Review

Re-examining the causes of campylobacteriosis

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The development of fluoroquinolone (FQ)-resistant strains of *Campylobacter* (CP) in chickens is favored by enrofloxacin, which is used to combat respiratory disease in chicken broilers. Thus, it seems plausible that eating chicken treated with FQs could increase the risk of FQ-resistant CP illness. We call this hypothesis 'Causal Model 1'. It is the dominant paradigm driving current regulatory efforts in the USA to ban FQ use in chickens. Although plausible, Causal Model 1 does not explain why several recent data sets indicate that eating chicken (and even touching raw chicken) at home can reduce the risk of CP illness. An alternative, Causal Model 2, instead attributes the risk of sporadic domestic CP cases primarily to commercial cooking of hamburgers, chicken, and other meats. This paper re-examines case–control data collected by the Centers for Disease Control (CDC), and re-analyzes previously published case–control data to assess the evidence for Causal Models 1 and 2. We apply causal graph, classification tree, conditional independence and Bayesian Model Averaging (BMA) methods of data analysis to identify potential causal relationships of interest in the case–control data. Available case–control data are generally consistent with Causal Model 2, but not Causal Model 1, because they indicate that chicken (and other meats) are protective against campylobacteriosis risk when prepared at home, and are only risky when consumed in commercial establishments such as restaurants. This suggests that poor hygiene in some restaurants may be a predominant cause of campylobacteriosis in humans, while chicken-borne CP plays at most a minor (statistically undetectable) role in human health risk. Both domestic and international data support this model. If true, Causal Model 2 implies that current regulatory efforts in the USA to protect human health by focusing on chicken-borne CP may be ineffective, conferring no detectable human health benefit. Instead, improving restaurant hygiene for a small minority of high-risk restaurants (as well, perhaps, as reducing over-use of FQs in human medicine) are the interventions most likely to create significant human health benefits, based on currently available data.

INTRODUCTION:
AN EPIDEMIOLOGIC PUZZLE

Chicken is usually considered the primary source of and vehicle for transmitting *Campylobacter* (CP) (mainly *Campylobacter jejuni*) to humans.[1] In July 2000, the Centers for Disease Control (CDC) published the following observations about the epidemiology of *Campylobacter* (CP):

> *Campylobacter* is the most common cause of bacterial gastroenteritis in the United States. The majority of *Campylobacter* infections ... occur as sporadic individual infections. We conducted a case–control study to determine risk factors for sporadic *Campylobacter* infections. ... In preliminary univariate analysis, foreign travel was strongly associated with illness (13% patients vs. 1.4% of controls, mOR 10.4, 95% CI 6.2–17.4). Among persons with no foreign travel the following exposures were significant risk factors for infection: eating undercooked poultry (7% patients vs 4% controls, mOR 1.9, 95%

CI 1.3–2.9), eating chicken or turkey that was cooked outside the home (46% patients vs 28% controls, mOR 2.4, 95% CI 2.0–2.9), eating non-poultry meat that was cooked outside the home (51% patients vs 34% controls, mOR 2.2, 95% CI 1.1–2.7), eating raw seafood (5% patients vs. 3% controls, mOR 1.8, 95% CI 1.1–2.7), drinking raw milk (2% patients vs 1% controls, mOR 3.5, 95% CI 1.4–8.7), living on or visiting a farm (16% patients vs. 9% controls, mOR 2.1, 95% CI 1.6–2.8), having contact with farm animals (11% patients vs. 5% controls, mOR 2.2, 95% CI 1.5–3.1) and having contact with puppies (11% patients vs. 6% controls, 2.0, 95% CI 1.5–2.8). Eating chicken or turkey cooked in the home was a protective factor (53% patients vs. 69% controls, mOR 0.5, 95% CI 0.4–0.6).[2]

The final sentence may surprise those familiar with CP risk assessments. If eating chicken cooked at home truly protects against campylobacteriosis, then current regulatory assumptions and risk models for the relationship between chicken consumption and illness risks must be radically revised, and the probable human health consequences of banning the veterinary use of drugs in chickens should be reassessed. This paper re-examines the CDC's preliminary findings, using multivariate statistical and causal modeling. It also analyzes additional data sets to test whether the patterns observed in

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the CDC data set hold more generally. Finally, it re-examines the risks of human CP illness in relation to fluoroquinolone (FQ) use in chickens in light of these findings.

ECOLOGICAL ANALYSIS OF CDC POPULATION SURVEY DATA

The CDC collects population survey data on food consumption patterns, including chicken consumption, among people in several FoodNet catchment areas.[3-5] For purposes of regulatory risk analysis, the the Food and Drug Administration (FDA) assumes that excess risks of CP (and FQ-resistant CP) illnesses in humans are directly proportional to the amount of chicken consumed:[1]:

> Excess risk of CP illness
> in humans=K × total chicken consumed

where

$K=(k_1k_2/k_3)$, k_2=fraction of chicken treated with FQ, k_3=fraction of all human CP cases that are identified as having FQ-resistant isolates, and k_1=(FQ-resistant CP isolates in humans/FQ-treated chicken consumed).

If this risk model is correct, then ecological fallacies do not arise.[6] The constant K can then be estimated from population-level data on chicken consumption and campylobacteriosis incidence rates in catchment areas, e.g. by linear or Poisson regression of CP case counts in different catchment areas over a time period (e.g. a year) against quantities of chicken consumed in those areas over the same time period.

Figure 1 plots CP prevalence (CASERATE=cases per 100 000 people) against a measure of chicken consumption per person per week (TOTCHICK, obtained by summing the numbers for different styles of chicken, such as fried or roasted) for seven FoodNet catchment areas for which the CDC collected data (all but Tennessee, which was added to FoodNet subsequently).[3] To account for the effects of multiple risk factors simultaneously, multiple linear regression with forward stepwise variable selection was also used. The main findings from multiple linear regression analysis of this ecological data set are as follows:

(a) Most chicken-related variables recorded in the data set, including eating pink chicken and touching or handling raw chicken, are not significantly associated with CP illness risk (CASERATE). The exceptions are ground chicken and chicken sausage, both of which are discovered in multivariate analysis to be confounded with other risk factors.

(b) Aggregate chicken consumption in the catchment areas (TOTCHICK on the x-axis in Figure 1) is not positively associated with risk of CP illness (Figure 1). This is also true in multivariate analyses.

(c) Several other factors do appear to be significantly associated with increases or decreases in campylobacteriosis risk, despite the small number of cases (n=7 catchment areas). For example, frequently dining out in restaurants is positively associated with CP risk, while dining out in restaurants infrequently is negatively associated with CP risk.

