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# Risk management of antimicrobial use and resistance from food-producing animals in Denmark

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# **Risk management of antimicrobial use and resistance from food-producing animals in Denmark**

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## *Introduction*

For the past 12 years Denmark has had an ongoing risk management strategy for optimization of antimicrobial usage and reduction of antimicrobial resistance. The aim of the strategy is to secure food safety and the future treatment possibilities for humans without jeopardizing animal health and welfare. This strategy has been possible due to the strong cooperation between the human and veterinary health authorities in Denmark on this issue, as well as strong collaboration between research and monitoring and risk management. The first major result of this cooperation was the ban of the antimicrobial growth promoter avoparcin and the establishing of DANMAP in 1995 and the latest is the establishing of a task force between the Danish Medicines Agency and the Danish Veterinary and Food Administration in order to cooperate on inspections of veterinary practices, among else securing no economical relationship between veterinary practitioners and the medical industry. The task force is a part of action plan 2007 from the Danish Veterinary and Food Administration, under the Ministry of Family and Consumer Affairs. All antimicrobials in Denmark, both human and veterinary products are prescription only, this places both the human and the veterinary practitioners as key persons in prudent antimicrobial usage.

The most important parts of this continuing evolving risk management strategy are outlined below.

## *Growth promoters*

In 1995 the current Danish Ministry of Agriculture, Fisheries and Food decided to ban the use of the growth promoter avoparcin, due to cross-resistance to vancomycin, a critically important antimicrobial for human use. In 1997 EU banned the use of avoparcin. In 1998 Denmark banned the use of virginiamycin due to cross-resistance to the critical important Synercid used in humans. Also in 1998 the Danish animal production industry voluntarily stopped the use of growth promoters, only swine up till 35 kg bodyweight was still treated with growth promoters until January 2000. In 1999 EU banned tylosine, spiramycin, virginiamycin and bacitracin and the remaining growth promoters were banned in EU from January 2006.

The gradual banning of growth promoters in Denmark resulted in a 50% reduction of the usage in the animal production from 1997 to 1998 and this large reduction was not directly compensated in an increased therapeutic use as documented in figure 1.

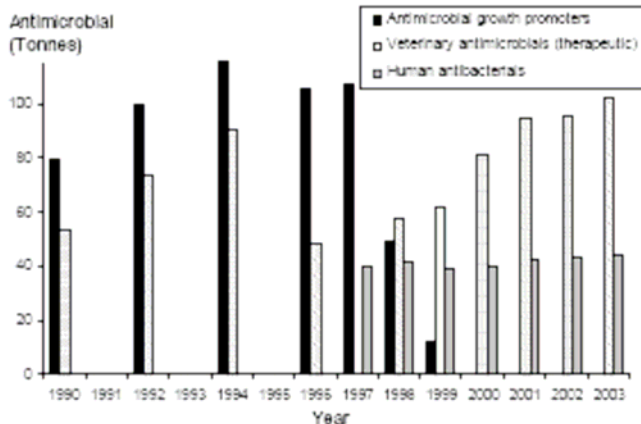


Figure 1. Antimicrobial use in animals and humans in Denmark, 1990-2003 (DANMAP 2003)

#### *No prophylactic use and restrictions on profits from sale of medicine*

In 1994/95 any prophylactic use of antimicrobials was prohibited and the veterinarians profit from direct sales of medicine was fixated at a very low level. This led to an immediate reduction in the total volume of antimicrobial drugs prescribed by veterinarians by 40%, as seen in figure 1.

#### *Implementing preventive veterinary strategies*

Since 1995 herd owners with food-producing animals are encouraged to sign a herd health contract with a veterinarian. This contract includes a regular monthly visit from the veterinarian, irrespective of the actual herd health situation, in order to promote preventive veterinary strategies, optimizing antimicrobial use. Thereby the role of the veterinarian should be of a more counseling type on herd health and management instead of prescription of medicine for acute disease. The herd owner benefits from the contract by having a right to hold and use prescribed veterinary medicine for the treatment of new cases for up to 35 days, instead of only for 5 days follow up treatment. About 95% of all swineherds and 70% of dairy herds have a herd health contract, whereas only approximately 20 % of the beef-herds have a contract. The effect of this regulation on antimicrobial usage has not been specifically assessed.

