DISCUSSION PAPER

Interventions Aimed at Reducing Antimicrobial Usage and Resistance in Production Animals in Denmark

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Antimicrobial Usage and Interventions: A Brief History from 1950 to the Present

Antimicrobials for veterinary purposes came on the market in the 1950s, followed shortly by antimicrobial growth promoters (AGPs), because of their growth-enhancing effects to animals when added in sub-therapeutic levels to their feed [1].

Growth Promotors

In the 1970s, the EU Council authorized that the usage of antimicrobials as feed additives was permitted if the antibiotic did "not endanger animal or human health nor harm the consumer of livestock products" [2]. However, this precaution did not account for bacterial evolutionary paths that lead to antimicrobial-resistant bacteria in livestock and transfer of such bacteria to humans, e.g., through food consumption. Subsequently it was recognized that usage of the growth promotor avoparcin in food-producing animals via cross-resistance caused vancomycin resistance in enterococci in humans [3].

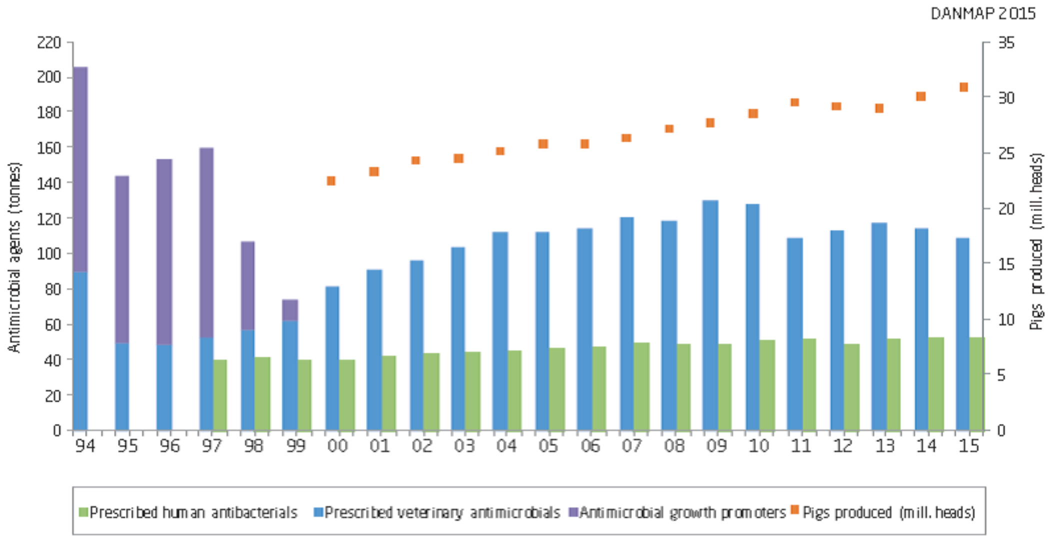
As early as 1994, using avoparcin as a growth promoter for food-producing animals was banned in Denmark because of the negative implications vancomycin-resistant enterococci could inflict on the health care system. The EU banned usage of avoparcin in 1997. Of note, by 2000, the agricultural industry in Denmark voluntarily banned usage of all AGPs in poultry and pig production [4]. The EU banned usage of AGPs for food-producing animals beginning January 1, 2006 [5].

To curb the usage of antimicrobials, in 1994–1995 additional interventions were established in Denmark. Foremost, limitations on veterinarians' profits from sales of prescribed medicines were introduced: (1) practicing veterinarians were not permitted to own a company that distributed prescription medications; and (2) veterinarians could resell only legally bought medicines (from pharmacies) to farmers with a fixed profit. Furthermore, actions were taken to increase the awareness of the Cascade rule [6], which established the Maximum Residue Limit (EEC 2377/90) in food-producing animals limiting the excessive magisterial production of prescribed medicines occurring at the time. Finally, Veterinary Health Advisory Contracts between farmers and veterinarians were established. These were intended to support preventive measures with respect to the occurrence of diseases based on regular farm visits [2,8].

Establishing the Copenhagen Recommendations

The European Union Chief Medical Officers launched the Microbial Threat conference in 1997, because of the increasing resistance to antibiotics and other antimicrobial agents in human medicine. The conference was hosted by the Danish government in Copenhagen in September 1998 and resulted in the Copenhagen Recommendations, relating to five main areas for action [9]:

1. Human health implications of the increasing resistance to antimicrobial agents
2. Surveillance of microorganisms resistant to antimicrobial agents
3. Monitoring the use of antimicrobial agents
4. Good practice in the use of antimicrobial agents
5. Framework for development of guidelines for research programs



Sources: Human therapeutics: The Danish Medicines Agency. Antimicrobials for animals: Until 2001, data are based on reports from the pharmaceutical industry of total annual sales from the Federation of Danish pig producers and slaughterhouses (1994-1995) and Danish Medicines Agency and Danish Plant Directorate (1996-2000). Data from 2004-2015 are based on data extracted from VetStat.

