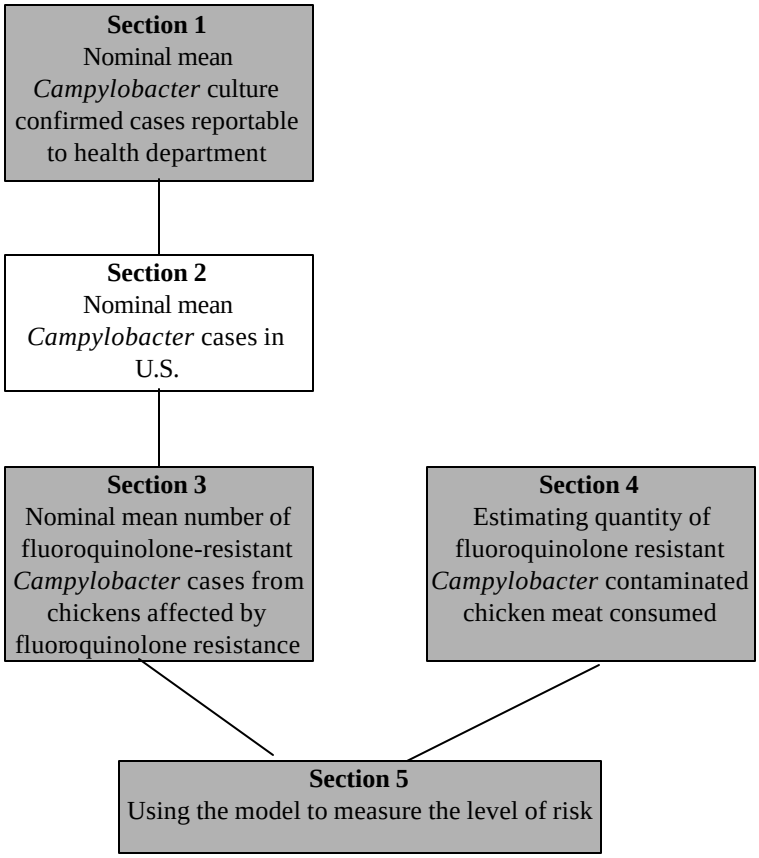
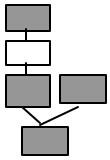
Section 2

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





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
$\lambda 2_n$ $\lambda 2_b$ $\lambda 2_I$ $\mathbf{I 2_T}$	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

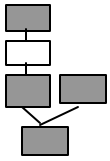
Two estimates were provided for this proportion, one for the probability that a person with enteric illness would seek care if they reported having no blood in their stool (p_{mn}) and one (p_{mb}) for bloody diarrhea.

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)

[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.

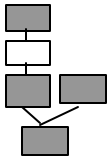
ASSUMPTION(s): The rate at which people reporting bloody stools seek care is similar to the rate at which people with campylobacteriosis reporting bloody stools seek care. The rate at which people with non-bloody stools seek care for diarrheal illness is similar to the rate at which people with campylobacteriosis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

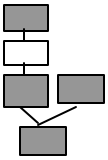
Invasive disease
There is no information on the rate of physician requests for diagnostic testing or rate of sample submission for cases of invasive disease caused by *Campylobacter*, see Section 1.3. In this assessment, we have assumed a rate of 100%.

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.

[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.

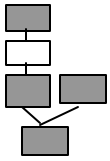
Because another, U.S. related, estimate of the sensitivity of stool culture was not available and to assess whether this estimate was a close approximation to the true value for the sensitivity of stool culture, Dr. Fred Angulo, from CDC and Dr. Irving Nachamkin, from the University of Pennsylvania Medical 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 ($\lambda 2_n$, $\lambda 2_b$, $\lambda 2_i$, $\mathbf{l\,2_T}$) – 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	$\mathbf{l\,2_n}$	822,273	1,307,500	1,999,114
	$\mathbf{l\,2_b}$	158,991	460,951	1,065,573
	$\mathbf{l\,2_i}$	433	567	715
1999	$\mathbf{l\,2_n}$	641,837	1,016,954	1,559,694
	$\mathbf{l\,2_b}$	124,414	358,581	829,404
	$\mathbf{l\,2_i}$	420	538	668

