Managing Dairy Cows with Less Antibiotics!

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Take Home Messages

- The prudent use of antimicrobials is of great importance for human and veterinary medicine (One Health).
- Losing the efficacy of antibiotics means no chemotherapy, no neonatal care and no surgery anymore.
- Following treatment protocols reduces the misuse of antimicrobials.
- Suboptimal hygiene and management is often compensated by extensive use of antimicrobials.
- Time consuming management improvement will be paid back by better herd performance.
- The most important step in preventing antimicrobial resistance is avoiding the use of the critical important antimicrobials (CIA's).

Antimicrobial Resistance

Antimicrobial resistance (AMR) happens when microorganisms (such as bacteria and parasites) change when they are exposed to antimicrobial drugs (such as antibiotics and anthelmintics). Microorganisms that develop antimicrobial resistance are sometimes referred to as "superbugs". As a result, the medicines become ineffective and infections persist in the body. Some bacteria are naturally resistant to certain types of antibiotics. For example, bacteria that have an outer membrane that is impermeable to antibiotics will never be reached by the antibiotic and are therefore resistant. But bacteria may also become resistant. This acquired resistance occurs when a previously susceptible bacterium becomes resistant through mutation or acquisition of new DNA. Several mechanisms of resistance have been described. Some bacteria contain enzymes that de-activate antibiotics.

Bacteria can be resistant to one antibiotic, or to two, or to almost all the available antibiotics. Multi-resistant bacteria are resistant to almost all the

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available bacteria. It should be clear that it is not the animal or human that are resistant, rather the bacteria in animals or humans

What Factors Effect the Development of AMR?

The extensive and often unnecessary use of antibiotics may induce AMR. Overuse of antibiotics and incorrect prescribing practices are significant problems. Antimicrobials are designed to either limit or prevent the growth of microbes and in so doing create a selective pressure upon microbial communities. Under antimicrobial treatment, only those microbes able to survive and reproduce will predominate within the microbial community, causing their “advantage” to become common. More aggressive and persistent use of antibiotics increases the selective pressure on the microbial community to which they are applied. The widespread and intense application of antibiotics provides a strong and polarized selective pressure that will continue to provoke a strong adaptive response in the microbial world.

Daily routine treatments do not always follow the labels anymore. Sometimes, therapies find their way based on recommendations of farmers or experts who are visiting farms. Another example of overuse is treating a disease with antibiotics that is not caused by bacteria. Viruses are not killed by antibiotics and nutritional diarrhoea in pre-weaned calves does not respond to antibiotic treatment.

What are the Consequences of Antimicrobial Resistance?

The consequences of AMR are that some bacteria will not react to antibiotics. Resistant bacterial infections decrease therapeutic options, increase the costs of health care and can contribute to increased morbidity. If the efficacy of antibiotics decreases many therapeutic options will be lost, such as chemotherapy, surgery and neonatal care. Resistant bacteria can spread from animal to animal, from human to human, but also from human to animal and vice versa. The biggest threat is the spread of multi-resistant bacteria over the world.

■ Prudent use of Antibiotics

Antibiotics should always be used and managed in relation to animal health and public health. Although the link between the use of antibiotics in animals and the development of antimicrobial resistance in humans is complex and not yet well understood, all veterinarians must promote the most prudent use possible of antibiotics. Producers are worried about bans and restrictions that have been imposed, their impact on the health and welfare of their animals as well as economic impacts on their businesses. In fact, the restrictions and precautions that are requested with regard to the use of antibiotics have more to do with the knowledge and respect of the categories of importance in human medicine for antibiotics. The veterinarian must make a decision based on a rigorous decision process, which is supported by current scientific knowledge and awareness of potential consequences (including the development of resistant strains).

■ What Happened in the Netherlands?

During the past decade the use of antibiotics in food-producing animals has been a frequently discussed topic in the Netherlands. Differences in the total number of antibiotics between human medicine and veterinary medicine led to intense discussions. Development of AMR resulting from agricultural use of antimicrobials that could impact the treatment of human diseases has become a global public health concern. In 2006 the use of antibiotics in human medicine in the Netherlands was almost the lowest compared with other European countries, whereas the antibiotic use in veterinary medicine was highest in the Netherlands compared to surrounding European countries. This discussion resulted in the formation of a Task Force on Antibiotic Resistance in Food Producing Animals in 2008. Representatives from all parties within the food-production chain (farmer organisations, meat processing industries, feed suppliers), the Royal Dutch Veterinary Association (KNMvD) and the Government were represented in the Task Force. Within each animal production sector (cattle, veal, poultry and pigs) action plans were developed. The main goal of the Task Force was to get more insight into the use of antimicrobials and to focus on a more prudent and restrictive use of antimicrobials. The Minister of Agriculture stated in 2010 that the total use of antibiotics in food-producing animals should be reduced by 20% in 2011, by 50% in 2013 and by 70% in 2015. These reductions are relative to total antibiotic use in 2009.

