Summary

The therapeutic use of fluoroquinolones in poultry: the effect on Campylobacter and the potential human health consequences

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On 31 October 2000, the Food and Drug Administration (FDA), Center for Veterinary Medicine (CVM) proposed to withdraw approval for the fluoroquinolone enrofloxacin for poultry (marketed under the tradename Baytril 3.23% Concentrate Antimicrobial Solution). Baytril was licensed by the CVM in 1996 for use in treating life-threatening diseases in turkeys and chickens. This proposal was based in part on concern that the use of Baytril in poultry may have resulted in an increase in human fluoroquinolone-resistant Campylobacter infections, which could reduce the effectiveness of fluoroquinolones in treating campylobacteriosis in humans.1,2

Bayer evaluated the data presented by the CVM, and consulted experts in microbiology, and veterinary and human medicine. As a result of its scientific evaluation of the data, Bayer concluded that the continued use of Baytril in poultry did not have an adverse human health impact. On 21 February 2001, Bayer presented its data and conclusions to the FDA, and requested that the FDA grant a hearing on its proposed withdrawal of Baytril.

Bayer understands and supports the CVM's mission to protect public health, and appreciates the difficulty of determining the cause of a reported increase in Campylobacter fluoroquinolone resistance. Bayer also believes that it is important to identify the causes of resistance to fluoroquinolones in Campylobacter, and to quantify the attributable risks so that targeted appropriate mitigation measures can be applied.

In 2002, Bayer assembled experts in poultry production and medicine, resistance monitoring, Campylobacter epidemiology and genetics, and risk assessment, and physicians involved in the diagnosis and treatment of human infectious diseases, to discuss the use of fluoroquinolones in poultry and its potential impact. The symposium was convened for the purpose of providing a scientific forum to examine the effects of the use of Baytril in poultry on the development of fluoroquinolone-resistant Campylobacter, and to evaluate the potential human health consequences of such use.

CONCLUSIONS

Campylobacter jejuni is currently the second most commonly recognized cause of bacterial gastroenteritis in humans in the USA. When antibiotics are indicated for the treatment of Campylobacter gastroenteritis, erythromycin or a fluoroquinolone such as ciprofloxacin is considered the drug of choice. Fluoroquinolones are frequently prescribed empirically for diarreal illness, including travelers' diarrhea, because of their effectiveness against a range of enteric bacteria. Since the late 1980s, the resistance of Campylobacter isolates to fluoroquinolones has been increasing, especially in Europe and in certain South American countries. Poultry have traditionally been considered to represent a major source of Campylobacter infections in humans, and some investigators have proposed a causal relationship between the use of fluoroquinolones in animals and the increase in fluoroquinolone-resistant Campylobacter infections in humans. The majority of Campylobacter infections occur as sporadic individual infections.

The objective of the symposium was to examine the evidence that the use of fluoroquinolones in poultry health management contributes to the emergence of fluoroquinolone-resistant Campylobacter species that may be transferable to humans, resulting in an increase in human fluoroquinolone-resistant Campylobacter infections, thus reducing the effectiveness of fluoroquinolones in treating campylobacteriosis in humans.

The current rate of fluoroquinolone resistance among human isolates in the USA is <15%, similar to a level noted in 1995, prior to the introduction of enrofloxacin for the treatment of confirmed poultry disease. It is important to note that <1% of all poultry in the USA are treated with enrofloxacin annually, which is a much lower rate than that of human quinolone administration in the same country (>40 million adults received a quinolone in 2001, representing >10% of the US population).

The fully integrated system of poultry production in the USA is characterized by the rearing of large numbers of birds under intensive conditions, which requires excellent animal health management veterinary services. When certain bacterial diseases occur in a population of broiler chickens, the veterinarian must diagnose the disease correctly, and select an antibiotic which will be cost-effective and will not result in illegal drug residues. Enrofloxacin is the most effective antimicrobial available for the treatment of airsacculitis in poultry production. Although it may be used empirically based on clinical experience, a definitive diagnosis based on necropsy, culture and susceptibility testing is the
procedure employed by poultry veterinarians in the majority of cases.

The CVM's proposal to withdraw approval for enrofloxacin for poultry was based in part on concern that use of the drug in poultry may have resulted in an increase in human fluoroquinolone-resistant Campylobacter infections (data derived from national surveillance sources), which could reduce the effectiveness of fluoroquinolones in treating campylobacteriosis in humans.