(d) To examine possible effects on risk of demographic variables such as ethnic group and income, we used
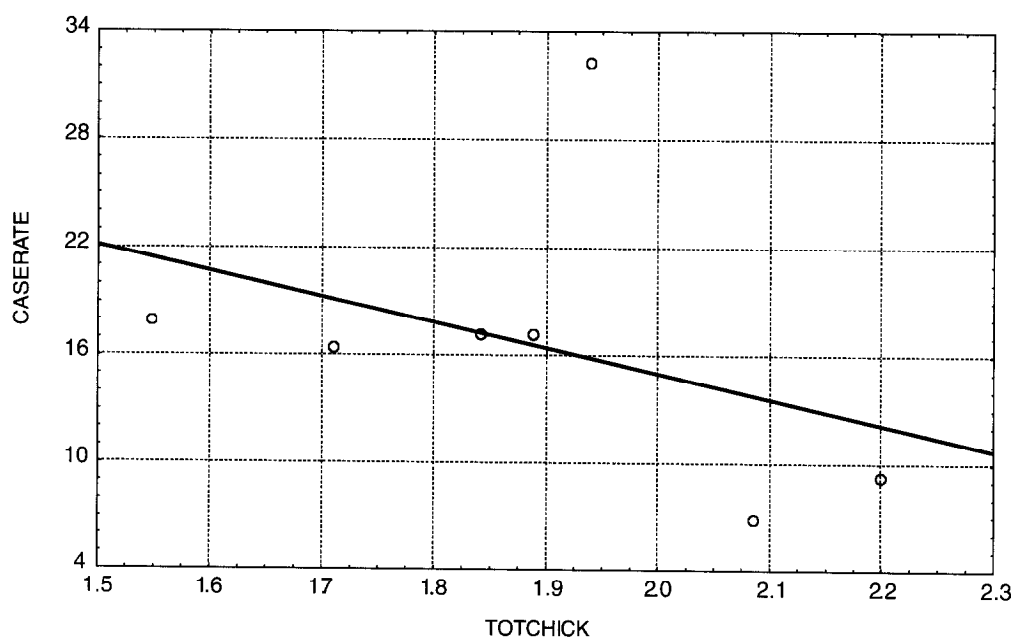
Figure 1. Linear regression of CASERATE against total chicken consumption. CASERATE=cases per 100 000 people; TOTCHICK= aggregate chicken consumption in the catchment areas, obtained by summing the numbers for different styles of chicken, such as fried or roasted).

1990 census data to estimate the proportion of Hispanic households with annual income less than $15 000 in each catchment area. This turned out to be strongly correlated with CP risk (Spearman's rank correlation of 0.92, Pearson's linear correlation coefficient of 0.86.) Thus, it may be valuable to include such demographic variables in future analyses of CP risk data.

(e) In a multiple linear regression analysis, washing hands (both in general and specifically after handling chicken) is protective against CP illness risk, even though handling raw chicken is not itself a risk factor. This suggests that good kitchen hygiene reduces the risk of CP illness, whether or not chicken is the source of CP.

ANALYSIS OF CDC INDIVIDUAL CASE–CONTROL DATA

If excess risk of CP illness is not directly proportional to the amount of chicken consumed, then aggregate population data may not accurately reflect individual-level relationships between chicken consumption and CP risk.[6] We therefore obtained individual-level case–control data from the CDC, to follow up on the preliminary study by Friedman et al.[2] The data set consists of 859 CP cases and 585 controls surveyed by the CDC, with stool sample data collected in 1998 and early 1999 and analyzed as part of the National Antimicrobial Resistance Monitoring (NARMS) program.

To extend the Friedman et al analysis, we first examined the relationships between the risks (CACO= case–control status, 1=case, 2=control) for the different types of chicken for both home preparation and commercial preparation. Figure 2 shows that home-cooked chicken of many types appears to be associated with reduced risk of campylobacteriosis, in that consumption of home-cooked chicken is more common among controls than among cases for each specific type of chicken.

This pattern is highly statistically significant (P<0.001) using a sign test. Similar exploratory plots establish that:

- Domestic cases (i.e. those with no foreign travel) are significantly more likely to have eaten chicken in restaurants (or other commercially prepared chicken) than are controls. Again, this holds for multiple specific types of chicken.
- Domestic cases are significantly more likely to have eaten specific other meats in restaurants than are controls, as a plot similar to Figure 2 makes clear.
- Domestic cases are significantly less likely than controls to have eaten any specific other meats at home.

These results suggest that the underlying common risk factor is restaurant (or commercial establishment) food preparation, rather than chicken consumption per se.

To analyze this possibility more thoroughly, we applied the non-parametric multivariate data modeling technique of classification tree analysis[7,8] to simul-
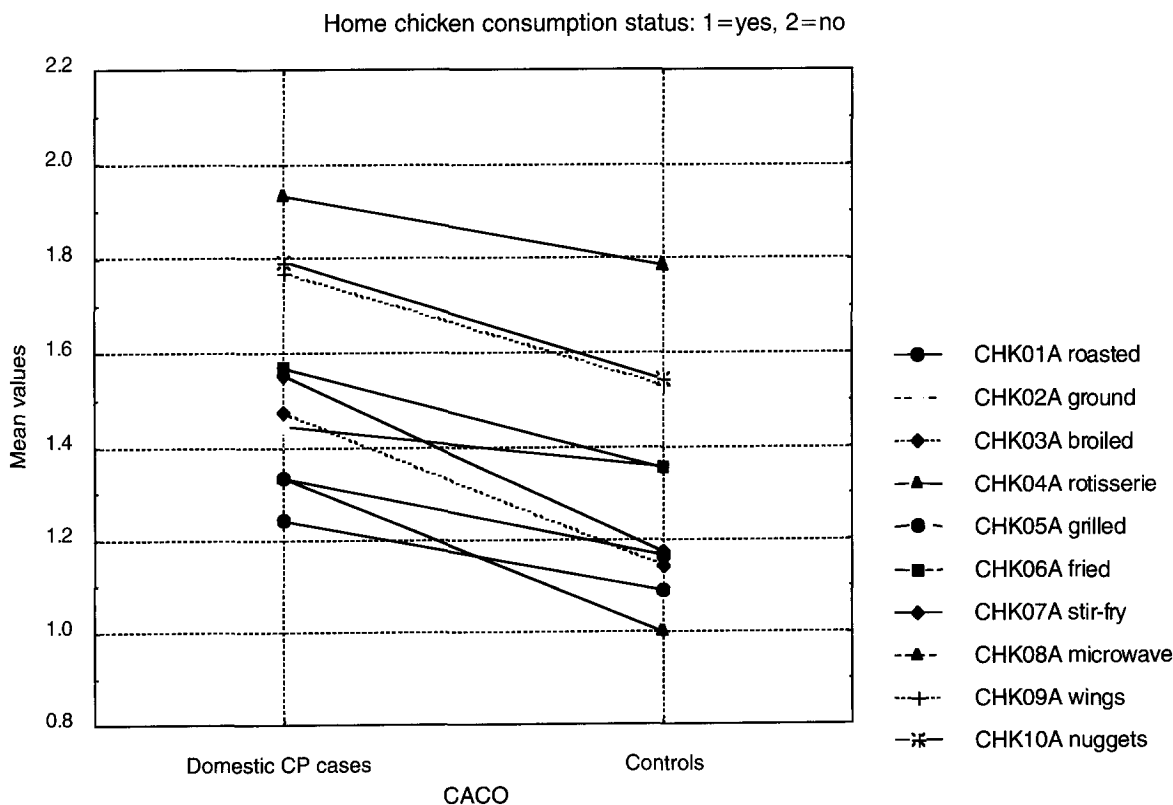
Figure 2. Domestic cases eat less chicken at home than controls. A=cooked at home.

