The effects of antibiotic usage in food animals on the development of antimicrobial resistance of importance for humans in Campylobacter and Escherichia coli

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ABSTRACT – Modern food animal production depends on use of large amounts of antibiotics for disease control. This provides favourable conditions for the spread and persistence of antimicrobial-resistant zoonotic bacteria such as Campylobacter and E. coli O157. The occurrence of antimicrobial resistance to antimicrobials used in human therapy is increasing in human pathogenic Campylobacter and E. coli from animals. There is an urgent need to implement strategies for prudent use of antibiotics in food animal production to prevent further increases in the occurrence of antimicrobial resistance in food-borne human pathogenic bacteria such as Campylobacter and E. coli. © Elsevier, Paris

1. Introduction

A zoonosis is an infection or infectious disease transmissible under normal conditions from vertebrate animals to man and may be enzootic or epizootic [1]. The zoonoses which occur most frequently in the industrialised world today are food-borne infections caused by bacteria enzootic to food animals namely, species of Salmonella, Campylobacter, Yersinia, Listeria, and enterohaemorrhagic Escherichia coli. The main reservoir of zoonotic agents is the gastrointestinal tract (GI tract) of healthy food animals, and most food-borne infections originate from faecal contamination during slaughter or cross-contamination during subsequent processing.

In the complex epidemiology of food-borne zoonoses, the GI tract of the animals serves not only as the main reservoir and major site of bacterial propagation but also, as a hot spot for the exchange of genetic information [2]. It is generally agreed that usage of antimicrobial agents is the most important factor in the selection of resistance in bacteria, and that, in general, a close association exists between the rate of resistance development and the quantities of antimicrobial agents used [3, 4]. In specific human pathogens, development of resistance has been associated with use of antibiotics for human therapy either in hospital (methicillin-resistant Staphylococcus aureus) or in the community (penicillin-resistant pneumococci). For the bacterial zoonoses, development of resistance is associated with the use of antimicrobial agents for both humans and animals.

Animals in modern intensive production systems frequently receive antibiotics for therapy, prevention and control of diseases. Furthermore, most food animals receive antibiotics as feed additives for growth promotion. In Denmark in 1997, approximately 35 tonnes of antibiotics were used for human therapy, 53 tonnes for animal therapy and prophylactics and 107 tonnes for growth promotion. Similar figures for the Netherlands amount to 80 300 and > 300 tonnes, respectively [2]. In light of the amounts used it seems reasonable to assume that resistance development in zoonotic bacteria primarily is driven by the use of antibiotics for animals and to a lesser extent by the use of antibiotics for treatment of human infections.

Development of resistance in zoonotic bacteria constitutes a public health risk, primarily through the increased risk of treatment failures [5, 6]. In addition, development of resistance, notably by acquisition of transmissible genetic elements, may affect other properties such as the ability to colonise an animal host or persist in the farm- or food processing environment.
This review will focus on the development of antimicrobial resistance of importance for humans in Campylobacter spp. and E. coli among food animals, and the transmission of resistant bacteria of these species and resistance determinants between animals and humans.

2. Campylobacter coli/jejuni

Campylobacter spp. are common causes of infections in humans in most countries. The typical symptoms of campylobacteriosis are bloody diarrhea and fever. Campylobacter infections usually occur as sporadic cases following ingestion of improperly handled or cooked food. Usually the infection is self-limiting and does not require treatment (table I). However, in immunocompromised patients, for example HIV patients, the infection can lead to bacteraemia. Campylobacter bacteraemia can have a very high mortality rate (>30%) and fatalities due to treatment failure have been reported [6]. In these cases macrolides and fluoroquinolones are commonly used for treatment [7–10]. In Denmark, macrolides are standard empirical therapy for diagnosed campylobacteriosis in humans, whereas fluoroquinolones are the standard therapy for nondiagnosed gastrointestinal infections (table I).

Two Campylobacter species are usually associated with most infections in man: Campylobacter jejuni and Campylobacter coli [11, 12]. The epidemiology of the infection is not entirely elucidated. However, food animals are considered the primary reservoir of Campylobacter causing infections in humans. C. jejuni is predominant among cattle and broilers, but only found in low frequency among pigs where C. coli predominate [13, 14].

