ORIGINAL ARTICLE

Reduction of Veterinary Antimicrobial Use in the Netherlands. The Dutch Success Model

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Impacts

- Veterinary overuse of antimicrobials contributes to the selection and spread of antimicrobial resistance which poses a public health risk.
- A series of events and discoveries of significant reservoirs of antimicrobial resistant pathogens in the Netherlands resulted in a successful collaboration between government and stakeholders to reduce antimicrobial use in farm animals.
- Total use of antimicrobials in farm animals in the Netherlands decreased with 56% in the period 2007–2012.

Keywords:
Antimicrobial resistance; veterinary antimicrobial use; public health; livestock; preventive medicine

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Received for publication May 19, 2014

doi: 10.1111/zph.12167

Summary

Use of antimicrobials in animals poses a potential risk for public health as it contributes to the selection and spread of antimicrobial resistance. Although knowledge of the negative consequences of extensive antimicrobial use in humans and animals accumulated over the decades, total therapeutic antimicrobial use in farm animals in the Netherlands doubled between 1990 and 2007. A series of facts and events formed a window of opportunity to reduce antimicrobial use in farm animals. The recent discovery of significant reservoirs of antimicrobial-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and extended spectrum beta-lactamase-producing bacteria (ESBL) in farm animals, with potential public health implications, combined with an increasing lack of confidence of the public in intensive livestock industries, and discrepancy between the very low antimicrobial use in humans and high use in animals, resulted in intensive collaboration between the government, veterinary professional organizations and important stakeholders within the livestock sector. A combination of compulsory and voluntary actions with clear reduction goals resulted in a 56% reduction in antimicrobial use in farm animals in the Netherlands between 2007 and 2012 and aims at accomplishing a 70% reduction target in 2015. This article describes and analyses the processes and actions behind this transition from an abundant antimicrobial use in farm animals towards a more prudent application of antimicrobials in farm animals in the Netherlands.

Introduction

The introduction of antimicrobials in the second half of the 20th century has been of major importance in human and veterinary medicine. In addition to therapeutic and preventive use, they were also applied as antimicrobial growth promotors (AGP) to increase the efficiency of animal production (van den Bogaard and Stobberingh, 1999; McEwen and Fedorka-Cray, 2002; McEwen, 2006). Although debate exists about the quantitative attribution of antimicrobial use in food animals to antimicrobial resistance in human pathogens, there are strong indications that there is animal–human transmission of antimicrobial resistance which justifies the application of the precautionary

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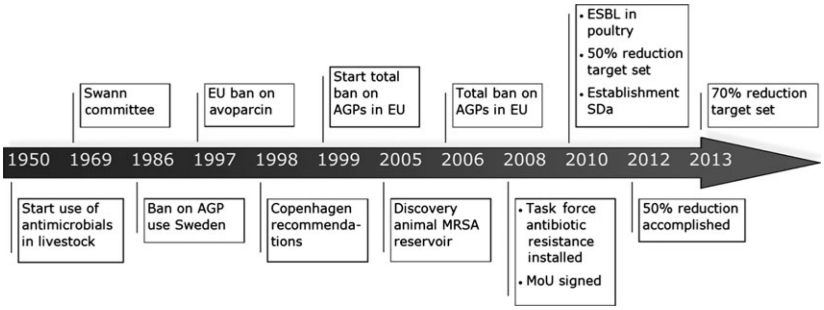

Fig. 1. Timeline of events resulting in a successful reduction of antimicrobial use in farm animals in the Netherlands.

principle to reduce veterinary antimicrobial use (Swann et al., 1969; European Commission, 1999, 2000; Bager et al., 2000; Smith et al., 2005; Aarestrup et al., 2008). In the Netherlands, sales of veterinary antimicrobials doubled between 1990 and 2007 (MARAN, 2002, 2009). Recently, however, a combination of compulsory and voluntary actions with clear reduction goals resulted in a 56% reduction in antimicrobial use in farm animals in the Netherlands between 2007 and 2012. The aim of this article was to describe and discuss this rapid process of transition.