taneously quantify the effects of multiple risk factors. Figure 3 shows the main results. In this figure, CACO is the risk variable indicating case or control status (CACO=1 for cases, CACO=2 for controls; this figure keeps the CDC's variable names and codes, with 1= yes, 2=no, and 7=no answer; ??? indicates missing data). In each box, the bottom number is the total number of subjects in that box (i.e. described by the splits along the path leading from the top of the tree to that node). The top and middle numbers are the fractions of cases and controls, respectively.
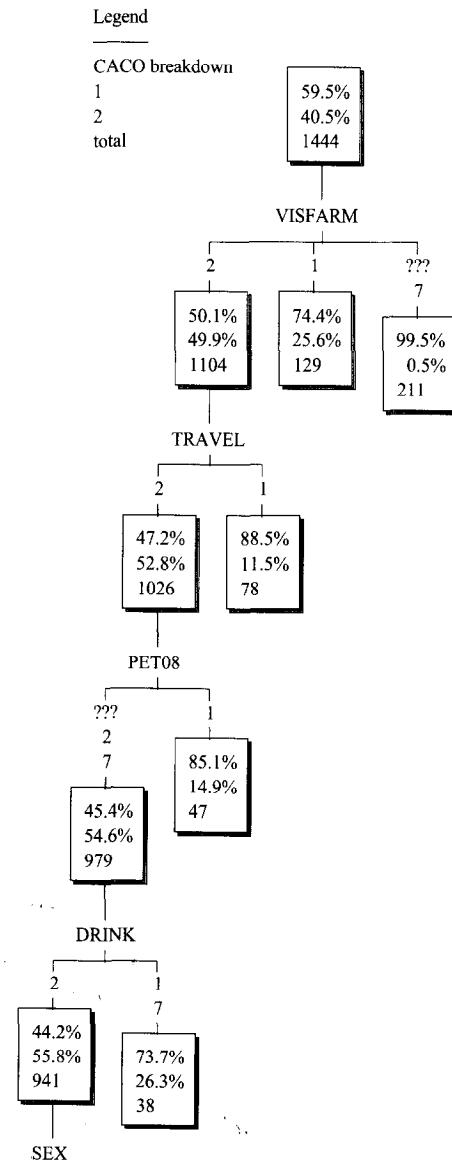
Figures 3a and 3b are two parts of one tree grown using the KnowledgeSeeker™ commercial software.[7] In a classification tree, the dependent variable (at the top of the tree) is conditionally independent of all variables not in the tree (so far as the tree-growing algorithm can discover), given the variables that are in the tree. The 'splits' in the tree indicate variables that are statistically significantly associated with the dependent variable after correcting for multiple testing bias and conditioning on the values of preceding splits (those higher in the tree). Thus, the sub-tree in Figure 3a indicates that visiting a farm (VISFARM), traveling outside the USA (TRAVEL), having a puppy as a pet (PET08) and drinking unprocessed water (DRINK) are all significantly associated with increased risk of campylobacteriosis. These findings are expected, based on the earlier literature on risk factors for sporadic cases of campylobacteriosis.

Figure 3b focuses on risk factors for campylobacteriosis in the sub-population for which these previously identified risk factors do not hold, i.e. for cases that remain after excluding those associated with foreign travel, farm visits, puppies, and drinking raw water. New findings for this group, as revealed by the tree analysis, are that:
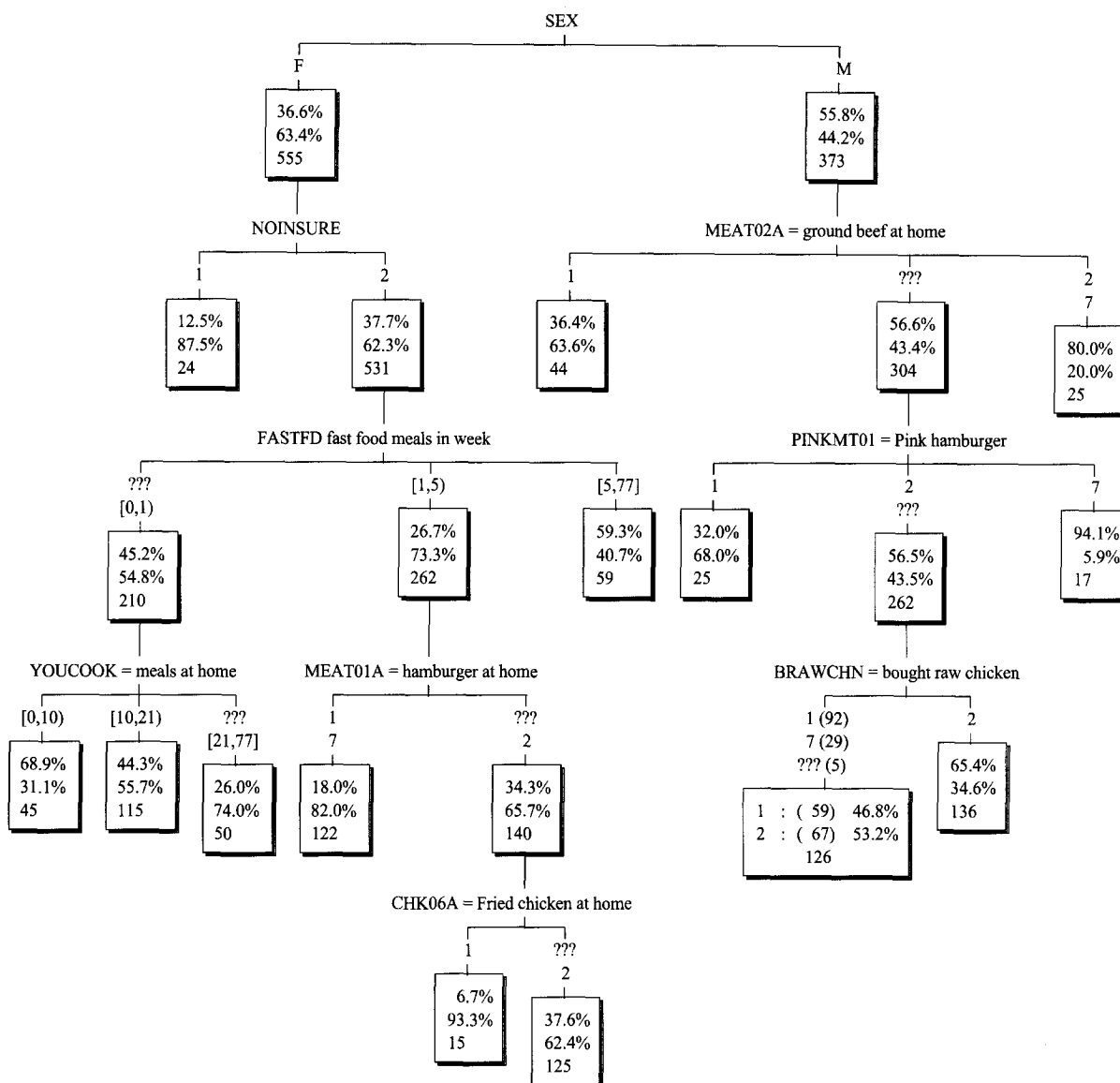
- Eating hamburgers, other ground beef and fried chicken prepared at home is significantly associated with a decreased risk of campylobacteriosis.
- Home cooking (YOUCOOK) is significantly associated with decreased risk.
- People who eat five or more fast-food restaurant meals per week are at greater risk than people who eat only one to four. People who eat no fast-food meals (and who may therefore eat more at non-fast-food restaurants) are at increased risk compared to those who eat one to four fast-food restaurant meals per week.
- Buying raw chicken (BRAWCHK) is significantly associated with decreased risk.
- Having no insurance is significantly associated with decreased risk of (reported) campylobacteriosis.
- Other specific chicken variables such as CHK01A etc., shown in Figure 2, are not associated with risk after conditioning on the other variables in Figure 3. This suggests that they are not causal drivers of risk.

