Risk assessment for antibiotic resistance: use of macrolides in Danish pig production

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Abstract

What is the risk that use of antibiotics in farm animals will result in treatment failure in humans? Different approaches can address this. One approach is to make a risk profile and another to conduct a risk assessment. Use of macrolides in Danish pigs will be used as an example that demonstrates how the conclusion depends on the approach. A risk profile includes a description of the hazard and a qualitative assessment of the risk, similar to hazard identification. Accordingly, macrolide-resistant Campylobacter might develop as a result of usage of macrolides in pig production. This is of concern for human health, because it might reduce the effect of erythromycin, a macrolide used in children for treatment of Campylobacter infections. A full risk assessment contains an assessment of release, exposure, and consequences related to the unwanted outcome. Release deals with the probability that Campylobacter will be present in the gut, and how often the isolates found are resistant to macrolides. Exposure relates to the probability of a person being exposed to macrolide-resistant Campylobacter, and here the prevalence in pork - and not live pigs - is of interest. The consequences deal with the outcome of exposure: likelihood of disease/adverse effects. Campylobacter is commonly occurring in the pig gut, and so is macrolide-resistance in Campylobacter in pigs. However, the prevalence of Campylobacter in Danish pork at retail is negligible because of use of blast-chilling after slaughter. Human campylobacteriosis is usually self-limiting. One study describes adverse effects related to infection with macrolide-resistant Campylobacter — but the effect was severely confounded with age and co-morbidity, and no children got adversely affected. So according to the risk assessment, the risk associated with veterinary use of macrolides in Danish pigs for the health of humans seemed low. This is contrary to the result obtained by the risk profile.

Introduction

Veterinary usage of antibiotics might result in development of resistance among zoonotic bacteria or non-pathogenic microorganisms. The fear is that treatment failure of humans will occur as a result of infection with zoonotic bacteria originating from e.g. pigs or poultry treated with antibiotics. Moreover, transfer of resistance from non-pathogenic microorganisms to human pathogens might occur, and examples of this have been observed. The World Health Organization (WHO) has reservations about veterinary use of macrolides, because of the risk of development of macrolide-resistant Campylobacter. In particular, children are of concern, because macrolides are the drug of choice for treatment of intestinal disorders in children (WHO, 2005). In line, The US Federal Drug Agency (FDA) considers veterinary usage of macrolides as a risk for human health (FDA, 2003). To mitigate this risk, usage of antibiotics as growth promoters has gradually been banned within the European Union (EU) (Anon., 1998; Anon., 2003). In July 1999, the EU suspended four antimicrobial growth promoters: bacitracin, virginiamycin, spiramycin and tylosin (Anon., 1998).

In 2006, the Danish Veterinary & Food Administration decided to redraw macrolides from the list of drugs recommended for treatment of diarrhea in pigs. The decision was driven by a political interest in reducing the antibiotic consumption per se as well as evidence pointing at a specific risk related to macrolides. The decision to leave out macrolides was taken based on a risk profile, in line with the precautionary principle, which can be used to take preliminary decisions.

A full risk assessment is then a natural step — to study whether in fact the decision taken is justified or not. Therefore, a risk assessment following international guidelines was conducted by the Danish Meat Association aiming at assessing the risk for human health associated with usage of
macrolides in Danish pigs. In the following it will be demonstrated how the estimated risk depends on the approach taken: risk profile or quantitative risk assessment.

Materials and Methods

Initially, we identified macrolide-resistant *Campylobacter* as the agent of interest based on two criteria: 1) it should be a zoonotic bacterium that causes disease in humans and 2) macrolides should be the drug of choice for treatment of disease. Data on prevalence of *Campylobacter* in beef, pork, poultry meat and humans as well as on macrolide-resistant *Campylobacter* were obtained from national and international surveys primarily from 2004. In particular, data from EU surveillance were obtained from the EFSA report (EFSA, 2005). Moreover, information on antibiotic consumption, meat import statistics and consumption patterns were obtained. Information from published papers on the consequences related to human infection with *Campylobacter* was also incorporated.

We decided to include pork and poultry in the analysis, whereas we interpreted pets as carriers of *Campylobacter* from pork and poultry, because pets often share food with their owners. Beef was ruled out because it was an insignificant source of macrolide-resistant *Campylobacter*.