Historical Developments of Veterinary Antimicrobial Use

Europe

Veterinary antimicrobial use increased from the 1950s onwards in the fast-developing modern livestock production systems (Fig. 1) (Manten, 1963; EMEA, 1999). The Swann Committee in 1969 was the first international body to raise serious concerns about extensive veterinary antimicrobial use and related risks for human health care. Nevertheless, despite increasing knowledge about the potential impact of veterinary antimicrobial use on public health, veterinary antimicrobial use still increased during the following decades (Endtz et al., 1991; van den Bogaard et al., 1994; EMEA, 1999). It took until 1986 when, as precautionary measure, Sweden banned all AGP use in animals (Wierup, 2001).

In the nineties of the last century, individual European countries (Denmark, Germany) decided to ban the use of avoparcin as AGP in livestock in response to the finding of vancomycin-resistant enterococci (VRE) in avoparcin-fed pigs and poultry, followed by a ban in the complete European Union (EU) in 1997. The recommendations of the World Health Organization (WHO) in 1997 and the Copenhagen recommendations in 1998 regarding the use of non-therapeutic antimicrobials in animals further accelerated EU policymaking, which resulted in the withdrawal of specific AGPs in 1999 and a complete ban on all AGP use in animals by 2006 (WHO, 1997; Mevius et al., 1999; Barton, 2000; Aarestrup, 2005; Cogliani et al., 2011).

The Netherlands

Notwithstanding these interventions, in the Netherlands, the total sales of antimicrobials for therapeutic veterinary use increased from an estimated 275 tons in 1990 to almost 600 tons in 2007 (MARAN, 2002, 2009). In 2007, the Netherlands was ranked as the highest veterinary antimicrobial consumer out of 10 EU countries from which data were available (Grave et al., 2010). Parallel to the increase in use, the Dutch monitoring programme in production animals, MARAN (Monitoring of Antimicrobial Resistance and Antimicrobial Use in Animals in the Netherlands), reported that commensal *E. coli* isolates from the gastrointestinal tract of most farm animals showed increasing antimicrobial resistance levels between 1998 and 2009 (MARAN, 2009).

In 2005, livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) was reported to be widely spread in the Dutch pig population with occupational transmission to humans (farmers, veterinarians). This had a high impact on Dutch hospitals that had controlled MRSA very successfully by restricted antimicrobial use and strict infection control measures and was followed by societal and political pressure to reduce veterinary antimicrobial use (Voss et al., 2005). Discussions on the future of antimicrobial use in animals between government and stakeholders of the livestock industry resulted in 2008 in the set-up of the Taskforce Antibiotic Resistance in Animal Husbandry. This taskforce comprised representatives from all parties within the animal production chain (advocacy organizations of farmers, meat processing industries, feed suppliers), the Royal Dutch Veterinary Association (KNMvD), the Ministry of Agriculture[1] and the Ministry of Health). This Taskforce developed action plans per animal production sector (cattle, veal calves, poultry and pigs) as part of a

[1] Agriculture was till 2010 part of the Ministry of Agriculture, Nature and Food Quality. From 2010 to 2012, it was part of the Ministry of Economic Affairs, Agriculture and Innovation. It is currently in the Ministry of Economic Affairs. Throughout this manuscript, we use consequently 'Ministry of Agriculture'.

Memorandum of Understanding (MoU), with the aim to control antimicrobial resistance in livestock. This MoU was signed in 2008 by mentioned stakeholders involved in animal production and supported by the government (Anonymous, 2008). The action plans aimed at detailed monitoring of antimicrobial use at herd level, the monitoring of antimicrobial resistance, a clear separation of responsibilities for veterinarians and farmers in antibiotic prescriptions and the introduction of Farm Treatment Plans and Farm Health Plans. However, no strict targets or regulations for antimicrobial use were formulated yet. Although the MoU was the basis for further discussions, it did not have a direct effect on the total veterinary antimicrobial use in the following year (MARAN, 2009).

