

February 10, 2000

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Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**RE: Docket Number 98D-0969**

Dear Sir or Madam,

The following comments on the draft "Risk Assessment on the Human Health Impact of Fluoroquinolone Resistant *Campylobacter* Associated with the Consumption of Chicken" are submitted on behalf of the pork production industry, as represented by the National Pork Producers Council and the American Association of Swine Practitioners.

The pork production industry is the fourth largest agricultural sector in the U.S., generating approximately \$11.0 billion in annual farm gate sales (although farm gate sales were reduced to approximately \$9.0 billion in 1998 as a result of the lowest prices in history in deflated dollars), while creating an estimated \$64.0 billion in economic activity and employing 600,000 people.

The American Association of Swine Practitioners (AASP) is a professional organization with a membership of over 1,100 veterinarians in the United States. AASP's members have an abiding interest in swine health and production. The issue of continued availability of effective antimicrobials for use in swine is of great importance to the AASP. The safe and effective use of antimicrobials is a critical component of maintaining a healthy and safe supply of pork for the consuming public, as well as providing for the health and well-being of the nation's swine herd.

The National Pork Producers Council (NPPC) is one of the largest commodity organizations in the nation. NPPC is headquartered in Des Moines, Iowa, with an office in Washington, DC. The Council works to build a strong and vital pork industry by solving problems efficiently for the nation's pork producers. With approximately 85,000 producer members in 44 affiliated state associations, NPPC draws its strength from the nation's grassroots pork producers. Every producer, regardless of production size, has a voice in policy-making through a state-elected delegate system.

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AASP and NPPC share the concerns of government agencies, physicians, veterinarians, and other meat and poultry producers about changes in microbial susceptibility that could threaten the health of people and animals. Farmers and their veterinarians are also consumers. They also are very proud of their role in maintaining the health and productivity of their animals. They enjoy what they do and strive to be good stewards so subsequent generations can also participate in animal agriculture.

AASP and NPPC have each previously commented that a scientifically defensible assessment of the actual risk to the public health from antimicrobial use in animal agriculture is critical. The agency deserves congratulations for the good faith effort that was put forth to produce this document. It appears to be a disciplined approach to a very complicated question; it is mathematically defensible in its modeling of each of its components; it is generally (with a few exceptions) careful in its attempt to specify the assumptions that have had to be made; and it is an important attempt to quantify the uncertainty inherent in the arguments.

However, this should not be construed to be an unconditional endorsement of the risk assessment document. Recognizing the statistical and mathematical foundation of the effort, AASP and NPPC enlisted the assistance of a statistician on the faculty of the Iowa State University Department of Statistics to review the work and offer comments on its statistical and mathematical structure. This review, offered in its entirety in Attachment A, answered the questions (1) What are the positive aspects of the model?; (2) What aspects would you consider changing?; (3) Do you feel there are significant data gaps?; (4) What do you see are limitations of the model?; and (5) Other comments. It points out that before this risk assessment can be used for its stated purpose as a model for developing subsequent assessments, there are basic flaws that go beyond the choice of phrasing and wording in the model. These are flaws that must be addressed and rectified to complete the work that has begun.

For example, the review points out that one strength of the risk assessment is in its attempt to break down this complex issue into a series of simpler, more workable models. However, therein lies one of its major weaknesses as well. It is rarely the case that the final model is as simple as that presented in this document. The effects of clustering and spatial heterogeneity, for example, are not accounted for in this simplistic model. To adequately perform the assessment one should construct each of the model components in a statistically correct manner even though this may not yield as simple of an overall model as presented in this document.

Also, while using the Bayesian approach to estimating some of the model components key to the risk assessment is reasonable, its application is inconsistent. There are instances in which it is applied using a noninformative prior and a likelihood to construct a posterior. There are other examples in which the prior is constructed from the data that are already available, which leaves the conclusion (posterior) the same as the prior that was constructed. Attachment A, page 5 "Specify likelihoods as well as priors", will give a more complete discussion of these inconsistencies.