A causal graph model[9,10] shows variables as nodes, and shows the causal parents of each variable by arrows

from other nodes/variables pointing into it. (Formally, a causal graph model is a directed acyclic graph (DAG) with the conditional probability distribution for the value of each variable determined by the values of the nodes that point into it.) Generically, all of a variable's parents in a correct causal graph model will appear in any classification tree for that variable, while more remote ancestors will not appear in the tree after all the parents have been introduced (since the variable, considered as the dependent variable in a classification tree, is by definition conditionally independent of its more remote ancestors, given the values of its parents). Thus, classification trees provide a method to test (or learn) the conditional independence relationships represented by a causal graph model. Applying this technique to identify the direct causal predecessors of CACO reveals that no subset of the variables in Figure 3 explains away the effects of the others. Moreover, in

Figure 3. (a) Step 1: exclude subjects with four known risk factors.

SEX

F — 36.6% / 63.4% / 555

M — 55.8% / 44.2% / 373

NOINSURE
- 1 — 12.5% / 87.5% / 24
- 2 — 37.7% / 62.3% / 531

MEAT02A = ground beef at home
- 1 — 36.4% / 63.6% / 44
- ??? — 56.6% / 43.4% / 304
- 2 / 7 — 80.0% / 20.0% / 25

FASTFD fast food meals in week
- ??? [0,1) — 45.2% / 54.8% / 210
- [1,5) — 26.7% / 73.3% / 262
- [5,77] — 59.3% / 40.7% / 59

PINKMT01 = Pink hamburger
- 1 — 32.0% / 68.0% / 25
- 2 ??? — 56.5% / 43.5% / 262
- 7 — 94.1% / 5.9% / 17

YOUCOOK = meals at home
- [0,10) — 68.9% / 31.1% / 45
- [10,21) — 44.3% / 55.7% / 115
- ??? [21,77] — 26.0% / 74.0% / 50

MEAT01A = hamburger at home
- 1 / 7 — 18.0% / 82.0% / 122
- ??? 2 — 34.3% / 65.7% / 140

BRAWCHN = bought raw chicken
- 1 (92), 7 (29), ??? (5):
  - 1 : (59) 46.8%
  - 2 : (67) 53.2%
  - 126
- 2 — 65.4% / 34.6% / 136

CHK06A = Fried chicken at home
- 1 — 6.7% / 93.3% / 15
- ??? 2 — 37.6% / 62.4% / 125

Figure 3. (b) Step 2: identify risk factors among remaining subjects.

addition to the findings shown in Figure 3, eating commercially prepared hamburgers or other ground beef outside the home is a risk factor for campylobacteriosis. Specific chicken variables such as those in Figure 2 are not risk factors for campylobacteriosis.

Compared to the results from the preliminary univariate analyses of Friedman et al,[2] our multivariate analyses show no significant effects (i.e. no direct causal effects in a causal graph) of eating undercooked poultry, drinking raw milk, eating chicken or turkey cooked outside the home, or eating raw seafood. The apparent effects of these variables in univariate analyses are fully represented and/or explained away in multivariate analyses by their associations with other variables. For example, the significant association between raw milk and risk (i.e. between RAWMILK and CACO) disappears after conditioning on no foreign travel and on no farm visits. On the other hand, our multivariate analysis fully confirms the suggestions from the Friedman et al study that commercially prepared food is a risk factor, while home-prepared food (including home-prepared chicken) is not. Analysis of specific variables such as touching raw chicken indicate that chicken handled, prepared or eaten at home does not increase (but may decrease) the risk of campylobacteriosis.

RE-ANALYSIS OF HAWAII CASE-CONTROL DATA

Effler et al[11] conducted a case–control study of campylobacteriosis risk factors in Hawaii. This data set provides a useful check in an independent data set of the conclusions from the CDC study. Key conclusions reported by Effler et al were as follows: 'In matched logistic regression analyses, eating chicken prepared by a commercial food establishment in the 7 days before case illness onset (adjusted odds ratio [AOR], 1.8; P=.03) and consuming antibiotics during the 28 days before illness onset (AOR, 3.3; P=.03) were significant independent predictors of illness.' These results were

based on particular selections of variables to include as potential explanatory variables, but without correcting for resulting variable-selection bias.[12]

To more thoroughly and correctly analyze the case–control data set of Effler et al, we obtained the same data via a Freedom of Information Act (FOIA) request, and then applied Bayesian Model Averaging (BMA)[13] to account for model uncertainty about what variables should be included as significant predictors of risk. The BMA methodology identified explanatory variables having a high posterior (i.e. conditioned on the data) probability of belonging in the model. This improves on earlier stepwise variable-selection techniques that do not quantify the probabilities that variables should be included in the model. Table 1 shows the main results. The first six variables were those selected in the original analysis by Effler et al. Most turned out to have a zero probability of inclusion as relevant explanatory variables based on BMA analysis; however, HAM was confirmed as a very probably significant risk factor. The next nine variables were dropped from the Effler et al model using stepwise variable selection. Of these, six actually turn out to have positive probabilities of inclusion based on the BMA analysis, with under-cooked (i.e. pink inside) chicken cooked outside the house a significant risk factor, while chicken cooked at home is a significant protective factor. The remaining variables considered in Table 1, including drinking un-

treated water and various restaurant-related variables, were assigned zero probabilities of inclusion in the BMA analysis.