The discovery of ubiquitous presence of extended spectrum beta-lactamase-producing bacteria (ESBLs) on Dutch poultry meat in 2009 and a possible relationship with a human casualty was greatly disseminated in the media in 2010 and led to serious public concerns (Leverstein-van Hall et al., 2011). This further prioritized the issue of extensive veterinary antimicrobial use on the political agenda. A debate in parliament followed where the public health concerns of extensive use of antimicrobials in farm animals were discussed. Subsequently, the government introduced a compulsory 50% reduction target in antimicrobial use in farm animals in 2013 compared to 2009 (Anonymous, 2010).

Veterinary Medicines Authority

In response to the need for an independent body to monitor antimicrobial usage at herd level, in 2010, the independent Netherlands Veterinary Medicines Authority (SDa) was established as a public–private partnership between the government, the KNMvD and livestock industries. The task of the SDa is (i) to collect and report reliable antimicrobial usage and prescription data from all individual farms and veterinarians and (ii) to set annual targets for antimicrobial use in the different major livestock sectors, including species-specific (and categories within species) benchmark indicators that differentiate between moderate, high and very high users (farmers) and prescribers (veterinarians). High users and high prescribers can be subjected to disciplinary sanctions by the private IKB systems (integrated chain control; quality assurance systems) and the KNMvD, respectively. They can also be subjected to additional controls of the Dutch Food and Consumer Product Safety Authority (NVWA) of the Dutch Government (SDa, 2013).

Restricting the Specific Use of Antimicrobials

In August 2011, the Dutch Health Council (HC), an independent scientific advisory body for the government and parliament, presented on request of the Ministers of Health and Agriculture scientifically based recommendations to prevent further development and spread of antimicrobial-resistant bacteria in animal production (Anonymous, 2011a). Most of these recommendations showed similarities with the advice of the European Food Safety Authority (EFSA) Panel on Biological Hazards also published in 2011 (EFSA, 2011). Particularly, the development and spread of ESBLs were targeted as this was considered as the major resistance problem. There were indications that the use of 3rd and 4th generation cephalosporins in group treatments (e.g. extensive systematic and illegal use in hatcheries) had promoted the occurrence of ESBLs. There are no data about the amount of antimicrobials used in hatcheries. Among the recommendations of the HC were the exclusive use of newly developed antimicrobials for humans, an immediate ban on preventive and systematic therapeutic group treatments of animals with the as critically important considered 3rd and 4th generation cephalosporins and fluoroquinolones (Collignon et al., 2009), a future ban on the use of colistin and the phasing out of all preventive and systematic veterinary use of β-lactam antibiotics and aminoglycosides in animals. The different existing private IKB systems translated these recommendations into specific regulations that radically restricted the use of 3rd and 4th generation cephalosporins and fluoroquinolones in farm animals. The Veterinary Antimicrobial Policy Working Group (WVAB) of the KNMvD subsequently reclassified veterinary antimicrobials into first, second and third choice for use in the existing veterinary treatment guidelines (formularies) and veterinary practice, based on the recommendations of the HC. The government took the responsibility for enforcement of these private regulations and made proposals to incorporate these private regulations into legislation. Further on, the government banned the preventive use of all antimicrobials in animals (Anonymous, 2011b).