#### *The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP)*

The Danish monitoring for antimicrobial resistance (DANMAP) was established in 1995 and is based on the examination of representative bacterial isolates from both healthy and diseased animals. Pathogenic, zoonotic and indicator isolates are sampled. All major food animal sources are covered and the programme is coordinated with a similar sampling of data from bacteria causing infections in humans. In addition, information on the usage of antimicrobial agents is collected. The results are published annually and are available on: [www.danmap.org](http://www.danmap.org)

The objectives of DANMAP are:

- To monitor the usage of antimicrobial agents for food animals and humans
- To monitor the occurrence of antimicrobial resistance in bacteria isolated from food animals, food of animal origin and humans
- To study associations between usage and resistance and identify their trends
- To identify routes of transmission and areas for further research studies

The monitoring of antimicrobial resistance among food animals is based on three categories of bacteria: animal pathogens, zoonotic bacteria and indicator bacteria. Animal pathogens are included because these cause infections and treatment failures can be expected. Animal pathogens are collected from samples submitted for diagnostic purpose and were selected to represent some of the bacterial species most commonly associated with disease in production animals in Denmark. Zoonotic bacteria are included because they can develop resistance in the animal reservoir and may compromise therapy when causing infection in humans. The zoonotic bacteria in DANMAP are *Salmonella* and *Campylobacter coli/jejuni*. The indicator bacteria were selected to represent bacteria, which easily acquire resistance and are commonly found in the intestinal tract of different animals and humans. In this monitoring programme *Escherichia coli* was chosen to represent Gram-negative bacteria and *Enterococcus faecalis/faecium* to represent Gram-positive ones. The occurrence of resistance among bacteria isolated from animals is compared to results of the surveillance among bacteria isolated from food and humans. The results have been published once every year since 1997 in the DANMAP reports ([www.danmap.org](http://www.danmap.org)).

The establishment of DANMAP has made it possible to follow the changes in occurrence of antimicrobial resistance as a consequence of changes in usage, especially the changes in the usage of antimicrobial growth promoters. Since the ban of avoparcin in 1995 the occurrence of vancomycin resistance decreased significantly among enterococcal isolates from broilers, whereas no significant change occurred in pigs during the first three years. All VRE isolated from pigs were also simultaneously resistant to macrolides and tetracycline. These two antimicrobials have been commonly used for growth promotion and therapy, respectively, in the pig production in Denmark. It was shown that all VRE isolated from pigs in Denmark belonged to the same clone and that the genes encoding resistance to macrolides (*ermB*) and glycopeptides (*vanA*) were located on the same mobile DNA-element. The consumption of tylosine for growth promotion decreased substantially during 1998. During 1999 and 2000 a significant decrease in the occurrence of VRE among *E. faecium* isolates from pigs have been observed. These findings strongly suggest that the persistence of VRE among the pig population was caused by the continued use of macrolides, mainly tylosine, for growth promotion and therapy. Similarly the occurrence of resistance to other antimicrobial growth promoters (avilamycin, tylosine and virginiamycin) has decreased since the ban.