The main conclusions from this re-analysis are as follows:

- Eating chicken at home is significantly associated with a decreased risk of campylobacteriosis (RR=0.6 in the original analysis of Effler et al). This confirms the results from the Friedman et al study and from our new analysis given above.
- Eating chicken or pink chicken in restaurants is a risk factor; that is, it is statistically significantly and positively associated with risk.
- No variable involving preparation or consumption of food at home is a risk factor.
- Prior antibiotic use is not a risk factor for campylobacteriosis, in contrast to the findings of Effler et al without using BMA.
- Having health insurance or belonging to a Health Maintenance Organization is a significant risk factor for reported CP, though this factor was not identified by Effler et al, and hence is not shown in Table 1.

The main results were also confirmed by classification tree analysis (not shown), to avoid possible dependence on the assumptions of the logistic regression model's

Table 1. Results of BMA analysis for case–control data of Effler et al[11]

Variables	Description	Inclusion[a] probability (%)	Sign
CHNCKN or RSTCKN	Consumed chicken from a restaurant in the past 7 days		
P4ABX	Consumed antibiotics in the past 28 days		
P4NTAC	Consumed medications to lower stomach in the past 28 days	25	+
OVNTKY or GRDTKY or FRZTKY or DELTKY or OTTKEY	Consumed turkey in the past 7 days		
HAM	Consumed ham in the past 7 days	94.1	
P7CTCKN	Had contact with a live chicken in the past 7 days		
P7ECKNOS	Chicken eaten outside the house		
PNCKN	Chicken eaten outside the house, pink inside	100	+
P7HMDCKN	Chicken eaten at home	98	−
HKORWCKN	Cooking raw chicken at home		
TCHWRCKN	Touched any raw chicken at home		
JKY	Beef jerky	47	−
STK	Steak	80.6	−
CTPUP	Contact with puppy	3.5	+
DIPUP	Contact with puppy with diarrhea	91.2	+
FSTFOOD	Number of fast-food meals in the past 7 days		
RSTRANT	Number of sit-down restaurant meals in the past 7 days		
"BOOLRST"= RSTRANT>0	Any sit-down restaurant food in the past 7 days		
P7ECKN	Consumption of any chicken		
MILK	Drinking unpasteurized milk		
DRUTRH20	Drinking untreated water		
IMUNEDIS	Immune disease		
P7OTISLE	Travel to another Hawaiian island		

[a]Blanks in this column indicate zero inclusion probabilities.

functional form. The above findings generally support those from the CDC data set.

RE-ANALYSIS OF RISK FACTORS FOR HUMAN FQ RESISTANCE

Smith et al[14] performed a case–control study among campylobacteriosis patients to determine risk factors for FQ-resistant strains of CP. Their main conclusions and interpretations are as follows:

> The proportion of quinolone-resistant *C. jejuni* isolates from humans increased from 1.3 percent in 1992 to 10.2 percent in 1998 (P<0.001). [Human] quinolone use could account for no more than 15 percent of the cases from 1996 through 1998 ... Molecular subtyping showed an association between resistant *C. jejuni* strains from chicken products and domestically acquired infections in Minnesota residents.
>
> CONCLUSIONS: The increase in quinolone-resistant *C. jejuni* infections in Minnesota is largely due to infections acquired during foreign travel. However, the number of quinolone-resistant infections acquired domestically has also increased, largely because of the acquisition of resistant strains

from poultry. The use of fluoroquinolones in poultry, which began in the United States in 1995, has created a reservoir of resistant *C. jejuni*.

This attribution of increases in FQ resistance among human CP isolates to consumption of FQ-exposed poultry (mainly chickens) raises a potential problem. Our epidemiologic results suggest that chicken consumption per se is not a significant risk factor for campylobacteriosis. It appears to be risky only in the context of restaurant dining, where other meats are equally associated with increased risk. Yet, if chicken were the main source of CP illness in humans (either directly or by cross-contamination of other foods), then it should lead to excess risk of campylobacteriosis even among people who prepare it at home. However, if chicken itself is not a significant carrier of CP to humans, then how can it be a significant carrier of FQ-resistant CP to humans?

To address this question, we obtained the original data of Smith et al and re-analyzed them using classification tree analysis and BMA. The main results (see classification trees in Figure 4) are as follows:

* The non-chicken factors that were individually statistically significantly associated with increased
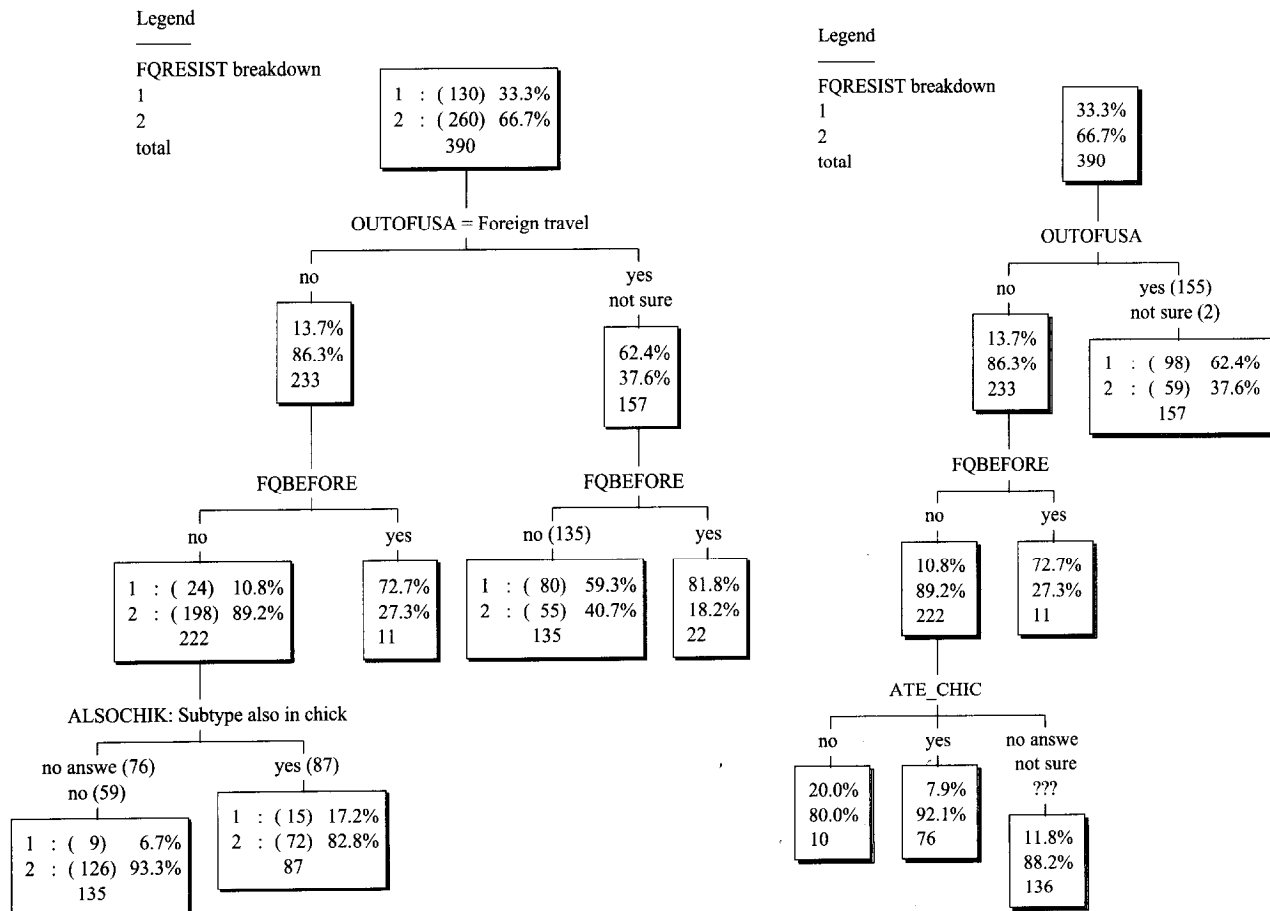
Figure 4. Classification tree analysis of FQ resistance in Smith data set.[14] Comparison of risk factors for FQ-resistant CP isolates (FQRESIST=1) in humans: eating chicken is not a risk factor, but multi-species subtype is.