To get more insight and transparency in the quantitative and qualitative use of antibiotics a study was conducted in the University Farm Animal Practice (ULP) in the Netherlands. In this veterinary practice the use of antibiotics was calculated based on the information of the practice management system (PMS). After the so-called baseline measurement of 2009 and 2010, strategies were undertaken to make farmers and vets more aware of prudent antibiotic use and explain to farmers the public health concerns around antimicrobial resistance.

How to Reduce if We Don't Know What We Use?

The collection and analysis of veterinary use data was not very standardized. Most European countries reported data based on sales figures of the pharmaceutical industry or prescriptions by veterinarians. In some countries a specific veterinary antimicrobial use monitoring program was developed, like in the Netherlands and Belgium (Catry et al., 2007; MARAN, accessed February 2011).

It is necessary to express the amount of sold or prescribed antibiotics relative to the number of treatments such that antibiotic use is related to a relevant denominator. This allows for correct interpretation and fair international comparisons of antimicrobial usage data. In human medicine, antimicrobial usage is expressed in defined daily doses (DDD) per 1000 inhabitants for general practitioner prescription and per 100 hospital bed-days for hospitals.

The DDD provide a fixed unit of measurement independent of price and dosage form (e.g. tablet strength) enabling the researcher to assess trends in drug consumption and to perform comparisons between population groups. For veterinary antimicrobial consumption evaluation, therefore, it is essential to calculate Defined Daily Dose Animal per year (DDDA/Y) for each antimicrobial pharmaceutical compound per animal species (Jensen et al., 2004). Drugs are classified in groups at five different levels. This classification, combined with administration route for systemic drugs, enables characterization of prescriptions at a therapeutic group level and at an administration route level, e.g. intra-mammary (drying-off and mastitis), intra uterine, oral and per injection (parenteral).

In the Netherlands the use of antibiotics is reported as Defined Daily Doses per Animal Year (DDDA/Y). This should be interpreted as follows: if the DDDA/Y of a herd is 5.3 it means that on average each cow of the herd has been exposed for 5.3 days per year to antibiotics.

Use of Antibiotics in Dairy Cows

The University Farm Animal Practice is a veterinary practice in the centre of the Netherlands. In this practice students from the Veterinary Faculty follow their ambulatory. The practice consists of 400 dairy herds, representing approximately 28,000 adult cows. Average herd size in 2010 was 71 cows (min = 18, max = 320). Antibiotic use was calculated over three years: 2009, 2010 and 2011. The mean antibiotic use per herd was 4.3, 4.3 and 4.2 Defined Daily Dose Animal/Year, for 2009, 2010 and 2011, respectively. Figure 1 shows the frequency distribution of all herds.

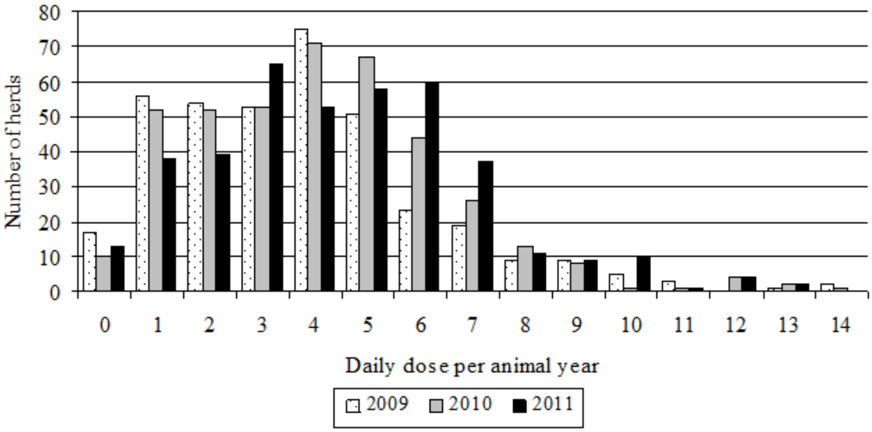


Figure 1. Frequency distribution of antibiotic use in 400 herds expressed as Defined Daily Dose per Animal Year (DDDA/Y), over three consecutive years.

