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Reduction of antibiotic use in animals "let's go Dutch"

Dik Mevius · Dick Heederik

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1 Background

Use of antibiotics for animals in the Netherlands has reduced considerably over the last 5 years. This reduction is the result of a change in policy towards the use of antibiotics in veterinary practice and is characterized by a series of coherent political decisions which changed the playing field for farmers and veterinarians considerably. In the years before the reducing trend in use of antibiotics started off, the Netherlands was a relative high consumer of antibiotics in veterinary practice. The trends in antibiotic use will be explored in this paper, in particular focussing on the reducing trends in recent years, and the measures which led to the strong reducing trend which can be observed over a period of more than 3 years now.

The authors are the former and present chair of the expert panel of the Netherlands Veterinary Medicine Authority (SDa). The opinions expressed in this manuscript are their personal opinions and not of the SDa.

D. Mevius (✉)
Department of Bacteriology and TSEs, Central Veterinary Institute of Wageningen UR, Lelystad, The Netherlands
e-mail: dik.mevius@wur.nl

D. Mevius
Department of Infectious Diseases and Immunology, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands

D. Heederik
Department Veterinary Public Health, Faculty of Veterinary Medicine, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands

2 The years of high use of antibiotics in livestock production

Antibiotic use in animals in the Netherlands is measured as sales data since 1999 by the Association of Veterinary Pharmacy in the Netherlands (FIDIN) (Anonymous 2013). The sales data are considered to provide a good estimate of the use of antibiotics in animals licenced for therapy on prescription by veterinarians. However, specification by animal species is not possible, since many products are licensed to be used in multiple animal species. Sales of antibiotics increased from approximately 300 tons in 1999 till almost 600 tons in 2007 (Fig. 1). In that period the use of antimicrobial growth promoters in the Netherlands was phased out and reduced from a use of 250 tons in 1999 to zero tons in 2006, the result of the ban of these substances by the European Commission. Because the number of Dutch livestock animals produced remained stable, it can be concluded that the antimicrobial growth promoters were fully replaced by increased therapeutic use by veterinarians (Anonymous 2013). Animal treatments outside the livestock industry only contributed marginally to the overall sales data.

Apparently, systematic use of cheap antibiotics was considered more cost effective for intensive animal production, than implementing stringent health and infection control programs. Moreover, the control on prudent antibiotic use was insufficient until 2008.

Based on these sales data, the European Surveillance of Antibiotic Use working group (ESVAC) of the European Medicine Agency in London reported in 2012 that in the Netherlands most antibiotics were used per kg live weight produced (Grave et al. 2012).

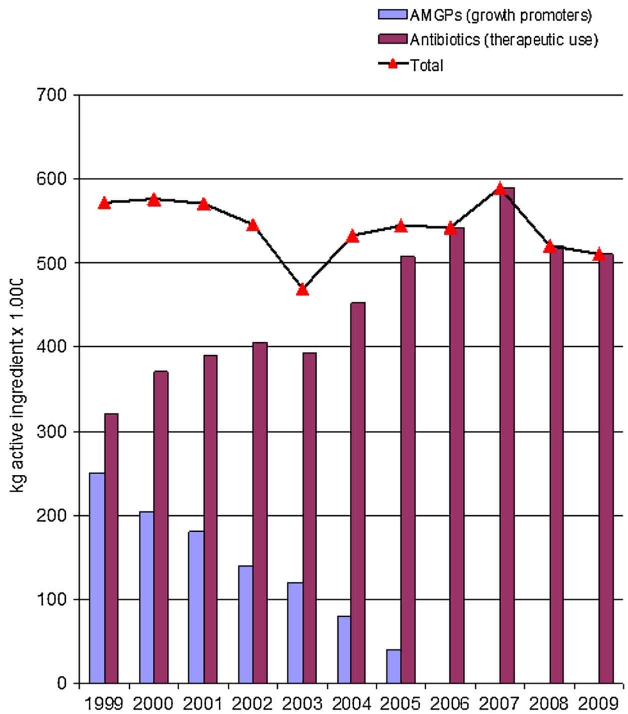

Fig. 1 Sales of antimicrobials for therapeutic use on prescription in animals (*purple bars*) and sales of antimicrobial growth promoters from 1999 to 2009 in the Netherlands (*Source*: FIDIN) (color figure online)

3 Prudent use of antibiotics in human medicine in the Netherlands

In contrast, in Dutch human medicine, use of antibiotics can be considered as essentially prudented. In patients in the Netherlands, antibiotic use is among the lowest of Europe (Elseviers et al. 2007; Vander Stichele et al. 2006). As a result microbial resistance levels in health care are low, as illustrated by the low level of Methicillin Resistant *Staphylococcus aureus* (MRSA) infections. These occur only incidentally in invasive infections in hospitals (EARSNET-2013[1]). Also the occurrence of cefotaxime resistant isolates suspected to produce Extended Spectrum Beta-Lactamases (ESBLs) in infections in hospitals, is lower than in most other European countries (EARSNET-2013). This enormous contrast in antibiotic use in veterinary and human medicine practice feeds the negative perception of medical doctors, authorities and the public about live-stock production in the Netherlands. Moreover, the consequence is also that any potential contribution of resistant organisms from animals to human infections in health care is more visible in routine statistics and has a higher potential contribution to disease load than in countries with high usage in human health care and with endemic occurrence of multi-drug resistant organisms in hospitals.

