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# Evidence-based policy for controlling antimicrobial resistance in the food chain in Denmark

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A B S T R A C T

Emergence of antimicrobial resistance (AMR) in the animal reservoir forms a risk for human health. The use of antimicrobials in animals is the major cause of development of AMR in bacteria in animals. In the 1990s, the use of antimicrobials in animals, particularly as a growth promoter, led to alarming levels of AMR in many countries. This paper analyses the emergence of AMR in Denmark in terms of contributing factors that formed fertile ground from which AMR could develop. New technologies in combination with scientific unknowns led to the unexpected development of cross-resistance and an uncertainty about transmission to and risk for humans. Conflict of interests and varying susceptibility to risk between agriculture, health and commercial stakeholders complicated intervention. In addition, unintended economic incentives from old legislation resulted in a situation where the use of antimicrobials in general was stimulated. Complications of alarming high levels of AMR in animals, and a general discontent about this situation (including with farmers and vets) demanded a solution. National surveillance in DANMAP involving all stakeholders from the farm-to-fork food chain was setup to counteract scientific unknowns and conflicts of interest; new legislation was developed; and unintended economic incentives reduced. The current analysis may help to better understand the AMR problem in general and what may be done to counteract it.



## 1. Introduction

Recent data show that antimicrobial resistance (AMR) in bacteria in animals and food forms an increasing problem for human health (Aarestrup, 2012; DANMAP, 2010; ECDC, 2010; WHO, 2001). In particular, the emergence of multidrug-resistant bacterial strains, and strains resistant against antimicrobials considered critically important in human medicine (WHO, 2011) is of concern (Kumarasamy et al., 2010; Potron, Kalpoe, Poirel, & Nordmann,, 2011). The phenomenon of AMR is not new, and the prolonged use of antimicrobials[1] in general may lead to the occurrence of resistant microorganisms, simply through survival of the fittest.

Through food, direct contact, and via the environment, bacteria and other microorganisms from animals may end up in humans, and vice versa, microorganism from humans may end up in the animal reservoir (Price et al., 2012) (see Fig. 1). Because many bacteria are non-pathogenic commensals (part of the natural flora), or host specific, and do not survive in different hosts, much of this exchange goes unnoticed. However, the exchange of zoonotic microorganisms capable of living both in humans and animals and AMR microorganisms may cause problems, either directly because of the pathogenic nature of the microorganism, or because an opportunistic harmful infection develops during antimicrobial treatment.

In the early 1940s, antimicrobials were first introduced to control bacterial infections in humans. The success in humans led to their introduction in veterinary medicine in the 1950s, being used in food- and companion-animals. Currently, antimicrobials are also used for intensive fish farming, and some are used to control diseases in plants. Antimicrobial use is thus widespread in food production.

In animals antimicrobials are used essentially in three different ways: for therapy of individual cases; for disease prevention (prophylaxis) by treating groups of animals; and as antimicrobial growth promoters (AGP) (Prescott, 2008). The last application has been under debate almost since its introduction. Since the 1950s, AGP has been intensively applied to food animals, regardless of the animals' health status or the risk of bacterial infection. For AGP use, antimicrobials are added to animal feed at sub-therapeutic concentrations to improve animal growth. There are, however, conflicting results on whether it leads to a significant improvement of

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[1] It does not concern the effect of residues of antimicrobial use, which were below or near the physical limit of detection as tested in pig and chicken samples (WHO, 2003).

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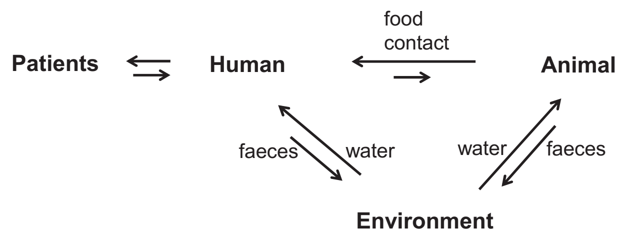


**Fig. 1.** Several important transmission routes via which the human and animal microbial flora are in contact with each other.

growth or not (Aarestrup, Jensen, Emborg, Jacobsen, & Wegener, 2010; Lee et al., 2012; WHO, 2003). Notwithstanding these uncertainties, the use of AGP led to a steep increase in the use of antimicrobials in animals worldwide as many farmers saw advantages in the use of AGP. As a result, in many countries, including Denmark, the use of antimicrobials as a growth promoter at some point exceeded therapeutic use.

