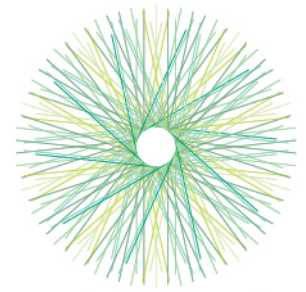


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AGRICULTURE & INNOVATION

Brief overview of strategies to reduce antimicrobial usage in pig production

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Introduction and background

Antimicrobials have been a key tool used to fight against infectious diseases since the 1940s. However, the efficacy of antimicrobials in human and livestock health is being increasingly threatened. Multiple reports have shown the increased costs and mortality rates associated with resistance. The World Health Organization (WHO) has recently classified antimicrobial resistance (AMR) as one of the top three threats to human health.

Resistance is a natural and ancient phenomenon, but there is evidence that the current global levels of resistance are, in part, due to the use of antimicrobials in livestock. Defining boundaries between the use of antimicrobials in humans and its use in animals proves extremely challenging. Any use of antimicrobials in animals can ultimately affect humans, and *vice versa*, due to the connectedness of microorganism populations. Resistant bacteria and resistance genes carried by commensal bacteria in food-producing animals can reach people, mainly directly via the food chain. Resistant bacteria can also spread through the environment (e.g. via contaminated water) or through direct animal contact on farms or at home with pets.

This paper aims to provide a concise overview of the problem and possible options to reduce antimicrobial usage in pig production. In order to avoid misunderstandings, a glossary of terms is provided at the end of the document. The terms “antimicrobials” and “antimicrobial resistance” are used to include all substances that might have public health impact keeping in mind that currently antibacterial resistance is most relevant.

This paper is primarily directed at the focus group. The focus group is meant to explore ways to reduce the use of antimicrobials which have a positive or at least neutral effect on the economics of production. This paper provides an overview of all available strategies, not all of which will fall in the focus category of the working group but are included for completeness. This particularly relates to the chapter on good governance. It is anticipated that the focus group will consider changes in general farm and husbandry management practices that are most likely to lead to a reduced usage of antimicrobials. Practical consequences of such changes will also be considered.

Brief problem description

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. The overall quantities used depend on the species, production system and the common bacterial problems faced on a specific farm. It is estimated that around 80% of total global antimicrobial use occurs in livestock. There are 27 different anti-bacterial classes used in animals, most of which are also used in humans, but there are nine exclusively used in animals. 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 disease) or **methaphylaxis** (when antimicrobials are administered to clinically healthy animals belonging to the same flock or pen of animals with clinical signs). In the past, antimicrobials were also used for **growth promotion**, an application now banned in the EU. The goal was to decrease the time and total feed consumption needed to grow an animal to market weight. In the EU, growth promoting use of antimicrobials was discontinued in 2006; in the USA and most other parts of the world, growth promoters can still be legally used at present.

The effect of the use of an antibiotic in an animal is multidimensional. These drugs will not only affect the pathogen triggering the treatment, but have a general impact. Most public health and food safety concerns derive from the unintended effects of antimicrobials in the bacteria normally resident in the gastrointestinal tracts of food animals, the so-called microbiome. Additionally, the continued use of a specific antimicrobial can lead to resistance to multiple structurally related or unrelated antimicrobials, because the genes coding for this resistance are located on the same mobile genetic element. This amplifies the negative impact by causing so-called **co-resistance**. Also, some resistance mechanisms acquired by bacteria are effective against several antimicrobial molecules, a situation called **cross-resistance**. The direct consequences of resistance are treatment failure - potentially also for humans - and related reduced productivity of livestock as well as animal welfare issues. Considering these risks it is likely that public authorities will increasingly focus on the use of antimicrobials and further restrictions in their use may be introduced.

Overview of strategies

The World Organisation for Animal Health (OIE) and the European Commission (EC) as well as the WHO have described strategies to address the issue of antimicrobial resistance. The strategies can be summarised under the four following key headings (also see Figure 1):

1. Good governance and usage principles
2. Monitoring of usage and resistance
3. Unspecific prevention
4. Specific prevention

