or food preparation. These guidelines also provide advice on management strategies to reduce such risks.

Food system risks

The association between antimicrobial use and the prevalence of resistance in bacteria has been indicated above. The use of fluoroquinolones (e.g. enrofloxacin) in food animals has been linked to the development of ciprofloxacin-resistant *Salmonella*, *Campylobacter* and *E.coli*, which were responsible for human infections. It is recognised that resistance generated to these antimicrobials through the use in animals is a part of the resistance profile as these antimicrobials are widely used in human medicine and the spread can be through travel and food contamination. However, several reports suggest that multiple *E.coli* (EPEC) human infections may have originated in food animals, mainly poultry (Warren et al, 2008; Johnson et al, 2007).

Table 5. Studies on the risks associated with the development of resistance from using antimicrobials in livestock in the United States

Country	Purpose of the study	Antimicrobial class	Bacterium analysed	Food animal species in question	Risk estimates obtained	Author, year, reference
US	Public health impact Of Fluoroquinolone resistance in Campylobacter, attributed to using fluoroquinolone in chicken	Fluoroquino-lones	*Campylobacter*	Broiler; chickens	1999 human cases: estimated to be between 5 230 (5th percentile), 15 330 (95th percentile)	Bartholomew et al.; Data from 1999; published in 2003
US	Annual risk to US population on successful treatment of Campylobacter and E. faecium due to resistance to macrolides	Macrolides	*Campylobacter, Enterococcus faecium*	Poultry, pigs, non-dairy beef cattle	Human illness due to macrolide-resistant campylobacteriosis from farm level attribution resulted in <1 in 10 million cases in human medicine. Similarly for cases due to macrolide-resistant *E. faecium <1 in 3 billion*	Hurd et al.; 2004[1]
US	Potential effect of a ban in virginiamycin	Streptogramin	*Enterococcus faecium*	Chicken	A modelling approach was used that produced a wide spread of predictions on the impact of antimicrobial use in livestock. There appeared to be greatest benefits from reductions in use of virginiamycin	Kelly et al.; 2004[2]
US	Quantify the harm from use of penicillin drugs in food animals by estimating the number of ampicillin-resistant non-nosocomial fatal *E. faecium human* infections	Penicillins	*Enterococcus faecium*	Food animals	0.04 to 0.14 excess mortalities of people per year prevented, if current uses of penicillin drugs in food animals were discontinued	Cox et al.; 2009[3]

1. Hurd HS, Brudvig J, Dickson J, et al. (2008) “Swine health impact on carcass contamination and human foodborne risk”, *Public Health Reports* , Vol. 123(3):343-51. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2289987&tool=pmcentrez&rendertype=abstract. Accessed 5 May 2014

2. Kelly L, Smith DL, Snary EL, et al. (2004), “Animal growth promoters: to ban or not to ban? A risk assessment approach”, International Journal of Antimicrobial Agents, Vol. 24(3):205-12. doi:10.1016/j.ijantimicag.2004.04.007.

3. Cox, L.A.T., D.A. Popken and J.J. Mathers (2009), “Human health risk assessment of penicillin/aminopenicillin resistance in enterococci due to penicillin use in food animals”, Risk Analysis, Vol. 2009;29(6):796-805. doi:10.1111/j.1539-6924.2009.01202.x.

Source: Adapted from McEwen S.A. (2012), “Quantitative human health risk assessments of antimicrobial use in animals and selection of resistance: a review of publicly available reports”, *Revue Scientifique et Techniques* (International Office of Epizootics), Vol. 31(1):261-76. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22849281.

In terms of looking at the impacts on the human health McEwen (2012) published a review paper, summarising the available American quantitative human health risk assessments of antimicrobial use in animals (McEwen, 2012). Risk estimates ranged from a few additional illnesses per million at risk, to many thousands (Table 5). Comparison between studies is however far from straightforward, as few of them consider the same drug/bacterium combination or the same risk question, and the methodologies used also differ substantially (McEwen, 2012). The risk being assessed in the table is the risk of treatment failure in human illness, an appropriate measure since resistance alone is not a risk.