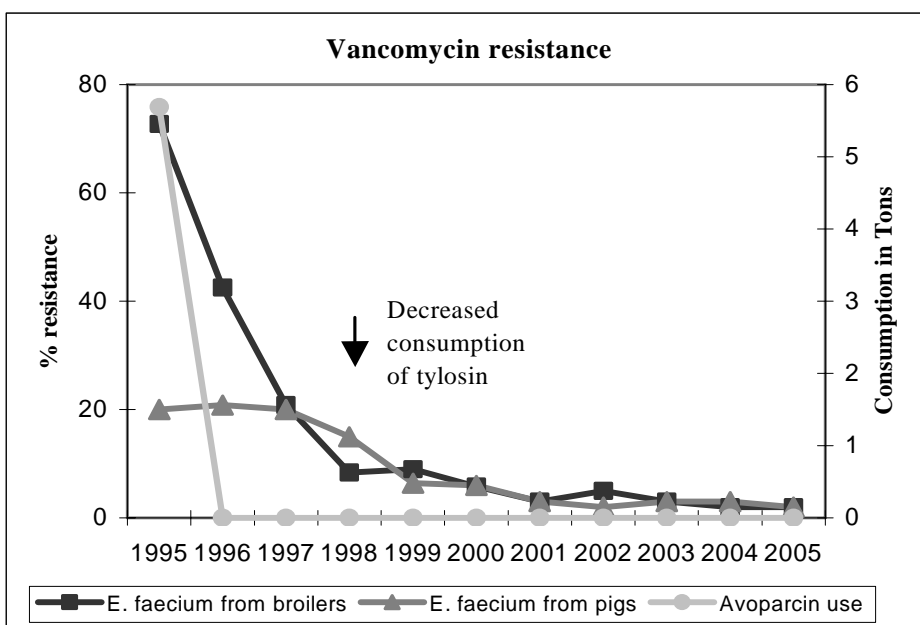


Figure 2. Occurrence of vancomycin resistance and consumption of avoparcin from 1995-2005

Tylosine is used for both growth promotion and therapy. This usage will also select for resistance in *Campylobacter*. As shown in figure 3, the occurrence of macrolide resistance in *Campylobacter coli* from pigs has closely followed the consumption of tylosine in the food animal production.

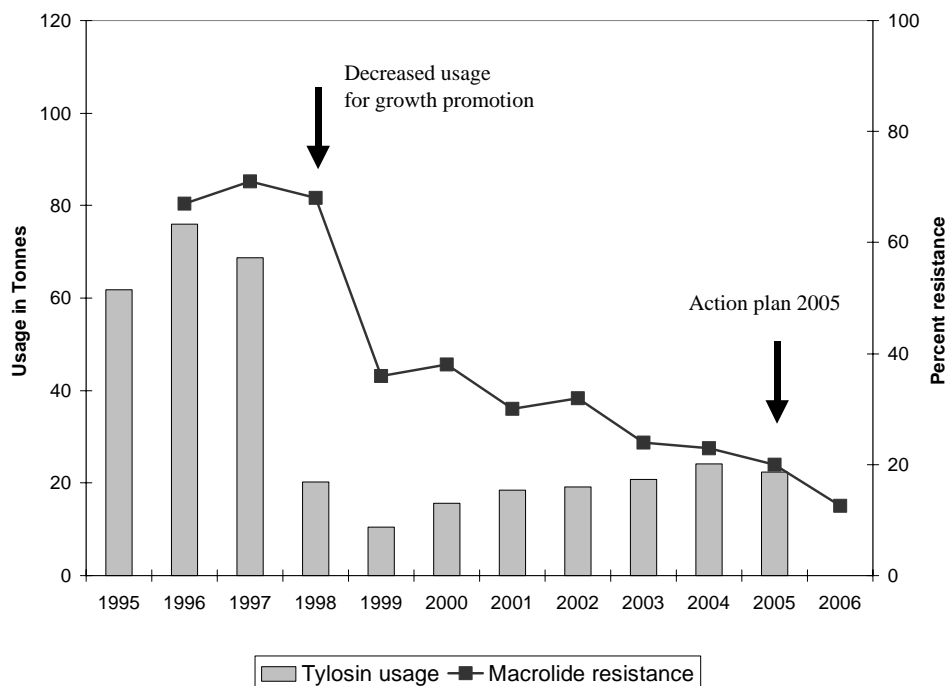


Figure 3. Macrolide resistance among *Campylobacter coli* from pigs and consumption of tylosine for growth promotion and therapy, 1995-2006.

#### Source attribution of *Salmonella*

##### *Quantifying the Contribution of Animal-food Sources to Human Salmonellosis*

To better explain the mechanisms in the occurrence of *Salmonella* infections in humans, the Danish Zoonosis Centre has developed a method that estimates the number of human cases attributable to each of the major animal-food sources. The principle is to compare *Salmonella* subtypes found in animals and food with subtypes found in humans. Some subtypes of *Salmonella* are almost exclusively found in a particular food animal reservoir or food type. These subtypes are used as anchor points for the distribution of subtypes occurring in several sources. Detailed knowledge of the distribution of *Salmonella* types in relevant food sources, generated through intensive and continuous monitoring, is a prerequisite for the analysis. The principle of *Salmonella* case attribution generates annual estimates for the impact of major animal-food sources. The results are published in the "Annual Report on Zoonoses in Denmark". The method has proven to be a powerful decision-support tool for risk managers for allocating resources to achieve the optimal public-health benefit.