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

$\mathbf{l\,2_T} = \lambda 2_n + \lambda 2_b + \lambda 2_i$

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	$\mathbf{l\,2_T}$	1,113,895	1,769,018	2,773,268
1999	$\mathbf{l\,2_T}$	867,090	1,376,073	2,156,934
Difference (99-98)			-392,945	

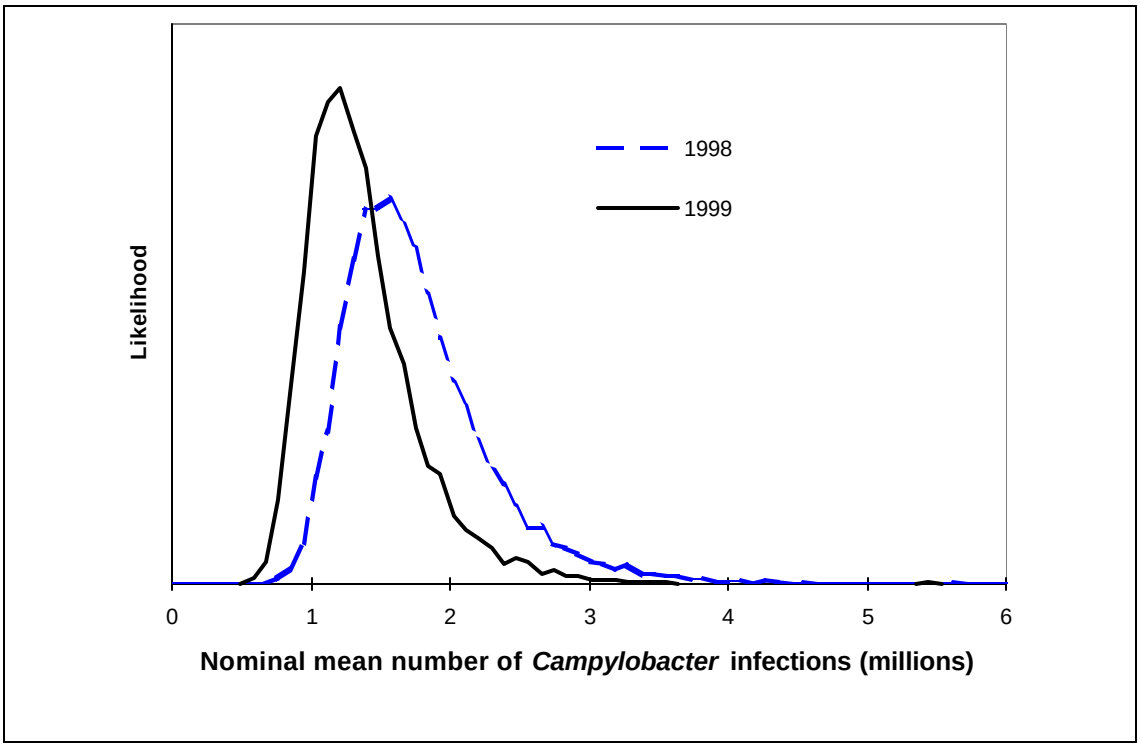


Figure 2.1. The confidence distribution (distribution of uncertainty) for the nominal mean total number of cases of campylobacteriosis in the U.S. for 1998 and 1999. *Note that the vertical axis for this and all other figures showing histogram (relative probability) representations of probability distributions 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 $\mathbf{l}\,\mathbf{2}_{\mathbf{T}} = \lambda 2_i + \lambda 2_n + \lambda 2_b$. The estimates for 1998 and 1999 using this model are given in Figure 2.1. The mean estimate of the distribution for 1998 is 1.77 million cases, with a 5th percentile estimate of 1.11 million and a 95th percentile estimate of 2.77 million. The mean estimate of the distribution for 1999 is 1.38 million, the 5th percentile estimate is 0.867 million and the 95th percentile estimate is 2.16 million. Relative contributions of the various components of the model to the model uncertainty will be presented in Section 5, Sensitivity Analysis.