

ANTIMICROBIAL USE IN FOOD-PRODUCING ANIMALS



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Replies to EFSA/EMA questions on the use of antimicrobials in food-producing animals in EU and possible measures to reduce antimicrobial use.

Antimicrobial use in food-producing animals

REPLIES TO EFSA/EMA QUESTIONS ON THE USE OF
ANTIMICROBIALS IN FOOD-PRODUCING ANIMALS IN EU AND
POSSIBLE MEASURES TO REDUCE ANTIMICROBIAL USE.

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SUMMARY

FVE was approached on 23 December 2015 by an *ad hoc* joint EFSA–EMA Working Group to provide input on antimicrobial use in food-producing animals in Europe and on possible measures to reduce antimicrobial use. Six questions were asked for all main food-producing species.

FVE collected and compiled, in the short time frame given, as much as possible information. This information is based on scientific publications, governmental reports and other formal data and complemented by expert opinions from many veterinarians working with the species concerned.

In general, it was found that limited formal data exist with detailed analysis on the antimicrobial use of the main indications/production systems; especially for the minor food-producing species such as small ruminants and rabbits. Therefore, much of the report is based on expert opinion.

It should be noted that there are great differences between husbandry and management conditions of food producing animals in Europe between countries. This also applies to the relative share of the various animal species/sub-species kept, climate, epizootiology, the infectious disease and the availability of veterinary antimicrobial products and alternatives.

Therefore, great care should be taken when reading and interpreting this report, as it might not reflect the situation in the whole of Europe, nor give a total picture. It should be recognized that while the results presented in this document are indicative, a more representative picture of the situation in the different regions of Europe requires a more thorough analysis per species/ country/ production systems/ etc.

INTRODUCTION

On 31 March 2015, European Commission sent to the European Food Safety Authority (EFSA) and to the European Medicines Agency (EMA) a request for a Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in European Union (EU) Member States, and the resulting impacts on food safety. The Opinion is expected to be completed by the end of 2016.

This mandate is being addressed jointly by the EFSA Panel on Biological Hazards (BIOHAZ) and by the EMA Committee on Veterinary Medicinal Products (CVMP). An ad hoc joint EFSA–EMA Working Group (WG) of experts has been set up to draft the Opinion.

During preliminary discussions, the experts identified the need to collect some information in relation to the use of antimicrobials in food-producing animals, with particular focus on the cattle, pig and poultry (all poultry species) EU production systems, and on possible measures to reduce the need to use antimicrobials and the use of antimicrobials in food-producing animals. The WG identified FVE as the body with the best links to European veterinarians who are professionals with the appropriate expertise to address this need.

The ad hoc joint EFSA–EMA Working Group (WG) approached FVE on 23 December 2015 and requested the FVE input to six questions for the different categories of food-producing animals/sectors, such as cattle, pigs, poultry, aquaculture, equids, rabbits, farmed game and bees. The information provided by FVE is planned to be used by the WG to inform the assessment and may be annexed to the Joint EFSA–EMA Opinion, once published.

On 29 February 2016, FVE submitted its answers, as contained in this document to the WG.

SIX QUESTIONS

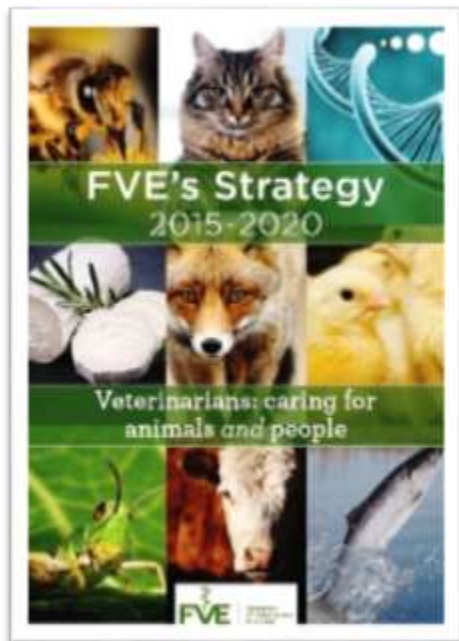
1. Please advise which 'production systems/life stages' and 'syndrome/disease' combinations use the greatest amount of antimicrobials in the target species.
2. For which of these combinations is it considered most difficult to implement measures aimed at reducing the need for antimicrobials?
3. For which of these combinations is it considered most easy to implement measures aimed at reducing the need for antimicrobials?
4. In relation to the above, do you have specific examples of where vaccination can be used to directly or indirectly reduce the use of antimicrobials?
5. In relation to the above, do you have other examples of where vaccines would be needed and could be used to directly or indirectly reduce the use of antimicrobials?
6. Stakeholders were previously requested by the AMEG¹ to provide examples of the impact of risk management measures in regards to antimicrobial use on animal health, welfare and husbandry. Are you aware of any further specific examples where measures have successfully reduced the use of antimicrobials in cattle and, if available, the impact on the occurrence of resistance to such antimicrobials?

¹ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/07/WC500170253.pdf

ABOUT FVE

Founded in 1975, FVE represents national veterinary organisations from 38 European countries and includes four vibrant sections, each representing a key group in the veterinary profession: the Union of European Veterinary Practitioners (UEVP); the European Association of State Veterinary Officers (EASVO); European Veterinarians in Education, Research and Industry (EVERI); and the Union of European Veterinary Hygienists (UEVH).

FVE strives to enhance animal health, animal welfare, public health and the protection of the environment by promoting the veterinary profession. Together with its members, FVE aims to support veterinarians in delivering their professional responsibilities to the best possible standard, and that this expertise is recognised and valued by society.



One of the FVE goals as defined in the FVE Strategy 2015–2020 is to promoting responsible use of veterinary medicines, including antimicrobials. Veterinarians have an important role to play in controlling the use of antimicrobials, medicines that have to be used correctly to avoid them becoming ineffective, so they can continue to protect animal and human health now and in the future.

NOT SPECIES-SPECIFIC FEEDBACK

1. Species kept for food production as well as the husbandry and management conditions of how these animals are reared **differs greatly between countries in Europe**. This also applies to the relative proportion of the various animal species/sub-species/category of animals, the climate, epizootiology, the infectious disease and the availability of veterinary antimicrobial products and alternatives. As a result, indications to prescribe antimicrobials for and amounts used per species, vary greatly per species.
2. Different definitions of the **term antimicrobials** exist. The EPRUMA definition (EPRUMA 2013) of antimicrobials is ‘a general term for any compound with a direct action on micro-organisms used for treatment or prevention of infections. Antimicrobials are inclusive of anti-bacterials, anti-virals, antifungals and anti-protozoals’. As these questions relate to the ongoing work controlling antimicrobial resistance, the focus of our answers was on the use of antibiotics. As such, throughout the document the term ‘antimicrobial’ has been used in place of ‘antibiotic’ or ‘antibacterial’.
3. Looking at antimicrobial use per country per species **significant fluctuations per year** are seen. The reasons often are a changed disease pattern (e.g. a widespread outbreak of respiratory problems in turkeys), changed climatic condition (e.g. higher water temperatures in aquaculture with as a result more bacterial diseases in fish and in the need for more antimicrobials).
4. There is considerable variation between countries in terms of the **availability of number of authorized veterinary medicines**; from 296 products in Iceland to 2,944 products in France (EPEC 2011). Smaller countries tend to have fewer authorised veterinary medicinal products. In addition, a high proportion of products authorised in these small countries are not placed on the market as it is seen as not-profitable. Especially for minor species such as rabbits, turkeys and fish, there are very few

available authorised veterinary medicines. Off-label use, mainly using a product authorized for another indication or another species or in another country (thought 'Cascade prescription'), is often the only solution to treat these animals and is therefore essential. Without the flexibility provided by the legislation to prescribe off-label, animal health and welfare would suffer.

5. In Question 1, FVE is asked to list the 'production systems/life stages'–'syndrome/disease' combinations that use the greatest amount of antimicrobials. However, **the 'greatest amount' can be interpreted in different ways**, such as in greatest volume or in greatest amount of treatment days. Consideration also needs to be made to the average live weight of animals, the dosing of the active substance, the interval and duration of the treatment according to the protocol for each disease/syndrome, the resistance patterns and how critical the antimicrobial used is for human health.
6. For all animal species and from all experts came back that **"prevention is better than cure"** and that this is the best way to reduce the use of antimicrobials. **Antibiotics are for cure**. Moreover, preventing disease improves production and increases food safety. Prevention of diseases can be done through a wide choice of tools such as improving biosecurity, good housing and ventilation, good hygiene, appropriate nutrition and robust animals, regular veterinary visits to monitor animal health and welfare and to develop herd health plans, use of diagnostics both to diagnose the disease as to do antimicrobial sensitivity testing, vaccination and responsible use of veterinary medicines.
7. The use of **biosecurity practices** can help greatly in boosting productivity and reducing the use of therapeutics with positive impacts on farm economy and food safety. All in, all out has proven very successful for many species. Veterinarians may be challenged with very different scenarios going from large-scale properties to hobby farmers, consequently the number of measures that can be put in place to mitigate biosecurity risks will differ. Multiple scientific publications demonstrate and quantify the clear link between biosecurity and both production- and antimicrobial treatment-related criteria (Laanen M. 2013). A biosecurity checking system exist for both poultry and pigs (Biocheck.ugent®).

8. **Regular animal health and welfare visits** and an effective herd health planning system, build on a good relationship between the veterinarian and the farmer allows to make a farm specific risk-assessment and prevention plan. The Regulation on transmissible animal diseases ('Animal Health Law') which is expected to be adopted in 2016 stipulates that professional animal owners are to receive regular animal health visits from a veterinarian for disease prevention, detection and biosecurity. Herd health planning allows the farmer and veterinary practitioner to collect information from many sources (including collection and communication of inspection results from the slaughterhouse), to identify and manage key animal health risks so that stressful and costly diseases can be reduced, production can improve and farm profits can increase.
9. Nevertheless, as it happens even when preventive and biosecurity plans are carefully applied, **animals still may get sick**. It is therefore of vital importance for the veterinarian to have access to the right medicines to treat the animals under his care and that way prevent from spread of disease to other animals or people. Veterinarians are concerned about the potential total ban or restrictions on use for certain veterinary antimicrobials and to restrict the use of these substances to humans only. FVE supports that these products should only be prescribed after sensitivity testing and as a very last resort, when no other alternatives are available. While the nature of these potential restrictions is not yet known, if they were to cover all classes of antimicrobials this could limit treatment options, particularly in countries where only a small number of veterinary medicinal products are authorised. In such circumstances, an unsuitable antimicrobial choice may be the consequence, for example, a broad spectrum one when a narrow spectrum one is the better option, so acting contrary to the goal of ensuring responsible use. A single market for veterinary medicines would increase the range of antimicrobial products available as well as the number of alternatives to antimicrobials in many countries.
10. It is without doubt that **vaccination strategies** against bacterial as well as viral infections tend to diminish antimicrobial consumption. This has been demonstrated such as with vaccination for Clostridial diseases, *L. Intracellularis* for pigs, Infectious Bronchitis for poultry and in Salmon farming. Nevertheless, the effect of vaccination

on the antimicrobial use cannot be estimated by simply comparing the total consumption of antimicrobial agents and application of different groups of vaccines. Correlations between the two strategies for prevention and treatment of infectious diseases must be analysed applying herd level data.

11. Another factor that has to be carefully considered is the **availability of vaccines** in the different countries. Some countries have no vaccine success stories, simply because vaccines are unavailable in their country and are too difficult to import even with the existence of the 'cascade system'. This has a direct effect to animal health and welfare, preventive practices and use of antimicrobials.
12. Also, efforts should be made to increase **vaccines efficacy**. Vaccines should be tested in real-life situations and in different local settings. In this way, the most effective vaccines can be identified, for the sake of the whole population. Stimulating such studies would help to identify effective vaccines, and to quantify their effects in relation to the costs.
13. Autogenous or autologous vaccines are used for many food-producing animals. They allow veterinarians to develop vaccines in quite a large variety of epidemiological circumstances where no commercial or effective vaccines are yet available. There is limited scientific value of these products and their efficacy, mostly because they are difficult to compare. However, it is reported that they may work well for certain diseases and in certain species. Autogenous vaccines are excluded from Community legislation. A harmonised set of requirements should be developed to guarantee an acceptable standard in the development, use and control of this particular category of veterinary immune-biologicals.
14. There is an imperative need for rapid, reliable and better **veterinary diagnostics** available in EU, which will facilitate correct diagnosis, strengthen veterinarians' confidence to not prescribe antimicrobials, improve the correct use of antimicrobials and therefore restrain from the development of antimicrobial resistance. The increase of analysis addressed to the identification of the etiological agent and possibly to determine the sensitivity to antimicrobials is crucial. An adequate diagnosis (possibly etiology), although not always so easy, is of paramount

importance. Many times the use of antimicrobials might be useless because the agent is not sensible to antimicrobials.

15. Breeding programs should be balanced and not focus on productivity alone. They should focus on **producing robust animals** who are less susceptible to diseases. Genetic selection can be one of the tools that can increase the reduced specific and specific immunity, performances and general response to diseases.
16. Regardless the type of diseases a very useful role might be played by the **monitoring of livestock resistome**. The understanding of the livestock resistome will become a key feature in planning and implementing modern sustainable animal husbandry concepts.
17. The **environment should be designed to fit the needs of animals**, not the other way around. A positive association can be seen often between reduced antimicrobial use and animal welfare. Animals which are well cared for and appropriately housed, will be less prone to infections and will need less antimicrobials. In other words, the more successful the actions aiming at improving animal health and welfare are, the more successful will be the attempts to reduce the use of antimicrobials and to curb bacterial resistance in food animals.
18. Setting up active **epidemiological disease surveillance systems**, encompassing data received both from veterinary practitioners as from laboratories, allows to monitor the disease status of a specific animal population in a region. It allows veterinary practitioners to be warned of possible emerging disease treats so that preventive actions can be taken. It also allows to plan group efforts to bring down the cases of certain indications. All this can allow practitioners to improve prevention (e.g. by vaccinating for an emerging disease) and can lower the need to use antimicrobials. Examples of successful surveillance networks are the Small Animal Veterinary Surveillance Network (SAVSNET) and the French epidemiological surveillance network in poultry (ANSES RNOEU).
19. To understand the development and spread of antimicrobial resistance mechanisms in animal husbandry, as well as in the entire food chain, **effective monitoring systems** are necessary. They help to understand the dynamic of antimicrobial resistance traits and are of importance during the (re)search, development and application of

alternative treatments. The level of detected resistant bacteria before and after the application of antimicrobials provides valuable information about the antimicrobial resistance dynamics in the bacterial community. Collected data would be a useful tool to gain the knowledge about occurrence of resistant bacteria on the farms, which could lead to reduced usage of antimicrobials and therefore prevent further development and spread of resistance. Knowing the potential decrease or increase of some resistances during the production cycle may help support the decision making process to minimize the application of antimicrobials on the farms.