risk of FQ resistance were travel (OUTOFUSA, OUTSTATE), prior use of FQs in human medicine (FQBEFORE), and drinking or swimming in untreated water (RAWWATER, SWIMMING).
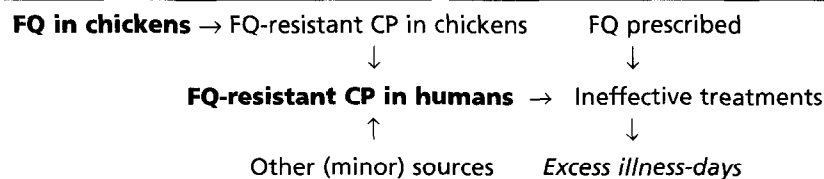
- RAWWATER and SWIMMING are not significantly associated with FQ resistance risk after conditioning on travel outside the USA. Foreign travel is positively associated with both those variables and with FQ resistance. It explains away the significant univariate associations between RAWWATER and SWIMMING and risk.

- Subtypes of CP that are found in both human and chicken isolates (denoted in the left panel of Figure 4 by the variable ALSOCHIK) are more likely to be FQ resistant than subtypes that appear only in humans.

- Eating chicken (ATE_CHIC in Figure 4) is non-significantly negatively associated with FQ resistance of human CP isolates. This variable does not appear in the tree unless forced in (which was done in Figure 4), as there is no significant relationship between chicken consumption and FQ resistance.

- We confirmed that chicken consumption is also unrelated to FQ resistance in the CDC data set given above. Classification tree analyses (not shown) indicate absence of any statistically significant associations between chicken variables and FQ resistance (CIPRES) among domestic CP cases in the CDC data set. There is also no significant association between FQ resistance in domestic adult cases and duration of diarrhea (DAYSDIAR). (The association is non-significantly negative.)
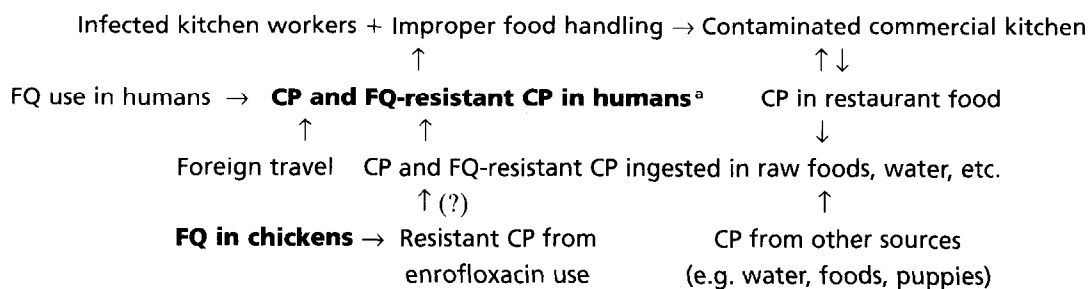
DISCUSSION

Figures 5a and 5b show two different alternative causal hypotheses about the relationship between FQ use in chickens and resulting human health risks. In Causal Model 1, chickens comprise the primary vehicle for conveying CP, and especially FQ-resistant CP, to human targets. In Causal Model 2, both FQ-responsive and FQ-resistant strains of CP originate from multiple sources. While chicken-derived CP may play some role in transmitting CP to people, e.g. among farm visitors having contact with live chickens, it is a relatively small contribution, not detectable in human data. The main vehicle transmitting CP to humans in the continental USA is contamination in commercial kitchens. Moreover, the contamination in question may come from human handling of food. It does not appear to be specifically chicken-derived (e.g. via cross-contamination of other foods by chicken in restaurant kitchens), as eating chicken in restaurants does not appear to be more associated with risk than eating other meats.

The epidemiologic evidence examined in this paper is generally not consistent with Causal Model 1 (the 'contaminated chicken' hypothesis). That chicken prepared at home is significantly negatively associated with risk in both univariate analyses (e.g. Figure 2) and in multivariate analyses based on classification trees and conditional independence (e.g. Figure 3) suggests that processing of chicken prior to retail is highly effective in eliminating most of the dangerous CP microbial load. Other vehicles must be primarily responsible for carrying CP to human targets. By contrast, the epidemiologic

(a) Causal model 1: Current Regulatory Paradigm ('Chickens transmit resistant CP' model)

FQ in chickens → FQ-resistant CP in chickens   FQ prescribed
↓   ↓
FQ-resistant CP in humans → Ineffective treatments
↑   ↓
Other (minor) sources   *Excess illness-days*

(b) Causal model 2: ('Restaurants transmit resistant CP' model)

Infected kitchen workers + Improper food handling → Contaminated commercial kitchen
↑   ↑↓
FQ use in humans → **CP and FQ-resistant CP in humans**[a]   CP in restaurant food
↑   ↑   ↓
Foreign travel   CP and FQ-resistant CP ingested in raw foods, water, etc.
↑ (?)   ↑
FQ in chickens → Resistant CP from   CP from other sources
enrofloxacin use   (e.g. water, foods, puppies)

Figure 5. (a) Causal Model 1: current regulatory paradigm ('chickens transmit resistant CP' model). (b) Causal Model 2: ('restaurants transmit resistant CP' model). [a]The health consequences of human CP infections are the same as in (a), but routine CP exposures in home-cooked chicken may contribute to acquired immunity instead of to infections.

data are generally consistent with Causal Model 2 (the 'contaminated restaurants' hypothesis). They also suggest the possibility that the comparatively low levels of CP contamination found in food cooked at home may tend to contribute to a protective effect, perhaps due to acquired immunity. Levels of CP contamination found in some restaurants may be more extreme, creating high CP doses that cause CP illness. These conjectures are consistent with the US data given earlier.

