Human Health Impact of Fluoroquinolone Resistant Campylobacter Attributed to the Consumption of Chicken

Food and Drug Administration
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Introduction to the risk assessment

The human health impact from 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, which is 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 (insert refs from above). 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.

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[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).

Nonetheless, 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:

$$x \Rightarrow x * a \Rightarrow x * a * b$$

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:

$$x \Rightarrow x * a \Rightarrow x * a ^\wedge b$$

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:

$$\lambda 4_n(t) = K_n * V_i(t) * p_{mn}(t) * p_{an}(t) * p_{FQ}(t)$$
$$\lambda 4_b(t) = K_b * V_i(t) * p_{mb}(t) * p_{ab}(t) * p_{FQ}(t)$$
$$\lambda 4_i(t) = K_i * V_i(t) * p_{FQ}(t)$$
$$\lambda 4_T(t) = \lambda 4_n(t) + \lambda 4_b(t) + \lambda 4_i(t)$$

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. $= \text{Poisson}(\lambda 4_n(t))$, $\text{Poisson}(\lambda 4_b(t))$, and $\text{Poisson}(\lambda 4_i(t))$ for non-bloody and bloody diarrhea and invasive case respectively, and a total number of cases given by:

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

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:

$$\lambda 4_n(t) = K_n * (1\text{-}q) * V_i(t) * p_{mn}(t) * p_{an}(t) * p_{FQ}(t)$$
$$\lambda 4_b(t) = K_b * (1\text{-}q) * V_i(t) * p_{mb}(t) * p_{ab}(t) * p_{FQ}(t)$$
$$\lambda 4_i(t) = K_i * (1\text{-}q) * V_i(t) * p_{FQ}(t)$$
$$\lambda 4_T(t) = \lambda 4_n(t) + \lambda 4_b(t) + \lambda 4_i(t)$$

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. $L = 10\text{^Expon}(\beta)$) 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:

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

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 (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} = $\dfrac{\text{Nominal mean number of } Campylobacter \text{ cases attributable to chicken}}{\text{Estimated amount of } Campylobacter\text{-contaminated chicken meat consumed}}$

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

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. 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

Exposed group	1998			1999		
	5th percentile	Mean	95th percentile	5th percentile	Mean	95th percentile
U.S. citizens	0.0018%	0.0032%	0.0054%	0.0023%	0.0042%	0.0070%
U.S. citizens with campylobacteriosis	0.31%	0.50%	0.72%	0.44%	0.68%	0.97%
U.S. citizens with campylobacteriosis seeking care	1.40%	2.11%	2.95%	1.94%	2.89%	3.98%
U.S. citizens with campylobacteriosis seeking care and prescribed antibiotic	3.03%	4.49%	6.17%	4.22%	6.16%	8.33%

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

Exposed group	1998			1999		
	5th percentile	Mean	95th percentile	5th percentile	Mean	95th percentile
U.S. citizens	55,687	34,651	18,397	42,526	26,639	14,369
U.S. citizens with campylobacteriosis	316.9	214.3	138.6	226.3	155.5	103.5
U.S. citizens with campylobacteriosis seeking care	71.63	50.07	33.86	51.45	36.34	25.10
U.S. citizens with campylobacteriosis seeking care and prescribed antibiotic	33.00	23.38	16.20	23.70	16.97	12.00

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 34,651 people were affected in 1998 and 1 in 26,639 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 1.70 million expected cases of campylobacteriosis and 5th and 95th percentile estimates of 1.07 and 2.68 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 11,477 people were expected to be infected with fluoroquinolone resistant *Campylobacter* from consuming chicken and received fluoroquinolones as therapy. The model gives 5th and 95th percentile estimates of 6,412 and 18,978 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 1,240,000,000 with 5th and 95th 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.

Overview of the Risk Assessment

The risk assessment document details the risk assessment model development in Sections 1 through 4. Section 5 discusses how the model can be used to measure the level of risk.

To guide the reader through these five sections, the following flow diagram is presented on the cover sheet for each section and in the header of subsequent pages. Within a given section, the other sections will be grayed out and the current section will be illustrated with a white background.
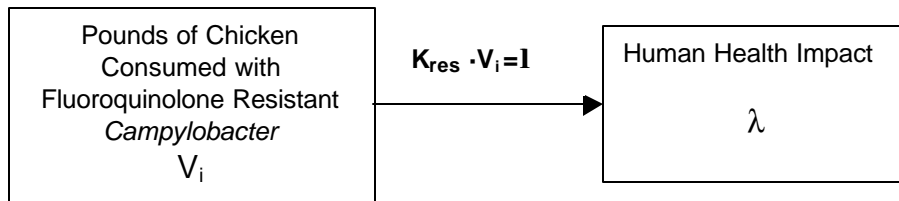
Overview of the Document Structure

Section 1
Nominal mean *Campylobacter* culture confirmed cases reportable to health department

Section 2
Nominal mean *Campylobacter* cases in U.S.

Section 3
Nominal mean number of fluoroquinolone-resistant *Campylobacter* cases from chickens affected by fluorquinolone resistance

Section 4
Estimating quantity of fluoroquinolone resistant *Campylobacter* contaminated chicken meat consumed

Section 5
Using the model to measure the level of risk

Introduction to Overview

The model brings together two branches to match an estimate of the human health impact due to fluoroquinolone resistant *Campylobacter* from domestically reared broilers (Sections 1 to 3) with an estimate of the quantity of fluoroquinolone resistant *Campylobacter* contaminated broiler meat consumed domestically (Section 4). This section of the report presents overviews of the general logic used in the modeling sections 1 through 4. The purpose in bringing together the two branches as described in Section 5 is to estimate the proportionality constant K_{res} which relates the exposure, the quantity of fluoroquinolone resistant *Campylobacter* contaminated broiler meat consumed domestically, to the human health impact due to fluoroquinolone resistant *Campylobacter* from domestically reared broilers.

```
┌─────────────────────────┐                    ┌─────────────────────────┐
│    Pounds of Chicken     │   K_res · V_i = 1  │   Human Health Impact    │
│     Consumed with        │ ─────────────────► │                          │
│ Fluoroquinolone Resistant│                    │           λ              │
│     Campylobacter        │                    │                          │
│          V_i             │                    │                          │
└─────────────────────────┘                    └─────────────────────────┘
```

The model is also used to generate the proportionality constant K_{all} that relates exposure in terms of all *Campylobacter* contaminated broiler meat consumed domestically to the human health impact due to *Campylobacter* from domestically reared broilers (λ). The human health impact is determined in Sections 1 to 3 and the quantity of contaminated broiler meat consumed domestically is calculated in Section 4. The proportionality constant K_{res} allows one to predict the human health impact associated with various levels of fluoroquinolone resistance in domestically reared broilers.
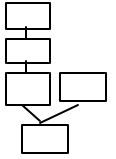
A table is provided after the section overviews that is a brief summary of the mathematics used in each section of the model. Each section output is emphasized in bold type both in the tables and in the text. After the mathematics table there will be a list of changes that were made to the model between the draft risk assessment report presented at a workshop on December 9-10, 1999 and this final version of the risk assessment report. The section ends with a table that displays the results from the draft model and from the final model for comparison. The Excel/@RISK model can be downloaded from the FDA-CVM website at : http://www.fda.gov/cvm/ .

Overview for Sections 1 and 2

Section 1 is Nominal mean *Campylobacter* culture confirmed cases reportable to health departments in the FoodNet catchment area. **Section 2** is Nominal mean *Campylobacter* cases in U.S.

The Centers for Disease Control and Prevention (CDC) obtained data for the determination of the annual burden of *Campylobacter* infections through active surveillance, surveys and case control studies. These data sources will be described in detail in Sections 1 and 2. Assumptions made in the risk assessment are presented in the sections adjacent to the data points to which they apply and are listed separately in Appendix B.

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. The enteric cases are further apportioned into those with bloody diarrhea and those without. These three distinct categories of cases, confirmed cases with invasive disease and enteric cases with and without bloody diarrhea, are required in the next step of building the annual number of culture-confirmed *Campylobacter* cases in the U.S.

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. Only a small number of cases are reported in FoodNet surveillance, because only a small fraction of persons with campylobacteriosis will progress along the medical care path to the point of becoming a culture-confirmed case. The path includes: seeking health care, having a specimen requested, submitting a specimen when requested to do so, having the laboratory test for *Campylobacter*, and having the laboratory that tests for *Campylobacter* actually finding it. The probabilities of these events occurring differ at points among the three distinct categories listed above.

To illustrate the basic steps of the method used to determine the annual burden of *Camplyobacter* illness, the calculations for 1999 are described here using point estimates. Calculations for 1998 are similar. The risk analysis calculations of the annual burden of campylobacteriosis are described in Sections 1 and 2 and follow these basic steps but incorporate confidence distributions in place of the point estimates used for demonstration purposes in the pyramids below.

Example – Basic Steps in Calculation of total number of *Campylobacter* infections in the U.S. in 1999

The number of enteric culture-confirmed cases for the U.S. is calculated by multiplying the number of enteric culture-confirmed cases in the FoodNet sites for the year by the ratio of the U.S. population to the FoodNet catchment size. There were 3,851 *Campylobacter* culture-confirmed cases ascertained in FoodNet sites in 1999. Of these cases, 51 were isolated from body sites considered invasive and 3,800 were from stool samples or were of unknown origin. For a FoodNet population of 25,859,311 and a national population of 272,690,813 that translates into approximately 50,001 culture-confirmed enteric *Campylobacter* cases. Similarly, there are an estimated 671 culture-confirmed *Campylobacter* cases with invasive disease. Therefore, the total number of culture-confirmed cases, combining those with enteric disease and those with invasive disease, is the sum of these two estimates: 50,001 + 671 or 50,672.

Of those culture confirmed cases in FoodNet in 1999, 46.5% came from cases with bloody diarrhea (see Section 1.9). This means that 50,001 x 0.465= 23,250 cultures came from cases with bloody diarrhea, and 26,751 cultures came from cases without blood in the stool.
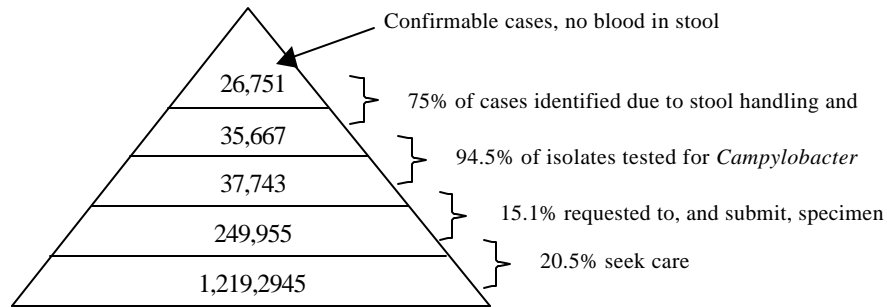
The way the number of culture-confirmed cases is built up to the total number of cases is best illustrated by means of pyramids in the example given below. The values of parameters in the pyramid that apply to

cases without bloody diarrhea are different from the values of parameters in the pyramid for cases with bloody diarrhea. The pyramid for *Campylobacter* cases without blood in the stool is as follows:
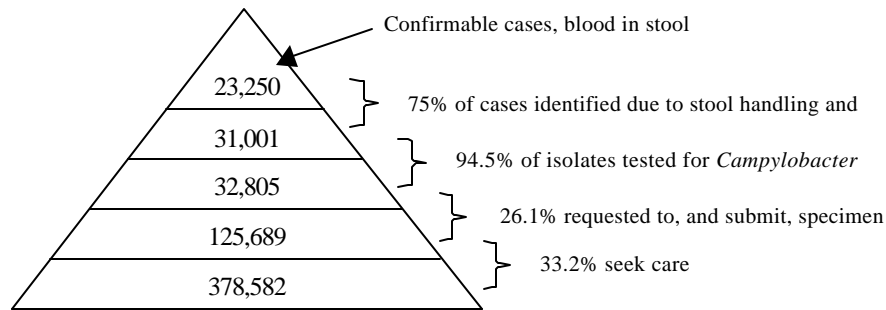
The calculation begins with the 26,751 cases one would have expected to be confirmed if FoodNet active surveillance were extended over the entire U.S. population. That number is divided by 0.75 to adjust for losses in isolations due to stool handling procedures and lack of test sensitivity, which are the cases that were tested but failed to yield a positive result. This process of adjustment for the various steps along the medical care path continues down the pyramid until the predicted number of campylobacteriosis cases without blood in the stool in the U.S. is attained at the bottom of the pyramid, 1,219,294 cases.

Non-bloody stool pyramid:

The pyramid for cases with bloody diarrhea contains the assumptions that a larger percentage of persons with bloody diarrhea will seek care, will be requested and will submit specimens when they are requested to do so (Section 2.3).

Bloody stool pyramid:

Finally, all cases of invasive campylobacteriosis were assumed to have been reported , obviating the need to use calculations. Thus, the estimated total burden of campylobacteriosis for 1999 is the sum of the three values for cases without bloody diarrhea, with bloody diarrhea, and with invasive disease. That is 1,219,294 + 378,582 + 671 = 1,598,547 cases.

This basic calculation makes use of point estimates derived from CDC data. The remainder of Sections 1 and 2 describe the data points with their inherent uncertainty or confidence distributions that were used in modeling the risk to provide an estimate of the total annual burden of campylobacteriosis.
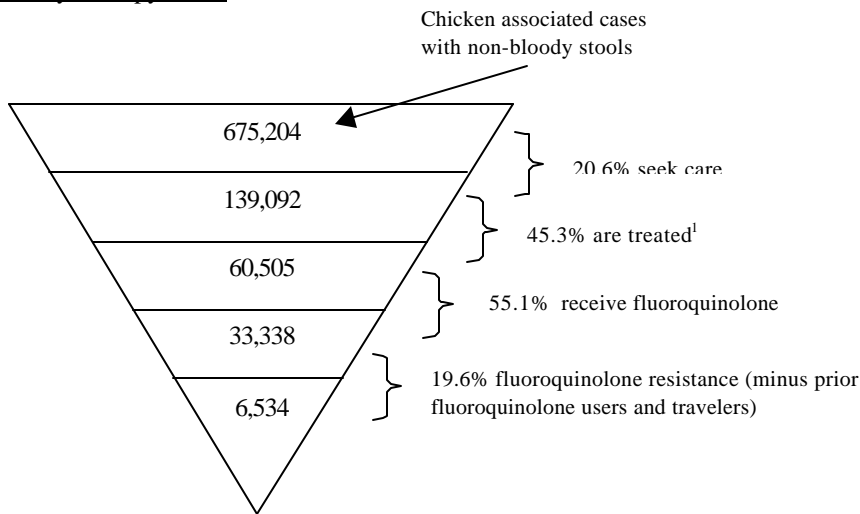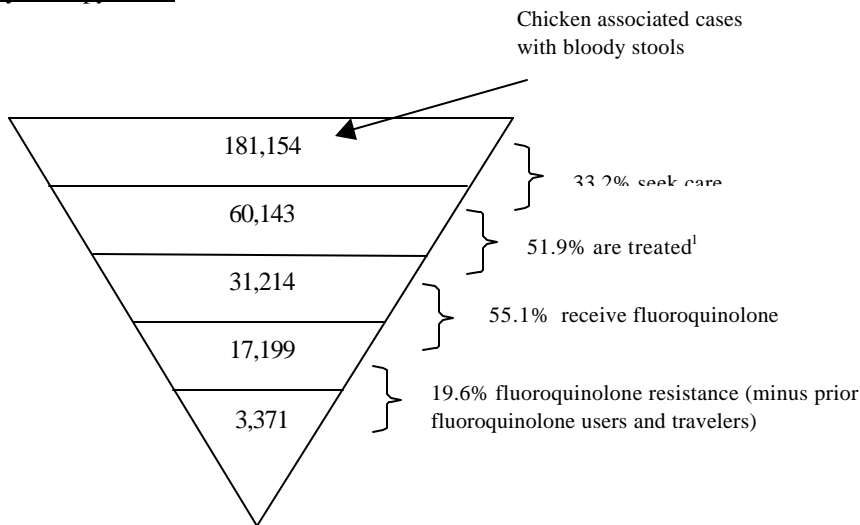
Overview for Section 3

Section 3 determines the Nominal mean number of fluoroquinolone-resistant *Campylobacter* cases attributable to chicken, seeking care, treated with a fluoroquinolone and therefore affected by fluoroquinolone resistance.

Having taken the path down the pyramid from the number of all *Campylobacter* cases ascertained by the health departments to the number of all *Campylobacter* cases in the U.S. for the year, it is then necessary to travel down a similar, but inverted, pyramid from the number of all *Campylobacter* cases attributable to chicken, to those who seek care, who are treated with an antibiotic, who receive fluoroquinolone and who have resistant fluoroquinolone *Campylobacter* attributable to domestic reared broilers.

Non-bloody stool pyramid:

Chicken associated cases
with non-bloody stools

675,204

20.6% seek care

139,092

45.3% are treated[1]

60,505

55.1% receive fluoroquinolone

33,338

19.6% fluoroquinolone resistance (minus prior
fluoroquinolone users and travelers)

6,534

Bloody stool pyramid:

Chicken associated cases
with bloody stools

181,154

33.2% seek care

60,143

51.9% are treated[1]

31,214

55.1% receive fluoroquinolone

17,199

19.6% fluoroquinolone resistance (minus prior
fluoroquinolone users and travelers)

3,371

These estimates are point estimates for the number of cases of chicken associated illness with non-bloody and bloody stools. These are cases who have sought care and received a fluoroquinolone. The infection
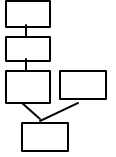
causing the illness was fluoroquinolone resistant. The resistance was domestically acquired and not attributed to the affected person having taken a fluoroquinolone prior to submitting a culture. Thus, the estimated total for 1999 is the sum of the three values for cases without bloody diarrhea, with bloody diarrhea, and with invasive disease. That is $6,772 + 3,371 + 42 = 10,185$ cases[1]. Section 3 describes in detail how uncertainty was modeled.

Overview for Section 4

Section 4 Estimates the quantity of fluoroquinolone resistant *Campylobacter* contaminated chicken meat consumed. The estimate is based on the per capita consumption of meat, the size of the U.S. population, the prevalence of *Campylobacter* among carcasses and the prevalence of resistance among contaminated carcasses.

Overview for Section 5

Section 5 is entitled Using the model to measure the level of 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.

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[1] These pyramids demonstrate the logic used in the model. While these pyramids give a general overview of the main steps used in the model, not every step is included in this description. Differences in prescribing rates for patients submitting, not submitting stools and invasive disease were modeled but are not demonstrated here (See Section 3.5).
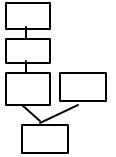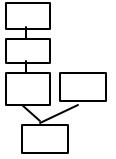
Table O.1 Table of Parameters, Notation and Formulas Used in the Model by Section

| Symbol	Description	Formula
Section 1 Nominal mean *Campylobacter* culture confirmed cases reportable to health department		
n_{US}	U.S. population	Data
n_{FN}	FoodNet catchment site total population	Data
o_{ej}, o_{ij}	Expected observed FoodNet enteric/invasive disease by site {j}	Data
λ_e λ_i	Expected observed FoodNet enteric/invasive disease in catchment	$= n_{US} / n_{FN} * \Sigma_j \text{Gamma}(o_{ej},1)$ $= n_{US} / n_{FN} * \Sigma_j \text{Gamma}(o_{ij},1)$
p_b	Proportion of culture confirmed enteric infections with bloody diarrhea	Beta distribution based on data
$\lambda 1_n$ $\lambda 1_b$ $\lambda 1_i$ $\pmb{\lambda 1_T}$	Nominal mean *Campylobacter* culture confirmed cases reportable to health department (non-bloody, bloody and invasive and total)	$= \lambda_e * (1 - p_b)$ $= \lambda_e * p_b$ $= \lambda_i$ $= \lambda 1_n + \lambda 1_b + \lambda 1_i$
Section 2 Nominal mean *Campylobacter* cases in U.S.		
p_{mn}, p_{mb}	Probability a person with campylobacteriosis seeks care (non-bloody, bloody enteric cases)	Beta distribution based on data
p_{cn}, p_{cb}	Probability a person with campylobacteriosis who has sought care is then requested to supply a stool and complies (non-bloody, bloody enteric cases)	Composite distribution based on data
p_t	Probability a lab tests a stool sample for *Campylobacter*	Beta distribution based on data
p_+	Probability a stool with *Campylobacter* is cultured positive	Beta distribution based on data
$\lambda 2_n$ $\lambda 2_b$ $\lambda 2_i$ $\pmb{\lambda 2_T}$	Nominal mean number of *Campylobacter* cases in U.S. population (non-bloody, bloody, invasive and total)	$= \lambda 1_n / (p_{mn} * p_{cn} * p_t * p_+)$ $= \lambda 1_b / (p_{mb} * p_{cb} * p_t * p_+)$ $= \lambda 1_i$ $= \lambda 2_n + \lambda 2_b + \lambda 2_i$
Section 3 Nominal mean number of fluoroquinolone resistant *Campylobacter* cases attributable to chicken, seeking care, treated with a fluoroquinolone and therefore affected by the fluoroquinolone resistance		
p_{ca}	Probability a *Campylobacter* case is attributable to chicken	Based on referenced estimates
p_{rh}	Probability a *Campylobacter* case from chicken is fluoroquinolone resistant	Weighted estimate based on data
$\lambda 3_n$ $\lambda 3_b$ $\lambda 3_i$ $\pmb{\lambda 3_T}$	Nominal mean number of fluoroquinolone resistant *Campylobacter* cases attributable to chickens (non-bloody, bloody, invasive and total cases)	$= \lambda 2_n * p_{ca} * p_{rh}$ $= \lambda 2_b * p_{ca} * p_{rh}$ $= \lambda 2_i * p_{ca} * p_{rh}$ $= \lambda 3_n + \lambda 3_b + \lambda 3_i$
p_{mn}, p_{mb}	Probability a person with campylobacteriosis seeks care(non-bloody and bloody)	From Section 2
p_{an}, p_{ab}	Probability a *Campylobacter* case who has sought care is treated with an antibiotic	Composite estimate based on data
p_{FQ} [2]	Probability a *Campylobacter* case who has sought care and has been treated with an antibiotic is treated with a fluoroquinolone	Weighted estimate based on data
$\lambda 4_n$	Nominal mean number of fluoroquinolone resistant	$= \lambda 3_n * p_{mn} * P_{an} * P_{FQ}$

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[2] FQ-fluoroquinolone

$\lambda4_b$ $\lambda4_i$ $\mathbf{14_T}$	*Campylobacter* cases attributable to chicken, seeking care, treated with a fluoroquinolone and therefore affected by the fluoroquinolone resistance (non-bloody, bloody, invasive and total cases)	$= \lambda3_b* p_{mb}*P_{ab}*P_{FQ}$ $= \lambda3_i *p_{FQ}$ $= \lambda4_n + \lambda4_b + \lambda4_i$

Symbol	Description	Formula
Section 4 Estimating quantity of fluoroquinolone resistant *Campylobacter* contaminated chicken meat consumed		
p_c	Total prevalence of *Campylobacter* among broiler carcasses	Beta distribution based on data
p_{rc}	Prevalence of fluoroquinolone resistant *Campylobacter* among *Campylobacter* contaminated broiler carcasses	Beta distribution based on data
p_p	Estimated prevalence of fluoroquinolone-resistant *Campylobacter* in broiler carcasses	$= p_c *p_{rc}$
c	Consumption of boneless domestically reared chickens in U.S. per capita (lbs)	Data
V_c	Total consumption of boneless domestically reared chicken in U.S. (lbs)	$= c * n_{US}$
$\mathbf{V_i}$	Total consumption of boneless, domestically reared chicken contaminated with fluoroquinolone resistant *Campylobacter* in U.S. (lbs)	$=V_c*p_p$

List of changes to the model since the December Draft report

- Calculations done for 1998 in the draft report were repeated for 1999;
- Updated the 1998 per capita consumption of boneless domestically reared chicken;
- Updated 1998 NARMS chicken isolate data from 11.3% resistance (18/159 isolates) to 9.4% (12/128). This removed samples that tested inconsistently on PCR and hippurase biochemical assay or upon further analysis were identified as *C. coli* and were not considered in this model;
- Changed the calculations of the level of resistance in humans from *Campylobacter* Case Control (CCC) study derived estimate for 1998 that directly removed travelers and prior fluoroquinolone users from *Campylobacter* isolates (included *C. jejuni* and *C. coli* species) collected in the CCC to a two step procedure: 1) determination of an adjustment factor from *Campylobacter* Case Control study to represent the proportion of resistant and susceptible isolates from travelers and prior fluoroquinolone users 2) This factor was used to adjust *C. jejuni* data reported by NARMS in 1998 and 1999 and determine an adjusted level of resistance by state;
- Used only survey data to estimate p_{cn}, p_{cb}, (i.e. removed physician survey data at CDC's advice).
- Removed Study #3 used to estimate the lower bound of the attributable risk due to inconsistencies in the data.
- Changed the parameter named by z from Proportion of persons treated with an antibiotic – not submitting a stool (now referred to as y) to Proportion of persons treated with an antibiotic – submitting a stool.;
- FoodNet data were broken down by FoodNet site;
- Nosocomial data used in estimating p_b used in the draft risk assessment was removed;
- Uncertainty estimates were assigned to p_{ca-min} and p_{ca-max};
- 1998/9 CDC population survey data replaced 1996/7 population survey;
- Deleted Appendix B and provided a table of expected values in this Overview.
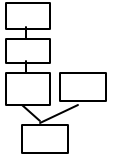
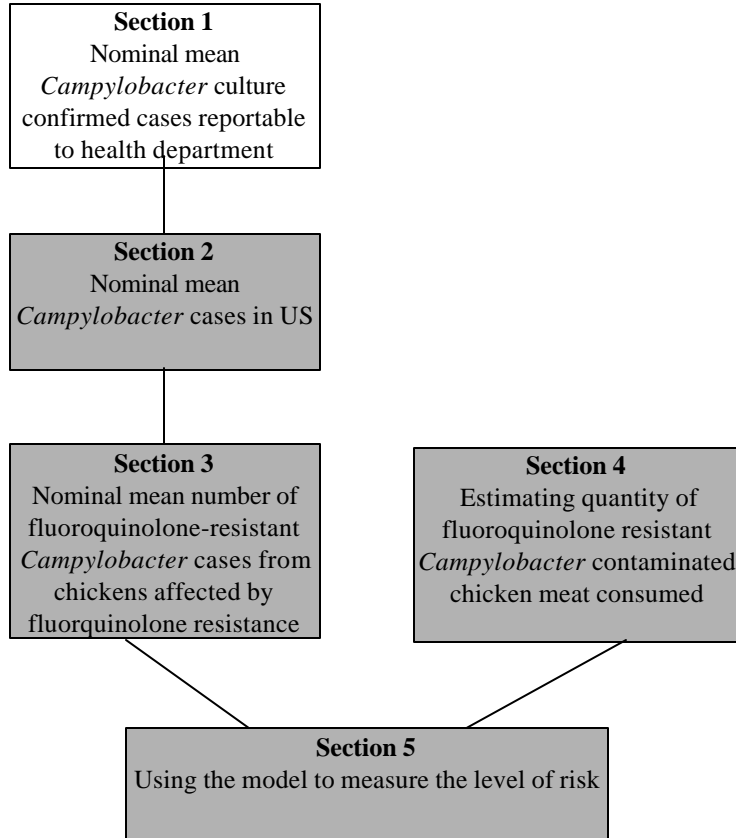**Changes in results in the final risk assessment**

The table below illustrates how the model results have changed since the draft risk assessment. The figures shown represent the spreadsheet calculation when all distributions are set to their expected values and give an indication of the magnitude of the effect of the above changes.
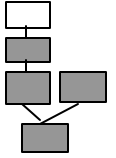
Table O.2: Comparison of modeled values, between the draft and final risk assessments. These results are based on one run of the 1998 model and one run of the 1999 model. The complete distributions of the outputs are displayed in the relevant Sections of this risk assessment.

| | Draft report | | | Final report | | | | | |
| | 1998 | | | 1998 | | | 1999 | | |
	Non-bloody	Bloody	Invasive	Non-bloody	Bloody	Invasive	Non-bloody	Bloody	Invasive
Section 1									
nUS	270,298,524			270,248,003			272,690,813		
nFN	20,723,982			20,723,982			25,859,311		
li	561			571			671		
le	51,976			52,436			50,001		
pb	46.0%			46.5%			46.5%		
$\lambda 1n, \lambda 1b, \lambda 1i$	28.077	23.898	561	28.061	24.375	571	26.758	23.243	671
Section 2									
pmn, pmb	12.2%	26.7%		20.6%	34.3%		20.6%	34.3%	
pcn, pcb	19.1%	55.4%		15.6%	30.4%		15.6%	30.4%	
pt	94.5%	94.5%		94.5%	94.5%		94.5%	94.5%	
p+	75.0%	75.0%		75.0%	75.0%		75.0%	75.0%	
$\lambda 2n, \lambda 2b, \lambda 2i$	1.702.043	228.040	561	1.229.299	329.815	571	1.172.230	314.503	671
$\lambda 2T=\lambda 2n+\lambda 2b+\lambda 2i$	1.930.644			1.559.685			1.487.404		
Section 3									
pca-min	47.0%			48.5%					
pca-max	70.0%			66.7%					
pca	58.5%			57.6%			57.6%		
prh	10.4%			14.2%			21.8%		
$\lambda 3n, \lambda 3b, \lambda 3i$				100.627	26.998	47	132.529	35.557	76
$\lambda 3T=\lambda 3n+\lambda 3b+\lambda 3i$				127.671			168.162		
pmn, pmb	12.2%	26.7%		20.6%	34.3%		20.6%	34.3%	
pan, pab	47.9%	63.7%		45.3%	51.9%		45.3%	51.9%	
pFQ	55.1%			55.1%			55.1%		
$\lambda 4n, \lambda 4b, \lambda 4i$	3.324	1.300	19	5.172	2.646	26	6.812	3.484	42
$\lambda 4T=\lambda 4n+\lambda 4b+\lambda 4i$	4.642			7.844			10.338		
Section 4									
pc	88.1%			88.1%			88.1%		
prc	11.8%			10.0%			9.5%		
c	51.4			50.8			54.3		
Vi	1,445,209,653			1,210,103,568			1,243,017,872		

Section 1
Nominal mean
Campylobacter culture
confirmed cases reportable
to health department

Section 2
Nominal mean
Campylobacter cases in US

Section 3
Nominal mean number of
fluoroquinolone-resistant
Campylobacter cases from
chickens affected by
fluorquinolone resistance

Section 4
Estimating quantity of
fluoroquinolone resistant
Campylobacter contaminated
chicken meat consumed

Section 5
Using the model to measure the level of risk

Overview for Sections 1 and 2

The Centers for Disease Control and Prevention (CDC) obtained data for the determination of the annual burden of *Campylobacter* infections through active surveillance, surveys and case control studies. These data sources will be described in detail in Sections 1 and 2. Assumptions made in the risk assessment are presented in the sections adjacent to the data points to which they apply and are listed separately in Appendix B.