The next step was to divide the total antibiotic use over the different routes of administration. Figure 2 shows the distribution of the five routes of administration. Distribution showed a stable pattern over the three consecutive years. Antimicrobial dry cow treatment (DCT) varied between 1.5 and 2 DDDA/Y followed by approximately 1 DDDA/Y of antibiotics for the treatment of sub-clinical and clinical mastitis. Expressed as a percentage, more than 60% of antibiotic use in dairy cows was for intra- mammary treatment. Included in the 60%, more than 40% was for antimicrobial dry cow treatment and another 22% for treatment of sub-clinical and clinical mastitis. On top of that, about 5% of the parentally used antibiotics were for mastitis treatment. Thus, about 70% of the total antibiotic use is related to the control or treatment of mastitis.

Oral use of antibiotics accounts for 20% of the total use. A substantial part of the antibiotics are fed to unweaned calves to treat diarrhoea. This vulnerable group of animals is already exposed to antibiotics in the first two months of life. Parentally used antibiotics were stable over the years and accounted for 10%-12% of the total use.

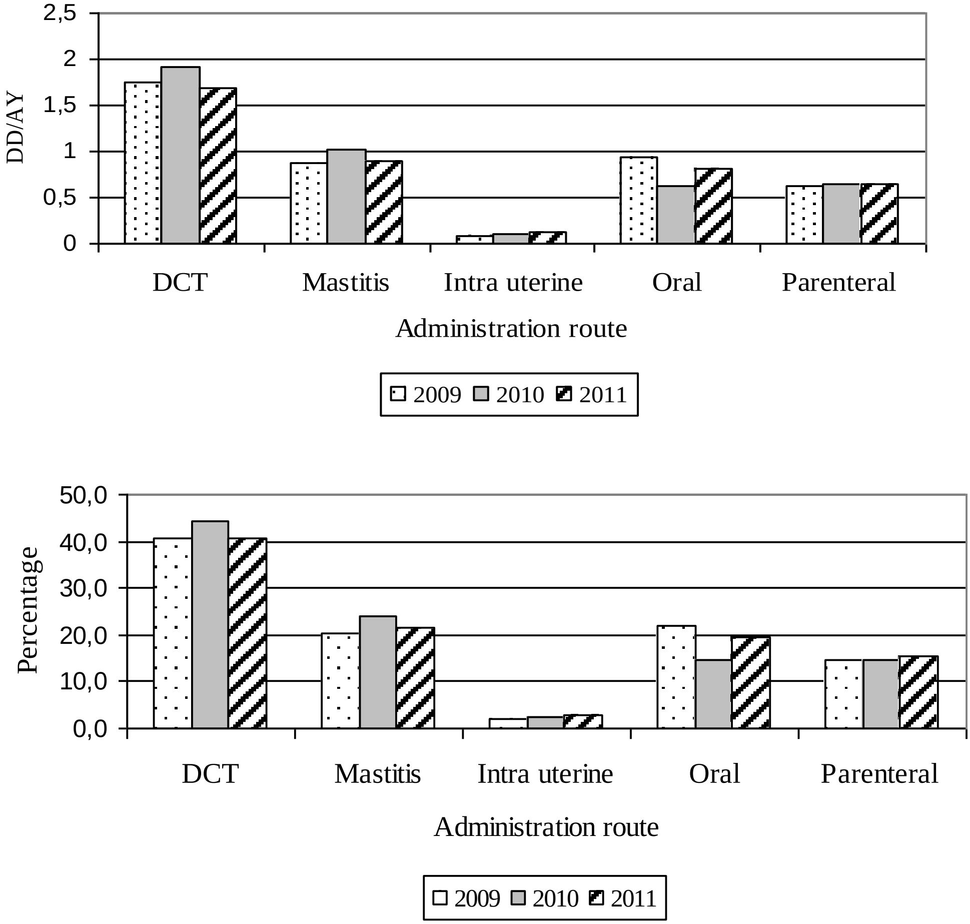


Figure 2. Distribution of the routes of administration expressed as Defined Daily Dose per animal year (DDDA/Y) (upper figure) and as percentage of the total use (lower figure) for the years 2009, 2010 and 2011 calculated for 400 herds. (DCT= dry cow treatment)

How was the Antibiotic Reduction Realized?

Creating Awareness

The first step in reducing the use of antibiotics was creating awareness in both farmers and veterinarians on the prudent use of antibiotics. Since 2010 the University Farm Animal Practice invested a lot of energy into informing and training farmers about the prudent use of antibiotics. Written information was provided, and meetings and study clubs were organized. Farmers and vets expressed anxiety that a reduction of antibiotics would negatively affect animal health and animal welfare. They were afraid that delayed or non-treatment would lead to deteriorating consequences for animal productivity and the economic performance of their farms. It was explained that diseased animals should always be treated as deserved, but treatment should be done in a responsible way!