20. The ease or difficulty to implement all the above measures is related to local practicality of these measures, their effectiveness, their technical applicability and last, but not least, **their economic feasibility**. Economic sustainability is an essential prerequisite for farmers to invest in prevention and ensure the sustainable production of animals. This means that public policy and associated incentives must allow for food, feed and energy crop production to develop on an economically sound basis. Consumers must understand that food prices must be realistic and based on real costs. This cannot be left to the market alone. The ongoing retail competition based on low pricing of food of animal origin has a detrimental effect on the way animals are kept and treated. Raising awareness, promoting good practices and setting standards should be encouraged.
21. One possibility to promote this, is through a **certification system**, in which buyers pay more for a vaccinated animal (less risk) and animals kept in better welfare status. Similar preconditioning systems are done with success in feedlots in the US and in the UK for young calves (Surecalf).

SPECIES SPECIFIC FEEDBACK

Cattle

1. Please advise which 'production systems/life stages'–'syndrome/disease' combinations use the greatest amount of antimicrobials in cattle.

The overall national consumption is strongly influenced by the type of rearing system present in the different countries.

Diary

- **Mastitis** is the biggest consumer of antimicrobials
- **Lameness/ foot disease, uterine problems** (e.g. metritis) and **surgery** also require the use of antimicrobials, but they are only occasionally observed.

Dairy production systems are present in every European country, and mostly involve farms with adult animals and their calves (male calves depart to the veal industry). Major indication for antimicrobial use in dairy cattle is mastitis and especially the dry cow treatment for mastitis. Blanket dry cow therapy signifies that every cow receives a long acting antimicrobial veterinary product in the 4 quarters of its udder before the dry period to prevent new infections.

The effect of intra-mammary application of antibiotics on AMR development is smaller than the effect of parenteral treatment. Bacterial exposure in the udder to intra-mammary administered antimicrobials is limited, especially when compared to the exposure of gastrointestinal flora after, for example, parenteral treatment. The udder tissue is an environment with few bacteria, besides the strain that causes the infection. Moreover, the bovine udder is separated from the body through the blood-milk barrier. Diffusion across this barrier depends on the pharmacokinetic properties, such as ionization and lipid solubility (Kietzmann and Bäumer, 2008). Exchange of specific antibiotics between the udder tissue and systemic circulation in healthy cows, therefore, is limited, which was shown for various antibiotics (Erskine et al., 2003, Kietzmann et al., 2010, Lainesse et al.,

2012, Zonca et al., 2011). However, this might not always be the case in cows affected by mastitis, where bacteria and inflammation impair the blood–milk barrier (Lainesse et al., 2012). This is clearly seen after IMM administration of for example florfenicol and gentamicin (Soback et al., 1995, Sweeney et al., 1996). This may lead to exposure of intestinal bacteria to residues from IMM applied antibiotics, although concentrations will likely not reach the levels of parenteral administration.

Important remarks are:

- Current standard daily dose methodology does not take into account the long acting nature of dry cow antimicrobial formulations (active concentrations up to 2 months after intramammary administration), which off course artificially reduces antimicrobial use in this branch
- Antimicrobial use in calves is underestimated (neonatal diarrhoea and bovine respiratory disease)
- Because 3rd and 4th generation cephalosporins do not have a withdrawal time for milk, they are overused in lactating dairy cattle, frequently without a clear diagnosis.

Calves / Veal

- **Respiratory disease**
- **Diarrhoea**

Calves aged 2–4 weeks, originating from a multitude of herds of origin (including from other countries) arrive at large fattening farms (150–2000 animals), where they are fattened in an 8 months period maximum. Predominantly oral, group antimicrobial treatments (metaphylaxis) in the milk are used. Industrial white veal industry is present (in order of amount of herds) in France, the Netherlands, Italy, Belgium and Germany (Switzerland has a different, small scale system). Production of rosé calves, characterised by roughage provision (development of working rumen) is predominantly present in the Netherlands, and rosé start (first 3 months) and rosé finish farms are distinguished.

Veal calves are the major antimicrobial consumers of all cattle production systems, including extensive use of critically important antimicrobials (CIAs) (e.g. Belgium: average veal calf treated for 153 animal daily dosages (ADD_{veal}) per year).

Main reason for antimicrobial use is bovine respiratory disease (60%). Antimicrobial resistance levels for commensals, pathogens and zoonotic agents are very high in the veal industry.

Important remarks:

Current daily dose methodology systems underestimate antimicrobial use in calves since standard weights used for the dose calculation are often much higher than the real weights at the age of disease. For example, veal calves get sick 3 weeks after arrival, i.e. weighing around 50/60 kg, whereas the calculation of the dose is done on 160 kg; another example is observed on dairy herds, where the antimicrobial use in calves is underestimated because the standard weight of an animal is set at 600 kg (adult dairy cow).

Beef

- **Respiratory diseases** mainly at the beginning of the fattening period
- **Legs diseases** (lameness, arthritis) where antimicrobial treatments are done based on the personal knowledge of the farm.
- **Neonatal diarrhoea**

Beef breeds are more susceptible for diseases than dairy breeds, and within beef breeds susceptibility differences exist (e.g. Belgian blue very susceptible).

General remarks

Critically important cephalosporins can be used in these animals at the end of the fattening period, because of their short withdrawal time.

- In the survey of De Briyne *et al.* (2014, see table below) it is indicated that for cattle **the predominant use of antimicrobials was for the control of mastitis in dairy cows**, where antimicrobial treatment may be given for clinical or subclinical mastitis. Dry cow therapy has traditionally used intramammary antimicrobial therapy immediately after the last milking of lactation.
- De Briyne *et al.* (2014) reports that **CIAs** were mostly mentioned **for respiratory diseases in cattle**, urinary and periodontal diseases in cats, **diarrhoea in cattle** and pigs, **locomotion disorders in cattle** and postpartum dysgalactia syndrome complex in pigs and dental disease in dogs. **Antimicrobials defined as CIAs were mentioned in 26 per cent in cattle.**
- Of the CIAs used in cattle, **third and fourth generation cephalosporins** are cited most frequently, for example, they are specified in 22 per cent of locomotion cases. The reason for the use of these classes rather than a non-CIA, especially in dairy cattle, may be the very short withdrawal period (zero days for milk in some cases) (De Briyne *et al.*, 2014).
- The following table shows the antimicrobials most used to treat cattle in Europe (De Briyne survey, 2014).

Therapeutic area	Percentage mentioned	Percentage critically important antibiotics (CIAs) v percentage other antibiotics	Frequency of citation of the different classes of antibiotics (top 5)
Mastitis	40%	CIAs: 22% Non-CIAs: 78%	Penicillins 41%, 1st and 2nd generation cephalosporins 12% 3rd and 4th generation cephalosporins 11% Aminoglycosides 10% Macrolides 6%
Respiratory disease	22% (27%)	CIAs: 45% (44%) Non-CIAs: 55% (56%)	Macrolides 27%, (28%) Phenicolols 22%, (19%) Tetracyclines 19%, (18%) (Fluoro)quinolones 13%, (12%) Penicillins 7%

Therapeutic area	Percentage mentioned	Percentage critically important antibiotics (CIAs) v percentage other antibiotics	Frequency of citation of the different classes of antibiotics (top 5)
Diarrhoea	14% (57%)	CIAs: 29% (26%) Non-CIAs: 71% (74%)	Polymyxins 40%, (44%) (Fluoro)quinolones 20%, (18%) Penicillins 13% (13%) Aminoglycosides 9% 3rd and 4th generation cephalosporins 8% (8%)
Uterine	8%	CIAs: 21% Non-CIAs: 79%	Penicillins 37%, 3rd and 4th generation Cephalosporins 18%, Aminoglycosides 16%, Tetracyclines 16%, 1st and 2nd generation cephalosporins 7%
Locomotion	8%	CIAs: 31% Non-CIAs: 69%	Penicillins 33%, Tetracyclines 24%, 3rd and 4th generation cephalosporins 22%, Macrolides 9%, Aminoglycosides 9%
Other = in order: perioperative (including caesarean-section), sepsis, infection, peritonitis, traumatic reticulitis, wounds, abscess, urinary, meningitis, nephritis, eye disease and abortion	8% (16%)	CIAs: 13% (10%) Non-CIAs: 87% (90%)	Penicillins 60%, (55%) Aminoglycosides 12%, (18%) 3rd and 4th generation cephalosporins 8%, Lincosamides 7%, (12%) Tetracyclines 4%

Figure 1: Antibiotics mentioned and frequency with which they were mentioned for the top five indications where antibiotics are said to be prescribed for cattle and calves. Numbers in brackets relate to calves only. Other figures relate to all cattle including calves.

Source: De Briyne N et al 2014 Antibiotics used most commonly to treat animals in Europe

2. For which combinations is it considered most difficult to implement measures aimed at reducing the need for antimicrobials?

Undoubtedly intensive rearing systems, whatever it will be, remain the situation at most risk of use of antimicrobials, bovine respiratory complex being the most risky, especially in systems which purchase animals.

Bovine respiratory disease (BRD) is the most difficult disease to control on cattle farm because of

- The multitude of pathogens involved (viruses and bacteria)
- The multitude of possible risk factors, especially those that are inherent to the production system (e.g. purchase)
- Vaccination before exposure to the pathogens is not always possible (purchase–no contact with seller), and vaccination at exposure questionable (no evidence provided)
- Knowledge on how to contain BRD in every production system is incomplete, and new insights into the pathogenesis (interaction pathogen–risk factor) are still needed.
- Advantage is that a massive amount of antimicrobial consumption for BRD is based on ‘farmers sentiment’ and marked reductions can be realised (up to 70% in a Flemish demonstration project (ADLO) + see national data from the Netherlands), just by avoiding combination of antimicrobial medicinal products (1 / 3 treatments), target it to the dominant pathogen (e.g. *Mycoplasma bovis* in veal calves)
- The disease and its prevalence is frequently underestimated (e.g. on dairy farms) + poor detection by the farmer
- Dominant risk factors are frequently inherent to the system (purchase, commingling) and cannot easily be changed

3. For which combinations is it considered most easy to implement measures aimed at reducing the need for antimicrobials?

The concept of “*prevention is better than cure*” remains one of the most important instrument for reducing the use of antimicrobials.

Potentially all systems and all disease-groups may be linked to a reduction of the need for antimicrobials if preventive measures are undertaken in order to prevent infectious diseases.

For the following diseases, sufficient knowledge on the key risk factors is available and can be used to prevent from their establishment and consequently decrease the need to use antimicrobials. More precisely measures could be implemented in

Mastitis, since

- Involved pathogens and associated risk factors (even pathogen specific) are well-known
- Effective control measures for each pathogen are well established as well as technical necessities
- Knowledge on how to manage udder health problems is well distributed among veterinarians. Selective dry cow treatment is possible, although it leads to some increase of clinical mastitis. Selective treatment of clinical mastitis cases, i.e. not treating culture negative or Gram negative cases is an option but in order not to compromise animal welfare, it should only apply in herds which already have a good udder health management
- Lactating cattle have priority for the farmer, so a close follow is possible

Neonatal diarrhoea, since

- All priority risk factors are known: colostrum management and hygiene. Use of farm's own colostrum is recommendable (antibodies against farms specific strains within time)
- Vaccines available
- Basically a compliance problem and lack of follow-up

- Good response on intervention

Endometritis, since

- Preventive measures (hygiene calving, avoiding dystocia, trace elements) well known (again compliance).

Regardless the type of disease a very useful role might be played by the monitoring of livestock resistance.

A precise diagnosis (also etiological) is of paramount importance.

4. Do you have specific examples of where vaccination can be used to directly or indirectly reduce the use of antimicrobials?

There is agreement on the efficacy of vaccine in reducing the use of antimicrobials.

Vaccination against viral diseases has also an indirect effect on bacterial infections and the need to use antimicrobials. Nevertheless, vaccination on its own is not that beneficial. It has to be combined with adequate housing in a well-ventilated stable. Hygiene management is of crucial importance.

Respiratory diseases

Efficacy proven for most viral vaccines. Less convincing evidence for bacterial vaccines, but meta-analyses show an effect (e.g. not available for *Histophilus somni*). In several systems, vaccination cannot be done before the risk period/exposure (e.g. veal calves/feedlot) therefore reducing its efficiency.

In respect to vaccination against respiratory diseases supportive data from well-designed clinical trials are the best measure of efficacy of any vaccine. Unfortunately, in dairy calves information are available mainly from experimental challenge. Although experimental challenge studies can prove vaccine efficacy, the artificial nature of the experimental challenge study limits the degree to which results can be extrapolated to

the field. Therefore there is a potential bias in the transposing of the results to field conditions. For example, most published BRD vaccine trials have been completed in feedlots. Few clinical trials have evaluated BRD vaccines in dairy calves.

Neonatal diarrhoea

Vaccines administered to the mother can increase the amount of specific antibodies in colostrum. Use of farm's own colostrum is strongly recommendable (antibodies against farms specific strains within time). However, should be noted that there is an important issue with insufficient colostrum delivery, which hampers the vaccines efficacy.

A **certification system**, in which buyers pay more for a vaccinated animal (less risk) and animals kept in better welfare status should be carefully looked at. Similar preconditioning systems are done with success in feedlots in the US and in the UK for young calves (Surecalf). For example, a protective effect of having received enough colostrum is described for veal calves. Calves can be tested by gammaglobuline determination even at the age of arrival (2–4 weeks) (Pardon et al., 2015). This offers all the tools to test calves, and pay less for calves which did not receive enough colostrum and more for those with adequate transfer. Sellers and buyers need to find each other, and most likely authorities will be needed to convince the buyers of its importance.

5. Do you have other examples of where vaccines would be needed and could be used to directly or indirectly reduce the use of antimicrobials?

- Vaccines against *Mycoplasma bovis*

The incidence of *Mycoplasma bovis* has markedly increased in the last decade, and this pathogen poorly responds on antimicrobial therapy. Mycoplasmoses continue to be a major reason for the administration of antimicrobial medicinal products to intensively farmed livestock, so improved control of these diseases by vaccination will have a significant effect on the use of antimicrobial medicinal products in agriculture.

- Vaccines against *Cryptosporidium parvum*
- Vaccine against foot infections
- Vaccine against puerperal metritis
- Mastitis

The efficacy of the currently available vaccine is quite questionable. We need to look further into developing efficient vaccines against mastitis.

As in human medicine, there is a need for government supported clinical trials to determine vaccine efficacy in every production system (local). In this way, the most effective vaccines can be identified, for the sake of the whole of the populations (and of the animals off course). Nowadays, all trials are company sponsored, and do not include comparison with other vaccines in a local setting. Stimulating these studies would help to identify effective vaccines, and to quantify there effects in relation to the costs.

6. Are you aware of any further specific examples where measures have successfully reduced the use of antimicrobials in animals and, if available, the impact on the occurrence of resistance to such antimicrobials.

- **Monitoring of use:** ESVAC report shows stable decrease in the amount of the antimicrobials used over the years.

Data from 26 EU countries in 2013 show a general trend to decrease the use of antimicrobials.

Overall, for 23 of the countries reporting sales data to the ESVAC for the years 2011 – 2013, a 7.9 % decrease in the sales (mg/PCU) was observed; the reduction in PCU was 2.8 % and the decline in tons sold was 10.5 %. However, the sale (mg/PCU) of fluoroquinolones and 3rd- and 4th-generation cephalosporins in these countries remained stable during this period (Figure 57.).

For the 20 countries that delivered sales data to ESVAC for four years (2010–2013) the current data analysis indicates that the overall sales (mg/PCU) for these countries continues to decline; for this period, the overall reduction was 11.1 %.