A result of the high use of antibiotics in animals, is that resistance levels are high in food-producing animals as reported in the annual reports of the Dutch Monitoring of Antibiotics use and Resistance in Animals program (Anonymous 2013). Resistance levels are most optimally measured in the intestinal flora of healthy animals (Anonymous 2008). Commensal *E. coli* isolated according to EFSA protocols is used as indicator organism of the Gram-negative intestinal flora. Multi-drug resistance levels in *E. coli* are high and increased up to 2009 in isolates from broilers, pigs, and veal calves and to a lesser extend in those from dairy cattle (Anonymous 2008). This indicates that the gastro-intestinal tract of food-animals is a (potential) reservoir of multi-drug resistant organisms.

4 Events leading to increased attention for high veterinary use of antimicrobials

Livestock MRSA (ST398) was first detected in a Dutch pig farm in 2005 (Voss et al. 2005). Surveillance targeted at MRSA prevalence showed that most pig and veal calf farms are positive for MRSA, and that this organism can also be found in companion animals, horses, poultry and meat products.[2] The transmission route of MRSA to humans is direct contact, and farmers and veterinarians are considered to be at risk to be MRSA carriers (Dorado-Garcia et al. 2013; Gilbert et al. 2012; Graveland et al. 2011). Patients at risk to carry MRSA are nursed and treated in isolation in hospitals to prevent spread of MRSA (Voss 2004; Wassenberg et al. 2010). The frequent occurrence of MRSA ST398 has resulted in human infections, although MRSA ST398 is generally not considered a highly pathogenic micro-organism, but in particular had a major effect on increased costs in health care, which has increased the level of concern of health care authorities regarding Dutch livestock

[1] European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2012. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2013. http://www.ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/map_reports.aspx.

[2] Analysis of the baseline survey on the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in holdings with breeding pigs, in the EU, 2008, Part A: MRSA prevalence estimates; on request from the European Commission. EFSA Journal 2009; 7(11):1376 [82 pp.]. doi:10.2903/j.efsa.2009.1376. Available online: www.efsa.europa.eu.

production. The emergence of MRSA was paralleled by occurrence of ESBL-producing organisms in livestock production. Since 2002 the occurrence of ESBL-producing organisms has been observed in broilers (Dierikx et al. 2010). Both in *E. coli* and in *Salmonella* a rapid increase was observed of ESBL-producers in these animals. A prevalence study showed that all broiler farms were positive and virtually all animals shed ESBL-producing *E. coli* in their faeces (Dierikx et al. 2013). As a result almost all broiler meat products were positive for ESBL-producing organisms (Cohen Stuart et al. 2012; Overdevest et al. 2011). A large study conducted with the University Medical Centre of Utrecht (UMCU) and the Dutch Institute for Public Health and the Environment (RIVM) showed that one in five human clinical ESBL-producing isolates harboured genes and plasmids that seemed indistinguishable from poultry genes and plasmids (Leverstein-van Hall et al. 2011). Poultry meat was considered a potentially likely route of transmission to humans. Data from poultry sources and from subsequent screening in other food-animals, dogs and wild birds demonstrating high prevalences further raised concerns about the possible attribution of ESBLs from animal related sources to infections in humans.

5 Reducing the use of antimicrobials in veterinary practice

The concerns about public health consequences of antibiotic usage and resistant organisms in animals to human health have resulted in drastic changes in the policy of the Dutch authorities. In 2008 already the Dutch minister of Agriculture, Nature and Food Quality, installed a task force on Antimicrobial Resistance in Food Animals and demanded the combined stakeholders involved in animal production and the Dutch Royal Veterinary Association (KNMvD) to sign memoranda of understanding in which measures to reduce antibiotic use and antimicrobial resistance are described. After a debate in parliament about ESBLs in poultry, mandatory reduction targets in antibiotic usage in animals in the Netherlands were defined as 20 % reduction in 2011 and 50 % in 2013. In 2012 this target was renewed to 70 % reduction for total livestock production. As reference year 2009 was defined. Different initiatives were taken resulting in a measurable reduction in the use of antibiotics:

