Introduction to the risk assessment

The human health impact of fluoroquinolone-resistant *Campylobacter*

Food borne diseases caused by bacteria have a major public health impact in the United States. Recent estimates describe 5,000 deaths and 76 million cases of food borne illness annually (70). Emergence of antimicrobial resistant and multi-drug resistant bacteria are evident in both human and veterinary medicine (6, 124). Bacterial food borne disease is a growing problem worldwide and has been addressed in many reviews and reports on the topic. In industrialized countries, the food borne pathogens, *Salmonella* and *Campylobacter* are infrequently transferred from person to person. In these countries, epidemiological data has demonstrated that a significant source of antibiotic resistant food borne infections in humans is the acquisition of resistant bacteria from animals via food (36, 92).

Although *Campylobacter* infections are usually self-limiting, antibiotic therapy is used for patients: 1) who demonstrate symptoms of high fever, bloody diarrhea, or more than eight stools in 24 hours; 2) who are immunosuppressed; 3) who have bloodstream infections; or 4) whose symptoms worsen or persist for more than 1 week (12). Antimicrobial therapy can reduce the duration of illness (30, 42). Empiric treatment of patients with enteric disease seeking treatment is the norm because when treatment is delayed (e.g., until *C. jejuni* infection is confirmed by a medical laboratory), therapy may not be effective (12). Fluoroquinolone drugs are frequently used in the empiric treatment of patients presenting to a physician with gastrointestinal symptoms because they exhibit good activity against most enteric pathogens (12, 86).

Campylobacter is the most common known cause of bacterial food borne illness in the United States (22, 95). Campylobacteriosis has been estimated to comprise 14.2% of total food borne illness in the United States and represents 17.3% of total food borne disease hospitalizations (70). Estimates attribute 99 deaths to food borne campylobacteriosis annually, which comprises 5.5% of the total estimated deaths due to food borne pathogens. (70). The incubation period for campylobacteriosis is 1 day to 1 week and infections usually result in mild to moderate symptoms including diarrhea, abdominal pain and fever. Symptoms may last 1 day to 1 week or more, and in up to 20 percent of cases, illness lasts for more than a week (12). Although most cases of campylobacteriosis are self-limiting, some patients experience symptoms sufficiently severe to seek care and take antibiotics for their illness. Relapses occur in approximately 5 to 10% of untreated patients. More invasive disease such as blood infections occur in less than 1% of patients with *C. jejuni* infections and are more common in the elderly or very young individuals (21). Rare manifestations of *C. jejuni* can include meningitis, endocarditis and septic abortion. Persons with immunoglobulin deficiencies may manifest prolonged, severe and recurrent infections (12). Campylobacteriosis has been associated with chronic sequelae that include reactive arthritis, inflammation of the liver and kidney and Guillain-Barré syndrome, a disease that may result in a reversible paralysis (12).

Antimicrobial drugs are used in food-producing animals to treat, prevent and control disease and to improve growth and feed efficiency. In the United States, regulatory terminology names these products "new animal drugs." Before any new animal drug can be approved in the United States, the drug's sponsor must demonstrate that the product is safe and effective for its intended use. If the antimicrobial is intended for use in food producing animals, the drug sponsor must demonstrate safety for consumers of edible animal products, as well as safety for use in the animal.

Selection for antimicrobial resistant and multi-drug resistant bacteria is a hazard associated with drug use in both human and veterinary medicine (6, 124). Animals serve as reservoirs for many food borne pathogens, including *Salmonella* and *Campylobacter*. Antibiotic resistant food borne pathogens may be present in or on animals as a result of drug use in animals. When an animal is treated with an antimicrobial drug, a selective pressure is applied to all bacteria associated with that animal. Bacteria that are sensitive to the antimicrobial are killed, while bacteria that have the ability to resist the antimicrobial can persist and

replace the sensitive bacteria. In addition, bacteria can become resistant when resistance genes are passed from a resistant bacterium to a sensitive one. Thus, antimicrobial agents may increase the prevalence of resistant bacteria among both target pathogens and normal bacterial flora. These resistant food borne pathogens, like susceptible pathogens, may contaminate a carcass at slaughter (100, 101), and can be transmitted to humans through consumption and handling of contaminated food (32, 33, 45, 46). When these bacteria cause an illness that needs treatment, medical therapy may be compromised if the pathogenic bacteria are resistant to the drug(s) used for treatment (42, 80).

