Risk assessment of antimicrobial usage in Danish pig production on the human exposure to antimicrobial resistant bacteria from pork - DTU Orbit (09/12/2018)

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During the last decades, bacteria with resistance to all commonly used antimicrobial agents have been detected, thereby posing a major threat to public health. In worst case, infections with resistant bacteria can lead to treatment failure and death of humans. The evolution of bacteria resistant to antimicrobials are influenced by the use of antimicrobial agents, and the prudence of antimicrobial use have been emphasized since the Swann report in 1969 recommended that antibiotics used in human medicine should not be used as growth promoters in food-producing animals. In 2007, the World Health Organisation (WHO) pronounced a list of the antimicrobial classes critically important for the treatment of infectious diseases in humans. On this list occurred among others the third and fourth generation cephalosporins.

Cephalosporins have been used increasingly worldwide throughout the recent years to treat various infections in veterinary and human medicine and the occurrence of resistance to this antimicrobial class have been detected with increasing frequency.

The purpose of this thesis was to perform a quantitative assessment of the association between the use of antimicrobial agents for treatment of slaughter pigs and the occurrence of extended-spectrum cephalosporinases (ESC) producing E. coli in pigs and pork. The thesis addresses this purpose by estimating the effect of the antimicrobial usage on the occurrence of resistance. And by using the obtained results in a risk assessment model where the human exposure to cephalosporin resistance from pork purchased in retail shops was assessed using different scenarios for the amount of antimicrobial used in the primary production. Also, farm-related factors affecting the antimicrobial usage were investigated as a part of this thesis.

The thesis addresses this in the following sections:

Objective 1: Estimating the association between antimicrobial usage and the detection of ESC producing E. coli

Objective 2: Quantifying the effect of antimicrobial usage on the proportion of ESC producing E. coli

Objective 3: Identification of management factors in the Danish finishing pig production important for antimicrobial usage

In Objective 1, the occurrence (presence/non-presence) of ESC producing E. coli in samples from healthy pigs at slaughter was investigated using selective agar plates supplemented with ceftriaxone. The occurrence of ESC producing E. coli was used as the outcome in the data analysis, where the effect of using cephalosporins, extended spectrum penicillins and tetracyclines was estimated using regression analysis.

In Objective 2, the samples collected for Objective 1 were diluted in 10 fold and spread on selective plates in two set of triplicates (one set containing three MacConkey agar plates, and one set containing three MacConkey agar plates supplemented with ceftriaxone). This provided quantitative data for the ESC producing E. coli and total concentration of E. coli in each sample. The proportion of ESC producing E. coli was thereafter estimated using a Poisson regression adjusting for applied dilution factor. The resistance proportion was subsequently used as outcome in a regression model to estimate the effect of the antimicrobial usage on the proportion of ESC producing E. coli.

The prevalence, concentration and proportion of ESC producing E. coli obtained in Objective 1 and Objective 2 was used as input in a human exposure assessment model. In Objective 2, a significant effect on the resistance proportion was found from the quantitative use of tetracyclines one year prior to the sampling date. This effect was used in the exposure assessment model. This model also used data from additional sources to estimate the human exposure to ESC producing E. coli from the purchase of Danish pork chops. By using the ESC producing E. coli prevalence of 41 % (obtained in Objective 1), the resulting prevalence in pork chops was found to vary from 19.70 % to 21.80 %. The prevalence of ESC producing E. coli was increasing as the usage of tetracyclines increased. However, this prevalence was found in pork chops originating from the study population, which was chosen based on their usage of cephalosporin.

In an attempt to check the validity of the model, the data from a national survey was used as input. This survey also used selective enrichment, but did not estimate the concentration of E. coli or the proportion of ESC producing E. coli, therefore the prevalence obtained from the healthy pigs at slaughter was used as input in the model, whereas the remaining steps of the model were not changed. The resulting effect on the estimated prevalence of ESC producing E. coli in 100,000 pork chops was compared to the observed prevalence from the national survey. This analysis estimated the prevalence to 5.3 % ESC producing E. coli, which is 2.6 times higher than the observed prevalence on 2 %. However, the data from the national survey was obtained at retail, whereas the model was not considering the growth or inactivation taking place under the transport and storage of the meat.

In Objective 3, the risk factors for a high usage of tetracycline were investigated by assessing the effect of tetracycline usage on the occurrence of tetracycline resistance in pigs originating from three different production types. The effect of the tetracycline usage and the effect of the production type was estimated using logistic regression. The results of this objective showed a highly significant effect of the production type, where the organic production had significantly lower occurrence of tetracycline resistance, and also had a much lower average usage of tetracycline. No significant difference in the tetracycline resistance could be found between the conventional and free range productions. When estimating the effect of the tetracycline usage in general using all the production types, a significant effect on the occurrence of resistance was found on the quantitative usage of tetracycline.

Data in this study unfortunately did not have enough power to point out single factors within the production types that could be responsible for the size of the tetracycline usage.

The overall conclusion of this thesis is that there is a significant effect of the quantitative antimicrobial usage (i.e. the amount of antimicrobial used) on the occurrence of ESC producing E. coli. A high antimicrobial usage gives an increased prevalence of resistance, but also an increased proportion of resistance. Furthermore, the occurrence of cephalosporin...
resistance appears to be influenced by a generic use of antimicrobial agents rather than the effect of a single antimicrobial class. The exposure assessment indicate that human exposure to ESC producing E. coli is to some degree affected by the generic use of antimicrobial agents in the primary pig production. However, this thesis also found big differences in the occurrence of resistance and antimicrobial usage, when comparing conventional and free range production to organic production. There seems to be a huge potential to lower the generic antimicrobial usage in the conventional and free range productions. Future studies evaluating the effect of specific risk factors in the organic production could lead to useful recommendations on how to lower the antimicrobial usage in the other production types. However, welfare issues need to be investigated to rule out the possibility of untreated diseases in the organic production.