In general, there are a number of studies that indicate an association between antimicrobial use in livestock and resistance in bacteria. However, few have quantified what this subsequently means in terms of public health. There is a void in data and information which can lead to uninformed policy making at international and national levels, poor development of private standards and uninformed choice of production systems at farm-level. Snary et al. (2004) indicate that much data are available for food system risk assessments of resistance, but it is rarely in a form that allows strong quantitative analysis. The *Codex Alimentarius* guidelines on assessing antimicrobial resistance risks in the food system are important in this context as they provide an analytical structure to guide data collection and enhance data capture.

Environmental risks

Two environmental risks are identified: (i) the hazard of emission of antimicrobials into the environment, for example a significant quantity (75-90%) of tetracycline antimicrobials used in food animals are excreted largely unmetabolised into the environment, and (Chee-Sanford et al, 2001) (ii) the hazard of bacteria with resistance genes being disseminated into the environment when manure and urine from livestock production are spread. The data on this dissemination is limited and requires further work to draw hard conclusions. An additional concern is the waste water from pharmaceutical manufacturers which if left untreated has been shown to create pockets of resistance.[13]

Table 1 presented the different types of antimicrobials according to their chemical classification, which in part also relates to the mechanisms by which they limit microbial growth or kill microbes. Another important consideration of the nature of antimicrobials is their chemical nature and in particular whether they are hydro-philic or phobic. The hydrophilic antimicrobials will largely be excreted in the urine. This in turn means that they will have less impact on the intestinal flora – the microbiome. Hydrophobic antimicrobials on the other hand are excreted less rapidly from the body and are ideal in terms of long acting nature in animals that might be difficult to catch and manage. These antimicrobials are more likely to be excreted in the bile and hence into the intestine with potential impact on the microbiome.

In the UK, between 2006 and 2011, each year, an estimated 70 million tonnes of animal manure (that could contain residues of antimicrobials) were spread, as fertiliser, onto agricultural land. Heuer et al. (2011) analysed the contribution of manure to resistance levels in agricultural soils and concluded that manure has become a reservoir of resistant bacteria (Heuer, 2011). Antimicrobials excreted from humans and animals either go as waste water to rivers or to treatment plants. This "grey water" can then be used for a wide variety of purposes, including irrigation of agricultural crops, watering of golf courses or creating artificial snow at ski resorts. Antimicrobial residues can be removed by adsorption, complex formation and degradation (chemical or biological) (Acar, 2012) or remain in soil, manure and/or water for different periods of time, according to their stability and the local

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[13] http://www.nature.com/news/2011/110216/full/news.2011.46.html

environmental conditions. This leaching into the environment effectively exposes countless environmental organisms to minute quantities of antimicrobial (Marshall et al., 2011). The outreach/spread of this leaching effect can also reach geographical remote areas, such as the pole areas (Sjolund et al, 2008; Hernandez et al, 2012). Environmental contamination might also be one of the reasons that explain the recovery of antimicrobial resistant bacteria in wild animals (Robb et al, 2013; Carson et al, 2012; Schaumburg et al, 2012; Wardyn et al, 2012).

Ultraviolet disinfection of water and wastewater seems to have limited potential to damage antimicrobial resistant bacteria and antimicrobial resistance genes (McKinney et al, 2012), so different treatments need to be developed and tested.

In summary, most antimicrobials given to livestock are excreted. Their impact can be localised in terms of influencing the microbiome of the animal and also more generalised through the antimicrobial coming into contact with the environment as it is excreted in the manure and urine. Some data indicate the problems this appears to cause with an association between the spread of manure and the existence of resistance genes in the environment (Wegener, 2012). Again, there are gaps in our knowledge of the overall impact of the environmental externality created by using antimicrobials in livestock systems.

Overall economic impact of antimicrobial resistance

From an economic perspective it is important to recognise that low-level antimicrobial use in livestock influences the efficiency of feed inputs and hence the overall productivity of a system. Yet there are trade-offs in terms of animal health. For example, whilst antimicrobials may enhance the growth and efficiency of livestock, that could well lead over time to the emergence of resistance to antimicrobials and any outbreaks of disease of organisms with resistance genes would require the use of more expensive antimicrobials. Conversely not using antimicrobial prophylactically may increase feed costs and perhaps costs associated with disease and death loss, but diseases are less likely to be caused by resistant pathogens and can often be treated with less expensive first-line antimicrobial drugs (Mathews, 2001). The balance between the short-term gains from using antimicrobials prophylactically versus medium- to long-term costs of resistance build up illustrate in a localised sense the trade-offs that need to be made at animal production level.