The magnitude of the public health risk associated with antimicrobial use in animals has been debated for over thirty years. Since the approval of fluoroquinolones for use in food producing animals, reports have identified a relationship between the approval of fluoroquinolones for therapeutic use in food producing animals and the development of fluoroquinolone resistance in *Campylobacter* in animals and humans (36, 79, 92). The approval of these drugs in food-producing animals in the Netherlands, (36, 58, 80), Spain (79, 116) and the United States (92) temporally preceded increases in resistance in *Campylobacter* isolates from treated animals and ill humans. Despite several restrictions placed on the use of the two approved poultry fluoroquinolone products in the United States, fluoroquinolone-resistant isolates were recently identified on 24 percent of domestic retail chicken products from which *Campylobacter* were isolated (82). Molecular subtyping revealed an association between resistant *C. jejuni* strains from chicken products and *C. jejuni* strains from domestically acquired human cases of campylobacteriosis (92). To date, fluoroquinolone resistance has not been observed in *Salmonella* species associated with poultry in the U.S. (23).

Based upon emerging scientific evidence that therapeutic uses of antimicrobials in food-producing animals, in addition to subtherapeutic feed uses, may select for resistant bacteria of human health concern, the FDA announced in November 1998 draft guidance for industry (GFI # 78) on this subject. This GFI which was finalized in December 1999 (available at http://www.fda.gov/cvm/) states that FDA believes it is necessary to consider the potential human health impact of the microbial effects associated with all uses of all classes of antimicrobial new animal drugs intended for use in food-producing animals when approving such drugs. In December 1998, CVM issued a discussion document entitled "A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals." This document set out FDA's concept of a regulatory system that could be used for antimicrobials for use in food producing animals to address microbial safety concerns. To assess microbial safety, the document discussed the need to consider both the importance of the drug to human medicine and the potential human exposure to resistant bacteria acquired from food producing animals that are human pathogens or that can transfer their resistance to human pathogens. The document articulated the need to determine acceptable levels of resistant bacteria in animal products (thresholds) to ensure that the effectiveness of human antimicrobials would not be compromised.

To evaluate the human health impact of antimicrobial use in animals, the FDA Center for Veterinary Medicine (CVM) developed a quantitative risk assessment model. The risk assessment was intended to estimate the risk to human health from antibiotic resistant food borne pathogens associated with the domestic use of antimicrobials in food producing animals. Specifically, a mathematical model was derived to relate the prevalence of fluoroquinolone resistant *Campylobacter* infections in humans associated with the consumption of chicken to the prevalence of fluoroquinolone resistant *Campylobacter* in chickens.

Rationale for this risk assessment

The use of fluoroquinolones in chickens and the development of resistant *Campylobacter* in chickens were of concern for several reasons. First, chickens are reservoirs for many food borne pathogens including *Campylobacter* and *Salmonella*. For example, broiler carcass contamination measured in the processing plant estimates that 20% of broiler chickens in the United States are contaminated with *Salmonella* and over 80% are contaminated with *Campylobacter* (104). Consumption of food contaminated with these bacteria can lead to illness in susceptible individuals (12, 28, 45). Second, *Campylobacter* is the most common known cause of bacterial food borne illness in the United States (21, 22, 95). Sporadic cases of *Campylobacter* account for approximately 99% of all *Campylobacter* cases (95). Epidemiological investigations of sporadic infections have indicated that chicken is the most common source of human infection (3, 92, 95). Also, slaughter and processing of chickens may result in bacterial contamination on

the carcass that can survive on retail product and result in human exposure during food preparation and consumption (29, 101, 104). Third, *Campylobacter* has been reported to develop resistance when fluoroquinolones are used. (57, 58, 79, 80). Finally, fluoroquinolones are used in human medicine empirically to treat gastrointestinal infections, such as campylobacteriosis and are important for use in many other therapeutic indications in human medicine (86). Increasing levels of resistance reduce the utility of fluoroquinolones in the empiric treatment of enteric illness (12, 42, 80, 125).

The model assumes that resistant bacteria pass through the food supply, infect humans and are treated in the same manner as susceptible bacteria. The health risk associated with antimicrobial resistant bacteria represents an increase in risk to consumers because resistance to an antimicrobial used in human medicine can compromise the effectiveness of therapy. Using this approach, the incremental human health impact of resistant food borne disease can be determined without assessing all the factors influencing the cause of the food borne illness itself.

To limit the complexity of the assessment, only the human health risk associated with the use of fluoroquinolones in chickens was assessed. Fluoroquinolones were chosen because of their importance in treating enteric infections in humans (86). Information from USDA and CDC on sources of food borne disease indicated that chicken carcasses carry a relatively high level of *Campylobacter* and are associated with a large number of cases of food borne illness (95, 104). *Salmonella* was not included in the model because, as indicated earlier, fluoroquinolone resistance has not been observed in *Salmonella* species associated with poultry.

