ORIGINAL

UNITED STATES OF AMERICA
BEFORE THE FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

In the Matter of:	
Enrofloxacin for Poultry: Withdrawal of Approval of Bayer Corporation's New Animal Drug Application (NADA) 140-828 (Baytril)	FDA DOCKET NO. 00N-1571

03 MAY -9 P1:07

Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland

Wednesday, April 30, 2003

THE HEARING in the above-entitled matter commenced at 9:30 a.m., pursuant to notice.

BEFORE:

DANIEL J. DAVIDSON, Administrative Law Judge

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00N-1571

~~TR 3~~
TR 11

APPEARANCES:

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C O N T E N T S

P R O C E E D I N G S

JUDGE DAVIDSON: We are on the record.

Do we have any preliminary matters from the parties?

MS. ZUCKERMAN: No, your Honor.

MR. NICHOLAS: No, your Honor.

MR. KRAUSS: No, your Honor.

JUDGE DAVIDSON: Well, I have one myself. As you know, I think I have said before, the record in this proceeding is rather large. It contains an awful lot of things which I feel are duplicative and some of which are unnecessary.

I've reviewed my notes from the last couple of days and I assume everyone -- counsel all have copies of the joint stipulations, the revised joint stipulations. And my notes indicate that too many questions have been asked of witnesses on the stand that are already covered by the joint stipulations.

Now, that just adds to a voluminous record that I don't need. I have enough problem going through this record. Now, I'm not going to say -- of course the cross examination this point has been conducted by

Bayer but it's not limited to the cross. Some of the redirect has done the same kind of things.

So I'm giving you fair warning that if I see questions asked that are covered by joint stipulations and it continues, it will violate my original warning that I want cross examination to be conducted efficiently and succinctly, not to burden the record with unnecessary questions, unnecessarily information.

So if it continues and I notice more than one question that's already covered by joint stipulations, you run the risk of having your cross examination terminated.

MR. KRAUSS: Your Honor, may I address that just briefly?

JUDGE DAVIDSON: Yes.

MR. KRAUSS: Thank you, your Honor. Gregory Krauss on behalf of Bayer.

In some instances, the witness's testimony may somewhat contradict a joint stipulation, so would we be allowed to address --

JUDGE DAVIDSON: No, because you have -- unless it's preliminary to getting the witness to

change his testimony. But if it's in the record as a joint stipulation, that's evidence. The witness can say what he wants to say. You gentlemen and ladies stipulated that that's the evidence in the case.

MR. KRAUSS: That's right, your Honor. Thank you.

JUDGE DAVIDSON: Okay. All right. I think we're ready for Dr. Angulo.

MS. ZUCKERMAN: Your Honor, the Center for Veterinary Medicine would like to call Dr. Angulo to the stand.

Whereupon,

FREDERICK ANGULO

was called as a witness and, having been duly sworn, was examined and testified on his oath as follows:

JUDGE DAVIDSON: Please be seated. Give your full name and address to the reporter.

THE WITNESS: My name is Frederick James Angulo. My address is 2520 Oak Crossing Drive, Decatur, Georgia 30033.

MS. ZUCKERMAN: Your Honor, may I approach the witness?

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JUDGE DAVIDSON: Certainly.

MS. ZUCKERMAN: I'm handing the witness Exhibit G-1452.

DIRECT EXAMINATION

BY MS. ZUCKERMAN:

Q Dr. Angulo, do you recognize this?

A I recognize this.

Q Would you please identify it?

A This is my direct witness testimony and its attachments ~~attachment~~.

Q Would you please turn to page 17? Is that a copy of your signature at the bottom of the page?

A This is a copy of my signature.

Q Have you reviewed your testimony since you signed it?

A Yes.

Q Is there anything that you would like to correct in your testimony or in any attachment to your testimony?

A I would like to make a correction on page 9 of my testimony.

Q Would you please explain what that correction

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is?

A On page 9, line number 48, where it says the 12-month population-based case-control study was conducted in the seven FoodNet sites; Connecticut, Georgia, Minnesota, Oregon, and selected counties in California, Maryland, and New York, that's an imprecise statement.