A review of the United States National Antimicrobial Resistance Monitoring System (NARMS) data on fluoroquinolone-resistant Campylobacter isolates from humans with campylobacteriosis revealed no evidence to indicate a rise in resistant isolates associated with the introduction of the use of fluoroquinolones in poultry. A number of shortcomings in the NARMS program include a lack of overall sampling design, biases in the collection of isolates from animal samples, non-compliance of state departments of health with NARMS protocols, lack of such basic data as genotype information of the organisms isolated, and, for animal samples, lack of measurements of bacterial load. When combined, these inadequacies indicate that the present NARMS data probably overestimate the resistance levels, and do not provide reliable information with which to quantify the extent and temporal trends of antimicrobial resistance in Campylobacter and other enteric bacteria from human and animal populations. The NARMS system is useful as a qualitative monitoring system which can provide an indication of emerging resistance, but in its present form is not useful as a quantitative tool.

In order to support the CVM proposal, it is essential that specific and reliable methods of proving relatedness of isolates be available. Genotyping methods are used to differentiate Campylobacter jejuni isolates. However, the data are complex and do not support simple models of transmission. Several observations have apparently weakened their value and complicated the interpretation of genotyping methods. The epidemiologic tools currently available to demonstrate the transmission of Campylobacter strains from poultry to humans, and that poultry represent the source of the disease, are inadequate. The relatively small number of fluoroquinolone-resistant strains further highlights the likelihood that drug-resistant disease may be uncommon and therefore difficult to establish a clear causality for. The measurement of resistance in poultry and human isolates using one single phenotyping or genotyping method to prove identity of clones is insufficient to conclude that particular resistant strains isolated from humans and poultry are identical.

Campylobacter jejuni, and its close relative C. coli, are Gram-negative thermophilic, microaerophilic bacteria that colonize the intestinal mucosa of various hosts and are considered to be ubiquitous in the general environment. Humans may become infected from poultry and other contaminated meats, and from water contaminated with feces from livestock, wild animals, birds, and other humans. The organism cycles in the environment through all potential hosts. Campylobacter species have been isolated from the feces of dogs with and without diarrhea. The outcome of host colonization is variable. Evidence suggests that the organisms have evolved to preferentially and chronically colonize a relatively unique niche in the avian gut as a commensal. Infection in most animals, and many humans, is also asymptomatic and transient. However, infection in susceptible humans may lead to an acute but self-limiting enteritis. There are several possible explanations for such a range of outcomes, including the host immune status and variations in bacterial virulence, particularly invasiveness and toxin production. There is also increasing evidence that the bacterium can respond to its host environment during growth in the host intestine by switching on gene expression and possibly by genetic rearrangement.

Relevant to this symposium, in a recent publication the fluoroquinolone-resistant strains of Campylobacter from human clinical sources and chickens originating in Northern Ireland were compared. The study was largely self-contained, because most of the poultry consumed had been produced locally and there was relatively little foreign travel. Overall, there were no isolates from either source which shared complete phenotypic homology. A high degree of phenotypic diversity was observed among the biotypes from chickens and humans, with only two common biotypes. The prevalence of antibiotic-resistant organisms was similar in both humans and chickens, with the exception of a higher rate of tetracycline resistance in chickens. Fluoroquinolone resistance was higher in the human isolates than in the animal isolates. This higher level of fluoroquinolone resistance in human isolates possibly suggests acquisition from another source, where fluoroquinolones are more frequently used than in poultry production, e.g. small animals and pets. A small proportion of human infections are reportedly acquired from dogs. The study illustrated the difficulty in deducing the origins of fluoroquinolone resistance in campylobacters, which may come not only from poultry but also from other animal sources, especially domestic pets, in addition to human sources.

Analysis of case-control data on campylobacteriosis in humans revealed that fluoroquinolone resistance in human isolates is not positively associated with the consumption of chicken. According to the CDC data, chicken consumed at home appears to be protective against campylobacteriosis. Even handling and preparing chicken at home seems to be associated with a decreased risk of campylobacteriosis. This poses the question of whether chicken really is a common source of infective doses to people. If chicken by itself is not transmitting Campylobacter to humans, then it is probably not transmitting fluoroquinolone-resistant Campylobacter to people. The CDC's own studies
illustrate the wide range of other potential sources of *Campylobacter* infections.

