Reducing Antimicrobial Drug Use in Dutch Veal Calves and Antimicrobial Resistance

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The use of antimicrobials in food animal production induces antimicrobial resistance not only in bacteria that can cause disease (e.g. Salmonella) but also in normal gut bacteria (so called commensal flora). These resistant bacteria can be passed on from animals to humans by direct contact or through food. There is great concern about the increasing antimicrobial resistance in bacteria and the threat for human and animal health as they may lead to treatment failures.

Different specific phases can be considered in antimicrobial resistance (AMR). These can be either (1) development, (2) selection, (3) spread, (4) persistence and (5) reduction.

Development of resistance occurs when a bacterium which is sensitive to antimicrobials changes into a bacterium which is resistant to antimicrobials. Most often (but not always) this is the result of changes in the DNA of the bacterium by so called mutations or horizontal gene transfer.

The presence of antimicrobials might result in selection of these resistant bacteria. Antimicrobial usage might allow the resistant bacteria to grow as a result of the space which is created by killing or inhibition of the sensitive bacteria. Next, resistant bacteria can spread (transfer) to people, animals and/or environment. Development of AMR, selection and spread are highly dependent on antibiotic use. Whether resistant bacteria in the original host remain in the new host (persistence) depends partly on antimicrobial pressure. Most often resistance gives a relative disadvantage to resistant microorganisms what means that they may grow a little bit slower and are competed out by sensitive ones.

The total sales of antimicrobials for therapeutic use in animals in the Netherlands increased from 322 to 590 tonnes in the period between 1999 and 2007. When we calculate these amounts of antimicrobials for use in animals relative to the sum of the weight of live food producing animals in the Netherlands, it was shown that in this country the use of antimicrobials in animals was one of the highest in Europe. This was in contrast with the use in humans, with the Netherlands being one of the lowest in the world. It has to be noted that use of antimicrobials as growth promotor is not allowed in the EU since 2006.

To prevent further development of bacterial resistance, the Dutch government, food animal production sector, and veterinarians felt a shared responsibility and agreed to reduce the use of antimicrobials in food animal production. In 2010 the Ministry of Economics, Agriculture and Innovation (now: Ministry of Economic Affairs) set the objectives for reduction: 20 per cent reduction by 2011 and 50 per cent reduction by 2013 and added later the 70 per cent for 2015 (compared to the use in 2009 – 565 tonnes sales of antimicrobials for therapeutic use in animals).

Dutch veal production and antimicrobial use

In the Netherlands there are approximately 921,000 veal calves. About half of these animals (53 per cent) are imported from many different European countries with Germany as the most important supplier of veal calves for the Netherlands. The majority of veal production (62 per cent) originates from animals younger than eight months old (white veal). The remaining 38 per cent originates from calves aged between eight and twelve months (rosé veal). The Netherlands is the major exporter of veal in the world. For decades, more than 80 per cent of the total export of the meat has been exported to the same three countries – Italy, Germany and France.

In the Netherlands, more than 90 per cent of the antimicrobials in veal calves are orally administered. The main reasons for the preference for orally administrable antimicrobials in the veal industry are the easy administration in the milk during the feeding routine and the low cost per calf.

Data from 2014 revealed that 50 per cent of the total antimicrobial use on the veal calf farms in the Netherlands originated from the administration of tetracyclines, 20 per cent from intestinal anti-infectives (e.g. neomycin, colistin) and 10 per cent from trimethoprim/sulfonamides. Fluoroquinolones and 3rd and 4th generation cephalosporins use were respectively 0.1 and 0 per cent of the total use (Table 1 and Figure 1). The sector is in the process of a considerable reduction of the use of colistin.

The relatively high antimicrobial drug use in veal calves can partly be explained by the structure of this industry and the age of the animals. Where pig herds and poultry flocks are mainly closed or only combine animals from a limited number of origins, the veal industry commingles young, recently transported, calves that originate from multiple farms, both domestic and foreign. The combination of these factors is known to cause a higher disease risk.

Reduction of veterinary antibiotic use; the Dutch approach

To reduce veterinary antibiotic use, the Dutch approach aims to achieve a combination of quantitative reduction and qualitative improvement (see below). In addition, a crucial part of the approach is to provide a complete transparency of antimicrobial use in animal husbandry, by registration of all prescribed and administered antibiotics for each individual farm.

To create transparency and set bench mark indicators for the use of antimicrobials, an independent institution, the Netherlands Veterinary Medicines Authority (Stichting Diergeneesmiddelenautoriteit - SDa) was established in 2010.

Quantitative reduction and qualitative improvement

A reduction in the number of group treatments will substantially contribute to the reduction of antimicrobial use in animals. This approach will reduce the increase of antimicrobial resistance. The ultimate goal is to get a reduction of resistant bacteria. However, this reduction has to be obtained through a natural shift from resistant to susceptible bacteria. It is hard to predict what the timeframe is for such a shift.