Optimisation of Management

The second step in reducing antibiotic use was the optimisation of management, housing and nutrition. Keeping cows healthy is the best way to reduce antibiotic use, because healthy cows don't need to be treated. Keeping cows healthy requires a daily challenge of finding the right balance between immune status of the cow and infection pressure from the environment. Incidence of infectious diseases at the farm level can be minimized through strict biosecurity measures and eradication of infectious diseases such as Bovine Viral Diarrhea (BVD). Spending a lot of antibiotics to treat cases of clinical mastitis without knowing the BVD status of the herd is a waste of antibiotics. BVD is a disease that lowers the immune status of the dairy cow in a substantial way and therefore a BVD free herd is the first step to a healthier herd.

Avoiding Misuse and Overuse of Antibiotics

In the first years, the biggest steps towards reduction were made by verifying the current treatment rules on each farm. It seemed that many farms had developed treatment procedures that were not in accordance with the label use and proper treatment rules. Therefore, written treatment protocols were provided and explained. Protocols that described the choice of antibiotic treatment, dose, dose interval and withdrawal time were developed for all diseases of dairy cows. At the beginning of 2010 most farmers did not know about the existence of different classes of antibiotics and had no idea which antibiotics belonged to the critically important antibiotics (CIA), such as 3rd or 4^{rth} generation cephalosporins or fluoro-quinolons. After all the oral and written information sessions, use of these antibiotic groups was reduced by 46% in less than two years!

Therapeutic or Prophylactic Use?

Antimicrobial drugs are used on dairy farms as therapeutics and prophylactics. Therapeutic usage is intended to treat bacterial infections associated with diseases such a pneumonia, metritis and mastitis (Schwarz et al., 2012). The use of prophylactic antibiotics is for treating healthy animals to prevent a disease during periods of increased susceptibility. Antibiotics may also be used for therapeutic and preventive use, such as in dry cow treatment. In 2012 a ban on the preventive use of antimicrobials in Dutch livestock was implemented.

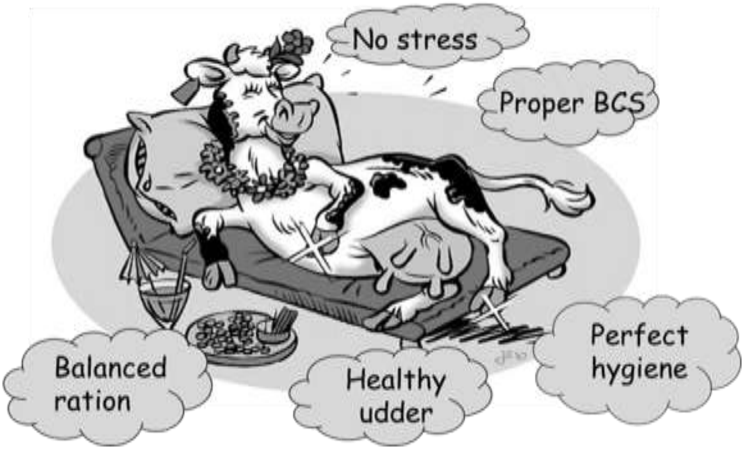
Forced to Selective Dry Cow Treatment

The ban on preventive antibiotic use meant that one significant antimicrobial dry cow treatment, prevention of new infections in the dry period, was not allowed anymore. Labels of dry cow tubes were adjusted and the claim of prevention of new intra-mammary infections during the dry period was omitted. As a result, Dutch dairy farmers were forced to use Selective Dry Cow Treatment (SDCT) rather than Blanket Dry Cow Treatment (BDCT). In January 2014, the Royal Dutch Veterinary Association provided a guideline, ‘The use of antimicrobials at dry-off in dairy cattle’, to support veterinarians in advising dairy farmers in the practice of SDCT (KNMvD, 2014).

The somatic cell count (SCC) thresholds to select cows for SDCT were based on a simulation study by Scherpenzeel et al. (2106) and were assumed to result in an optimal tradeoff between reduced antimicrobial usage associated with udder health versus increased risk of new intra-mammary infection (IMI). It was decided that multiparous cow with a cow SCC > 50,000 cell/ml and first calf heifers with a SCC > 150,000 cells/ml were allowed to dry off with antimicrobials. The interval between last milk recording and drying off should not be longer than 6 weeks.