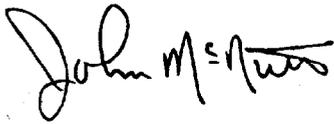
Additional specific concerns with the construction of and assumptions within the risk assessment (some of which are discussed in greater detail in Attachment A) are:

1. The use of the FoodNet data as a model for *Campylobacter* infections in the general population. On page 1.6 it is correctly pointed out that "Sentinel surveillance systems provide incidence estimates for the catchment area being monitored, and are not necessarily representative of the U.S. population. Incidence rates from sentinel surveillance systems are intended to be indicative of, but not necessarily the same as, disease rates in other parts of the country." Yet, the risk assessment then goes on to attempt to justify the use of the FoodNet surveillance system as a reflection of the status of the rest of the U.S. We refer you to Attachment A and the discussion of the 1987 book *Women and Love: A Cultural Revolution in Progress* in which the author uses the same flawed arguments that are used in this portion of the risk assessment to assert that 79% of all women married five or more years are having sex outside of their marriages.
2. Unpublished, non-peer reviewed correspondence is used to support multiple basic assumptions that are key to the risk assessment. For example, reference 97, "Preliminary data analysis *Campylobacter* Case Control Study Working Group and personal communication" is used on page 3.11 to support the assumption that the population survey proportion of cases of all acute diarrheal illness seeking care, not submitting a stool sample and receiving an antibiotic is similar to that for persons ill with campylobacteriosis. It is also used on page 2.4 in estimating  $p_{nc}$ ; on page 3.10 in estimating  $p_{ab}$ ,  $p_{an}$ , and  $p_{ai}$ ; and in other sections of the document. Building a scientifically sound risk assessment on personal communication and unpublished data is dangerous in that it lends the appearance and credibility of scientific review to something that could be no more than opinion. Without the peer-review process, there is no way to know this is not the case.
3. Studies used to support the assumptions in each of the modeling sections receive equal weighting of importance regardless of the reliability of the data. This puts data from unpublished sources as pointed out in item number 2 on equal weighting with peer-reviewed, published data sources.
4. The issue of spatial heterogeneity, whether in reference to the unsuitability of the FoodNet data to extrapolate to the U.S. population or the assumed lack of independence between processing plants in the prevalence of *Campylobacter* in chicken product, is a primary concern. A thorough discussion is offered in Attachment A.
5. On page 1.10, data from a nosocomial case-control study is brought forth as being representative of the general population. What is the scientific basis for this assumption? Are there data to support the generalization?
6. On page 5.19, assumption number 2 states that preharvest and postharvest practices will remain constant. Therefore there is a very basic assumption that the level of *Campylobacter* on the carcass is what consumers will be exposed to in their food. This does not take into account the effects of cooking on the potential level of exposure. It also does not allow the application of new technologies such as irradiation to mitigate exposure and therefore have a profound effect on the level of potential exposure and subsequent risk.

In conclusion, we assert that physicians and their patients and veterinarians and their clients have to share in the responsibility to properly use the antimicrobial products that play such an important role in human and animal health as well as in food safety. The industry will continue to monitor newly available scientific data and will assess this information in relation to the production of a safe, wholesome product.

We welcome the opportunity to discuss and debate the specifics of the risk assessment document and the FDA's Framework document. We offer our assistance as the Agency considers practical alternatives to the safety standard of "reasonable assurance of no harm." And we continue to ask that our previous comments regarding an inclusive process in which all stakeholders have the opportunity for meaningful input will be heeded.

Sincerely,



John McNutt  
President  
National Pork Producers Council



Dr. Alan Scheidt  
President  
American Association of Swine Practitioners

Encl. Attachment A: Report on "Risk Assessment on the Human Health Impact of Fluoroquinolone Resistant Campylobacter Associated with the Consumption of Chicken", Breidt, F. Jay, December 17, 1999.

**Report on  
“Risk Assessment on the Human Health Impact of Fluoroquinolone  
Resistant *Campylobacter* Associated with the Consumption of  
Chicken”<sup>1</sup>**

**F. Jay Breidt<sup>2</sup>**  
December 17, 1999

On December 2, 1999, the FDA’s Center for Veterinary Medicine posted the document “Risk Assessment on the Human Health Impact of Fluoroquinolone Resistant *Campylobacter* Associated with the Consumption of Chicken” on its website. This report will review the statistical and mathematical aspects of the risk assessment model as described in the December 2 document.