It should read it was conducted in seven FoodNet sites, Georgia, Minnesota, Oregon and selected counties in California, and the rest. It was not -- so --

Q Is there anything else?

A I'd like to correct on page 10 -- excuse me -- on page 8 -- pardon me.

I'd like to correct on page 8, line 17, when we talked about the proportion of ~~jejune~~ jejuni isolates resistant to Ciprofloxacin, the variation from year to year in between sites should -- incorrectly states at the end of that statement on line 17, 30 percent in Connecticut and Georgia in 2001. That clause -- that end of that sentence should say 30 percent in Connecticut in 1999.

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Q Is there anything else?

A I'd like to add for clarification that although my witness testimony reference -- or statement is correct, for clarity, on attachment number 3, the risk -- the case control study draft manuscript by Cindy Friedman, that there are a coup -- that there are -- an inversion in both the abstract and in the text, although the table is correct, and I cite the table in my testimony so my testimony is correct.

But just for clarity, on page 3 of the abstract in the middle where it states in parentheses adjusted odds ratio, the second adjusted odds ratio of 1.7 should actually be 2.5 and the third adjusted odds ratio should be 1.7 instead of 2.5. And it is the same correction in the text.

Q And what page is that in the text?

MR. KRAUSS: Your Honor --

THE WITNESS: That's on page 10 in the text. The last paragraph of page 10 in the text.

MR. KRAUSS: Your Honor, the witness is correcting an attachment to his testimony that he didn't ~~offer~~ author? I don't understand that.

JUDGE DAVIDSON: I don't understand it, either. Could you explain that? Did you author the attachment?

THE WITNESS: I'm a member of the -- my branch authored that attachment. I cited -- it's from our team and --

JUDGE DAVIDSON: Did this error occur before it was published, after it was published? When did the mistake occur in the attachment, if it is a mistake?

THE WITNESS: The attachment is a draft manuscript that's going through CDC clearance and when it was in the clearance process, we detected this error which I only raise because in the -- as I read through the commentary of my witness testimony, there was an issue raised about this error. So for clarity I thought I would demonstrate -- agree with this correction. My written testimony --

JUDGE DAVIDSON: I understand your written testimony already has that information in it. I don't think you can correct the attachment unless it's something that you personally authored by yourself.

I'll give you an opportunity, which I've

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already done, I think, to explain what happened and why there's a difference, and that's as far as you can go. But you can't correct the attachment, okay?

THE WITNESS: Okay.

JUDGE DAVIDSON: I think he's already explained it. If you want to ask him another question about it, feel free.

MS. ZUCKERMAN: Those were the only questions.

BY MS. ZUCKERMAN:

Q Anything else, Dr. Angulo?

A No, thank you.

Q Thank you, Dr. Angulo. Dr. Angulo is now ready for cross examination.

JUDGE DAVIDSON: Mr. Krauss, you may proceed.

MR. KRAUSS: Thank you, your Honor.

CROSS EXAMINATION

BY MR. KRAUSS:

Q Dr. Angulo, good morning.

A Good morning.

Q My name is Gregory Krauss. I represent Bayer Corporation. Before we get started, can I just set one ground rule, that would you wait ~~till~~ until I finish my

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questions before you start to answer and I will wait until/~~till~~ you finish your answer before I start the next question, as I'm sure Madam Court Reporter will appreciate that.

Is that okay?

A Yes.

JUDGE DAVIDSON: As long as we're setting ground rules, you also have the opportunity to explain your answer when counsel wants a yes or no. You can explain the yes or no before he asks the next question -- he or she.

Go ahead. Proceed.

MR. KRAUSS: Thank you, your Honor.

BY MR. KRAUSS:

Q Dr. Angulo, you work for the Centers for Disease Control and Prevention, don't you?

A Yes.

Q And what is your title there?

A I am a medical epidemiologist. That's my position title.

Q You're the chief of a certain branch, aren't you?