Tables 2 and 3 summarize potentially relevant findings from other countries, recently reviewed by Neimann and Engberg[15] (originally presented at a 1999 conference).

These findings generally support the conclusion that preparing and eating chicken at home is protective. Evidence from New Zealand shows an association between eating undercooked chicken and increased risk of CP illness. However, it is not known what other undercooked foods those who eat undercooked chicken might also tend to eat, or whether consumption typically takes place at home or in other settings (e.g. social gatherings, restaurants) that may carry high CP illness

risks. Therefore, this observation does not necessarily conflict with data from the UK and from the USA showing that handling raw chicken is a protective factor. Neimann and Engberg[15] identified eating in restaurants in Denmark as a protective factor, suggesting that the restaurant or commercial preparation effects that are so prominent in the USA are not necessarily present in all other countries. However, there is evidence from Mexico that a small number of restaurants with poor food preparation hygiene,[16] perhaps combined with restaurant workers who are asymptomatic but shed CP (see Tochin and Machado[17] for Brazil), may contribute to human CP exposures in other countries.

We are not aware of comparable studies in the USA with which to test and validate Causal Model 2. However, if relevant restaurant practices and contamination processes in at least some US restaurants are similar to those in these studies, then the possibility of frequent sporadic contamination due to unsafe food-handling practices and/or infected but asymptomatic restaurant workers ('carriers')—considered very unlikely in some previous risk assessments in the USA[1]—should be taken seriously.

If Causal Model 1 is correct, then strategies that reduce the microbial load of CP in chickens before they reach the consumer's kitchen will be effective in reducing the risk of human CP illness. Reducing FQ-resistant CP in and on chickens reaching humans can then prevent or reduce FQ-resistant CP cases. In Causal Model 2, by contrast, eliminating chicken-borne CP loads before they reach kitchens may have little or no impact on human health. The contribution of chicken-borne CP to human illnesses is postulated to be minor to non-existent. There may even be a protective effect, e.g. due to acquired immunity. Rather, the focus of risk management efforts should be on kitchens where unsafe food preparation, handling or hygiene contribute enough CP to served food to increase CP illness risks among customers.

Table 2. International evidence on protective factors for CP illness

Protective factor	OR	Country
Eating chicken	<1	USA
Eating chicken at home	0.36	New Zealand
Whole chicken	0.59	New Zealand
Chicken prepared at home	0.67	New Zealand
Baked/roasted chicken	0.75	New Zealand
Chicken purchased frozen	0.61	New Zealand
Chicken leg	0.55	Denmark
Preparing main meals	0.9	UK
Handling raw chicken	0.41	UK

Source: Neimann and Engberg,[15] Tables 1 and 2, p. 153.
OR, odds ratio.

Table 3. References on chicken and human CP risk outside the USA

Findings	Country	Reference
'Risk of campylobacteriosis was strongly associated with recent consumption of raw or undercooked chicken (matched odds ratio 4.52, 95% confidence interval 2.88, 7.10). There was also an increased risk with chicken eaten in restaurants (matched odds ratio 3.85; 2.52, 5.88).'	New Zealand	18
'Recent consumption of baked or roasted chicken seemed to be protective.'	New Zealand	18
'Handling any whole chicken in the domestic kitchen that had been bought raw with giblets [was] significantly associated with a decrease in the risk of becoming ill with campylobacter.'	UK	19
'Eating any dish cooked from chicken of this type in the home (OR 0.41–0.44; CI 0.24, 0.79) [was] significantly associated with a decrease in the risk of becoming ill with campylobacter.'	UK	19
'Eating poultry at a friend's house (OR=3.18, CI 1.0, 10.73, p=0.03), at a barbecue (OR=3.00, CI 0.99, 9.34, p=0.03) or eating undercooked chicken (OR=4.94, CI 1.03, 23.62, p=0.05) was a risk [for CP illness].'	New Zealand	20
'Eating at home was protective (OR=0.36, CI 0.14, 0.9, p=0.02).'	New Zealand	20

OR, odds ratio.

CONCLUSIONS

This paper has re-analyzed available case–control data on campylobacteriosis using statistical models and methods that do not involve the usual assumption that chicken is a primary source of CP in humans. The results suggest that current regulatory assumptions about the causes of campylobacteriosis must be revised. We have confirmed and extended the results of Friedman et al[2] on the protective effects of home-cooked chicken (or, more generally, home-cooked meals), as well as their findings that chicken (and other meats) in restaurants are risk factors for CP. This leads to a proposed new framework for understanding and interpreting CP data, summarized in Causal Model 2 (Figure 5b.)

The sources of FQ-resistant CP in people remain unclear, but they do not appear to be associated with chicken consumption in the available data of Smith et al[14] or the CDC.[2] International evidence that asymptomatic human carriers of campylobacteriosis are found among restaurant kitchen staff in other countries,[17] and that a few restaurants with poor hygiene contribute disproportionately to CP microbial loads in customer food,[16] suggest a need for comparable studies of restaurant-transmitted CP illness in the USA, especially in states such as California that have relatively high CP illness rates.

The main practical implications of this work are that risk management strategies that focus on restaurant kitchen hygiene rather than on chickens may be much more productive in preventing human CP illnesses. Attempts to reduce FQ-resistant isolates among human campylobacteriosis patients by banning FQ use in chickens may be unsuccessful, since there does not appear to be a detectable causal link between them. Instead, the most beneficial strategy to protect human health may be to improve restaurant hygiene and to reduce the overuse of FQs in human medicine, both of which have been shown to have detectable impacts on human health.