Although the predominant feature of this risk assessment is to quantify the risk to human health, it is important that the level of risk be viewed in context of the data used to model the risk. This risk assessment has provided insight into the strengths and limitations of the data available to quantify the impact of fluoroquinolone resistant *Campylobacter* associated with consumption of chicken on human health. Data used in the risk assessment were relevant to the model design and were selected based upon the robustness and validity of the scientific methods used by the investigators. The data met high standards for validity of associations/relationships and were selected based upon a strong body of scientific evidence, consistent across studies. While assembling the data to be used, some limitations were raised and were addressed as data gaps and assumptions. Where feasible, the use of data requiring an assumption is evaluated and the impact of that use is stated and discussed. In addition, with inclusion of 1999 data some assumptions needed for the draft version were no longer necessary. Benefits of conducting this risk assessment include a review of surveillance data collection methods and recommendations for enhancing the relevance of data collection for the quantification of the impact of resistant food borne pathogens on human health (See Sections 3 and 5). Significantly, this risk assessment has quantitatively demonstrated that resistance development in bacteria from food-producing animals presents a risk to human health.

The major strengths of this model are its mathematical simplicity and ease with which it can be updated as new data become available. The model provides a quickly and continuously updateable method of estimating the current human health impact. Given a projection of future prevalence of resistance in poultry carcasses for example, or projections of any other modeled parameter, it will allow a prediction of a future human health impact.

The model assumes that the presence of resistant C*ampylobacter* on the animal carcass was due to antimicrobial drug use. Because of data supporting the linkage between antimicrobial drug use and antimicrobial resistance in animals in studies and surveillance, this assumption is considered to be scientifically sound (36, 58, 79, 92, 116). The model quantifies the level of risk due to consumption of chicken and has not quantified the impact of the spread of the pathogen from chicken to other food sources due to lack of data. This can occur from cross contamination of other foods by chicken (29) or from the spread from chicken sources to other animal reservoirs of human exposure more proximate to the farm.

Modeling method used

While the safety assessments for food additives, veterinary drugs and pesticides are very standardized and accepted internationally, microbial risk assessments are relatively new, with no formal procedures. Microbial food safety problems are generally extremely complicated and assessment requires a great deal of data. To date, about a half-dozen microbial risk assessment models have been published that attempt a full quantitative assessment of the public health risks of microbial contamination[1]. These models use only very specific products and very limiting assumptions and have not been used by regulatory agencies to set limits on the amount of bacterial contamination permitted in food. Under the President's Food Safety Initiative, the charge to government agencies with respect to risk assessment is to develop better data and modeling techniques to help characterize the nature and size of risks to human health associated with foodborne hazards (5).

The risk assessment developed for FDA estimates the relationship between the level of fluoroquinolone resistance in poultry and the human health impact that results.

The model achieves the following goals:

- Assessment of the human health impact of fluoroquinolone-resistant *Campylobacter* from broilers;
- Provision of a transparent and robust assessment, based on published and, where necessary, regularly revised data to the extent that it is available;
- Allowance of future important changes in the system being modeled

This section provides an overview of the modeling approach FDA has taken in assessing this risk issue. It explains why a more traditional microbial risk assessment was not adopted and how the model that has been developed can be used as a predictive tool for evaluating future human health impact resulting from fluoroquinolone resistant *Campylobacter* in poultry.

Comparing a more traditional 'farm-to-fork' risk assessment with the FDA-CVM approach

The approach used by the FDA model is innovative. The approach that has more typically been taken in addressing a microbial food safety problem has been to model the microbial pathways at all stages from production of the animal to final ingestion and any resultant illness (69A). Thus, the approach used here has been misunderstood and questions have been raised as to why a full microbial risk assessment, or some of its components, were not developed. This sub-section explains why the FDA approach was taken, its advantages and disadvantages.

A food safety microbial risk assessment typically tracks the prevalence and level of bacterial contamination of food products from the farm to the table (69A). These risk assessments consider various cross-contamination and microbial growth and reduction events during every stage of the farm to table process, for example slaughtering, processing, transportation, storage, retail and food handling prior to consumption. They take considerable time and effort to complete. The models are necessarily quite complex but still make very general assumptions. For example, it is extremely difficult to model inter-individual variability (differences between elements at each stage of the process, e.g. due to flock sizes, carcass sizes, variations in processing methods and their interactions), stochastic variability (randomness) and uncertainty (lack of complete knowledge of the values of the model's parameters). Including all three correctly requires a three-dimensional model, which would be enormously complex and impractical to either write or run. Simplification is therefore necessary: for example calculating mean values throughout rather than inter-individual or stochastic distributions and simulating only the model parameter uncertainty. Nonetheless,

[1] Examples of microbial risk assessments are available at USDA-Food Safety Inspection Service (http://www.fsis.usda.gov) and FDA- Center for Food Safety and Nutrition (http://vm.cfsan.fda.gov).

these models are useful because they model the entire process and can therefore provide some information on the effect on microbial contamination of changes in practice or conditions at any point in the process.