There are studies that have attempted to estimate the monetary externalities of antimicrobial resistance. Kaier and Frank (2010) measured the externality of antibacterial use in human medicine and concluded that consumption of a single defined daily dose of second-generation cephalosporins, third-generation cephalosporins, fluoroquinolones and lincosamides is associated with a negative externality of about EUR 5, EUR 15, EUR 11 and EUR 12, respectively. This estimate relates to increased likelihood of the emergence of resistance and the increases costs in healthcare and human health loss associated with that increased resistance (Kaier et al., 2012).

In contrast, use of one litre of alcohol-based hand rub solution for hand disinfection is associated with a positive externality of about EUR 61 (Kaier et al., 2012). Kaier and Moog concluded that a 32% reduction in the cost of MRSA to the German healthcare system could be reached, if the use of fluoroquinolones and third-generation cephalosporins (in humans) was reduced by 10%, together with the same increase in the use of antiseptics for hand disinfection. Tansarli et al. (2013) looked at the in-hospital costs attributable to antimicrobial multidrug resistance on (human) inpatient care cost and concluded that these costs are alarmingly high. For example, with respect to MRSA, the attributable mean total costs varied from USD 1 014 to 40 090, and they varied from USD 1 584 to 30 093 among studies on extended-spectrum β-lactamase-producing *Enterobacteriaceae*. The large spread on the estimates relate to uncertainties on the parameters and outcomes in individual cases.

Vagsholm and Hojgard (2010) presented a careful analysis of how the externalities need to be incorporated into a taxation mechanism on antimicrobial pricing. Their analysis is useful in putting into context the need for government policies on taxation of antimicrobials and the fact that this element of policy making should be aiming to rectify market failure. One area of weakness within the paper surrounds the underlying science in terms of resistance emergence and transmission.

Smith et al. (2005) highlighted that much work is done on resistance issues in terms of micro level impacts and interventions to avoid or minimise the risks. They argued that macro-level impacts need to be examined carefully for wider implications on the economy, as evaluations tend to concentrate on the economic impact to the healthcare sector alone, with poor estimation of the social costs and benefits of a disease or intervention. Further work indicates (Smith et al., 2013) that an increase in resistant organisms coupled with no new antibacterial discovered since 1987 (Davies, 2013) and very few antivirals and antifungals suggesting a crisis and a need to change how current human and animal health systems will need to manage infectious diseases in the future. The currently available estimates of the economic costs of antimicrobial resistance fail to recognise that antimicrobials are integral to modern healthcare.

4. Policy options and private standards

The use of antimicrobials in livestock is common, yet the institutional setting in which they are used is variable. International and regional organisations have recognised the need to understand and manage antimicrobial use, and many countries have mechanisms for approval and use of antimicrobials in livestock in place. In addition to these public mechanisms often backed with legislation, there are private standards promoted by organisations that govern livestock food production systems and also farmer and animal health organisations that have an interest in the health and welfare of animals as well as the need to provide safe food and protect the environment. This section summarises the important issues in this institutional setting.

International policy

Considering the importance and the global dimension of AMR, it is not surprising that multiple international organisations have made this topic a priority. The WHO has pursued the issue for a number of years, involving several expert groups in the development of a global strategy. The strategy includes a push for a total ban of antimicrobials for growth promotion purposes. WHO also published a list of “Critically Important Antimicrobials for Human Medicine.” Antimicrobial classes were categorised as “critically important”, “highly important” or “important” on the basis of two criteria: i) the antimicrobial was the sole therapy or one of the few alternatives to treat serious human disease, and ii) the antimicrobial was used to treat diseases caused by organisms that may acquire resistance genes from non-human sources. The general expectation is that those antimicrobials seen as “critically important” for public health may have to be limited in their non-human usage in order to preserve efficacy. In terms of a generic strategy, the WHO has a policy on containment of antimicrobial resistance.[14]

From the animal health perspective, OIE has been working on the issue of antimicrobials for over a decade, and of particular importance is the document on prudent use of

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[14] http://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf?ua=1.

antimicrobials (Chapter 6.9 of the Terrestrial Animal Health Code).[15] It has also developed, in parallel with the WHO for human medicines, a list of antimicrobial agents of veterinary importance which was adopted originally by the World Assembly of Delegates in May 2007. A revision, undertaken with the participation of the WHO, took into account concerns for human health and was adopted by the 178 OIE member countries in May 2013.

