Fluoroquinolone-Resistant *Campylobacter* Species and the Withdrawal of Fluoroquinolones from Use in Poultry: A Public Health Success Story

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Campylobacter **species cause 1.4 million infections each year in the United States. Fluoroquinolones (e.g., ciprofloxacin) are commonly used in adults with *Campylobacter* infection and other infections. Fluoroquinolones (e.g., enrofloxacin) are also used in veterinary medicine. Human infections with fluoroquinolone-resistant *Campylobacter* species have become increasingly common and are associated with consumption of poultry. These findings, along with other data, prompted the US Food and Drug Administration to propose the withdrawal of fluoroquinolone use in poultry in 2000. A lengthy legal hearing concluded with an order to withdraw enrofloxacin from use in poultry (effective in September 2005). Clinicians are likely to continue to encounter patients with fluoroquinolone-resistant *Campylobacter* infection and other enteric infection because of the continued circulation of fluoroquinolone-resistant *Campylobacter* species in poultry flocks and in persons returning from foreign travel who have acquired a fluoroquinolone-resistant enteric infection while abroad. Judicious use of fluoroquinolones and other antimicrobial agents in human and veterinary medicine is essential to preserve the efficacy of these important chemotherapeutic agents.**

CAMPYLOBACTER SPECIES

Campylobacter species are a leading cause of bacterial gastroenteritis in the United States, causing an estimated 1.4 million infections, 13,000 hospitalizations, and 100 deaths annually [1,2]. Approximately 95% of human *Campylobacter* infections are caused by *Campylobacter jejuni*, and 5% are caused by *Campylobacter coli;* human infections caused by other *Campylobacter* species are rare. Most *Campylobacter* infections are mild, self-limiting diarrheal illnesses, but severe infections do occur [3]. Approximately 1 of 1000 *Campylobacter* infections results in Guillain-Barré syndrome, a neurologic complication characterized by paralysis [4].

The primary risk factors associated with *Campylobacter* infection are consuming and handling foods of animal origins, especially poultry products. The epidemiological association between campylobacteriosis and eating undercooked poultry or foods cross-contaminated by raw poultry juices is well documented [5–7]. During 1998–1999, the US Centers for Disease Control and Prevention (CDC) Foodborne Diseases Active Surveillance Network (FoodNet) conducted a case-control study of *Campylobacter* infection and demonstrated that persons with *Campylobacter* infection were twice as likely to have eaten poultry outside of the home than were persons without *Campylobacter* infection [7]. Eating chicken and turkey at a restaurant accounted for 24% and 4% of *Campylobacter* infections, respectively [7].

In addition to epidemiological evidence, microbiological evidence supports poultry as the primary source of human *Campylobacter* infection, including fluoroquinolone-resistant *Campylobacter* infection [8–10]. A pilot survey conducted in the FoodNet sites found that 44% of the 180 retail chicken products tested were contaminated with *Campylobacter* species; 10% of the retail chicken products were contaminated with fluoroquinolone-resistant *Campylobacter* species [9].

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FLUOROQUINOLONES

Many persons with *Campylobacter* infection seek medical care and receive antimicrobial therapy, especially persons with persistent or bloodstream infection and immunocompromised persons. For persons with severe infection, antimicrobial agents may be life saving. Common antimicrobial agents prescribed for *Campylobacter* infection are erythromycin, for children, and a fluoroquinolone, such as ciprofloxacin, for adults [11, 12]. Fluoroquinolones have been available in the United States for human use since 1986 and have been shown to reduce the severity and duration of symptoms associated with campylobacteriosis [13]. Several studies have demonstrated that fluoroquinolone-resistant *Campylobacter* infections are associated with longer symptoms [14, 15] and more frequent hospitalizations (CDC, unpublished data) than fluoroquinolone-susceptible *Campylobacter* infections.

The US Food and Drug Administration (FDA) licensed 2 fluoroquinolones—sarafloxacin in 1995 and enrofloxacin in 1996—for treatment of respiratory diseases in poultry. Fluoroquinolones used in poultry are added to the drinking water and, thereby, administered on a poultry house–wide basis (to 10,000–30,000 birds). Sarafloxacin- and enrofloxacin-resistant *Campylobacter* species are also resistant to ciprofloxacin and other fluoroquinolones used in human medicine [8]. Prior to approving fluoroquinolone use in poultry, a FDA joint advisory committee, consisting of members of the FDA's Veterinary Medicine Advisory Committee and Anti-Infective Drugs Advisory Committee, recommended several conditions for licensure, including no off label use and the establishment of national surveillance of antimicrobial resistance in foodborne bacteria.