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. The enteric cases are further apportioned into those with bloody diarrhea and those without. These three distinct categories of cases, confirmed cases with invasive disease and enteric cases with and without bloody diarrhea, are required in the next step of building the annual number of culture-confirmed *Campylobacter* cases in the U.S.

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. Only a small number of cases are reported in FoodNet surveillance, because only a small fraction of persons with campylobacteriosis will progress along the medical care path to the point of becoming a culture-confirmed case. The path includes: seeking health care, having a specimen requested, submitting a specimen when requested to do so, having the laboratory test for *Campylobacter*, and having the laboratory that tests for *Campylobacter* actually finding it. The probabilities of these events occurring differ at points among the three distinct categories listed above.

To illustrate the basic steps of the method used to determine the annual burden of *Camplyobacter* illness, the calculations for 1999 are described here using point estimates. Calculations for 1998 are similar. The risk analysis calculations of the annual burden of campylobacteriosis are described in Sections 1 and 2 and follow these basic steps but incorporate confidence distributions in place of the point estimates used for demonstration purposes in the pyramids below.

Example – Basic Steps in Calculation of total number of *Campylobacter* infections in the U.S. in 1999

The number of enteric culture-confirmed cases for the U.S. is calculated by multiplying the number of enteric culture-confirmed cases in the FoodNet sites for the year by the ratio of the U.S. population to the FoodNet catchment size. There were 3,851 *Campylobacter* culture-confirmed cases ascertained in FoodNet sites in 1999. Of these cases, 51 were isolated from body sites considered invasive and 3,800 were from stool samples or were of unknown origin. For a FoodNet population of 25,859,311 and a national population of 272,690,813 that translates into approximately 50,001 culture-confirmed enteric *Campylobacter* cases. Similarly, there are an estimated 671 culture-confirmed *Campylobacter* cases with invasive disease. Therefore, the total number of culture-confirmed cases, combining those with enteric disease and those with invasive disease, is the sum of these two estimates: 50,001 + 671 or 50,672.

Of those culture confirmed cases in FoodNet in 1999, 46.5% came from cases with bloody diarrhea (see Section 1.9). This means that 50,001 x 0.465= 23,250 cultures came from cases with bloody diarrhea, and 26,751 cultures came from cases without blood in the stool.
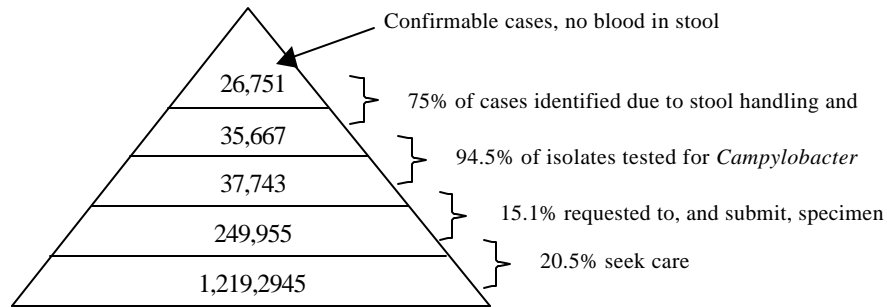
The way the number of culture-confirmed cases is built up to the total number of cases is best illustrated by means of pyramids in the example given below. The values of parameters in the pyramid that apply to

cases without bloody diarrhea are different from the values of parameters in the pyramid for cases with bloody diarrhea. The pyramid for *Campylobacter* cases without blood in the stool is as follows:
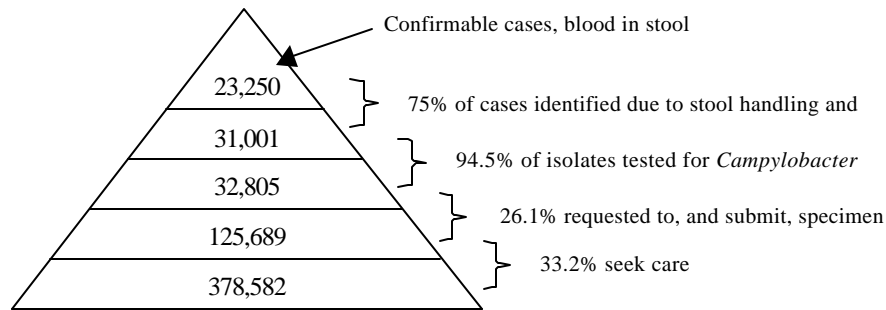
The calculation begins with the 26,751 cases one would have expected to be confirmed if FoodNet active surveillance were extended over the entire U.S. population. That number is divided by 0.75 to adjust for losses in isolations due to stool handling procedures and lack of test sensitivity, which are the cases that were tested but failed to yield a positive result. This process of adjustment for the various steps along the medical care path continues down the pyramid until the predicted number of campylobacteriosis cases without blood in the stool in the U.S. is attained at the bottom of the pyramid, 1,219,294 cases.

 Non-bloody stool pyramid:

The pyramid for cases with bloody diarrhea contains the assumptions that a larger percentage of persons with bloody diarrhea will seek care, will be requested and will submit specimens when they are requested to do so (Section 2.3).

Bloody stool pyramid:

Finally, all cases of invasive campylobacteriosis were assumed to have been reported , obviating the need to use calculations. Thus, the estimated total burden of campylobacteriosis for 1999 is the sum of the three values for cases without bloody diarrhea, with bloody diarrhea, and with invasive disease. That is 1,219,294 + 378,582 + 671 = 1,598,547 cases.

This basic calculation makes use of point estimates derived from CDC data. The remainder of Sections 1 and 2 describe the data points with their inherent uncertainty or confidence distributions that were used in modeling the risk to provide an estimate of the total annual burden of campylobacteriosis.

Symbol	Description	Formula

n_{US}	U.S. population	Data
n_{FN}	FoodNet catchment site total population	Data
o_{ej}, o_{ij}	Expected observed FoodNet enteric/invasive disease by site {j}	Data
λ_e λ_i	Expected observed FoodNet enteric/invasive disease in catchment	$= n_{US} / n_{FN} * \Sigma_j Gamma(o_{ej}, 1)$ $= n_{US} / n_{FN} * \Sigma_i Gamma(o_{ij}, 1)$
p_b	Proportion of culture confirmed enteric infections with bloody diarrhea	Beta distribution based on data
$\lambda1_n$ $\lambda1_b$ $\lambda1_i$ $\mathbf{\lambda1_T}$	Nominal mean *Campylobacter* culture confirmed cases reportable to health department (non-bloody, bloody and invasive and **total**)	$= \lambda_e * (1 - p_b)$ $= \lambda_e * p_b$ $= \lambda_i$ $= \lambda1_n + \lambda1_b + \lambda1_i$

Parameter estimations

1.1 (n_{us}) – <u>U.S. population</u>
The numbers used in the calculation of FoodNet incidence rates for the catchment areas and the size of the total U.S. population are obtained from the U.S. Census Bureau post-census estimates. These post-census estimates are calculated annually, based upon the most recent census survey. More information about how these population estimates are calculated is available from the U.S. Census Bureau (114) (available at http://www.census.gov/).

For 1998, n_{US} = 270,248,003
For 1999, n_{US} = 272,690,813

1.2 (n_{FN}) - <u>FoodNet Catchment site total population</u>
FoodNet is a sentinel surveillance network of Emerging Infections Program Sites. FoodNet was initiated in 1996 in five sites (California, Connecticut, Georgia, Minnesota, Oregon) to provide more accurate national estimates of the burden of foodborne disease than was previously available through passive surveillance (19). By 1998, the FoodNet catchment area had expanded to include the states of Minnesota (MN), Connecticut (CT), Oregon (OR), and selected counties in California (CA), Georgia (GA), Maryland (MD), and New York (NY) (21). Expansion in 1999 included the entire state of Georgia. The seven sites represented approximately 7.7%, and 9.5% of the U.S. population in 1998 and 1999 respectively. Because FoodNet is an active surveillance system, all clinical laboratories within the catchment areas and outside the catchment area, if they receive specimens from persons who reside within the catchment area, are contacted by FoodNet representatives to identify culture-confirmed cases of campylobacteriosis occurring among catchment area residents. Cases are identified from laboratory reports collected for the previous month or are collected more frequently, depending on laboratory volume. Active surveillance is considered more accurate than passive surveillance because it does not rely upon laboratories to provide reports of cases to the surveillance system. Instead, the system contacts and collects the information from the laboratories. FoodNet incidence rates are based upon laboratory-confirmed cases of campylobacteriosis and are being used to document the effectiveness of new food safety control measures. FoodNet incidence rates of culture-confirmed campylobacteriosis therefore include only those persons with campylobacteriosis who sought care for their illness and had a specimen submitted that was tested for and yielded the organism. FoodNet reporting limits case reports to a single report per affected individual within any 12-month period. If more than a single isolation of *Campylobacter* from a single individual occurs from multiple specimens, only one, with priority given to the most invasive isolation, is reported to FoodNet for incidence rate estimates. While this sentinel surveillance system is not designed specifically to be representative of the U.S. population, based on a comparison of the demographic characteristics the disease incidence is likely to be representative of the U.S. population. Although comparison of risk factors is preferable to comparison of demographic characteristics for extrapolating data, the data are not available to make this comparison.
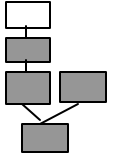
 The comparison of FoodNet and U.S. populations by demographic characteristics (sex, age, race, and rural-to-urban distribution), indicated that the population distributions appeared to be similar (Table 1.1). The exception may be the lower proportion of Hispanics represented in FoodNet catchment areas compared to the U.S. population. The demographic characteristics available for comparison are, in most instances, only markers for other risk factors that influence the rates of disease in populations. The ideal extrapolation of FoodNet incidence rates to the U.S. population would require knowledge of the distribution of risk factors that affect the rates of disease. However, many of these risk factors are not well described. Some risk factors for campylobacteriosis are age (the most susceptible are the very young and elderly), immune status (the immunocompromised are most at risk), and antibiotic therapy in the month prior to illness onset (74). Because the comparison of demographic characteristics between the FoodNet and the U.S. populations was similar, this indicates that the risk factors that affect disease rates may also be distributed similarly. Therefore, the rates of disease obtained from FoodNet are likely to be representative of disease rates in the U.S.

Table 1.1. Comparison of the distribution of demographic characteristics by FoodNet total catchment to U.S. population (1998)

Demographic Characteristic		FoodNet Total Catchment Area	U.S. Population
Rural vs. Urban[1]	Rural	4,076,398 (21.78)	61,656,386 (24.80)
	Urban	14,637,400 (78.22)	187,053,487 (75.20)
Age Distribution	0-<1 year	280,015 (1.35)	3,776,389 (1.40)
	1-<10 years	2,907,058 (14.03)	39,050,749 (14.45)
	10-<20 years	2,865,920 (13.83)	38,050,749 (14.29)
	20-<30 years	2,767,848 (13.36)	36,296,139 (13.43)
	30-<40 years	3,591,391 (17.33)	43,608,568 (16.13)
	40-<50 years	3,201,640 (15.45)	39,778,258 (14.72)
	50-<60 years	2,047,441 (9.88)	26,692,895 (9.88)
	60+ years	3,062,669 (14.78)	42,472,248 (15.71)
Sex	Male	10,148,135 (48.97)	132,046,334 (48.85)
	Female	10,575,847 (51.03)	138,252,190 (51.15)
Race	Native American	126,418 (0.61)	2,000,000 (0.74)
	White	15,913,196 (76.79)	195,439,508 (72.31)
	Black	2,534,928 (12.23)	32,717,955 (12.10)
	Hispanic	1,147,715 (5.54)	30,250,255 (11.19)
	Asian	1,001,725 (4.83)	9,890,223 (3.66)

[1]1990 U.S. Census Estimates

ASSUMPTION: An extrapolation from FoodNet catchment populations to the U.S. population at large assumes that the FoodNet catchment populations will, in aggregate, be reasonably representative of the U.S. population (Table 1.1).

FoodNet data for 1999 were preliminary.

DISCUSSION: Although the incidence rates varied by site, from 6.8/100,000 in Maryland to 32.1/100,000 in California in 1999 (22), the overall rate of *Campylobacter* isolation is likely to reflect isolation rates in the U.S. population. Comparisons of demographic characteristics between the FoodNet sites and the U.S. population show similar distributions of sex, age, race and rural/urban distributions (Table 1.1).
In addition to demonstrating similarity in population composition, an evaluation of potential exposure is important. In a 1994-5 United States Department of Agriculture, Food Safety Inspection Service, survey, 88% of chicken carcasses were reported to carry *Campylobacter* at slaughter (Table 1.2)(104). Another estimate, of *Campylobacter* carriage on retail chicken products was demonstrated at a level of 88% in a Minnesota survey of chicken products in 1997 (92).

Sporadic cases of *Campylobacter* account for approximately 99% of all *Campylobacter* cases. Epidemiologic investigations of sporadic infections have indicated that chicken is the most common source of human infections (3, 92, 95). The frequency of chicken consumption was evaluated to assess exposure to this risk factor in the U.S. population. The National Chicken Council provided a chicken consumption survey, conducted by Bruskin Goldring Research in June 1999 (18). The survey utilized computer-assisted telephone interviewing and evaluated the frequency of chicken consumption at home or away from home by sex, age, income and region. The sample consisted of 1,019 completed interviews of males and females, at least 18 years of age, in approximately equal numbers. The selection of interviewees was based upon a computer-based random-digit dialing sample of all households with telephones in the continental U.S. There was equal probability of selection for each household with a telephone, including listed and unlisted numbers. Each number was subject to an original and at least four follow-up attempts to complete the interviews. Findings, at a 5% significance level, indicated that there was no difference in frequency of chicken consumption at home or away from home by sex. Frequency of chicken consumption at home or away from home was slightly greater for younger respondents 18-24 years of age (mean=8.3 times per month, $p<0.05$) compared to other age groups (range of means=6.6-7.6 times per month, $p<0.05$). Respondents from the Northeast (mean=8.2 times per month, $p<0.05$), consumed chicken at home more frequently compared to other parts of the country (range of means=6.1-7.5 times per month, $p<0.05$), but when eating chicken away from home all regions were similar. The proportion of people rarely or never consuming chicken was low and did not vary significantly by sex, age, income or region of the U.S. at a 5% significance level (18).

Table 1.2. Percent isolation of *Campylobacter* and level of contamination

Food Animal	Source	No. Sampled	Percent Positive	Concentration[1] MPN/cm^{2}	Year[2]	Ref
Cattle						
Slaughterhouse	Carcass (Strs[4] & Heifers)	2064	4	0.1 (CI NA)[3]	1992-3	106
Slaughterhouse	Carcass (Cows & Bulls)	2109	10	0.1 (CI 0.1- 0.2)	1993-4	105
Slaughterhouse	Ground Beef[5]	562	0	NA	1993-4	107
Swine						
Slaughterhouse	Carcasses	2,112	32	0.1 (CI 0.08-0.13)	1995-6	108
Broiler Chickens						
Slaughterhouse	Carcasses	1297	88	4.4 (CI 3.8-5.1)	1994-5	104
Processing Plant	Grd. Chicken[6]	283	60	4.8 (CI 4.0-5.7)	1995	109
Turkeys						
Slaughterhouse	Carcasses	1221	90	0.18 (CI 0.16-0.20)	1996-7	111
Slaughterhouse	Ground Turkey[7]	295	25	2.8 (CI 0.42-18.52)	1995	110

[1]MPN-Most Probable Number indicates most likely level of contamination, not actual level because enrichment steps were required to isolate *Campylobacter*. Carcass units are MPN/cm^{2} and ground product units are MPN/g.

[2] These studies are nationally representative and well designed, more recently conducted surveys were not available.
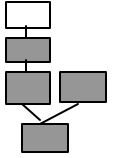
[3] Strs=Steers, CI- 95% Confidence Interval

[4] Not applicable

[5] Sampling period omitted sampling between March through August

[6] Grd=Ground, Sampling period omitted collection between June through September.

[7]Sampling period omitted collection between March through and September.

ASSUMPTION: The incidence rates for culture-confirmed *Campylobacter* infections in the FoodNet catchment are representative of incidence rates for culture-confirmed *Campylobacter* infections in the U. S.

For 1998, n_{FN} = 20,723,982
For 1999, n_{FN} = 25,859,311

1.3 (o_{ej} , o_{ij}) – Expected observable FoodNet enteric/invasive disease by site {j}

Culture-confirmed cases of campylobacteriosis represent only a fraction of all *Campylobacter* illnesses. The majority of persons with *Campylobacter* illnesses do not seek care and most patients who do seek care are not asked and do not submit specimens for culture (70).

(o_{ej}) – Expected o*bserved FoodNet **enteric** cases of Campylobacter by site*
FoodNet reported the number of laboratory-confirmed isolations from stools submitted by persons ill and visiting a health care provider. A FoodNet case is defined as an isolation of *Campylobacter* from a catchment area resident without an isolation in the preceding 12 months.

Table 1.3 Total number of enteric cases of *Campylobacter* by FoodNet site, 1998 and 1999

Year	CA[1]	CT	GA	MD	MN	NY	OR	Total
1998	780	595	460	248	998	221	693	3985
1999	683	517	728	156	782	356	578	3800

[1]CA-California, CT-Connecticut, GA-Georgia, MD-Maryland, MN-Minnesota, NY-New York, OR-Oregon

For 1998, the total number of enteric cases of *Campylobacter* was 3985. For 1999, the total number observed was 3800. Uncertainty distributions for the numbers of expected observable reportable cases, o_{ej}, where j is the index for site, were modeled as Gamma distributions with o■$_{ej}$, the actual observed number of enteric cases of *Campylobacter*, as input. This was done for the data for each year.

o_{ej} = Gamma(o■$_{ej}$, 1).

(o_{ij}) – *Expected Observable FoodNet **invasive** cases of Campylobacter by site*
Invasive *Campylobacter* infections were ascertained in FoodNet as an isolation of *Campylobacter* from blood, cerebrospinal fluid (CSF), or other normally sterile site. Invasive isolations represent approximately 1.0% of all culture-confirmed *Campylobacter* cases and the vast majority are bloodborne infections (19, 20, 21, 95).

DISCUSSION: It is not precisely known the completeness of ascertainment of invasive *Campylobacter* infections. However, because persons with invasive *Campylobacter* infections will be moderately to severely ill, it is likely that most of these patients will seek care and be reported.

Little is known about the completeness of ascertainment of invasive campylobacteriosis. We do not know the frequency with which laboratories are requested to test blood, CSF or other sterile specimens for *Campylobacter,* and we do not know the sensitivity of the diagnostic tests used for isolation from blood and other sterile sites. The lack of this information may result in an underestimate of actual invasive disease rates. However, an increase in isolation of specimens classified as invasive is unlikely to have much impact on the overall number of cases of campylobacteriosis in the U.S. because the currently ascertained proportion of invasive cases is approximately 1.0% of all confirmed cases, and most cases are likely to seek care.

ASSUMPTION: All invasive campylobacteriosis cases seek care, have a specimen collected that yields *Campylobacter*, and is ascertained by FoodNet.
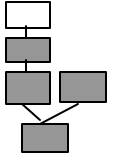
DATA GAP: Data are not available describing rates or cases of invasive disease seeking care, requests for diagnostic tests, and the sensitivity of diagnostic procedures, such as blood culture.

Table 1.4 Total number of invasive cases of *Campylobacter* by FoodNet Site, 1998 and 1999

Year	CA[1]	CT	GA	MD	MN	NY	OR	Total
1998	10	8	9	8	6	0	2	43
1999	11	11	8	10	3	2	6	51

[1]CA-California, CT-Connecticut, GA-Georgia, MD-Maryland, MN-Minnesota, NY-New York, OR-Oregon

For 1998, the total number of observed invasive cases of *Campylobacter* was 43. For 1999, the total number was 51. Uncertainty distributions for the expected numbers of observable reportable cases, o_{ij}, where j is the index for site, were modeled as Gamma distributions with $o\blacksquare_{ij}$, the actual observed number of invasive cases of *Campylobacter*, as input[1]. This was done for the data for each year.

$$o_{ij} = \text{Gamma}(o\blacksquare_{ij}, 1).$$

1.4 (λ_e) and (λ_i) - Expected observed FoodNet enteric/invasive disease in catchment

The number of enteric and invasive infections in the FoodNet catchment sites that are observed is affected by random chance. The true measure of the health burden is the mean number of observations we would see if we were able to repeat each year many times. The confirmed cases of *Campylobacter* are rare events when compared to the population size, so it is reasonable to assume that the frequency of confirmed cases is a Poisson process. In this case, the mean number of observations are the Poisson means $\mathbf{l}_i$ and $\mathbf{l}_e$ for invasive and enteric infections respectively.

(λ_e and λ_e) *Nominal mean **enteric** and **invasive** Campylobacter culture confirmed infections reportable to health department*
The FoodNet sites cover only (n_{FN} / n_{US}) of the population, so estimates of the mean number of cases that would apply to the population are calculated by dividing the sum of the modeled FoodNet mean observable cases by this fraction. That is,

$$\mathbf{l}_e = \frac{n_{US}}{n_{FN}} \sum_j \text{Gamma}\left(o_{ej}\right)$$

and

$$\mathbf{l}_i = \frac{n_{US}}{n_{FN}} \sum_j \text{Gamma}\left(o_{ij}\right).$$

1.5 (p_b) - Proportion of culture confirmed enteric infections with bloody diarrhea

The estimation of this parameter used two sources of data. The proportion of culture-confirmed enteric infections with patients reporting bloody diarrhea was calculated from the *Campylobacter* Case Control study for each FoodNet site (CA=18.2% (2/11), CT=40.2% (70/174), GA=53.6% (15/28), MD=47.6% (10/21), MN=49.1% (113/230), NY=50.8% (32/63), OR=54.6% (6/11) and weighted by catchment site population (18). The estimate weighted by catchment population was 46.2%, and the crude estimate was 46.1%. See Table 1.5.

Table 1.5. Catchment populations and cases reporting to have had blood in their stools. (*Campylobacter* Case Control Study)

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[1] One exception occurred for NY in 1998 where there were no reported invasive cases. The uncertainty distribution for o_{ij} in that case was taken to be $-\ln(\text{Beta}(2,1))$ because a Gamma(0,1) model is not possible.
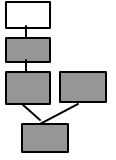
Site j	Catchment population	Weighting Fraction W_j	Number for whom response was known A_j	Number who had bloody diarrhea B_j
CA	2,146,096	0.103556	11	2
CT	3,274,069	0.157985	174	70
GA	3,746,059	0.18076	28	15
MD	2,444,280	0.117945	21	10
MN	4,725,419	0.228017	230	113
NY	1,106,085	0.053372	63	32
OR	3,281,974	0.158366	11	6
Total	20,723,982	1	538	248

The FoodNet data for reporting blood in the stool was used as follows to determine an estimate for p_b:

$$p_b = \sum_j W_j * Beta(B_j + 1, A_j - B_j + 1)$$

where W_j is the weight for site j (site j size divided by total catchment size), B_j is the site-specific number of cases reporting bloody diarrhea and A_j is the site-specific number of cases providing a response to whether blood had been observed in their stools. The Beta distribution is used here to describe the uncertainty about a proportion, as explained in Appendix A. Each of the summed Beta distributions is approximately normally distributed because there are reasonably large samples (94) and because the Beta distributions are centered at values near 0.5 (i.e. B_j/A_j are approximately 0.5). The distribution of p_b can thus be approximated by first replacing each Beta distribution with a Normal:

$$Beta(B_j + 1, A_j - B_j + 1) \approx Normal(\boldsymbol{m}_j, \boldsymbol{s}_j)$$

where

$$\boldsymbol{m}_j = \frac{B_j + 1}{A_j + 2} \text{ and } \boldsymbol{s}_j = \sqrt{\frac{(B_j + 1)(A_j - B_j + 1)}{(A_j + 2)^2 (A_j + 3)}}$$

and then noting the identity:

$$p_b \approx \sum_j W_j * Normal(\boldsymbol{m}_j, \boldsymbol{s}_j) = Normal\left(\sum_j W_j \boldsymbol{m}_j, \sqrt{\sum_j (W_j \boldsymbol{s}_j)^2}\right)$$

1.6 ($\lambda 1_n$, $\lambda 1_b$, $\lambda 1_i$) - <u>Nominal mean number of *Campylobacter* culture confirmed enteric infections in the FoodNet catchment area with self reported bloody and non-bloody diarrhea and the nominal mean number of culture confirmed invasive infections in the catchment reportable to health department</u>

These enteric infection parameters are calculated by multiplying the nominal observed mean enteric infections in the population by the probabilities a case will report visible blood in the diarrhea p_b and ($1-p_b$) the probability of reporting no visible blood in the diarrhea respectively. The number of invasive cases is not subdivided, thus:

$\lambda 1_b = \lambda_e * p_b$
$\lambda 1_n = \lambda_e * (1 - p_b)$
$\lambda 1_i = \lambda_i$
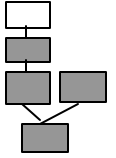
In mathematical terms, $\lambda 1_b$ and $\lambda 1_n$ are the mean values (intensities) of Poisson distributions and p_b has been interpreted as the probability that an individual contracting campylobacteriosis will report visibly bloody stools. An alternative interpretation of p_b would be the predictably constant fraction of the population contracting campylobacteriosis that would report visibly bloody stools because of some mechanism. The approach used in this model allows for greater variability in the observable incidence of bloody diarrhea and, therefore, produces greater uncertainty in our estimates of the mean incidence.

1.7 ($\mathbf{1}1_T$) - Nominal total mean number of *Campylobacter* culture confirmed cases reportable to health department in the FoodNet catchment area

The total number of reportable cases is the sum of the reportable cases of the three types, enteric non-bloody, enteric bloody, and invasive. The parameter for the nominal total mean is modeled as the sum of the parameters for numbers of reportable cases of the three types.

$$\mathbf{1}1_T = \lambda 1_n + \lambda 1_b + \lambda 1_i.$$

$\mathbf{1}1_T$ was modeled for 1998 and for 1999. The results are displayed here.

Year	Model output	5th percentile	Mean	95th percentile
1998	$\mathbf{1}1_T$	51,586	53,008	54,384
1999	$\mathbf{1}1_T$	49,316	50,672	51,994
Difference (98-99)			-2,336	

Section 1 Summary

The model predicts that in 1999 there was a mean estimate of 26,758 reportable cases of campylobacteriosis with non-bloody diarrhea with a 5th percentile estimate of 23,993 and a 95th percentile estimate of 29,586 in the FoodNet catchment area. In 1999 there was a mean estimate of 23,243 reportable cases with bloody diarrhea with a 5th percentile estimate of 20,449 and a 95th percentile estimate of 26,040 and a mean estimate of 671 confirmed invasive disease cases with a 5th percentile estimate of 523 and a 95th percentile estimate of 833 in the catchment. Relative contributions of the various components of the model to the total model uncertainty will be presented in Section 5, Sensitivity Analysis.
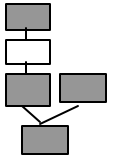
Table 1.6. 1998 and 1999 FoodNet active surveillance for *Campylobacter* from culture confirmed cases

Site	Catchment Population Estimate		Enteric Cases		Invasive Cases	
	1998	1999	1998	1999	1998	1999
CA	2,146,096	2,162,359	780	683	10	11
CT	3,274,069	3,282,031	595	517	8	11
GA	3,746,059	7,788,240	460	728	9	8
MD	2,444,280	2,450,566	240	156	8	10
MN	4,725,419	4,775,508	998	782	6	3
NY	1,106,085	2,084,453	221	356	0	2
OR	3,281,974	3,316,154	691	578	2	6
Totals for Catchment	20,723,982	25,859,311	3985	3800	43	51

Section 2

Nominal mean *Campylobacter* cases in the U.S. population

Section 1
Nominal mean
Campylobacter culture
confirmed cases reportable
to health department

Section 2
Nominal mean
Campylobacter cases in
U.S.

Section 3
Nominal mean number of
fluoroquinolone-resistant
Campylobacter cases from
chickens affected by
fluorquinolone resistance

Section 4
Estimating quantity of
fluoroquinolone resistant
Campylobacter contaminated
chicken meat consumed

Section 5
Using the model to measure the level of risk

Symbol	Description	Formula
p_{mn}, p_{mb}	Probability a person with campylobacteriosis seeks care (non-bloody, bloody enteric cases)	Beta distribution based on data
p_{cn}, p_{cb}	Probability a person with campylobacteriosis who has sought care is then requested to supply a stool and complies (non-bloody, bloody enteric cases)	Beta distribution based on data
p_t	Probability a lab tests a stool sample for *Campylobacter*	Beta distribution based on data
p_+	Probability a stool with *Campylobacter* is cultured positive	Beta distribution based on data
$\lambda 2_n$ $\lambda 2_b$ $\lambda 2_I$ $\mathbf{\lambda 2_T}$	Nominal mean number of *Campylobacter* cases in U.S. population (non-bloody, bloody, invasive and total)	$=\lambda 1_n/(p_{mn}*p_{cn}*p_t*p_+)$ $=\lambda 1_b/(p_{mb}*p_{cb}*p_t*p_+)$ $=\lambda 1_i$ $=\lambda 2_n+\lambda 2_b+\lambda 2_i$

Parameter estimations

2.1 (p_{mn}, p_{mb}) – Probability a person with campylobacteriosis seeks care

Two estimates were provided for this proportion, one for the probability that a person with enteric illness would seek care if they reported having no blood in their stool (p_{mn}) and one (p_{mb}) for bloody diarrhea.

The proportion of cases that sought care for "diarrheal illness" is based upon a 1998-9 population survey of 12,755 persons. The people interviewed were from the general population of the FoodNet sites (selected counties in California, Connecticut, Maryland and New York and the states of Georgia, Minnesota and Oregon), representing 8.6% of the U.S. population (26). The survey was conducted for the entire year. Approximately 150 persons per site were interviewed per month. People were randomly selected using a random digit dialing, single stage, Genesys-ID sampling method and were interviewed using methods similar to those used in the Behavioral Risk Factor Surveillance System. Cases excluded from the survey included persons with chronic illness, colitis, prior surgery to remove part of their stomach or intestine and irritable bowel syndrome (n=680); resulting in a total number of 12,075 usable interviews. Of the 12,075 usable interviews, **645** individuals reported having a "diarrheal illness," defined as three or more loose stools within a 24-hour period, or diarrhea lasting for more than one day or which resulted in an inability to perform normal activities. Of the 645 persons with a diarrheal illness, 30 reported bloody stools, 609 reported non-bloody stools and 6 were unknown.