- In Belgium empirical data from experts suggest a reduction in the use of antimicrobials in veal calves in Belgium by 50%.
- In Denmark only 40% of cows received dry-cow therapy in 2009 when the average cell count was 235,300 cells/mL. Since 2010, Danish veterinarians have been required to examine a milk sample before prescribing antimicrobial medicinal products other than simple penicillin for mastitis treatment. This constrains the use of antibiotics during lactation and encourages a shift toward curative dry-cow therapy. In 2013, when the national cell count was 212,100 cells/mL, 43% of cows received dry-cow therapy. The use of antimicrobials tubes during lactation decreased by 48.5% from 2009 to 2013, whereas the use of tubes for dry-cow therapy increased by 13.4% in the same period (Katholm (2014), McDougall (2012)) reported that, in New Zealand, selective dry-cow therapy was used in about one-third of herds in 2011, whereas approximately 10% of cows and heifers were treated with a teat sealer.

In Denmark, the restriction on third-choice lactation antimicrobials, in force since 2010, has led to a decrease in the use of third- and fourth-generation cephalosporins, and almost no fluoroquinolones have been used since 2000 (Katholm, 2014).

- In the Netherlands, the UK, NZ, some US states, and likely some other countries, (national) udder health programs have been executed with the goal to reduce mastitis. They may have, or have not led to reduction of antimicrobial use too, although that generally has not been the specific goal. In the Netherlands an obligatory program started in 2013.

In the Netherlands, the combination of awareness-raising and restrictive measures appears to be effective in reducing antimicrobial use (–17% in 2012 compared with 2009), although the contribution of the dairy sector to the national reduction goal (–50% by 2013) was modest. Where dairy farms have to make a herd level disease prevention and herd level treatment plan, specifically with the

goal to reduce antimicrobial use. Antimicrobial use has decreased enormously since then, but that likely is the effect of the total of activities (including obligatory selective dry cow therapy) rather than these herd plans only.

Antibiotic use for mastitis treatment fell considerably in the final year of the study period, whereas farmers were reluctant to reduce use for dry-cow therapy.

Use of third- and fourth-generation cephalosporins and fluoroquinolones dropped from 18% of ADDD during 2005 to 2010 to 1% in 2012, with a shift toward penicillins and broad spectrum antimicrobials.

The reduction in third-choice antimicrobials in the present study was partly replaced by an increase in first- and second-choice ones. For mastitis, a relative increase in cephalosporin combinations was observed; for drying-off, an increase in procaine penicillin combinations was noted; and for other ailments, an increase in narrow-spectrum penicillins and trimethoprim-sulfadoxine was recorded. Therefore, although a reduction in use of third-choice antimicrobials occurred, there was also an increased use of penicillins and certain broad-spectrum antimicrobial medicinal products. The use of third-choice antimicrobials (i.e., third- and fourth-generation cephalosporins and fluoroquinolones) decreased from 18% of total usage from 2005 to 2010 to 1% in 2012.

➤ **Guidelines/ existence of a clear national strategy**

52 % drop in sales in the Netherlands from 2010 to 2013

16,3 % overall for all species and 10,3% in cattle drop in sales in France from 2010 to 2013

15 % drop in sales in the Germany from 2010 to 2013

Czech Republic: In some pharmaceutical forms, trends in sales can be clearly linked to measures such as intramammary veterinary medicinal products used in mastitis in cattle and a stepwise decline in consumption influenced, for example, by the introduction of 'in-house' ready-to-use tests, better husbandry hygiene measures and better feed balance.

Italy: Overall, there was a 29 % drop in sales, expressed as mg/PCU, in the period 2010 to 2013. This decrease would appear to be correlated mainly with a progressive decline in sales of tetracyclines and sulfonamides but also of macrolides and polymyxins. The reduced sales are likely to have been caused by the following factors:

- In 2009, the Ministry of Health launched awareness campaigns¹² against the prophylactic use of antimicrobial agents in breeding farms. Furthermore, an online training course on veterinary medicines surveillance and pharmacovigilance was published.
- In 2010, an information system was implemented in order to estimate the number of prescriptions of veterinary antimicrobials issued throughout each Italian region. These data allow the local competent authorities to identify the most problematic sectors where antimicrobial resistance has to be tackled in the following year. Furthermore, training courses were held in collaboration with the National Reference Laboratory for Antimicrobial Resistance in Rome, in 2010 and 2011. At the same time, in accordance with Regulation (EC) No 852/2004, the Ministry of Health validated and published species-specific good husbandry practices manuals in which basic principles for medicines management in farms are addressed.

A joint project between the Regional Veterinary Service of Emilia Romagna (an intensive farm area in northern Italy) and the University of Bologna has been carried out, with two important objectives: to produce a reliable assessment of the use of antimicrobials and of the related critical aspects in the various production chains, and to issue specific guidelines on the basis of such outcomes.

Of paramount importance the education of farmers veterinarians and future veterinarians (students). In an effort of preparing the next generation of veterinarians with the wealth of knowledge they need, the Department of Veterinary Medical Sciences (University of Bologna), in collaboration with the local veterinary state office–Public Health Area, included on farm biosecurity training in the fifth year of

the veterinary curriculum to prepare the students to think holistically about different livestock systems and to understand the regulatory requirements.

Slovenia: The Slovenian Buiatric Association and Veterinary Chamber of Slovenia start to implement practice of responsible use of antimicrobials in practice actually before the European Movement actually started. While consumption of antimicrobials in Slovenia has never been very high, after introducing some principles directly in everyday practice, usage of antimicrobials additionally diminished.

➤ Enforcement of **Animal Health visits**

Source: Antibiotic consumption and the veterinarian's right to dispense

The Netherlands, which has recently introduced mandatory herd health visits, has observed an impressive 59% drop in antimicrobial use since the time of introduction. In Belgium, poultry farms that received one-to-one veterinary management advice reduced their antimicrobial consumption by 29%¹. (<http://www.vilt.be/pluimveehouders-slaagden-in-grote-antibioticumreductie>)

➤ Use of specific **diagnostic tools**

Pigs

1. Please advise which 'production systems/life stages'–'syndrome/disease' combinations use the greatest amount of antimicrobials in pigs.

In intensive pig-farming the most commonly faced problems are the following:

- **Suckling piglets:** locomotory infections (arthritis), neurological disorders and diarrhoea (*Escherichia Coli*)
- **Weaners:** diarrhoea and respiratory diseases (e.g. *Mycoplasma hyorhinis*, *Lawsonia intracellularis*), neurological disorders (e.g. infections by *Streptococcus Suis*, *Haemophilus Parasuis*) and edema disease (*E. coli*).
- **Fatteners:** respiratory (e.g. Porcine Respiratory Disease Complex (PRDC)) and digestive disorders (e.g. Proliferative Enteropathy (PE) by *Lawsonia intracellularis*, Swine dysentery, Ileitis, Salmonella).
- **Sows:** urogenital disorders with Leptospirosis being important, Postpartum dysgalactia syndrome (PPDS), *Actinobacillus pleuropneumonia* (APP) in gilts.

The above mentioned conditions are not observed equally throughout Europe.

It should be underlined that when considering the cases where the greatest amount of antimicrobials are used, we should be mindful about other parameters like live weight of animals, dose of active substance, interval and duration of the treatment according to the protocol for each disease/syndrome. The relative importance of these parameters will depend on the indicators selected to measure antimicrobial usage.

Another parameter has to do with authorisation and availability of veterinary medicines in each country. An important indicator when considering the use antimicrobials in piglets is the authorisation and availability of Zinc Oxide (ZnO) for treatment and/or prevention and control of diarrhoea in post weaning pigs in the different countries. In countries where ZnO is authorised in high doses, there is a significant impact on reduced need to use certain antimicrobials.

Additionally, co-existing infections in a farm, for example farms endemic to porcine reproductive and respiratory syndrome (PRRS) and Influenza, which are viral infections, may have a significant impact on increased need for antimicrobials in order to cover bacterial superinfections.

Additional information about common indications in pigs where antimicrobials are mainly used is also provided in publication of De Briyne N., Atkinson J., Borriello S.P., Pokludová L. (2014) Antibiotics used most commonly to treat animals in Europe, Veterinary Record doi:10.1136/vr.102462

<http://veterinaryrecord.bmj.com/content/early/2014/06/04/vr.102462.full>

- In this survey De Briyne *et al.* (2014, see table below) indicated that for pigs respiratory disease and diarrhoea in weaning pigs are the most often indications for using antibiotics.
- De Briyne *et al.* (2014) reports that CIAs (critically important antibiotics) were mostly mentioned for postpartum dysgalactia syndrome complex in pigs.
- Of the CIAs used in pigs, macrolides and third and fourth generation cephalosporins are cited most frequently (De Briyne *et al.*, 2014).

The following table shows the antimicrobials most used to treat pigs in Europe (De Briyne survey, 2014).

Therapeutic area	Percentage mentioned*	Percentage critically important antibiotics (CIAs) v percentage other antibiotics used for treatment	Frequency of use of the different classes of antibiotics (top 5)
Respiratory disease	31%	CIAs: 12% Non CIAs: 88%	Tetracyclines 47%, Penicillins 21%, Macrolides 10% , Potentiated sulphonamides 8%, Phenicol 5%
Diarrhoea including Colibacillosis Dysentery	31% (8%) (4%)	CIAs: 34% Non-CIAs: 66%	Polymyxin 30%, Macrolides 22% , (Fluoro)quinolones 12% , Potentiated sulphonamides 11%, Pleuromutilin 7%
<i>Streptococcus suis</i> infection including Arthritis Lameness Meningitis	17% (4%) (2%) (1%)	CIAs: 5% Non-CIAs: 95%	Penicillins 81%, Lincosamide 5%, Potentiated sulphonamides 4%, 3rd and 4th generation Cephalosporins 3% , Aminoglycosides 4%

Therapeutic area	Percentage mentioned*	Percentage critically important antibiotics (CIAs) v percentage other antibiotics used for treatment	Frequency of use of the different classes of antibiotics (top 5)
Postpartum dysgalactia syndrome (PPDS)	12%	CIAs: 31% Non-CIAs: 69%	Penicillins 41%, (Fluoro)quinolones 21%, Potentiated sulphonamides 21%, 3rd and 4th generation Cephalosporins 7%, Macrolides 3%
Others	9%	CIAs: 14% Non-CIAs: 86%	Penicillins 56%, Aminoglycosides 12%, Tetracyclines 12%, Macrolides 7%, (Fluoro)quinolones 5%
Figure 2: Antibiotics mentioned and frequency with which they were mentioned for the top five indications where antibiotics are said to be prescribed for pigs and piglets.			
Source: De Briyne N et al 2014 Antibiotics used most commonly to treat animals in Europe			

Data from 2014 and 2015 collected by Belpork in connection with AMCRA (Antimicrobial Consumption and Resistance in Animals) show that the main antibiotic use for pigs are for weaned piglets to treat neurological disorders, respiratory diseases and digestive disorders. For slaughter pigs and suckling piglets, the most important indication is respiratory disorders. Belpork/AMCRA also found for the same period that the most used antibiotics are aminopenicillins, tetracyclines, sulfonamides + diaminopyrimidines, polymyxins and macrolides.

2. For which combinations is it considered most difficult to implement measures aimed at reducing the need for antimicrobials?

Difficulty (or ease) to implement measures can be related to existence of these measures, their effectiveness and their technical applicability or economic feasibility.

- **Post-weaning diarrhoea** by *E. coli* and other disorders at this life-stage are the most difficult to manage.

It is worth mentioning here that colistin main indication is digestive disorder due to *E. coli* in weaners. It is used in many countries as it is still very effective and cheap.

Alternatives for treatment are aminoglycosides (e.g. neomycin, apramidine, gentamicine, amikacin), toward which ones resistance can be rapidly selected (and in such a case first generation quinolones might be re-used...). Some nutritional active substances (i.e, feed additives) (Zinc oxide, acids, bio-flavonoids, mono glycerides, etc.) could also substitute colistin, however prevention through use of ZnO is raising a lot of concerns such as environmental impact and co-selection. Additionally the economic aspect is very important as the alternative options to the use of colistin seem to be much more expensive.

If usage is restricted (to a therapeutic purpose only after sensitivity testing), it is worried by practitioners that due to the acute character of the disease, animals would suffer and economical losses would be experienced.

Prevention through feed management, composition and additives optimisation could be helpful, but at the moment this cannot be achieved at the same cost and imply the same level of disease control.

- **PRRS:** Pig flow, environmental conditions and herd stabilization in PRRS are difficult to be properly managed. PRRS and Influenza are not directly managed by antimicrobials – but can destabilize herd health and immunity, leading to antimicrobial usage for secondary infections. If PRRS and APP eradicated, respiratory disorders can be managed through rearing conditions improvement which often requires holdings renovation difficult to realize for economic reasons.
- **Leptospirosis:** Reducing antimicrobial treatments against leptospirosis in sows is difficult once it is established; it is preferable to prevent it from entering into the herd with high biosecurity. Leptospirosis requires group treatments, no authorized vaccine is available, and diagnosis is difficult (no convenient diagnostic tool) and therefore mainly based on the observed therapeutic efficiency.

3. For which combinations is it considered most easy to implement measures aimed at reducing the need for antimicrobials?

- **Diarrhea in weaners:** It is possible to handle diarrhoea in weaners through feed management by improving feed intake before weaning; weaning age above 25 days; improving feed intake in the first week after weaning; improving feed quality by using high quality raw materials and special additives (probiotics and acidifiers) as well as the use of organic acids and the use of CCM (Cobb-corn mix) in the feed.

Zinc Oxide can also help to prevent or alleviate post-weaning diarrhoea in early weaned piglets and as an alternative to antibiotics, such as colistin. However, we should be mindful of its high environmental impact and the co-selection effect.

- ***S. Suis* infections in weaners** are perhaps easier to control and prevent. Autogenous vaccination for Streptococcus infections can also be possible and effective.
- **PRDC** can be managed better through the implementation of best practices, such as holdings renovation in light of economical context.
- **Arthritis** in maternity be prevented with good piglet management practices (e.g. castration).
- **PRRS** and **APP** should be eradicated. National and European programs should be in place and enforced by the Member States and the European Union.

4. Do you have specific examples of where vaccination can be used to directly or indirectly reduce the use of antimicrobials?

Most vaccines for pigs are used for prevention of systemic viral and respiratory diseases, which are infections that often cannot be treated by antimicrobials. It is without doubt that the vaccination strategies against bacterial as well as viral infections tend to diminish antimicrobial consumption, if they are combined with best management practices, like

good pig flow, proper hygiene and biosecurity measures. However the high cost of vaccinations (there are farms who have to deal with 15–17% of the production costs are costs for using all these vaccines) is a dissuasive factor.

Vaccines that have a positive impact on reducing the need for use of antimicrobials are the following:

- The use of vaccination against *L. Intracellularis* (ileitis) usually replaces a significant amount of antimicrobial treatments for diarrhea in some countries (e.g. Denmark, Germany, Spain);
- *M. Hyopneumoniae* and *Actinobacillus pleuropneumonia* vaccination;
- PCV2 vaccination;
- E.Coli (against edema disease);
- *C. Perfringens* (both A and C) for the sows to control enteritis in suckling piglets;
- **Autogenous vaccines** (made with agents isolated in the farm) for certain strains like *S. suis*, *H. parasuis*, *M. hyorhinis*, etc. can in some cases give very good results.

5. Do you have other examples of where vaccines would be needed and could be used to directly or indirectly reduce the use of antimicrobials?