New Obligations for Farmers

The private IKB systems introduced in 2009 the prerequisite for farmers to only procure veterinary services and veterinary medicines from one veterinary practice (1-in-1 relationship) to reduce competition between veterinary practices and to ensure a proper knowledge of the farm of the prescribing veterinarian. This measure was already proposed in the MoU in 2008 and was in 2012 imposed for all farmers by the Product Boards for Livestock, Meat and Eggs (PVE; public–private organization with legislative powers for the whole livestock sector) (Beemer et al., 2011). The PVE in 2011 decreed – as mentioned in the MoU – the introduction of the Farm Health Plan (FHP) and Farm Treatment Plan (FTP) and central registration of all prescribed and delivered antimicrobials on farms. These measures were subsequently incorporated in the existing private IKB systems for different livestock sectors. The FHP and FTP must be developed in collaboration between the farmer and the farm veterinarian and evaluated annually. The FHP should contain information about farm-specific risk factors for the introduction and spread of infectious diseases and the specific management measures as proposed by the farmer to control these risk factors and improve the health status of the animals. The FTP is a farm-specific treatment protocol for the most common (infectious) diseases on that farm that can be empirically treated by the farmer. This FTP should be in accordance with the formularies developed by the KNMvD and other relevant farm-specific information like susceptibility patterns of cultured pathogens and historical treatment results. In principle, only first-choice (non-critically important) antimicrobials from the WVAB formularies are allowed in this FTP.

Effects of Measures

The SDa reported a decrease in the use of antimicrobials in pigs, veal calves, dairy and poultry, expressed as defined doses per animal year (DDD/Y), with a 10–17% reduction among most animal species and farm categories in 2012 compared to 2011. Furthermore, it reported a 56% reduction in antimicrobial use in farm animals in the period 2007–2012 (SDa, 2013). In the period 2009–2012, the veterinary sales of the as critically important considered 3rd and 4th generation cephalosporins and (fluoro)quinolones decreased from 92% and 59% to 0.03% and 1.3% of the total sales, respectively (Bondt et al., 2012). Already in 2012, the 50% reduction goal as set for 2013 was almost met (Fig. 2). Abandoning preventive use of antimicrobials, restricting therapy lengths to the SPC (Summary of Product Characteristics), replacement of antimicrobial combinations by single substances and individual or partial herd treatment as replacement for whole herd treatments attributed most to this reduction (personal communication). In 2013, based on the measures that were initiated by private

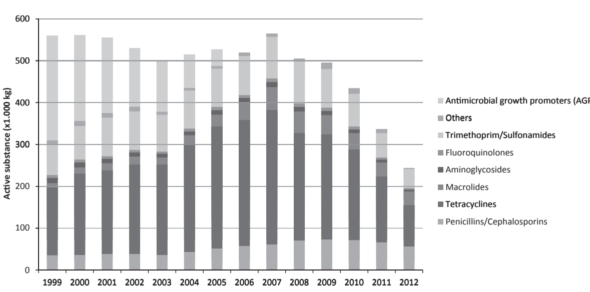

Fig. 2. Sales figures for antibiotics licensed for therapeutic use in animals (kg × 1000) in the Netherlands from 1999 up to and including 2012. (source: FIDIN)

parties involved in animal production, the government set a new goal of 70% reduction in veterinary antimicrobial use in 2015 compared to 2009 (Anonymous, 2012).

Position of Veterinarians

Veterinarians are in a complex playing field. They are supposed to guard public health as an independent professional, which is a moral and legislative obligation. However, they are hired and paid by farmers who have specific interests which are largely economically driven and sometimes conflicting with public health interests (e.g. preventive application of antimicrobials). Therefore, the independent position of veterinarians had to be reinforced to be able to act as an independent professional and a gatekeeper for prudent use of antimicrobials in animals. Initiatives hitherto taken by the veterinary profession and the government are expected to contribute to this aim (Beemer et al., 2011).

In 2011, the KNMvD proposed the development of a quality system for veterinarians. Incorporated in this quality system are the development of treatment guidelines for veterinarians and the introduction of compulsory post-academic education. The KNMvD in 2013 has started the development of these disease-specific guidelines that should support veterinarians in their clinical decision-making. As these guidelines will be incorporated in existing private quality systems, the implementation of these guidelines can be enforced.