A That's correct. My task is I'm the chief of the Foodborne Disease Active Surveillance Network, FoodNet, and the National Antimicrobial Resistance Monitoring System, NARMS, and also Global Salmonella Surveillance System, the unit that covers those three activities.

Q Now, CVM's counsel gave you a copy of your testimony and directed you to the signature page, which was page 17. You signed that on or about December 6, 2002, didn't you?

A I believe I did.

Q And at the time you signed it, you declared that you were signing it under penalty of perjury, that the foregoing is true and correct, didn't you?

A Yes.

Q Did you draft your testimony yourself?

A Yes, I did.

Q All of it?

A I drafted the testimony myself, in its entirety.

Q I understand from your testimony you're a veterinarian, is that right?

A That is correct.

Q And you have a Ph.D. in epidemiology?

A Yes.

Q And you're the lead scientist at the CDC on the epidemiology of antimicrobial resistance in foodborne bacteria. Is that right?

A Yes.

Q And you've testified that you've conducted extensive research on antimicrobial resistance in foodborne pathogens. Isn't that right?

A Yes.

Q And in fact, in your testimony you describe yourself as a veterinary epidemiologist, right?

A Yes.

Q This morning you said you were a medical epidemiologist. What's the difference?

A Medical epidemiologist is the job series title or position I'm assigned to, which can -- veterinarians can apply to and physicians can apply to and Ph.D. epidemiologists can apply to. I'm in a billet of a medical epidemiologist.

Q You're not a medical doctor, are you?

A No.

Q And you do not have any advanced degrees in microbiology, do you?

A Let me just -- excuse me. Your question was are you not a medical doctor, are you? And the answer is yes, I am not a medical doctor. I'm sorry. I said no.

JUDGE DAVIDSON: That's the previous question.

THE WITNESS: The previous question was -- sorry. Your question --

MR. KRAUSS: Let me ask it again.

THE WITNESS: Yes. Thank you.

BY MR. KRAUSS:

Q You are not a medical doctor, are you?

JUDGE DAVIDSON: How about are you a medical doctor?

MR. KRAUSS: Thank you, your Honor.

BY MR. KRAUSS:

Q Are you a medical doctor?

A No.

Q Do you have any degrees in -- advanced degrees in microbiology?

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A No.

Q Do you have any advanced degrees in veterinary microbiology?

A No.

Q Are you a poultry veterinarian?

A I am not. I have a master's in ~~microbiology~~ biology with an emphasis in microbiology from the University of San Francisco in 1979.

Q Okay. I asked you whether you were a poultry veterinarian. Are you?

A No.

Q Are you a diplomate of the American College of Poultry Veterinarians?

A No.

Q Are you a member of the American Association of Avian Pathologists?

A Yes, but my dues are past due.

(Laughter.)

MR. KRAUSS: Let me show you this invoice.

(Laughter.)

BY MR. KRAUSS:

Q Now, Dr. Angulo, let me go over some terms

with you.

MR. KRAUSS: I know I did this with the prior witness, but, your Honor, I want to make sure that this witness and I can come to an understanding of certain epidemiology terms, if you don't mind.

JUDGE DAVIDSON: Go ahead.

BY MR. KRAUSS:

Q As an epidemiologist, would you agree that an incidence rate for a disease is that number of cases over a defined period of time in a defined population?

A I would not agree with that statement because I don't agree with the term incidence rate. I understand the term incidence and I agree that the incidence is the defined number of cases over a population for a specific period of time. That's incidence. I would not call it incidence rate.

Q So if a textbook on epidemiology defined incidence rate as the number of cases over a defined time period in a defined population, that would be wrong, in your view?

A It gets to an issue of terminology and in most modern epidemiology textbooks, which at this Ph.D.

program where I was trained, the textbook was by Rothman and by Greenland, and my advisor was Sander Greenland.

And we stuck very closely to a strict terminology and in that terminology, incidence is a term but incidence rate is redundant because of course incidence -- it means rate. So you wouldn't -- so incidence is a specific epidemiological term. Incidence rate, which exists in some old textbooks, is not the modern term.

Q I see. So you don't have a problem with the definition. You just don't like to add on the word rate as being extraneous. Is that right?