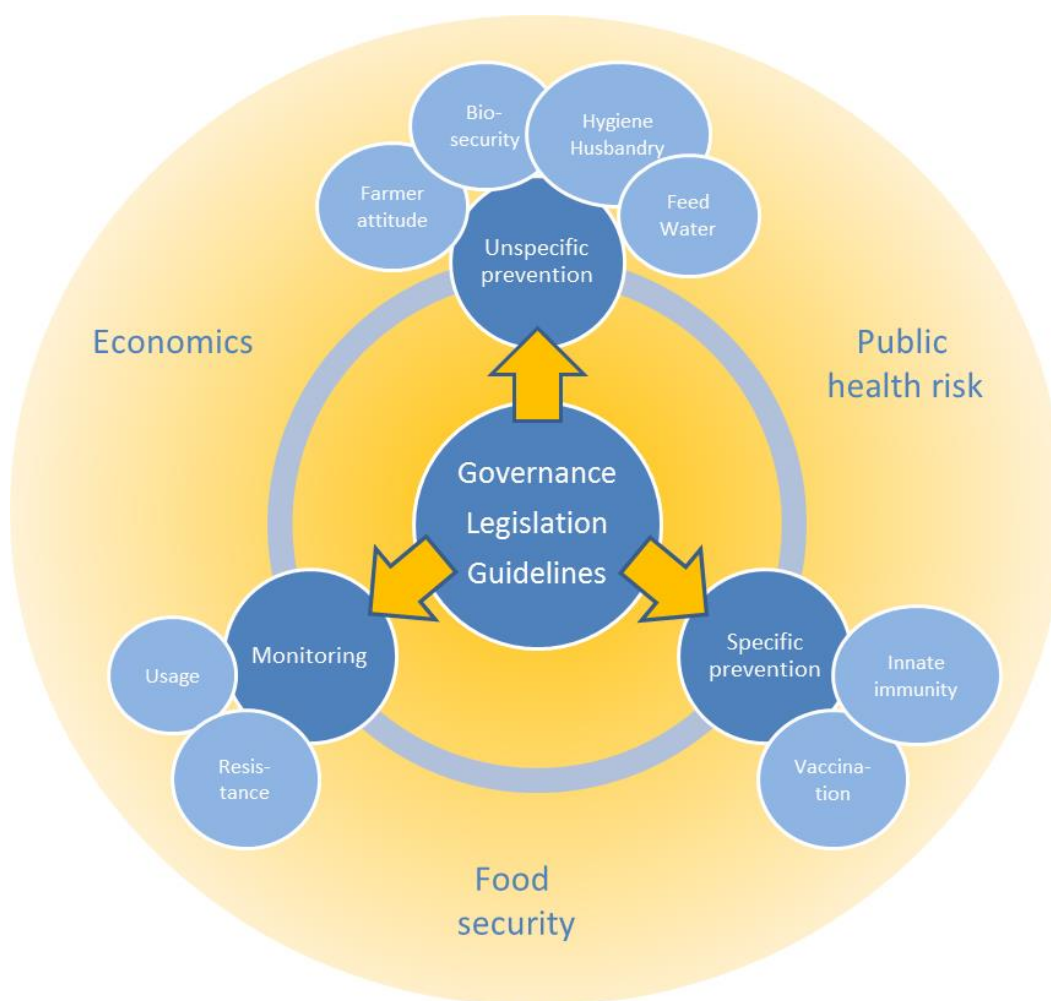


Figure 1: Overview of approaches to reduce antimicrobial usage in livestock

Good governance and usage principles

Good governance refers to the legal framework within which antimicrobials are used. It requires a legal process for registration of antimicrobial substances including documentation of effectiveness and safety. It also includes licensing of personnel involved in the sale and administration of antimicrobials, typically pharmacists and veterinarians, and sale conditions (e.g. prescription-only).

“Prudent usage” principles (sometimes also referred to as “responsible” or “judicious” usage) describe criteria for best practice in the context of antimicrobial use. Guidelines have been developed by a number of organisations including veterinary associations and stakeholder platforms. Prudent usage principles typically cover points of registration and legal basis, need for diagnosis, selection of appropriate substance, formulation and spectrum, correct dosage as well as emphasis on resistance testing. Some countries have developed more detailed usage guidelines based on these general principles. A significant fault in usage may occur in relation to the amount of a drug that is applied to an individual or group. There is substantial evidence of **over- and under-dosing** of drugs in group treatments in poultry and pigs. The extent of such deviance from best practice and the extent of consequences on resistance development are currently not well understood, but accepted as a significant component in the prevention of resistance. Also, the impacts of specific delivery pathways, treatment durations and varying combinations of the two yet have to be systematically investigated. Thus prudent usage guidelines could become more evidence-based.