**What are positive aspects of model?**

The document takes a systematic, disciplined approach to quantifying uncertainty in the risk assessment. The complex problem of assessing human health impact of fluoroquinolone-resistant *Campylobacter* is decomposed into smaller, simpler problems. For each such problem, the available data are reviewed, necessary assumptions are discussed, and a mathematical model of the small problem is proposed.

The document adopts a Bayesian approach for drawing conclusions about unknown quantities in the problem. The idea of the Bayesian approach is to describe an unknown parameter not with a single “best guess” but with a probability distribution on all possible values. The probability distribution reflects the state of knowledge about the parameter. If little is known, then the distribution is relatively flat, assigning substantial probability across a wide range of possible values. If much is known, then the distribution is relatively peaked, assigning substantial probability to only a narrow range of possible values.

The probability distribution for a parameter is constructed in three steps in the Bayesian approach. First, a “prior” probability distribution is constructed to describe the state of knowledge about the parameter before the collection of data. Second, a “likelihood” is constructed to describe how the data are related to the parameter of interest. The likelihood is simply a data-generating model. Third, the prior probability distribution is updated using the information in the likelihood. The updated distribution, called the “posterior,” is proportional to the product of the prior and the likelihood.

The Bayesian approach is very useful for analyzing the model, as it allows a formal accounting of the uncertainty in the risk assessment even though data sources are disparate and sample sizes

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<sup>1</sup> This report was prepared on behalf of the American Association of Swine Practitioners and the National Pork Producer’s Council.

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are often small. The approach is particularly convenient when new data become available. To update the probability distribution, the old posterior becomes the new prior, and the new prior is updated with the new data to get the new posterior.

In the document, prior probability distributions are often chosen to be fairly uninformative (flat), and sensitivity to these prior distributions is discussed.

Many key assumptions in the document are explicitly detailed, clearly labeled as assumptions, and gathered and prioritized in an appendix. A sensitivity analysis is performed to assess the impact of uncertainty in model inputs on the uncertainty of key model outputs.

Off-the-shelf software is employed (Palisade @RISK add-in for Microsoft Excel), allowing other researchers to try the risk assessment model or experiment with alternatives. This software generates hundreds or thousands of replicates of a spreadsheet by sampling from probability distributions on cell entries. The resulting ensemble of cell entries and quantities derived from them can be used to answer quantitative risk assessment questions not with single numbers, but with probability distributions which reflect the uncertainty in the answers.

### **What aspects would you consider changing?**

While the simplicity of the model is appealing, it is also probably misleading. An oversimplified model may understate the actual uncertainty about the unknown model parameters.

#### *Choose priors and likelihoods appropriately*

One area with major potential for oversimplification is the choice of priors and likelihoods. It appears that the priors and likelihoods in this document are chosen largely for mathematical and computational convenience. Mathematically, it is convenient that the models have the conjugacy property: certain combinations of prior and likelihood lead to a posterior in the same distributional family as the prior. For example, a gamma prior with a Poisson likelihood leads to a gamma posterior, and a beta prior with a binomial likelihood leads to a beta posterior. Computationally, it is convenient that these distributions are provided in the Palisade @RISK software. In spite of these conveniences, the statistical appropriateness of these models must be considered carefully.

It appears that more or less the same beta-binomial and Poisson-gamma models are employed whether the data are obtained from a monitoring network, a case control study, a complex sample survey, or an expert opinion. It seems unlikely that the same data-generating mechanisms are at work in all of these cases. The binomial model is appropriate if the data have been generated as the number of successes in a fixed number of *independent* success/failure trials with a *constant probability* of success. The Poisson model is a limiting case of the binomial, appropriate (roughly speaking) for the binomial model with a very large number of independent trials and a very small constant probability of success.

In real-world problems, the assumptions of independence and constant probability may not be valid. Whenever the population of interest breaks down naturally into groups receiving similar treatment, the binomial assumptions are suspect. Examples include chickens within farms, carcasses within slaughterhouses, patients within insurance plans, doctors within hospitals, and

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so on. Processing of one carcass may infect another carcass, violating the assumption of independence. *Campylobacter* infection rates may vary across farms, stool sample request rates may vary across insurance plans, and antibiotic prescription rates may vary across hospitals, violating the assumption of constant probability.