A That's correct. It's not a precise term.

Q Okay. And in your work in terms of studying foodborne illness, would you agree that incidence is often reported as cases per 100,000 per year for foodborne illnesses?

A Yes.

Q And in your work, annual incidence are used by epidemiologists to track trends over time, aren't they -- or isn't it?

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A Would you please ask a more precise -- again, it's also -- I -- the terminology annual incidence is also not a precise epidemiological term because incidence is a specific -- is number of cases in a period of a time which can be a year or it can be 10 years. So we don't tend to use the term annual incidence. We talk about incidence in a specific period of time.

So that's a terminology question. We use incidence to compare changes -- to compare an incidence of today's ~~date~~ data versus a previous year's ~~date~~ data which, you must be careful because that's not necessarily a trend analysis.

A trend analysis is actually -- has also a jargon or epidemiological term -- there's a statistical science or approach of trend analysis. So if -- so we definitely use incidence to track changes in disease over time, but I would not say we use incidence necessarily to track a trend because that implies trend analysis, which actually is a -- again, is a terminology issue.

Q And that's why we're going through this, Dr.

Angulo, so I can make sure we get -- that I get the terminology down.

So you would agree with me that incidence is used by epidemiologists to track trends over time?

A No.

Q But not annual incidence.

A No. I'm sorry. I would agree that incidence is used to track changes in disease between certain times, yes, but I would not use the word trend unless we introduce the science -- or the approach of trend analysis.

Trend, as I -- trend is -- trend implies trend analysis, which is actually a whole approach to trying to look at the changes in incidence over time and we don't -- so I have to disagree with your statement. But I agree that we use incidence to track changes in disease.

Q Okay. That's good. Thank you. Let me ask you about another term. Confounding. Now, let me make sure I get this right and that you and I can come to an understanding of what this concept in epidemiology is, okay?

Would you agree that confounding is the distortion of an exposure disease association by the effect of some third factor?

A That's an overly broad statement because I can influence -- I agree that a confounder will have that -- can have that effect but there's other things that can cause that effect, also. The distortion between exposure and outcome can be distorted by the effect of modifiers or co-variates. In other words, a strong risk factor for the outcome can distort the impact from exposure.

So that is -- I wouldn't use the definition you've provided as a precise definition of confounding or confounder.

Q Well, let me make sure that I got it right out of the textbook. Are you familiar with Field Epidemiology by Gregg?

A It was not the textbook that we studied. I don't believe it would be judged in schools of public health as a lead textbook.

Q Have you heard of it?

A I have heard of it, yes.

Q Do they use it at the CDC?

A Some groups may. We tend to use Rothman and Greenland, which is Modern Epidemiology, which is the textbook at the University of California - Los Angeles, and it's the one that's most widely used, in my understanding.

Q So when this textbook says confounding is a distortion of an exposure disease association by the effect of some third factor, you don't agree with that definition? Do you want to see it?

A I don't believe that's a definition. That's just stating what confounding can occur but that's not a precise definition of confounding.

Q But do you agree that confounding is a distortion in the exposure disease association by a third factor?

MS. ZUCKERMAN: Objection, your Honor. Asked and answered.

JUDGE DAVIDSON: I'll let him answer. Go ahead.

THE WITNESS: I agree it can have that effect. I do not agree that it is solely related -- has that

impact -- has that consequence. As I explained, there's other factors that can cause that distortion, not confounders.

BY MR. KRAUSS:

Q And what are those other factors?

A Effect modification. Effect modifiers can distort the effect between exposure and outcome.

Q Anything else?

A I think a strong independent risk factor, not necessarily effect -- again, effect modification has a very strict epidemiological definition but there are also just strong co-variates. In other words, a variable that's strongly associated with an outcome, that variable can influence the association between the exposure and the outcome.

Q So, so far, if I've got this right, you've got three things that can affect or distort an exposure disease association, right? It can be, by your view, the confounder can do that --

A Yes.

Q -- an effect modifier can do that --

A Yes.

Q -- and a strong co-variate will do that.