At the end of a full microbial food safety risk assessment, one has to translate the prevalence and level of microbial contamination of the food consumed, including any cross-contamination of otherwise unrelated food products, into the resultant human health impact. This necessitates a good knowledge of both the consumption patterns of the population at risk and the appropriate dose-response relationships. The dose-response relationship describes the probability of being infected (or becoming ill, or suffering various degrees of illness, or death) given some ingested dose. Each individual consumption event has associated with it some dose-response relationship. This is because for any specific number of organisms ingested the probability of infection, etc. depends on the age, size, health status, etc. of the exposed person, as well as the immediate circumstances surrounding the ingestion event, (e.g. did the person consume the product in a small or large meal? what condition were the bacteria in at the moment of ingestion? was the product consumed in a fatty matrix? had the person recently undergone any antibiotic therapy? etc.).

Data, if available for the dose-response part of a microbial risk assessment, usually come from old dose-response experiments on a small number of students or armed forces personnel, with little background information on the condition and medical history of the participants. Occasionally, one can learn from outbreaks where the food source has been preserved, but the lack of control (knowing how much each person consumed, etc.) makes the data difficult to analyze. The type of dose-response model to use, the uncertainty in the available data and the use of other bacteria as a surrogate where no directly relevant data are available, can add orders of magnitude of uncertainty to the risk assessment model.

The FDA-CVM model described in this report is not an attempt at a full microbial food safety risk assessment. The modeling approach we have used has been designed to address the effect of specific risk management actions, while also providing the facility to take into account the effect of the most important future changes in the physical system, for example changes in: consumption volumes; the prevalence of contaminated food; the microbial load on contaminated product and the fluoroquinolone prescription rate. For most parameters relevant *Campylobacter* data were available and there was thus little need to use surrogate data. The approach we have used does not model the many processes between farm and table for which we have little or no information. Instead, it relies on connecting what has been observed in the human population with the contaminated food to which they were exposed.

One must be cautious in using a sequential (i.e. one step following on from the previous) risk assessment model like a more usual microbial risk assessment that follows bacteria from ‘farm to fork’ when it is not possible to verify the accuracy of the intermediary steps. To illustrate, suppose that the model assumed to apply in a given situation is:

$$x \Longrightarrow x * a \Longrightarrow x * a * b$$

where x and y =x * a * b are quantities that can be observed. Once the parameters a and b have been quantified, we can observe a value for x and predict the value of y. One can later check that the predicted and observed values of y correspond. Now, based on the assumed model, if something were done that reduced b to half its value, the value of y would be expected to correspondingly drop by a factor of 2. But if the true relationship had been:

$$x \Longrightarrow x * a \Longrightarrow x * a \wedge b$$

then by reducing b to half its value, the value of y would actually drop by a factor of $a \wedge (b/2)$ rather than by the factor of 2 predicted under the incorrectly assumed model. If we were able to observe an intermediary step, like x * a, we would be able to check that the model was reasonable, but without any intermediary data we cannot.

It is therefore very helpful to have constructed a model whose parameter values and moreover whose structural assumptions can be readily verified by comparing predicted and observed values. The level of

complexity of a full microbial food safety risk assessment means that it is at best difficult, and frequently impossible without considerably more data, to validate a model in terms of both its structure and model parameter values. The FDA-CVM model on the other hand has a very simple logic with one fundamental model assumption (that the amount of contaminated meat is roughly proportional to the number of people who become ill from consuming it), which can be tested. It is unlikely that this assumption is statistically exact, but it makes logical sense and is likely accurate..

Using the FDA model to predict future human health impact

Accounting for future changes in medical practice, patient behavior, and resistant Campylobacter prevalence in poultry

The ratios $\lambda 3_n/V_i$, $\lambda 3_b/V_i$ and $\lambda 3_i/V_i$, which have the labels K_n, K_b, and K_i respectively, estimate per pound of contaminated meat the expected number of people who would suffer non-bloody and bloody enteric infections and invasive fluoroquinolone resistant *Campylobacter* infections respectively. These ratios can then be used to predict the expected number of cases of fluoroquinolone resistant *Campylobacter* human infection that would seek care and be prescribed a fluoroquinolone in the future as follows:

$$\left.\begin{aligned}
\lambda 4_n(t) &= K_n * V_i(t) * p_{mn}(t) * p_{an}(t) * p_{FQ}(t) \\
\lambda 4_b(t) &= K_b * V_i(t) * p_{mb}(t) * p_{ab}(t) * p_{FQ}(t) \\
\lambda 4_i(t) &= K_i * V_i(t) * p_{FQ}(t) \\
\lambda 4_T(t) &= \lambda 4_n(t) + \lambda 4_b(t) + \lambda 4_i(t)
\end{aligned}\right\} \quad \text{Equation set 1.}$$

Where:

Subscript (t) represents an estimation of the parameter value at some year t;

$p_{mn}(t)$, $p_{an}(t)$, $p_{FQ}(t)$, etc. are the model parameter values (with the (t) subscript added), described in Section 3, estimated for year t. ($p_{mi}(t)$ and $p_{ai}(t)$ are equal to 1.) These can be updated if there are any changes in medical practice and willingness to seek health care between now and year t or left at the estimates used in the current model otherwise.