A risk profile includes a description of the hazard and a qualitative assessment of the risk, similar to hazard identification. A risk assessment is an extension because it implies an evaluation of each of the following steps:

1. Hazard identification
2. Release assessment
3. Exposure assessment
4. Consequence assessment
5. Risk estimation

A quantitative model was constructed in the software programme @Risk.

Results

**Risk profile**

According to the risk profile, macrolide-resistant *Campylobacter* might develop as a result of usage of macrolides in animal production. This is of concern for human health, because it might reduce the effect of erythromycin, a macrolide used in children for treatment of *Campylobacter* infections. In 2004, approximately 13t of macrolides were used for therapeutic treatment in Denmark (DANMAP, 2004). Around 92% of this was used for a production of 23m finishers as well as an export of 2m piglets (DANMAP, 2004; Anon., 2005b). This corresponds to around 0.5g macrolides per produced pig (13t x 0.92 /25m pigs = 0.48g macrolides / pig). The main part (87%) of the consumption in pigs was used for weaners and finishers. Only around 50kg of macrolides were used in cattle, and here, half of it was used in adult cattle and half in calves <12months of age. In poultry, around 15kg were used (DANMAP, 2004). This common use selects for development of macrolide-resistance in *Campylobacter* (Frimodt-Møller and Hammerum, 2004). Secondly, a Danish study, recently published, demonstrated an excess risk of invasiveness or dying among patients infected with macrolide-resistant *Campylobacter* (Helms et al., 2005). Based on this information it was judged that use of macrolides for treatment of pigs might lead to development of macrolide-resistant *Campylobacter* which again constitutes an increased risk for humans.

**Risk assessment**

The release assessment showed that thermophilic *Campylobacter* spp. are widespread in nature and the principle reservoirs are the alimentary tract of wild and domestic birds and mammals. In poultry and cattle, *C. jejuni* is the most commonly found species, whereas *C. coli* is most common in pigs (Stern & Line, 2000). There is a moderate to high prevalence of macrolide-resistant *Campylobacter* in live pigs, including Danish pigs, presumably as a result of usage of macrolides in pig production. In poultry, the macrolide-resistance in *Campylobacter* is less common and probably
a result of the use of antimicrobial growth promoters (virginiamycin and spiramycin) in broilers in EU before year 2000.

The exposure assessment showed that the prevalence of Campylobacter in pork is low, and especially low in Danish pork due to blast chilling. In poultry, the proportion of Campylobacter isolates that are macrolide-resistant is much lower than in pork however; this is counteracted by the high prevalence of Campylobacter found in poultry in general. The exposure model for 2004 data showed that the usage of macrolides in Danish pig production was associated with seven human cases only. The main part of the cases was related to imported meat; pork (83 cases) or poultry meat (74 cases).

Table 1
Description of input parameters used in a model describing the source of exposure of Danes to macrolide-resistant Campylobacter due to consumption of pork or poultry meat, 2004