(p_{mn}) *Probability a person with campylobacteriosis and* **non-bloody** *diarrhea seeks care*
Of those **609** cases with a diarrheal illness and non-bloody stools, **20.5%**, a weighted estimate (131/609), sought care (26). The estimate was adjusted to account for unequal probabilities of selection to allow population estimates to be made. Factors that affected selection probabilities included the number of people in a household. Age and sex were also weighted, creating an "external weight" so that the sample population resembled that of the U. S[1]. Because a confidence interval was not available for the estimate, uncertainty about the parameter was modeled using a Beta distribution as follows:

p_{mn} = Beta(609*0. 205+1, 609*(1-0.205)+1)

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[1] In the draft risk assessment the 1996-7 population survey (25, 49) was used to estimate the probability of seeking care and submitting a stool. A second population survey was conducted in 1998-9 (26) and was used to update these parameters in the model. The 1998-9 data were considered more relevant to the years modeled.
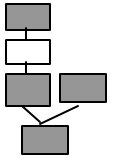
(p_{mb}) *Probability a person with campylobacteriosis and **bloody** diarrhea seeks care*
The same population survey identified **30** people who reported bloody diarrhea. Of the thirty persons with bloody diarrhea, nine sought care and an adjusted estimate of **33.2%** for p_{bm} was given (26). Uncertainty about the parameter was modeled using a Beta distribution as follows:

$$p_{mb} = Beta(30*0.332+1, 30*(1-0.332)+1)$$

Invasive disease
No information is available to estimate this parameter, see Section 1.3. It was assumed that, due to the severity of illness, 100% of people with invasive *Campylobacter* illness sought care.

DISCUSSION: These estimates are for diarrheal illness, and not campylobacteriosis specifically. Data describing care seeking behavior for campylobacteriosis was not available. Bacterial foodborne disease is typically more severe than viral foodborne disease (42) and rates of seeking care may differ by pathogen.

In the population survey, factors that were most important in influencing the decision to seek care were fever, vomiting, "how sick they felt," stomach cramps, reporting blood in stool and duration of diarrhea (26). Some of these factors were evaluated for diarrheal illness in the telephone survey and compared with the same characteristics in individuals who had culture-confirmed *Campylobacter* infections or diarrheal disease (Table 2.1). Comparing the groups, a greater proportion of people with culture-confirmed *Campylobacter* cases were affected by fever and blood in the stool than the people seeking care for diarrheal illness. Therefore, the actual rate of seeking care for campylobacteriosis may be underestimated by the 20.5% for persons with non-bloody and 33.2% for persons with bloody stools. However, because a greater proportion of people with fever and bloody stools would be cultured and enrolled in the case control study, such comparisons are difficult.

ASSUMPTION(s): The rate at which people reporting bloody stools seek care is similar to the rate at which people with campylobacteriosis reporting bloody stools seek care. The rate at which people with non-bloody stools seek care for diarrheal illness is similar to the rate at which people with campylobacteriosis reporting non-bloody stools seek care.

DATA GAP: Additional studies to define the rate at which people with campylobacteriosis seek care (123) would be helpful and would provide a more accurate estimate. These data would require very large community-based surveys.

Table 2.1. Comparison of characteristics of illness most important in seeking care between the telephone population survey of all diarrheal illness (26) and culture confirmed campylobacteriosis and a survey of diarrheal disease

Characteristic	Diarrheal Illness Seeking Care & Submitted Cultures – 1998-9[a]	Culture-confirmed *Campylobacter* Cases (CCCC) 1998[b]	CCCC 1980-1[c]
Sample size	21	1461	239
Fever	48%	83%	74%
Vomiting	50%	30%	38%
Stomach Cramps	75%	86%	79%
Blood in stool	15%	46%	46%

[a]Population Survey,(Ref. 26)
[b]*Campylobacter* Case Control Study (Ref. 28)
[c]Survey conducted in eight hospitals in the National Nosocomial Infections Study (Ref. 17, Table 2).
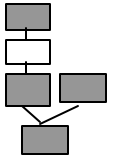
2.2 (p_{cn}, p_{cb},) – Probability a person with campylobacteriosis who has sought care is then requested to submit a stool and complies, for non-bloody and bloody diarrhea

Two estimates were provided for this proportion, equivalent to the probability that a person with an enteric illness would be requested to submit a stool sample and comply, if they reported having no visible blood (p_{cn}) or having visible blood (p_{cb}) in their stool.

The probability that a specimen was requested and submitted was determined from the same population survey of the seven FoodNet sites as listed in Section 2.1.

(p_{cn}) *Non-bloody diarrhea*
From the CDC population survey that identified 18 people reporting non-bloody diarrhea that were requested to submit and did submit a stool sample for culture of **128** persons reporting non-bloody diarrhea and seeking care and responding to the survey question, CDC provided an adjusted estimate of **15.1%** for p_{cn} (26). The estimate was adjusted to account for the number of people in a household, see Section 2.1.

Confidence intervals were not available with the weighted population estimates and in the absence of confidence intervals, uncertainty about the parameter was modeled using a Beta distribution as follows:

p_{cn} = Beta(128*0.151+1, 128*(1-0.151)+1).

(p_{cb}) *Bloody diarrhea*
In the population survey, the proportion of persons with a diarrheal illness that reported blood in their stools were requested to submit a stool sample and did submit was **26.1**% (weighted estimate based on 3/**9**)(26)[2].

Confidence intervals were not available with the weighted estimates and in the absence of confidence intervals, uncertainty about the parameter was modeled using a Beta distribution as follows:
p_{cb} = Beta(9*0.261+1, 9*(1-0.261)+1).

Invasive disease
There is no information on the rate of physician requests for diagnostic testing or rate of sample submission for cases of invasive disease caused by *Campylobacter*, see Section 1.3. In this assessment, we have assumed a rate of 100%.

ASSUMPTION: The probability that a stool specimen was requested among people with diarrheal illness reporting bloody stools is similar to the probability that a stool specimen was requested among people with campylobacteriosis reporting bloody stools. The probability that a stool specimen was requested among people with diarrheal illness reporting non-bloody stools is similar to the probability that a stool specimen was requested among people with campylobacteriosis reporting non-bloody stools.

2.3 (p_t) – Probability a lab tests a stool sample for *Campylobacter*
Non-Bloody Stool and Bloody Stool
In a survey of 309 laboratories in the five original FoodNet sites (CA, CT, GA, MN, OR, population 14,281,096 million persons), **389,255** stools were submitted during 1996. In the laboratories surveyed, **367,846** (94.5%) of submitted stool specimens were tested for *Campylobacter* (115).

Thus, this parameter was modeled using a Beta(367846+1, 389255-367846+1) distribution which is essentially a single point estimate of 94.5% because of the very large data set.

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[2] From the draft version of the risk assessment the physician survey (27,48) was dropped because reponses to the physician survey questionnaire were not data-driven, but rather based on physician recall.
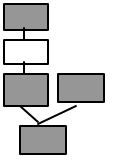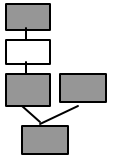
Invasive disease
No information is available for an estimate, see Section 1.3. The proportion is assumed to be 100% for invasive disease.

2.4 (p₊) – Probability a stool with *Campylobacter* cultures positive

The problems with the lack of sensitivity of stool culture are two-fold. First, stool culture techniques lack sensitivity as *Campylobacter* are fastidious microaerophillic organisms that, when exposed to oxygen or other stress, may enter a non-culturable state. Secondly, sensitivity of stool culture is limited by the amount of *Campylobacter* present in the stool. Finally, handling of the specimen is important and contributes to the lack of sensitivity of culture of *Campylobacter*. Sub-optimal specimen handling and storage may allow competitive growth by other bacteria or result in low numbers of *Campylobacter* in the stool that could reduce the likelihood that *Campylobacter* will be identified during culture. In addition, there are no standardized methods for isolation of *Campylobacter* and the increased costs associated with enrichment procedures and the utilization of highly selective media that would improve isolation discourages their routine use.

In an outbreak at a camp in New Zealand of *Campylobacter* enteritis, in 1990, associated with exposure to spring water, of 116 persons attending or resident at the camp, 44 showed clinical symptoms. Of the 44 clinical cases, 14 showing signs of enteric disease submitted stools for culture. Of the **14** specimens submitted from clinically affected individuals only **11** (78.6%) cultured positive for *Campylobacter* (55). Serology was not conducted to determine if rising titers of immunoglobulins were evident in persons ill and culture negative to determine if they may have been exposed to the pathogen.

Because another, U.S. related, estimate of the sensitivity of stool culture was not available and to assess whether this estimate was a close approximation to the true value for the sensitivity of stool culture, Dr. Fred Angulo, from CDC and Dr. Irving Nachamkin, from the University of Pennsylvania Medical Center, were surveyed for their expert opinions of the sensitivity of stool culture for *Campylobacter* (personal communications). Their estimates of 70% and 75%, respectively were close to the mean value of the parameter modeled.

DISCUSSION: There is little information on the sensitivity of stool culture methods and the methods for culturing stools are extremely diverse. Specimen handling is another factor that can greatly decrease the sensitivity of stool culture methods. In a review of non-typhoidal salmonellosis, an assumed estimate of the sensitivity of culturing *Salmonella* was 70% and was used to estimate the burden of salmonellosis in the U. S. (117). This estimate was adopted for determining the burden of campylobacteriosis in a recent review of foodborne disease (70).

DATA GAP: There is incomplete knowledge of the sensitivity of culturing specimens for *Campylobacter* and an estimate with a large degree of uncertainty was used from the literature. A study to estimate the sensitivity of stool culture as commonly practiced in labs testing stool for *Campylobacter* would provide a more precise estimate.

Thus, this parameter was modeled:

p₊= Beta (11+1,14-11+1).

2.5 (λ2ₙ, λ2ᵦ, λ2ᵢ, λ2ₜ) – Nominal Mean number of *Campylobacter* cases in the U.S.
Estimate of expected number of people in U.S. population ill with enteric *Campylobacter* infection and bloody and non-bloody diarrhea and with invasive disease *Campylobacter* in year in population and the sum of the three
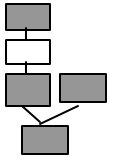
Calculation of the estimate of illness caused by *Campylobacter* in the U.S. population is done by combining the results determined by category of disease, enteric without observable blood in stools, enteric with observable bloody stools and invasive disease.

$(\lambda 2_n, \lambda 2_b, \lambda 2_i)$: *The estimates of illness caused by Campylobacter in the U.S. population*
The estimate of expected number of people in U.S. population ill with enteric disease was modeled separately for non-bloody and bloody diarrhea. Invasive disease caused by *Campylobacter* in a year is determined as equal to $\lambda 1_i$. This assumes that, due to the severity of the illness, all invasive cases of campylobacteriosis would seek care and provide a stool sample. The estimates, by category of disease, enteric with observable bloody stools and enteric without observable blood in stools and invasive disease are calculated as follows:

For non-bloody stool:
$\lambda 2_n = \lambda 1_n/(p_{mn}*p_{cn}*p_t*p_+)$

For bloody stool:
$\lambda 2_b = \lambda 1_b/(p_{mb}*p_{cb}*p_t*p_+)$

For invasive disease:
$\lambda 2_i = \lambda 1_i$

Year	Model output	5th percentile	Mean	95th percentile
1998	$\lambda 2_n$	825,620	1,320,768	2,032,490
	$\lambda 2_b$	160,392	466,253	1,105,344
	$\lambda 2_i$	436	572	723
1999	$\lambda 2_n$	786,079	1,259,425	1,944,018
	$\lambda 2_b$	152,970	444,599	1,057,061
	$\lambda 2_i$	526	671	828

Therefore the sum of the total number of cases in the U.S. population is:

$\lambda 2_T = \lambda 2_n + \lambda 2_b + \lambda 2_i$

The statistical characteristics of the distribution of the sum of the total number of cases in the U.S. population are given below:

Year	Model output	5th percentile	Mean	95th percentile
1998	$\lambda 2_T$	1,125,078	1,787,315	2,798,647
1999	$\lambda 2_T$	1,072,805	1,704,372	2,680,447
Difference (98-99)			-82,681	
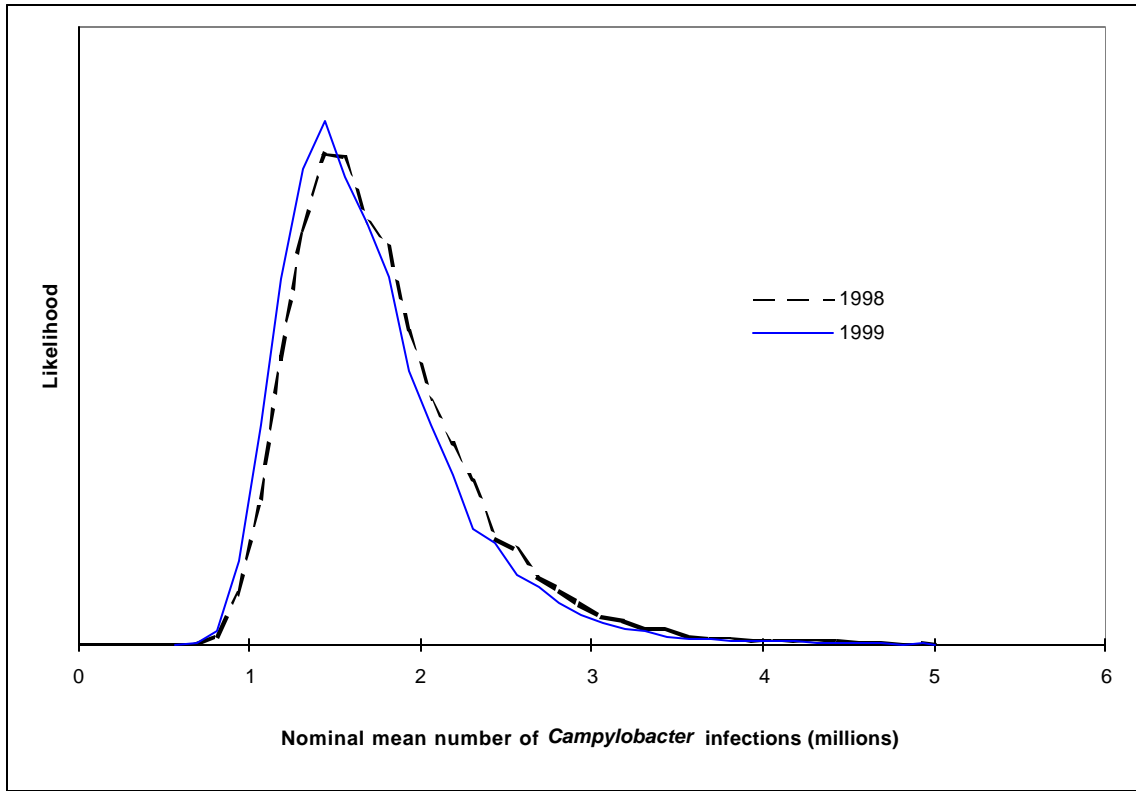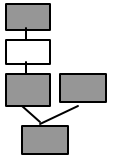
Figure 2.1. The confidence distribution (distribution of uncertainty) for the nominal mean total number of cases of campylobacteriosis in the U.S. for 1998 and 1999. *Note that the vertical axis for this and all other figures showing histogram (relative probability) representations of probability distributions have no scale: this is because the y-axis scale simply normalizes the curve to contain an area equal to unity. Values associated with higher likelihoods are more probable than values associated with lower likelihoods, but the height does not represent a probability for any given value.*

Section 2 Summary

The expected total number of cases of campylobacteriosis is then estimated as $\lambda_T = \lambda_i + \lambda_n + \lambda_b$. The estimates for 1998 and 1999 using this model are given in Figure 2.1. The figure shows the similarity in the estimates for the two years. The mean estimate of the distribution for 1998 is 1.79 million cases, with a 5th percentile estimate of 1.13 million and a 95th percentile estimate of 2.80 million. The mean estimate of the distribution for 1999 is 1.70 million, the 5th percentile estimate is 1.07 million and the 95th percentile estimate is 2.68 million Relative contributions of the various components of the model to the model uncertainty will be presented in Section 5, Sensitivity Analysis.

Section 3

Nominal mean number of fluoroquinolone resistant *Campylobacter* cases attributable to chicken, seeking care, treated with a fluoroquinolone and therefore affected by the fluoroquinolone resistance

Section 1
Nominal mean *Campylobacter* culture confirmed cases reportable to health department

Section 2
Nominal mean *Campylobacter* cases in US

Section 3
Nominal mean number of fluoroquinolone-resistant *Campylobacter* cases from chickens affected by fluorquinolone resistance

Section 4
Estimating quantity of fluoroquinolone resistant *Campylobacter* contaminated chicken meat consumed

Section 5
Using the model to measure the level of risk

Symbol	Description	Formula
p_{ca}	Probability a *Campylobacter* case is attributable to chicken	Based on referenced estimates
p_{rh}	Probability a *Campylobacter* case from chicken is fluoroquinolone resistant	Weighted estimate based on data
$\lambda 3_n$ $\lambda 3_b$ $\lambda 3_i$ $\lambda 3_T$	Nominal mean number of fluoroquinolone resistant *Campylobacter* cases attributable to chickens (non-bloody, bloody, invasive and total cases)	$= \lambda 2_n * p_{ca} * p_{rh}$ $= \lambda 2_b * p_{ca} * p_{rh}$ $= \lambda 2_i * p_{ca} * p_{rh}$ $= \lambda 3_n + \lambda 3_b + \lambda 3_i$
p_{mn}, p_{mb}	Probability a person with campylobacteriosis seeks care (non-bloody and bloody)	From Section 2
p_{an}, p_{ab}	Probability a *Campylobacter* case who has sought care is treated with an antibiotic	Composite estimate based on data
p_{FQ}	Probability a *Campylobacter* case who has sought care and has been treated with an antibiotic is treated with a fluoroquinolone	Weighted estimate based on data
$\lambda 4_n$ $\lambda 4_b$ $\lambda 4_i$ $\lambda 4_T$	Nominal mean number of fluoroquinolone resistant *Campylobacter* cases attributable to chicken, seeking care, treated with a fluoroquinolone and therefore affected by the fluoroquinolone resistance (non-bloody, bloody, invasive and total cases)	$= \lambda 3_n * p_{mn} * P_{an} * P_{FQ}$ $= \lambda 3_b * p_{mb} * P_{ab} * P_{FQ}$ $= \lambda 3_i * p_{FQ}$ $= \lambda 4_n + \lambda 4_b + \lambda 4_i$

Overview for Section 3.

Epidemiology of campylobacteriosis

Major differences in the epidemiology of common source outbreaks and sporadic cases have been described in the literature (12, 14, 95). The majority of *Campylobacter* cases are classified as sporadic cases (single cases of campylobacteriosis), while outbreaks account for a small proportion of all cases (11). In outbreaks, where a common source was identified, the predominant source of infection was consumption of unpasteurized milk, and less commonly involved contaminated water, or poultry (9, 16, 95). The seasonality of outbreak related disease differs from patterns observed for sporadic disease. Outbreaks peak in May and October while sporadic disease cases occur throughout the year and peak in the summer (61, 95, 96, 97) The proportion of disease due to person to person transmission is considered low, as outbreaks of *C. jejuni* and *C. coli* have rarely been identified in day care or nursing home settings where transmission of disease may be more likely (96, 97). Because outbreaks represent a small number of all cases and the predominant type of infection is sporadic disease, the major focus of this analysis was on risk factors for sporadic disease.

Sporadic campylobacteriosis accounts for more than 99% of all cases (95) and consumption of chicken (14, 32, 42, 43, 45, 51, 52) especially undercooked chicken (35, 45, 55) and handling or preparation of raw chicken (52, 56, 62) are the major risk factors identified in epidemiologic investigations. However, one study showed a protective effect when handling or consuming meals prepared from whole chicken (1). Cross-contamination of foods from contaminated poultry has been demonstrated to be associated with certain kitchen practices involved in the preparation of food (45, 62). Other risk factors for sporadic disease identified in the literature are; consumption of contaminated water (84) drinking unpasteurized milk or eating raw milk food products (61) contact with pets or diarrheic animals (1, 64) and travel to developing countries (92).

Campylobacter jejuni is the predominantly isolated *Campylobacter* spp, accounting for more than 90% of human isolates. Other *Campylobacter* spp may cause disease but are not routinely isolated from cases of campylobacteriosis. When methods other than the commonly utilized enrichment techniques are used in the
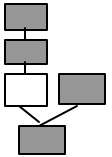
isolation of *Campylobacter*, such as filtration, other species are more commonly found. This indicates that current culture methods are not sufficiently developed to optimize isolation of all species of *Campylobacter*. The lack of knowledge of the magnitude of disease caused by unculturable *Campylobacter* spp potentially creates an unmeasurable impact on the estimate of risk. In this assessment, we have assessed only the measurable risk.

Sources of Infection and Level of Carriage
Campylobacter infections are predominantly foodborne infections associated with animal derived food products (51). *Campylobacter* spp are often found as commensal microbes carried in the intestines of food animals and can contaminate food during slaughter and processing. USDA-FSIS has recently conducted surveys of recovery rates and estimated the mean number per unit (gram, cm^2) of product for some of the major foodborne pathogens found on raw animal products at slaughter and processing. Raw product isolation rates vary by species, with turkeys and chickens appearing to have the highest rates of *Campylobacter* recovery (Table 1.2) (90, 103). Broilers carry the highest carcass and ground product load (Most Probable Number [MPN]/cm^3) of *Campylobacter* when compared to other food animals at slaughter (108, 109) (Table 1.2), consistent with the repeated observations in epidemiologic studies of the increased risk of campylobacteriosis associated with exposure to chicken.

In other surveys of retail food products, *Campylobacter* was isolated from: 2-20% of raw beef; 40% of veal; up to 98% of chicken meat; low proportions in pork, mutton and shellfish; 2% of fresh produce from outdoor markets and 1.5% of mushrooms (33).

Campylobacter Speciation
In some of the references cited for human campylobacteriosis in this risk assessment the distinction between *C. jejuni* and *C. coli* was not made. *Campylobacter* speciation has been difficult to determine and the methods used to characterize the organisms have changed over time. Currently methods are not standardized. Due to the lack of standardization, laboratories have established unique methods for the identification of *Campylobacter* spp. This can result in discrepancies between laboratories (77). Often studies that were published in the literature did not make the distinction between species and when the distinction was made, the studies often relied solely upon biochemical hippurate hydrolysis which does not identify hippurate negative *C. jejuni* (99). Because of the potential for species misclassification, additional tests using polymerase chain reaction (PCR) primers to identify the hippuricase gene were added to protocols to identify hippurase negative *C. jejuni*. Recently, PCR based assays have been developed to allow genotypic species characterization (47). The majority of human disease reported in the United States has been *C. jejuni,* typically comprising over 90% of human isolates (95). The consistently reported preponderance of *C. jejuni* human isolates made the lack of speciation in studies of risk factors less relevant to human campylobacteriosis.

Campylobacter Strains and Epidemiologic Typing Methods
Subtyping of *Campylobacter* strains using phenotypic methods such as biotyping, serotyping, phage typing, and genotypic methods using pulsed field gel electrophoresis, restriction endonuclease analysis, ribotyping, multilocus enzyme electrophoresis (MEE) and PCR fingerprinting have all been used to characterize strains for epidemiologic studies (34). Serotyping has identified similar strains present in *C. jejuni* isolated from chickens, cattle and human cases (76). For serotyped *C. coli* isolates, similar strains have been identified in humans, swine and poultry (76). Using genotypic strain typing methods, similar strains were identified in humans and poultry (34, 64, 78).

Some researchers have proposed that genomic rearrangement may occur in *Campylobacter* (44) suggesting that identification of strains using genotypic methods may have less sensitivity and specificity than was previously thought. However, in laboratory studies genomic instability was not demonstrated in in-vitro and in-vivo tests (44, 121). Strain typing using a gene, for example the *flaA* and *flaB* genes with PCR-RFLP typing, is considered a sound epidemiologic tool for strain identification (73, 75).
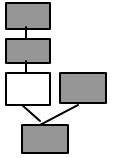
Other Sources of Human Exposure to Campylobacter:

Pet associated cases

Acquisition of puppies and kittens and contact with diarrheic animals has been shown to be associated with human campylobacteriosis (1, 85). Cats and dogs, especially puppies and kittens have been identified as potential sources of human infections (15, 79). Exposure to diarrheic animals was a risk factor in one study and approximately 6.3% of cases were attributed to this exposure (OR 4.3, 95% CI 1.9 to 9.7). Analysis of isolates obtained from animals and ill persons in the same household indicated the presence of similar Penner serotypes from both sources (85).

Cattle (beef and raw milk) associated cases

C. jejuni is a commensal bacteria inhabiting the intestinal tract of cattle (61). In Canada and Denmark, Penner serotypes and biotypes identified in *C. jejuni* and *C. coli* isolated from cattle were similar to and commonly isolated from human sources (39, 41). In one of the surveys (39). *Campylobacter* spp were recovered from 50% of steers, 40% of bulls and heifers and 22% of cows. Carcasses are contaminated with *Campylobacter* during slaughter and processing and the results of recent estimates of prevalence and load surveys conducted by FSIS are shown in Table 1.2.

Consumption of contaminated milk has often been associated with outbreaks of disease (9, 97). Contamination of milk most often occurs via exposure to feces but mammary excretion of *Campylobacter* has been demonstrated (61, 65).   In a survey of Tennessee dairies *C. jejuni* was recovered from 12.3% of bulk tank raw milk samples (61).

A reduction in the number of outbreaks and associated cases has been observed since 1987 when the FDA implemented a ban on the interstate marketing of raw milk (46). The mean annual number of reported outbreaks was much lower for the period after the 1987 ban compared to the period before 1987 (1.3 vs. 2.7) (46). In 1995, for the 28 states that allowed the intrastate sale of raw milk, it was stated that approximately 1% of total milk sold was unpasteurized, although a source for this consumption data was not provided. In Iowa, cases associated with the consumption of raw milk were the result of the ready availability of unpasteurized milk on farms where it was produced, never entering a market (87). The number of reported outbreaks per 10 million person-years in states that allowed the sale of raw milk was 0.14, compared to 0.03 outbreaks per 10 million person-years in states where the sale was illegal (46). It is difficult to assess whether a reduction in disease rates may have changed after the 1987 FDA ban because raw milk consumption data is not readily available and outbreaks associated with exposure to raw milk have not been reported since 1992.

Water associated cases

Contaminated surface water has been associated with human outbreaks, sporadic campylobacteriosis and as a source of infection for animals. In the U.K., a spring was contaminated with *C. jejuni* that was only present when other fecal indicator species were concurrently isolated. The spring was monitored for a 12-month period and some biotypes of the *C. jejuni* strains isolated from the groundwater were identical to strains isolated from a dairy farm located within the same rainwater catchment area (93). Contamination of municipal water sources has been reported and is typically associated with large outbreaks in the community. Drinking water contamination may occur from wild animal reservoirs, especially birds and domestic animal sources by contamination with feces (71, 84).

Isolation of *Campylobacter* from ground water occurs predominantly in the spring and fall. *Campylobacter* in water may be difficult to isolate as they may be present in low numbers, sub-lethally injured by temperature extremes, osmotic stress, nutrient depletion, and by competition from other organisms (68). They may enter a "viable but non-culturable" state but maintain the ability to infect and cause disease in people and animals (68). *Campylobacter* has been isolated from stream water at 4 degrees C for 4 weeks. Isolation was temperature dependent and duration of isolation was less at 25 degrees C compared to 4 degrees C. This indicates that environmental exposures may be temperature dependent and the environment may provide a source of *Campylobacter* that is the result of fecal contamination from animal sources (57).
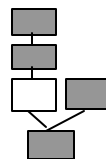
In a wastewater survey in the Netherlands, three sources of water were tested for the presence of resistant *Campylobacter*. Poultry abbatoir effluent and two sewage purification plants, one receiving mixed sewage from poultry and humans and one not receiving meat-processing sewage, isolated *Campylobacter* and conducted susceptibility testing. Fluoroquinolone resistance in *Campylobacter* isolates was identified at levels of 29%, 18% and 11% respectively, indicating that water can be a medium for resistant and susceptible *Campylobacter* (87).

Turkey associated cases

The presence of *Campylobacter* in the intestinal tract of turkeys is common. Of 650 cecal samples taken from turkeys on eight farms, 100% were positive for *Campylobacter* and contamination of raw product can occur during slaughter and processing (67). In the King County study, cases exposed to processed turkey sandwich meats demonstrated an increased risk of infection (RR 1.7, 95% CI 1.0 to 2.9) compared to controls. In a companion survey of retail meats, fresh turkey samples were contaminated with *Campylobacter* in 1.8% of samples (45). In a study of members of a Southern California Health Maintenance Organization, a significantly higher proportion of 11 bacteremic cases, not associated with enteric symptoms, compared to 22 controls had consumed processed turkey meat (45, 89). FDA has shown the persistence of *C. jejuni* in processed meat for up to 21 days at 4 degrees C (57, 89). In an USDA-FSIS survey of turkey carcasses (110) and ground turkey (109) the recovery of *Campylobacter* was 90% and 25% respectively. Although the prevalence of carcass isolation was slightly higher than in broilers, the level of contamination of the carcass was lower than the level found on chicken carcasses and approximately half that of the ground product.

Swine associated cases

The majority of *Campylobacter* isolated from swine under currently used microbial species typing is *C. coli* (4, 76) and is usually present in pigs without signs of disease. *C. coli* recovered from swine and typed using Penner serotyping indicated that pig serotypes do not appear to overlap with human: serotypes in Denmark (76); biotypes in the Netherlands (7); and biotypes and serotypes in the United States (72). *C. coli* reportedly represents approximately 4 and 6 % of human disease in the U.S. and Denmark respectively (23, 76). In studies to determine risk factors for human disease, the finding of an association between human illness and the consumption of pork is rare. One study in Norway identified risk associated with consumption of sausages at a barbecue that could not be attributed to cross-contamination from poultry (62).

Sheep associated cases

Few investigations of *Campylobacter* have been conducted in sheep to determine the frequency of isolation from sheep and sheep food products. Little work characterizing strain serotypes, biotypes or use of genetic typing methods has been reported for ovine associated *Campylobacter* (4, 61).

Shellfish and other associated cases

Few studies have shown an association between disease and exposure to shellfish and other fish (45). *Campylobacter* have been isolated from mushrooms (33) but little is known of other produce nor the magnitude of human cases from exposures to these sources.

Human to human transmission

The amount of human-to-human transmission of *Campylobacter* is considered to be low and infrequent outbreaks in day care settings and nursing homes confirm the low risk of human to human spread of disease (95).

Fluoroquinolones have been available for human use since 1986 when the first drug was approved in the United States (91, 92). Emergence of fluoroquinolone resistant human *Campylobacter* infections occurred between 1996-8 (92). Although human fluoroquinolone use can lead to the emergence of resistant isolates, human to human transmission of *Campylobacter* is uncommon and is unlikely to contribute to a greater

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fluoroquinolone and therefore affected by the fluoroquinolone resistance
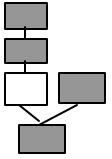
proportion of resistant human infections relative to the contribution of poultry associated resistant infections (91).