This model can therefore estimate the level of human health impact from fluoroquinolone-resistant *Campylobacter* from poultry with new predicted levels of contamination of the food, changes in quantity of food consumed, plus any significant changes in the health practice. The number of actual affected *Campylobacter* cases in year t is thus calculated using the Poisson distribution, i.e. = Poisson($\lambda 4_n(t)$), Poisson($\lambda 4_b(t)$), and Poisson($\lambda 4_i(t)$) for non-bloody and bloody diarrhea and invasive case respectively, and a total number of cases given by:

Total affected cases = Poisson($\lambda 4_n(t) + \lambda 4_b(t) + \lambda 4_i(t)$)

Accounting for changes in the number of U.S. citizens

Changes in the number of U.S. citizens are irrelevant to the problem except to the degree it affects the quantity of poultry meat that is consumed, which is accounted for in the estimation of V_i.

Accounting for changes in the bacterial load of contaminated carcasses
Adjustments can be made in the model for changes in the bacterial load of contaminated carcasses. For example, if irradiation was to be introduced into some plants that processed the fraction q of all domestically reared poultry, and if this irradiation effectively killed all bacteria on carcasses that were so processed, the model would be revised as follows:

$$\left.\begin{aligned}
\lambda 4_n(t) &= K_n * (1-q) * V_i(t) * p_{mn}(t) * p_{an}(t) * p_{FQ}(t) \\
\lambda 4_b(t) &= K_b * (1-q) * V_i(t) * p_{mb}(t) * p_{ab}(t) * p_{FQ}(t) \\
\lambda 4_i(t) &= K_i * (1-q) * V_i(t) * p_{FQ}(t) \\
\lambda 4_T(t) &= \lambda 4_n(t) + \lambda 4_b(t) + \lambda 4_i(t)
\end{aligned}\right\} \quad \text{Equation set 2.}$$

Other *changes in farm and slaughterhouse practices* that reduced the microbial load on contaminated carcasses can be taken into account in an approximate way. We can do this by making use of a property of the logexponential distribution. If a random variable is logexponentially distributed, dividing that variable by some factor greater than 1 has the effect of simply shifting the distribution to the left, which means that the resultant distribution, conditional on the variable being greater than zero, is identical to the original distribution.

Let us assume that the *Campylobacter* load L on contaminated carcasses is logexponentially distributed (i.e. L = 10^Expon(β)) and that some improvement in production practices has decreased the load on contaminated carcasses by some factor d. Then the new load L^{∇} takes the form:

$$\text{Log}_{10}(L^{\nabla}) = \text{Expon}(\beta) - \text{Log}_{10}(d)$$

The probability that L^{∇} is less than 1 (i.e. there are no bacteria on the carcass) is given by:

$$\begin{aligned}
P(L^{\nabla}<1) &= P(\text{Log}_{10}(L^{\nabla}) < 0) \\
&= P(\text{Expon}(\beta) < \text{Log}_{10}(d)) \\
&= 1 - \text{Exp}(-\text{Log}_{10}(d)/\beta)
\end{aligned}$$

Thus to correct for a reduction in microbial load of carcasses in some year t, we would first fit a logexponential distribution to data on past carcass load to determine a value for β. Then, we would make a correction to our estimate of human health impact by reducing the effective prevalence of contaminated carcasses to $p_p * \text{Exp}(-\text{Log}_{10}(d)/\beta)$, where p_p is the model parameter described in Section 4. Our predictive estimate of human health cases would be as in equation set 2, except that now $V_i(t) = p_p * \text{Exp}(-\text{Log}_{10}(d)/\beta)$

FDA model as a generic method

This risk assessment was developed to address a significant risk issue, but had several other goals:

- To evaluate how results from survey programs and laboratory tests and other data sources can be used most effectively in risk assessments and to identify collection methods that would maximize the value of data for risk assessment. This point is addressed in Discussion of Results below.
- To develop a methodology that could be used across a range of antimicrobial resistance issues.