From a food chain perspective, it is important to recognise the guidance from *Codex Alimentarius* through its *ad hoc* group Intergovernmental Task Force on Antimicrobial Resistance on best practice to minimise and contain antimicrobial resistance. These detail the need for surveillance and management measures based on risk analyses that focus on a combination of animal health and human health.

Harmonisation and common actions worldwide for human health, animal health and environment require dialogue between all sectors and organisations. A general discussion on how to reconciliate the different interest will require dialogue between all sectors and organisations. A perfect example would be an agreement on the harmonisation for the protocols used in data collection for quantifying usage by substance and species as well as for determination of resistance. In this regard, it is important to note the meeting between OIE, FAO and WHO in November 2007 to discuss the use of antimicrobials in humans and animals and initiate common actions (FAO, 2008).

National level: Legal basis for antimicrobial use in livestock

The majority of countries have regulations or legislation in place to control the use of antimicrobials in livestock, e.g. in terms of having antimicrobials as prescription only medicines (Pagel et al., 2012). However, the implementation, coverage and enforcement of these regulations are far from perfect (Pagel et al., 2012). The US, for example, has a regulatory system that requires an authorisation prior to a drug entering the market which will look at efficacy, residues, toxicology, environment and animal safety. Risk management options can include restrictions on sale and use yet a prescription is often not required when livestock producers want to have access to an antimicrobial drug (Green et al., 2010). The same is true for the availability of antimicrobials without a prescription for humans. In Kerala, India, there is no restriction on over-the-counter dispensing of antimicrobials without a prescription, no matter the class of antimicrobial in question (Saradamma et al., 2000). Other countries have reported very high percentages of self-medication (Jordan 40%; China 59.4%, Sudan 73.9%[16]). Nevertheless, a number of countries have no legislation in place for antimicrobials based on their effect, safety and quality. Improved legislation and enforcement is therefore one of the focus areas in the WHO's and OIE's goals for antimicrobial use as communicated at the World Health Day in 2011, this mirrors earlier calls from WHO (WHO Berlin, 1997).[17]

In the US, the Food and Drug Administration (FDA) builds its policy partly on voluntary adoption of judicious use principles and partly on regulatory limitation of use. The latter was applied to the non-human use of cephalosporins, which is now generally limited for off-label usage.

In the EU, antimicrobials for animal use are classified as prescription-only drugs and need to be obtained from an authorisation dealer, wholesaler, pharmacy or a veterinarian. It is unclear whether this led to a reduced use of antimicrobials. There can be additional restrictions and requirements, for example the need for a veterinary visit before a prescription

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[15] http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_1.6.9.htm.

[16] Respectively, Al-Azzam et al, 2007; Bi et al., 2000 ; Awad et al., 2005).

[17] http://www.who.int/world-health-day/2011/policybriefs/en/.

can be issued for livestock, or the establishment of a consultant contract before drugs can be left on the farm for use by the farmer. As up to two thirds of veterinary antimicrobial products in livestock are administered via feed, there is an additional issue related to dosage and administration details. Many countries impose recording duties on farmers, requiring them to keep records on which animals have received which substance and dosage on a given date. When introducing such regulations, resistance is common from both farmers and veterinarians due to costs of collecting the data and the limited private benefits. This will have impact on the enforcement of such regulations by government authorities. Additionally, in Europe, treatments have to be mentioned on documents for animals being sent to the abattoir, if the treatment is given within a withdrawal period (a period dependent on the antimicrobial and species). It is the responsibility of the owner to declare the use of the medicine.