C. jejuni isolated from clinical infections is generally susceptible to erythromycin [14–16], whereas a higher level of resistance among isolates of C. coli has been reported [14, 16–18]. An increase in resistance, especially to fluoroquinolones has been reported among human clinical isolates in several countries [16, 18–21], but resistance to erythromycin and other antimicrobial agents has also been observed [15–18, 21].

Several studies have shown that resistance to fluoroquinolones develops very rapidly in Campylobacter following introduction of fluoroquinolones for veterinary use. In the Netherlands, a direct association between the licensing of fluoroquinolones for water medication for poultry production and development of resistance in animal isolates was shown [19]. At the same time, fluoroquinolone resistance levels increased in human isolates [19], indicating a direct transmission of resistant Campylobacter from poultry to humans. Sanchez et al. [18] reported increased levels of fluoroquinolone resistance following the licensing of fluoroquinolones for poultry in Spain. More than half of the Campylobacter isolates from human cases were reported to be resistant two years after fluoroquinolones were licensed for animals compared to none before licensing. Recently, increasing levels of fluoroquinolone resistance have been reported from the USA [22]. Also in this study, the authors explain the increasing occurrence of resistance by exposure to fluoroquinolone-resistant Campylobacter from poultry. It must be expected that as the use fluoroquinolones for animals increases, resistance increases also, making fluoroquinolones less useful for therapy of humans. A combination of resistance to fluoroquinolones and macrolides is an unwanted combination in Campylobacter, because these drugs are used for standard treatment of infections with Campylobacter (table I).

The genetic bases for antimicrobial resistance in Campylobacter have only been examined in a few studies. However, conjugative transfer of resistance to chloramphenicol, erythromycin, kanamycin, neomycin, streptomycin, and tetracycline has been observed in Campylobacter species [21, 23]. Genes encoding resistance have also been found transferable between Campylobacter and other bacterial species [24]. The genes encoding kanamycin (aphA-3), streptomycin (aadA), and streptomycin/spectinomycin (aadE) resistance in Gram-positive cocci have also been identified in Campylobacter [25, 26]. However, a novel gene encoding resistance to kanamycin has also been identified among Campylobacter [27] and it is not known to what extent different Campylobacter species share genes with other pathogenic bacterial species.

3. E. coli

E. coli is one of the most common causes of infection in humans and animals world-wide. E. coli is associated with a wide variety of diseases, but a large degree of host and disease specificity exists for the different serotypes. Thus, certain pathogenic E. coli serotypes predominate as causes of intestinal infections in humans and different
animal species. In contrast, extraintestinal infections are caused by \textit{E. coli} types also found in the normal intestinal flora [28]. Even though a number of different \textit{E. coli} serotypes might be zoonotic [29–31], most of the emphasis has been put on enterohaemorrhagic \textit{E. coli} of serotype O157.

Few studies describe antimicrobial susceptibility patterns among \textit{E. coli} O157 isolates from humans and animals. In general, most isolates has been fully susceptible, even though resistance to ampicillin, streptomycin, sulphonamides, and tetracyclines has been observed [32–39]. However, recent surveillance data from the USA showed that 20% of isolates from several states were resistant to at least one antimicrobial agent, and 7% were resistant to two or more antimicrobials. The most common resistance was against sulphamethoxazole 13% [40].

The range of different \textit{E. coli} types colonising humans and animals is not entirely characterised. However, the O serogroups commonly isolated from the gut of food animals and humans are relatively similar [41, 42].

Antimicrobial-resistant \textit{E. coli} from the gut of food animals will contaminate the carcasses of animals during slaughter. These strains may enter the human alimentary tract via food. In a study by Linton et al. [43], antibiotic-resistant \textit{E. coli} from chickens were found to colonise humans for at least 10 days.

Besides the well-established zoonotic \textit{E. coli} of serotype O157:H7, there is no compelling evidence that \textit{E. coli} isolates from food animals reaching humans through the food chain can cause infections. However, during the perhaps temporary colonisation of \textit{E. coli} of animal origin of the human gut, they have the potential to transfer resistance genes to the indigenous flora of the gut, that might in tum transfer the resistance genes to pathogenic bacteria.