The purpose of the last goal is to allow the maximum amount of transparency and consistency between all risk assessments FDA undertakes to address microbial resistance issues. The modeling approach used here achieves that goal because it requires the minimum amount of data to perform the assessment, as well as making as few assumptions as possible. The concepts of the approach should be applicable wherever one can:

- Identify source items of contamination and estimate their number;
- Identify and estimate the level of impact that these contaminated items result in; and
- Identify risk management options that FDA can take, and estimate the level to which they will reduce or contain the impact.

Despite having developed a generic approach, each risk assessment will nonetheless require sufficient amounts of data to estimate the necessary parameters before a quantitative assessment like the one carried out in this report can be accomplished.

Discussion of results

This risk assessment model has provided a quantitative estimate of the human health impact resulting from fluoroquinolone-resistant *Campylobacter* on poultry. 1998 and 1999 were modeled side-by-side in an @RISK/Excel spreadsheet simulation model. Any parameter that was common to both years was modeled in one cell and referred to wherever necessary, which ensured consistency between model iterations.

The model produced a number of outputs for both 1998 and 1999:

- Estimates of the probability a person would be affected by the risk in question for various U.S. sub-populations. Probabilities were provided as fractions and 1 in x estimates;
- Estimates of nominal mean number of *Campylobacter* cases in U.S. population ($\lambda 2_T$);
- Estimates of nominal mean number of fluoroquinolone resistant *Campylobacter* cases attributable to chicken ($\lambda 3_T$);
- Estimates of nominal mean number of fluoroquinolone-resistant *Campylobacter* cases attributable to chicken, seeking care, treated with fluoroquinolone and therefore affected by the fluoroquinolone resistance ($\lambda 4_T$); and
- Estimates of total consumption of boneless, domestically reared chicken contaminated at slaughter plant with fluoroquinolone-resistant *Campylobacter* in U.S. in pounds ($\mathbf{V_i}$).

These estimates all attempted to assess the recent level of the problem, and are discussed in Sections 2 to 4.

K_{all} and K_{res}

Aside from the probabilities, two 'K' values were calculated, K_{all} and K_{res}, which represent the potential of poultry meat contaminated with *Campylobacter* and fluoroquinolone resistant *Campylobacter* respectively to result in human illness. These parameters are calculated as follows:

$$K_{all} = \frac{\text{Nominal mean number of } \textit{Campylobacter} \text{ cases attributable to chicken}}{\text{Estimated amount of } \textit{Campylobacter}\text{-contaminated chicken meat consumed}}$$

$$K_{res} = \frac{\text{Nominal mean number of fluoroquinolone resistant } \textit{Campylobacter} \text{ cases from chicken}}{\text{Estimated amount of fluoroquinolone resistant } \textit{Campylobacter}\text{-contaminated chicken meat consumed}}$$

The K values can be thought of as the probability that a pound of *Campylobacter* contaminated chicken meat (in general, and resistant) will result in a case of campylobacteriosis (in general and resistant). If the

distributions of the total number of *Campylobacter* that reside on resistant and susceptible *Campylobacter*-contaminated carcasses are the same, and if resistant and susceptible *Campylobacter* have similar survivability and virulence, it is reasonable to assume that these values will be roughly equivalent. The importance of these K-values as a predictive tool has been discussed in this section and will be again in Section 5 where the theory behind them is presented. Figures 5.2 to 5.4 plot these K estimates. There is strong agreement between years: i.e., the differences between the 1998 and 1999 distributions for both parameters are very small compared to the total uncertainty being described by the distributions' ranges. The difference in the spread of the 1998 and 1999 K_{all} distributions noted in Figure 5.2 is due to the increase in the catchment population and the concomitant decrease in uncertainty.There is also reasonable overlap between K_{res} and K_{all}, though K_{res} is consistently estimated as larger than K_{all}. Two of the most logical reasons for this difference are that the prevalence estimate of fluoroquinolone resistant-*Campylobacter* on carcasses is too small (about half of what it should be) because:

1. The estimate used in this analysis came from an unweighted analysis of NARMS chicken isolate test results. An analysis that weighted the state prevalence by the production in pounds of chicken gives a significantly higher result (12.0% for the weighted modeled result vs. 10.3% for the unweighted modeled result in 1999).

2. NARMS testing procedures take one isolate from a cultured dish, and test that isolate for resistance. This would provide a good estimate of resistance prevalence if all *Campylobacter* on a fluoroquinolone resistant-contaminated carcass were resistant. However, if there are also susceptible *Campylobacter* present, the isolate selected from a cultured dish may be a susceptible *Campylobacter* mixed in a population of resistant *Campylobacter*. So, for example, if a carcass contaminated with resistant-*Campylobacter* had, on average, a 50% mix of resistant and susceptible *Campylobacter*, the observed resistance prevalence from NARMS isolates would be about half the true prevalence. Data are not currently available on the distribution of ratio between susceptible and resistant *Campylobacter* on a carcass, but would be extremely useful to get a clearer picture of the risk issue.