Below you may find examples, where vaccines could be very helpful. Please note that no priority listing applies.

- **PRRS** vaccines are not covering all the strains. There is a need or better more efficient vaccines for PRRS that cover several circulating strains. Those vaccinations should be considered as part of a broader eradication program in the European Union.
- More effective *E. coli* vaccines for post-weaning diarrhoea are necessary. The existing vaccine containing F4 E.coli has not always so good results. A vaccine covering **F4** and **F18** strains could be more beneficial. Additionally strains **F5** and **F6** are a risk for piglets in their first two weeks and should be considered to be included in vaccines.
- *Clostridium perfringens*, **especially type A**

- Effective **APP** vaccines should be developed as part of a broader eradication programme
- Vaccines against **Rotavirus**
- **Leptospirosis**,
- **Influenza**

Additional comments:

For PRRS deleted vaccines would be useful to allow differentiating infected from vaccinated animals.

Vaccines association has also to be studied as feasibility of administration might become complex.

For some of the existing vaccines, balance between antimicrobial and vaccines costs is not always in favour of vaccines.

EU officials support the development of autogenous vaccines as in certain case can work very well (see also above-question 4).

6. Are you aware of any further specific examples where measures have successfully reduced the use of antimicrobials in animals and, if available, the impact on the occurrence of resistance to such antimicrobials

Risk management measures on farm level

In the Emida-Era net MINAPIG project, 70 farrow-to-finish pig herds from Belgium, France, Germany and Sweden took part to an intervention study aiming at reducing antimicrobial usage while implementing alternative measures, i.e. measures to reduce the need for AM usage. These included vaccination, improved biosecurity, changes in feed (e.g. ZnO) or water schemes (e.g. acidification). Overall, median usage was reduced by 37% in suckling pigs and 54% in weaners (when expressed in terms of treatment incidence). Yet, it is very difficult to state which alternative measure was the most promising, as each herd was

implementing a different intervention, which was adapted to its specific context and health problems. The impact on the occurrence of resistance was not monitored.

Postma M (2015) observed a negative association between the biosecurity level and the estimated frequency of treatment against certain clinical signs of disease. This is consistent with the hypothesis that a higher biosecurity level results in healthier animals. These findings promote an improved biosecurity status at pig farms and are of relevance in the discussion on alternative ways to keep animals healthy with a reduced necessity of antimicrobials; Prevention is better than cure!

Risk management measures at national and European Union level

➤ **Enforcement of Animal Health visits by veterinarians**

Proper risk management measures of farm level is fundamental. The Netherlands, which has recently introduced mandatory herd health visits, has observed an impressive 59% drop in antimicrobial use since the time of introduction. In Belgium, poultry farms that received one-to-one veterinary management advice reduced their antimicrobial consumption by 29%. (<http://www.vilt.be/pluimveehouders-slaagden-in-grote-antibioticumreductie>)

A [study](#) was carried out on reasons which led to a decrease in antimicrobial usage between 2010 and 2013 in different farms. Most cited positive measures implemented were good farming practices (decrease in density, less mixing ...) castration stopped, feed improvements, hygiene improvement, holdings renovation, water quality improvement... Practices changed were mainly related to withdrawal of preventive usage and vaccination optimisation.

FVE has been advocating the need for enforcement of the one-to-one relationship between farmers and veterinarians, obligatory animal health visits and efficient herd health schemes for all species (http://www.fve.org/uploads/publications/docs/fve_10_054_hhplan_uevh_uevp_final_2010%20%28%29.pdf)

➤ **Monitoring of use:** [ESVAC report](#) shows stable decrease in the amount of the antimicrobials used over the years. Data from 26 EU countries in 2013 show a general

trend to decrease the use of antimicrobials. For the 20 countries that delivered sales data to ESVAC for four years (2010–2013) the current data analysis indicates that the overall sales (mg/PCU) for these countries continues to decline; for this period, the overall reduction was 11.1 %.

However, FVE proposes that more indicators, like monitoring of ZnO, should be used when proceeding with the analysis of data of use of antimicrobials in pigs. It should be also considered that resistance against heavy metals is positively correlated to resistance to AMR.

➤ **Guidelines/ existence of a clear national strategy** (see also ESVAC report)

In Denmark the overall sales (mg/PCU) of veterinary antimicrobial agents decreased by 5 % from 2010 to 2013, mainly due to new regulations directed towards the 5–10 % of pig producers using most of the antimicrobial agents. Following a decrease of 9 % between 2010 and 2011, the consumption increased slightly during 2012 and 2013 (Table 10.). Approximately 90 % (mostly tylosin) of the macrolides are used in pigs.

Denmark managed to decrease use of tetracyclines and to a lesser extend pleuromutilins and macrolides which were mainly used in feed and water medication for gastro-intestinal disease. It has voluntarily banned cephalosporins and ban on use of fluoroquinolones in pigs (DANMAP 2014).

In France, 16.3 % overall for all species and 21.7 % for pigs drop in sales in France from 2010 to 2013. Following a voluntary restriction by the pig industry in 2010 on the use of 3rd- and 4th-generation cephalosporins, the consumption of 3rd- and 4th-generation cephalosporins fell by 65.6 % in pigs in 2013 compared to 2010. The [National Plan](#) endorsed by Ministry of agriculture also favoured antimicrobial usage reduction and amongst main changes observed, reduction of in feed medication has to be mentioned.

Italy reported overall a 29 % drop in sales, in the period 2010 to 2013. This decrease would appear to be correlated mainly with a progressive decline in sales of tetracyclines and sulfonamides but also of macrolides and polymyxins. The reduced sales are likely to have been caused by the following factors:

- In 2009, the Ministry of Health launched awareness campaigns against the prophylactic use of antimicrobial agents in breeding farms. Furthermore, an online training course on veterinary medicines surveillance and pharmacovigilance was published.
- In 2010, an information system was implemented in order to estimate the number of prescriptions of veterinary antimicrobials issued throughout each Italian region. These data allow the local competent authorities to identify the most problematic sectors where antimicrobial resistance has to be tackled in the following year. Furthermore, training courses were held in collaboration with the National Reference Laboratory for Antimicrobial Resistance in Rome, in 2010 and 2011. At the same time, in accordance with Regulation (EC) No 852/2004, the Ministry of Health validated and published species-specific good husbandry practices manuals in which basic principles for medicines management in farms are addressed.
- In February 2012, a 'Manual for prudent use of antimicrobials in poultry, pig and rabbit production', addressed to farmers and veterinarians, was developed by the Italian authorities. Also, a ministerial 'Guideline for official controls on distribution and use of veterinary medicines' for local official veterinary services was published in January 2012.

In the Netherlands there was a 52 % drop in sales in the Netherlands from 2010 to 2013. The sales of 3rd- and 4th-generation cephalosporins declined by 94 % and the sales of fluoroquinolones decreased by 45 % from 2011 to 2012, and continued to decline in 2013. This result was achieved by the efforts of private quality production systems, which put in place certain rule/ legislation, such as:

- Obligatory visits for all pig farms at least once a month by the responsible veterinarian of the farm;
- Voluntary ban on in feed medication within a quality system;

- Only a herd or group medication is allowed after a farm visit;
- The use of the fluoroquinolone enrofloxacin and 3rd- and 4th-generation cephalosporins is banned in animal production within the quality system;
- Monitoring of the use of antimicrobials on a farm level, on a way that bench marking could be done. It is also possible to bench mark prescribing vets.

In Spain, an overall decline of 6 % in sales was observed for the same period (2010 to 2013). However, tetracyclines had the highest sales during the period 2011 to 2013, while sales of penicillins and macrolides increased slightly. Tetracyclines and macrolides were the most commonly used antimicrobial classes in pig production, which is the largest food-animal production sector in Spain.

The sales of macrolides in Sweden dropped by 20 % of total sales expressed as mg/PCU, which is entirely explained by lower sales of products for the group medication of pigs.

➤ **Use of specific diagnostic tools**

From June 2014, all pig-vets in Denmark (Danmap 2014), when wanting to treat pigs for respiratory or gastro-intestinal infections for administration in feed or water with antimicrobials, have to take a lab sample to verify their diagnosis.

Easy and accurate diagnostic tools can enforce veterinarians to make the right diagnosis and prescribe the right antimicrobial.

Poultry

Poultry production in Europe is very diverse and accounts for 13% of the PCU in the 26 countries. (ESVAC). Most poultry meat produced in Europe is broiler meat, followed by turkey and duck. Poultry kept for meat are kept in professional farms of more than 5000 broilers but also in more than 2Mj small farms or back-yard farms. Different production systems exist. Mostly used are broilers of fast growing genotypes to produce poultry meat but increasingly gaining attention in many EU countries is the use of slower growing genotypes. The number of farms with free range or organic production is small, except in France, where a large number of farms is involved in alternative broiler production. (Remark: At the end of this year the supermarkets in the Netherlands will only sell meat coming from slow growing broilers.)

Next to broilers or chickens for fattening, Europe is also home to more than 350 Mj laying hens who also are kept in different husbandry systems from enriched cages, to free range or barn, in large scale professional farms, small or backyard farms, conventional or organic farming.

Despite growing concerns about the emergence of antimicrobial-resistant strains of bacteria and the measuring of sales data, little work has been carried out to investigate reasons for prescription of antimicrobials and almost no quantitative data exist on which production systems use the greatest amount of antimicrobials.

The underneath answers which can be found are mostly by expert opinion and by analysing the little published research available. Therefore, these answers cannot be taken as representative for all over Europe. It should also be noted that incidence risks of underneath mentioned conditions differ between countries and productions systems throughout Europe. Depending on the type of production type, the climate conditions and management system, different problems can be observed. To get in-depth answers to the questions answered a research project should be done, taking into account all the different production systems over Europe.

1. Please advise which 'production systems/life stages'–'syndrome/disease' combinations use the greatest amount of antimicrobials in poultry.

The most commonly faced problems are the following:

- **Broilers or chickens for fattening:**
 - gastro-intestinal disorders (such as Coccidiosis, Necrotic Enteritis, dysbacteriosis, feed quality)
 - respiratory diseases (such as *E. Coli*, but also Infectious Bronchitis, Newcastle Disease, Infectious Laryngotracheitis, *Mycoplasma gallisepticum* (diseases often followed by secondary infection with *E. coli*), Fowl Cholera)
 - locomotion (bacterial arthritis (e.g. due to *E. Coli*, *Staphylococcus aureus* or *Enterococcus*), secondary bacterial infections connected with tenosynovitis, necrosis of the femur heads, etc)
 - Septicemia, Omphalitis (*E. Coli*)

- **Laying hens:**
 - Have generally a lower antimicrobial use than broilers
 - Mostly to treat gastro-intestinal disorders (such as *E. Coli*, avian intestinal spirochaetosis (AIS)
 - locomotory system, respiratory system (*E. Coli*, *Mycoplasma*)
 - Very often treatment necessary of secondary *E. coli* infection such as after red mite infestation
 - In free range layers also taeniosis can be seen

- **Turkeys:** respiratory (e.g. *Ornithobacterium* Infection), gastro-intestinal (e.g. coccidiosis), ..

In all of the above groups, **young birds** are the most sensitive group needing most treatment with antimicrobials.

In France, the broilers 'label' which mostly see slow growing breeds which are often kept in a more extensive manner, observe a slightly lower disease incidence and as a consequence less antimicrobial use is seen. (Anses – RNOEA 2014)

E. Coli O1 K1, O2K1 and O78 K80 and others are very important pathogen.

Most used antimicrobials are amoxicillin, ampicillin, fluoroquinolone, macrolide, tetracyclines, sulphonamide/diaminopyrimidine combination and polypeptides.

The decision on which antimicrobial to use depends not only on sensitivity but also on efficacy, solubility, withdrawal time, acceptance, side or adverse effects, availability of alternative registered products (antimicrobials should be registered for all bacteria that are sensitive to that antimicrobial and not for specific diseases or organ systems).

In some countries the use of fluoroquinolones or cephalosporins is prohibited. In other countries, such as the UK, the sector has voluntarily banned the use of all cephalosporins in broilers and has commitment to reduce the prophylactic use of fluoroquinolones in day old broilers.

In laying hens, the waiting period is very important and therefore not many antimicrobials are authorized and suitable. The most used antimicrobials are oxytetracycline and colistin.

It was also noted that in some countries e.g. the Netherlands, in the recent year's antimicrobial use has decreased enormously. Currently, the usage of antimicrobials in general in poultry in the Netherlands is already so low that the loss of any of the remaining antimicrobials would directly have a huge impact on animal health and welfare.

2. For which combinations is it considered most difficult to implement measures aimed at reducing the need for antimicrobials?

Young birds coming from diseased parent stock or from low quality hatcheries have a difficult start of life. When these birds are kept under less optimal circumstances (e.g. old houses with bad heating, ventilation, insulation) or when they get low quality feed they will get diseases easily and they will need antimicrobials probably more than once.

Quality of feed plays a very important role and can be difficult to control. As an example, in the UK in 2013 more antimicrobial was given to poultry due to poor quality feed raw materials. This was caused due to bad weather during growth and harvest of mainly wheat and barley. Poorer quality feed is less easy digested and significantly impacts the intestinal health of the birds. Issues with feed in feed mill companies are not easily shared with veterinarians in the field out of fear for negative impact on sales.

In turkey production, economic reasons often cause that farmers cannot invest in better housing, prevention control or management systems.

3. For which combinations is it considered most easy to implement measures aimed at reducing the need for antimicrobials?

The respiratory system because there are good vaccines available and because ventilation systems are well developed.

4. Do you have specific examples of where vaccination can be used to directly or indirectly reduce the use of antimicrobials?

Many authorized poultry vaccines exist such as for Marek's disease, Turkey herpesvirus, Tenosynovitis, Salmonellosis, Newcastle/infectious bronchitis, Infectious bursal disease, Chicken Infectious Anemia, Encephalomyelitis, Fowl cholera, Chicken infectious anemia, Laryngotracheitis, Viral Arthritis, Infectious Coryza, etc. For turkeys, the main vaccines are against Rhinotracheitis and Hemorrhagic Enteritis.

Autogenous vaccines are also used in some countries, sometimes because it is felt that the authorized vaccines lack efficiency or due to new field variants.

Vaccines that specifically had a positive impact on reducing the need for use of antimicrobials are the ones against:

- Infectious Bronchitis vaccines helped a lot in reducing respiratory problems
- *E. Coli*
- Coccidiosis vaccines helped a lot in reducing gastro-intestinal disorders

Although vaccines exist for a lot of diseases, sometimes the problem is getting them implemented. It is crucial to set up vaccination plans, tailored to fit every farm or epidemiological situation, shared between operators and veterinarians, and being applied properly.

Also, even with the best vaccination schedules implemented, at times a disease outbreak can occur. Then treatment with antimicrobials will be needed to treat bacterial infections.

5. Do you have other examples of where vaccines would be needed and could be used to directly or indirectly reduce the use of antimicrobials?