FLUOROQUINOLONE-RESISTANT *CAMPYLOBACTER* SPECIES

To monitor antimicrobial resistance in foodborne pathogens, the CDC, in collaboration with the FDA Center for Veterinary Medicine, the Agricultural Research Service of the US Department of Agriculture, and selected state health departments, launched the National Antimicrobial Resistance Monitoring System (NARMS) [16]. In 1997, NARMS began surveillance for antimicrobial-resistant *Campylobacter* species in FoodNet sites; in 2004, these sites included Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, and Tennessee and selected counties in California, Colorado, and New York.

Each week, participating sites selected and forwarded a *Campylobacter* isolate to the CDC for susceptibility testing [17]. Isolates were presumptively identified as *Campylobacter* species by dark field microscopy and the oxidase test. *C. jejuni* isolates were further identified using the hippurate hydrolysis test. Hippurate-negative *C. jejuni* isolates and *C. coli* isolates were identified by PCR [18, 19]. Isolates were then tested for susceptibility to antimicrobial agents, using the Etest system (AB Biodisk) to determine the MIC for 8 antimicrobial agents (azithromycin, chloramphenicol, ciprofloxacin, clindamycin, erythromycin, gentamicin, nalidixic acid, and tetracycline). *Campylobacter* isolates with a ciprofloxacin MIC $\geqslant 4$ μg/mL were considered to be resistant.

Fluoroquinolone-resistant *Campylobacter* species in humans were first reported in the late 1980s and have been documented in numerous countries [20, 21]. Several investigations have demonstrated that an increased prevalence of fluoroquinolone resistance among human *Campylobacter* isolates is temporally related to the introduction of fluoroquinolones in veterinary medicine [9, 21, 22]. Fluoroquinolone-resistant *Campylobacter* species have become increasingly common in the United States. A survey conducted in selected counties by the CDC in 1990 found that none of the 297 human *C. jejuni* or *C. coli* isolates tested resistant to ciprofloxacin. In 1999, 18% of human *Campylobacter* isolates submitted to NARMS were fluoroquinolone resistant [9]. Other evidence supports the conclusion that there was little fluoroquinolone resistance among *Campylobacter* species during the early 1990s in the United States [8, 23, 24]. A study conducted in the University of Pennsylvania Health System did not identify any fluoroquinolone resistance among *C. jejuni* isolates recovered from patients during 1982–1992, but 41% of isolates were found to be resistant in 2001 [23, 24].

The rapid increase in the prevalence of fluoroquinolone resistance among human *Campylobacter* isolates was a cause for concern during the late 1990s. To estimate the risk posed to human health by fluoroquinolone-resistant *Campylobacter* species that were associated with the domestic use of fluoroquinolones in poultry, the FDA Center for Veterinary Medicine developed a quantitative risk assessment model [25]. The model estimated that 153,580 persons were infected with fluoroquinolone-resistant *Campylobacter* species in 1999 as a result of chicken consumption; 9261 of these persons were estimated to have been treated with a fluoroquinolone. The model also estimated that 1.2 billion pounds of boneless chicken contaminated with fluoroquinolone-resistant *Campylobacter* species were consumed in the United States during 1999.

PUBLIC HEALTH ACTION

These data, in addition to FoodNet and NARMS data, prompted the FDA to propose withdrawal of the approval of the new animal drug applications for fluoroquinolone use in poultry, an action that would prohibit fluoroquinolone use in chickens and turkeys in the United States [26]. In October 2000, the FDA issued a Notice of Opportunity for Hearing based on evidence that fluoroquinolone use in poultry caused development of fluoroquinolone-resistant *Campylobacter* species, fluoroquinolone-resistant *Campylobacter* species were transferred

to humans, and fluoroquinolone-resistant *Campylobacter* infections were a hazard to human health. Prior to the issuance of this Notice of Opportunity for Hearing, Abbott Laboratories, sponsor of sarafloxacin, requested withdrawal of the new animal drug application applicable to sarafloxacin, thereby removing sarafloxacin from the market and making the Notice of Opportunity for Hearing only applicable to enrofloxacin use in poultry. In November 2000, Bayer Corporation, sponsor of enrofloxacin, requested a hearing. In February 2002, the FDA's acting deputy commissioner issued a Notice of Hearing, which granted Bayer a formal hearing and identified subjects of discussion for the evidentiary hearing. The Animal Health Institute joined Bayer as a participant in the case.