In addition to the two reasons for underestimation of K_{res} above, it may also be that the assumptions, i.e. same distribution of number of *Campylobacter* reside on resistant and susceptible *Campylobacter*-contaminated carcasses, and resistant and susceptible *Campylobacter* have similar survivability and virulence, in comparing the two K values may need to be reevaluated. If differences are observed in K_{res} or K_{all}, when making comparisons between years, these differences may be explained by changes in the: 1) prevalence of resistance in travelers, 2) prevalence of resistance on imported food or 3) use of the drug in other food animal species and many other factors.

Measuring the human health impact

1. Probability

First of all, we can assess the level of risk by calculating the ratio of the nominal mean number of fluoroquinolone-resistant *Campylobacter* cases attributable to chicken, seeking care, treated with fluoroquinolone and therefore affected by the fluoroquinolone resistance each year ($\lambda 4_T$), to the size of the population at risk. There are various options one may select as the population at risk, shown in the table below:

Table I.1: Confidence intervals for estimates of **probability** of being affected by fluoroquinolone resistant *Campylobacter* for various groups

	1998			**1999**		
Exposed group	5^{th} percentile	Mean	95^{th} percentile	5^{th} percentile	Mean	95^{th} percentile
U.S. citizens	0.0018%	0.0032%	0.0053%	0.0019%	0.0034%	0.0056%
U.S. citizens with campylobacteriosis	0.31%	0.50%	0.72%	0.44%	0.68%	0.98%
U.S. citizens with campylobacteriosis seeking care	1.38%	2.11%	2.95%	1.94%	2.89%	3.99%
U.S. citizens with campylobacteriosis seeking care and prescribed antibiotic	3.01%	4.49%	6.17%	4.24%	6.15%	8.28%

Table I.2: Confidence intervals for estimates of 1 in **x** of being affected by fluoroquinolone resistant *Campylobacter* for various groups

	1998			**1999**		
Exposed group	5^{th} percentile	Mean	95^{th} percentile	5^{th} percentile	Mean	95^{th} percentile
U.S. citizens	56,795	34,945	18,808	52,166	32,912	17,792
U.S. citizens with campylobacteriosis	319	214	139	227	156	102
U.S. citizens with campylobacteriosis seeking care	72	50	34	51	36	25
U.S. citizens with campylobacteriosis seeking care and prescribed antibiotic	33	23	16	24	17	12

Table I.1 gives estimates of the probability, with confidence intervals, that an individual randomly chosen from the selected denominator population at risk in 1998 and 1999 would have numbered among those for whom fluoroquinolone resistant *Campylobacter* in broilers resulted in a health impact ($\lambda 4_T$). Table I.2 offers an alternative expression of the probability as 1 in x that many people find easier to interpret. The tables show mean estimates and the uncertainty around these values.

The size of the risk may be viewed differently depending on an individual's personal circumstances. For the average U.S. citizen, the risk may well be perceived presently as being very small: we have estimated that 1 in 34,945 people were affected in 1998 and 1 in 32,912 in 1999, for example. On the other extreme, people with reduced immunity who may be more likely to seek medical help, may perceive the risk as quite significant. The results are presented with four different denominators.

The first denominator distributes the risk among the entire U.S. population. The great majority of the U.S. population consumes chicken, and the consumption of a fluoroquinolone resistant *Campylobacter* contaminated chicken product, or consumption of another food item contaminated by chicken (e.g. salad) is a random process. Thus, the great majority of people are exposed to the risk and the randomness of the process means that most people are not in full control of that risk. They may consume the food at a restaurant, other type of food outlet or the home of someone else. Considering only those people in the U.S. population who consume chicken could refine this denominator a little.

The second denominator distributes the risk among people who contract campylobacteriosis from any source. These people will potentially seek medical care and may be prescribed a fluoroquinolone. This denominator puts the risk from fluoroquinolone resistant *Campylobacter* from broilers into context with the total sources of *Campylobacter* infections. Thus, one can make statements like "0.68% of people contracting campylobacteriosis in 1999 were affected by the risk".

The third denominator distributes the risk among those people who contract campylobacteriosis from any source and then seek some medical care. These people are sufficiently ill that they decide they need help. This denominator includes consideration of those people who may be more susceptible to *Campylobacter* than most.

The fourth denominator distributes the risk among those people who contract campylobacteriosis from any source, seek some medical care and are prescribed a fluoroquinolone. Both they themselves and their medical practitioner consider these people sick. The definition represents the group that is most seriously at risk from the failure of fluoroquinolone therapy.

2. Number of cases

The level of human health burden may alternatively be measured simply as the number of people who contract fluoroquinolone resistant campylobacteriosis in a year where the *Campylobacter* is associated with domestically reared broilers ($\lambda 4_T$).