Vaccinations against the following diseases would be extremely beneficial:

- More effective vaccines against Coccidiosis, Enterococci and *Ornithobacterium* infection.
- Vaccines against Histomoniasis and Coccidiosis for turkeys
- Better control against colibacillosis (different vaccine strains; besides vaccines there is a big need for alternative antimicrobials against *E. coli* because colistin needs to be spared for sporadic cases)

6. Are you aware of any further specific examples where measures have successfully reduced the use of antimicrobials in animals and, if available, the impact on the occurrence of resistance to such antimicrobials

Risk management measures on farm level

Need for better surveillance with regular visits by private independent veterinarians to the farms and lab checks, so that the vet can give advice on farm management, biosecurity, feeding, vaccination and prevention programs. Also the breeding of chickens should be regularly inspected by the veterinary services in order to prevent Salmonellosis, Avian Influenza, or other zoonotic diseases for which specific (national or regional) plans and control measures are provided.

It is important to prevent environmental stress (e.g. through high concentrations of ammonia and carbon dioxide), to ensure proper application of "all in all out", to have a robust breed of good parent stock and to prevent management problems of technological nature (e.g. bad management of mortality, ventilation problems, inadequate bedding).

Risk management measures at national and European Union level

- ***Enforcement of Animal Health visits by veterinarians***

The Netherlands, which has recently introduced mandatory herd health visits, has observed an impressive 59% drop in antimicrobial use since the time of introduction. This is due to regular health visits, better awareness of the problem and due to a penalty system when the antimicrobial use gets over a certain set level and due to a benchmark system. In Belgium, poultry farms that received one-to-one veterinary management advice reduced their antimicrobial consumption by 29%¹. (<http://www.vilt.be/pluimveehouders-slaagden-in-grote-antibioticumreductie>) For broilers, at least one animal health visit should be done per flock or every 2 months. For turkeys, every 3 months.

- ***Monitoring of use***

- ***Guidelines/ existence of a clear national strategy***

Biosecurity

Very important is to have only one age group on a farm (all in – all out).

Quality of the breeding stock

Extra attention should be paid to the development of robustness of birds during the breeding process. The more robust young chicks are the less diseases they get and the less antibiotics are needed. Furthermore guidance of farms where breeding stock is kept is important to get good quality eggs going to the hatcheries. The quality of feed going to breeder birds is even more important than the feed quality for broilers.

Use of alternatives

The use of probiotics (total flora) and the use of organic acids show effect in reducing the use of antimicrobials. This, however, does not mean there will be a reduction in resistance. The majority of organic chicken meat samples are also found to be contaminated with ESBL producing *E. coli*, and the ESBL genes and strain types were largely the same as in conventional meat samples (Cohen S et al 2012).

Other veterinary medicines needed by poultry vets are acetylsalicylic acid (aspirin) and broomhexine.

Better diagnostics

Rapid tests for checking the health status of flocks would be helping the vet in making decisions whether to treat the birds with antimicrobials or not. Not only rapid tests to find out the nature of the disease but also tests which give quickly a reliable answer to the sensitivity of bacteria for antimicrobials.

Further research

There is a need for further research efforts to be focused on the epidemiology of enteric, locomotory and respiratory disease in poultry. The cost of disease to the broiler industry is great, resulting in the need to use antimicrobials in a preventive way to safeguard against large financial losses. Although preventive use of antimicrobials is regarded as incorrect use of antimicrobials the end-effect very often is better in terms of use of antimicrobials. When antimicrobials are used in very early stages of the development of disease (metaphylactic use) the total use of antimicrobials in kg and in frequency is less than when antimicrobials are used only when disease symptoms are clearly present.

More research into alternative disease control measures is required. Especially alternatives for antimicrobials should be checked for their efficacy in preventing or curing disease. Too many products come to the market without proper proof of efficacy, resulting in financial losses, animal welfare problems and in the end again a drive towards the use of antimicrobials.

Sheep/Goat

1. Please advise which 'production systems/life stages'–'syndrome/disease' combinations use the greatest amount of antimicrobials in sheep/goats.

The most commonly faced problems considered by life-stage are the following:

- Lambs in their first month of life:
 - o Enteritis
 - o In cases of intensive motherless rearing, *Mannheimia* infections, as well as arthritis (especially observed in intensive goat farming)
- Growing/fattening lambs:
 - o Mainly, bacterial respiratory infections, e.g. *Mannheimia* infections, especially during the end of housing period and first time on pasture
 - o Lameness due to arthritis/ polyarthritis, including problems as the result of tick pyaemia or footrot
 - o Infectious conjunctivitis (sporadic problems)
- Ewes/does and Adults
 - o Bacterial abortion, e.g. *Chlamydia* spp., *Campylobacter* spp., *Listeria* spp., *Coxiella burnetii*
 - o Post-partum disorders of the genital system
 - o Diarrhoea due to clostridial infections
 - o Bacterial mastitis and contagious agalactia
 - o Lameness, e.g. footrot, scald, contagious ovine digital dermatitis (CODD).
 - o Tick-borne fever
 - o Listeriosis (sporadic problems)

To note that incidence risks of above mentioned conditions differ between countries and productions systems throughout Europe.

Small ruminant management systems vary throughout Europe from intensive to extensive, with meat, milk and wool production types prevalent in the continent. Depending on the type of production type and management system, different problems can be observed. Overall, it seems that the use of antimicrobials is more frequent in intensive and semi-intensive management systems. The use of antimicrobial seems to be similar in both sheep and goats kept under the same conditions. However, the use of antimicrobials is often less when those species are reared under extensive management system. Antimicrobials are

especially used when animals are housed, as well as around the lambing/kidding period and at end of the lactation period. Frequent administration of antimicrobials may also be practiced in areas with ectoparasites, against vector-transmitted diseases or secondary infections.

Some examples on the way that management system affects establishment of certain diseases are the following:

- Winter fattening of lambs and young adults, where housing, overcrowding and poor ventilation can lead to increased incidence risk of respiratory disease.
- Lameness of ewes, lambs and goats, especially in lowland grazing, where muddy gapways and grazing can predispose to increased incidence risk of lameness (footrot, scald, CODD).
- Infectious conjunctivitis is a common bacterial disease especially where ewes, goats and lambs are fed in troughs with direct contact
- Milking sheep/goats that are housed may have increased incidence risk of mastitis due to increased housing and environmental challenges

2. For which combinations is it considered most difficult to implement measures aimed at reducing the need for antimicrobials?

- **Enteritis** in newborn lambs. Several enteropathogens are associated with diarrhoea in neonates. Their relative incidence varies geographically, but the most frequently occurring microorganisms in most areas are *E. coli*. Cases of neonatal diarrhea are commonly associated with more than one infectious agents (including non-bacterial ones), e.g. rotavirus, coronavirus or *Cryptosporidium parvum*, and most outbreaks are also multifactorial.
- **Infectious conjunctivitis** is very difficult to manage especially due to crowding and transport and where sheep are being fed in troughs where there is considerable eye to eye contact. This feeding is normal practice during sheep lifecycle especially with fattening lambs and pregnant ewes.

- **Abortions and post-partum disorders** in ewes/does. In commercial sheep flocks there is a tendency to have less strict biosecurity as sheep are bought and sold. This presents challenges in preventing in controlling infectious abortions.
- **Listeriosis** in intensive goat farming appears sometimes difficult to treat. Even when the cause is removed, new cases can occur for many weeks.

3. For which combinations is it considered most easy to implement measures aimed at reducing the need for antimicrobials?

- In growing/fattening lambs:
 - o **Bacterial respiratory infections.** Fattening of lambs and young adults indoors predisposes to increased incidence risk of respiratory disease. Management improvements include the use of vaccines (*Mannheimia*), reducing stocking density and increasing ventilation.

Additionally the use of food chain information and in particular communication and inspection of results from the abattoir back to the farmer/vet can facilitate on farm management changes to reduce pneumonia and the use of antimicrobials.

- o **Arthritis /polyarthritis** in young animals through best practices management
- In pregnant females:
 - o **Bacterial abortion.** Through increased biosecurity measures and the administration of effective, commercially available vaccines, it is possible to prevent infection of healthy pregnant animals by bacteria that can lead to abortion at the last stage of pregnancy.
- In lactating ewes/does
 - o **Bacterial mastitis** and **contagious agalactia** through improved biosecurity and vaccination schemes, as well as by implementing an udder health

management scheme. The use of the appropriate milking machine and milking technique is an important factor preventing from mastitis.

- Young and adults
 - **Footrot disease** caused could be decreased by improving biosecurity, including better quarantine, and using the existing vaccines as well as by using genomics to identify individuals of sheep/goats with genetic resistance to withstanding infection.
 - **Clostridial infections** through appropriate vaccination programs

4. Do you have specific examples of where vaccination can be used to directly or indirectly reduce the use of antimicrobials?

Vaccines that have a positive impact on reducing the need for use of antimicrobials are the ones against:

- Clostridial infections
- Respiratory infections, e.g. *Mannheimia haemolytica*, *Bibersteinia trehalosi*
- Contagious agalactia
- Footrot disease
- Chlamydia infections (causing abortions)

To reduce disease occurrence, spread of infections and production losses, vaccination is only one factor. It is also important to improve the management system, e.g. improved hygiene, reduced stocking rate, increased ventilation and lower the stress level in general. Additionally food chain information and feedback from the abattoir to the veterinarian and the farmer can significantly help as well.

The veterinarian plays a key role with the farmer in using the combination of these tools to reduce disease.

5. Do you have other examples of where vaccines would be needed and could be used to directly or indirectly reduce the use of antimicrobials?

- **Mastitis** has been documented as a very significant welfare problem in sheep (EFSA 2014), but nevertheless no modern-technology vaccines are available commercially. Development and commercialisation of vaccines against mastitis in sheep/goats will contribute to minimise use of antimicrobials in those species. Anti-mastitis vaccines, integrated within an udder health management program, will contribute to reduction of the incidence of the disease and hence to the frequency and the extent of use of antimicrobials.
- In areas with **ticks and tick-borne infections**, a vaccine against tick-borne fever (*Anaplasma phagocytophilum*) will increase the animal welfare on tick pasture and reduce the use of antimicrobials.

6. Are you aware of any further specific examples where measures have successfully reduced the use of antimicrobials in animals and, if available, the impact on the occurrence of resistance to such antimicrobials

Risk management measures on farm level

Use of best practices such as proper vaccination, improved biosecurity with emphasis on quarantine measures, balanced nutrition, etc., in intensive farming.

Risk management measures at national and European Union level

- **Enforcement of Animal Health visits by veterinarians**
Proper risk management measures of farm level is fundamental. It is noteworthy that in The Netherlands, which has recently introduced mandatory farm health visits, an impressive 59% drop in antimicrobial use has been observed since introduction of the scheme.

- **Monitoring of use:** [ESVAC report](#) shows stable decrease in the amount of the antimicrobials used over the years. Data from 26 EU countries in 2013 show a general trend to decrease the use of antimicrobials. For the 20 countries that delivered sales data to ESVAC for four years (2010–2013) the current data analysis indicates that the overall sales (mg/PCU) for these countries continues to decline; for this period, the overall reduction was 11.1 %.
- **Guidelines/ existence of a clear national strategy** (see also ESVAC report)
- Use of improved **diagnostic tools** will improve detection of diseases, hence antimicrobials will be used only in cases that are really necessary.

Horses

1. Please advise which 'production systems/life stages' – 'syndrome/disease' combinations use the greatest amount of antimicrobials in horses.

The issue with horses is more complex as some horses are kept as food producing animals, some as companion animals and some for sport, and often they are switched between these categories during their lifetime. The category of a horse influences the treatment options. Horses held as companion animals and declared as not for food production, can be treated with a much wider range of veterinary medicines as medicine residues in food would not be a consideration.

(Note: numbers are not in order of importance, but are used to refer to in question 2)

- 1 – Racing yards with young horses at risk of disease or low grade performance limiting respiratory infections.
- 2 – Stables and studs with large numbers of horses at high risk of disease (young horses, different age groups of horses, yards with a high throughput of horses, horses travelling frequently to competitions and being exposed to/stabled with a variety of horses). Mostly respiratory conditions.
- 3 – All horses – Wounds, very common disease and potentially life threatening.
- 4 – Studs: broodmares being treated for in/hypo-fertility – intrauterine treatment
- 5 – Some specific conditions in large studs, namely *Rhodococcus equi* – specific treatment routinely used for extended time.
- 6 – Perioperative antimicrobials

Scicluna et al (2013) found that respiratory diseases, skin disease and reproductive disorders were the predominant citation of use, which is similar to the study of De Briyne

(2014) who found that the predominant citation of use of antibiotics was said to be to deal with skin diseases and respiratory conditions.

2. For which combinations is it considered most difficult to implement measures aimed at reducing the need for antimicrobials?

1–2 – Client pressure extremely strong, particularly with racehorses – difficult to limit use of antimicrobials in subclinical conditions. Additionally, availability/route/ease of administration, often favour use of critically important antimicrobials over first line ones.

5 – Difficult to implement measures to limit use of antimicrobials in studs where *R. equi* is established. However on-going research shows that reduced use is possible – Continuing education of veterinarian is of paramount importance.

3 – Wounds –Difficult to limit use of antimicrobials when deep wounds or when synovial structures are involved. See point below

3. For which of these combinations is it considered most easy to implement measures aimed at reducing the need for antimicrobials?

4– Goal is to educate veterinarians involved in reproductive work to limit use of antimicrobials to treat mares with hypo-fertility problems.

3– Wounds. With more superficial wounds and no proximity to synovial structures antimicrobials are overused. Again continuing education of veterinarians most important in walking away from long established routine administration of antimicrobial even for minor wounds. Evidence supports the use of antimicrobials only to treat major and complicated wounds (see point 2 above).

6 – In the case of surgery improving standard of surgery and implementing current international guidelines in elective procedures would significantly reduce the use of perioperative antimicrobials.

4. Do you have specific examples of where vaccination can be used to directly or indirectly reduce the use of antimicrobials?

Viral diseases. Equine Influenza (already widely in use) and EHV1,4 vaccination would strongly reduce the use of antimicrobial to treat bacterial infections secondary to viral disease

Bacterial disease: Bacterial respiratory disease caused by *Streptococcus equi* var *equi* can be prevented by submucosal vaccination. However, uptake is limited amongst horse owners with no mandatory programme within the industry. Development of a strangles vaccine with a longer duration of immunity and better availability may result in more widespread use. If this could be tied in with an annual influenza vaccination it may be used more widely.

5. Do you have other examples of where vaccines would be needed and could be used to directly or indirectly reduce the use of antimicrobials?

Vaccination against *Rhodococcus equi*.

Leptospirosis / Ehrlichiosis / Lyme disease/Babesiosis: commonly treated with antimicrobials when serology is positive. Availability to vaccination in endemic regions would be beneficial.

6. Are you aware of any further specific examples where measures have successfully reduced the use of antimicrobials in animals and, if available, the impact on the occurrence of resistance to such antimicrobials.

Clear guidelines (such as the HBLB guidelines in the event of a strangles outbreak which are freely available online) with regards to management and hygiene practices in the event of disease outbreaks will have reduced the spread of disease and therefore the number of horses affected and numbers requiring antimicrobial treatment.

In 2012, The British Equine Veterinary Association launched its Antimicrobial stewardship programme (www.beva.org.uk/protectme) to develop a framework for establishing local guidelines for stewardship of antimicrobials, especially the highest priority critically important antimicrobials. At the same time, its journals (Equine Veterinary Journal and Equine Veterinary Education) introduced antimicrobial stewardship guidelines into its author guidelines, requiring discussion of judicious use of such antimicrobials where used or recommended in any publication⁶.