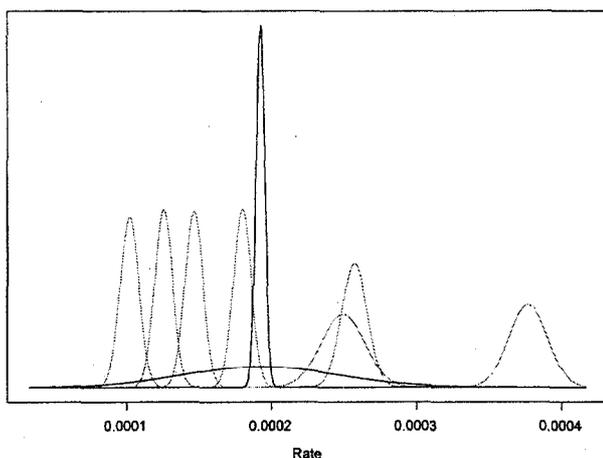
### *Investigate spatial heterogeneity*

In particular, there is evidence of possible differences across catchment areas (spatial heterogeneity) in the Poisson-gamma model of Section 1. The observed 1998 FoodNet incidence rates of enteric cases of *Campylobacter* are, from page 1.5,  $10.2/100,000=249/2,444,280$  for Maryland and  $37.7/100,000=809/2,146,096$  for California. If the Poisson process was homogeneous across sites with constant rate  $3985/20,723,982$ , we would expect incidence rates of  $(470.0 \pm 42.5)/2,444,280$  for Maryland, which are much higher than those observed, and incidence rates of  $(412.7 \pm 39.8)/2,146,096$  for California, which are much lower than those observed. A more formal test could be conducted given the complete data, but this argument suggests the presence of variation across regions in the Poisson rates.

The reasons for spatial heterogeneity could include differences across catchment areas in population demographics (age, occupation, education, income), environmental characteristics (weather, drinking water supply), health care (providers, insurance plans, testing laboratories), food distribution network (farms, slaughterhouses, processing plants, retail outlets), and so on. For similar reasons, spatial heterogeneity may exist and should be explored for the data on antibiotic use in culture confirmed cases (page 3.11), submitting a stool for culture (page 3.11), and rate of fluoroquinolone resistance (page 3.12).

What is the impact of spatial heterogeneity? If there are differences across regions in the Poisson rates, but the simple, constant-rate Poisson model is used, then the uncertainty about the overall incidence rate will be underestimated. The figure below illustrates this phenomenon using a hypothetical set of data constructed to resemble the incidence rates of enteric cases of *Campylobacter*. The leftmost curve summarizes the hypothetical data from Maryland, the rightmost curve summarizes the hypothetical data from California, and the remaining five light curves summarize hypothetical data from the other catchment areas. Combining the information in these seven curves, we obtain the lowest (flattest) curve, representing our uncertainty about the overall rate. If, however, we ignore the differences across regions in the rates, then we obtain the highest (most peaked) curve. This highest curve is centered at the same point as the lowest curve, but the highest curve severely underestimates the actual uncertainty about the overall rate.

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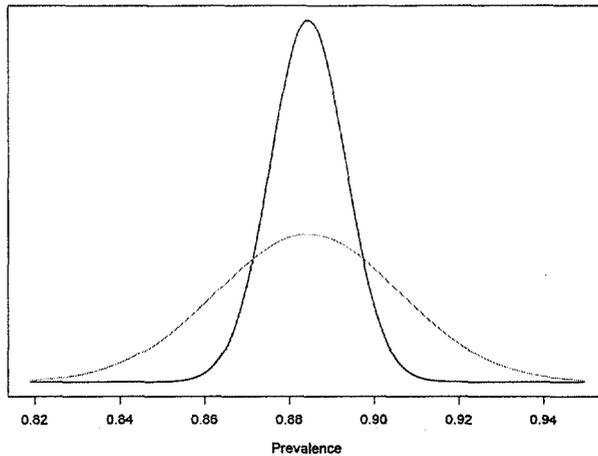
### *Account for complex survey designs*

The clustering and stratification in a complex survey design are often inconsistent with the independence and constant probability assumptions of a binomial model. An example is the broiler carcass survey on page 4.3, in which carcasses are clustered by slaughterhouse. Carcasses within the same slaughterhouse are likely to have similar *Campylobacter* prevalence; that is, measurements on carcasses within the same slaughterhouse are likely to be correlated. Intra-cluster correlation is common in data from complex sampling designs. Typically cluster-specific random effects are needed to capture variance and correlation structure appropriately. Ignoring the clustering as is done in this document usually leads to standard errors that are too small.<sup>3</sup>