In 2014, new legislation (UDD measure, administration by veterinarians only) has been introduced by the government. Under this legislation, the administration of all veterinary antimicrobials should be performed by veterinarians. When farmers meet specific conditions, they are permitted to apply antimicrobials to their animals without physical intervention of a veterinarian. These conditions comprise the 1-in-1 relationship, mandatory periodical herd inspections by the veterinarian and annual evaluation of the FHP and FTP. Under these conditions, farmers are allowed to have first-choice antimicrobials in stock for one treatment of 15% of the susceptible animals (Staatscourant, 2013). Until 2016, exemptions have been made for a few second-choice antimicrobials that were regarded essential to treat animals for specific indications and where no first-choice alternatives are available. These antimicrobials may be applied by farmers in advance to identified animals for a period of maximum 14 days under the condition that their veterinarian has made a clinical diagnosis.

Veterinary Pharmacy

Dutch veterinary practices hold their own veterinary pharmacy. This implies that they make a direct profit from the drugs they prescribe to farmers. Similar to other countries, this became a point of concern in the public debate and at governmental level, and questions arose whether the veterinary pharmacy should be separated from veterinary practices (Wegener, 2006). However, the Dutch government concluded, based on an independent advisory report, that decoupling prescription and selling of veterinary drugs as sole measure would not lead to the desired reduction. Instead, the economic motives to prescribe would greatly be eliminated by the proposed benchmarking of antimicrobial prescription and use and introduction of strict 1-to-1 relationships (Anonymous, 2011c; Beemer et al., 2011).

Role of the Public Opinion

Public opinion is known to be very influential in political agenda setting, which might result in policy decisions (Freimuth et al., 2000; Baumgartner et al., 2007). Experiences in Sweden, Denmark and Germany showed that consumer concerns initiated restrictions in antimicrobial use (Bager et al., 2000; Hayes et al., 2002; Ungemach et al., 2006). Also the Dutch experience clearly showed that not much changed in veterinary antimicrobial use until societal concerns put this issue prominent on the political agenda. The discovery of a reservoir of MRSA in the livestock sector in a country with a very low MRSA incidence in hospitals worried medical professionals (van Rijen et al., 2008). Dramatic stories about how MRSA affected the lives of individual people fed the public's fear for these new 'superbugs', and the potential threat for public health was quickly disseminated by the media (Freimuth et al., 2000). There clearly was an important role for mass media in altering public opinion, but also the current interest of the general public in disease germs and increased anxiety for infectious disease pandemics might have contributed (Tomes, 2000).

Another possible influential factor was the increase of socioethical concerns about the contemporary large-scale livestock industry which is perceived to be associated with impaired animal welfare, misuse of antimicrobials, risks of animal for human transmission of pathogens and environmental pollution (Croney et al., 2012). From 2007 onwards, the Netherlands faced the largest Q-fever outbreak ever seen which affected thousands of people (Schimmer et al., 2008). This showed the public the possible serious adverse effects of large-scale livestock production systems. The message of excessive veterinary antimicrobial use with potential adverse public health consequences increased the opposition towards extensive antimicrobial use in food animals. Also farmers and their family members themselves became critical about antimicrobial overuse in animals. They were confronted with the potential personal health risks of antimicrobial use in their animals as they were subjected to strict isolation measures at hospital admission to prevent possible MRSA transmission within hospitals (van Rijen et al., 2008).

Window of Opportunity

A window of opportunity can be an important driver for policy changes and exists when several conditions are present: (i) clearly measurable indicators describing the problem, (ii) a 'focusing event' that draws attention to the problem, (iii) policy entrepreneurs drawing attention to the problem and iv) the existence of practical policy alternatives to replace a certain policy (Bovens et al., 2007).

Regarding veterinary antimicrobial overuse, all the aforementioned events led to a situation in which extensive veterinary antimicrobial use and resistance became a common concern of the public, government and the private sectors, and herewith, a window of opportunity was created in which a substantial part of the stakeholders became motivated to jointly resolve this problem (Table 1).

