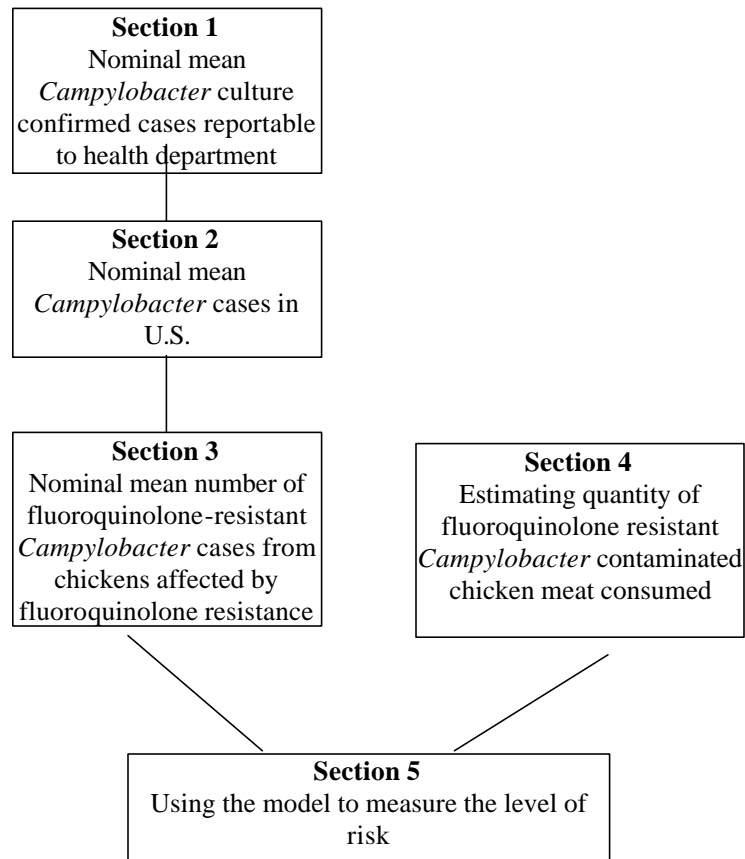## Overview of the Risk Assessment

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 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

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.

$$\boxed{\begin{array}{c}\text{Pounds of Chicken} \\ \text{Consumed with} \\ \text{Fluoroquinolone Resistant} \\ \textit{Campylobacter} \\ V_i\end{array}} \xrightarrow{\;K_{res}\cdot V_i = 1\;} \boxed{\begin{array}{c}\text{Human Health Impact} \\ \\ \lambda\end{array}}$$
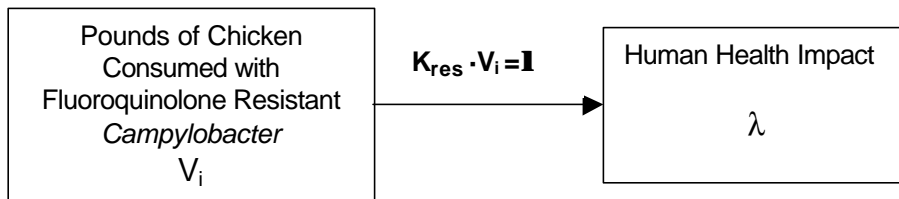
The model is also used to generate the proportionality constant K_{all} that relates exposure in terms of all *Campylobacter* contaminated broiler meat consumed domestically to the human health impact due to *Campylobacter* from domestically reared broilers (λ). The human health impact is determined 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 means of the distributions from the draft report and from the revised January, 2001 report for comparison. The October 18, 2000 risk assessment is revised in the January 5, 2001 report. The updated 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 the nominal mean *Campylobacter* culture confirmed cases reportable to health departments in the FoodNet catchment area. **Section 2** is the nominal mean *Campylobacter* cases in the 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 *Campylobacter* illness, the updated 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 in the pyramids below. These pyramids are provided for demonstration purposes only and show calculations of point estimates. Since the calculations in these examples do not use the distributions as is done in the model the output numbers will not exactly agree with the modeled values.

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 3,884 *Campylobacter* culture-confirmed cases ascertained in FoodNet sites in 1999. Of these cases, 51 were isolated from body sites considered invasive and 3,833 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 40,419 culture-confirmed enteric *Campylobacter* cases. Similarly, there are an estimated 538 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: 40,419 + 538 or 40,957.

Of those culture confirmed cases in FoodNet in 1999, 46.5% came from cases with bloody diarrhea (see Section 1.9). This means that 40,957 x 0.465= 19,045 cultures came from cases with bloody diarrhea, and 21,912 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 21,912 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, 998,753 cases.