The figure below illustrates the difference in uncertainty about the prevalence proportion for two hypothetical cases, with different levels of intra-cluster correlation. In each case, 6 carcasses are sampled at each of 216 slaughterhouses, for a total of 1296 carcasses, and 1146 of the carcasses test positive. In the first case (dark line), measurements on all carcasses are independent. In the second case (light line), measurements on carcasses within the same slaughterhouse are perfectly correlated; that is, if one carcass tests positive, then all 6 carcasses test positive. Note that the distribution is much flatter when the measurements are dependent than when the measurements are independent. In practice, the correlation within a cluster would be less than perfect, and the probability distribution for prevalence would fall somewhere between the extremes shown in the figure.

<sup>3</sup> See for example Skinner, C.J., Holt, D., and Smith, T.M.F., (1989), *Analysis of Complex Surveys*, Wiley.

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### *Specify likelihoods as well as priors*

The Bayesian paradigm for statistical inference is not consistently applied in this document. In some cases, non-informative prior distributions are assigned and likelihoods (data generating models) are evaluated to make posterior inferences on the unknown parameters, such as the Poisson means in Section 1. In other cases, however, the prior distributions are constructed directly from the data, and no likelihood is specified. In Section 1, for example,  $p_b$ , the proportion of enteric infections with bloody diarrhea, is modeled as a linear combination of Beta-distributed random variables (but condensed back to a single Beta after some normal approximation arguments). Another example is  $p_{bc}$ , the proportion of patients with enteric bloody diarrhea infections seeking care who are requested to supply stool samples and comply. In Section 2, this parameter is assigned a uniform prior distribution based on data. Many other examples appear in the document:  $P_{ca}$ ,  $P_{an}$ ,  $P_{ab}$ ,  $P_{FQ}$ ,  $P_{rh}$ .

Since no likelihood is specified, there is no data-generating model. For example, if the prior is beta and the likelihood is binomial, then we know that the data should have been generated as the number of successes in a fixed number of independent, success/failure trials with a constant probability of success. We can think about the data and decide if these modeling assumptions are reasonable.

On the other hand, if the prior is constructed directly from the data, and no likelihood is specified, then critical assessment of modeling assumptions is impossible. There is no data-generating model to critique. All of the data-generating models must be made explicit in this document.

### *Make modeling assumptions explicit*

Other parts of the document would also benefit from more explicit modeling assumptions. In the most complex parts of the model, probabilities of complex events are decomposed via the “chain rule” into products of conditional probabilities. For example, the probability of a complex event like “A occurs and B occurs and C occurs” can be written as

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$$\Pr(A \text{ and } B \text{ and } C) = \Pr(A | B \text{ and } C) \Pr(B | C) \Pr(C),$$

where the vertical bar “|” is read “given”. Each conditional probability is an unknown quantity, and the uncertainty about these quantities can be modeled using available data.

There are a number of built-in assumptions in the applications of the chain rule in this document. These assumptions are made clear if all conditional probabilities, with their full conditioning events, are written out in detail. For example, on page 3.11, parameters  $y$  and  $z$  appear in two computations. By writing out the associated conditional probabilities, we can see that

$$y = \Pr(\text{antibio} | \text{nonbloody diarrhea, seek medical care, comply with stool request})$$

$$= \Pr(\text{antibio} | \text{bloody diarrhea, seek medical care, comply with stool request})$$

and

$$z = \Pr(\text{antibio} | \text{nonbloody diarrhea, seek medical care, no stool request})$$

$$= \Pr(\text{antibio} | \text{bloody diarrhea, seek medical care, no stool request}).$$

The hidden assumption that non-bloody and bloody diarrhea cases have similar antibiotic prescription rates is made explicit when the conditioning events are written out.

### *Modify models to reflect uncertainty of extrapolation*

It has been mentioned above that the same models are used throughout this document regardless of the data source: monitoring network, case-control study, sample survey, or expert opinion. A related problem is that the same models are used regardless of the directness of the evidence to the risk assessment problem.