Role of the Government

There was no reduction of total veterinary antimicrobial use after the ban on growth promoters. The MoU also did not result in a significant reduction in the first year after signing in 2008. The introduction of strict usage targets by the Dutch government was clearly required to enforce further measures in the production sectors, with a further reduction as a result. Also in Denmark, strict governmental regulations were effective in reducing veterinary antimicrobial use (Cleveland-Nielsen et al., 2007; Danish Veterinary and Food Administration, 2010). This indicates that simply banning AGPs or developing general agreements without strict flanking targets is insufficient to reduce antimicrobial

Table 1. Window of opportunity of the Dutch situation

Condition	Example
Measurable indicators describing problem	Increasing level of antimicrobial resistance in indicator bacteria and quantifiable high veterinary use of antimicrobials
Focusing event	Discovery of animal-human transmission of antimicrobial resistant bacteria and high prevalence of resistant bacteria on animal derived products (i.e. MRSA and ESBL)
Policy entrepreneurs	Medical doctors raising public concern, thereby assisted by several media
Policy alternatives	Possible policy alternatives were a compulsory reduction of veterinary antimicrobial use, decoupling of prescribing and dispensing of antimicrobials by veterinarians and increasing transparency by central registration of antimicrobial prescription

use in food animals. Non-committal intentions might not work in the reduction of veterinary antimicrobial use as other interests of the livestock industry (e.g. economic ones) might eventually be prevailing above interests such as public health.

There is, however, a clear difference between the Danish and the Dutch approach. The Danish measures to reduce veterinary antimicrobial use were mainly established and carried out by the government (Beemer et al., 2011). The Dutch government adopted a more facilitating role in the reduction of veterinary antimicrobial use with the primary responsibility for the reduction of veterinary antimicrobial use with the private parties through self-regulation. The government set reduction targets and further facilitated the co-funding of the SDa, incorporated private regulations into legislation, intensified inspection and enforcement of legislation and supported the strengthening of the independent position of veterinarians through the introduction of the UDD measure.

Reduction and Resistance

The reduction targets as given by the government were not based on any evidence-based dose (antimicrobial use)–effect (antimicrobial resistance) relation. However, faced with increasing public pressure and concerns, decisions need to be taken. Studies on a total ban of certain specific antimicrobials used as AGP (tetracyclines, glycopeptides and macrolides) and for therapeutic purposes (cephalosporins) indicates a relation between antimicrobial use and antimicrobial resistance (van Leeuwen et al., 1979; Aarestrup, 2005; Cleveland-Nielsen et al., 2007; Danish Integrated Antimicrobial Resistance Monitoring, Research Programme, 2012). The effect of an overall reduction of all therapeutically used antimicrobials is unknown and hard to predict based on the complexity of the association between antimicrobial use and resistance due to, for example, co-resistance. Since 2010, in the routine monitoring, an apparent trend is visible, for example, in commensal indicator *E. coli* isolates from broilers, veal calves and slaughter pigs towards a systematic and substantial decrease in resistance levels for a number of antimicrobials. This trend is also visible in *Campylobacter* spp. for the fluoroquinolones (*C. jejuni* from poultry) and macrolides (*C. coli* from pigs) (MARAN, 2013). However, these data should be interpreted with caution. Only long-term monitoring over a period of several years might reveal robust changes in resistance patterns.

Feasibility of Antimicrobial Reduction

Animal welfare and health could negatively be affected by delayed or non-treatment with antimicrobials, although evidence suggests that lower antimicrobial use can be realized without deteriorating consequences for animal health and productivity (Wierup, 2001; Aarestrup et al., 2010; Innovatienetwerk, 2011). Optimal housing and hygiene practices, climate control, and feed and water quality are major prerequisites for the reduction of antimicrobial use in farm animals. Several authors concluded that a reduction in antimicrobial use might probably be accompanied with higher production costs per unit (Wierup, 2001; Cromwell, 2002; Phillips et al., 2004; Jensen, 2006). However, others dispute this adverse economic effect (Graham et al., 2007; van der Fels-Klerx et al., 2011). It should be noted that all analyses have up to now focused on the economic consequences of a ban on AGPs, not on the effects of a drastic reduction in total antimicrobial use. Many veterinarians believe that the high use of antimicrobials in Dutch livestock can largely be explained by the economic benefits of using (cheap) antimicrobials instead of taking (more expensive) measures to prevent infectious diseases (Speksnijder et al., 2014). A rise in production costs would be a challenge in a competitive international market in which the Dutch agro-food sector highly relies on export.