Non-bloody stool pyramid:
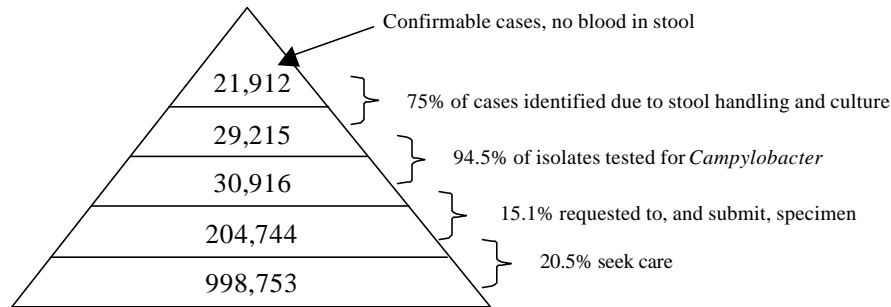
The pyramid for cases with bloody diarrhea contains the assumptions that a larger percentage of persons with bloody diarrhea will seek care, will be requested and will submit specimens when they are requested to do so (Section 2.3). This pyramid begins with 19,045 cases with bloody stool.

Bloody stool pyramid:
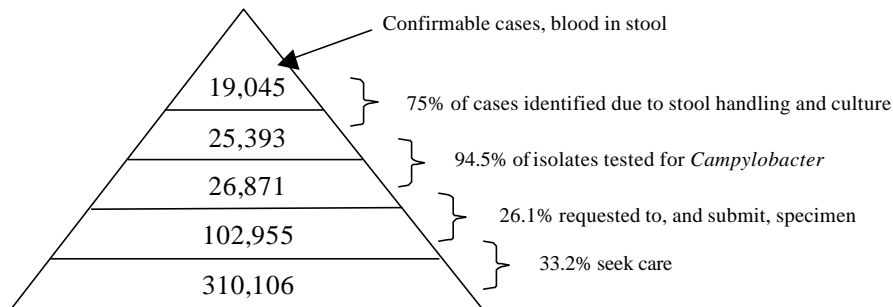
Finally, all cases of invasive campylobacteriosis were assumed to have been reported, obviating the need to use calculations. Thus, the estimated total burden of campylobacteriosis for 1999 is the sum of the three values for cases without bloody diarrhea, with bloody diarrhea, and with invasive disease. That is 998,753 + 310,106 + 538 = 1,309,387 cases.
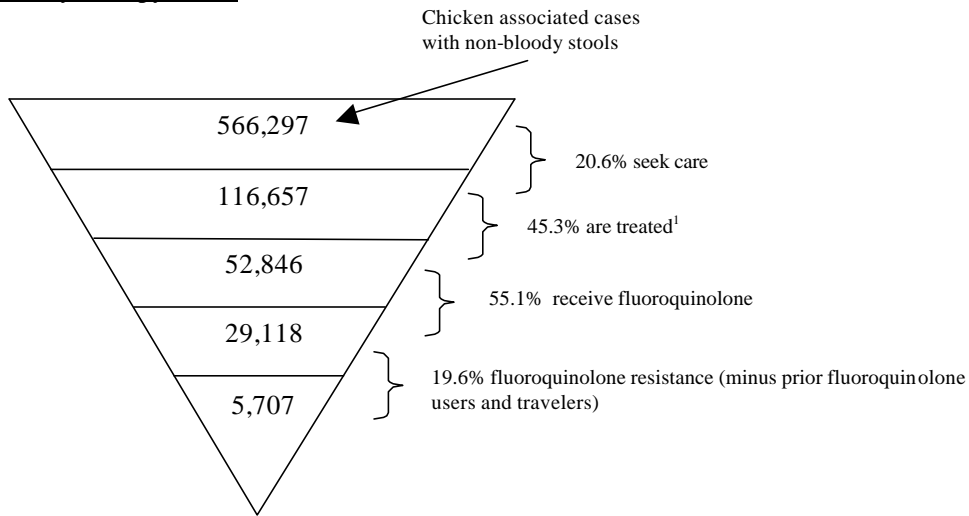
This basic calculation makes use of point estimates derived from CDC data. Sections 1 and 2 describe the data points with their inherent uncertainty or confidence distributions that were used in modeling the risk to provide an estimate of the total annual burden of campylobacteriosis.
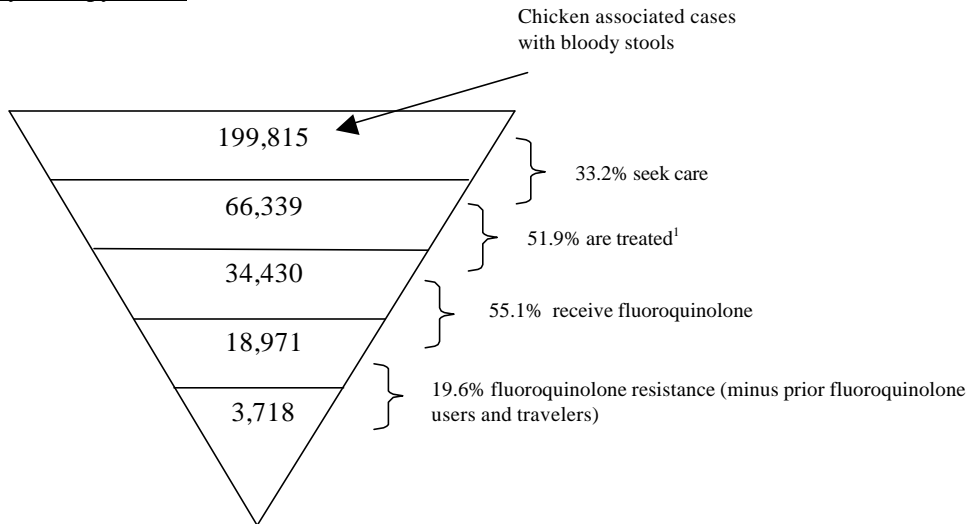
Overview for Section 3

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 fluoroquinolone resistant *Campylobacter* illness.