Travel Associated Cases
In numerous studies, travel to developing countries has been associated with increased risk of *Campylobacter* infection and since the late 1980's with quinolone resistant *Campylobacter* infections (13, 81, 91).

In the CDC FoodNet *Campylobacter* Case Control Study preliminary results of 580 cases, the proportion of cases that traveled was 12.1%. The level of fluoroquinolone resistance in the travelers was 37.5%, higher than the overall level of *Campylobacter* fluoroquinolone resistance in 1998 of 13.6% (23, 28).

Overview Summary
To summarize, sporadic disease represents the greater proportion of human campylobacteriosis and although many other sources of infection have been determined, consumption of chicken has been the most consistently identified risk factor in epidemiologic studies. Strain typing of isolates has confirmed epidemiologic findings, that similar strains are present in humans and chickens, as well as other animal species. Prevalence surveys indicate a high prevalence and burden of *Campylobacter jejuni* and *C. coli* on chicken carcasses (Table 1.2). *C. jejuni* is isolated from approximately 95% of human cases. The risk assessment question was to determine the measurable impact of fluoroquinolone resistant *Campylobacter* associated with the consumption of chicken on the treatment of human campylobacteriosis. This section determines the number of fluoroquinolone resistant human cases attributed to consumption of chicken that are treated with a fluoroquinolone.
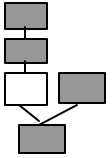
The number of fluoroquinolone resistant cases attributed to chicken related exposures was determined from the total number of cases using the following parameters, (refer to Appendix B for summary reference to mean expected estimates of each parameter):

- Probability a *Campylobacter* case is attributable to chicken
- Probability a *Campylobacter* case from chicken is fluoroquinolone- resistant

Output: Nominal mean number of fluoroquinolone resistant *Campylobacter* cases attributable to chicken

- Probability a person with campylobacteriosis seeks care (Bloody diarrhea, Non-bloody diarrhea and invasive cases)
- Probability a *Campylobacter* case who has sought care is treated with an antibiotic (no stool submitted or culture; culture confirmed cases: Bloody diarrhea and Non-bloody diarrhea; and invasive cases)
- Probability that, for a *Campylobacter* case who has sought care and has been treated with an antibiotic, the antibiotic is a fluoroquinolone (no stool submitted or culture; culture confirmed cases: Bloody diarrhea and Non-bloody diarrhea; and invasive cases)

Output: Nominal mean number of fluoroquinolone resistant *Campylobacter* cases attributable to chicken, seeking care, treated with a fluoroquinolone and therefore affected by the fluoroquinolone resistance

Parameter estimations

3.1 (p_{ca}) Probability a *Campylobacter* case is attributable to chicken: Chicken associated cases (Studies 1-2)[1]

STUDY 1, Seattle-King County Study:
A case control study was conducted to explore a wide variety of potential risk factors associated with sporadic campylobacteriosis (travel, food, water, animal and human contacts) and to evaluate the degree to which consumption of various meats played an etiologic role in disease (45). The study was conducted from April 1982 to September 1983 of enrollees in the Group Health Cooperative (GHC), a 320,000 member health maintenance organization located in Western Washington State. Cases and controls were GHC enrollees and residents of King, and southwest Snohomish Counties. Cases were identified as persons from whom *C. jejuni* or *C. coli* was isolated from stool. Cases were excluded if they did not have a telephone, had moved from the study area or did not speak English. Only the first case from each household was included in the study. Cases were matched to controls by age and month of case interview and were interviewed an average of two weeks after onset of symptoms. Of 32 randomly selected controls out of the total number of 526 controls and 90 contacts of controls that were cultured, no enteric pathogens were isolated from either group. Risk factors identified in this study were chicken consumption (relative risk (RR) 2.4, 95% CI 1.6 to 3.6), eating undercooked chicken (RR 7.6, 95% CI 2.1 to 27.6), consumption of Cornish game hen (RR 3.3, 95% CI 1.1 to 9.8), processed turkey meats (RR 1.7, 95% CI 1.0 to 2.9), shellfish (RR 1.5, 95% CI 1.1 to 2.1) and raw or rare fish (RR 4.0, 95% CI 1.1 to 14.5). (Table 3.1)

This study also surveyed practices relating to food preparation surfaces on a "cutting board scale" that ranged from 0-10 points, higher scores indicating safer practices. Controls scored higher on average than cases and a linear trend in risk ($p \leq 0.02$) was associated with decreasing score on the "cutting board scale" that was strongest in chicken consumers and absent in non-chicken eaters. Chicken consumption was quite common in the study population and the estimate of the etiologic fraction, the proportion of cases that would not have occurred had chicken not been consumed, was **48.5%**, (CI 27.9 to 63.2). No other fresh red meats or poultry were associated with campylobacteriosis. Another survey conducted in King County was unable to isolate *Campylobacter* from fresh fish and shellfish (45).

This study was limited to cases with enteric illness, submitting stools for culture. The authors indicated a potential non-respondent bias due to lack of participation by controls that may have resulted in a higher estimate of the relative risk (RR 3.0) associated with chicken consumption. The results of this study are now 17 years old and exposures and other factors may have changed in the interim, potentially affecting the level of risk attributable to chicken. Demographic characteristics of the population, the frequency, preparation and amount of chicken consumption, the proportion of the population consuming chicken and many other factors may have changed since this study. For example, the amount of chicken consumed has increased since 1982, and in 1998 people consumed 64.8% (77.5/47.02) more chicken, calculated in RTC pounds consumed per capita (102, 103).

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[1] In the draft risk assessment a third study, Hopkins, R., Olmstead, R., and Istre, G., Endemic *Campylobacter jejuni* Infection in Colorado: Identified Risk Factors. Am. Jour. Pub. Health. 1984. 74(3); 249-50.) was used to define the attributable risk of campylobacteriosis from consumption of chicken. The study was dropped from the final risk assessment because of inconsistencies in the reported results.
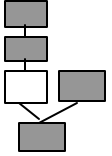
Table 3.1. Odds Ratios and etiologic fraction associated with statistically significant exposure variables for campylobacteriosis, April 1982-September 1983, Group Health Cooperative, King County, Washington (Adapted from Table 4, Ref. 85)

Risk Factor	Odds Ratio	95% Confidence Interval	Etiologic Fraction
Chicken Consumption	2.4	1.6-3.6	48.2
Non-household member with enteritis	2.5	1.6-4.0	11.7
Travel to underdeveloped countries	32.9	10.2-133.6	9.0
Household member with enteritis	1.9	1.2-3.0	8.0
Non-home well or surface water	1.8	1.1-2.9	7.6
Any animal with diarrhea	4.3	1.9-9.7	6.3
Raw Milk Consumption	4.6	2.1-10.4	5.2

STUDY 2, University of Georgia Study:

In 1983-1984 at the University of Georgia a case control study was conducted to identify risk factors for *C. jejuni* enteritis (32). Cases were students ill with diarrhea that submitted a stool sample from which *C. jejuni* or *C. coli* was isolated. Controls that were not ill were matched to the cases by sex, residence and age (+/-5years). Interviews were conducted by local public health personnel covering demographic, clinical and other potential exposures. 95 students submitted stools during the fall and winter quarters, all met the case definition and 45 were included in the study. In a breakdown of the 50 exclusions: 27 students were excluded because they could not be contacted, 11 refused to be interviewed, five because a matching control was not found and for seven cases a reason for exclusion was not given. Those excluded from the study did not differ significantly from the included cases based upon date of illness, sex, age, or campus residency.

Overall, 40 cases reported consumption of chicken, 9 undercooked chicken and 11 reported contact with a cat. In an evaluation of the demographic characteristics between the cases and controls, males were at greater risk of infection than female students. One explanation proposed for this difference was that male student cooking practices were less safe than those of the female students.

In univariate analysis of potential risk factors, three statistically significant factors were identified; consumption of chicken within six days of onset of illness (odds ratio=4.7, $p \leq 0.02$), consumption of raw or undercooked chicken (odds ratio=9.10, $p \leq 0.05$) and contact with a cat in the week before onset of illness (odds ratio 9.0, $p \leq 0.05$). Multivariable analysis indicated the same risk factors as in univariate analysis; eating any undercooked chicken (odds ratio 48.7, 95% confidence interval [CI] 2.1 to 1,135), eating any chicken (cooked only) (odds ratio 7.2, 95% CI 1.2-43.7) and contact with a cat (odds ratio 28.2 95% CI 1.02-777) (32). Those who had eaten raw or undercooked chicken were more likely to have eaten barbecued chicken than the cases who had eaten completely cooked chicken. No foreign travel or raw milk consumption was reported by any of the respondents. Illness was not associated with untreated water, contact with a dog or puppy, exposure to another person with diarrhea, consumption of pork, beef, or turkey or place of food preparation. The number of chicken meals consumed by cases peaked in the period two to four days before onset of illness compared to the controls where frequency of consumption was more consistent and only half as frequent as cases. Illness was not associated with preparation of chicken, consumption of chickens cooked whole or the duration between preparation and consumption of chicken. Overall **66.7%** (95% CI 20.2 to 86.1) of cases were attributed to eating chicken (95).

Limitations of this study include the lack of representativeness of the study population and the absence of some exposures, such as travel and raw milk that are frequently associated with risk in the population at large. In addition, the study was limited to enteric illnesses because more invasive infections were not eligible for inclusion in the study, although these usually comprise less than 1% of cases. These differences result in difficulty in generalizing the findings to the United States population but may represent the level of risk in some subgroups of the population.

DISCUSSION: In the two case control studies there was an increased risk of illness associated with consumption of chicken especially consumption of undercooked chicken. One study indicated a risk
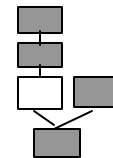
associated with raw milk consumption although the proportion of attributable risk was much less than that attributed to chicken. The proportions of disease attributable to chicken consumption were 48.5% and 66.7%. The higher estimate of attributable risk from study 2 of 66.7% in the university student population indicates that in some subgroups of the population exposures are likely to differ and risk attributable to consumption of chicken will vary accordingly. These estimates of the etiologic fraction represent a range of risk that is likely to reflect the level of risk in the early 1980's. More recent data do not exist for United States populations.

ASSUMPTION: The current level of risk of contracting campylobacteriosis from consumption of chicken is contained within the range of risk ascertained from studies conducted in the 1980's.

DISCUSSION: The definition of the attributable risk included all cases of disease which may be attributed to a specific risk factor (122, 83). One limitation of epidemiologic tools used to determine the attributable risk or etiologic fraction is that those cases that were exposed to the risk factor of interest, even though the exposure may not have been the cause of the disease, would be included in the calculated level of risk, thereby potentially overestimating the level of actual risk. Conversely, another limitation of the epidemiologic tools used to determine the risk from the specific exposure of interest is that spread from the primary source of the pathogen, in this case chickens, is not included in the calculation of the level of risk. The magnitude of the bias introduced by false associations with chicken exposures (false positive associations) may well be much smaller than the lack of inclusion of the undeterminable cases from spread of the chicken associated resistant *Campylobacter* to other sources of human exposure as such a large proportion of the population, over 80%, consumes chicken. In addition, the risk assessment does not take into account the spread of the pathogen from chicken to other food sources. This can occur from cross contamination of other foods (29) or spread from chicken sources more proximate to the farm. For example: from chicken litter to birds, insect and water; use of chicken litter in aquaculture to fertilize fish ponds and to increase the non-protein nitrogen content of cattle feeds. Therefore, the risk assessment is likely to underestimate the overall risk of acquiring a resistant *Campylobacter* infection from exposure to chicken due to the spread of *Campylobacter*.

ASSUMPTION: The level of risk as calculated does not account for cases originating from chicken and contaminating other foods or the spread from chicken to other animal hosts and resulting in human exposure.
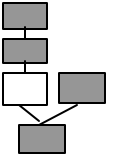
A Uniform distribution was used to model the uncertainty in the proportion of *Campylobacter* illness attributed to domestically consumed chicken, p_{ca}. The Uniform distribution assigns the same probability to all parameter values in its range, indicating maximum uncertainty about the true parameter value. The lower and upper bounds of the range of the Uniform are themselves unknown parameters. These parameters were estimated from the confidence intervals for the attributable risks from the two studies as follows.

Walter (122) demonstrated that for attributable risk estimator θ and $\xi = 1 - \theta$, the log of ξ is asymptotically Normal. This is the basis for the derivation of the confidence intervals for θ. If, then, θ_L, θ_U are the limits of a 95% confidence interval for θ, the uncertainty distribution of $\log_{10}(\xi)$ is modeled as

Normal $\{\log_{10}(1-\theta), [\log_{10}(1-\theta_L) - \log_{10}(1-\theta_U)]/1.96\}$.

The uncertainty distribution for p_{ca-min} is based on the estimated 95% confidence interval for the smaller attributable risk point estimate 48.5%, from Study 1, and is $10^{\wedge}$Normal(-0.66, 0.34). The uncertainty distribution for p_{ca-max} is based on the estimated 95% confidence interval for the larger attributable risk point estimate 66.7%, from Study 2, and is $10^{\wedge}$Normal(-1.10, 0.89). These two Normal distributions overlap very slightly; the smaller of p_{ca-min} and p_{ca-max} was taken as the sampled value for the lower bound of the Uniform and the larger was taken as the sampled value for the upper bound of the Uniform uncertainty distribution for p_{ca}.
That is,

Section 3

Nominal mean number of fluoroquinolone resistant *Campylobacter* cases attributable to chicken, seeking care, treated with a fluoroquinolone and therefore affected by the fluoroquinolone resistance

$p_{ca\text{-}min} = 10^{\wedge}\text{Normal}(-0.66, 0.34)$,

$p_{ca\text{-}max} = 10^{\wedge}\text{Normal}(-1.10, 0.89)$, and

$p_{ca} = \text{Uniform}(\text{MIN}(p_{ca\text{-}min}, p_{ca\text{-}max}), \text{MAX}(p_{ca\text{-}min}, p_{ca\text{-}max}))$.

3.2 (p_{rh}) - Probability a *Campylobacter* case from chicken is fluoroquinolone resistant:

Ciprofloxacin is one of two antimicrobials used to monitor losses of susceptibility to the class of fluoroquinolone drugs in the National Antimicrobial Resistance Monitoring System: Enteric Bacteria (NARMS:EB) and represents the most widely used member of the class in human medicine. The breakpoint below which isolates are considered susceptible, 4 mcg/ml, was formally established for other *Enterobacteriaceae* by NCCLS and is used as a predictor of *Campylobacter* susceptibility to Ciprofloxacin. The breakpoint indicating loss of clinical effectiveness has not been set for fluoroquinolone drug use in *Campylobacter* infections but a breakpoint of 4 mcg/ml is used by many diagnostic labs and surveillance systems to monitor shifts in susceptibility.

E-Test strips (AB BIODISK, Solna, Sweden) contain an antimicrobial gradient on the opposite surface of a scale indicating increasing concentrations of the test drug. Growth along the strip is inhibited where the concentration of the drug exceeds the minimum inhibitory concentration (MIC) of the microorganism being tested. *Campylobacter* E-test MIC's to Ciprofloxacin have been compared with agar dilution susceptibility testing and although the E-Test tended to produce lower results, indicating higher activity than that observed on agar dilution testing, the overall correlation of MIC's between methods was good at 90.4% of the tests in one study (53).

Fluoroquinolone resistance has been significantly associated with human infections that are travel related (80, 92) foodborne, particularly chicken associated infections (71) and treatment of human illness with a fluoroquinolone (88).

580 isolates were obtained from the FoodNet catchment area from cases enrolled in the *Campylobacter* Case Control Study. *C. jejuni* comprised 92.4%, *C. coli* 2.7% and *C.* "other" 4.8% of the total number of isolates. The isolates were cultured and speciated in clinical laboratories and forwarded to the FoodNet State Health Department where susceptibility testing was performed. Isolates (150/580) were forwarded to CDC for NARMS:EB surveillance susceptibility testing using E-Test and compared to state health department findings. The correlation of susceptibility testing results between laboratories was good.

From the 580 isolates collected for the *Campylobacter* Case Control study, the proportion of travelers and persons taking fluoroquinolones prior to culture was calculated for susceptible and resistant isolates for each state in the study, see Table 3.2 located at the end of Section 3 or the worksheet labeled "Data" in the Excel model. These proportions were used to remove travelers and persons taking fluoroquinolones prior to culture, adjusting total susceptible and total resistant NARMS:EB isolates from each site for 1998 and 1999 (23, 24). Because the number of isolates that were tested was disproportionately distributed by site and the rate of resistance varied by site, the level of resistance was weighted by the site population size to better represent the relative contributions of each FoodNet site, Table 3.3 below (21, 22).
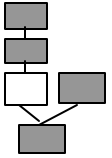
Table 3.3 Weighted levels of domestically acquired resistance by FoodNet site, 1998 and 1999[1]

State	CA[2]	CT	GA	MD	MN	NY	OR	TN	Level of DA Resistance (%)
1998	0.0176	0.0285	0.0241	0.0363	0.0164	0.0133	0.0059	ND	14.2
1999	0.0172	0.0375	0.0587	0.0286	0.0288	0.0131	0.0064	0.0059	19.6

[1]See model data sheet for calculation of weighted levels of domestically acquired resistance or Table 3.5 at the end of this section.

[2]CA-California, CT-Connecticut, GA-Georgia, MD-Maryland, MN-Minnesota, NY-New York, OR-Oregon, DA-Domestically Acquired, ND-Not Determined

DISCUSSION: It is difficult to know what proportion of resistance in human campylobacteriosis may be attributable to a single commodity or source of human illness when human exposures are multiple and varied. A single source of resistant bacteria may be disseminated from its origins or maintained in secondary hosts further spreading resistant *Campylobacter* to additional sources of human exposure.

Fluoroquinolone use has been associated with the development of fluoroquinolone resistance in *Campylobacter* in clinical trials in poultry production units (58) in the Netherlands (36) and in the United States (92) after the introduction of veterinary fluoroquinolones. In countries where fluoroquinolones have been approved for human and companion animal use but are not allowed in food animals the level of fluoroquinolone resistance in food animals and human clinical cases is low (8, 54)

An Extra Label Use Prohibition of fluoroquinolone use in food-producing animals was published in 1997 (21CFR530.41), limiting food animal drug use to species listed on the product label. Approvals of fluoroquinolone drugs for use in animals include feline and canine oral and canine injectable products (available beginning in 1989), poultry water soluble and in-ovo injectable products (available in 1995) and feedlot cattle injectable products (available beginning in October 1998). There are no fluoroquinolones currently approved for use in swine.

Although drugs were used in humans and companion animals in the U.S. since the late 1980's, domestically acquired levels of fluoroquinolone resistance were not reported until 1996, after approval of the poultry fluoroquinolones. The level of domestically acquired resistance in Minnesota has increased annually from 0.8%, in 1996, to 4.2% in 1999 (92, personal communication K. Smith).

Campylobacteriosis is primarily an animal derived foodborne disease, with the predominant source of human infections attributed to poultry (32, 45, 51, 85). There is little surveillance data available to describe the level of fluoroquinolone resistance in *Campylobacter* isolated from other animal derived food and other food products in the United States, either before or after the approval of these drugs for food animal use. Chicken *Campylobacter jejuni* isolates collected in 1998 and 1999 indicated a level of 9.4% resistance to Ciprofloxacin (see Section 4.2). Because there was no food animal fluoroquinolone use other than use in poultry until late 1998, and only rare sporadic and isolated resistance was observed prior to 1992 in human cases[2] it is unlikely that the increase in domestically acquired fluoroquinolone resistance observed in people since 1996[3] can be attributed to origins other than poultry.

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[2] In two surveys encompassing 474 human isolates from 1982 to 1992 in the United States, only a single Ciprofloxacin resistant isolate was identified and subsequently speciated as *C. lari* which is intrinsically resistant to fluoroquinolones (91).

[3] After removal of persons who had traveled within 7 days of illness onset and removal of those taking fluoroquinolones prior to culture, quinolone resistance in Minnesota was observed in 0.8% of isolates in 1996 and had increased to 3.0% in 1998 (chi square for linear trend, 9.8; $p \leq 0.002$) (92). In Minnesota quinolone resistance, screened by nalidixic acid disc diffusion was highly correlated with resistance to ciprofloxacin using the E-Test, (sensitivity 99.6%, specificity 98.4%) (92). A survey of *Campylobacter* isolated from 88% of 91 chicken products resulted in *C. jejuni* from 67(74%) and *C. coli* from 19 (21%) of
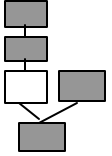
ASSUMPTIONS: The fluoroquinolone resistance observed in persons ill from campylobacteriosis, (after removal of travelers, those who took a fluoroquinolone prior to culture and those for whom the time of taking the fluoroquinolone was unknown) is largely attributed to chickens.

DATA GAP: Quantification of the proportion of human disease attributable to various sources and the determination of the level of resistance carriage within the specific exposures would more precisely allow the determination of the relative contributions of the various exposures to fluoroquinolone resistant human disease. A model intended to determine the human health impact of the level of resistance in *Campylobacter* attributable to fluoroquinolone use in food animals will need to distribute the burden of susceptible and resistant human disease amongst many different food animal species and potentially other food sources.

From the CCC study the number of resistant cases: 1) who had traveled internationally within the past 7 days; 2) who had taken fluoroquinolones prior to submitting cultures; and 3) who did not remember when the fluoroquinolone was taken, was known per catchment site for the total number of resistant cases and the total number of cases tested. From that it was possible to estimate the proportion of all resistant isolates that came from cases who had either traveled internationally or had taken a fluoroquinolone prior to culture at site j. Call those proportions a_j. Conversely, it was possible to estimate proportion of all susceptible isolates that came from cases who had either traveled internationally or had taken a fluoroquinolone prior to culture at site j. Call those proportions b_j. G_j is the number of human isolates that tested positive for resistant *Campylobacter* for site j, shown in Table 3.2 at the end of this section. F_j is the number of human isolates that were tested for resistance that is found by adding the number susceptible and the number resistant in the table. $F_j - G_j$ is therefore the number of susceptible isolates.

The parameter p_{rh} is then modeled as:

$$p_{rh} = \sum_j W_j \, Beta \, (g_j + 1, f_j - g_j + 1)$$

for $g_j = G_j*(1-a_j)$
and $f_j = g_j + Binomial (ROUND(F_j-G_j)*(1-b_j),0),p_{ca})$

3.3 ($\lambda 3_n$, $\lambda 3_b$, $\lambda 3_i$, **13$_T$**) – Nominal mean number of fluoroquinolone resistant *Campylobacter* cases attributable to chickens (non-bloody, bloody, invasive and total cases):

The nominal mean number of people with fluoroquinolone resistant *Campylobacter* infection from chicken is estimated as the nominal mean number of *Campylobacter* illnesses times the proportion that are chicken associated times the proportion of *Campylobacter* infections from chicken that are resistant to fluoroquinolone. This is determined separately for enteric *Campylobacter* infections with non-bloody

---

samples and six samples were the source of both pathogens. Products carrying resistant isolates were purchased from 11 stores representing 8 franchises and originated in seven processing plants in five states (91, 92) indicating widespread resistance in chicken *Campylobacter* isolates. Molecular subtyping was performed using PCR restriction endonuclease length polymorphism typing of the flagellin gene in *the C. jejuni* human and chicken product isolates. 12 subtypes were identified from 13 *C. jejuni* positive chicken products. Six of seven resistant subtypes in the chicken products were also identified in the quinolone resistant human isolates. For people acquiring infections during 1997, excluding cases that had taken fluoroquinolones prior to culture, persons with non-traveler resistant infections were more likely to *have C. jejuni* subtype also found in the quinolone resistant *C. jejuni* from chicken products (odds ratio 15.0, 95% CI 1.9 to 321.8) (91)

diarrhea, enteric *Campylobacter* infections with bloody diarrhea and invasive *Campylobacter* infections and lastly, the three estimates are summed.
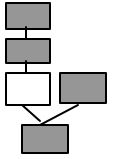
($\lambda 3_n$, $\lambda 3_b$) *Enteric disease:*

($\lambda 3_n$) *Non-bloody diarrhea*

$\lambda 3_n = \lambda 2_n * p_{ca} * p_{rh}$

($\lambda 3_b$) *Bloody diarrhea*

$\lambda 3_b = \lambda 2_b * p_{ca} * p_{rh}$

($\lambda 3_i$) *Invasive disease*

$\lambda 3_i = \lambda 2_i * p_{ca} * p_{rh}$

The distributions have the following characteristics:

Year	Model output	5th percentile	Mean	95th percentile
1998	$\lambda 3_n$	57,921	107,620	179,625
	$\lambda 3_b$	11,805	38,001	92,834
	$\lambda 3_i$	29	47	68
1999	$\lambda 3_n$	75,654	140,716	233,746
	$\lambda 3_b$	15,948	49,551	118,300
	$\lambda 3_i$	48	75	107

Therefore the sum of nominal mean number of fluoroquinolone resistant *Campylobacter* cases attributable to chickens for non-bloody, bloody and invasive cases is:

$\lambda 3_T = \lambda 3_n + \lambda 3_b + \lambda 3_i$

Section 3
Nominal mean number of fluoroquinolone resistant *Campylobacter* cases attributable to chicken, seeking care, treated with a
fluoroquinolone and therefore affected by the fluoroquinolone resistance
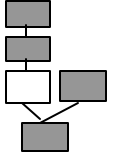
The distribution has the following characteristics:

Year	Model output	5th percentile	Mean	95th percentile
1998	**13**$_T$	77,596	145,766	246,674
1999	**13**$_T$	103,471	190,421	318,321
Difference (98-99)			44,655	
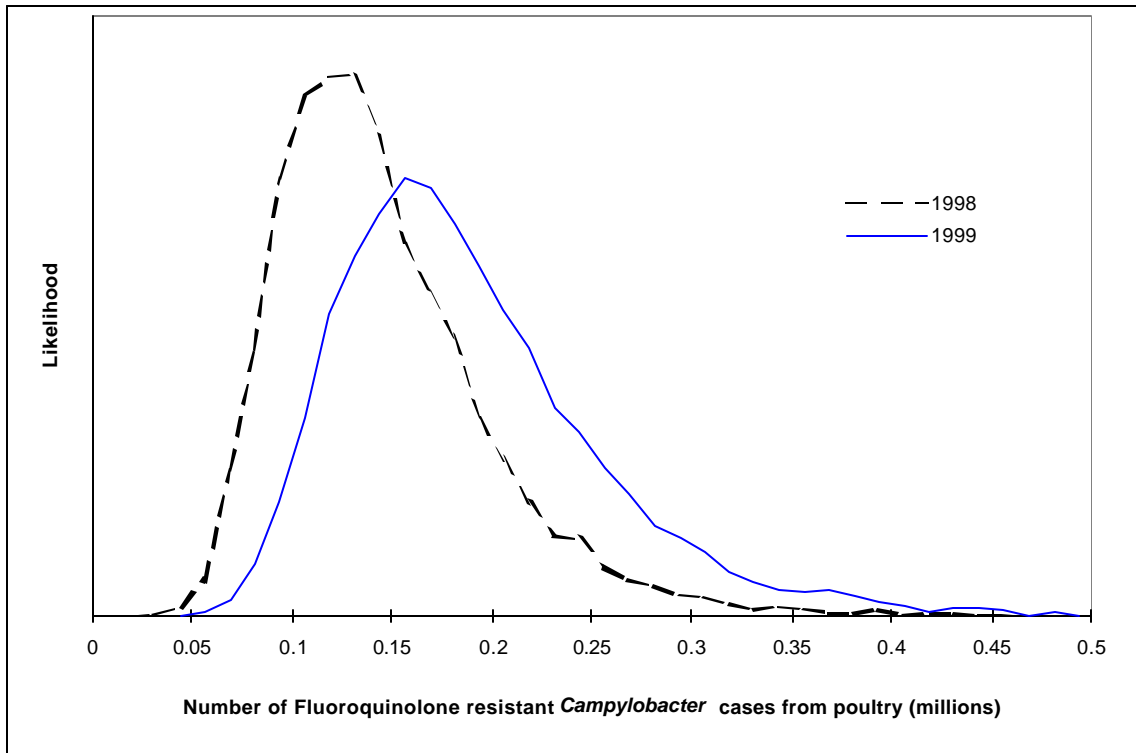
Figure 3.1 Uncertainty distribution for **13**$_T$

3.4 (p_{mn}, p_{mb}) - Probability a person with campylobacteriosis seeks care (non-bloody and bloody):

In the population survey, described in Section 2.1, the most important factors in seeking care for acute
diarrheal disease included having fever, vomiting, "how sick they felt", stomach cramps, reporting blood in
stool and duration of diarrhea. The highest rates for seeking care were amongst children less than 5 years of
age, urban residents, and those with health insurance. This estimate was for all diarrheal illness, and not
specific to campylobacteriosis.

(p_{mn})– *Reported **non-bloody** stool rate for seeking care*
Of cases with a diarrheal illness and reporting non-bloody stools 20.5%, a weighted estimate, sought care
(131/609) (28).

(p_{mb})– *Reported **bloody** stool rate for seeking care*
Of cases with a diarrheal illness and reporting bloody stools 33.2%, a weighted estimate, sought care (9/30)
(28).

In the model, these parameters were set equal to those of Section 2.1. As in Section 2.1, the proportion of those seeking care with invasive infection was estimated at 100%.

3.5 (p_{ab}, p_{an}) - Probability a *Campylobacter* case who has sought care is treated with an antibiotic (not submitting a stool, submitting a stool and invasive disease):

Persons ill with campylobacteriosis may take antibiotics for their illness with or without having sought care. The population survey indicated 5.9%, a weighted estimate, of persons that do not seek care with diarrheal illness take antibiotics, 28/524 (26). To assess the magnitude of impact this group may have on the total number of persons with a fluoroquinolone resistant illness taking fluoroquinolones, the total number of persons was estimated. Approximately 190,000 persons acquired fluoroquinolone resistant illnesses from chicken in 1999. Of these 88% did not seek care and 5.9% reported taking an antimicrobial (26). There were no data describing the types or sources of antimicrobials that were actually used. From data reporting recorded prescriptions of fluoroquinolones (69) it was determined that the cases prescribed fluoroquinolones were likely to make a small contribution to the total number of affected cases and hence were not included in the modeled estimate of cases.

Those cases that seek care present to the physician with varying severity of illness and complicating medical conditions. Cases that were not requested to submit a stool for culture took antimicrobial drugs less commonly than those submitting stools for culture did. Cases of invasive disease represented severely ill patients that were all likely to be prescribed antimicrobial drugs for their illness. Both of these groups were included in the estimate of the number of affected individuals.