Private veterinarians usually earn their income by charging for their services and – in most countries – also by selling drugs directly to the producers. This is a scenario that can provide an incentive for over-prescription for financial benefit.

Monitoring of usage and resistance

Several international organisations have formulated guidelines for the monitoring of both usage of antimicrobials as well as for monitoring resistance in micro-organisms. Regarding **usage monitoring**, there are significant differences in terms of the extent and methods used between countries, even at the European level as documented by the European Medicines Agency (EMA)¹. In general, the comparison of usage data between countries should be treated with caution and conclusions should only be drawn with great care. Grave *et al.*² compared the sales of veterinary antimicrobial agents between 10 European countries and found a wide variation between countries ranging from 18 to 188 mg/kg – mg of antibacterial drug sold/kg of biomass of slaughtered food animal. The authors concluded that the difference could not be explained only by differences in the animal species demographics. Speculative explanations include differences in animal husbandry practices. To facilitate data comparison, the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) has suggested the use of two standardized units of measurement³. Unless usage data are collected systematically and at sufficient level of detail, it will be difficult to make the link between

¹ European Medicines Agency (2012). Sales of veterinary antimicrobial agents in 19 EU/EEA countries in 2010. Second ESVAC report.

² Grave K, Torren-Edo J, Mackay D. Comparison of the sales of veterinary antibacterial agents between 10 European countries. *J Antimicrob Chemother.* 2010;65(9):2037-2040.

³ **Defined Daily Dose Animal (DDDA)**: This is an adaptation of the DDD used in human medicine, “the assumed average maintenance dose per day for a drug used for its main indications in adults”. **Defined Course Dose Animal (DCDA)**: This is a technical unit of measurement usually based on recommendations as described in antimicrobial product information and in some cases on information from experiments or scientific literature.

frequency of usage and resistance. In the absence of this linkage, the utility of usage data remains limited.

The Netherlands, Belgium and France now all formally aim at reducing the total amount of antimicrobial usage, some with specific reduction targets expressed as percentage of usage reduction measured at the national level. Some countries intend to go one step further in that they aim to measure usage at individual farm level. A leader in the field of usage registration and reduction is Denmark, where the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) reports since 2005 not only on usage but also on the occurrence of antimicrobial resistance in zoonotic, indicator and pathogenic bacteria from animals, food and humans. Denmark has recently also introduced usage reduction targets. Under this policy, a farmer receives a “yellow card” if he/she uses antimicrobials in a quantity two times higher than the national average. He/she then needs to take measures to reduce usage. This scheme has led to a reduction in antimicrobial use for therapy of almost 25% during the past two years. The Netherlands use a similar “traffic light” system.

Regarding the **monitoring of resistance** in micro-organisms, an EU-wide report is collated by EFSA and ECDC. Harmonized monitoring programmes for antimicrobial resistance in zoonotic and indicator bacteria have been established for this purpose. The data 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. Sweden and Finland were found to have no resistance.

Measures aiming at unspecific disease prevention

“Prevention is better than cure” is the EC’s motto in the animal health strategy. Preventive measures can either be specific (i.e. effective for a defined pathogen) or unspecific with general efficacy. The need for the use of antimicrobials is heavily influenced by **husbandry practices** and their direct link to animal health. The better the husbandry and environmental conditions, the higher the general health status of the animals and the smaller the need for treatment. High-health schemes and pathogen-free production such as the specific pathogen free (SPF) programme provide sanitary protocols to manage both the risk of disease incursion as well as spread. The sanitary measures include access control, physical barriers for pets and wildlife as well as special hygiene protocols. In conventional husbandry systems, high-risk moments during the production cycle are generally known, for example, when new batches of young animals are added and/or mixed. 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 are treated with antimicrobials before the development of clinical signs (prophylaxis). Because many management factors can impact on health and therefore antimicrobial usage on a farm, it is difficult to identify individual factors that are consistently and strongly correlated with resistance and/or usage.

These observations have led to the promotion of so-called “**good farming practice**” specifically **biosecurity** and **general hygiene** measures. Efforts to increase biosecurity have been implemented for a range of diseases. Biosecurity has been identified as a factor that negatively correlates with resistance of bacteria on pig farms. However, biosecurity is a complex concept which includes many components and is therefore difficult to measure. Also, farmer perception of biosecurity has been shown to be affected by a lack of incentives and by underestimation of risk. Recently, an online tool

has been developed to support classification of farms in terms of biosecurity⁴. While such developments are welcome, there is a need for evaluation and quantification of effects.