A That is correct. But the first two are much more -- have much more influence than the latter. But yes, that's correct.

Q Is there anything else in your view that can distort the exposure disease association other than what you just mentioned?

A There's many things that can distort an exposure disease association. Inherent bias in the way that you classify either the outcome or the -- or not just even inherent. Bias in the way you classify the exposure and classify the outcome, either/or can influence the association between the exposure and the outcome.

Q Would that include biases introduced by data collection methods, for example?

A Certainly they could.

Q Okay. Now, I gave you what I thought as a non-epidemiologist my definition of confounder was. I'd like to get your definition.

What is a confounder, Dr. Angulo?

A Well, a confounder -- in my mind it can be a

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ital, a priori

apriority confounder, a confounder that we understand is expected to be present in a data set and that can -- and also you can have potential confounders that might occur in the data set that may not necessarily be -- that may not be apparent before the analysis.

But regardless, in both instances, confounder is -- to be a confounder, a confounder has to be an independent risk factor for the outcome and associated with the exposure. To actually show up in a data set, it would have to have both those associations, independent risk factor for the outcome associated with the exposure.

Q Okay. So, now, I'm following you and learning here. A confounder is a third factor that is an independent risk factor for the outcome you're studying and is associated with the exposure. Is that right, Dr. Angulo?

MS. ZUCKERMAN: Objection, your Honor. Asked and answered.

JUDGE DAVIDSON: It's all right. Let him answer.

THE WITNESS: That's correct.

BY MR. KRAUSS:

Q Would you agree with me that in epidemiology, the fact that an outcome is associated with an exposure does not mean that the outcome is caused by the exposure?

A Caused -- causation has also a very strict epidemiological definition and there actually is a whole approach to trying to create enough -- to create the body of evidence that would allow someone to make the judgment of causation.

Q Is that known as causal analysis?

A No.

Q What is it known as?

MS. ZUCKERMAN: Objection, your Honor. It seems like the witness was interrupted when he was giving his answer.

JUDGE DAVIDSON: Well, he has the right to explain, as I said before.

Go ahead and explain your answer.

THE WITNESS: Could you repeat the question? I was trying to answer so --

BY MR. KRAUSS:

Q Let me go back to my original question, Doctor.

A Thank you. Thank you.

Q Would you agree with me that in epidemiology, just because an outcome is associated with an exposure does not mean that the outcome is caused by the exposure?

A Very good. Yes. I would agree that -- again, the problem is the term in causation in that I agree that a central feature of agreeing on causation is having studies that show an association between exposure and the outcome.

I also agree that it's not sufficient to just have a single piece of epidemiological evidence that is -- that demonstrates an association between an exposure and outcome that most -- to conclude that it is in fact -- that that exposure caused that outcome.

What -- the judgment of causation, and it is a judgment, is based upon a body of evidence that allows people to then conclude or to have their judgment that there is a causation involved.

JUDGE DAVIDSON: Excuse me. I think you read too much into the question, okay? As I recall, the question was is it necessarily -- if there's an association, does it necessarily equate with causation. It seems to me -- I mean, I'm not a scientist, but it seems kind of simple. You know, when you use the word "necessarily," that means, well, of course not.

That doesn't mean that the rest of your answer isn't correct, but I don't think that was part of the question.

MR. KRAUSS: Thank you.

THE WITNESS: All right.

BY MR. KRAUSS:

Q So, Dr. Angulo, when epidemiologists conduct case control studies and study risk factors and they find an association between an exposure and an outcome and they define -- and it's an association, that doesn't mean it's a cause, does it?

A It's a -- it does not mean it's a cause. It's part of the evidence necessary to judge it as being a cause but it's not sufficient in and of itself to judge causation.

Q Let me get back to confounding for just a minute. This case is about the use of Enrofloxacin in poultry, isn't it?

A Yes.

Q And whether the use of Enrofloxacin in poultry is having some human health impact on the United States population, right?

A Yes.

Q And whether it has an adverse human health impact on the United States population, right?

A I believe so.