In 2011, the EU published an action plan with policies targeted at the reduction of antimicrobial resistance. The key measures are focusing on appropriate use (in both animal and human health), strengthening the regulatory framework, general infection control and prevention, development of novel antimicrobial substances through research efforts as well as international collaboration through multi-lateral bodies such as WHO. One option to be considered is also the withdrawal or partial withdrawal of substances from veterinary usage. Several technical documents, including such recommendations, have already been published (Vågsholm, I.; Höjgård, S. 2010).

Substance withdrawal

A last resort preventive strategy would be to ban non-human antimicrobial use for certain indications. An example is the withdrawal of antimicrobials for growth promotion in livestock in the EU in 2006. In 2011, the WHO issued a call for a global phasing out of growth promotion use. One of the major fears among the food animal industries is that prohibiting the use of growth promoters will have a significant negative economic impact. Nonetheless, some evidence, while controversial, indicates that, in the long term, the consequences could be minimal (Aarestrup et al., 2010). Improved management (e.g. improved farming practices, hygiene and breeding programmes), reduced stress (e.g. reduced animal density) and investment in prophylaxis (e.g. vaccines, prebiotics) could provide producers the same benefits that the use of growth promoters claims to deliver (Marshall et al., 2011). There is a need for intensified research activity to develop strategies that provide alternatives to antimicrobial growth promoters. Some research programmes, for example Horizon 2020 from the EU, are starting to focus on this, but there remains a significant gap at present in terms of effective and efficient options for farmers and their advisors.

Avoparcin, a growth promoter glycopeptide, which selects for vancomycin-resistant Enterococci (VRE), was withdrawn in 1995 in the EU. In Denmark, this was followed by a reduction in the prevalence of human and animal VRE. However, VRE have persisted in poultry farms for up to 12 years, emphasising the complex relationship between the use of antimicrobials and the presence of resistant bacteria.[18]

A similar, more recent example stems from Quebec, Canada, where the use of ceftiofur was voluntarily ceased in egg hatcheries. The subsequent drop in ceftiofur resistance in *Salmonella* and *E.coli* isolated from humans provides very strong evidence for the effectiveness of this intervention. This was confirmed by the fact the resistance increased again after the temporary ban was lifted (Dutil et al., 2010). Consistent evidence was found in Denmark after a voluntary ban of cephalosporin use in pig production. A

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[18] DANMAP reports http://www.danmap.org/Downloads/Reports.aspx.

significant drop in ESBL-producing *E.coli* was observed two years after the ban (Agerso et al., 2013).

There is currently an increasing debate about general withdrawal of certain substances or substance classes for all or specified indications in non-human use. The European Medicine Agency (EMA) has published a reflection paper on the limitation of use of third and fourth generation cephalosporins in animals in 2008 (finally published in 2009); a referral took place later on addressing the recommendations from the reflection paper. Subsequently, the matter was considered by the European Food Safety Agency (EFSA), concluding that while there was indirect evidence to link non-human use with food-borne exposure and subsequent public health outcomes, there were insufficient data to quantify the link.[19]

Decisions on the bans of antimicrobial use in livestock have to take into account multiple criteria, most importantly the evidence on the potential positive public health impact. However, these need to be balanced against animal welfare, food safety and food security considerations. In this debate, discussions need to be initiated on why the antimicrobials are used, for therapeutic or prophylaxis measures. As there are significant knowledge gaps in several of these aspects, precautionary measures are being discussed in the meantime. While the World Trade Organisation (WTO), does not include explicit rules for precautionary measures, the WTO's Sanitary and Phytosanitary (SPS) Agreement does include rules for provisional SPS measures that may be taken when scientific information is insufficient to assess risks. According to the SPS Agreement, these measures should be temporary and should be reviewed as new scientific information becomes available.

Antimicrobial use has been integrated into trade standards, such as the OIE Terrestrial and Aquatic Codes and *Codex Alimentarius* code of practice on food system risk assessment and also code of practices to containment and minimisation of risk. The intention is to reduce trade disruption as a consequence of food contamination if antimicrobial residues occur. In principle, a country that has phased out a substance, could build a case against import of food produced using the substance, if evidence of a public health risk was available. Owing to the complexity of the ecology of resistant bacteria and their gene transfer, it seems difficult to provide clear-cut arguments. However, in the absence of alternative production practices, industries in countries reducing antimicrobial consumption probably pay a price in terms of reduced international competitiveness, related to changes in production practices at least in the short term. If requirements for a regulatory framework and availability of consumption data were accepted as minimum standards for international trade, this could have substantial negative consequences for low-income countries aiming to participate in international food trade, because low-income countries have yet to develop systems of data collection and analysis that would be able to demonstrate controlled use of antimicrobials and the tracking of antimicrobial resistance.