REFERENCES

1. FDA-CVM. Risk assessment on the human health impact of fluoroquinolone resistant Campylobacter associated with the consumption of chicken. US Food and Drug Administration, Center for Veterinary Medicine, 2000. http://www.fda.gov/cvm/antimicrobial/ra/risk.html
2. Friedman C, Reddy S, Samual M, et al. Risk factors for sporadic *Campylobacter* infections in the United States: a case–control study on FoodNet Sites. In: 2nd International Conference on Emerging Infectious Diseases, Atlanta, GA, July 2000. Atlanta: CDC, 2000, http://www.cdc.gov/foodnet/pub/iceid/2000/friedman_c.htm
3. CDC-FoodNet. Population survey atlas of exposures: 1998–1999. Atlanta: Centers for Disease Control and Prevention. Foodborne Diseases Active Surveillance Network (Food Net), 1999.
4. CDC-FoodNet. 1998 Surveillance Results Final Report.
Centers for Disease Control and Prevention, National Center for Infectious Diseases, Division of Bacterial and Mycotic Diseases, Foodborne and Diarrheal Diseases Branch, 1998. http://www.cdc.gov/foodnet/annuals.htm
5. CDC-FoodNet. 1999 Surveillance Results Preliminary Report. Centers for Disease Control and Prevention, National Center for Infectious Diseases, Division of Bacterial and Mycotic Diseases, Foodborne and Diarrheal Diseases Branch, 2000. http://www.cdc.gov/foodnet/annuals.htm
6. Greenland S. Ecologic versus individual-level sources of bias in ecologic estimates of contextual health effects. Int J Epidemiol 2001; 30(6):1343–1350.
7. Biggs D, de Ville B, Suen E. A method of choosing multiway partitions for classification and decision trees. J Appl Statistics 1991; 18(1):49–62.
8. Breiman L, Friedman JH, Olshen R, Stone CJ. Classification and regression trees. Belmont, CA: Wadsworth Publishing (now Chapman & Hall/CRC Press), 1984.
9. Glymour C, Cooper CF. Computation, causation, and discovery. Cambridge, MA: AAAI Press and MIT Press, 1999.
10. Pearl J. Causality: models, reasoning, and inference. New York: Cambridge University Press, 2000.
11. Effler P, Leong MC, Kimura A, et al. Sporadic *Campylobacter jejuni* infections in Hawaii: associations with prior antibiotic use and commercially prepared chicken. J Infect Dis 2001; 183(7):1152–1155.
12. Burnham KP, Anderson DR. Model selection and inference. New York: Springer, 1998.
13. Raftery AE, Madigan D, Hoeting JA. Bayesian model averaging for linear regression. J Am Statist Assoc 1997; 92:179–191.
14. Smith KE, Besser JM, Hedberg CW, et al. Quinolone-resistant *Campylobacter jejuni* infections in Minnesota, 1992–1998. Investigation Team. N Engl J Med 1999; 340(20):1525–1532.
15. Neimann J, Engberg J. Exposures being protective for Campylobacter infection. Paper V in Neimann J, 2001. The epidemiology of sporadic campylobacteriosis in Denmark investigated by a case control study and strain characterization of patient isolates. PhD thesis. Copenhagen, Denmark: The Royal Veterinary and Agricultural University, Department of Animal Science and Animal Health, Danish Zoonosis Center, 2001.
16. Quinones-Ramirez EI, Vazquez-Salinas C, Rodas-Suarez OR, Ramos-Flores MO, Rodriguez-Montano R. Frequency of isolation of Campylobacter from roasted chicken samples from Mexico City. J Food Prot 2000; 63(1):117–119.
17. Tosin I, Machado RA. Occurrence of Campylobacter spp among food handlers in hospital kitchens in urban areas of the southern region of Brazil. Rev Saude Publica 1995; 29(6):472–477.
18. Eberhart-Phillips J, Walker N, Garrett N, et al. Campylobacteriosis in New Zealand: results of a case–control study. J Epidemiol Community Health 1997; 51(6):686–691.
19. Adak GK, Cowden JM, Nicholas S, Evans HS. The Public Health Laboratory Service national case–control study of primary indigenous sporadic cases of Campylobacter infection. Epidemiol Infect 1995; 115(1):15–22.
20. Ikram R, Chambers S, Mitchell P, Brieseman MA, Ikam OH. A case control study to determine risk factors for Campylobacter infection in Christchurch in the summer of 1992–3. NZ Med J 1994; 107(988):430–432.

PANEL DISCUSSION

M. Ginevan: Have you tried splitting the data into urban versus rural?

T. Cox: No, although somebody suggested today that this could be worthwhile. I simply excluded those who lived on or visited a farm, because there is a known association with risk of campylobacteriosis. Most of what I have shown you starts with people who don't have any obvious cause of campylobacteriosis. My analyses look at risk factors among that subset.

M. Ginevan: I wasn't thinking of that, but of difference in lifestyle. Who is usually eating out? People in the city. Who is usually cooking their food at home? People in less urban areas. The latter group has an acquired immunity because of multiple exposures, and so the risk factor is not the restaurant. The difference you are seeing is the response of the host to an exposure.

T. Cox: People who live on farms have a higher risk of campylobacteriosis than people who don't, so I wonder if that hypotheses is correct.

M. Ginevan: The difference arises through people who visit.

T. Cox: Visitors are also in this data set, and people who live on farms also have a higher risk. If you live on a farm, you have a 60% chance of being a case instead of a control; if you don't live on a farm, you have a 46% chance, conditional on you not visiting a farm, not drinking raw milk, not drinking raw water, and not traveling outside the USA. Living on and visiting a farm are two separate variables. People who live on farms are more likely to swim in and drink raw water, if you look at the correlations among these factors. I think a potential contribution of classification tree analysis is to go beyond just looking at the direct marginal associations. What one should ask is, after we correct for the other factors that we know about, what is the influence of other factors, singly and in combination?

M. Ginevan: Much of what you have said has illustrated the difficulty of separating confounders from causal factors in case–control data. For example, you find that living on a farm and drinking raw milk are risk factors. Yet, someone living in a city can't find raw milk. So, is farm living or raw milk consumption the risk factor? They are hard to disentangle.

T. Cox: I agree with that. In fact, my analysis did look at cause-and-effect relationships and carefully separated direct from indirect causes. I extracted a causal graph from the data using a program (the 'PC algorithm' from causal graph modeling). This program doesn't know what any of the variables mean, but it produces a causal graph that points to most of the same conclusions as the classification trees I have described. For example, it shows that dining out in fast-food and what the CDC calls slow-food restaurants are associated with each other and with risk of campylobacteriosis. Causal graph modeling is a much more sophisticated and useful kind of analysis than just identifying factors that are statistically associated with risk.

M. Pasternack: Do you have any data on nursing homes or summer camps?

T. Cox: I don't have data on those groups. I have read about outbreaks in both settings.

R. Carnevale: An important thing to remember is that if you want to get your name in the newspaper, you can talk about getting infections from animals. If you want to get a more prominent mention in the newspaper, you can mention *Salmonella*. If you want to get close to the front page, you can mention antibiotics and animals. If you want to get on the front page, you can mention the use of fluoroquinolones in animals and subsequent human infection.

T. Cox: I think, to be fair to the newspaper editors, that Causal Model 1 is a very compelling commonsense story. In this story, poultry act as a conveyor belt that carries *Campylobacter* through an imperfect screening process to the consumer, and people are getting sick because of it. I think this story has all the right elements from a risk communication point of view to motivate outrage and action. It grab's people's attention and excites them. I just don't see much evidence for it in the data–it is exciting, but does not seem to be true.

R. Carnevale: If you talk about fluoroquinolone resistance being a function of chicken consumption, then you are going to get a lot more attention paid to your paper than you would otherwise.

T. Cox: If you take a pure public health perspective, and ask what actions we can take to prevent the greatest number of illness-days or total cases of *Campylobacter* infection, then the whole fluoroquinolone issue is largely irrelevant. We are talking about a small fraction of 1% of all cases. If the chicken-as-conveyor belt model were right, then a focus on reducing microbial load at the processing plant could provide a 600-fold greater reduction in risk than eliminating fluoroquinolone use on the farm. Obviously, development of fluoroquinolone-resistant strains is currently a big news item and huge focus of political attention, but it is a very minor component of the total public health problem.