It might be worth considering modification of the models to account for the fact that some studies are less reliable than others for generalizing to the population, and consequently should have greater uncertainty (for a given sample size).

### **Do you feel there are significant data gaps?**

The document contains extensive discussion of limitations of existing data. In some cases, further consideration of the appropriateness of generalizing from samples to the population might be necessary. For example, on page 1.6, the document contains the following statement: “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.” Though this argument seems reasonable, it is false, as numerous studies have shown (often inadvertently). Agreement of sample demographic characteristics with population demographic characteristics does not imply that the sample is representative of the population. Perhaps the most famous example is Shere Hite’s book *Women and Love: A Cultural Revolution in Progress* (1987), which contained widely quoted (and criticized) statistics such as 70% of all women “married five or more years are having sex outside of their marriages” (p. 856). Though Hite showed that age, educational, and occupational characteristics of the women in her sample matched the corresponding population

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characteristics, this matching served only to disguise the sample's enormous selection bias.<sup>4</sup> The risk assessment document should attempt a more careful appraisal of the risk factors affecting disease rates. These risk factors presumably depend not only on characteristics of the people living in the catchment area, but also on characteristics of their environment (weather, food, health care, etc.)

### What do you see are limitations of model?

As pointed out in the introduction to the document, the model does not directly link the level of resistance in bacteria from food producing animals to drug use in animals. It also does not address infection rate or pathogen load as a function of drug use in animals. This means that the model is not able to answer questions about some interesting alternative scenarios. For example, what would be the human health impact if fluoroquinolone use in chickens was curtailed? Is it possible that infection rate and/or pathogen load in chickens would increase, leading to more (non-resistant, but still potentially dangerous) *Campylobacter* cases?

### Other comments

Much of the statistical notation and terminology in this document is non-standard and has the potential to be misinterpreted. For example, in the statistical literature, it is standard that Gamma(), Normal(), Beta(), Poisson(), and so forth refer to probability distributions, not random variables. This is particularly important, for example, when taking weighted linear combinations of Beta( $a_j, b_j$ ) with different parameters. In the notation of this document, such a linear combination means a *sum* of beta random variables with weights adding to one. In standard notation, this means a *mixture* of beta distributions: that is, sample from the  $j$ th beta distribution with probability  $w_j$ . The two approaches are quite different.

Along the same lines, it is improper to refer to a random variable or its distribution as an "estimate" of an unknown parameter. Estimates such as posterior means, medians, or modes can be derived from posterior distributions, but posterior distributions are not estimates.

"Confidence" has a very specific meaning in statistics and is not used in Bayesian analysis. The plotted distributions are "posterior distributions" and the interval estimates based on posterior distributions are "credible intervals."

Page I-3: References to the "half-dozen microbial risk assessment models" should be included.

Page 1.4: Here and elsewhere, capital ( $N_{US}, N_{FN}, O_i, O_e$ ) and lower-case ( $n_{US}, n_{FN}, o_i, o_e$ ) notation should not be used for the same quantities.

Table 1.1: Percentages of males and females in the U.S. population do not sum to 100%.

Page 1.7: "Findings, at a 5% level of confidence" presumably should be level of significance.

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<sup>4</sup> See Lohr, S.L., (1999), *Sampling: Design and Analysis*, Duxbury Press, for an excellent discussion.

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Page 2.6: The quantity  $p_m$  should be replaced by  $p_{bm}$  and  $p_{nm}$ . See also page O-2.

Page 3.2: Where in the model does it imply that infection from fluoroquinolone-resistant *Campylobacter* results in a longer illness?

Page 3.6: Why are much higher levels of fluoroquinolone resistance seen in travelers?

Page 3.10: Should empirical bloody stool rate for seeking care be 2/9 rather than 2/4? In those cases requested to submit a stool, did the antimicrobial drug use always come after the stool for culture?

Page 4.4. Does the estimate of about one pound of boneless chicken per person per week account for wasted meat (that is, purchased but ultimately discarded)?

Page 5.2: How many replications are done in the simulations for the sensitivity analysis? Also, the ranges 3100-6600 and 4600-4900 are not consistent with what is shown in the spider plot.

Table 5.1: Probabilities are not percentages. Also, the columns do not agree: for example,  $1/521=0.001919$ , not 0.002265. Finally, the numbers do not agree with those in Appendix B.