The Dutch Ministry of Economic Affairs has prepared regulations for use of antimicrobials (partly based upon a report of the Dutch Health Council published in 2011) and the Royal Netherlands Veterinary Association (KNMvD) has initiated the update and quality-assured implementation of guidelines. Some important measures are: the use of medication with antimicrobials should meet clear and strict criteria on therapeutic necessity, it should be based on proper diagnostics, and the type of antimicrobial (including dosage and duration) should be chosen on evidence-based guidelines ("formularia"). Group treatments should be replaced as much as possible by individual treatments. Antimicrobials like tigecycline, glycopeptides, daptomycin, oxazolidinones, and mupirocin should be reserved for use on humans and never be used (and approved) for animals. The use of 3rd and 4th generation cephalosporines and fluoroquinolones should be preferably banned from veterinary use or only be used for individual treatments after proper identification of the bacterium causing the disease. Susceptibility testing must show that there are no alternative treatment options for these reserved antimicrobials. Apart from therapeutic use in individual animals (based on proper diagnostics and according to professional guidelines), on the long term, the use of colistin, aminoglycosides (e.g. neomycin, gentamicin), and all beta-lactams (penicillins and cephalosporins) should be banned from veterinary use. To protect animal health and welfare and to reduce the risk of infection, additional measures should be developed to replace these medications, such as improvement of hygiene, housing, nutrition, vaccination and animal/stable management. Several animal production sectors

have taken their responsibility and banned 3rd and 4th generation cephalosporins on their own initiative.

The independent expert panel of the Netherlands Veterinary Medicines Authority (SDa) defines bench mark indicators for prudent use of antimicrobials. The bench mark indicators serve as guidelines for farmers and veterinarians and are specified per animal species (poultry, pigs, dairy cows and veal calves) and subsectors (sows, fatteners). The SDa expert panel analyses the data concerning the usage of antimicrobials for each production sector and reports the findings annually. Based on these findings, farms and veterinarians are classified with a green, orange or red label. The corrective actions for farmers are carried out through the private (quality) production systems. (http://www.autoriteitdiergeneesmiddelen.nl/).

Over the past few years, it can be concluded that antimicrobial sales for animals in the Netherlands have decreased substantially. Currently the total decrease in sales is 58.1 per cent (2014 compared to 2009). The veal farming sector achieved a 37.4 per cent reduction in the usage of antimicrobials over the 2009 to 2014 period. The veal farming sector however has already been working on antimicrobial reduction since 2007. Over the period from 2007 to 2014 a reduction of 46.3 per cent was achieved. It should be noted that in 2014, the reduction in use levelled off in most animal species including veal farming.

Association between reduction in antimicrobial usage and antimicrobial resistance

The SDa recently investigated the relation between antimicrobial usage and the occurrence of antimicrobial resistance in food animals. This was done using the antimicrobial consumption data as described by the SDa on the one hand and on the other hand using the resistance data of the fecal samples from different animal species collected by the Dutch Food Safety Authority (NVWA), which were part of the national antimicrobial resistance monitoring program carried out by the Central Veterinary Institute of Wageningen UR. Since there has been a decline in the use of antimicrobials in Dutch livestock these data provide the opportunity to examine the impact of this decline on the circulating resistant bacteria.

It was shown that the usage pattern reflected the resistance data. The decline in usage was accompanied by a decline in the prevalence of antimicrobial resistant Escherichia coli bacteria from fecal samples of several animal species (veal calves, pigs, chickens and dairy). However the magnitude of the decline varied widely and seemed to be dependent on the specific form of resistance.

In veal farming a 37.4 per cent decrease in total antimicrobial usage was associated with a 26 per cent drop in resistance to one or more classes of antimicrobials.

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Like the antimicrobial usage, the resistance levels stabilized in 2014 in bacterial organisms sampled from all animal species. These findings indicate that reductions in the total quantity of antimicrobials used in the Netherlands are associated with a reduction of the general levels of antimicrobial resistance. These associations are indicative of a direct causal association between usage of antimicrobials and antimicrobial resistance. The current levelling off in antimicrobial use was directly followed by a stabilization of resistance levels.

In conclusion: the actions performed by farmers and veterinarians with thresholds set by the government resulted in a huge reduction in antimicrobial use in Dutch animal sectors, including veal production. The reduction in use resulted in a reduction of resistance which is a very promising outcome.

Usage in antibiotics in DDDAF in veal calves in the Netherlands

(SDa report: 'Usage of Antibiotics in Agricultural Livestock in the Netherlands in 2014' - http://www.autoriteitdiergeneesmiddelen.nl/en/publications)

White veal calves

Number of white veal farms: 864

Number of white veal farms that used third- and fourth-generation chephalosporins:1

Number of white veal farms that used fluoroquinolones: 107

DDDAF= Defined Daily Dose Animal expressed in the antimicrobial usage data of a farm per animal year.

Table 1: Usage of antimicrobials in DDDAF at white veal farms in the Netherlands.

N	Mean	Median	P75	P90
864	24.5	23.4	31.0	37.8

Figure 1: Mean antibiotic use at white veal farms in 2011, 2012, 2013 and 2014, by ATCvet group (left) and by first-, second- and third-choice product (right).