In the 1990s, the use of antimicrobials in animals, in particularly as growth promoters, led to alarming levels of AMR in bacteria in the animal reservoir, which like any other zoonotic microorganism, could spread to humans and formed a risk for human health. This situation occurred in many countries; however, particularly in Denmark, it attracted much attention and has been well documented (Aarestrup et al., 2010; Hammerum et al., 2007; Wegener, Aarestrup, Jensen, Mammerum, & Bager, 1999; WHO, 2003). Using this information, the current paper describes the factors that contributed to the emergence of AMR, it summarizes the main stakeholders and events that played a role in this process, and it describes the measures that were taken to mitigate the problem. As a starting point, the use of avoparcin as an AGP, and the emergence of vancomycin-resistant *Enterococci* (VRE) in 1995 in Denmark have been chosen (Aarestrup, 1995). To further generalize the emergence of AMR, other developments around the use of other antimicrobials in animals and the international context will be described.

## 2. Materials and methods

### 2.1. Risk contributing factors

Several factors contributed to the emergence of AMR in the animal reservoir in Denmark in the 1990s. The different events and stakeholders involved in this process are related to the 12 risk development contributing factors (CF) identified by the International Risk Governance Council (IRGC) (IRGC, 2010). The IRGC uses CFs to systemize how emerging risks become real risks, where the IRGC defines an emerging risk as a risk which is perceived to be significant but not yet fully understood, thus preventing the development of effective risk management. The 12 risk development CFs identified by the IRGC are the following:

- CF1, scientific unknowns
- CF2, loss of safety margins
- CF3, positive feedback
- CF4, varying susceptibility to risk
- CF5, conflicts of interests, values and science
- CF6, social dynamics
- CF7, technological advances
- CF8, temporal complications
- CF9, communication
- CF10, information asymmetries
- CF11, unintended or perverse economic incentives
- CF12, malicious motives and acts

To understand these factors, one may compare them in a metaphorical way to the key factors that contribute to soil fertility and that increase the probability that a plant will emerge from a seed. Similarly, for the AMR, there was a set of key factors that contributed to the fertile ground from which AMR could emerge.

### 2.2. Stakeholders

Among the people and groups involved in this case in Denmark, five distinct stakeholders can be identified that played important roles: farmers, veterinarian practitioners, industry that profited from antimicrobial sales, scientists and the government. Next to these, the public played an important role through public opinion.

- The farmers, through their associations, were important stakeholders. They stood both as the source of the AMR risk and were part of the solution to reduce this risk. Farmers literally paid the price for antimicrobial use and the wellbeing of their animals. The farmers were also the first to react to the evidence showing that use of antimicrobials might have led to increased risk to human health.
- The veterinarian practitioners played a complicated role. On the one hand, they had to defend prudent antimicrobial use in animals and animal health. On the other hand, it was in their financial interest to use antimicrobials, because legislation at the time allowed that veterinarian practitioners could sell antimicrobials and for some veterinarian practitioners it amounted to about a third of their total income.
- The industry, the pharmaceutical industry and the AGP feed-preparing industry, who promoted the) use of antimicrobials in animals.
- Scientists from universities and public health institutes, aided by hospitals and food inspection laboratories, were part of the group that identified the risk of AMR in animals. They collected scientific evidence and were able to evaluate the effects of control measures.
- At the government level there were the Ministries of Health, of Food, Agriculture and Fisheries and of Science, Technology and Innovation. Together with the Ministry of Science, Technology and Innovation, the Ministry of Food, Agriculture and Fisheries and the Ministry of Health financed the required research and surveillance of antimicrobial use, and the occurrence of AMR in Denmark.

### 2.3. The avoparcin case

In the early 1960s, concern about AGP causing AMR and the possible adverse effects on human health started to build. The main reasons for concern were 1) the same classes of antimicrobials were used in humans and animals, both for therapy and AGPs, 2) there was a steep increase in the animal antimicrobial use which in animal-producing countries exceeded the human consumption, and 3) many different classes of antimicrobials were used as AGPs. In England this led to the appointment of the Joint Committee on the Use of Antibiotics[2] in Animal Husbandry and Veterinary Medicine, chaired by M.M. Swann (Swann and the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine, 1969). In 1969, the Committee recommended that specific antimicrobials should not be used as AGPs when they were

[2] Meaning the same as antimicrobials.