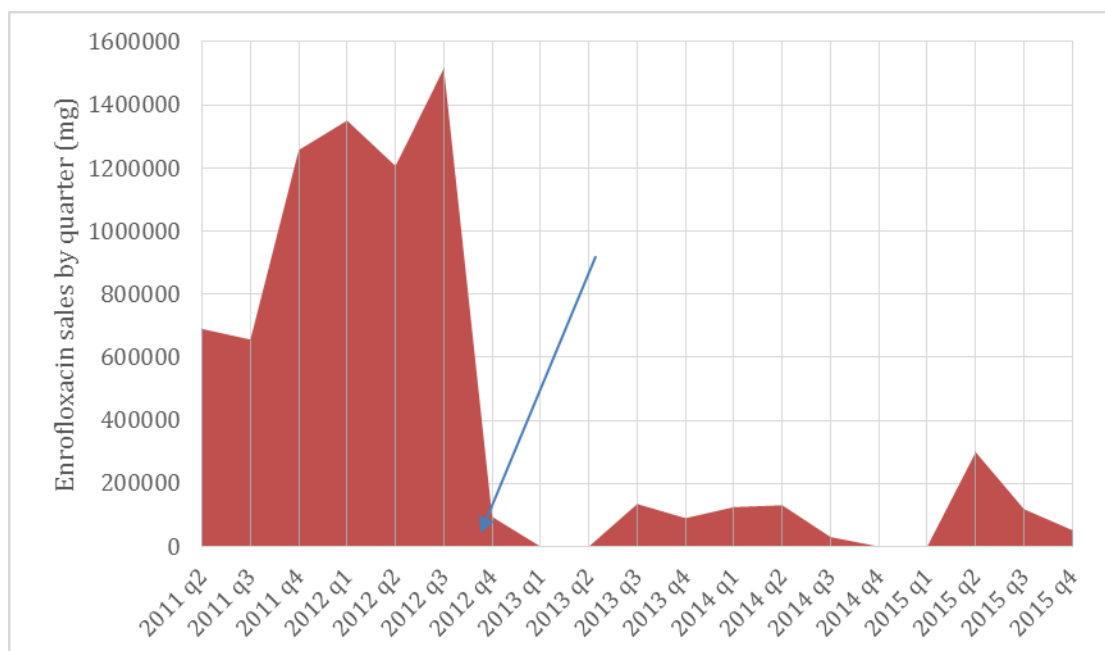


Figure 3: Graph showing quarterly sales of enrofloxacin before and after implementation of a voluntary antimicrobial stewardship programme within one veterinary practice in the United Kingdom. Blue arrow representing implementation in 4q of 2012

Source: www.beva.org.uk/protectme

In 2014, 2/3rd of UK based equine veterinary practices had adopted a program of antimicrobial stewardship. Although national data on the use of fluoroquinolones is not available since these medicines are used under the cascade, unpublished data from one veterinary business saw a reduction in sales that has been sustained since this time (Figure 1) representing over a 90% (91–96%) reduction in sales over the three years since implementation. National sales of equine doses of equine specific 3rd and 4th Generation

cephalosporins have reduced each year since the launch of this project in Autumn 2012 (20% reduction in 2013, 23 % reduction in 2014, 38% reduction in 2015 compared to pre-2012 sales data of over 80,000 doses sold per year).

In France, the “ecoantibio 2017 Plan” in France: decrease of 30% of the AM use between 2012/2013, -23% in the 5 previous years 2009–2014. 2017 Plan = -25% for 2013–2016 (ANSES 2015).

Aquatic animals

1. Please advise which 'production systems/life stages'–'syndrome/disease' combinations use the greatest amount of antimicrobials in aquatic animals

For aquaculture this question is difficult to answer as **European aquaculture include more than 35 different species**. In addition, it takes a **variety of production systems**: extensive or intensive, in natural settings or tanks, in fresh water or sea water, in cold, moderate or warm water, in flow-through or recirculation systems, traditional or modern, classic or organic, sheltered or exposed, etc.

Marine cold water fish species (Atlantic salmon, trout and cod) represent the largest production sector, followed by freshwater species (trout and carp) and marine Mediterranean species (sea bass, sea bream and turbot) (FEAP Production 2015). Farmed crustacean and mollusc's production seldom use antimicrobials.

In general there is **very little antimicrobial use in European aquaculture** (when compared to terrestrial farmed animals and humans), most especially in salmon (EMA/387934/2015).

As with other species, **considerable variation** in terms of use of various antimicrobials can be seen between countries which can be partly explained as different species are farmed in different production systems and authorised veterinary medicines vary per country (Table 1). One also can observe significant fluctuation per year, e.g. in warmer years, higher water temperatures will result in more bacterial disease.

In aquaculture, unrelated to the species, **most of the antimicrobials (including anti-parasitic) are given to treat bacterial and parasitic diseases**. The most common route for the administration of antimicrobials in aquaculture is the oral route via medicated feed and far more seldom antimicrobials can be administered by bath (added to the water). Antibacterial substances are used in metaphylactic treatments but not in preventive treatments, apart from exceptional and specific cases.

The **Salmon production** which is mostly located in Norway, Scotland and Ireland makes very little use of antimicrobials in the last decades. In 2014, Norwegian salmonid production exceeded 1.3 million tons, with Atlantic salmon being the most important species and rainbow trout accounting for approximately 5% of production volume. The same year, total sales of antibacterial agents for use in farmed fish were 523 kg active substance, corresponding to 0.39 mg/kg produced salmonids. In comparison, this is approximately one tenth of the antibacterial consumption per kg of meat from farm animals in Norway, which is also very low, having the

lowest consumption of all European countries (Lillehaug & Grave 2016). Also the use of antimicrobials for salmons in Scotland is almost nil.

In respect to life stages: approximately $\frac{3}{4}$ of the prescriptions are for the fresh-water phase, but the volume is bigger in marine farming, due to the bigger size of the fish. (personal comment Lillehaug, Norwegian Veterinary Institute, 10.11.2016).

For **seabass/bream production**, most antimicrobials are likely used in combating bacterial diseases in hatcheries, such as in the juvenile early life stages of sea bass in the Mediterranean (for tenacibaculosis, photobacteriosis (pasteurellosis) and vibriosis).

For **trout**, no precise data is available, but most likely slightly more antimicrobials are used in the trout sector than in salmon/seabass/bream production. This is mostly used in the early life stages (fry) for rainbow trout fry syndrome (RTFS)). Some other diseases can be prevented by vaccination, like enteric redmouth disease (yersiniosis) or furunculosis but with frequent lack of efficiency of vaccination.

Among French animal productions intended for human consumption in 2013, fish farming had the lowest “animal level of exposure to antimicrobials” (ANSES 2014).

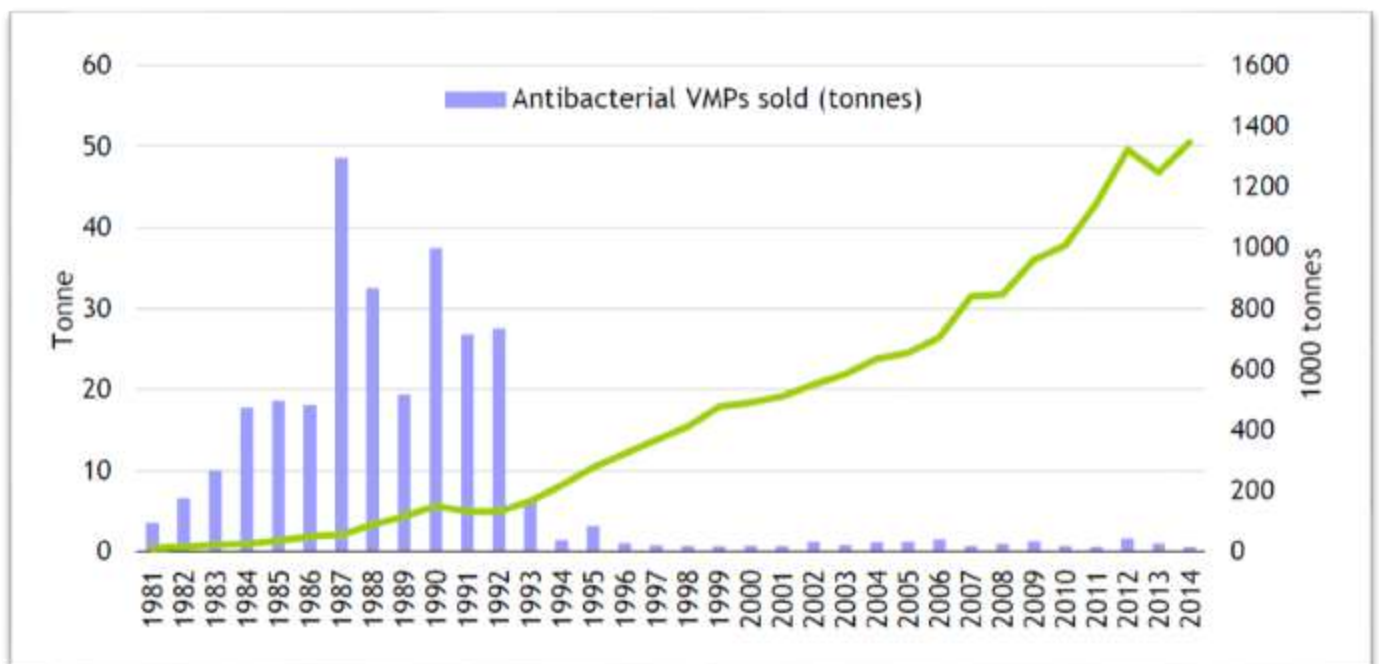


Figure 4: Total sales, in tonnes of active substance, of antimicrobial veterinary medicinal products (VMPs) for therapeutic use in farmed fish in Norway in the period 1981-2014 versus produced biomass (slaughtered) farmed fish. **Source:** Report on use of antibiotics in Norwegian Aquaculture Kari Grave Feb 2016

Rainbow (and brown) trout production (whatever the farming system):

life stages	syndrome/disease	Main used Antimicrobial(s)
Young fry	“Rainbow trout fry syndrome” or BCWD – septicemic infection by <i>Flavobacterium psychrophilum</i>	Florfenicol >> oxytetracycline high frequency, small biomass treated
Fry, young and sometimes big trout	Enteric redmouth disease – septicemic infection by <i>Yersinia ruckerii</i>	Sulfadiazine-trimethoprim; “old” quinolones (1 st and 2 nd generations) (oxolinic acid and flumequine).
“portion-sized trout” (> 200 g)	“Strawberry disease” – idiopathic skin disease	Oxytetracycline (still efficient for more than 30 years); frequent diseases in France and Denmark, rather rare in Italy, significant amount of antimicrobial for a “disease” which does not kill any fish.
Sometimes young but mostly “portion-sized” and big trout	Furunculosis – septicemic infection by <i>Aeromonas salmonicida</i>	Mostly sulfadiazine-trimethoprim; “old” quinolones (1 st and 2 nd generations) (oxolinic acid and flumequine); florfenicol; sometimes others, in case of resistance.

Sometimes young but mostly “portion-sized” to big trout	Streptococcosis – septicemic infection by <i>Lactococcus garvieae</i> or <i>Streptococcus iniae</i>	oxytetracycline, erythromycin, Sulfadiazine-trimethoprim, florfenicol ; sometimes others, in case of resistance (not common in France, high incidence in Italy, but luckily good i.p. vaccines exist)
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Figure 5: Use of antimicrobials in trout production.

Sturgeon production, for the caviar and sturgeon meat markets, is increasing in Europe but its annual volume remains very small compared to other farmed fish species.

life stages	syndrome/disease	Main used Antimicrobial(s)
Young fish	“columnaris disease” – gill/skin and sometimes septicemic infection by <i>F. psychrophilum</i>	Florfenicol >> oxytetracycline
Big fish (> 2or 3 years old)	Streptococcosis – septicemic infection by <i>Streptococcus dysgalactiae</i>	Florfenicol ; sulfadiazine-trimethoprim ; erythromycine

Figure 6: Use of antimicrobials in sturgeon production.

However, in some countries, such as Belgium, vaccines for fish are not available because of the small market. As such they have to resort to using antimicrobials to treat preventable diseases as furunculosis and yersiniosis (ERM) in trout. In other Countries the application of the “cascade principle” for vaccines it is not clear or competent authorities do not allow the using the cascade to import vaccines as they are not ‘if unnecessary suffering’ but are tools for prevention.

For **carp** (cyprinids), in Czech Republic mostly tetracycline is used after having done a susceptibility testing. In Czech Republic, consumption of oxytetracycline in aquaculture covered 1.28% of overall consumption of tetracyclines, based on collected data of veterinary medicinal products consumption in 2014.

For **tilapia**, produced in farms in Belgium, Poland, etc, *Streptococcus* infections at times has to be treated with antimicrobials.

Where **wild fish** are ranched or restocked (wild brood fish caught, stripped and juveniles released) as occurs with some salmonids there are some bacterial disease challenges (atypical furunculosis) which require treatment.

Negligible amount of antimicrobials are also used for individual treatment of **breeding fish**.

Treatment of breeding of ornamental **aquarium fish** also uses antimicrobials. The estimated number of aquaria containing ornamental fish in the EU is 8,272,000 and in all of Europe there are an estimated 9,221,000 aquaria. The breeding of aquarium fish is uncontrolled area and probably uncontrollable. Regularly it is reported that antimicrobial treatments (e.g. quinolones) for aquarium fish is sold over the counter in hobby shops without the need for any prescription. *Aeromonas sp.*, *Pseudomonas sp.*, *Staphylococcus sp.*, *Acinetobacter sp.*, *Flexibacter sp.*, *Alcaligenes sp.*, *Shewanella putrefaciens* and many *Mycobacteria spp.* are seen in diseased imported ornamental fish. These bacterial isolates possess also zoonotic potential. Antimicrobial resistance was identified in many bacteria cultured from imported ornamental fish often via the internet (Dobiasova et al. 2014, Declercq et al. 2013).

Also, when using antimicrobials in the wider senses, if biocides used as antiparasitic treatments are counted as antimicrobial treatments (such as the use of hydrogen peroxide, chloramine T, copper sulfate, formalin or even sea salt against ectoparasites, bacterial infections, or fungal problems) those likely come first in frequency of application and probably quantity used in all aquaculture operations.

In respect to **antimicrobials availability**, only a few are authorised for fish in the different countries (Figure 7) Another consideration is that in some countries treatment with medicated feed is not possible. The application of antimicrobials (and some antiparasitic agents) against bacterial diseases is then done by “coating” or “top-dressing” of extruded pellets on already pelleted (or bulk) feed in dedicated mixers, distinct from the feed production line machinery. While mixing at feed mill level is preferable in order to ensure a homogeneous and optimal distribution of pharmaceutical substances in the feed, unfortunately, there is very limited number of feed mills or fish feed producing companies who are willing to do this for fish farmers even when proper veterinary prescription is presented. Simply, small quantities (<1,000 kg, but frequently not more than a few dozen Kg) of pre-medicated food are not economically viable for producer to make (or keep equipment at hand to make it), or for a feed mill to prepare.

Care should also be taken that in certain circumstances when the daily feeding ratio is lowered (too high or too low temperature, too low appetite for different causes), some premixes have too weak a concentration of active substance and thus require to coat the feed with too much premix so as to reach the therapeutic dosage (mg of active substance/kg live weight to treat). In such cases, the fish veterinarian is led to substitute a more concentrated presentation like oral powders (or solutions) to reach the proper dosage on the feed and in the fish.