3. Incremental days of illness

A third option is to measure the human health impact as the number of extra people-days of illness that occur as a result of fluoroquinolone resistant *Campylobacter* associated with domestically reared broilers. This would potentially recognize that those people with invasive infection would have a much larger incremental duration of illness than those with enteric infection. However, problems arise in the definition of duration. In addition, there is no substantial evidence to suggest that people with enteric infection and bloody diarrhea will be ill longer than those with enteric infection and non-bloody diarrhea. Since some 99.6% of estimated cases of campylobacteriosis are enteric infections, calculating the number of incremental days of illness would amount to multiplying the number of enteric infections by some constant factor which was a difference of two medians, equivalent to a 3 day difference (92) or a mean difference of 2 days in the CDC *Campylobacter* Case Control Study (28).

If fluoroquinolone–resistant *Campylobacter* were demonstrated to induce more severe or longer illness than susceptible strains, then incremental days of illness would become a more relevant measure of the human health impact. We have not included this measurement of human health impact in the report.

Using the model to determine the adverse human health impact

This risk assessment estimates the human health impact arising from the observed fluoroquinolone-resistant *Campylobacter* prevalence in broiler carcasses. It effectively derives a ratio (given the label K_{res} described below) between the number of affected people ($\lambda 4_T$ in the model) and the volume of contaminated meat (V_i in the model). The model as it stands provides a quickly and continuously updateable method of estimating the current human health impact. There is considerable uncertainty in estimating the ratio K_{res} because of imperfect data, but further data and more years of monitoring would improve this estimate.

The parameter K_{res} relates the *current* (i.e., year of human illness data used) ability of a pound of fluoroquinolone-resistant *Campylobacter* contaminated poultry meat to cause human illness. It implicitly takes into account the variety of paths that a quantity of poultry meat may take, including being thrown away, being well-cooked, cross-contaminating some other food product, etc. Change outside of the defined parameters of the model would make a past value of K_{res} irrelevant. However, approximate corrections can be made to K_{res} to take account of such effects.

The model discussed here can be improved by continuously collecting data on fluoroquinolone resistant and susceptible *Campylobacter* human health impacts. This will have two benefits:

1. one can verify that the model is working as it should (i.e. it is probabilistically predicting the observed infections)
2. knowledge of the value for K_{res} will improve with more data

Contents of this report

This risk assessment consists of this introduction, an overview, five sections describing outputs, two appendices and a list of references.

The Overview describes this report and the model structure.

Section 1 explains the process of determining the estimated number of reportable cases to the CDC's active surveillance system in the FoodNet catchment area from the total number of culture confirmed cases reported in a given year. It also details how the total number of culture-confirmed cases is apportioned into confirmed cases of invasive or enteric campylobacteriosis.

Section 2 uses the estimated number of reportable cases in the catchment, calculated in Section 1, to estimate the predicted total number of *Campylobacter* cases in the U.S. For 1999 the model gives a mean estimate number of 1.38 million expected cases of campylobacteriosis and 5^{th} and 95^{th} percentile estimates of 0.867 and 2.16 million cases. The large degree of uncertainty in the estimates reflects the compounding uncertainty from each parameter of the model.

Section 3 estimates the number of individuals that acquire fluoroquinolone-resistant infections associated with consuming chicken and subsequently receive fluoroquinolone treatment. The results of this section showed that in 1999 about 9,261 people were expected to be infected with fluoroquinolone resistant *Campylobacter* from consuming chicken and received fluoroquinolones as therapy. The model gives 5^{th} and 95^{th} percentile estimates of 5,227 and 15,326 cases. It was assumed that all individuals with a fluoroquinolone resistant infection would experience a longer illness when treated with a fluoroquinolone due to a decrease in effectiveness of the drug. The fairly broad confidence interval is reflective of the lack of certainty in the various parameters used in the model in this section.

Section 4 estimates the pounds of boneless product carrying fluoroquinolone resistant *Campylobacter* consumed in a year. The mean value in 1999 for this estimate is 1,243,017,872 with 5^{th} and 95^{th} percentile estimates of the distribution of 968,000,000 and 1,540,000,000.

Section 5 proposes options for measuring the risk. In Section 5, the human health risk is assessed for different population bases. A description of the calculation of the parameter K, relating human health impact to quantity of contaminated product consumed, is provided. An example of how K is used for prediction of human health impacts in light of changes in model inputs is also given. Properties of the model are explored. In particular, sensitivity analyses are presented. Graphs display the relative effects of uncertainty in the model input parameters on the uncertainty in the key model output parameters.

Appendix A describes Bayesian and frequentist approaches to uncertainty. Appendix B lists assumptions used in the model.