Figure 1| Prescribed Antimicrobial Agents for Humans and for All Animal Species, and the Number of Pigs produced in Denmark

SOURCE: DANMAP 2015 – Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. Open source permission granted through the Danish Integrated Antimicrobial Resistance and Monitoring Research Programme.

Establishing the Danish Veterinary Medicines Statistic Program (VetStat)

In response to point 3 of the Copenhagen Recommendations, the government and the agricultural industry in Denmark reached a common understanding on the importance of monitoring antimicrobial usage in production animals. In 2000, the Danish Veterinary Medicines Statistic Program (VetStat) was established. VetStat contains data on all purchased and prescribed veterinary medicines [10].

Although the amount of antimicrobial usage declined from 1994 to 1999, the use in food-producing animals, mainly pigs, increased from 2003 to 2009. Part of this increase can be explained by an increase in the production of pigs *(see Figure 1)*.

Establishing the "Yellow Card" Intervention

As a consequence, the Danish Veterinary and Food Administration (DVFA) established the "Yellow Card" intervention [11]. The Yellow Card intervention was designed to target pig farmers using high amounts of antimicrobials, by setting national threshold limits for use of antimicrobials in weaners, grower pigs, and adult pigs. If over a 9-month period a farm exceeds a threshold, the veterinary authorities may issue an injunction requiring the animal owner to bring down consumption. The decline in antimicrobial consumption seen after 2010 is assessed mainly to be a result of the Yellow Card initiative [12].

Additional Interventions

To further limit the usage of particular broad-spectrum antimicrobials and flock treatment, two interventions were adopted in 2013:

1. a differentiated tax on the active antimicrobial compound, thus favoring narrow-spectrum antimicrobials and vaccines compared with broad-spectrum compounds; and
2. a requirement of laboratory verification of the diagnosis on an annual basis for issuing prescriptions for group treatments of intestinal and respiratory infections [13-15].

To reduce the usage of critically important antimicrobials for human medicine [16] in food-producing animals, the most recent initiative involves the modifications of the national maximum thresholds in the Yellow Card scheme. In this, the critically important antimicrobials for human medicine have a lower maximum threshold of usage per animal than the antimicrobials of lesser importance for human medicine [17].

Together, these interventions, particularly those implemented from 2010, appear to have ended the otherwise increasing trend in antimicrobial usage observed since 1999 [12]. The antimicrobial resistance levels in Denmark continue to be lower than in most EU countries [18], which is most likely because of the detailed research and monitoring of antimicrobial use and resistance in food animals and in humans [12].

The Use of VetStat for Research Purposes

Data from VetStat contains records on all medicine prescribed by veterinarians for animals. Each record represents one prescription, and contains information on active substance, amount, target species, age group, diagnosis group, and farm ID [10]. Furthermore, in order to have comparable data across records, the active compounds are converted into a unit measuring how many kilograms of animal that can be treated per day—Animal Defined Daily Doses per kilogram (ADDkg) [19]. The data from VetStat are assessed to be complete and have a high degree of accuracy [10], as the majority of the prescribed medicines are handled by pharmacies and feed mills.