Florfenicol and flumequine are useful mainly in aquaculture of salmonids. But veterinary medicinal products containing florfenicol are only authorised in a few countries and in some countries not marketed, even when they are authorised. Unfortunately this percentage is not representative as it is based on consumption of authorised VMPs that is indicated for treatment of 5 different target species, and fish is one of them.

In respect to risk for transfer of antimicrobial resistance, the critical hazard points should be looked at, such as when close contact is involved and when crossing of facilities and technologies of aquaculture in case of carp and koi carp. Especially also when facilities for aquaculture of ornamental and food fish cross (e.g. hatcheries, recirculation systems, handling of fish, etc.). Care must also be taken not to introduce exotic disease or antimicrobial-resistant bacteria together with the introduction of ornamental exotic fish species or via contaminated water.

Antibiotic classes authorised to be used in fish in the different countries are:

- Amoxycillin (Italy – authorised but not available, UK)
- Chlortetracyclin, Oxytetracycline (Bulgaria, Croatia, Cyprus, Czech Republic, Finland, France, Greece, Italy, Ireland, Italy, Latvia, Lithuania, Romania, Spain, Turkey and UK)
- Florfenicol (Austria, Bulgaria, Croatia, France, Italy, Norway, UK)
- Flumequine (Bulgaria, Croatia, Czech Republic, France, Greece, Hungary, Italy, Latvia, Romania and Spain)
- Enrofloxacin (Romania and Turkey)
- Oxolinic acid (Denmark, France, Greece and Norway)
- Sulfamide + Trimethoprim (France, Greece, Germany, Italy, Norway, Portugal and Turkey)

Figure 7: Antibiotic classes authorised in different countries for aquaculture.

Note: Not all products authorised in a country are also marketed in that country. Countries that have no products authorised have to resort to the cascade, but often this is impractical.

2. For which combinations is it considered most difficult to implement measures aimed at reducing the need for antimicrobials?

This is considered for the following indications:

1. Infections of fish at early stages like fry which lack proper immunocompetence for an efficient vaccination, both in freshwater and seawater e.g. by and RTFS (*Flavobacterium psychrophilum*) But these only use small quantities and have a very long factual withdrawal period.
2. Bacterial or viral infections (viral diseases increase the risk bacterial septicemia and can give combo's of bacterial and parasitic diseases) for which no vaccines exist such as Bacterial Gill Disease (BGD), Salmonid alphavirus, Cardiomyopathy Syndrome (CMS) and Heart and Skeletal Muscle Inflammation (HSMI)
3. Strawberry disease of rainbow trout
4. *Flavobacterium branchiophilum*
5. Treatment of ornamental fish, mainly due to the impossibility to have any reliable control of/on the sanitary quality of fish before their introduction in Europe.
6. Furunculosis in farmed trout (with frequent and increasing AMR). Outbreaks of vaccinated rainbow trout may be attributed to high water temperatures (environmental conditions).
7. Streptococcosis of sturgeon due, firstly, to the lack of knowledge of the disease but also to the long farming cycle and the lack of efficiency of autogenous vaccination to date.

Infection with parasites such as **salmon/sea lice** are especially difficult. Parasites won't be easily managed with vaccines in near future, so reduction in antiparasitics would likely only be achieved by lowering their impact by supporting a robust immune system through fish welfare (feeding/nutrition, husbandry, prevention of stress, nonspecific immuno-stimulation during the transitional stages/phases, etc...). Increased biosecurity may help, but it needs to be recognised that most common ectoparasites like gyrodactylids and protozoa are a normal part of most open aquatic ecosystems.

3. For which combinations is it considered most easy to implement measures aimed at reducing the need for antimicrobials?

Prevention is always the best cure!

Most operations would benefit from **tightened biosecurity measures** that will reduce risk of ANY disease, by enhancing prevention and control measures that do not involve use of antimicrobials. But, if applying better biosecurity in conjunction with novel vaccinations/prophylaxis, it is likely that bacterial diseases would be the “easiest” to address (Palic et al 2015).

One of the best ways to prevent low welfare, disease and use of medicines in aquaculture, is continuous maintenance of good health and welfare among the stock. Use of medicines should never replace good hygiene, stockmanship or other management-related factors. Veterinarian knowledge and competence regarding these issues are key factors for success and every farm should have a **written veterinary health plan** including regular mandatory vet-visits as part of the biosecurity program.

The maintenance of good health and welfare and the food safety aspect in the aquaculture industry, should include continuous following up on plans covering control strategies, biosecurity, competent stockmanship and handling/transport/slaughter/killing, water quality and -flow, stocking density, feeding regimes, use of vaccines and focus on producing more robust aquatic animals through effective selection programs.

Before starting a treatment an examination should be done, followed by a diagnosis. If a diagnosis step is missing, perhaps unspecific symptoms –conditions related to management or viral diseases will be treated with antimicrobials, hoping the treatment “might help”. In general, vaccination of fish would most likely reduce the use of antimicrobials.

For recirculating aquaculture systems appropriate measures should be implemented. Bath treatments are not recommended in recirculating systems, where the treated water will contact the biological filter, because the antimicrobials may kill or inhibit the nitrifying bacteria in the biological filters and the abundance and diversity of the microbial community will favour the selection of antimicrobial resistant strains in the ecosystem.

For flow-through fish farms, it is important that the competent authority deals with contaminated rivers downstream and upstream to the farm.

Some bacterial diseases can be prevented with **autogenous vaccines or commercial vaccines**, while fungal diseases can be minimized by increased overall water quality, general health/condition and improved biosecurity. Examples of successful vaccinations are:

- ERM (yersiniosis) in rainbow trout and vibriosis in sea bass, thanks to vaccination (bath/dip & injection),
- *Streptococcus iniae* of rainbow trout thanks to vaccination before the primary exposition of fish to the etiological agent and booster vaccination by injection,
- RTFS due to *F. psychrophilum* if the vertical transmission is efficiently prevented (which is not that easy).

Autogenous vaccines are used a lot in aquaculture production in certain species e.g. against yersiniosis in Atlantic Salmon (Norway) and are perceived as very useful if not irreplaceable.

Another 'easy' measure would be to ***improve the availability of the existing vaccines*** throughout Europe and to allow also import of vaccines under the cascade regime.

4. Do you have specific examples of where vaccination can be used to directly or indirectly reduce the use of antimicrobials?

Vaccination in combination with other measures such as increased biosecurity have nearly eliminated the need for antibacterial treatment of Norwegian and Scottish farmed fish. During the early phase of the salmon industry in the 1980's, serious disease problems were experienced. In 1987, antibacterial use approached 50 tons, for a total fish production of 50,000 tons. The same year, vaccines against the main bacterial disease problem, coldwater vibriosis, were introduced, and the consumption of antimicrobials declined. However, in 1990, medicine use rose again, due this time to the disease furunculosis. Vaccines were tested and taken into use, and during the following years, development of more effective vaccines, including combined products against several infections, were developed. The prevalence of the most important bacterial diseases has now remained very low for more than 20 years (Lillehaug & Grave 2016)

This success is not only due to the efficient and safe vaccines developed, but needs to be seen together with advances in feed technology, production elements that incorporated biosecurity, and significant government and company investment in infrastructure, including research.

Unfortunately, the ***vaccine success is less impressive in other fish species and types of production.***

Some successes occurred for ERM and vibriosis (due to *Listonella* (*Vibrio*) *anguillarum* serotype I and *Vibrio ordalii* (= *Listonella* (*Vibrio*) *anguillarum* serotype II alpha) were vaccination by

commercial vaccines proved effective to protect rainbow trout and sea bass from the related diseases (injection is more efficient and long-lasting than dipping which, in turn, is more efficient than the oral route).

In general, viral vaccines should be improved; inactivated vaccines against viral agents have low effect (infectious pancreatic necrosis, pancreas disease, infectious salmon anaemia, viral haemorrhagic septicaemia, infectious haematopoietic necrosis). “Live” attenuated and genetically modified technologies should be the focus, as well as other vaccine.

There are also “local” success stories that frequently are based on use of *autogenous vaccines* instead of antimicrobials to combat/prevent bacterial disease outbreaks. Treatment of parasites however, remains very much dependent on antiparasitics, and vaccines do not appear as viable or widespread solution in near future. In such cases, reduction in antiparasitics use may be better achieved with feed delivery and biosecurity measures.

Some countries have no vaccine success stories, simply because vaccines are unavailable in their country and are too difficult to import even with the existence of the ‘cascade system’.

It must also be noted that for fish, some authorized vaccines e.g. for immunization against enteric redmouth disease (ERM), their application can at times be challenging. For example injectable vaccine is easy to use for individual treatment of breeding fish, but the vaccination of tens of thousands fish on the production farm can be challenging. Nevertheless in trout production, it has been shown that vaccination by injection, e.g. for Vibriosis, is worth its cost and efforts even for a single indication on tens or hundreds of thousands of fish each year. With an efficient vaccination team, 1000–1800 fish can be manually injected per hour. In Norway and Scotland, vaccinating machines are frequently used for the injection of large numbers of young fish to protect them from several viral and bacterial diseases

5. Do you have other examples of where vaccines would be needed and could be used to directly or indirectly reduce the use of antimicrobials?

Yes, new vaccines are needed, but also existing vaccines could be improved in regard to efficiency (e.g. furunculosis). Some examples:

- *Sea lice* (including salmon lice). Sealice are not treated with antimicrobials and it is not likely that a commercially useful sea lice vaccine will be available soon. Therefore other control strategies should have priority. “*The greatest quantities of pharmaceuticals*

prescribed today in the salmon industry are for the control of salmon lice. Long-time exposure to various medicinal products is now causing an increasing resistance problem. However, in contrast to antimicrobial resistance, resistance in salmon lice to chemotherapeutics does not pose any direct threat to human health” (Lillehaug & Grave 2016).

- ***Vaccines for cleaner fish*** (lumpfish and wrasse) being used for sea lice control in Northern Europe. These fish are particularly susceptible to atypical furunculosis and pasteurellosis and effective commercial vaccines are not yet available.
- Well-functioning ***vaccines against Vibriosis*** in marine fish as well as ***vaccines against CMS and HSMI in salmonids, against PKD ('proliferative kidney disease') or Ichthyophthiriosis and emerging bacterial diseases like mycobacteriosis or older ones like flavobacteriosis***
- ***Vaccines for early life stages such as against RTFS (flavobacteriosis) and tenacibaculosis.*** Vaccination in the early life stages are difficult due to the fish being too small to inject or having a too immature immunity system, but some dip vaccines have shown promise. Live attenuated vaccines could also be promising; they seem currently forbidden in Europe for aquaculture whilst some are authorized in other productions or elsewhere for fish (i.e. columnaris or Edwardsiella for catfish in US).

However, again we need to emphasise that ***vaccination alone is only part of the solution***. Except for specific infections such as furunculosis, vibriosis and cold-water vibriosis, where vaccination will remain the dominating solution. In addition, it can make us lose sight of other options that can (probably with less cost and similar efficacy) give us reduction in antimicrobial use. Fighting disease by disease with developing individual vaccines afterwards, may be not the most economical approach when compared to benefits that come from implementation of “proper” biosecurity programs and measures intended to support a robust immunity (prevention of excessive stress or compensation of its adverse effects) with an improved involvement of veterinarians.

6. Are you aware of any further specific examples where measures have successfully reduced the use of antimicrobials in animals and, if available, the impact on the occurrence of resistance to such antimicrobials

Yes, our suggestions would be:

- ***Increased veterinary presence and better choice of treatments and approved veterinary medicines*** (e.g. licensing of medicines on European basis and not by member state, proper veterinary care; reduction of illegal use of medicinal products...),
- ***All prescriptions of antimicrobials should be done by a veterinarian*** after examination and diagnosis and if necessary, sensitivity testing. Monitoring of all prescriptions written in order to allow a good knowledge and to ensure proper compliance by the farmer,
- ***Improved biosecurity*** (veterinary examinations and inspections prior to livestock movements),
- ***Improve water quality, water flow and fish density in closed production systems, particularly for fry production, to avoid unspecific infections.***
- ***Improving the availability of authorised aquatic veterinary medicines in all EU countries,***
- ***To shorten as much as possible the delay between diagnosis and the onset of medication, especially for the oral route in metaphylactic treatment,***
- Accommodating the preparation of small quantities of ***prescription pre-medicated feeds*** (restrictive on-farm medication mixing controls coupled with high analysis of medicated feed testing adds to significant problems for farmers and vets),
- ***Development and standardisation of rapid diagnostic methods for susceptibility testing of the bacteria isolated from the diseased fish and assess/improve the predictive values of such tests,***
- ***Better control of ornamental fish*** import, breeding and medication,
- ***Forbid and penalise*** over-the-counter (OTC) medicines with antimicrobials!
- ***Increased testing of imported fish products for antimicrobial resistance,***
- ***To assess the efficiency of non-steroidal anti-inflammatory medicinal products (NSAID's) in association to antimicrobials to improve the medicated feed intake in the context of oral metaphylactic treatments,***
- The competent authority to take responsibility in the flow-through fish farms because of the rivers' contamination,
- Favouring the SPF production and suppressing the sources of specific epizootics linked with aquatic systems.

The problem of emerging antimicrobial resistance may (should!) be addressed ***with increased veterinary presence and wider choice of treatments and approved medicines*** (e.g. medicated feed; proper veterinary care and reduction of illegal use of medicinal products). This crosses over significantly into what we try to do with the FishMedPlus Coalition.

Improving biosecurity:

General biosecurity measures should be implemented (and regulated by law), such as veterinary exams and inspections prior to movement of livestock, health controls in fish farms, regulation of transport of live fish, when possible, only single generation of fish at one site, fallowing between generations, etc.

In Norway: “The biosecurity measures implemented during the early 90’s contribute significantly to a favourable health situation in Norwegian aquaculture regarding infectious diseases in general (Lillehaug & Grave 2016)”. Marine salmon farming in Norway is an example of an animal production system in which biosecurity measures, such as vaccination, have almost totally replaced antibacterial treatment” (Lillehaug & Grave 2016). The aquaculture sector, however, also consists in sectors represented by the total and unit production for farm much smaller than that of salmon, which do not justify investment by the pharmaceutical industry to develop vaccines on an industrial scale, to that effect that they have to resort to the production of autogenous vaccines.

The Norwegian Veterinary Institute reports: “Vaccination and other biosecurity measures have nearly eliminated the need for antibacterial treatment of Norwegian farmed fish.

There is also a recent (09/2015) special edition of Journal of Applied Aquaculture that has several case studies of how biosecurity programs can reduce disease risks, and indirectly contribute to reduction of costs related to disease. One possible “reversed” example is emergence of salmon lice resistance to “Slice” (ivermectin based treatment) after (un)controlled use of bulk cheap replacements of antimicrobials in Chilean salmon farms in late 90’ and early to mid-2000’ and poor biosecurity practices that brought the ISA epidemics to almost destroy the industry. The salmon industry and Chilean government have since worked together with veterinary authorities to significantly improve their approaches to biosecurity, and the disease losses have been subsequently fairly reduced.