Non-bloody stool pyramid:

Chicken associated cases
with non-bloody stools

566,297

20.6% seek care

116,657

45.3% are treated[1]

52,846

55.1% receive fluoroquinolone

29,118

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

5,707

Bloody stool pyramid:

Chicken associated cases
with bloody stools

199,815

33.2% seek care

66,339

51.9% are treated[1]

34,430

55.1% receive fluoroquinolone

18,971

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

3,718

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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).

These estimates are point estimates for the number of cases of chicken associated illness with non-bloody and bloody stools 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 $5{,}707 + 3{,}718 + 33 = 9{,}458$ cases[2]. Section 3 describes in detail how uncertainty in the parameters 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 may be used for prediction of the human health impact 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.

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 enteric/invasive disease in the U.S.	$= n_{US} / n_{FN} * \Sigma_j Gamma(o_{ej},1)$ $= n_{US} / n_{FN} * \Sigma_j Gamma(o_{ij},1)$
p_b	Proportion of culture confirmed enteric infections with bloody diarrhea	Beta distribution based on data
$\lambda 1_n$ $\lambda 1_b$ $\lambda 1_i$ **$\mathbf{\lambda 1_T}$**	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

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[2] 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.

Section 2 continued Nominal mean *Campylobacter* cases in U.S.		
$\lambda 2_n$ $\lambda 2_b$ $\lambda 2_i$ **$\mathbf{12_T}$**	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
$\lambda 3_n$ $\lambda 3_b$ $\lambda 3_i$ **$\mathbf{13_T}$**	Nominal mean number of fluoroquinolone resistant *Campylobacter* cases attributable to chicken (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}[3]	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
$\lambda 4_n$ $\lambda 4_b$ $\lambda 4_i$ **$\mathbf{14_T}$**	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)	$= \lambda 3_n * p_{mn} * P_{an} * P_{FQ}$ $= \lambda 3_b * p_{mb} * P_{ab} * P_{FQ}$ $= \lambda 3_i * p_{FQ}$ $= \lambda 4_n + \lambda 4_b + \lambda 4_i$
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 chicken 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)	$= V_c * p_p$

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[3] FQ-fluoroquinolone

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, see Section 2.2).
- Removed Study #3, one of the studies 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 and modeled by FoodNet site;
- Nosocomial data used in estimating p_b used in the draft risk assessment was removed;
- Uncertainty estimates were assigned to $p_{ca\text{-}min}$ and $p_{ca\text{-}max}$;
- 1998/9 CDC population survey data replaced 1996/7 population survey;
- Deleted Appendix B and provided Table O.2 of mean values for the parameters used and the outputs in the draft and final report for 1998 and 1999;
- Updated the October 18, 2000 risk assessment to revise cell references indicating appropriate catchment populations for 1998 and 1999 and updated 1999 FoodNet reported cases to the final reported values, increasing total reported cases to 3,884 (See Table O.2);

Changes in results in the updated 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 mean values, between the draft and updated final risk assessments. The complete distributions of the outputs are displayed in the relevant Sections of this risk assessment.

	Draft Report			Updated Final Report					
	1998			1998			1999		
	Non-bloody	Bloody	Inv.	Non-bloody	Bloody	Inv.	Non-Bloody	Bloody	Inv.
Section 1									
nUS	270,298,524			270,248,003			272,690,813		
nFN	20,723,982			20,723,982			25,859,311		
li	561			567			538		
le	51,976			51,966			40,419		
pb	46.0%			46.5%			46.5%		
$\lambda 1n, \lambda 1b, \lambda 1i$	28,077	23,898	561	27,809	24,157	567	21,630	18,789	538
$\lambda 1_T$				52,533			40,957		
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	1,307,500	460,951	567	1,016,954	358,581	538
$\lambda 2_T$				1,769,018			1,376,073		
Section 3									
Pca-min	47.0%			48.5%					
Pca-max	70.0%			66.7%					
Pca	58.5%			57.6%			57.6%		
Prh	10.4%			14.3%			21.8%		
$\lambda 3n, \lambda 3b, \lambda 3i$				106,485	37,454	46	113,548	39,971	60
$\lambda 3_T$				143,985			153,580		
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	5,411	3,241	25	5,768	3,460	33
$\lambda 4_T$				8,678			9,261		
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		