In a study by Levy [44], tetracycline-resistant \textit{E. coli} isolates were found among pigs and farmers after the use of tetracycline for therapy of the pigs. Furthermore, transmission of \textit{E. coli} of animal origin with selective antimicrobial resistance markers from animals to caretakers has been observed [45]. It is, however, in general difficult to prove whether the emergence of resistance to therapeutic antimicrobial agents in \textit{E. coli} in humans is a consequence of spread of resistant bacteria or resistance genes from the animals or caused by selection by therapy of humans, because the same antibiotics are used for both humans and food animals.

In cases where an antibiotic is used for food animals, but not for humans, a stronger line of evidence exists. Thus, after the introduction of the streptothricin antibiotic nourseothricin in animal husbandry for growth promotion in the former East Germany in 1983, \textit{E. coli} harbouring a transferable plasmid mediating resistance appeared [46]. This plasmid was found among different \textit{E. coli} isolates from pigs, pig farmers, and their families and furthermore, was found in \textit{E. coli} isolates of the gut flora or causing urinary tract infections in humans without any contact with pig farms, but living in the same regions [47]. This demonstrated that resistance plasmids might spread from food animals through the food chain to humans and even end up in pathogenic strains of \textit{E. coli}.

Another example is the emergence of apramycin resistance after the introduction of the aminoglycoside antibiotic apramycin for veterinary medicine in the beginning of the 1980s. Soon after, apramycin-resistant \textit{E. coli} isolates were found in cattle and the pigs in France and the United Kingdom [48, 49]. The gene encoding resistance had not previously been observed and it also conferred resistance to gentamicin [50]. The same apramycin-resistance gene and similar resistance plasmids have since been observed in salmonella from animals and in human clinical isolates of \textit{E. coli}, \textit{Salmonella} and \textit{Klebsiella pneumoniae} [51–57].

Direct transfer of resistance plasmids mediating apramycin resistance from \textit{E. coli} in pigs to \textit{E. coli} from a stockman has also been observed [58]. These observations strongly indicate that this resistance gene primarily emerged among food animals because of selection by the use of apramycin and then afterwards was transmitted to humans and perhaps here selected for by the use of gentamicin for therapy.

Even though in several cases similar resistance genes have been observed among \textit{E. coli} causing human and animal infections, it is very difficult to trace the origin of resistance in the human pathogens, because the same drugs are used for both humans and animals. However, the examples with nourseothricin and apramycin give strong evidence that resistance genes can be transmitted from \textit{E. coli} living in the gut of food animals to commensal as well as pathogenic \textit{E. coli} in man.

4. Discussion

Modern food animal production provides favourable conditions for the spread and persistence of zoonotic bacteria such as \textit{Campylobacter} spp. and \textit{E. coli} O157. Moreover, these production systems depend on a high and constant input of antibiotics for growth promotion and disease control in order to be cost effective. Thus, not only does the risk of food-borne infections increase in these production systems, but also the public health risk associated with infections will increase with increasing levels of resistance. Among both species of \textit{Campylobacter} and \textit{E. coli} causing human clinical infections, the occurrence of antimicrobial resistance seems to be increasing [16, 18–21, 59, 60–62].

The question remains: what is the actual magnitude of this risk and how far we are from noncurable food-borne zoonoses? For organisms like \textit{Campylobacter} spp. and \textit{E. coli} O157, therapeutic failures due to development of antimicrobial resistance are probably still relatively rare. Standard empirical treatment are fluoroquinolones and gentamicin in many countries. Levels of resistance to these antimicrobial drugs will increase with increasing use in agriculture. At the same time, the rate of antimicrobial drug development has slowed down, and it is the general perception that no new classes of antibiotics are presented under development for Gram-negative bacteria. Thus, the stage is set for the occurrence of noncurable zoonoses.

To circumvent this development we only have two options: infection control (zoonosis control) and prudent use of antibiotics. In fact, the two options probably only
work in concert – prudent antibiotic use demands improved infection control strategies at herd level, and pre-harvest control of zoonotic agents to some extent relies on similar control principles. Thus, by aiming for one we may achieve both benefits at the same time.

References


Antimicrobial resistance in Campylobacter and E. coli from food animals


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