Increased availability of medicines

Although widely developed for warm-blooded animals, there is a total gap in the field of NSAID's use in fish treatment (non-steroidal anti-inflammatory medicinal products) which could yet improve the welfare of sick fish and improve the efficiency of antibacterial treatments (maybe even lower the risk of antimicrobial resistance). Some trials, in association with

antimicrobials were and are carried out in France which seem to show interesting benefits towards fish welfare and efficacy of antibacterial treatments.

Accommodating the preparation of small quantities of prescription *pre-medicated feeds* could significantly reduce quantities of antimicrobials used.

The availability of medicines registered in aquaculture is very limited and the few authorised are usually only for one or a few fish species. There is thus a need for many pharmacological studies in order to adapt the use of these medicines to other fish species.

It should also be recognised that with global warming some bacteria are becoming emergent pathogens for farmed fish (example: streptococcosis, mycobacteriosis among farmed fish). Besides, the extensive trade of exotic fish species (enhanced by the globalization) leads to the spread of new infectious/parasitic diseases which can dramatically threaten fish welfare (both farmed and wild) by the sudden contact between "naive" fish populations and new pathogenic organisms (current example in Europe : emergence of rosette disease thanks to the spread of *Pseudorasbora*).

The development of rapid diagnostic methods for susceptibility testing of the bacteria isolated from the diseased fish is also needed. Better epidemiological systems should be developed.

The regular monitoring of fish farms connected with cultivation of present bacteria and susceptibility testing with centralised data collection and access could help veterinarians with quicker diagnosis and targeted treatment of clinical bacteriosis in stock of fish. In our area the regular monitoring of pathogens needs to be focus on *Aeromonas salmonicida* *susp. salmonicida* and *Flavobacterium psychrophilum*, in case of salmonids.

It is clear that this proposed system would not be possible without greater involvement of specialists in fish diseases, veterinary diagnostic laboratories, management of farm registers and governmental participation (e.g. governmental contracts).

Another incentive to a producer may be in a form of a voluntary participation in a certification program (e.g. biosecurity certification) that has a part to specifically address reduced use of antimicrobials in the operation by any means available as long as it does not endanger the production and welfare of animals.

Rabbits

1. Please advise which 'production systems/life stages'–'syndrome/disease' combinations use the greatest amount of antimicrobials in rabbits.

Contrary to the other species kept for food production, little quantitative data or publications exist on the use of antimicrobials in rabbit production. Therefore, most of the underneath answers are from expert opinions.

Critical phases with an increased need for antimicrobials are:

- **Breeding females:** in this group most antimicrobials used is associated with Pasteurellose such as by *Pasteurella multocida* (respiratory form mostly, also genital infection). Antimicrobials are also used to treat metritis and mastitis (staphylococcal bacteria or others), Treponematosis (some countries) (Vent Disease, Rabbit Syphilis), etc.
- **Small kids before weaning:** Enterotoxemia such as by *Clostridium spiriforme*, colibacillosis such as by *Escherichia coli*, neonatal enteritis and staphylococcal infections.
- **Fattening phase:** the first part following weaning is the most critical phase. Young rabbits in that period are especially vulnerable for intestinal diseases, which are a major cause of death in young rabbits. In this period intestinal diseases such as Enzootic Rabbit Enterocolitis (ERE– etiology unknown) and colibacillosis are predominant. Other diseases are Proliferative enteropathy, caused by *Lawsonia intracellularis* bacteria, coccidiosis by *Eimeria spp* and Muroid enteritis (etiology unknown).

Risk factors for high antimicrobial use:

- different production 'bands' in the same housing system, with insufficient biosecurity, etc.
- difficulties to ensure the right micro-climatic conditions for every specific phase
- no adequate biosecurity measures implemented

- no all-in all-out management after each reproduction cycle, followed by adequate cleaning and disinfection)
- pressure put on the reproductive phase (intensive breeding systems) or the growth phase (early weaning, mixing)
- increase in antimicrobials administered to rabbits and systematic water acidification during the fattening period are shown to be associated with a decrease in the doe fertility and in viability of rabbits. (Chauvin 2012)

See Annex I for more information on rabbit production systems.

In France, for rabbits most used antimicrobials are tetracyclines, phenicols, fluoroquinolones and aminoglycosides. See graph.

In Italy, based on personal communication, they estimate that the most used antimicrobials are tetracyclines, sulphamidics, fluoroquinolones, polypeptidic substances and aminoglycoside."

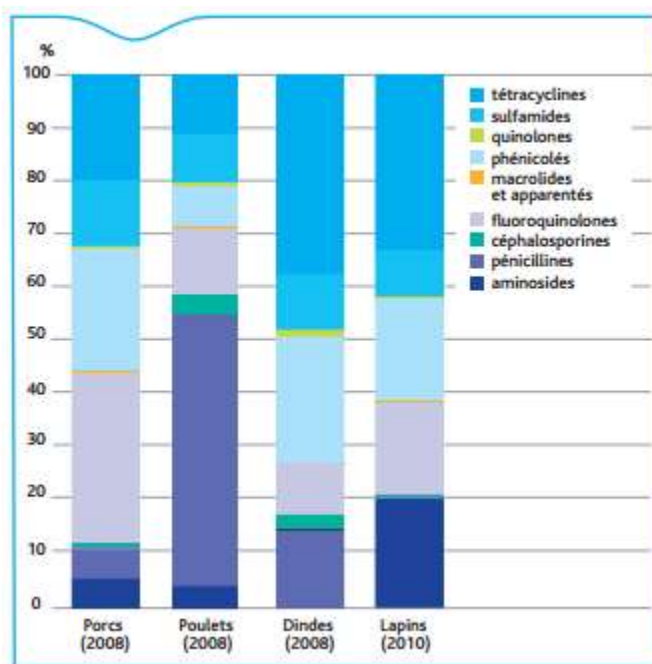


Figure 8: Percentage of use of different classes of antibiotics for rabbits in France in 2010

Source: Chauvin C et al, Usage des antibiotiques en filières porcine, avicole et cunicole en France. Resultats d'enquêtes. Bulletin épidémiologique santé animale - alimentation, 2012, pp.12-15

A survey done in France amongst rabbit breeders (2010) showed that about 1% antimicrobials was administered via injection (females only), 9% by drinking water (rabbits growth and females) and 90% via oral medication (and female rabbits growing).

2. For which combinations is it considered most difficult to implement measures aimed at reducing the need for antimicrobials?

Pasteurellosis and Enzootic Rabbit Enterocolitis (ERE).

Pasteurellosis is often treated with antimicrobials such as tetracycline, streptomycin, spiramycin and enrofloxacin or sulphonamides and tilmicosine or with the use of autogenous vaccines. Results are often disappointing. Best is to try to prevent pasteurellosis (starting with a healthy reproduction stock).

Enzootic Rabbit Enterocolitis, ERE is a syndrome of which the etiology is unknown. The diagnosis in field conditions is difficult because co-infection with other common rabbit pathogens occurs frequently such as with enterotoxemia due to *C. spiroforme*, coccidiosis and colibacillosis.

Implementing measures to reduce the need for antimicrobials is the most difficult in the breeding phase and with the kids before weaning, and is slightly easier in the fattening phase.

It is especially difficult in housing systems where all the different phases are done in the same housing environment. In these systems it is difficult to modulate correctly the internal microclimate (temperature, humidity, air velocity, concentration of harmful gases such as ammonia and carbon dioxide) and to prevent the spread of diseases.

In the breeding phase, the introduction of corrective measures (such as to ensure good internal micro-climate) are often insufficient to prevent pasteurellosis and limit the economic consequences of it. Farms using the "all in – all out" system are better from a biosecurity point of view.

In the fattening period, rabbits are extremely vulnerable to digestive diseases. Using a good balance between low digestible fibre (insoluble fibre) and fermentable fibre (soluble fibre) and possibly feed restriction of 20–25% in the first weeks after weaning, optimizes gut health and can reduce the losses in fattening rabbits without an excessive use of antimicrobials. However,

in the critical phase of 40–55 days of age even the best measures can at times be ineffective to prevent colibacilloses.

3. For which of these combinations is it considered most easy to implement measures aimed at reducing the need for antimicrobials?

The easiest to do, although not always the easiest from an economical point of view, are:

- Proper housing systems with good microclimate (temperature, humidity, air velocity, concentration of harmful gases such as ammonia and carbon dioxide)
- Good internal and external biosecurity (all-in all-out management)
- Suitable genetic selection of robust and disease free breeding rabbits (e.g. less susceptibility to pasteurellosis)
- Good maternity management and doe replacement systems
- Good husbandry methods to reduce stress around the critical periods
- Good feeding regime adapted to the different growth phases, with good balance between low digestible fiber (insoluble fiber) and fermentable fiber (soluble fiber)
- A feed restriction by restricting the feeding time after weaning (7–8h maximum) by using an automatic feeding system
- Regular health visits to ensure the farm having a good preventive health control plan including vaccination and parasite prevention

The use of medicines should never replace good hygiene, stockmanship or other management-related factors. The veterinary knowledge and competence regarding these issues and the peculiarities of rabbits breeding are key factors and provide an important opportunity for a more responsible and prudent use of VMPs.

In the last years, a French platform ‘interprofessionnelle’ has voluntarily started to implement measures to reduce the antimicrobials used in the different food producing animals, including rabbits. They use agreed indicators to calculate the amount of antimicrobials used; namely IFTAr (Indication Frequency Treatment Antimicrobials – reproduction) and IFTAc (fattening). Between 2010 and 2014, IFTAr decreased by 45% and IFTAc by 52%. The results of the RESAPATH network (Resapath 2014) over the same period shows that the % of isolates sensitive to most antimicrobials commonly tested went up for *Escherichia coli*, *Pasteurella multocida* and *Staphylococcus aureus*. This seems to indicate a decreased antimicrobial resistance.

4. Do you have specific examples of where vaccination can be used to directly or indirectly reduce the use of antimicrobials?

Only two vaccines exist. Vaccinations in rabbits exist for viral diseases; namely for myxomatosis and Rabbit Hemorrhagic disease virus.

Autogenous vaccines are used to prevent against pasteurellosis, however results are divergent.

Autogenous vaccines are frequently used in some countries, less in others. Some experts have very good experiences with autogenous vaccines, to the extent that they believe they reduce the numbers of antimicrobials used. Other experts are less convinced of the efficacy of autogenous vaccines, believing the results are uncertain and that often it takes too long to prepare them.

Autogenous vaccines are used against highly pathogenic colibacillosis (type O103), mastitis (by *Staphylococcus*) and klebsiellosis. Unfortunately all experts agree that autogenous vaccines against *Pasteurella*, the most important condition to prescribe antimicrobials for in the breeding phase, give disappointing results.

5. Do you have other examples of where vaccines would be needed and could be used to directly or indirectly reduce the use of antimicrobials?

Vaccines most needed are for:

- Pasteurellosis
- Enzootic Rabbit Enterocolitis (ERE) – etiology unknown!
- Coccidiosis
- *Staphylococcus*
- *Clostridium*

In addition to normal vaccines, also improved autogenous vaccines would be welcome.

However, it is doubtful whether in the near future it will be possible to develop vaccines for pasteurellosis and ERE. The availability of vaccines against coccidiosis (as existing for poultry) would be useful to reduce the need of coccidiostats as veterinary medical product or as feed additive.

Having additional vaccines against bacterial diseases, would be very useful, but will always be only one element in a holistic integrated approach to preventing and controlling rabbit diseases. Vaccination alone will not solve the problem.

As important is the list of measures in question 3 in relation to good housing, feeding, and management and biosecurity practices.

6. Are you aware of any further specific examples where measures have successfully reduced the use of antimicrobials in animals and, if available, the impact on the occurrence of resistance to such antimicrobials

See list of measures in question 3 in relation to good housing, feeding, and management and biosecurity practices.

Moreover, if highly pathogenic agents have been detected in the rabbits, an emptying of the stable followed by a thoroughly cleaning and disinfection AND repopulation with healthy reproduction stock is an adequate measure to reduce the use of antimicrobials.

Food reduction for 4 weeks after weaning has shown to decrease gastro-intestinal problems and mortality in rabbits (Maertens L 2015).

On serious staphylococcal disease (multi-antibiotic resistant *Staphylococcus*), the use of autogenous vaccines and treatment based on essential oils have reduced the use of antimicrobials and find a very correct sensitivity of the bacteria.

Bees

1. Please advise which 'production systems/life stages'–'syndrome/disease' combinations use the greatest amount of antimicrobials in bees.

Bees may be affected by bacterial diseases such as by **American foulbrood** and **European foulbrood**. These are diseases of the brood respectively due to *Paenibacillus larvae* and *Melissococcus pluton*.

American foulbrood disease (AFB) and European Foulbrood (EFB) could in theory be fought by the use antibiotics, however most experts discourage this and believe that the best way to control bacterial diseases in bees is via good beekeeping practices.

Many veterinary bee experts believe no antibiotics should be used to treat in honey bees.

US beekeepers since decades have applied oxytetracycline to honeybee colonies to prevent foulbrood. As a result, researchers (Moran et al, 2012) found that gut bacteria in US bees carry 8 genetic variants that confer resistance to tetracycline, compared with 1 or 2 such resistance-conferring variants in wild bees or in those from countries that don't use antibiotics on bees.

Adult bees may be affected by microsporidian diseases such as **Nosemosis** type-A and Nosemosis type-C respectively due to *Nosema apis* and *Nosema ceranae*.

Nosemosis is a fungal disease due to microsporidies: *Nosema apis* and/ or *Nosema ceranae*. It can cause major damages in apiaries, according to the countries, climate, and some contributing factors as Varroa infestation, beekeeping practices and miss-use (illegal) of antibiotics.

Nosema apis and *Nosema ceranae* have been found in asymptomatic colonies, and are considered by some veterinarians and researchers as a facultative pathogen. Other researchers, think that *Nosema spp.* should be considered as other pathogens.

At this time, no treatments have a marketing Authorisation against Nosemosis except in the United Kingdom. Most bee veterinarians believe good beekeeping management of

apiaries can be helpful and even sufficient against Nosemosis. In rare cases, Fumagillin treatment is necessary.

The fight against **Varroa destructor** is absolutely necessary because of the damages of this mite. Varroosis is a parasitical disease which can lead to weak colonies or even to the collapse of colonies. Varroa can be spread easily in an apiary or between apiaries.

There is a great responsibility for beekeepers to fight the best they can and according to scientific and reliable methods. The fight must be associated with good practical management and correct use of miticides.

The main miticides are Amitraz – Tau-Fluvalinate – Thymol – Oxalic acid (OA) – Formic acid. (In addition to: flumethrin, coumaphos, lactic acid, acrinathrin registered).

2. For which combinations is it considered most difficult to implement measures aimed at reducing the need for antimicrobials?

None

3. For which combinations is it considered most easy to implement measures aimed at reducing the need for antimicrobials?

All, need good beekeeping practices

4. Do you have specific examples of where vaccination can be used to directly or indirectly reduce the use of antimicrobials?

Vaccination is impossible in bees because they have no specific immune system and thus they have no lymphocytes or plasma cells --> no antibodies!

5. Do you have other examples of where vaccines would be needed and could be used to directly or indirectly reduce the use of antimicrobials?

See question 4

6. Are you aware of any further specific examples where measures have successfully reduced the use of antimicrobials in animals and, if available, the impact on the occurrence of resistance to such antimicrobials

Drafting, implementation and controlling Good Beekeeping Practices and fighting illegal use. Especially when diseases occur, is the best way to control them.

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