Since 2001 this estimate has also included antimicrobial resistant *Salmonella*. The model is used to guide the research and intervention for control of *Salmonella* and also specific types of salmonella such as antimicrobial resistance in general as well as fluoroquinolone and cephalosporin resistance. As an example, in 2005 it was estimated that approximately 60% of all infections with salmonella acquired in Denmark came from Danish meat and 40% from imported meat. However, when

looking at the multiple resistant isolates or fluoroquinolone resistant isolates more than 90% of infections were attributed to imported meat.

#### *Control of Salmonella Typhimurium DT104*

In 1998 the Danish Veterinary and Food Administration implemented a zero-tolerance for multi-resistant variants of *Salmonella* Typhimurium DT104. The aim was to offer the Danish consumers maximum protection against this type of *Salmonella*, because it was feared that it had a larger potential for spread in food animals than other *Salmonella* types, and also that it had increased virulence for humans. The regulation also covers imported foodstuffs, which has helped to reduce the introduction of resistant *Salmonella* by imported foodstuffs to some extent. The levels of antimicrobial resistance in *Salmonella* from imported foodstuffs in Denmark remains however, considerably higher than in domestically produced foodstuffs.

#### *Restrictions on fluoroquinolones*

In the year 2002, the veterinarians use and prescription of fluoroquinolones to food-producing animals were restricted. The aim is to reduce the public health risk from emerging fluoroquinolone resistance in food borne pathogens, particularly *Salmonella* and *Campylobacter*. Fluoroquinolones can only be used in food-producing animals if a current laboratory test of resistance patterns shows that no other antimicrobial will be effective in treatment of the disease in question and this has been reported to the regional veterinary officer. This reduced the usage of fluoroquinolones from 183 kg in 2001 to 53 kg in 2003. The effect on the occurrence of resistance has not been as clear as for the antimicrobial growth promoters.

#### *VetStat*

VetStat has been used for risk management purposes from year 2002. VetStat enables the authorities to enforce risk management not only on the country level but also on the herd and vet level and development over the years can be followed and unacceptable trends spotted. Using ADD enables comparisons between herds, animal species, age groups and veterinarians. With the data from VetStat the control of antimicrobial usage could be planned as a risk based control on both the herd and the veterinarian level and on animal species and even age-group level. From 2002 –2007 a risk-based control using data from VetStat was put in force for 200 herds and of 40 veterinarians yearly. The 200 herds represents approximately 0,5% of all food-producing herds in Denmark and the 40 veterinarians represents 10% of all veterinarians working with food-producing animals. Regional veterinary officers did this control. Different risk based selection criteria were chosen each year, for instance an abnormal use (high or low) in herds, abnormal prescription pattern by veterinarians or prescription of fluoroquinolones. In 2005 this control resulted in 14% of the herd owners and 48% of the veterinarians controlled were reported to the police for further investigations of violations of the legislation in veterinary medicine.

#### *The Medicine Control Task force*

In 2003 the Medicine Control Task Force, a special unit under the Danish Veterinary and Food Administration, was established. The special unit plans the risk-based control and assists the regional veterinary officers in difficult cases; the unit assists the police and the Prosecution. But the unit also carries out 4-6 special actions towards for instance dairy herds to control for herd owner initiated treatment of mastitis which is illegal or illegal import of veterinary antimicrobials. For this purpose VetStat is also used to select the herds and veterinarians involved.

### Action plan 2005

The background for the plan was an increase of 25% from 2002-2004 in antimicrobials used in the Danish pig production. As the Danish pig industry consumes 80% of the total amount of antimicrobials used for animals in Denmark, this ongoing increase in usage could give rise to an increased risk of antimicrobial resistance selection pressure on both veterinary and human pathogens and risk of decreased treatment possibilities. Therefore the Danish action plan for reduction and prudent use of antimicrobials in pigs was initiated in 2005. There seemed to be a potential for a reduced usage, as large regional differences and very large differences between veterinarians consumption per pig produced was observed through VetStat.