Another area of suggested unspecific intervention is water and feed. Particularly after weaning, there is a high risk of diarrhoea due to change in the piglets' diet, and a substantial proportion of antimicrobial usage is due to this indication. **Feed composition** impacts on the digestive tract, particularly digestible crude protein. So-called "protective diets" are recommended for certain age groups, particularly around weaning. However, the impact of fermentable protein and protein-carbohydrate ratio on the intestinal microbiome needs to be further explored. Additionally the source of protein appears to be influential, i.e. plant *versus* animal source protein. Although the impact of protein sources on growth has been studied extensively, knowledge of their effect on the microbiome is still sparse. Molecular techniques now offer new opportunities to investigate this area further.

There are also some **feed additives** that are used to reduce the risk of gastro-intestinal infection in weaned pigs. Zinc was demonstrated to be beneficial during diet transition. ZnO has been shown to reduce faecal shedding of bacteria such as *Campylobacter coli* in pigs. Zinc is, however, not approved as a feed additive for pigs in all Member States and there are concerns regarding environmental contamination. Similar issues relate to the use of other metals such as copper. **Probiotics** are live microbial feed supplements. Most commonly used are bacillus, yeast and lactic-acid producing bacteria. Probiotics yield variable and often inconsistent effects. Their mechanisms of action are diverse and not completely understood. Alternatively, **prebiotics** can be used, i.e. feed containing ingredients increasing gut health. Polysaccharides and dietary fibres fall into this category. Their effect is thought to be mostly linked to selective growth of bacteria associated with a healthy gut. Organic acids such as formic, lactic or benzoic acid can also have a beneficial effect around weaning when natural production of HCl is not yet adjusted to solid diets. Organic acids have been shown to reduce the occurrence of *Salmonella* and *E. coli*. Chinese herbs and other phyto-genic feed additives have also been demonstrated to have a positive effect on production performance of pigs thus offering an alternative to antimicrobials. However, there is generally limited quality control for such feed additives as this is currently not compulsory.

In the context of antimicrobial usage, **beliefs and attitudes** of farmers and veterinarians may be important factors determining prescription and usage patterns. A few studies examined pig farmers' psychosocial, demographic and farm characteristics regarding their use of antimicrobials. When comparing farmers and veterinarians, results indicated different knowledge levels, beliefs, attitudes, perceived risks. However, a comprehensive understanding of the psychosocial, external and demographical determinants of antimicrobial use or of alternative measures among pig farmers is lacking. Attitude towards antimicrobial use may also be influenced by information and education. Educational programmes may raise awareness and promote good practice in livestock production and veterinary prescriptions.

Measures aiming at specific disease prevention

Vaccination specifically increases an animal's resistance against a specific pathogen. Unfortunately, the complexity of pathogen biology and pathogenesis yet prevents success for many diseases. Nevertheless, there are some highly effective vaccines available against several relevant pathogens⁵ in pigs. As vaccination comes at a cost, economic evaluation of their application on a farm-by-farm basis

⁴ <http://www.biocheck.ugent.be/v4/home/>

⁵ *Mycoplasma hyopneumoniae* and *Lawsonia intracellularis*, porcine circovirus (PCV) 2

is important in decision making. It is expected that vaccination would also reduce the need for antimicrobial treatments. In pigs, it has been shown that vaccination against certain pathogens reduced the need for treatment. However, the efficacy of vaccination as an alternative to antimicrobials has not been systematically investigated. Study designs vary between experiments, and results are often not integrated to provide sufficiently robust evidence across production systems. Effectiveness under field conditions may depend on many factors such as vaccination scheme, general health status of the animals and management factors. The effectiveness of vaccination and its economic benefit therefore need to be more comprehensively assessed.

In this context, resistance of pigs against specific agents could be increased through targeted breeding programmes if the genes responsible for disease susceptibility can be identified and eliminated and provided that there are no negative side-effects. In the past, such projects based on phenotypic selection have yielded disappointing results. Yet, research looking into host resistance still suggests that such an approach might be effective, at least for some pathogens, for example PRRS virus. The traditional breeding approach is increasingly complemented and replaced by genomic approaches. Projects aiming at full genome sequencing are progressing and, in future, experimental insertion or deletion of genes may offer new, more rapid possibilities to manipulate and reduce the susceptibility of animals against specific agents. Genotyping may be used systematically for genomic selection and identification of phenotypic markers. The interaction of innate and adaptive immunity is a further research field that will inform future disease control strategies based on pig immunity.