Campylobacter Case Control Study Description, 1998-1999 (28)
A *Campylobacter* case control study was conducted at 7 FoodNet sites in 1998-1999 for a twelve-month period. (The start and end date of the 12-month enrollment period varied between sites). In total, 1314 matched sets of case patients and controls were enrolled in the study. The cases were defined as persons with diarrhea residing in the catchment area with a *Campylobacter* infection identified by a clinical laboratory isolation of *Campylobacter* from stool. Exclusion criteria from the case-control study were persons whose primary residence was outside the catchment area, persons without telephones, persons that were non-English speaking or unavailable for interview (including dead, and non-contactable). Additional exclusion criteria were persons not reporting diarrheal symptoms, or who could not recall the date of onset of their diarrhea, or whose onset of diarrhea was >10 days before the date of culture collection, or persons whose infections were outbreak associated; persons were also excluded if another member of the same household had a previous culture-confirmed infection within the past 28 days. A subset of case isolates were tested for antimicrobial susceptibility, either at the CDC (4 sites CA, GA, MD, OR) or by their own state public health laboratory as part of the study (3 sites CT, MN, NY). The number of submissions varied by site and is shown in Section 3.2.

One control per case was interviewed, matched on age and telephone exchange number of the case. Telephone interviews (using progressive and sequential telephone digit dialing based on telephone number of the case) were conducted within seven days of the matched case interview by trained personnel using standardized questionnaires for cases and controls. Questionnaires included questions about demographic characteristics, symptoms of illness, treatment, potentially complicating medical conditions, possible exposures such as travel, foods consumed and hygienic practices. For the seven participating sites during the study period, there were 3860 reported *Campylobacter* cases in surveillance; 2870 were eligible to be in the study (Table 1.3), 1461 cases were enrolled; 1314 were matched with a control, resulting in a 46% (1314/2870) enrollment rate for the case-control study.

(z) *Not submitting* a stool for culture
From the population survey, in the population seeking care, **38.1%** (**44/116**) of persons not requested to submit a stool sample by their health care provider took antibiotics for their illness (26). The estimated probability for taking an antibiotic given that a stool was not submitted, z, is estimated based upon 38.1%.
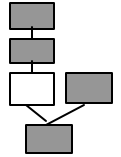
ASSUMPTION: The population survey proportion of cases of all acute diarrheal illness seeking care, not submitting a stool sample and receiving an antibiotic (38.1%) is similar to that for persons ill with campylobacteriosis.

DISCUSSION: Severity of illness is one of many factors that lead physicians to prescribe antibiotics to patients with a diarrheal illness.

(y) ***Submitting*** *a stool for Culture*
Preliminary analysis of the CDC FoodNet *Campylobacter* Case Control Study provided estimates of antibiotic use for culture confirmed cases (28). The proportion of cases treated with antibiotics was 84.4% unweighted estimate (488/578) and an overall summed weighted estimate of 83.1%. The individual state treatment rates were weighted: CA 8.9% (11/12), CT 13.3% (162/192), GA 16.5% (30/32), MD 10.3% (19/21), MN 18.7% (199/242), NY 4.6% (59/68) and OR 11.0% (8/11) (28).

ASSUMPTION: Patients who have sought care and been requested to submit stool cultures and have submitted stool cultures are prescribed antibiotics at a rate that is the same whether they had bloody or non-bloody diarrhea. Conversely, if patients have sought care but have not been requested to submit stool cultures, they are prescribed at another rate that is the same whether they had bloody or non-bloody diarrhea.

The parameters p_{an} and p_{ab} are modeled as:

$p_{an} = p_{cn}*y + (1-p_{cn})* z$
$p_{ab} = p_{cb}*y + (1-p_{cb})* z$
where $y = \sum_{j} W_j Beta(D_j + 1, C_j - D_j + 1)$,

$z = Beta(116*0.381+1, 116*(1-0.381)+1)$

and W_j are the weights for FoodNet sites as defined in section 1.9; C_j is the number of culture-confirmed cases for whom it is known whether they received an antibiotic or not for site j; and D_j is the number of culture-confirmed cases who did receive an antibiotic, shown in Table 3.4 below. z is the antibiotic prescription rate among patients who have sought care but have not been requested to submit stool samples.
y is the antibiotic prescription rate among patients who have sought care and been requested to submit stool samples.

ASSUMPTION: Because of the severity of illness upon presentation, all cases with invasive disease are presumed to seek care and are presumed to take antibiotics for their illness. Therefore p_{ai} is taken to be 1.

Section 3
Nominal mean number of fluoroquinolone resistant *Campylobacter* cases attributable to chicken, seeking care, treated with a
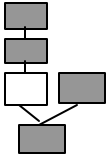fluoroquinolone and therefore affected by the fluoroquinolone resistance

Table 3.4 *Campylobacter* Case Control Study, unweighted and weighted proportions treated with antimicrobials and weighted proportions treated with fluoroquinolones, 1998-9 (Ref. 28)

Site	Weighting Fraction	Number for whom response was known	Number who were treated with antibiotics	Number who were treated with Fluoroquinolone	Unweighted proportion who were treated with antibiotics	Weighted proportion who were treated with antibiotics	Weighted proportion of those treated with antibiotic receiving Fluoroquin-olone
	W_j	C_j	D_j	E_j	[%]	(P_{em}) [%]	(p_{FQ}) [%]
CA	0.10	12	11	5	85.7	8.9	4.8
CT	0.16	192	162	93	84.0	13.3	9.1
GA	0.18	32	30	19	91.2	16.5	11.3
MD	0.12	21	19	8	87.0	10.3	5.1
MN	0.23	242	199	110	82.0	18.7	12.6
NY	0.05	68	59	31	85.7	4.6	2.8
OR	0.16	11	8	5	69.2	11.0	9.5
Total	1	578	488	271	84.4	83.1	55.1

3.6 (p_{FQ}) - Probability a *Campylobacter* case who has sought care and has been treated with an antibiotic is treated with a fluoroquinolone (not seeking care, seeking care but not submitting a stool , submitting a stool[non-bloody and bloody]):

Not seeking *care*
The 5.9% of persons with a diarrheal illness in the population survey that do not seek care and take antibiotics are not included in the assessment of fluoroquinolone treatment because they represent a small poorly described fraction of cases (See Section 3.4).

Submitting *a stool for Culture (Non-Bloody and Bloody Diarrhea)*
In preliminary results from the *Campylobacter* Case Control Study the proportion of cases treated with antimicrobials and receiving fluoroquinolone treatment was 55.5% (271/488) for both crude and weighted overall estimates. The individual state treatment rates were CA 4.8% (5/11), CT 9.1% (93/162), GA 11.3% (19/30), MD 5.1% (8/19), MN 12.6% (110/199), NY 2.8 % (31/59), OR 9.5% (5/8). (Table 3.4, above)

Not submitting *a stool for culture*
ASSUMPTION: Patients with campylobacteriosis who did not submit stools were treated by their health care provider with fluoroquinolones at the same frequency as those who submitted stools. (Table 3.4, above)

Invasive *Disease*
ASSUMPTION: The proportion of fluoroquinolone prescriptions of total antibiotic prescriptions is the same for patients with invasive campylobacteriosis treated by their health care providers as it is for patients with enteric campylobacteriosis treated by their health care providers. (Table 3.4, above)

The parameter p_{FQ} was thus modeled as:

$$p_{FQ} = \sum_j W_j Beta(E_j + 1, D_j - E_j + 1)$$

where, again, the W_j are the FoodNet site weights, E_j is the number of cases who have sought care and been treated with an antibiotic that is a fluoroquinolone and D_j is the number of cases who received antibiotics, shown in Table 3.4 above.
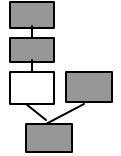
3.7 ($\lambda 4_n$, $\lambda 4_b$, $\lambda 4_i$, $\lambda 4_T$) - Nominal mean number of fluoroquinolone resistant *Campylobacter* cases attributable to chicken, seeking care, treated with a fluoroquinolone and therefore affected by the fluoroquinolone resistance (non-bloody, bloody and invasive and total):

This is the number of persons with fluoroquinolone resistant infections that are attributed to exposure to chicken, that seek care and are treated with a fluoroquinolone. The sum of non-bloody, bloody and invasive cases is:

($\lambda 4_n$, $\lambda 4_b$)*Enteric disease*

($\lambda 4_n$) *Non-bloody diarrhea*
$\lambda 4_n = \lambda 3_n * p_{mn} * P_{an} * P_{FQ}$

($\lambda 4_b$) *Bloody diarrhea*
$\lambda 4_b = \lambda 3_b * p_{mb} * P_{ab} * P_{FQ}$

($\lambda 4_i$) *Invasive disease*
$\lambda 4_i = \lambda 3_i * p_{FQ}$

The distributions have the following statistical characteristics[4]:

Year	Model output	5th percentile	Mean	95th percentile
1998	$\lambda 4_n$	3,016	5,459	9,084
	$\lambda 4_b$	1,422	3,276	6,817
	$\lambda 4_i$	16	26	38
1999	$\lambda 4_n$	4,003	7,135	11,609
	$\lambda 4_b$	1897	4278	8932
	$\lambda 4_i$	26	41	60

($\lambda 4_T$) - *Estimate of **total nominal mean** number of people with fluoroquinolone resistant Campylobacter infection from chicken who receive fluoroquinolone.*

The distribution of the sum, $\lambda 4_T = \lambda 4_n + \lambda 4_b + \lambda 4_i$ is shown in Figure 3.2. The distribution has the following statistical characteristics.

Year	Model output	5th percentile	Mean	95th percentile
1998	$\lambda 4_T$	4,849	8,782	14,689
1999	$\lambda 4_T$	6,412	11,477	18,978
Difference (98-99)			2,695	

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[4] Values incorporated in these tables will vary very slightly from graphed results due to small variations in repeating Monte Carlo simulations. The graphs are based on smaller simulation runs while the quoted values are based on large simulations and are more accurate.

Section 3
Nominal mean number of fluoroquinolone resistant *Campylobacter* cases attributable to chicken, seeking care, treated with a
fluoroquinolone and therefore affected by the fluoroquinolone resistance
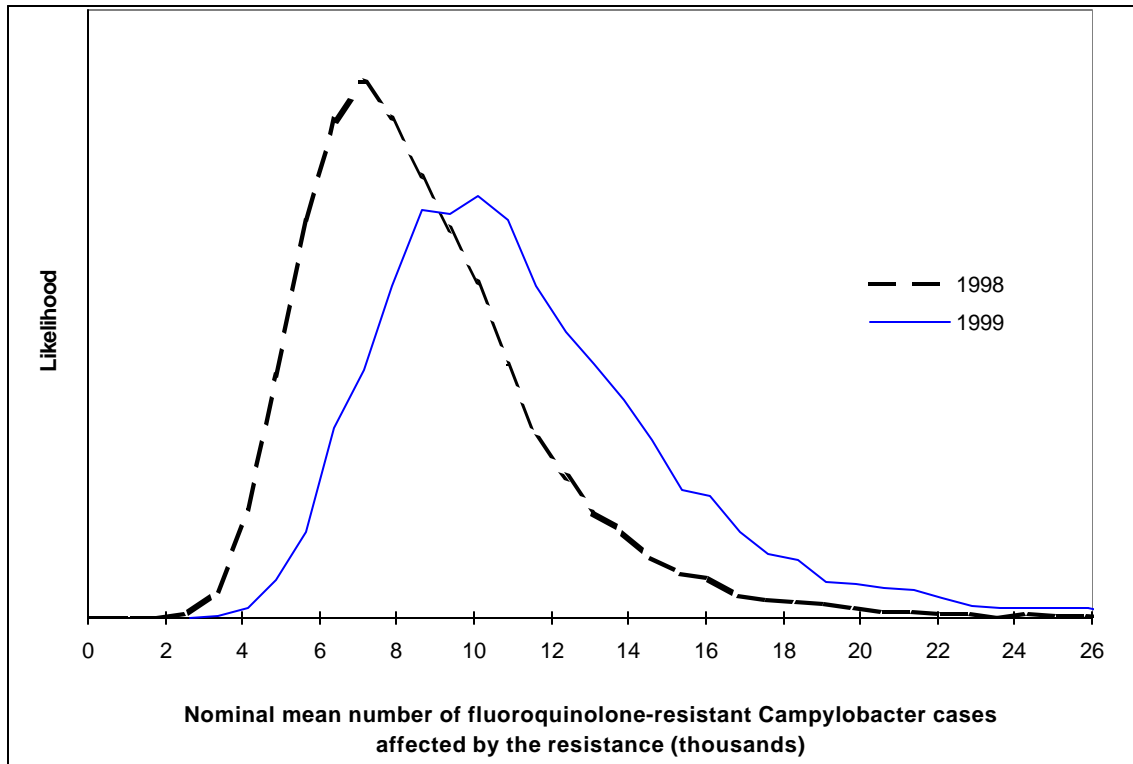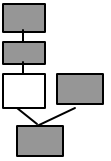
Figure 3.2. Relative confidence distribution of $I4_T$.

Section Summary

The model estimates that in 1998 a mean estimate of 8,782 people had fluoroquinolone resistant
Campylobacter illnesses from chicken and received fluoroquinolones. The 5th and 95th percentile estimates
for the number of people who had fluoroquinolone resistant *Campylobacter* infections from chicken
receiving fluoroquinolones is 4,849, and 14,689. In 1999 the mean estimate was 11,477 with wider 5th and 95th
percentile estimates of 6,412 and 18,978 compared to 1998. The fairly long length of the confidence interval is
reflective of the lack of certainty in the various parameters used in the model up to this point. Relative
contributions of the various components of the model to the model uncertainty will be presented in Section
5, Sensitivity Analysis.

Nominal mean number of fluoroquinolone resistant *Campylobacter* cases attributable to chicken, seeking care, treated with a fluoroquinolone and therefore affected by the fluoroquinolone resistance
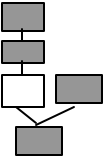
Table 3.2 *Campylobacter* Case Control study, the proportion of travellers and persons taking fluoroquinolones prior to culture for susceptible and resistant isolates by site

	1998 Catchment Pop.	1998 Population Weighting Fraction	98 Total Susceptible	98 Total Resistant	98 CCC Resistant Travelers and Prior FQ users	98 CCC Susceptible Travelers and Prior FQ users	98 CCC Proportion Resistant Travelers and Prior FQ users	98 CCC Proportion Susceptible Travelers and Prior FQ users
		W_j	$F_j - G_j$	G_j			a_j	b_j
CA	2,146,096	0.10	10	2	1	3	0.50	0.30
CT	3,274,069	0.16	166	26	15	49	0.58	0.30
GA	3,746,059	0.18	29	3	2	9	0.67	0.31
MD	2,444,280	0.12	19	3	0	6	0.00	0.32
MN	4,725,419	0.23	225	17	13	52	0.76	0.23
NY	1,106,085	0.05	59	10	4	16	0.40	0.27
OR	3,281,974	0.16	10	1	1	0	1.00	0.000
TOTAL	20,723,982	1.00	518	62	36	135	0.58	0.261

Table 3.5. Numbers of culture-confirmed cases with enteric campylobacteriosis where *Campylobacter* was tested for fluoroquinolone resistance and number fluoroquinolone resistant, by site, 1998-9.

Site	Catchment	Weighting Fraction	Number tested	Number fluoroquinolone resistant
j		W_j	F_j	G_j
CA	2,146,096	0.10	8	1
CT	3,274,069	0.16	128	11
GA	3,746,059	0.18	21	1
MD	2,444,280	0.12	16	3
MN	4,725,419	0.23	177	4
NY	1,106,085	0.05	49	6
OR	3,281,974	0.16	10	0
Total	20,723,982	1	409	26

Section 4

Estimating quantity of fluoroquinolone resistant *Campylobacter* contaminated chicken meat consumed

Section 1
Nominal mean *Campylobacter* culture confirmed cases reportable to health department

Section 2
Nominal mean *Campylobacter* cases in US

Section 3
Nominal mean number of fluoroquinolone-resistant *Campylobacter* cases from chickens affected by fluorquinolone resistance

Section 4
Estimating quantity of fluoroquinolone resistant *Campylobacter* contaminated chicken meat consumed

Section 5
Using the model to measure the level of risk
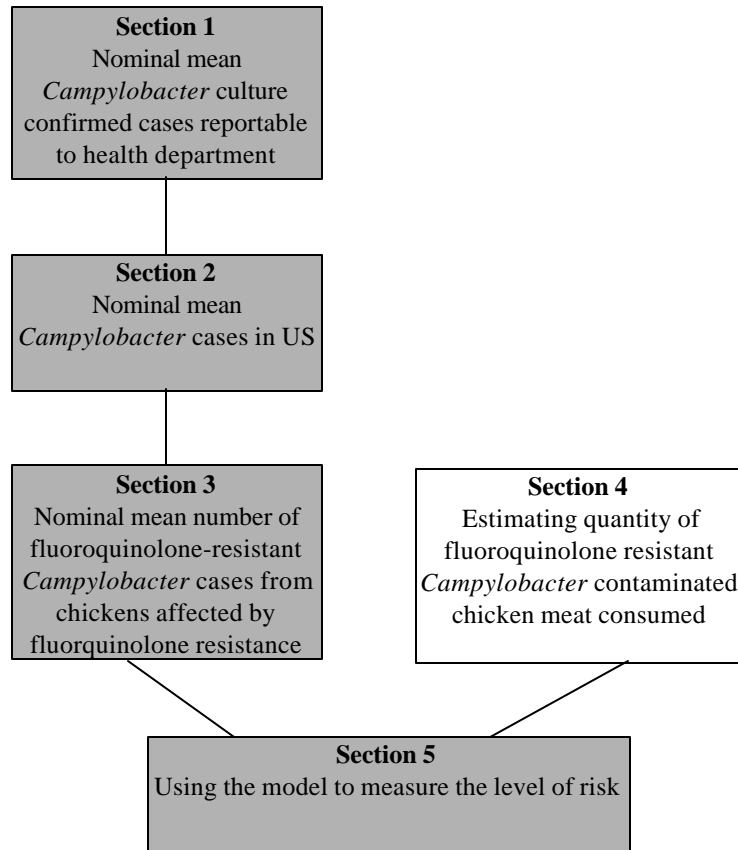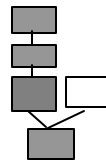
Symbol	Description	Formula
p_c	Total prevalence of *Campylobacter* among broiler carcasses	Beta distribution based on data
p_{rc}	Prevalence of fluoroquinolone resistant *Campylobacter* among *Campylobacter* contaminated broiler carcasses	Beta distribution based on data
p_p	Estimated prevalence of fluoroquinolone-resistant *Campylobacter* in broiler carcasses	$= p_c * p_{rc}$
c	Consumption of boneless domestically reared chickens in U.S. per capita (lbs)	Data
V_c	Total consumption of boneless domestically reared chicken in U.S. (lbs)	$= c * n_{US}$
V_i	Total consumption of boneless, domestically reared chicken contaminated with fluoroquinolone resistant *Campylobacter* in U.S. (lbs)	$= V_c * p_p$

Overview for Section 4

This section estimates the burden of fluoroquinolone resistant *Campylobacter* on chicken carcasses by multiplying the carcass *Campylobacter* prevalence by the level of resistance in isolates from chickens. An estimate of the proportion of domestically reared chicken with fluoroquinolone resistant *Campylobacter* using food disappearance data, less imports, was calculated to account for changes in chicken consumption from year to year.

Parameters modeled include:

- Total prevalence of *Campylobacter* among broiler carcasses
- Prevalence of fluoroquinolone resistant *Campylobacter* among *Campylobacter* contaminated broiler carcasses

Output: Estimated prevalence of fluoroquinolone-resistant *Campylobacter* contaminated broiler carcasses

- Consumption of boneless domestically reared chickens in U.S. per capita (lbs)
- Total consumption of boneless domestically reared chicken in U.S. (lbs)

Output: Total consumption of boneless, domestically reared chicken contaminated with fluoroquinolone resistant *Campylobacter* in U.S. (lbs)

Parameter estimations

4.1 (p_c) - Total prevalence of *Campylobacter* among broiler carcasses

Approximately 200 broiler slaughter establishments were included in the sample, representing 87% of all broiler slaughter establishments under Federal inspection in 1994. The broilers slaughtered at these establishments accounted for more than 99.9% of all broilers slaughtered during the period. Sample size, to provide reasonable levels of precision for a national prevalence, was estimated at 1200 samples. To achieve this number of samples a random number of 1871 broiler carcass samples were requested during the 52-week sampling period. Some samples were not collected, some were collected but not analyzed and the total number of samples providing laboratory results for the prevalence estimate was 1297 samples (104). Sampling frame was based upon weekly identification of randomly selected establishments using probabilities for sample selection that were proportional to the slaughter volume of the selected establishments, therefore those establishments slaughtering a greater number of chickens were sampled more frequently than other establishments. Sample delivery constraints resulted in the restriction of
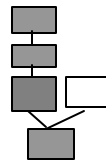
sampling to first shifts, Monday through Thursday. Carcasses were obtained from the drip line after the chill tank, the end point for slaughter and evisceration and prior to further handling and processing. Whole carcasses were randomly selected, and aseptically placed into a sterile bag that was securely closed, double bagged, packed with a gel pack and shipped to the laboratory via overnight delivery service. Only samples received at temperatures between 0 to 10 degrees C (inclusive) within one day of sample collection were analyzed. The analytical sample was obtained from rinse fluid recovered after shaking the broiler carcass in 400 ml of sterile Butterfield's Phosphate Diluent (104). Isolation was achieved using Hunt's Enrichment Broth, incubating the sample for 24 hours in a microaerophillic environment (5% O_2, 10% CO_2 and 85% N_2), followed by streaking onto Modified *Campylobacter* Charcoal Differential Agar for isolation of *Campylobacter* spp after incubation at 42 degrees C for 24 hours (81). Tests to identify *Campylobacter jejuni* and *coli* included wet mount examination, glucose fermentation, catalase, nalidixic acid, and oxidase tests. Nalidixic acid screening was performed to eliminate *Campylobacter* spp other than *jejuni* and *coli* from the prevalence estimate. Since fluoroquinolones were not licensed for use in poultry during the survey period, it was assumed that the level of nalidixic acid resistant isolates was low in 1994-5 because no selective pressure existed for chickens to develop fluoroquinolone resistance. Therefore, the prevalence estimate was unlikely to be affected by acquired resistance and potential misclassification of *Campylobacter* species.

ASSUMPTION: If a carcass was positive for *Campylobacter*, the predominant species isolated was *C. jejuni.*

The *Camplyobacter* prevalence estimate from the drip line was preferred because at this point carcasses were ready for further processing and had the least potential of human or other non-chicken sources of contamination. Post-chiller sampling of carcasses takes into account the cross-contamination from other chickens that occurs while in the chiller that leads to carriage of many diverse strains of *Campylobacter* on a single chicken product (92). The post-chiller location is a sampling point that is repeatable, practical, and provides isolates for susceptibility testing, closely linking these two parameters to provide a better estimate of the level of resistance. This would be more relevant for future surveys, when concurrent carcass prevalence and susceptibility testing could be conducted, as is currently underway in 1999.

The prevalence of *Campylobacter* in chickens was estimated from a 1994-95 survey of **1,297** broiler carcass rinse samples at 88.2% of carcasses, indicating that **1,144** carcasses tested positive (104).

The parameter was thus modeled as:

p_c = Beta(1144+1,1297-1144+1)

4.2 (p_{rc}) Prevalence of FQ resistant *Campylobacter* among *Campylobacter* broiler carcasses
Isolates were collected in a pilot survey by USDA-FSIS, from October to December 1998, from chicken carcass rinse samples (Section 4.1) and cultured as described previously (81). If growth was evident, a single colony was removed from the plate for susceptibility testing. A total of 128 *C. jejuni* isolates were collected from chicken carcasses for the period. The isolates were speciated using the biochemical hippurate assay and polymerase chain reaction (PCR) hippuricase primers to identify hippurase negative *C. jejuni* (74). The proportion of Fluoroquinolone resistant *C. jejuni* isolates was 9.4% (**12**/**128**), and *C.* "other" was 21.2% (14/66) (100). *C.* "other" were hippurate negative isolates, that were not *jejuni* as identified by PCR for the hippuricase gene and may include species such as *C. lari* that are intrinsically resistant to quinolones.

In 1999, collection of isolates was continuous throughout the year and a total of **481** *C. jejuni* isolates were obtained (101). Of these, **45** isolates were resistant so the proportion of isolates that were resistant was 9.4%.

The level of resistance to fluoroquinolone in *C. jejuni* from chickens was used in the risk assessment because the greater proportion of human disease, 92.7% in the *Campylobacter* Case Control Study, was due to *C. jejuni*. *C. coli* were not clearly distinguished from the group *C.* "other" which may have included *C.*
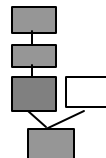
lari, a species intrinsically resistant to quinolones, therefore this precluded use of these isolates in the risk assessment.

DISCUSSION: Limitations in determination of the level of fluoroquinolone resistance in *Campylobacter* in 1998 included: the small number of isolates collected, the lack of seasonal representation. In addition, the presence of mixed colonies of organisms (*C. jejuni* and *C. coli*) when selecting a single colony makes species identification more complicated.

Unquantified Issues in the Assessment of the Prevalence of Resistance in Campylobacter isolates
Other problems were raised with the isolation and susceptibility testing of *Campylobacter*. Lack of agreement of MIC susceptibility test results occurs in up to 10% (2/20) of isolates subjected to repeat testing in one study (personal communication P. Fedorka-Cray). One explanation of the inconsistency is that the single colony may be composed of multiple isolates and that all isolates in the mixed colony may not have the same potential to survive storage, freezing, re-culture and testing. The effect of selecting a colony with multiple isolates decreases the reliability of susceptibility testing. The species of each reported isolate was confirmed by PCR of the *hipp-O* and *ceu* genes to identify *C. jejuni* and *C. coli* respectively.

In addition to the problem mentioned in the paragraph above, many varied *Campylobacter* colonies are present on a culture plate. The selection of a single colony from a plate of diverse colonies provides a "plate average," and the level reported will consistently underestimate the true carcass prevalence because a plate may carry resistant and susceptible isolates. A survey conducted in 1998-9 using a selective media for fluoroquinolone resistance indicated that of retail chicken products from which *Campylobacter* had been isolated, 24.5% (15/61) carried fluoroquinolone resistant isolates (82). Therefore, the actual prevalence of chicken carcasses carrying resistance may be much higher than the estimate obtained from testing a single isolate. Use of a quinolone-containing screening media would provide a better estimate of the true carcass prevalence and may give an indication of load of fluoroquinolone resistant *Campylobacter* on chicken. This may be a more accurate method to use to assess the impact of resistant pathogens.

The three issues described above; the lack of reliability of in identification of *Campylobacter* species using biochemical assay and the lack of accuracy in the determination of the level of resistance using a single isolate leading to an underestimation of the level of resistance in chicken carcasses are issues that are currently not quantifiable. These issues need to be better characterized and methods developed to allow more meaningful assessments of their impact on both human and foodborne isolates. This risk assessment determined the measurable risk, limiting the model to those parameters for which data were relevant, valid and available.

The parameter was thus modelled as:

1998: p_{rc} = Beta(12+1,128-12+1)
1999: p_{rc} = Beta(45+1,481-45+1)

4.3 (p_p) - <u>Estimated prevalence of fluoroquinolone-resistant *Campylobacter* in broiler carcasses</u>
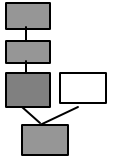
This parameter is calculated as:
$p_p = p_c * p_{rc}$

4.4 (c) - <u>Consumption of boneless domestically reared chickens in U.S. per capita (lbs)</u>
An annual value representing measurable human exposure to chicken in the United States less product sent for rendering, product diverted for pet food, exports, water added during processing and imports was the pounds of boneless broiler food disappearance, which in 1998 was 50.8 lbs per capita (102, 113).

1998 c = 50.8 lbs
1999 c = 54.3 lbs

4.5 (V_c) – Total consumption of boneless domestically reared chickens in U.S. per capita (lbs)

This parameter is calculated as:
$V_c = c * n_{US}$

4.6 (**V_i**) - Total consumption of boneless, domestically reared chicken contaminated with fluoroquinolone resistant *Campylobacter* in U.S. (lbs)

This parameter is calculated as:

$V_i = V_c * p_{rc}$

It represents the amount of boneless product contaminated with fluoroquinolone resistant *Campylobacter* consumed in the U.S. in the year. Figure 4.1 shows the uncertainty distribution for **V_i**.

Year	Model output	5th percentile	Mean	95th percentile
1998	V_I	7.34E+08	1.21E+09	1.77E+09
1999	V_I	9.68E+08	1.24E+09	1.54E+09
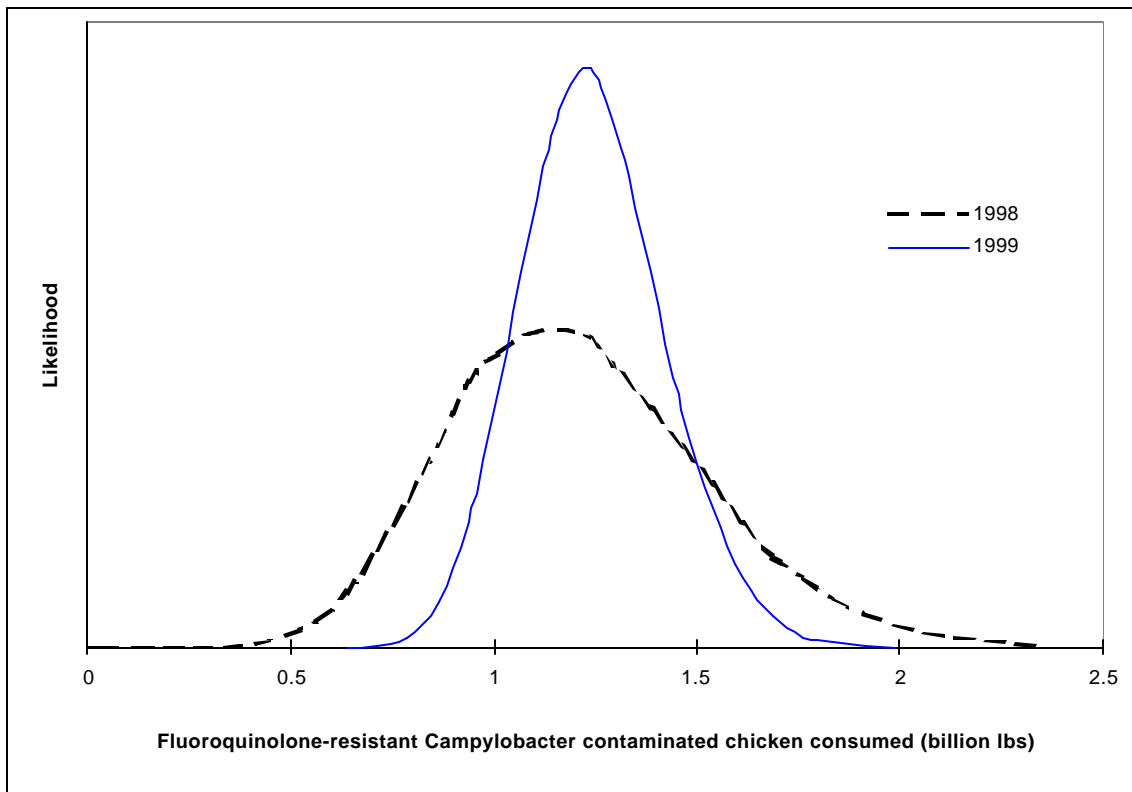
Figure 4.1. Uncertainty distribution for **V_i**.
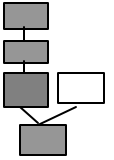
Section 4 Summary

The mean estimated value for pounds of boneless chicken carrying fluoroquinolone resistant *Campylobacter* consumed in 1998 is 1,210,000,000 pounds. The 5th percentile estimate is 734,000,000 and the 95th percentile estimate is 1,770,000,000 pounds. In 1999, the mean estimated value was 1,240,000,000 pounds with a 5th percentile of 968,000,000 and a 95th percentile of 1,540,000,000. Relative contributions of the various components of the model to the model uncertainty will be presented in Section 5, Sensitivity Analysis.