The action plan for antimicrobial use in pigs, initiated in 2005, consisted of two elements:

1. Treatment guidelines for veterinarians for the 10 most common swine diseases in Denmark
2. Audit and supervision of veterinarians with a high usage of antimicrobials for pigs. The usage was measured both as a high total usage and a high usage per pig produced.

In the audits, graphical displays of the veterinarians prescription patterns and usage per age group and administration route, were compared to their colleagues pattern and usage. Moreover, their prescriptions were compared to the new treatment guidelines. An example is given in Figure 4, which shows that the audit veterinarian prescribes more than twice the amount of macrolides compared to his colleagues. Therefore the audit for this veterinarian, for example, can focus on this overuse of macrolides for treatment of swine.

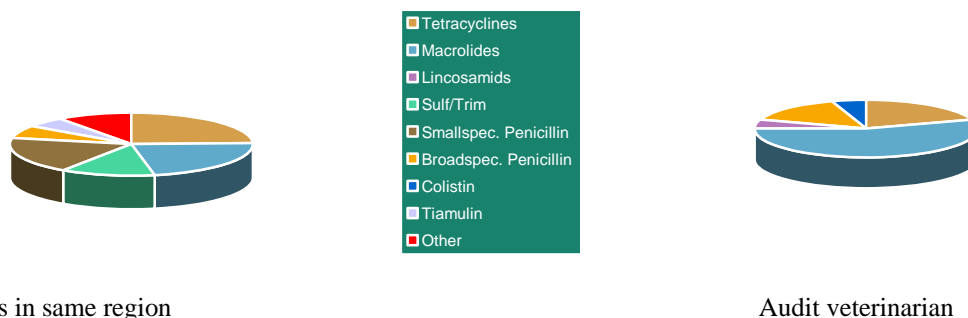


Figure 4. Example of an audit veterinarians prescription pattern for swine compared to all colleagues practising in the same region.

Furthermore the veterinarians were interviewed on treatment patterns for the most common swine diseases in Denmark. The objective of the audits was to discuss and clarify the veterinarians prescription and treatment patterns and by their self-recognition motivate them towards a reduced and more prudent use of antimicrobials.

The treatment guidelines for pigs excludes fluoroquinolones, macrolides, cephalosporins and apramycin due to their selection for resistance and/or their critically importance in human medicine. Moreover, the treatment guidelines list other antimicrobials just as effective in veterinary medicine, as the ones excluded, but without the risks of development of resistance and impaired human treatment possibilities.

Results from action plan 2005 show, that the approach with guidelines and audit and supervision visits is very effective. The fast increasing curve in the antimicrobial use seen from 2002 to 2004 of 25% has not only declined, but the usage has even decreased 0,2% in 2005 and this decrease has continued another 1,2% in 2006 despite a 1% increase in the pig production, as seen in figure 5.

Moreover, the action plan also changed the prescription patterns, as a more prudent use, following the new guidelines, has been adopted. The use of macrolides decreased respectively 5,5% and 6,5% in 2005 and 2006, simple penicillin's increased 7.5% in 2005 and tetracyclines increased 8,7% in 2006.