Legitimate concerns have been raised by farmers and veterinarians about the potential increase in both clinical and subclinical mastitis associated with SDCT and its consequential impact on animal welfare and production. Efficacy of dry DCT was not an issue because protection of BDCT against new IMI in the dry period is in general better than SDCT (Halasa et al., 2009). The challenge was to improve dry cow and transition management in order to minimize the risk of new IMI during the dry period. It was explained to producers that the protection of a dry cow tube should be replaced by improved management. To appeal to the imagination of producers we provided the following cartoon and explained to them that they should treat their dry cows like a princess.

"Treat your dry cow as a Princess"



▪ Situation in the Netherlands in 2017

Figure 3 shows the usage of antimicrobials by Dutch dairy herds over the last 6 years. After an initial decrease of 35% from 2009 – 2012, total usage of antimicrobials decreased from 2.9 DDDA/Y in 2012 to 2.09 DDDA/Y in 2017, which was a another decrease of 28%. Decrease in total antimicrobial use resulted from a decrease in intra-mammary antimicrobials for mastitis and by a decrease in intra-mammary antimicrobials for DCT.

Table 1 provides an overview of the antibiotic reduction during the last six years in the Netherlands. Decreased use of antimicrobial DCT started in 2013 and continued in 2014. A kind of steady state was reached by 2016 and 2017. From 2012 through 2017, usage of antimicrobials for DCT decreased by 50%. Usage of antimicrobials for mastitis also showed a decrease of 40% from 2012 until 2017. Use of antimicrobials for intra-mammary treatment decreased from 69% to 65% in 2017 and antimicrobials for DCT accounted for only 44% of the total use of intra-mammary antimicrobials.

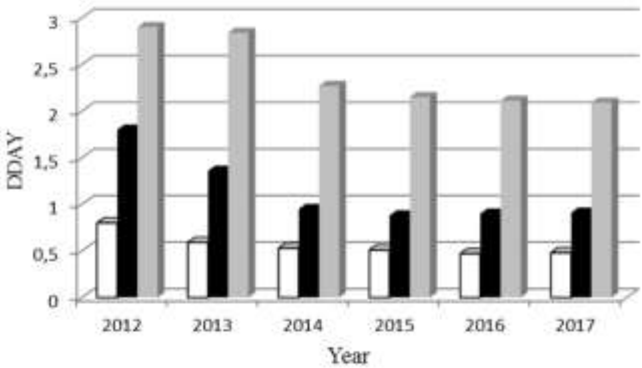


Figure 3. Dutch average of total use of antimicrobials (grey bars), intra-mammary dry cow tubes (black bars) and intra-mammary mastitis tubes (white bars) in defined daily dose per animal year (DDDA/Y) (n = approximately 18,000 dairy herds).

Table 1. Total use of antimicrobials and the intra-mammary (IMM) use of antimicrobials as Defined Daily Dose Animal Year (DDDA/Y) from 2012 through 2017 in all Dutch dairy herds (n = approximately 18,000 herds).

	Year					
Variable	2012	2013	2014	2015	2016	2017
Total use of AB (DDDA/Y)	2.90	2.84	2.27	2.15	2.11	2.09
IMM AB Mastitis (DDDA/Y)	0.8	0.59	0.53	0.51	0.47	0.48
IMM AB DCT (DDDA/Y)	1.8	1.36	0.95	0.88	0.90	0.91
IMM (mastitis + DCT) % of total	69%	70%	64%	63%	66%	65%
IMM DCT % of total IMM use	62%	48%	42%	41%	43%	44%

▪ Conclusion

Reduction in antibiotics was achieved in a relatively short period of time. This successful Dutch approach was enabled by several factors at the right time. The target that had been set by the government, a reduction of 50% in 4 years, helped to focus the initiative. The private sector, including the dairy industry, was motivated which forced farmers and vets to move quickly in the right direction.

The Dutch approach shows that reduction of antibiotics is possible without negative effects on animal welfare, but this requires improvement in management, nutrition and housing.

The forced transition from mainly BDCT to SDCT in the Netherlands resulted in a reduction in the number of intra-mammary antimicrobials used in dairy herds without having a deleterious effect on udder health during the dry period. Those big steps would probably not have been made if SDCT was promoted in a voluntary way. Awareness of the importance of improved management, nutrition and hygiene during transition to the dry period was critical. These management adaptations are not only beneficial for udder health but also improve total performance of the fresh cow, including reproductive performance, claw health, metabolic performance and milk production. Overall, the input of extra labor to improve management is paid back by lower antibiotic costs and better herd performance.

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