Section 5

Using the model to measure the level of risk.
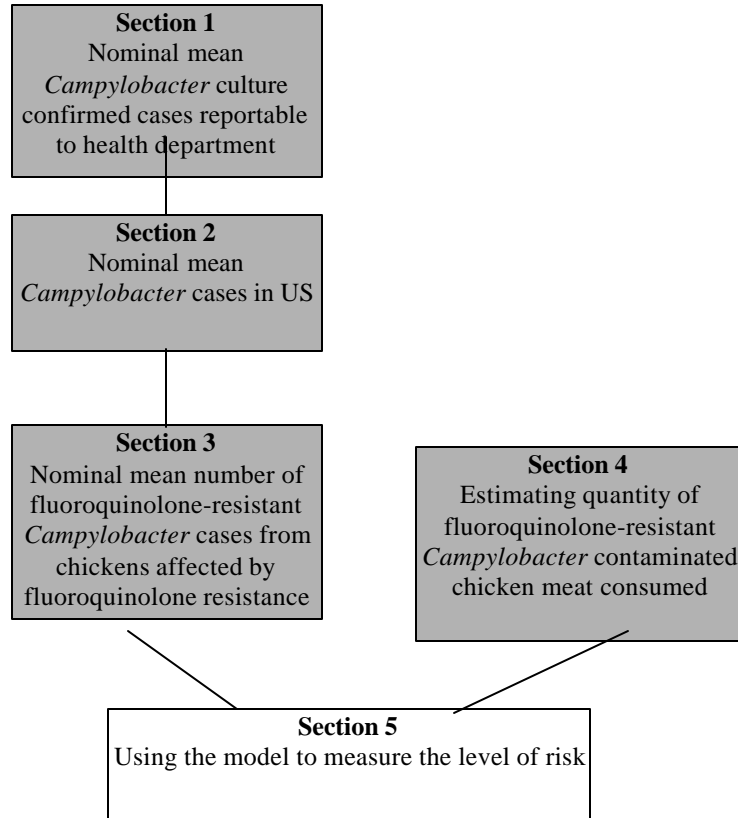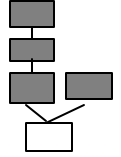
Section 1
Nominal mean
Campylobacter culture
confirmed cases reportable
to health department

Section 2
Nominal mean
Campylobacter cases in US

Section 3
Nominal mean number of
fluoroquinolone-resistant
Campylobacter cases from
chickens affected by
fluoroquinolone resistance

Section 4
Estimating quantity of
fluoroquinolone-resistant
Campylobacter contaminated
chicken meat consumed

Section 5
Using the model to measure the level of risk

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 was run for 10,000 iterations to produce the relative frequency plots and statistics. It was run for 300 iterations to produce points on the spider plots, a number sufficient to stabilize the reported means. All models used Latin Hypercube sampling.

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 ($I2_T$);
- Estimates of nominal mean number of fluoroquinolone-resistant *Campylobacter* cases attributable to chicken ($I3_T$);
- 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 ($I4_T$); and
- Estimates of total consumption of boneless, domestically reared chicken contaminated at slaughter plant with fluoroquinolone-resistant *Campylobacter* in U.S. in pounds (V_i).

Figures 5.1a and 5.1b, displayed on the next two pages, show cumulative uncertainty distributions. The estimates are all 'nominal mean' estimates assessing the human health illness rates rather than the actual number of cases there may be in a year as a result of random chance.
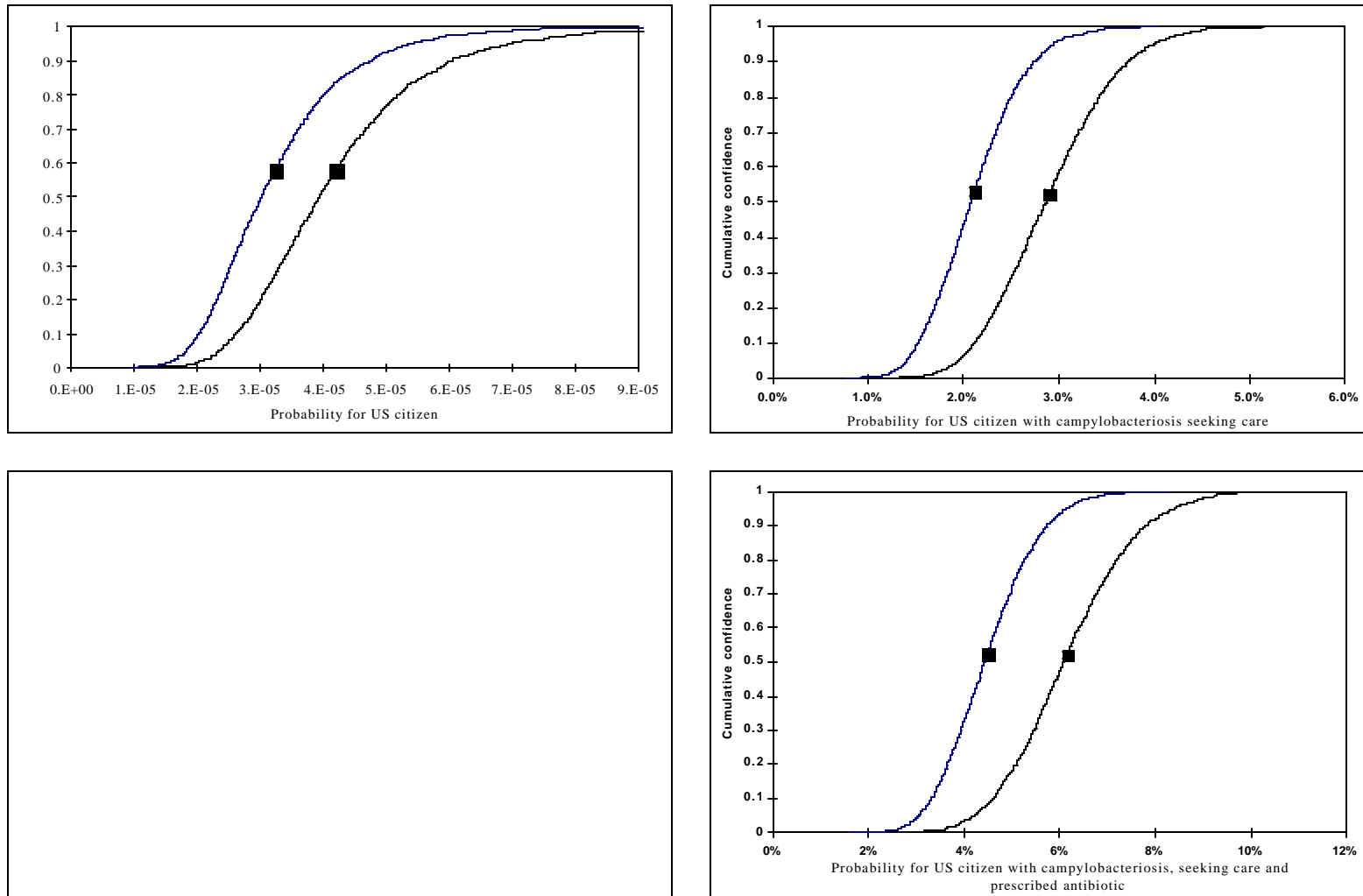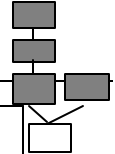
Figure 5.1a Confidence distributions for 1998 (heavier lines) and 1999 (lighter lines) values for the **probabilities** described in this section for the four different denominators representing different populations at risk – black squares denote expected values.
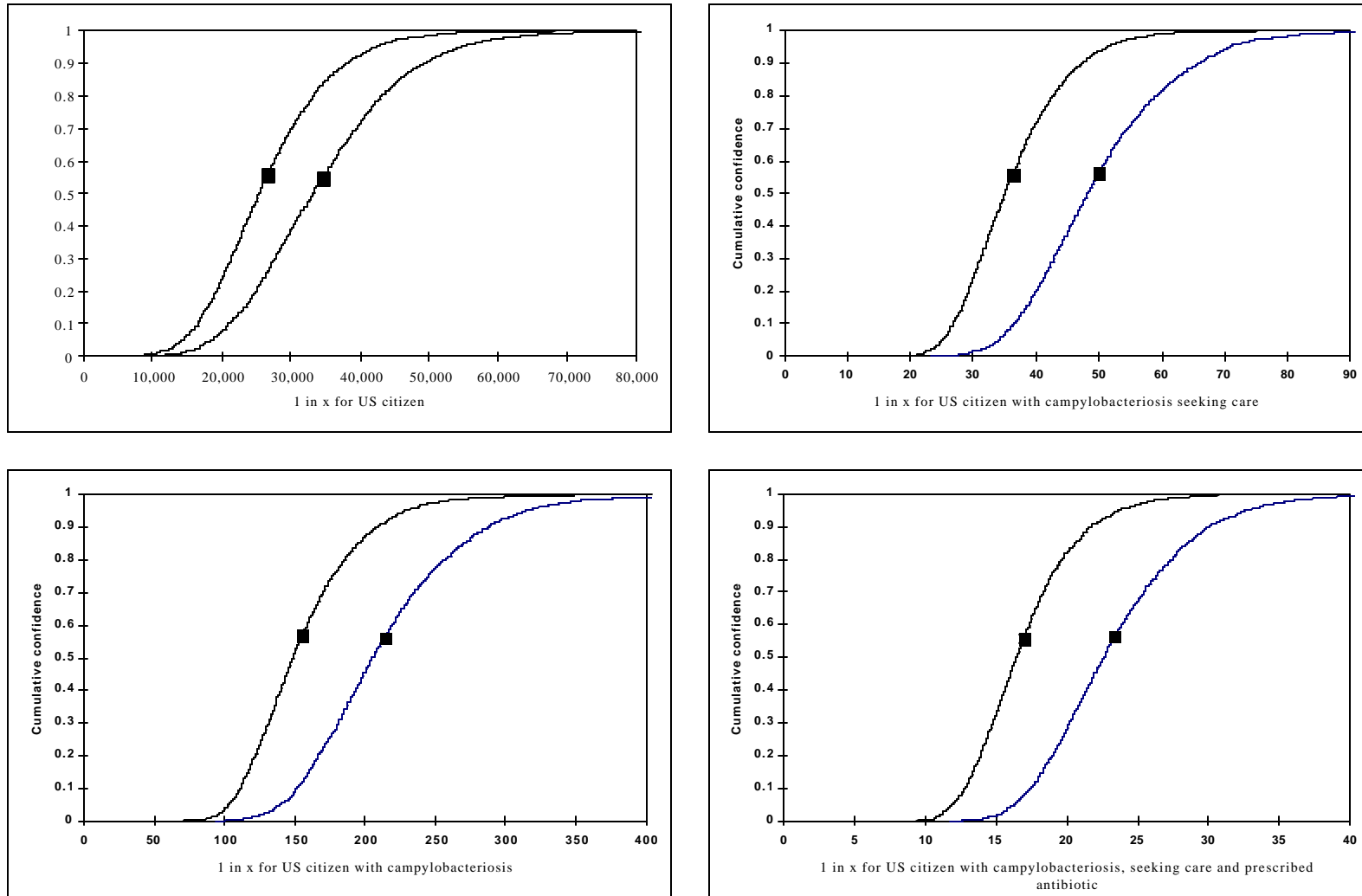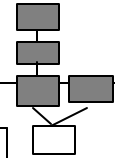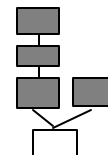
Figure 5.1b Confidence distributions for 1998 (heavier lines) and 1999 (lighter lines) values for the probabilities described in this section (in **1 in x** format) for the four different denominators representing different populations at risk – black squares denote expected values.

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 was discussed in the Introduction. The theory behind them is discussed later in this section. 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. 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 chicken 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.
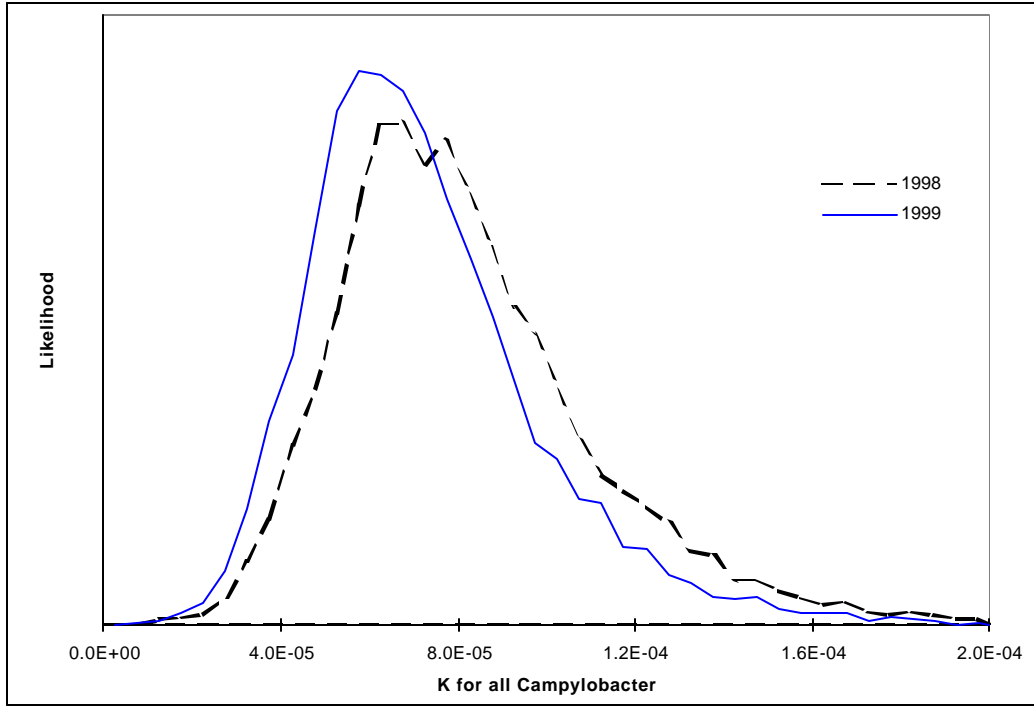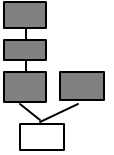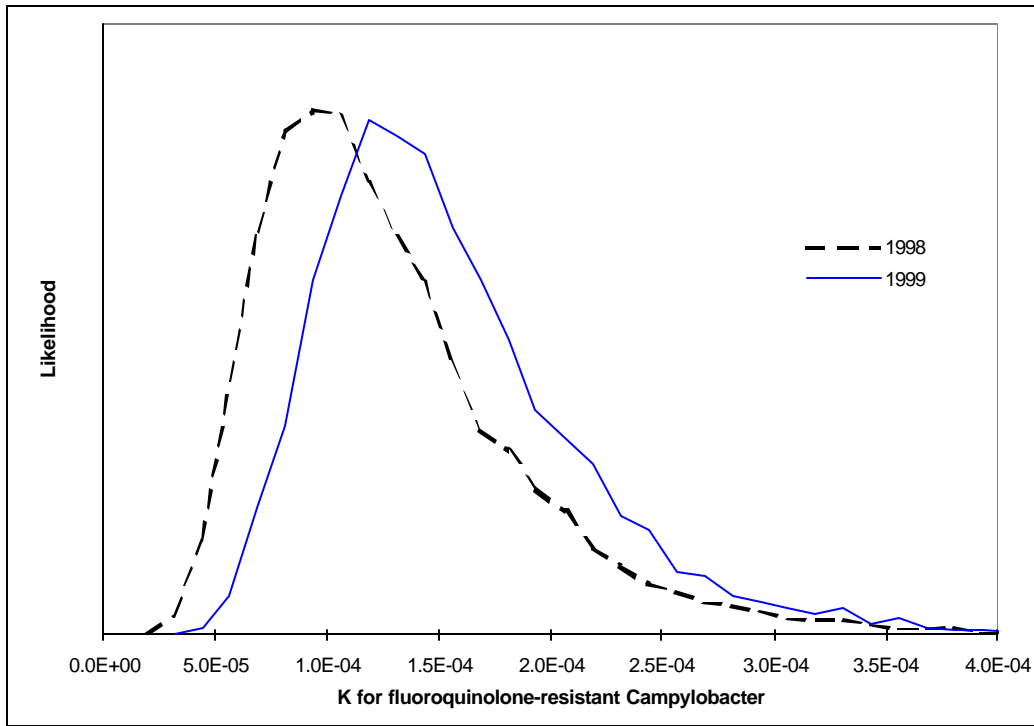
Figure 5.2. Estimates of K_{all} for 1998 and 1999

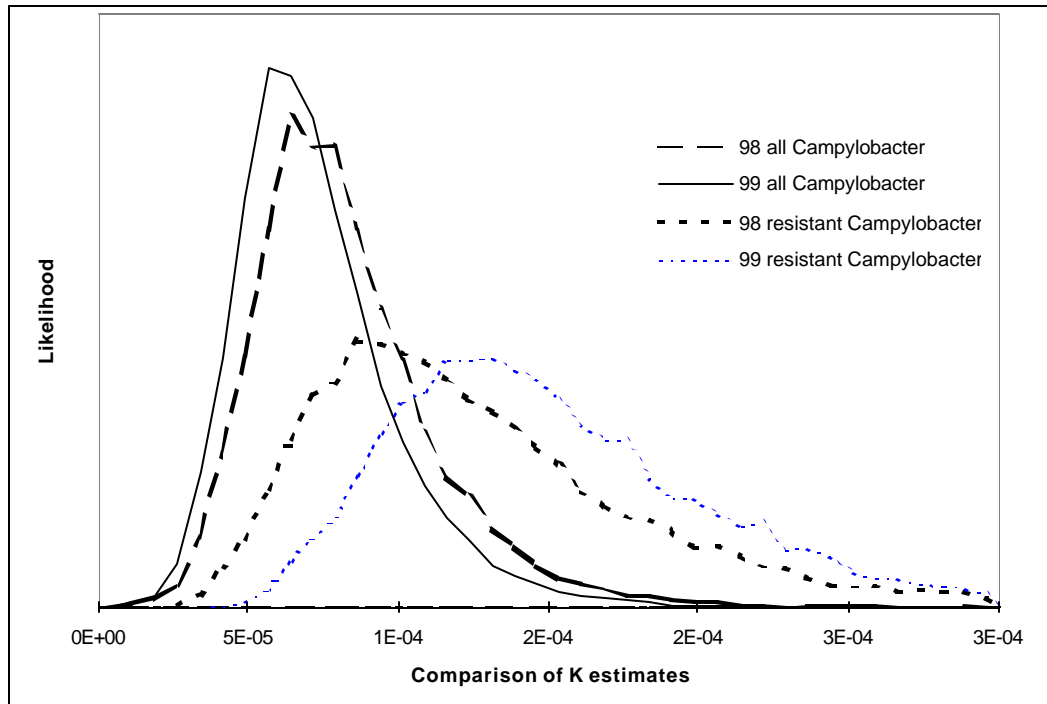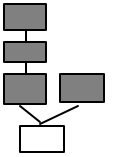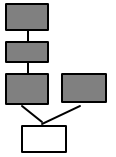Figure 5.3. Estimates of K_{res} for 1998 and 1999

Figure 5.4. Comparison of $\mathbf{K_{all}}$ and $\mathbf{K_{res}}$ for 1998 and 1999

Measuring the level of risk

The results and principles of Sections 1 to 4 of this model can be used to measure and monitor the level of risk to the U.S. population posed by fluoroquinolone resistant *Campylobacter* from domestically reared broilers.

Measuring the level of human health impact

1. Probability

The level of risk was assessed 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 5.1. Confidence intervals for estimates of **probability** of being affected by fluoroquinolone resistant *Campylobacter* for various groups

Exposed group	1998			1999		
	5th percentile	Mean	95th percentile	5th percentile	Mean	95th percentile
U.S. citizens	0.0018%	0.0032%	0.0054%	0.0023%	0.0042%	0.0070%
U.S. citizens with campylobacteriosis	0.31%	0.50%	0.72%	0.44%	0.68%	0.97%
U.S. citizens with campylobacteriosis seeking care	1.40%	2.11%	2.95%	1.94%	2.89%	3.98%
U.S. citizens with campylobacteriosis seeking care and prescribed antibiotic	3.03%	4.49%	6.17%	4.22%	6.16%	8.33%

Table 5.2. Confidence intervals for estimates of **1 in x** of being affected by fluoroquinolone resistant *Campylobacter* for various groups

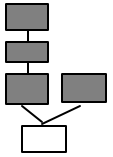| Exposed group	1998			1999		
	5th percentile	Mean	95th percentile	5th percentile	Mean	95th percentile
U.S. citizens	55,687	34,651	18,397	42,526	26,639	14,369
U.S. citizens with campylobacteriosis	316.9	214.3	138.6	226.3	155.5	103.5
U.S. citizens with campylobacteriosis seeking care	71.63	50.07	33.86	51.45	36.34	25.10
U.S. citizens with campylobacteriosis seeking care and prescribed antibiotic	33.00	23.38	16.20	23.70	16.97	12.00

Table 5.1 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 5.2 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 small: we have estimated that 1 in 34,651 people were affected in 1998 and 1 in 26,639 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.

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.
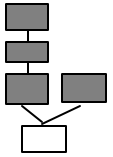
The fourth denominator distributes the risk among those people who contract campylobacteriosis from any source, seek some medical care and are prescribed an antibiotic. Both they themselves and their medical practitioner consider these people sick. This represents the group that is most seriously at 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 *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 the increased incremental days of illness would be a good measure of the human health impact. The current data describing duration of diarrhea for resistant and susceptible illnesses are not sufficiently robust to use in this model.

Theory behind, and use of, the parameter K

If one selects an infected item of food at some point in the production of a food product (e.g. an infected carcass at the spin chiller of a production plant which will contain some random number of servings), there are any number of potential probabilistic pathways for which the consumption of this item will result in the infection of one or more people. The paths are probabilistic because of the inherent randomness of the system, so there must be some (unknown) probability distributions of the number of people that could become infected, ill, etc. from an individual serving. The shape of this distribution cannot be known because of the myriad ways that a person can become affected as a result of the consumption of an infected serving. The persons affected need not even be direct consumers of the serving: for example, they can become affected from other food that has come into contact with the serving in question, through contact with others who have consumed the serving, or from pets who have consumed the product. The shape of the distribution is a result of any remaining processing of the item, the history of its handling during distribution, the current consumption and food handling behavior of the consuming population, as well as the distribution of the pathogen load among infected product and the dose-response relationships for the various segments of the consuming population.

In the case of chickens, the number of people infected by a food pathogen is orders of magnitude lower than the numbers of servings infected with that pathogen, so this distribution must have a mean *k* that is much smaller than 1 (Figure 5.5)[1]. Moreover, the probability of infecting two people from a serving will intuitively be considerably less than the probability of infecting just one person.

Applying the conditional probability identity principle, we can write:

$$\lambda = K_{res} * V_i$$

where:

$\boldsymbol{l}$ is the mean number of people per year who will experience an adverse human health effect as a result of consuming a pound of fluoroquinolone resistant *Campylobacter* contaminated broiler meat;
V_i is the quantity (lbs.) of fluoroquinolone resistant *Campylobacter* contaminated broiler meat consumed in a year in the U.S.

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[1] When K_{res} is much less than 1, the unknown parameter K_{res} can be interpreted as approximately equal to the probability that a random consumer will experience the human health impact by consuming 1lb of contaminated broiler meat . The relationship described by K essentially takes the role of the more traditional dose-response model, excepting that one has implicitly included some cross-contamination among people who have also consumed chicken, variations in pathogen load among infected servings and variation in organism-host interaction.
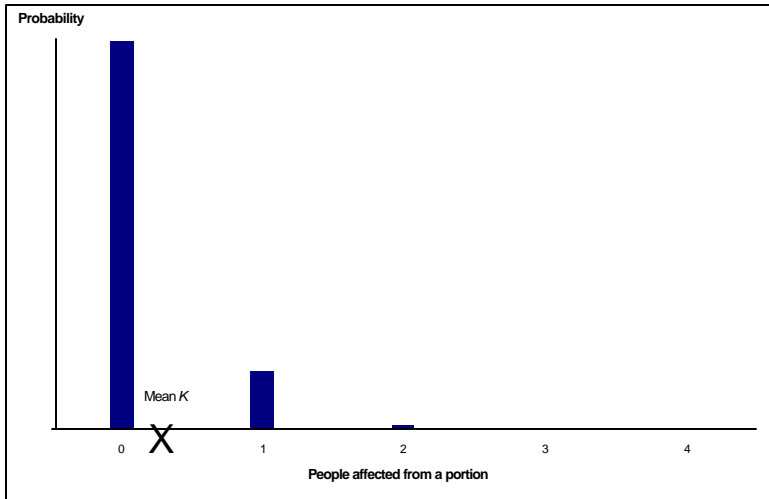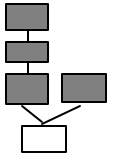
Figure 5.5. Probability distribution of number of affected people as a result of consuming one infected portion

Just as with the microbial pathogenicity approach to dose-response modeling using dose-response equations, the model parameter needs to be determined from data. In essence, this requires estimating the quantity of infected broiler meat consumed by the public in some recent time interval and estimating what *l* must have been, given the number of people experiencing the human health impacts of interest as a result of consuming those contaminated servings.

To use the model to predict the effects of various input parameters, K_{res} and V_i must be decomposed into products of the component inputs required in deriving them. For example, $V_i = V_c * p_c * p_{rc}$. Then λ can be modeled as a function of p_{rc} values chosen to be of interest while other inputs may or may not be held constant to reflect conditions of interest. The following graph displays the prediction of $\lambda 3$ as a function of p_{rc} ranging from 0 up to 25%. Further refinements of the predictive properties of the model are shown in Equation sets 1 and 2 in the Introduction.
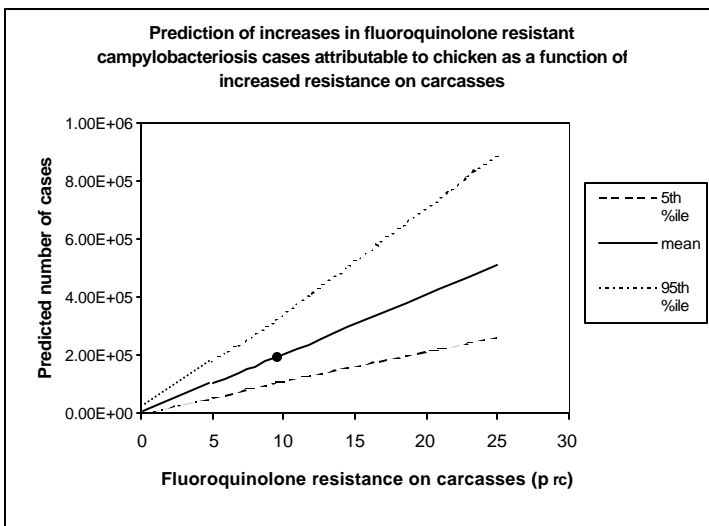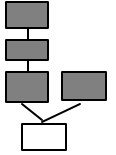

Figure 5.6. Using the risk assessment model to predict changes in $\boldsymbol{L3}$, on the vertical axis, due to increases in p_{rc}, on the horizontal axis.
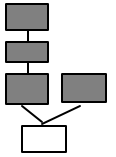
Sensitivity analysis

A sensitivity analysis was performed on the risk assessment model to determine which parameters are contributing to the model outputs' total uncertainty. The purpose of this exercise is to determine a) the model parameters to which the model outputs are most sensitive, and b) where extra information would be most useful in reducing the uncertainty about a model parameter and thus in the model outputs.
Five model outputs were used for the uncertainty analysis: $\lambda 3_T$ – the nominal mean number of fluoroquinolone resistant *Campylobacter* cases attributable to chicken: $\lambda 4_T$ - the nominal mean number of fluoroquinolone-resistant *Campylobacter* cases attributable to chicken, seeking care, treated with fluoroquinolone and therefore affected by the fluoroquinolone resistance; V_i – the total consumption of boneless, domestically reared chicken contaminated at slaughter plant with fluoroquinolone-resistant *Campylobacter* in U.S.(lbs); and the ratios K_{res} and K_{all} described above.

The sensitivity analysis was carried out by fixing each model parameter to the 5th, 25th, 50th, 75th and 95th percentiles of its uncertainty distribution in turn, whilst leaving all other model parameters with their uncertainty distributions. For each percentile, the model is simulated (with 300 iterations, sufficient to stabilize the output mean) to determine the mean output value. The result is a spider plot (118,119). The x-axis shows the percentile used for each model parameter and the y-axis shows the magnitude of the mean of the output in question. The degree of influence of an input parameter equates to the range of output mean values corresponding to the input percentiles. For example, Figure 5.8 shows that for 1999 eliminating the uncertainty about p_{th} could potentially move the estimate of $\lambda 4_T$ to be focused around a value anywhere between 8,000 and 17,000- a large movement, whereas eliminating the uncertainty about parameter p_b would not change the estimate of $\lambda 4_T$.

Sensitivity analysis for $\lambda 3_T$

Figure 5.7 illustrates the parameters that contribute the most to the uncertainty in the value for $\lambda 3_T$. The parameter p_{rh} produces the greatest vertical range for both 1998 and 1999 and therefore is the most influential input parameter. The next most important parameters are p_{ca} and p_+. The parameters p_{rh} and p_{ca} plot with positive gradients so $\lambda 3_T$ would be larger the larger the true value of p_{rh} and p_{ca}. The parameters p_{cn} and p_+ plot with a negative gradient, so the lower their true values, the higher the true value of $\lambda 3_T$.