Private standards: Responsible and prudent use principles and beyond

"Prudent use" principles (sometimes also referred to as "responsible" or "judicious" use) describe criteria for best practice in the context of antimicrobial use. Guidelines have been developed by a number of organisations including veterinary associations and multi-stakeholder platforms. Prudent use principles typically cover points of registration and legal basis, need for diagnosis, selection of appropriate substance, formulation and spectrum, right dosage as well as emphasis on resistance testing. Some countries have developed more detailed guidelines based on these general principles. For example in Sweden and Norway,

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[19] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004307.pdf

the Veterinary Association and the Norwegian Medicines Authority, respectively have developed guidelines for antimicrobial use in both food animals and pets.[20] These substantial documents specify the general use policy to be applied in relation to antimicrobials as well as detailed use recommendations for specific clinical case representations and substances. It also describes good practice for all procedures associated with surgery as well as treatment. The Swedish documents also mention some classes of antimicrobials that should not be used at all, including carbapenems, oxazolidonones and glycopeptides.

The identification of the bacteria causing a condition, the prescription of an antimicrobial drug and the administration of the correct dose in the appropriate manner are critical factors in the prevention of the development of resistance. Prudent use is therefore a prerequisite, but may not be difficult to achieve in a setting where livestock businesses are put at greater business risk if disease problems persist. Farmers and their expectations regarding services provided by veterinarians also play an important role. Campaigns addressing farmers are therefore important, but have not yet been used widely. One recent example is the campaign launched by a farming newsletter[21] in the UK using the title "Making sense of antimicrobials", supported by web based information accessible to the public on responsible use.

In the US, several species groups have education programs for producers that address antibiotic use and treatment records. For example, the Pork Quality Assurance Plus (PQA Plus)[22] Certification Program has a dedicated chapter to educate producers on responsible antibiotic use. The chapter outlines five principals and six guidelines on responsible antibiotic use including, for example, using veterinary input for as the basis for all antibiotic decision making and the importance of treatment records (when, how and with what drug the producer treated his/her animals). Record templates are provided and it is recommended that treatment records be maintained for at least 12 months after the last date of treatment. The US beef industry has a similar program, the Beef Quality Assurance (BQA).

To strengthen prudent use, principles may be turned into more binding rules or guidelines with appropriate oversight/enforcement. For example, in Denmark after the approval of fluoroquinolones for the use in food animals, a rapid emergence of resistance occurred. Between 1995 and 1996, 23% of *C. coli* isolates from pigs were found to be resistant. In response to this, fluoroquinolones could only be used in food-producing animals after 2002 for the treatment after laboratorial confirmation that fluoroquinolones would be the only therapeutic option. The antimicrobial could only be administered by injection by a veterinarian who had to report this use to the regional veterinary officer. As a consequence of these measures, the use of fluoroquinolones decreased from 183 kg in 2001 to 49 kg in 2006, and the percentage of resistant *C. coli* isolates dropped to 12%, in 2009 from 23% in the mid-1990s.[23]

There is also the need for effective dosing. The target is to reach bacterial cure rather than clinical cure, i.e. it is not enough that the sick animal looks healthier – it is essential that the bacteria that caused the disease are destroyed. On the development of dosing, there is a need to understand the dynamics of substance release, absorption and efficacy in a target organ or tissue. These can be quantified using mathematical models based on the physiological response to a drug and the effect of the drug to the condition. This task has

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[20] https://www.ddd.dk/organisatorisk/sektionsmaadyr/Documents/AntibioticGuidelines.pdf.

[21] http://www.fwi.co.uk/livestock/medicines/.

[22] http://www.pork.org/Certification/2341/pqaPlusMaterials.aspx#Section2.

[23] DANMAP reports http://www.danmap.org/Downloads/Reports.aspx.

traditionally focused on the individual animal rather than a population level. There is a gap in *in vivo* clinical trials to inform the setting of dosage such that the target of a 90% attainment rate can be reached.