Consequence assessments

The benefits of the use of antimicrobials are clear – livestock that are sick can be cured and become productive again. On the negative side, regular use of antimicrobials is likely to lead to the emergence of resistance, which limits the utility of antimicrobials in both animals and humans. There is a trade-off on the use of antimicrobials in livestock. The growing world population increases the demand for animal-derived food and increased livestock productivity. The latter was achieved through changes in the genetics of the livestock bred to efficiently utilise feeds, grow quickly, produce high individual quantities of milk or eggs and be able to be kept in confined and densely populated conditions. Such conditions increase the chance of transmission of diseases between animals and humans 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. The impact of changing production systems on the extent of antimicrobial usage across production systems is not well studied. The data available on antimicrobial use across countries seems to indicate that it may be possible to reduce antimicrobial use and retain highly intensive and productive systems of production. In order to pursue this approach, information is required on the impact of changes in production on disease occurrence and consequential usage of antimicrobials.

There is a risk of spread of resistant bacteria through the food chain, but significant research gaps remain for different livestock species and production system. An EU FP7 project called “EFFORT” is focus-ing on this topic and results will become available over the coming five years. A number of studies indicate already an association between antimicrobial use in livestock and resistance in bacteria, yet few have quantified how this impacts on public health. There is a lack of data and information which can lead to uninformed policy making at international and national levels, poor development of private standards and ignorant choice of production systems at farm-level. Even less

information is available on the significant quantity of antimicrobials used in food animals that are excreted largely un-metabolized into the environment.

Key questions for the working group

1. Are there additional approaches to reduce antimicrobial usage? Is Figure 1 complete?
2. Is there additional information/evidence to be added to the approaches listed above and in Figure 1?
3. Can the focus group report specific examples/case studies?
4. What are the most promising approaches mentioned above and in Figure 1? Which approaches should the focus group be exploring?
5. Is there evidence that some interventions will work in certain husbandry systems or climate zones or industries while being less effective in others?
6. Do you expect future changes in pig production that might have an impact on antimicrobial usage and/or on the effectiveness of strategies of usage reduction?

Glossary

Antibiotic	Generally used in the past to mean antimicrobials. However, it is now more often used to mean antibacterials and is understood by the public and professionals in this way. Almost exclusively now, when people talk about antibiotic resistance, they are talking about antibacterial resistance (HMA, 2012) ¹
Antimicrobials	General term for natural or synthetic compounds which at certain concentrations inhibit growth of, or kill, micro-organisms. The term antimicrobials is a collective for anti-virals, antibacterials, anti-fungals and anti-protozoals (HMA, 2012) ⁶
Antimicrobial resistance	Antimicrobial resistance (AMR) is resistance of a microorganism to an antimicrobial medicine to which it was originally sensitive. Resistant organisms (they include bacteria, fungi, viruses and some parasites) are able to withstand attack by antimicrobial medicines, such as antibiotics, antifungals, antivirals, and antimalarials, so that standard treatments become ineffective and infections persist increasing risk of spread to others (WHO, 2013) ⁷ .
Co-resistance	Bacteria can transfer genetic material to other bacteria, and when genetic information coding for several unrelated resistance mechanisms is transferred in a single event and expressed in the new bacterial host it is referred to as "co-resistance" (EC 2011 ⁸)
Cross-resistance	Bacteria that have developed survival methods effective against different types of antimicrobial molecules with similar mechanism(s) of action (EC 2011).
Prophylaxis	Antimicrobials are administered to a herd or flock of animals at risk of disease but not yet displaying clinical signs.
Metaphylaxis	Antimicrobials are administered to clinically healthy animals belonging to the same flock or pen as animals that are already displaying clinical signs.
Microbiome	The totality of microorganisms and their collective genetic material present in or on the human body or in another environment (Lederberg, 2001).
Multi-resistance	The term "multi-resistance" is used when a bacterial strain is resistant to several different antimicrobials or antimicrobial classes (EC 2011).

⁶http://www.hma.eu/fileadmin/dateien/Veterinary_medicines/00-HMA_Vet/02-HMA_Task_Force/03_HMA_vet_TF_AMR/2012_11_HMA_agreed_AB_AM_definitions.pdf

⁷ <http://www.who.int/mediacentre/factsheets/fs194/en/>

⁸ <http://ec.europa.eu/health/opinions/triclosan/en/glossary/abc/bacterial-resistance.htm>