From Figure 5.7 we can conclude that, to reduce the uncertainty in the human health impact of fluoroquinolone-resistant *Campylobacter* in broilers, the collection of the following data would be useful (in order of importance):

Proportion of *Campylobacter* infections from chicken that are fluoroquinolone resistant (p_{rh});
Probability a case of campylobacteriosis is attributable to chicken (p_{ca});
Probability that a stool will be requested and submitted from a patient with non-bloody diarrhea (p_{cn}); and
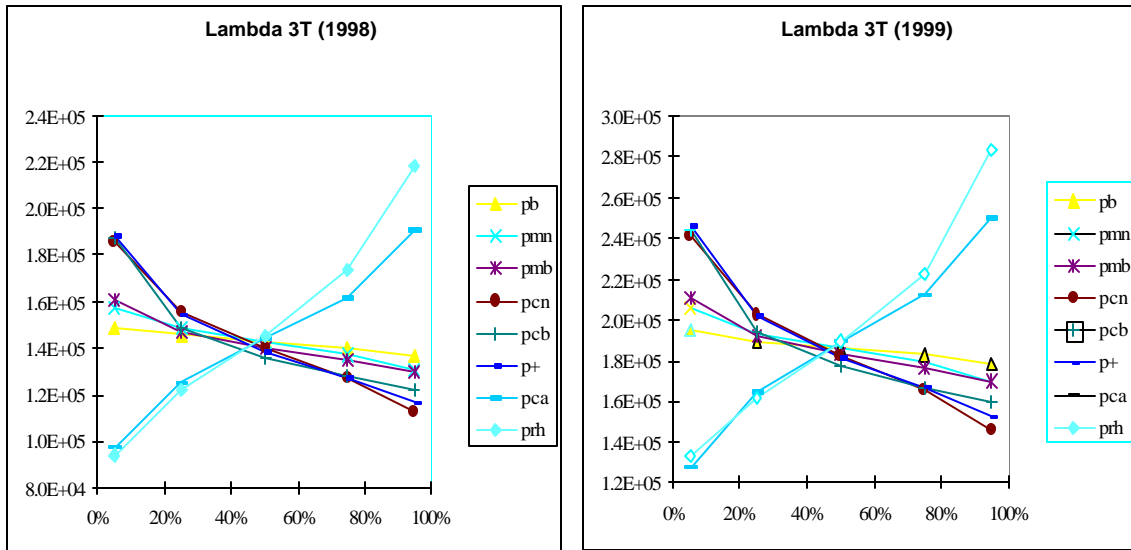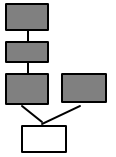Probability that the culture will confirm *Campylobacter* given it was tested (p_+).

Figure 5.7. The parameters that contribute the most to the uncertainty in the value for $\lambda 3_T$.

Sensitivity analysis for $\lambda 4_T$

Figure 5.8 illustrates the parameters that contribute the most to the uncertainty in the value for $\lambda 4_T$. The parameter p_{rh} produces the greatest vertical range for both 1998 and 1999 and therefore is the most influential input parameter. The next most important parameters are p_{cn} and p_+.

From Figure 5.8 we can conclude that, to reduce uncertainty in the human health impact of fluoroquinolone resistant *Campylobacter* in broilers, collection of the following data would be useful (in order of importance):

Proportion of *Campylobacter* infections from chicken that are fluoroquinolone resistant (p_{rh});
Probability that a stool will be requested and submitted from a patient with non-bloody diarrhea (p_{cn}); and
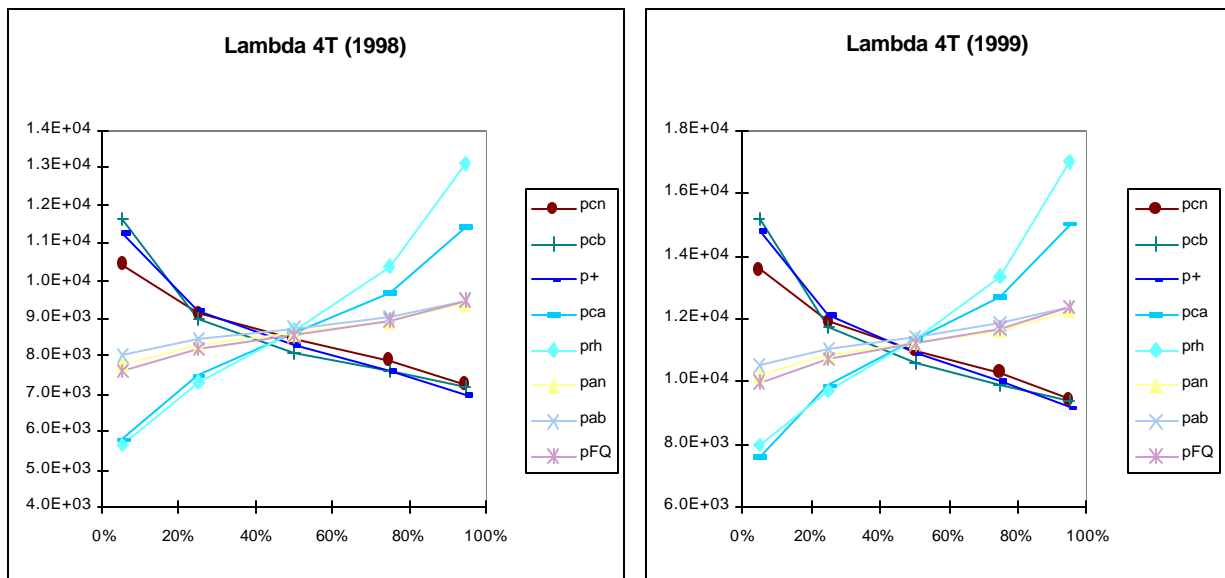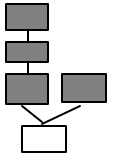Probability that the culture will confirm *Campylobacter* given it was tested (p_+).

Figure 5.8. The parameters that contribute the most to the uncertainty in the value for $\lambda 4_T$.

Sensitivity analysis for V_i

Figure 5.9 illustrates the parameters that contribute the most to the uncertainty in the value for V_i. There are only two uncertainty parameters in determining this output, p_c and p_{rc}, and p_{rc} (the prevalence of fluoroquinolone-resistant *Campylobacter* among *Campylobacter* contaminated broiler carcasses) is clearly contributing the greatest uncertainty to the determination of V_i.
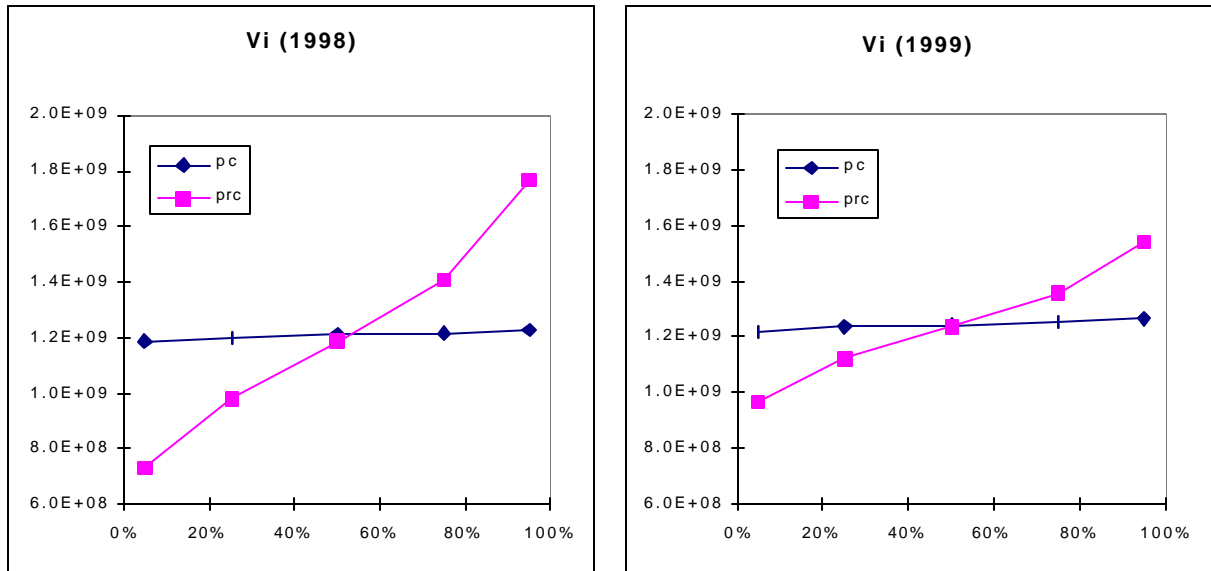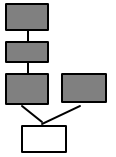

Figure 5.9. The parameters that contribute the most to the uncertainty in the value for **Vi**.

Sensitivity analysis for (K_{all})

Figure 5.10 illustrates the parameters that contribute the most to the ratio K_{all}. The parameters p_{ca} and p_{cn} produce the greatest vertical range and therefore are the most influential input parameters. While the parameter p_c is shown on the graphs for both 1998 and 1999, it does not add to the uncertainty in K_{all}, as indicated by the relative flatness of the line for p_c. The parameter p_{ca} is the only significant parameter plotted that contributes to the uncertainty from modeling contamination of chicken meat, i.e. all the other parameters correspond to determining the human health impact which means that we have more uncertainty about the human health side than the broiler side.
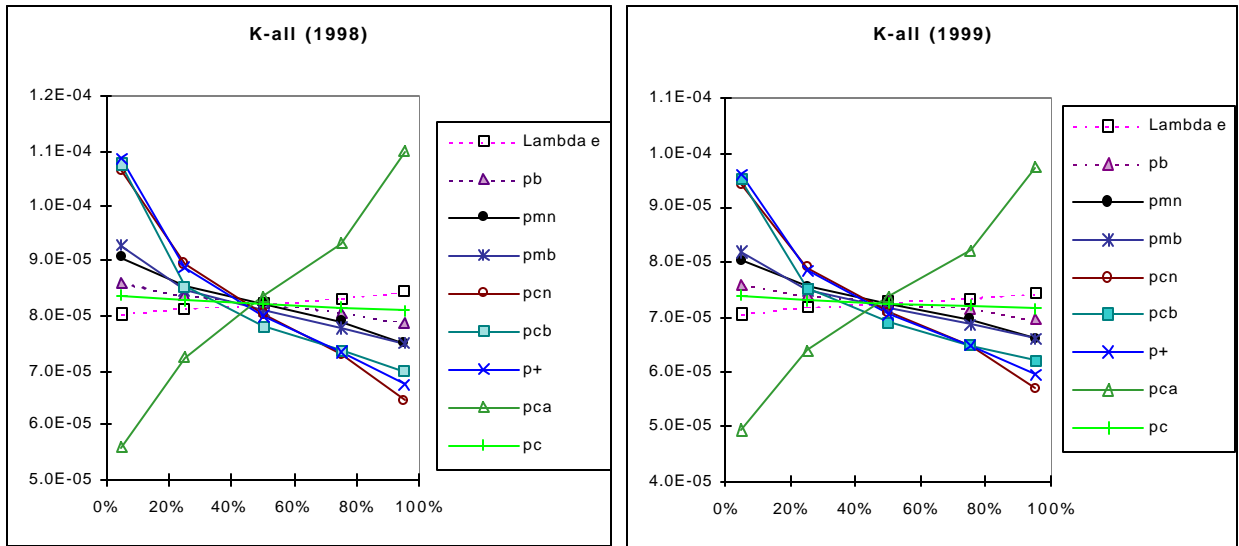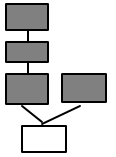

Figure 5.10. The parameters that contribute the most to the uncertainty in the value for **K_{all}**.

Sensitivity analysis for (K_{res})

Figure 5.11 illustrates the parameters that contribute the most to the ratio K_{res}. The parameters p_{rh} and p_{cn} produce the greatest vertical range and therefore are the most influential input parameters. The parameters p_{rc} and p_{ca} are the only significant parameters plotted that contribute to the uncertainty from the poultry side, i.e. all the other parameters correspond to determining the human health impact which means that we have more combined uncertainty on the human health side than the broiler side.
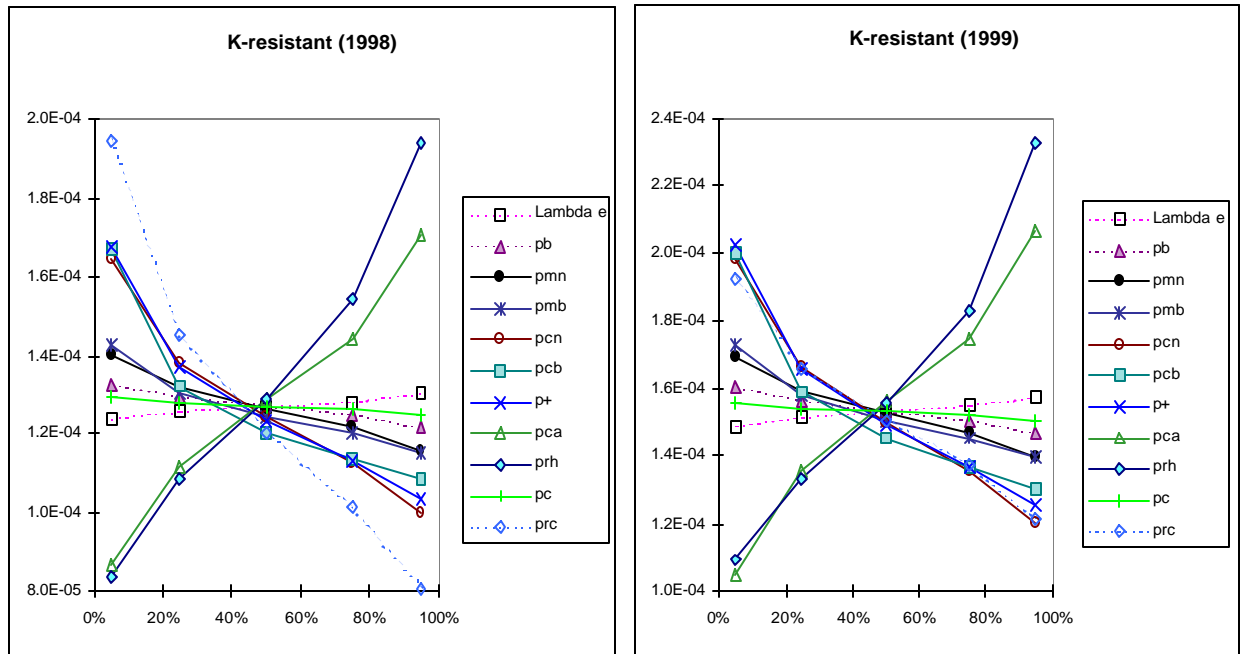

Figure 5.11. The parameters that contribute the most to the uncertainty in the value for K_{res}.

Sensitivity Analysis Summary

Quantitatively assessing the uncertainty for the parameters modeled indicates that there is more combined uncertainty on the human health side than the broiler side. Qualitative issues in assessing the data used in the risk assessment were raised in the Sections and given as limitations, assumptions and data gaps and are collectively listed in Appendix B. Other qualitative and methodological issues raised are described in the respective sections of the document. Consideration of both quantitative uncertainty and qualitative aspects of data are important in the collection of data useful for risk assessment.
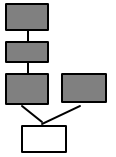
Effect of considering clustering of isolates by state in the estimation of resistance among *Campylobacter* isolates in poultry
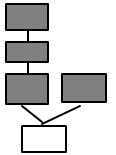
Chicken NARMS isolate susceptibility test results for 1999 were obtained for states with federally inspected poultry plants representing over 95% of chicken production. We obtained these data to allow us to assess whether an estimate of the resistance among *Campylobacter* isolates in poultry would be significantly different if we were able to weight isolate test results by the production in pounds of chicken for each state.

The data are shown in the spreadsheet model of Figure 5.12, which also illustrates the crude estimate (based on aggregating all isolate test results) and the estimate weighted by state production volume.

The results of this analysis are shown in Figure 5.13. The state-weighted estimate has almost the same degree of uncertainty (spread) but estimates the prevalence to be approximately 1.7% higher than the crude aggregate estimate. It would therefore be more accurate in the risk assessment model to use state-weighted estimates. However, since the state-by-state data were only obtainable for 1999, it was decided to use the crude method to estimate both years' prevalence to maintain consistency. If 1998 data became available, broken down by state, we would be able to update both years' estimates of the model parameter p_{rc} and therefore update estimates of K_{res}.

Effect on model of underestimating total prevalence of Campylobacter among broiler carcasses p_{rc}

The estimate of human health impact for the years 1998 and 1999 produced by the risk assessment model are unaffected by the consistent underestimation of p_{rc}. However, the model output K_{res} is inflated by a factor that is approximately 12%/10.4% = 1.15. This makes it difficult to validate the estimate for K_{res} by comparison with the estimate for K_{all}. Predicting any future human health impact is essentially unaffected since the inflation factor is a constant through the model and cancels out.

	STATE	Nr sampled	Nr Resistant Isolates	Relative Pounds Produced	Prevalence contribution by state
3	C	29	6	0	0.00%
4	BB	5	0	7	0.10%
5	A	3	0	3	0.07%
6	K	3	0	1	0.02%
7	O	6	1	18	0.47%
8	Q	4	0	5	0.09%
9	T	17	2	40	0.68%
10	U	8	1	6	0.13%
11	V	1	1	4	0.26%
12	E	63	1	139	0.45%
13	J	9	0	ND	0
14	P	44	2	90	0.62%
15	S	10	0	16	0.14%
16	AA	30	3	66	0.87%
17	F	54	3	119	0.90%
18	G	9	0	16	0.16%
19	L	52	4	142	1.40%
20	W	32	3	93	1.17%
21	X	9	1	27	0.52%
22	CC	10	0	24	0.22%
23	B	22	4	38	0.84%
24	D	15	4	23	0.73%
25	I	4	0	1	0.01%
26	M	6	0	1	0.01%
27	N	12	1	14	0.20%
28	R	20	6	41	1.38%
29	Y	5	3	9	0.53%
30				941	

	National prevalence estimate
Estimate weighted by each state's production	**11.96%**
Raw estimate determined by aggregating all isolate tests	**10.32%**
Difference between estimates (weighted-raw)	**1.65%**

Formulae table	
B3:E29	Data
E30	=SUM(F3:F29)
F3:F12, F14:F29	=RiskBeta(D3+1,C3-D3+1)*E3/E30
F13	0
F33 (output)	=SUM(F3:F29)
F34 (output)	=(RiskBeta(SUM(D3:D29)+1,SUM(C3:C29)-SUM(D3:D29)+1)*1000)/E30
F35 (output)	=F33-F34

Figure 5.12. Spreadsheet model containing isolate test data and methods of estimating prevalence (spreadsheet values in column F show a single random realization of the model) (Ref. 112)
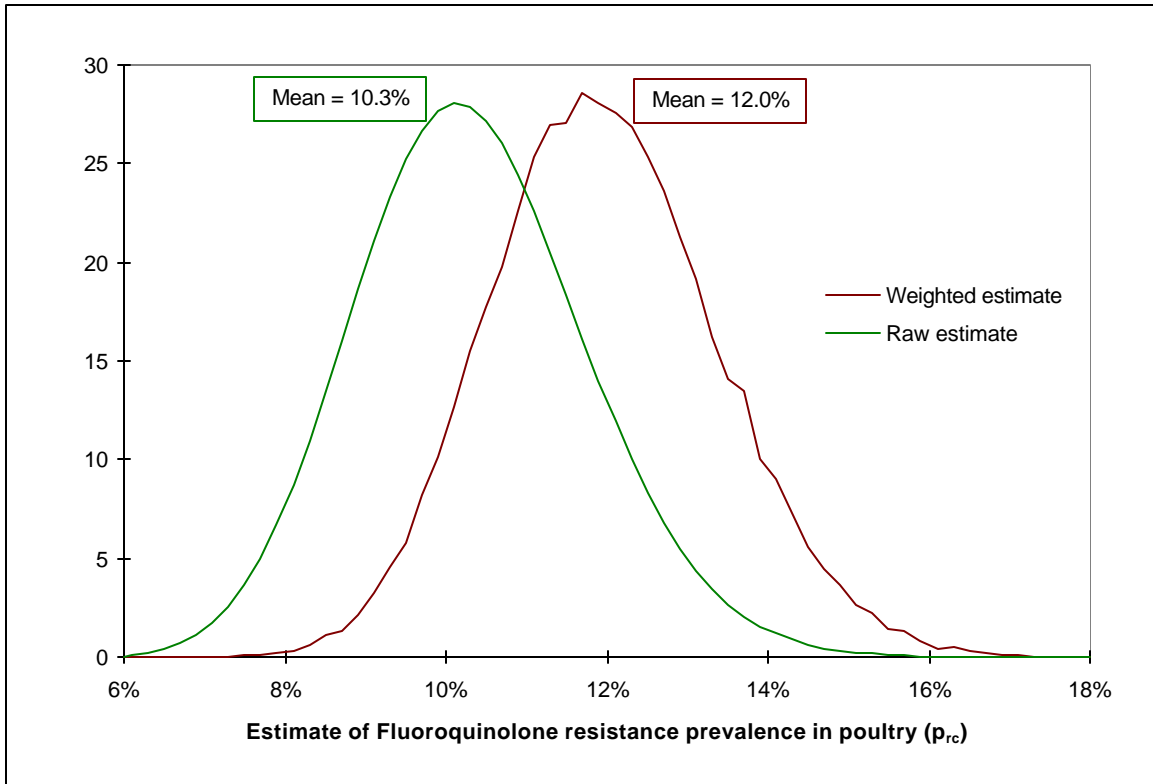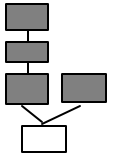
Figure 5.13. Estimates of fluoroquinolone resistance prevalence amongst *Campylobacter* contaminated poultry for 1999: Line labeled 10.3% – crude estimate aggregating all isolate test results; Line labeled 12.0% - estimate weighted by production volume from state of origin of each isolate.

Appendix A

Distributions Used in Uncertainty Analysis

The Beta distribution

The Beta distribution is one of three distributions associated with a binomial stochastic process. A binomial process is a random counting system where there are a discrete number of opportunities (trials) of some particular event happening (successes) and where each trial has the same probability of being a success. This means that each trial must be independent of every other trial.

There are many systems that closely approximate a binomial process. Random processes like the tossing of a coin are binomial, since one face of the coin can be defined as being a success and the probability of each coin being a success remains constant for all tosses. No matter how many "heads" there have been in a row, the probability of a "tails" for the next toss remains the same (e.g. 50% for a fair coin).

Random sampling from a population may also closely approximate a binomial process, where we are concerned with determining what proportion of that population has some characteristic of interest. If the population is much larger than the sample size (a rule of thumb is that the population should be at least 10 times the size of the sample) then the probability of an individual randomly sampled from the population having the characteristic of interest remains fairly constant and equivalent to the proportion of the population with that characteristic. So, for example, if we are interested in the proportion of U.S. citizens that eat meat, we can do a random survey of U.S. citizens. Providing that our sample is much smaller than the population size, the probability that each consecutive randomly selected person eats meat remains reasonably constant, though there are actually a finite number of people who eat meat and there is a finite population too, which means that the probability that the next randomly sampled person eats meat does, in fact, depend on the previous samples.

The example above for meat eaters assumes that we are sampling without replacement: in other words, we would not survey any person more than once. It also implicitly assumes that there are a fixed number of people who eat meat in the population and a fixed population size too. This would be a static system with a constant proportion of meat eaters.

The Beta distribution can be used to model the confidence one has about the probability of success of a binomial trial *p* where one has observed *n* independent trials of which *s* were successes (41, 66, 94, 118, 119) so that it is said that *p* is distributed as a Beta(*s*+1,*n*-*s*+1).

This distribution is the result of applying Bayes' Theorem with a Uniform(0,1) prior distribution and a binomial likelihood function. In layman's terms, Bayes' Theorem works as follows:

1. A prior statement of the knowledge of the variable to be modelled is given. In this case, we are saying that the probability *p* lies somewhere between zero and one, but we would not like to say that any value within that range was anymore likely than any other value (hence the Uniform(0,1) prior distribution.
2. For each allowed value within the prior distribution's range, we calculate the probability of observing the *s* successes we observed from the *n* trials. This probability is simply the binomial probability:

$$P(s;n,p) = {}_n C_s \, p^s (1-p)^{n-s}$$

3. These binomial probabilities then become the weightings given to each value of *p* in the prior distribution. By normalizing these weightings we arrive at a posterior (i.e. final answer) distribution.

Thus, the posterior distribution $f(p)$ for p is given by the product of the prior distribution density and the likelihood function:

$$f(p;s,n) = \frac{1 \cdot {}_nC_s p^s (1-p)^{n-s}}{1 \cdot \int\limits_0^1 {}_nC_s t^s (1-t)^{n-s} dt} \qquad 0 < p < 1$$

where the 1 in the equation is the probability density of the Uniform(0,1) prior distribution, the ${}_nC_s p^s (1-p)^{n-s}$ is the weighting given to the p value (the likelihood function) and the integral in the denominator normalizes the distribution so that the area under the curve equals unity. By omitting the 1, cancelling out the ${}_nC_s$ and using $a_1=s+1$, $a_2=n-s+1$, we arrive at the equation for the Beta(a_1, a_2) distribution's probability density $f(x;a_1,a_2)$:

$$f(x;a_1,a_2) = \frac{p^{a_1-1}(1-p)^{a_2-1}}{\int\limits_0^1 t^{a_1-1}(1-t)^{a_2-1} dt}$$

Note that the prior distribution for p is a Uniform(0,1) distribution, shown in Figure A1. The Uniform(0,1) prior distribution is an uninformed prior, meaning that no subjective opinion or any other information has been involved in determining the prior. This is logically the most conservative approach one could take where conservatism here means expressing the maximum degree of uncertainty possible. The selection of an appropriate prior is sometimes slightly contentious. For example, Beta(0,0) is sometimes suggested as an uninformed prior, though it does not in theory exist. One criticism for using a Beta(1,1) prior is that the mean of the estimated probability is biased towards 50%, away from the observed proportion. In fact, for all applications of the Beta distribution in this analysis, the information contained in the prior distribution is generally overwhelmed by the information contained in the sample data and the results are essentially equivalent to a more traditional frequentist statistics approach which would give the confidence distribution for the probability p as: $\hat{p} = \text{Binomial}(n, s/n) / n$. The frequentist also uses the central limit theorem in situations where a large number n of samples were taken, say $n > 30$. By the central limit theorem $\hat{p}$ has a Normal distribution Normal(p, $\sqrt{[p(1-p)/n]}$), where p is the true value of the probability of success. One then assumes (i.e. estimates) the confidence distribution for p to be :

$$\hat{p} = Normal\left(\frac{s}{n}, \sqrt{\frac{s(n-s)}{n^3}}\right)$$

Thus, from a practical viewpoint, there is little difference in using a Bayesian or frequentist approach to uncertainty estimating in this model, except that the Bayesian approach allows one to combine information from dissimilar data (66).