An additional fault in use may occur in relation to the amount of a drug that is applied to an individual or group. Previous reports have demonstrated the lack of accuracy when farmers and livestock owners estimate the weight of their animals (Machila et al., 2008; Besier et al., 1988). There is also evidence of over- and under-dosing of antimicrobials in group treatments in poultry and pigs (Callens et al., 2012; Persoons et al., 2012). The extent of such deviance from best practice and the extent of consequences are currently not well understood, but accepted as a significant component in the prevention of resistance. More research is now also focusing on the drivers and motivation of antimicrobial usage on farms to address the knowledge gap related to decision making (Mateus et al., 2011).

Private veterinarians usually earn their income both by charging for their services and – in many countries – by selling drugs directly to the producers. This is a scenario that can be perceived as providing an incentive for over-prescription of medication for financial benefit. To reduce the possibility of over-prescriptions, the Danish government introduced legislation in 1995 that reduced and fixed the profit of veterinarians from direct sales of antimicrobials to a maximum of 5%. The main sales point was to be the pharmacy. In Denmark, veterinarians can also only sell antimicrobials to a farmer during a visit, limited to a maximum of five days of treatment. The results of this policy implementation show that there was a 40% reduction in total use of therapeutic agents in Denmark, and the use of tetracyclines decreased from 37 tonnes in 1994 to 9 tonnes in 1995 (Aarestrup et al., 2008). It is worth noting that veterinarians in Finland, Norway and Sweden are not allowed to profit from the sale of antimicrobials, countries where use is relatively low.

As a further measure, Denmark recently introduced the “Yellow Card” scheme. Under this policy, a farmer receives a yellow card if he/she uses antimicrobials in a quantity two times higher than the national average. Classifications of farmers are based on recorded usage through pharmacies. This scheme has led to a reduction in antimicrobial use for therapy of almost 25% during the past two years (Aarestrup, 2012). The Netherlands also use a traffic light system. These initiatives have initially been effective in reducing antimicrobial use in livestock production, yet they are country specific and dependent on cultural norms and enforcement systems.

Similar to Denmark, some other European countries have introduced general policies aimed at reductions in non-human usage of antimicrobials. The Netherlands, Norway and France all have formal reduction targets expressed as percentage of previous use. The targets are high, up to 50% reductions, and mainly political rather than evidence-based. In the case of The Netherlands there has been success in reaching the target reductions and this has led to further target reduction between 2009 and 2015 of 70%.[24] This has led to renewed discussions around alternatives to antimicrobials, and these debates demonstrate the need for the public and private sector to work together in managing antimicrobial use. In conclusion public policy affects the institutional environment of antimicrobial use and thereby affects private decision making.

The institutional (or rule making and enforcement) landscape of antimicrobial use in livestock varies. In addition, there are major gaps of understanding and information in terms of the role of public and private organisations. One major gap is information from Latin America, Africa, Asia and the Pacific, which are all major holders of livestock and

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[24] http://www.agripress.be/_STUDIOEMMA_UPLOADS/downloads/wagenaar_benelux_december_2013.pdf.

important regions for the global production of livestock products. Even when information is available on major aspects of the institutional environment for antimicrobial use in livestock, there are differing cultural attitudes on use between US and the EU, and also differing cultural attitudes on use within the EU. This variation would appear to provide an explanation for the differences in antimicrobial consumption across the world in livestock systems. It therefore indicates that alongside the need for more detailed data on consumption, i.e. by species and production systems, there needs to be collection of the full institutional environment governing use and application of antimicrobials.

The OIE Global Conference on the Responsible and Prudent use of antimicrobial agents for animals recommend that the OIE collect harmonised quantitative data on the use of antimicrobial agents in animals with the view to establish a global database.[25] This will be based on its recently adopted standard on monitoring of the quantities of antimicrobials used in food producing animals and the questionnaire recently sent to member countries with the aim to collect first baseline information. This follows the *Codex Alimentarius* task force on antimicrobial resistance which was disbanded with the publication of risk analysis for AMR in the food system.