The CDC data also indicate that restaurant dining is significantly associated with *Campylobacter* risk in the USA, and *Campylobacter*-shedding restaurant workers have been identified as the source of *Campylobacter* outbreaks in the USA and Brazil. If restaurant workers represent an important source of *Campylobacter*, then fluoroquinolone resistance profiles in workers may influence fluoroquinolone resistance patterns in the population at large. This suggests that risk management strategies which focus on restaurant kitchen hygiene rather than on chickens may be more productive in preventing human *campylobacteriosis* and other intestinal infections. Attempts to reduce fluoroquinolone-resistant *Campylobacter* isolates among human *campylobacteriosis* patients by banning fluoroquinolone use in chickens may be unsuccessful, because there does not appear to be an incontrovertible causal link.

It is estimated that there are over 200,000,000 episodes of acute enteritis annually in the USA, of which approximately 75,000,000 are foodborne. Fewer than 20% of the estimated cases have a known etiology. Nearly half of the more than 4,000,000 cases of known foodborne bacterial enteritis are attributed to *Campylobacter* infections. The FoodNet active population-based surveillance system has demonstrated geographic variation in the incidence of *Campylobacter* infection, and the incidence of *Campylobacter* infections has been generally declining in the USA since 1996. *C. jejuni* infections may vary in severity and duration, and symptoms may persist for more than 1 week in 20% of patients. Antimicrobial therapy, especially if administered early, is thought to hasten clinical resolution by 2–3 days. Therapy is generally restricted to individuals with moderate-to-severe disease, and high-risk individuals, e.g., those with underlying immunodeficiency, extremes of age, or chronic illness. Approximately 10–15% of *C. jejuni* isolates exhibit in vitro resistance to fluoroquinolones, although most strains are susceptible to macrolides.

In 2001, *Campylobacter* was the second most frequent foodborne pathogen, with *Salmonella* being the most common, isolated from humans in Germany. Epidemiologic risk factors include consumption of poultry and untreated milk, and contact with surface water. Travel plays an important role, especially in Scandinavia, the UK, and certain states in the USA, where a high proportion of *Campylobacter* isolates of human infections are imported. Such isolates are much more often resistant to fluoroquinolones than are domestic strains. Fluoroquinolone resistance in human *Campylobacter* isolates is lowest in the UK and Denmark, at 12%. Estimates of resistance range from 20% to 40% in Finland, The Netherlands, Norway, Sweden, Austria, and Germany, with peaks of 70–80% in Spain. Usually, uncomplicated *Campylobacter* enteritis is symptomatically treated. If, in severe cases, anti-

microbials are indicated, in all European countries except Switzerland macrolides are used as first-line drugs, followed by fluoroquinolones or doxycycline.

In summary, the available evidence does not conclusively support the hypothesis that the veterinary use of fluoroquinolones in poultry in the USA has resulted in fluoroquinolone-resistant *Campylobacter* strains that were transmitted to people, causing disease in those people, and resulting in compromised treatment. The weight of evidence is insufficient to indicate that the therapeutic use of fluoroquinolones in poultry is a significant risk to public health and thus requires withdrawal of the approval of enrofloxacin for use in poultry in the USA. The symposium provided evidence that the increased risk of *campylobacteriosis* in humans is significantly associated with food prepared outside the home and not with chicken cooked at home. Proper handling and cooking of food can almost entirely eliminate the risk from *C. jejuni*. It appears unlikely that eliminating the use of fluoroquinolones in chickens would have any detectable human health benefit in reducing the incidence of resistant *Campylobacter* infections in humans. Nothing in the scientific data or the previously published data from various state and national studies examined suggests that the use of fluoroquinolones to treat chickens consumed in the USA is a risk to public health. A similar finding in northern Europe has recently been reported by de Neeling et al, who examined the possible relationship between fluoroquinolone resistance in *Campylobacter* in poultry and humans. Clear evidence showing that antibiotic-resistant bacteria arising in animals cause subsequent infection in humans which is then difficult to treat is difficult to find. Fluoroquinolone-resistant salmonellae and *Campylobacter* have been isolated from animals, foodstuffs, and humans, although evidence showing the full sequence of events, including the compromise of antibiotic choice by the clinician, has not yet been published.

REFERENCES
5. Anderson SA, Yeaton Woo RW, Crawford LM. Risk assessment of the impact on human health of resistant