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter estimate</th>
<th>Derived distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative consumption of pork compared to poultry</td>
<td>1.4 times more pork is consumed than poultry in Denmark on average</td>
<td>a</td>
<td>GfK Consumer Scan, GfK Denmark</td>
</tr>
<tr>
<td>Distribution of origin of pork</td>
<td>Domestic: 75%</td>
<td>a</td>
<td>Statistics from Danish Meat Association, 2006</td>
</tr>
<tr>
<td>Distribution of origin of poultry</td>
<td>Imported: 25%</td>
<td>a</td>
<td></td>
</tr>
<tr>
<td>Distribution of origin of poultry</td>
<td>Nationally: 65%</td>
<td>a</td>
<td>Statistics from Danish Meat Association, 2006</td>
</tr>
<tr>
<td>Prevalence of Campylobacter in pork</td>
<td>Domestic: 0.2%</td>
<td>Beta(ε=5, n=2,413)</td>
<td>EFSA, 2005</td>
</tr>
<tr>
<td>Imported: in general 5% or lower, however higher prevalences also observed</td>
<td>Beta(ε=5, n=2,413)</td>
<td>Beta(ε=13, n=584)</td>
<td>EFSA, 2005</td>
</tr>
<tr>
<td>Prevalence of Campylobacter in pork</td>
<td>Domestic: 23.5%</td>
<td>Beta(ε=13, n=584)</td>
<td>EFSA, 2005</td>
</tr>
<tr>
<td>Imported: varies greatly</td>
<td></td>
<td>Pert(2%, 30%, 89%)</td>
<td></td>
</tr>
<tr>
<td>Proportion that is macrolide-resistant</td>
<td>Domestic: 23%</td>
<td>Beta(ε=23,n=100)</td>
<td>DANMAP, 2004</td>
</tr>
<tr>
<td>Imported: varying greatly</td>
<td>Pert(16%,24%,78%)</td>
<td>Pert(16%,24%,78%)</td>
<td>EFSA, 2005</td>
</tr>
<tr>
<td>Prevalence of Campylobacter in poultry</td>
<td>Domestic: 23.5%</td>
<td>Pert(2%, 30%, 89%)</td>
<td>EFSA, 2005</td>
</tr>
<tr>
<td>Imported: varies greatly</td>
<td>Pert(2%, 30%, 89%)</td>
<td>Pert(2%, 30%, 89%)</td>
<td></td>
</tr>
<tr>
<td>Proportion that is macrolide-resistant</td>
<td>Domestic: C. jejuni: 0.5% C. coli: 3%</td>
<td>1.0%ab</td>
<td>DANMAP, 2004</td>
</tr>
<tr>
<td>Imported: C. jejuni: 3% C. coli: 12%</td>
<td>4.8%ab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human cases due to macrolide-resistant Campylobacter cases in 2004</td>
<td>3,724 human Campylobacter cases in 2004</td>
<td>5% 186 casesa</td>
<td>Anon., 2005a; Helms et al., 2005</td>
</tr>
<tr>
<td>Campylobacteriosis</td>
<td>1997-2000: 5.9% Mres C. 1997-2004: 0.5% Mres C.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a: No attempt was made to model the variability associated with these parameters.

b: The distribution between C. jejuni and C. coli in poultry meat was assumed to be 80:20 in line with Nielsen et al. (2005); hence in domestic produced poultry the proportion of Campylobacter isolates that is macrolide-resistant is 0.8 x 0.5% + 0.2 x 3.0% = 1%. Similarly, for imported poultry: 0.8 x 3% + 0.2 x 12% = 4.8%. In pork, all isolates were assumed to be C. coli.

The consequences assessment showed that in 2004 an incidence of human campylobacteriosis of 68.8 cases per 100,000 inhabitants in Denmark corresponding to 3,724 cases (Anon., 2005a). The disease is usually self-limiting with symptoms lasting less than seven days. Apparently, an excess risk of invasiveness and death among patients infected with Campylobacter has been observed by Helms et al. (2005). However, the effect of macrolide-resistance found in that study was confounded by age (only old people at risk) and co-morbidity, and non-significant when evaluated for 0 to 30 days of infection (Helms et al., 2005). In addition, in the study by Helms et al. (2005) no children infected with macrolide-resistant Campylobacter had invasive infection or died, and these were the ones that WHO were concerned with. Overall speaking, the consequences seemed to be negligible for children and adults, and low for old people. The crude data showed that patients infected with macrolide-resistant Campylobacter had a probability of 3.4% of experiencing invasive infection or death (Helms et al., 2005). This implies that for the year 2004, 7 cases x 0.034 = 0.2
human cases with adverse effect due to Danish pork could have been expected – when disregarding the confounding effect of age and co-morbidity, and the baseline risk associated with Campylobacter.

Discussion
The present study demonstrates that the use of the pre-cautionary principle is a preliminary activity that should be utilized when there is concern about a given activity/hazard. However, a full risk assessment is also required because it might yield a different conclusion about the concerned risk than when only undertaking a risk-profile. When performing risk assessments, international guidelines should be followed. Ideally, the assessment should be subjected to peer-review and an open debate should be held among stakeholders to ensure quality, validity and common understanding of the risk assessment. The results of such a risk assessment constitute the optimal scientific basis of management decisions (Vose et al., 2001).

Conclusions
The risk associated with veterinary use of macrolides in Danish pigs for human health because of macrolide-resistant Campylobacter seems to be negligible to low. A further reduction in the usage of macrolides in Danish pig production will therefore have limited effect on the number of human cases with adverse effects due to exposure of Danes to macrolide-resistant Campylobacter.

References

Please, contact the presenting author for a reference list for the remaining references.