5. Reviewing and responding to the challenges

Livestock are an important component of societies across the world, yet their role is changing and the systems in which we keep livestock have become more intensive. Part of this change in production has been an increased use of antimicrobials[26] in the management of animal health, in some cases to increase the efficiency of feed conversion in the animals. Antimicrobials have therefore become integral to the livestock systems that the world is increasingly dependent on. Yet the amount and frequency of use of antimicrobials across the world is different even in systems with similar levels of intensification. These differences in use are related to the rules and enforcement of antimicrobial use in livestock. This institutional environment is also evolving as antimicrobial resistance has become associated with the use of antimicrobials in livestock production. The emergence of resistance could be through the food systems, which are increasingly global in their reach, and can be through local contact and environmental contamination.

Antimicrobial resistance represents a global societal problem. Current antimicrobial use in livestock generates short term benefits for some in the livestock food systems, and over society in terms of greater availability of livestock products. However, this could lead to evolutionary pressures and antimicrobial resistance which have negative consequences for human health and wellbeing. This is generating a response from different organisations involved in safe guarding public health, yet there are major gaps in knowledge, data and information to assess the trade-offs. These gaps create weaknesses in terms of decision making on international and national public policy and also in setting private standards across livestock food systems. The following sections outline some of the areas that require further work to help clarify the issues and in the process improve evidence for future public policy and private standard setting processes.

Scientific gaps

Whilst general information exists that indicates that resistance is more likely to occur where antimicrobials are used, the exact mechanisms that lead to this situation are sparse

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[25] http://www.oie.int/eng/A_AMR2013/Recommendations_AMR_2013.pdf.

[26] The use could be as antimicrobial growth promoters or as medicines.

as is the impact on patterns of resistance in the microbiome. There are sparse data on how resistance genes are moved across the food system and also within the environment.

In general there are insufficient agreements on how to capture and utilise data on antimicrobial consumption and their impacts upon livestock production and productivity. Attempts by international organisations to standardise approaches are important, national governments supported by private sector groups need to support these initiatives. The OIE is establishing a database on the consumption of antimicrobial agents in animals and therefore information on a global level will become available with time is an important step.

Economics gaps: Impact of antimicrobial use

The use of antimicrobials in livestock production has contributed to an increase in the availability of livestock proteins and also the welfare of animals maintained. However, there seems to be no agreement on the desirable levels of antimicrobial consumption and the relationship with improved management systems to reduce the consumption. Further information is required on why national level data indicate that antimicrobial consumption can vary by ten-fold between similar types of intensive systems. Similarly, there are gaps on the negative impacts of the emergence of resistance from livestock systems using antimicrobials in terms of animal and human health.

Governance and policy

There are gaps of information on the institutional environment – the rule and enforcement structures – and patterns of antimicrobial consumption in livestock systems. Some regions have taken important steps towards processes of matching antimicrobial use and livestock production and in some places this is being backed by data collection and research on resistance. However, there are major gaps in understanding and these correspond to some of the major livestock producing areas of the world.

The lack of agreement on antimicrobial use and wording of rules leads to flexible interpretation at farm level and also variation in the provision of professional advice from the veterinarian. International recommendations on antimicrobial use need to be more carefully followed to improve this situation at national level in order to create clarity at farm-level.

Antimicrobial use in livestock is legislated in many countries with the veterinary profession being very heavily involved in the enforcement. To make best use of this public intervention, there should be an understanding of how public legislation and enforcement interacts with private standards and farm-level activities. However, very little is published on how public and private rules fit together and how they influence human behaviour. More information in such areas could help to identify gaps in the use of antimicrobial in livestock leading to both an improved efficiency of production and limiting the negative consequences of antimicrobial resistance emergence.

In addition to the rules introduced through legislation there is a need for resource allocations across societies in order to build capacity of organisations in terms of infrastructure and education in human capacities. These may come largely from the public sector, but need to coordinate with the strengths and interests of the private sector in order to develop a strong animal health system.

In summary, antimicrobial use in livestock requires regulations that are adapted to each country’s institutional environment (rules and enforcement). In some cases there may be a need for a single “agency” responsible for management of their use in agriculture, food animals and human medicine. Decisions that generate public benefits and protect the common good aspect of antimicrobials in this way will have to be supported by strong political awareness, leadership in the public interest and long-term view.

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