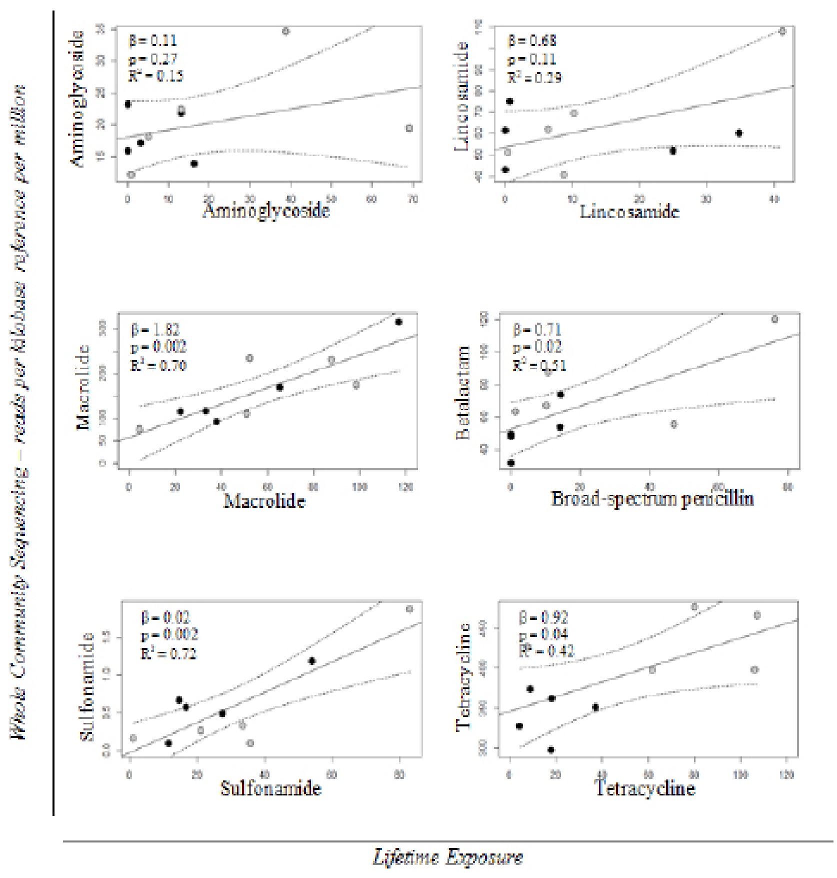


Figure 2| Univariable Linear Regression Plots (solid line) with 95% Confidence Interval (Dotted Lines) of Whole Community Sequencing—Reads per Kilobase References per Million (RPKM) as a Function of *Lifetime Exposure* for the Antimicrobial Groups: Aminoglycoside, Lincosamide, Macrolide, Betalactam/Broad-Spectrum Penicillin, Sulfonamide, and Tetracycline

SOURCE: Reproduced with permission from Cambridge University Press.
NOTES: Gray points represent the high antimicrobial-use herds and black points represent the low antimicrobial-use herds. The effect (β), the p-value (p), and the R-squared (R2) are shown in the top left corner of each model. Andersen, V., De Knegt, L., Munk, P., Jensen, M., Agersø, Y., Aarestrup, F., & Vigre, H. 2017. The association between measurements of antimicrobial use and resistance in the faeces microbiota of finisher batches. *Epidemiology and Infection:* 1-11.

VetStat is widely used in Danish studies of associations between antimicrobial use and occurrence of antimicrobial resistance, because of the detailed level of information. Thus, data on antimicrobial use can be extracted at farm-unit level [20], at farm level [20-21], and at farm-owner level [21-22] for a specified period.

Obtaining data at the unit or farm level has its limitations when animals are being moved between farms, which frequently occurs in Danish pig production. To overcome this obstacle, Andersen et al. (2016) developed a method described in the following section by which exposure to antimicrobials was calculated as the exposures during the entire rearing period that were independent of the rearing site [23]. This was achieved by combining data from the VetStat database and the Central Husbandry Register, where the latter registers movements of animals.

The effect of antimicrobial usage on occurrence of resistance genes in fecal samples from slaughter pig batches [23,24]

Introduction

The objective was to estimate the quantitative effect of three register-based measurements of antimicrobial use on antimicrobial-resistance results derived from cultivation and Whole Community Sequencing (WCS) at slaughter pig batch level.

Methods

Five integrated herds with a former low use of antimicrobials and five with a former high use were included. From the slaughter pig unit, fecal pen floor samples were collected from 30 randomly selected pens and pooled into one sample. The pig batches' exposure to antimicrobials were estimated as 1) a lifetime exposure for the sampled pigs (Lifetime Exposure), 2) a herd usage during the sampled pigs' lifetime from the overall use of antimicrobials on herd level (Herd Exposure), and 3) an exposure within the slaughter pig unit (Slaughter Pig3 Unit Exposure). The isolates were cultivated with and without tetracycline and ampicillin, and by using WCS, known resistance genes were identified. The results were assessed for possible quantitative effect of measurements of antimicrobial use on resistance.

Results

A univariable linear regression analysis showed a significant effect of Lifetime Exposure on antimicrobial resistance obtained from WCS for broad-spectrum penicillin, macrolide, tetracycline, and sulphonamide *(see Figure 2)*, and a significant effect on antimicrobial resistance obtained from cultivation for tetracycline. Furthermore, it showed a significant effect of Herd Exposure on antimicrobial resistance obtained from WCS for aminoglycoside, lincosamide, and tetracycline.

Conclusion

The study indicates that Lifetime Exposure provides a useful measure by which to identify potential quantitative effects of antimicrobial use on resistance obtained from cultivation or WCS in batches of slaughter pigs.

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