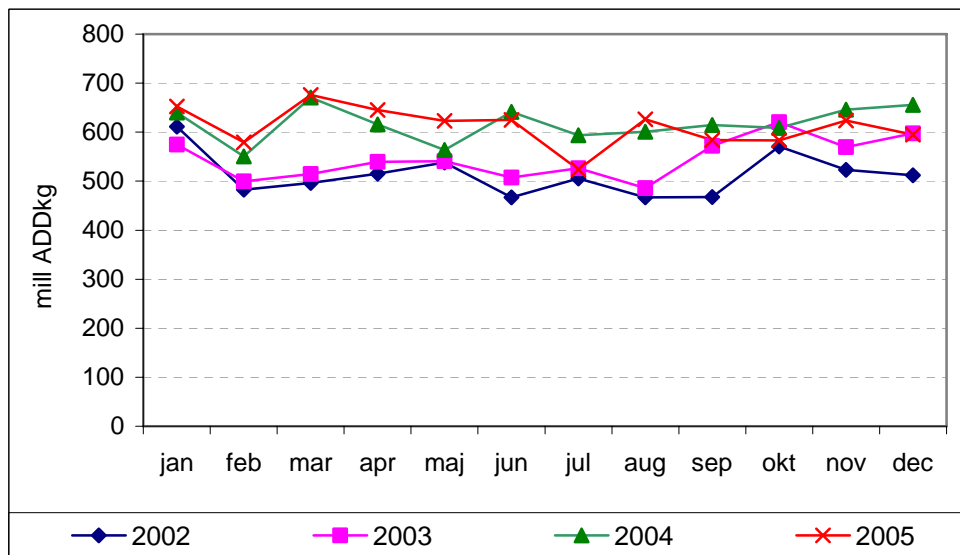


Figure 5. Development in antimicrobial use in swine year 2002-2005

Results from the audits concerning the treatment patterns (Figure 6) show that there is large variation in dose when treating Lawsonia diarrhoea with tetracycline in feed, whereas other treatment doses have a minor variation. Days of treatment on the other hand, show some variation despite disease and antimicrobial used for the treatment.

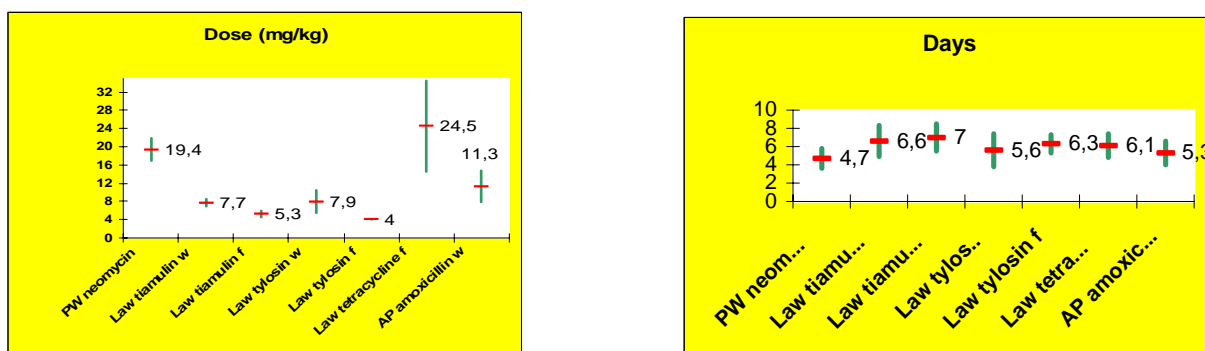


Figure 6. Results from interviews on treatment patterns on common swine diseases, giving dose and days of treatment for post-weaning diarrhoea (PW), Lawsonia diarrhoea (Law) and AP-infections and different antimicrobials used Red line =mean, green line =variation.

The conclusions from action plan 2005 were: there is an increasing focus on veterinarians usage of antimicrobials and their responsibility for animal antimicrobial consumption. The veterinarian plays the most important role in antimicrobial consumption in animals and has a large responsibility as prescribers of antimicrobial treatment and advisors in pig production.

The audits showed that there were large variations in especially days of treatment, so regulations in dose and days of treatment can reduce the consumption, though taking dose-effect and correlated risk of resistance into consideration. The audits increased the awareness of the veterinarians own

prescription patterns and resulted in a decreasing consumption and also alteration of the veterinarians prescription patterns for pigs.

#### *Case-by-Case investigation of meat for Salmonella*

Denmark has during the last decade reduced the content of *Salmonella* in the Danish meat production markedly. Especially in poultry, the level today is very low, and therefore Danish poultry meat is no longer an influential source of human infection with *Salmonella*. Imported poultry meat is nevertheless still infected with *Salmonella* and can therefore be a source of human infection.

To reduce the risk of human salmonellosis, Denmark in 2006 started testing Danish and imported meat for *Salmonella*. The testing determines whether the meat would impose a risk for the consumer, and if so, the meat would be deemed to be unsafe according to article 14 of Regulation (EC) No. 178/2002. In that case, the meat would be withdrawn from the market.