- An essential element in the approach of the task force was to make antibiotic use on all farms transparent. Since 2012 it is mandatory to register all antibiotics supplied by veterinarians. This was already partially implemented by the private stakeholders in animal production in 2011 in veal calves, broilers and pigs as part of their quality systems. In particular by means of the quality systems acting at the sector level, they were able to implement these policies swiftly and effectively. In 2012 cattle followed. Usage on farms is expressed as animal daily dosages per year (add/y) (Bos et al. 2013), which resembles the Danish system of reporting.[3] In this way farms and vets can be benchmarked and compared with each other and with independently defined targets (benchmarking). An essential part of this process was to install an independent institute to control the use data, report the data publically and to define targets for use. In spring 2011 the Netherlands Veterinary Medicines Authority (SDa: www.autoriteitdiergeneesmiddelen.nl) was installed for this purpose and the first targets for use in different animal production sectors were published in July 2011.
- Because of the concerns about MRSA and ESBLs in food-animals, the Dutch Heath Council was asked to advice the Ministers of Public health Welfare and Sports and the Minister of Economic Affairs about antibiotic usage in animals. The advice included a full ban in usage of any new antibacterial drug in animals and a restriction of the use of 3rd and 4th generation cephalosporins in animals. Moreover, it was advised to restrict the use of colistin, all beta-lactams, aminoglycosides and fluoroquinolones in food-animals. Since this advice lacked detail, the Antibiotics Policy Working Group (WVAB) of the KNMvD, wrote a guideline in which drugs were classified as first, second and third choice drugs for inclusion in treatment plans on farms (http://wvab.knmvd.nl/wvab). Moreover, the animal drug law was changed in 2013, ruling that only first choice drugs are allowed to be present on farms for empiric treatment of infections based on a mandatory treatment plan for each farm. This treatment plan has to be custom made by the veterinarian for each farm, based on treatment guidelines of the KNMvD (formularia: http://wvab.knmvd.nl/wvab/formularia/formularia).

[3] DANMAP 2012. Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. ISSN 1600–2032.

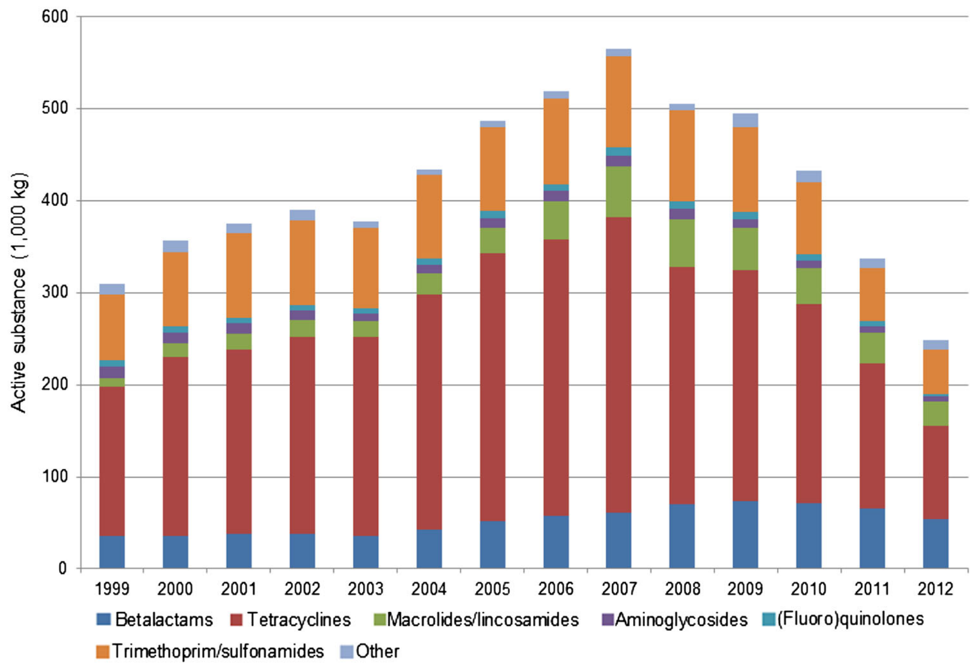

Fig. 2 Sales figures for antibiotics licensed for therapeutic use in animals (kg × 1,000) in the Netherlands from 1999 up to and including 2012. Usage of antibiotics in livestock in the Netherlands in 2012. June 2013. Netherlands Veterinary Medicines Authority (SDa). http://www.autoriteitdiergeneesmiddelen.nl/english

- In 2013 the SDa has defined quantitative reduction targets for antibiotic use for each food-animal species (in add/y) including zero add/y as quantitative target for fluoroquinolones and 3rd, and 4th generation cephalosporins. The latter two drugs are only allowed after it has been proven that no alternative treatment options are available. This is also regulated in 2013 by the change in the animal drug law. In the meantime, most animal production sectors have voluntarily decided to stop usage of these third choice drugs in animals on a voluntary basis.

As a result of all these measures taken, sales of antibiotics have decreased in 5 years by 56 % since 2007 and the target of 50 % reduction in 2013 is already reached in 2012 (Fig. 2). Moreover, clear indications exist that the occurrence of antimicrobial resistance in animal bacteria and the load of ESBLs in animals is decreasing (Anonymous 2013). This is a very important result of the governmental targets, the measures initiated by the private parties involved in animal production and the SDa, which can be considered to be critical success factors for the Netherlands.

However, to solve the current and future threats of multi-drug resistant organisms in (food)-animals to human health, a substantial further reduction may be warranted and on the longer term a change in animal production practices cannot be excluded. In 2014 next to livestock farms, veterinarians will also be benchmarked. A system has been developed which describes the use of antimicrobials on the population of farms for which a veterinarian is responsible. To facilitate this approach, regulations were put in place which resulted in unique one on one relations between veterinarians and livestock farmers. Further refinements in the benchmarking system are to be expected.

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