Perhaps the easiest way to understand the Beta distribution used in this manner is to look at a few plots of its shape for varying values of a_1 and a_2. Figure A1, the Uniform(0,1) distribution, is also the Beta(1,1), i.e. the Beta distribution where we have observed $s = 0$ successes and $(n-s) = 0$ failures: this is the distribution when we have not yet done any trials and hence remains the prior distribution.
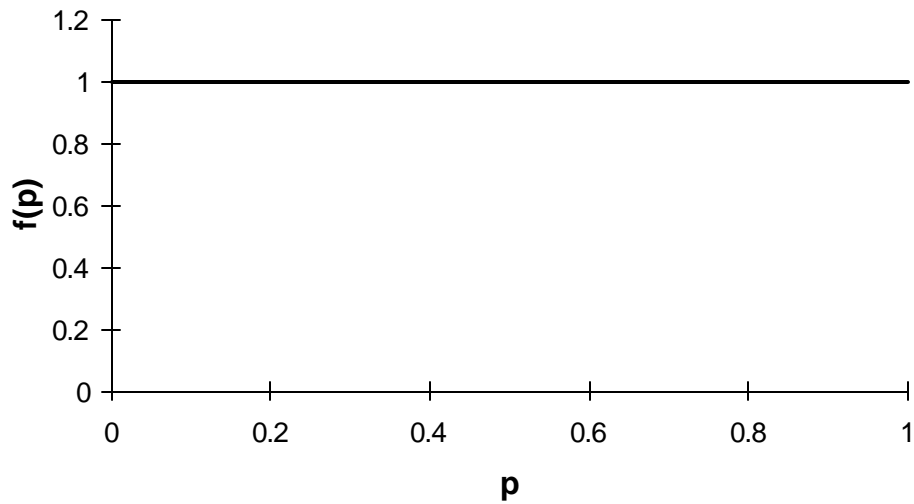
Figure A1: The Uniform(0,1) distribution, which is also the Beta(1,1) distribution

Figure A2 show the Beta(1,11)and the Beta(11,1) distributions: the former where we have observed zero successes in ten trials and the latter where we have observed ten successes in ten trials. Note that they are simply the reflection of each other since they essentially represent the same thing: one needs only to reverse the definition of a success to its opposite. Also note that, since all trials have been a success or a failure, the distributions peak at zero and one respectively. If this pattern continues with more trials, the distributions will become progressively more concentrated at zero and one.
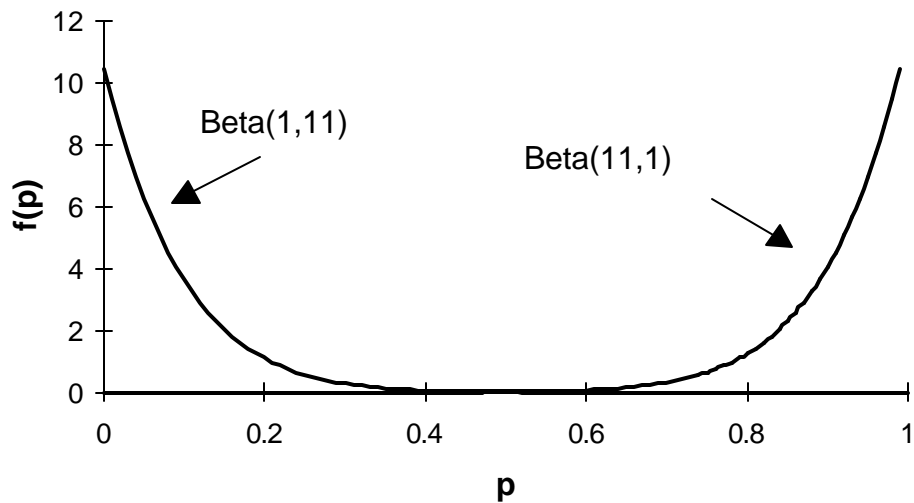
Figure A2: Examples of the Beta distribution where all trials are successes (peak at $p=1$)
or all are failures (peak at $p=0$)

Figure A3 shows the Beta(3,3), Beta(11,11) and Beta(21,21) distributions representing four, 20 and 40 trials where 50% have been successes. Note that as the number of trials increases, the distribution becomes progressively narrower: in other words, one is becoming progressively more confident about what the true value of p must be.
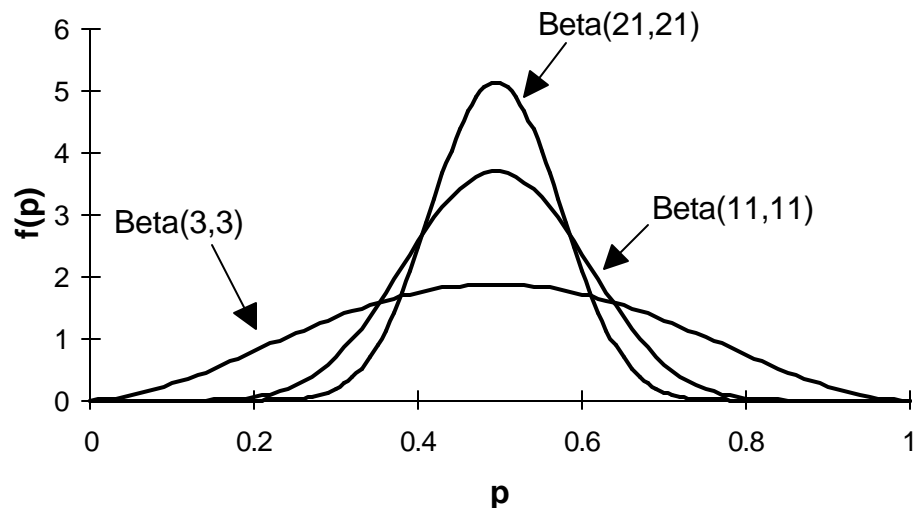
**Figure A3**: Examples of the Beta distribution where there are equal successes and failures (i.e. $a_1 = a_2$)

The figures below show that except for the case with very small n, the Binomial distributions or the Normal approximations to them that a frequentist would use to model the confidence distributions modeled as Beta posterior distributions above are practically indistinguishable from the Beta distributions. The cumulative probability distributions for the Binomial(4,0.5)/4, the Normal(0.5, 0.25), and the Beta(3,3) which are the ones for the case $n=4$, are shown in Figure A4a. One can see that for the proportion 0.5 the deviations between the Binomial and the Normal or Beta are fairly evenly arranged around the center of the graph. For a proportion of success less than 0.5, the deviations between the Binomial and the Normal or Beta are larger to the left half of the graph and very small toward the right side of the graph. Conversely, for a proportion of success greater than 0.5, the deviations between the Binomial and the Normal or Beta are larger to the right half of the graph and very small toward the left side of the graph. The major source of the deviation is the relative size of the steps in the Binomial when n is small. The cumulative distribution for the Binomial is a step function. As sample size increases the deviations between the discrete Binomial cumulative probability distributions and those of the corresponding continuous Normal or Beta distributions diminish. Figure A4b displays the cumulative probability distributions for the case $n=20$ and Figure A4c, for the case $n=40$. Because the Beta distribution is able to model success probability using non-integer numbers of successes it is extremely useful for risk assessment modeling where inputs are weighted survey results. Bayesian modeling is more conducive to combining various types of probability distributions than frequentist modeling is.

n = 4
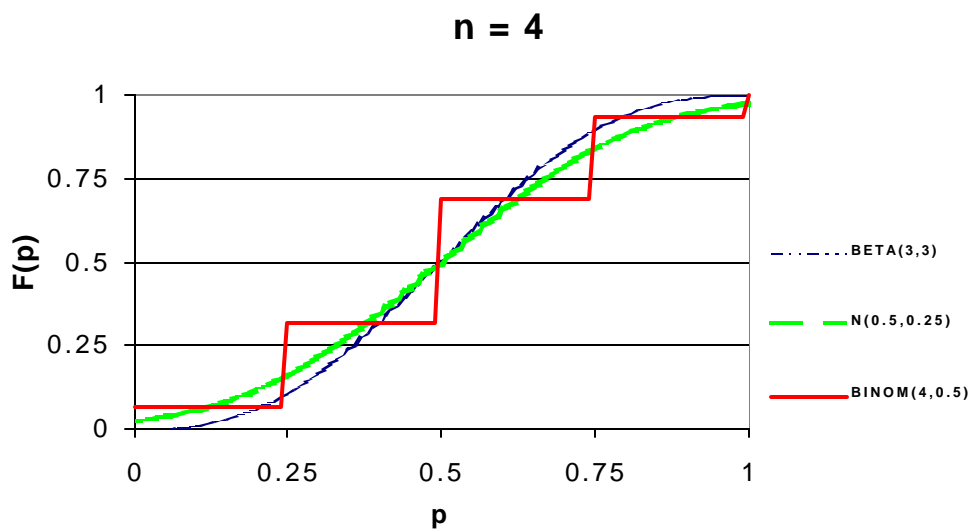
Figure A4a. Cumulative probability distributions for *p* based on the Beta, Binomial and Normal for the case n=4 and the number of observed successes is 2.

n = 20
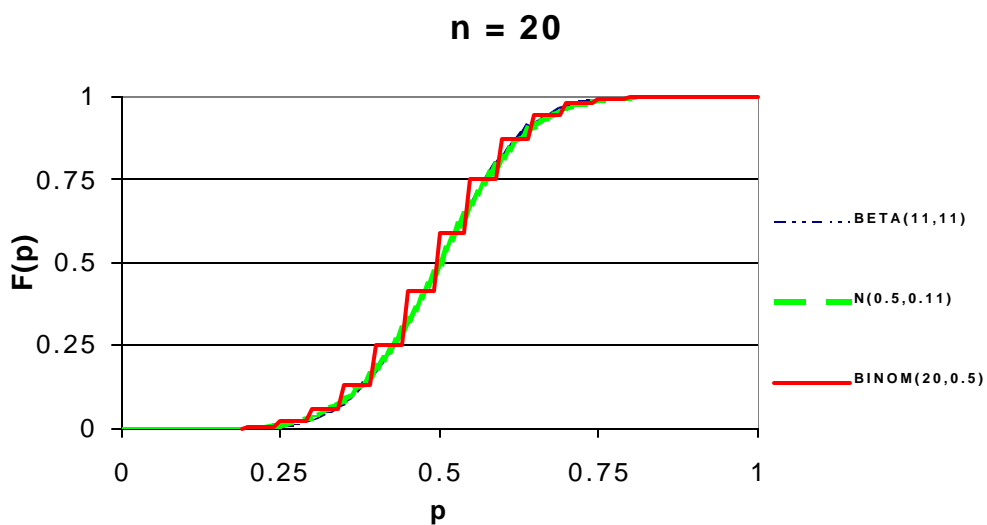
Figure A4b. Cumulative probability distributions for *p* based on the Beta, Binomial and Normal for the case n=20 and the number of observed successes is 10.

n = 40
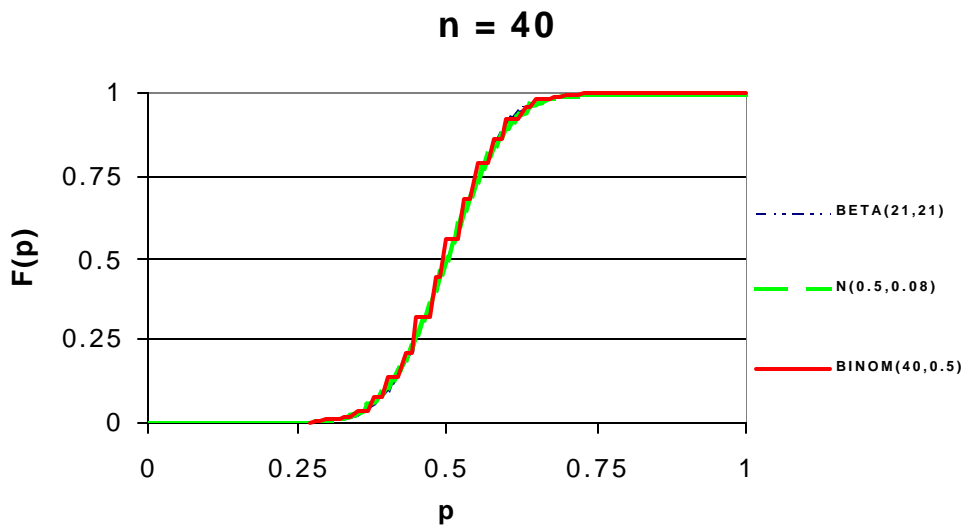
Figure A4c. Cumulative probability distributions for *p* based on the Beta, Binomial and Normal for the case n=40 and the number of observed successes is 20.

Use of the Gamma distribution to describe the uncertainty about a Poisson mean

Like the binomial probability p, the mean events per period λ is a fundamental property of the stochastic system in question. It can never be observed and it can never be exactly known. However, we can become progressively more certain about its value as more data are collected. Bayesian inference again provides us with a means of quantifying the state of our knowledge as we accumulate data.

Let us assume an uninformed prior $p(\lambda) = 1/\lambda$. The Poisson likelihood function for observing X events in period t is given by:

$$l(X\big|\lambda,t) = \frac{e^{-\lambda t}(\lambda t)^X}{X!} \propto e^{-\lambda t}(\lambda)^X$$

The posterior distribution density is the product of the prior density and the likelihood function. We can disregard terms that not involving λ, recognizing that the distribution will be normalized eventually, and we then get the posterior distribution:

$$p(\lambda\big|X) \propto e^{-\lambda t}\lambda^{X-1} \qquad \lambda > 0$$

which has the functional form of, and therefore is, a Gamma(X,1/t) distribution where λ is the variable.

The shape of the posterior Gamma distribution becomes progressively less sensitive to the prior distribution as data is collected. In essence, the sensitivity of the Gamma distribution to the prior amounts to whether (X-1) is approximately the same as X. So, if X was 100, the difference would be roughly 1% influenced by the prior and 99% influenced by the data. In this model, the information contained in the quantity of data available *always* overpowers the prior.

Gamma distributions used in the risk assessment to model the rate of invasive infection, λ_i which has a Gamma(43,1) distribution and the rate of enteric infection, λ_e which has a Gamma(3985,1) distribution. Those distributions are shown in the following graphs.
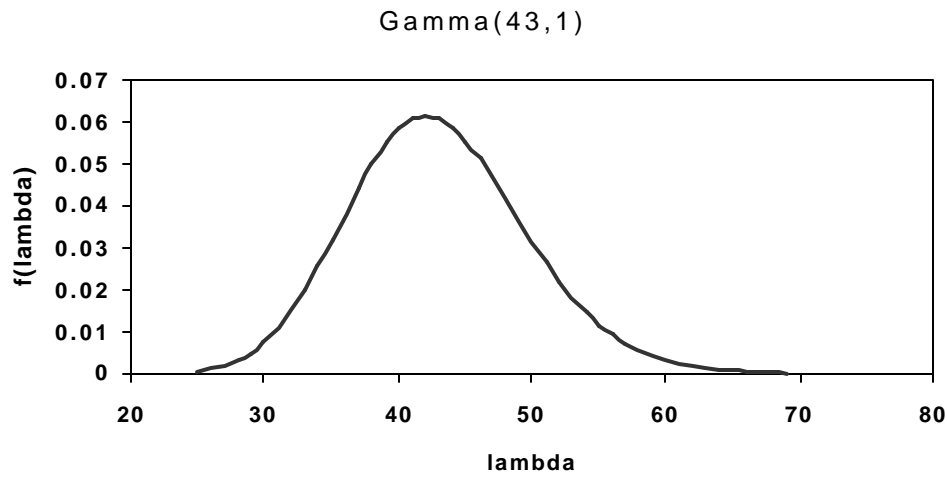
Gamma(43,1)

Figure A5a. The Gamma(43,1) distribution used to model the rate of invasive disease, λ_i.
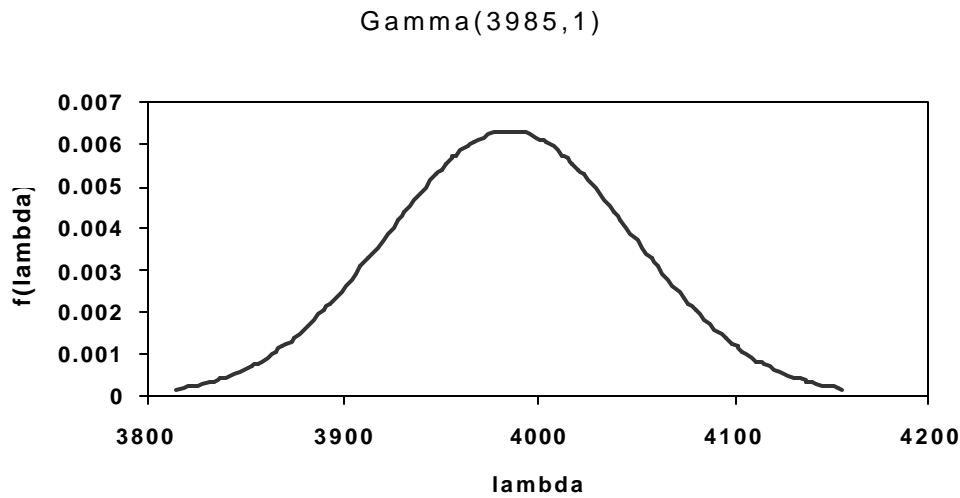
Gamma(3985,1)

Figure A5b. The Gamma(3985,1) distribution used to model the rate of enteric disease, λ_e.

As was the case for the Beta distribution, there is a distributional counterpart to the gamma that the frequentist would apply to this estimation problem. When X, the number of events in one unit of time (t=1), is distributed Poisson(λ), the maximum likelihood estimator for λ, $\hat{\lambda}$ is the observed value of X. Then the Poisson(X) distribution is used as the uncertainty distribution for λ. The Poisson distribution is the limiting distribution for a Binomial random variable when *n* is large and *p* is very small. Because of this relationship, the central limit theorem applies for the Poisson under the same limiting conditions. By the central limit theorem $\hat{\lambda}$ is normal with mean λ and variance λ, where λ is the true value of the parameter. This means that the confidence distribution for λ is estimated as:

$$Normal(X, \sqrt{X})$$

The three possible choices for the confidence distribution for λ when 43 cases were observed during the year are shown to demonstrate how similar they are.
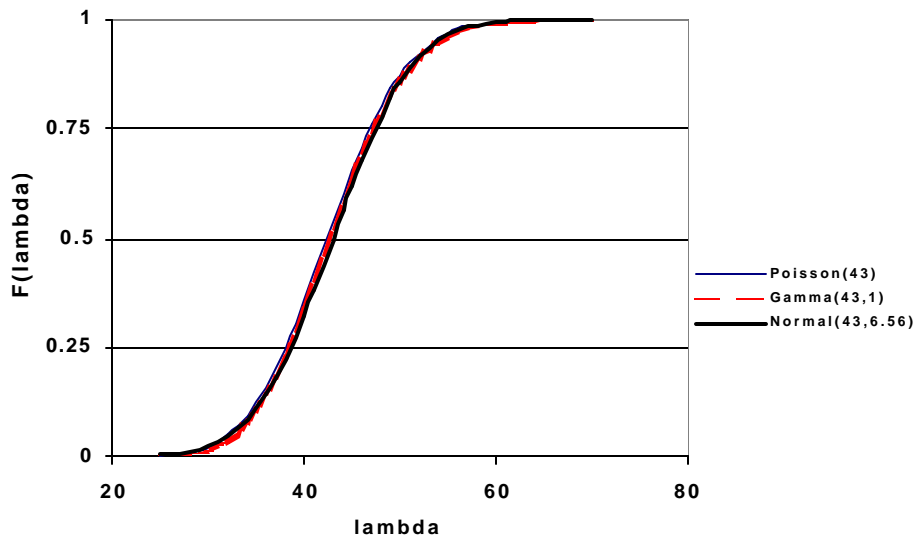
Figure A6. The cumulative distribution functions for Gamma(43,1), Poisson(43), and Normal(43,6.56)

Appendix B

List of Assumptions and Limitations of Data Used in the Risk Assessment

Below is a summary list of assumptions and a section reference for each assumption. The assumptions are listed in order of importance to the modeled risk.

Limitations in quantifying human health impact using attributable risk:
ASSUMPTION 1: The level of risk as calculated does not account for cases originating from chicken and contaminating other foods or the spread from chicken to other animal hosts and resulting in human exposure. (refer to Section 3.1)

DISCUSSION 1: The definition of the attributable risk included all cases of disease which may be attributed to a specific risk factor (122, 83). One limitation of epidemiologic tools used to determine the attributable risk or etiologic fraction is that those cases that were exposed to the risk factor of interest, even though the exposure may not have been the cause of the disease, would be included in the calculated level of risk, thereby potentially overestimating the level of actual risk. Conversely, another limitation of the epidemiologic tools used to determine the risk from the specific exposure of interest is that spread from the primary source of the pathogen, in this case chickens, is not included in the calculation of the level of risk. The magnitude of the bias introduced by false associations with chicken exposures (false positive associations) is likely to be much smaller than the lack of inclusion of the undeterminable cases from spread of the chicken associated resistant *Campylobacter* to other sources of human exposure. In addition, the risk assessment does not take into account the spread of the pathogen from chicken to other food sources. This can occur from cross contamination of other foods (29) or spread from chicken sources more proximate to the farm. For example, spread of Campylobacter can occur via many different pathways: from exposure of birds, insects and run-off surface water to chicken litter; from the use of chicken litter in aquaculture to fertilize fish ponds and from the use of litter in cattle feeds to increase the non-protein nitrogen content. Therefore, the risk assessment is likely to underestimate the overall risk of acquiring a resistant *Campylobacter* infection from exposure to chicken due to the secondary spread of *Campylobacter* from chickens to other sources of human exposure to the pathogen.

ASSUMPTION 2: The current level of risk of contracting campylobacteriosis from consumption of chicken is contained within the range of risk ascertained from studies conducted in the 1980's (refer to Section 3.1)

LIMITATIONS of studies used to determine the proportion of chicken associated cases:
Limitations of study 1 include: the demographic characteristics of the population, the frequency of chicken consumption, the proportion of the population consuming chicken and many other factors may have changed since this study. For example, the amount of chicken consumed has increased since 1982, and in 1998 people consumed 54.4% (72.60 lbs/47.02 lbs) more chicken, calculated in ready to cook pounds consumed per capita (80).

Limitations of study 2 include the lack of representativeness of the study population and the absence of some exposures, such as travel and raw milk that are frequently associated with risk in the population at large. In addition, the study was limited to enteric illnesses because more invasive infections were not eligible for inclusion in the study, although these usually comprise less than 1% of cases. These differences result in difficulty in generalizing the findings to the United States population but may represent the level of risk in some subgroups of the population.

DISCUSSION 2: In the two case control studies there was an increased risk of illness associated with consumption of chicken especially consumption of undercooked chicken. One study indicated a risk associated with raw milk consumption although the proportion of attributable risk was much less than that attributed to chicken. The proportions of disease attributable to consumption of chicken were 48.5% and 66.7%. The higher estimate of attributable risk from study 2 of 66.7% in the university student population indicates that in some subgroups of the population exposures are likely to differ and risk attributable to

consumption of chicken will vary accordingly. These estimates of the etiologic fraction represent a range of risk that is likely to reflect the level of risk in the early 1980's. More recent data do not exist for United States populations. Data analysis of a case control study, conducted by the CDC and participating State Health Departments (CA, CT, GA, MD, MN, OR), in 1998 within FoodNet sites is currently underway and will be published in the near future. The data from this study will provide updated risk factor information from which etiologic fractions associated with identified risk factors may be determined.

Limitations in data on resistant isolates:
ASSUMPTION 3: The fluoroquinolone resistance observed in persons ill from campylobacteriosis, (after removal of travelers, those who took a fluoroquinolone prior to culture and those for whom the time of taking the fluoroquinolone was unknown) is largely attributed to chickens (refer to Section 3.2).

DISCUSSION 3: It is difficult to know what proportion of resistance in human campylobacteriosis may be attributable to a source when human exposures are multiple and varied and when the data are limited. A single source of resistant bacteria may be disseminated from its origins into the environment or maintained in secondary hosts further spreading resistant *Campylobacter* to additional sources of human exposure further complicating the ability to measure the impact.

Fluoroquinolone use has been associated with the development of fluoroquinolone resistance in *Campylobacter* in clinical trials in poultry production units (58) in poultry production in the Netherlands (36) and in the United States (92) after the introduction of veterinary fluoroquinolones. In countries where fluoroquinolones have been approved for human and companion animal use but are not allowed in food animals the level of fluoroquinolone resistance in food animals and human clinical cases is low (8, 54).

An Extra Label Use Prohibition of fluoroquinolone use in food-producing animals was published in 1997 (21CFR530.41), limiting food animal drug use to species listed on the product label. Approvals of fluoroquinolone drugs for use in animals include feline and canine oral and canine injectable products (available in 1989), poultry water soluble and in-ovo injectable products (available in 1995) and feedlot cattle injectable products (available in October, 1998). There are no fluoroquinolones currently approved for use in swine.

Campylobacteriosis is primarily an animal derived foodborne disease, with the predominant source of human infections attributed to poultry (22, 31, 36 64). There is little surveillance data available to describe the level of fluoroquinolone resistance in *Campylobacter* isolated from animal derived food in the United States, either before or after the approval of these drugs for food animal use. Chicken *Campylobacter* isolates collected in 1998 indicated an overall level of 13.4% resistance to Ciprofloxacin (see Section 4.1). Because there was no food animal fluoroquinolone use other than use in poultry until late 1998, and only rare, sporadic and isolated resistance was observed prior to 1992 in human cases[1] it is unlikely that the increase in domestically acquired fluoroquinolone resistance observed in people since 1996[2] can be

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[1] In two surveys encompassing 474 human isolates from 1982 to 1992 in the United States, only a single Ciprofloxacin resistant isolate was identified and subsequently speciated as *C. lari* (70).

[2] After removal of persons who had traveled within 7 days of illness onset and removal of those taking fluoroquinolones prior to culture, quinolone resistance in Minnesota was observed in 0.8% of isolates in 1996 and had increased to 3.0% in 1998 (chi square for linear trend, 9.8; $p \leq 0.002$) (71). In Minnesota quinolone resistance, screened by nalidixic acid disc diffusion was highly correlated with resistance to ciprofloxacin using the E-Test, (sensitivity 99.6%, specificity 98.4%) (71). A survey of *Campylobacter* isolated from 88% of 91 chicken products resulted in *C. jejuni* from 67(74%) and *C. coli* from 19 (21%) of samples and six samples were the source of both pathogens. Products carrying resistant isolates were purchased from 11 stores representing 8 franchises and originated in seven processing plants in five states (70, 71) indicating widespread resistance in chicken campylobacter isolates. Molecular subtyping was performed using PCR restriction endonuclease length polymorphism typing of the flagellin gene in the C. jejuni human and chicken product isolates. 12 subtypes were identified from 13 *C. jejuni* positive chicken products. Six of seven resistant subtypes in the chicken products were also identified in the quinolone resistant human isolates. For people acquiring infections during 1997, excluding cases that had taken fluoroquinolones prior to culture, persons with non-traveler resistant infections were more likely to have C.

attributed to a consistently distributed source of resistant *Campylobacter* exposures. Distribution of resistance from foodborne sources is more likely to be associated with specific exposures and limited predominantly to poultry.

DATA GAP 3: Quantification of the proportion of human disease attributable to various sources and the determination of the level of resistance carriage within the specific exposures would more precisely allow the determination of the relative contributions of the various exposures to fluoroquinolone resistant human disease. This ability to determine the relative contributions of various sources of infection to the level of resistance in human cases becomes increasingly important once fluoroquinolones are available for use in more than one food animal species. A model intended to determine the human health impact of the level of resistance in *Campylobacter* attributable to fluoroquinolone use in food animals will need to distribute the burden of resistant human disease amongst many different food animal species and attribute levels of resistance to sources of human infection.

Limitations in microbiological methods:
LIMITATION 4: The lack of accuracy in the determination of the level of resistance using a single isolate leading to an underestimation of the level of resistance in chicken carcasses is currently not quantifiable. The limitation in the accuracy of reported carcass prevalence and the lack of reliability in the results needs further characterization and methods need to be developed to provide more accurate and reliable data which would improve the ability to measure the impact on human health. This risk assessment determined the measurable risk, limiting the model to those parameters for which data were relevant, valid and available.

ASSUMPTION 5: If a carcass was positive for *Campylobacter*, the predominant species isolated was *C. jejuni.* (refer to Section 4.1)

DISCUSSION: The prevalence of *Campylobacter* in chickens was estimated from a 1994-95 survey of **1,297** broiler carcass rinse samples at 88.2% of carcasses, indicating that **1,144** carcasses tested positive (104). The isolates were speciated using the biochemical hippurate assay and *C. jejuni* and *coli* were included in the carcass prevalence estimate.

Assumptions relating to the use of surrogate data on diarrheal illness for seeking care, submitting stools and rate of prescription of antimicrobials for campylobacteriosis:
ASSUMPTION(s) 6: The rate at which people reporting bloody stools seek care is similar to the rate at which people with campylobacteriosis reporting bloody stools seek care. The rate at which people with non-bloody stools seek care for diarrheal illness is similar to the rate at which people with campylobacteriosis reporting non-bloody stools seek care. (refer to Section 2.1 for discussion)

DISCUSSION 6: These estimates are for diarrheal illness, and not campylobacteriosis specifically. Data describing care seeking behavior for campylobacteriosis was not available. Bacterial foodborne disease is typically more severe than viral foodborne disease (42) and rates of seeking care may differ by pathogen.

In the population survey, factors that were most important in influencing the decision to seek care were fever, vomiting, "how sick they felt," stomach cramps, reporting blood in stool and duration of diarrhea (26). Some of these factors were evaluated for diarrheal illness in the telephone survey and compared with the same characteristics in individuals who had culture-confirmed *Campylobacter* infections or diarrheal disease (Table 2.1). Comparing the groups, a greater proportion of people with culture-confirmed *Campylobacter* cases were affected by fever and blood in the stool than the people seeking care for diarrheal illness. Therefore, the actual rate of seeking care for campylobacteriosis may be underestimated by the 20.5% for persons with non-bloody and 33.2% for persons with bloody stools. However, because a greater proportion of people with fever and bloody stools would be cultured and enrolled in the case control study, such comparisons are difficult.

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jejuni subtype also found in the quinolone resistant C. jejuni from chicken products (odds ratio 15.0, 5th and 95th percentile 1.9 to 321.8) (70).

DATA GAP 6: Additional studies to define the rate at which people with campylobacteriosis seek care would be helpful and would provide a more accurate estimate. These data would require very large community-based surveys that are likely to require considerable resources to conduct.

ASSUMPTION 7: The probability that a stool specimen was requested among people with diarrheal illness reporting bloody stools is similar to the probability that a stool specimen was requested among people with campylobacteriosis reporting bloody stools. The probability that a stool specimen was requested among people with diarrheal illness reporting non-bloody stools is similar to the probability that a stool specimen was requested among people with campylobacteriosis reporting non-bloody stools. (refer to Section 2.2)

ASSUMPTION 8: The population survey proportion of cases of all acute diarrheal illness seeking care, not submitting a stool sample and receiving an antibiotic (38.1%) is similar to that for persons ill with campylobacteriosis. (refer to Section 3.5)

DISCUSSION 8: Severity of illness is one of many factors that lead physicians to prescribe antibiotics to patients with a diarrheal illness.

Assumptions relating to bloody vs. non-bloody diarrhea:
ASSUMPTION 9: Patients with campylobacteriosis who have sought care and been requested to submit stool cultures and have submitted stool cultures are prescribed antibiotics at a rate that is the same whether they had bloody or non-bloody diarrhea. Conversely, if patients have sought care but have not been requested to submit stool cultures, they are prescribed at another rate that is the same whether they had bloody or non-bloody diarrhea.(refer to Section 3.5)

FoodNet to US extrapolation:
ASSUMPTION 10: The incidence rates for culture-confirmed *Campylobacter* infections in the FoodNet catchment are representative of incidence rates for culture-confirmed *Campylobacter* infections in the U. S. (refer to Section 1.2)

DISCUSSION 10: Although the incidence rates varied by site, from 10.2/100,000 in Maryland to 37.7/100,000 in California in 1998 (21), the overall rate of *Campylobacter* isolation is likely to reflect isolation rates in the U.S. population. Comparisons of demographic characteristics between the FoodNet sites and the U.S. population show similar distributions of sex, age, race and rural/urban distributions (Table 1.1).

In addition to demonstrating similarity in population composition, an evaluation of potential exposure is important. In a 1994-5 United States Department of Agriculture, Food Safety Inspection Service, survey, 88% of chicken carcasses were reported to carry *Campylobacter* at slaughter (Table 1.2)(104). Another estimate, of Campylobacter carriage on retail chicken products was demonstrated at a level of 88% in a Minnesota survey of chicken products in 1997 (92).

Another factor affecting incidence rates may be the sensitivity of stool culture methods as the methods for culturing stools are extremely diverse. Specimen handling is another factor that can greatly decrease the sensitivity of stool culture methods. In a review of non-typhoidal salmonellosis, an assumed estimate of the sensitivity of culture was 70% and was used to estimate the burden of salmonellosis in the United States (2). This estimate was adopted for determining the burden of campylobacteriosis in a recent review of foodborne disease (9).

DATA GAP 10: Incomplete knowledge of the sensitivity and specificity of culturing specimens for *Campylobacter* exists.

Invasive disease assumptions:
ASSUMPTION 11: All invasive campylobacteriosis cases seek care, have a specimen collected that yields *Campylobacter*, and is ascertained by FoodNet. (refer to Section 1.3)

DISCUSSION 11: It is not known precisely what proportion of persons with invasive *Campylobacter* infections seek care, but because persons with invasive *Campylobacter* infections will be moderately to severely ill, it is likely that most of these patients will seek care.

There is little knowledge of the completeness of ascertainment of invasive campylobacteriosis; the frequency with which laboratories are requested to test blood, CSF or other sterile specimens for *Campylobacter* and the sensitivity and specificity of the diagnostic tests used for isolation from blood and other sterile sites. Blood cultures usually represent more than 99% of all invasive isolations and most currently used blood culture systems are good for isolating *Campylobacter,* when it is present. The lack of information on the frequency of diagnostic requests and sensitivity may result in an underestimate of actual invasive disease rates. However, because the currently ascertained proportion of invasive cases is very small, approximately 1.0% of all confirmed cases, and most cases are likely to seek care, an increase in isolation of specimens classified as invasive is unlikely to have much impact on the overall number of cases of campylobacteriosis in the U.S.

DATA GAP 11: Data describing rates or cases of invasive disease seeking care, requests for diagnostic tests and the sensitivity of diagnostic procedures, such as blood culture, are not available.

ASSUMPTION 12: The proportion of fluoroquinolone prescriptions of total antibiotic prescriptions is the same for patients with invasive campylobacteriosis treated by their health care providers as it is for patients with enteric campylobacteriosis treated by their health care providers. (refer to Section 3.6)

ASSUMPTION 13: Because of the severity of illness upon presentation, all cases with invasive disease are presumed to seek care and are presumed to take antibiotics for their illness. (refer to Section 3.5)

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