As parameters in determination whether the meat will impose a risk for the consumers, numbers of infected samples, type of *Salmonella* and antimicrobial resistance profile are included.

Until now the evaluation is done for each case individually, but it is hoped that the future will provide microbiological criteria, so this can be done internationally using the same standardized procedure.

#### **Action plan 2007**

##### *Audit and supervisions*

In Action plan 2007 audit and supervision, every second year, of all veterinarians working with food-producing animals will be carried out in order to motivate prudent use of antimicrobials in all food-producing animals. The Medicine Control Task Force will be extended in order to accomplish this task. Moreover treatment guidelines also for cattle and poultry will be enforced.

The audits will follow the same procedure as in plan 2005, but furthermore regulations on diagnostic testing has also been enforced and the audits will discuss the veterinarians use of diagnostic testing and use of post-mortems in their counselling of herds, in an attempt to stop continuous use of antimicrobials in herds without diagnostic testing.

##### *Treatment guidelines*

In the treatment guidelines, antimicrobials for every disease and its pathogen(s) are listed and scored within the following four categories, efficacy, resistance, human importance and WHO criteria for Critically Important Antimicrobials (CIA):

- **Efficacy:** scored from + to +++ depending on the documentation in their SPC's for their effectiveness. One plus being applied for documented effect in clinical trials. Two plusses if it furthermore has a good and recognised effectiveness in clinical practice. Three plusses are given if it furthermore is approved, in the SPC, specifically for the indication and/or the clinical effectiveness is documented in peer-reviewed papers.

It should be noted that antimicrobials with two plusses could be as effective as those with three plusses, if the difference is merely an old SPC opposed to a new SPC with specific approval for the indication taking pharmacokinetics into account.

- **Resistance in the veterinary pathogen on the national level:** one plus <30% susceptible, two plusses 30-60% susceptible and three plusses >60% susceptibility.

- Significance for human treatment: scores 1-5 depending on the following elements
  - a. Selection for resistance in bacteria in the veterinary population
  - b. Selection for resistance in zoonotic bacteria or transferable resistance
  - c. Risk of transmission of resistant bacteria or resistant genes through the food chain or directly to humans
  - d. Risk of those bacteria either directly giving rise to human infections or resistant genes could be transmitted to bacteria which would give rise to human infections
  - e. The significance of lost human treatment possibilities

The scores 1-5 will be given as follows:

1. Are not used for human treatment or only very limited
2. Scored high in one of the following: Important or less important for human treatment; indirect transmission not likely or unlikely.
3. Important in human treatment; indirect transmission likely.
4. Important in human treatment; direct transmission likely.
5. First choice for treatment of serious human infections. Direct transmission from animals to humans detected. Treatment failure detected. Should not be used in animals.

- The WHO list of critically important antimicrobials for human medicine with its scores on Important Antimicrobials (IA), Highly Important Antimicrobial (HIA) and Critically Important Antimicrobials (CIA).

It should be emphasized that the treatment guidelines are, as stated, guidelines and the veterinarians can use other antimicrobials than listed, but they will have to document the rationale for not following the list, for the Danish Veterinary and Food Administration during the audit and supervision visit.

#### *Task force between the Danish Medicines Agency and the Danish Veterinary and Food Administration*

Another part of the action plan 2007 is to secure that there are no economical relationships between veterinary practitioners and the medical industry, therefore a task force between the Danish Medicines Agency and the Danish Veterinary and Food Administration has been established and they will cooperate on inspections of veterinarians and sometimes also in cooperation with the taxation authorities in order to get documentation on business transactions, for instance on suspicion of illegal import of veterinary medicine.

#### *Future plans*

The Danish authorities will continue to monitor the occurrence of antimicrobial resistance, usage of antimicrobial agents and utilize the most recent research results in a continues effort to reduce the consequences of antimicrobial usage in food-producing animals for the consumer.

Currently internationally accepted criteria for what should be accepted in meat products seems a reasonable way forward, especially to control the increasing amounts of infections attributable to imported meat.