The interim period, from November 2000 to February 2002, was used by the FDA and Bayer to gather documentary evidence and written, expert witness testimony. After the Notice of Hearing was issued, these supporting documents were submitted in December 2002 to the federal docket, which eventually contained >5000 documents related to this hearing. Both the FDA and the participants (Bayer and the Animal Health Institute) submitted testimony from several expert witnesses. Many of Bayer's expert witnesses reanalyzed data, including FoodNet and NARMS data, that had been used by the FDA to support their position. To obtain these data, Bayer submitted Freedom of Information Act requests to the CDC. During 2001–2005, Bayer submitted 32 Freedom of Information Act requests to the CDC.

An oral hearing for cross-examination of witnesses was held before an FDA administrative law judge from 28 April through 7 May 2003. Of Bayer's expert witnesses who had provided written testimony, the FDA chose only to request oral testimony from Dr. Louis Anthony Cox. Bayer and the Animal Health Institute requested oral testimony from many of the FDA's expert witnesses, including F.J.A., Dr. Mary Bartholomew, Dr. Marja-Liisa Hanninen, Dr. Heidi Kassenborg, Dr. Kirk Smith, Dr. Linda Tollefson, and Dr. Robert Walker. After the hearing, the administrative law judge reviewed all information obtained, including written and verbal expert witness testimony, posthearing briefs, and documentary evidence that had been submitted to the federal docket. An initial decision supporting the withdrawal of the new animal drug application for enrofloxacin in poultry was released in March 2004 [27]. During May 2004, each participant submitted exceptions, challenging legal and factual points to the administrative law judge's initial decision, and in July 2004, each participant submitted responses to each other's exceptions. After review of the entire record and proceedings, the FDA commissioner upheld the administrative law judge's initial decision, ordering that the new animal drug application for enrofloxacin be withdrawn, thereby prohibiting the use of enrofloxacin in poultry (effective in September 2005) [28]. The FDA commissioner's final decision is available on the FDA Web site (http://www.fda.gov/oc/antimicrobial/baytril.html).

CLINICAL IMPLICATIONS OF REGULATORY ACTION

Although the withdrawal of enrofloxacin for use in poultry in the United States became effective in September 2005, it is unlikely that national surveillance will observe a marked decrease in fluoroquinolone-resistant *Campylobacter* infection for several years. Studies have shown that fluoroquinolone-resistant *Campylobacter* species replace the environmental niche once filled by fluoroquinolone-susceptible *Campylobacter* species and may remain in the environment [29]. There is likely to be continued circulation of fluoroquinolone-resistant *Campylobacter* species in poultry flocks. Until fluoroquinolone-susceptible *Campylobacter* species reestablish this environmental niche, clinicians will encounter patients with domestically acquired, fluoroquinolone-resistant *Campylobacter* infection.

Furthermore, 13% of *Campylobacter* infections in the United States are a result of international travel; US regulatory actions are not effective internationally. Clinicians are likely to continue to observe persons returning from foreign travel who have acquired a fluoroquinolone-resistant enteric infection while abroad. Foreign travel, especially to southeast Asia, is a documented risk factor for fluoroquinolone-resistant enteric infections, including *Campylobacter* and *Salmonella* infections [8, 15, 30, 31]. Fluoroquinolones and other antimicrobial agents continue to be widely used in human and veterinary medicine in other countries. Thus, clinicians should consider travel history before empirically treating patients with enteric infections with fluoroquinolones.

The withdrawal of enrofloxacin for use in poultry in the United States may additionally reduce the selective pressure on nontyphoidal *Salmonella* species and other foodborne pathogens. Nontyphoidal *Salmonella* isolates with a decreased susceptibility to fluoroquinolones rapidly emerged following the approval for enrofloxacin in poultry [32]. When this selective pressure is removed, clinicians may observe a reduction in domestically acquired, nontyphoidal *Salmonella* infections that have a decreased susceptibility to fluoroquinolones.

CONCLUSIONS

The decision to withdraw the new animal drug application for enrofloxacin use in poultry was a seminal event, marking the first time an animal drug was removed from the market because of the associated emergence of resistance in humans. These events prompted the FDA to develop an evidence-based approach for approving animal antimicrobial drugs that are of clinical importance to humans. Both new animal antimicrobial drugs and those currently approved and marketed will be evaluated using a system that looks at the probability of emerging

antimicrobial resistance in animals as a result of drug use, the probability that these resistant bacteria will be transferred to humans, and the probability that these resistant bacteria will adversely affect human health [33]. This new animal drug approval system will help preserve the efficacy of antimicrobial agents, such as fluoroquinolones, that are essential to human medicine.

Although improvements to the process for approving new animal antimicrobial drugs have been made, fluoroquinolones and other antimicrobial agents continue to be widely used in human and veterinary medicine. Judicious use of antimicrobial agents should be stressed to preserve the efficacy of these important chemotherapeutic agents.

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