Basically, two major routes can promote prudent use of antimicrobials. The first is to minimize the incidence of infectious diseases at farm level by strict biosecurity measures, eradication of infectious diseases and vaccination (Wierup, 2000; Baker, 2006; McEwen, 2006; European Food Safety Authority, 2008). It is shown that the use of preventive or growth-promoting antimicrobials has the greatest beneficial effect on farms with poor hygiene, suggesting that improvement of overall hygiene might lead to the reduction of antimicrobial use (Wierup, 2000; Jensen, 2006).

The second route is a prudent application of antimicrobial therapy when preventive measures have failed and treatment is indicated. Ideally, antimicrobial selection should be based on proper diagnosis, preferably confirmed by susceptibility testing and pharmacokinetics. Many general recommendations for prudent use have been proposed including the implementation of treatment guidelines to support prescribers in the choice of the right antimicrobial (WHO, 2000; Alliance for the Prudent Use of Antibiotics, 2001; Schwarz et al., 2001; McEwen and Fedorka-Cray, 2002; Ungemach et al., 2006; Wegener, 2006; Federation of Veterinarians of Europe, 2010). Translation of these guidelines into the proposed action, however, is difficult. Many cultural, personal and psychological aspects are involved as shown in the human domain (Butler et al., 1998; Cabana et al., 1999; Grol and Wensing, 2004; Arnold and Straus, 2005; McEwen, 2006; Wegener, 2006; Hulscher et al., 2010).

Both routes to reduce veterinary antimicrobial use demand the adoption of new practices and behavioural changes. Forced behavioural changes have usually no sustainable effect and only last in the presence of enforcement of rules and regulations. This enforcement requires high efforts and human capital of governments and quality systems. A more sustainable approach for behavioural change is the voluntary motivated route in which internal and external motivators (social pressure, provisions and subsidies) are used to induce behavioural changes (Cleveland-Nielsen et al., 2007).

Need for European and Global Action

The livestock sector is internationally oriented and has large economic impact. Unilateral policy measures of one country might introduce a competitive disadvantage for its own livestock sector, promote illegal imports of antimicrobials and at the end of the day sort only moderate effects because antimicrobial-resistant pathogens will simply enter the country from abroad.

An increased global awareness of the possible adverse effects of veterinary antimicrobial use is now visible, especially in the highly industrialized countries and at supra-governmental levels (EU, WHO, FAO, OIE) and by public discussions. These developments might well be used by governments and other interest parties to expand and exploit the evolving window of opportunity to change antimicrobial policy and practices.

Concluding Remarks

The successful Dutch approach was enabled by the presence of several factors at the right time, which created a window of opportunity. The government set a specific target of 50% in 4 years as a clear focus. However, it left the responsibility to accomplish these unambiguous targets with the private sectors. It should be noted that the ‘Dutch approach’ is not a general blueprint for a veterinary antimicrobial reduction policy that is applicable in all circumstances and at all times. National and local contexts (e.g. culture, economy) ask for a specific translation of the universal principles for the containment of antimicrobial resistance into practical applicable measures to combat the global threat of antimicrobial resistance (WHO, 2000).

Acknowledgements

Contents of this article were presented in an international expert meeting, ‘Reducing antimicrobial usage in agriculture and aquaculture: beyond regulatory policy’, held in Utrecht, the Netherlands, 1–3 July 2013. The Workshop was sponsored by the OECD Co-operative Research Programme on Biological Resource Management for Sustainable Agricultural Systems, the Netherlands Organization for Health Research and Development (ZonMW), and the Dutch Ministry of Economic Affairs.

Disclaimer

DJM and JAW are a member and the former 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. The opinions expressed and arguments employed in this publication are the sole responsibility of the authors and do not necessarily reflect those of the OECD or of the governments of its Member countries.

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