Q And it's about whether use of Enrofloxacin in poultry is creating resistant -- Fluoroquinolone resistant Campylobacteriosis or -- I'm sorry -- Fluoroquinolone Campylobacter that can be transferred to humans and cause resistant -- Fluoroquinolone resistant Campylobacteriosis in humans, right?

A Correct.

Q Campylobacteriosis is a gastrointestinal disease, right?

A In most cases, yes. It also can cause blood stream infections, but in most cases, yes.

Q Those are rare, aren't they?

A There are hundreds of cases a year in the United States.

Q But compared to the total number of Campylobacter infections, blood stream infections are rare, aren't they?

A Because there are millions of cases of Campylobacter.

Q Millions or 1.4 million?

A There are millions -- there are over -- there are millions of cases of Campylobacter. There's 1.4 -- we estimate that there are 1. -- with the latest data, 1999, that there are 1.4 million cases a year. There are millions of cases.

JUDGE DAVIDSON: Let's not quibble.

THE WITNESS: I didn't say number of years.

MR. KRAUSS: Thank you, your Honor.

BY MR. KRAUSS:

Q And the adverse human health impact of a Fluoroquinolone resistant Campylobacter infection, if I understand CVM's position, is a longer duration of diarrhea in a resistant infection versus a susceptible

infection, right?

A That's one of the adverse effects.

Q And there have been some studies that you referred to in your testimony, for example the Kirk Smith study that you say supports the idea that resistant infections will result in a longer duration of illness, right?

A There are reports -- I have most knowledge of the study that CDC did but there was also a study in Kirk Smith that -- Kirk Smith study in Minnesota that demonstrated a longer duration of diarrhea associated with a resistant infection.

Q Okay. Now, you've testified that a confounder is an independent risk factor for the outcome and also something that's associated with the exposure, right?

A Independent risk factor for the outcome and associated with the exposure, yes. That's a definition of confounder.

Q Now, in the Kirk Smith study, if -- this is a hypothetical -- if foreign travel -- persons in the study who had undertaken foreign travel -- is an independent risk factor for the outcome in resistant --

Fluoroquinolone-resistant Campylobacter infection, and foreign travel is also associated with -- strike that.

MR. KRAUSS: Your Honor, I need to start over on that one.

JUDGE DAVIDSON: Go ahead.

BY MR. KRAUSS:

Q If foreign travel is an independent risk factor for the outcome, a longer duration of diarrhea, and foreign travel is also associated with the exposure for Fluoroquinolone-resistant Campylobacteriosis, would that be a confounder?

A Would you mind rephrasing the question, since it's hypothetical, out of the Kirk Smith context?

Q Sure. Take it out of --

A Because -- thank you.

Q In general, in a case-controlled study that's looking at duration of diarrhea, okay, if foreign travel is associated with both resistant infections and longer duration of illness, would you agree that that would be a confounder?

A If international travel is associated as an independent risk factor for the outcome of interest,

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duration of diarrhea and is associated with the exposure of interest, Fluoroquinolone resistance, I would say international travel is a confounder and needs to be -- would need to be addressed.

Q Now, your testimony discusses FoodNet and that's the Foodborne Diseases Active Surveillance Network, isn't it?

A Yes.

Q And FoodNet conducts surveillance or clinical laboratory isolations of certain enteric bacteria; isn't that right?

A That's correct.

Q And what's an enteric bacteria?

A Enteric means intestinal tract and so it's bacteria that are largely in the intestinal tract. And those are the ~~grahms~~ gram negative bacteria which include the E. coli and Campylobacter and Salmonella.

Q Okay. So FoodNet surveillance includes Campylobacter, doesn't it?

A Yes.

Q And it includes Salmonella, right?

A Yes.

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Q And E. coli?

A Yes, E. coli -- pardon me -- ~~Chicatoxin~~ shiga toxin-producing E. coli of which O157 is one type. It's not all E. coli.

Q And ~~Chagilla~~ Shigella?

A Yes.

Q And others, right?

A Yes.

Q And NARMS is National Antimicrobial Resistance Monitoring System for Enteric Bacteria. Is that right?

A Yes.

Q And that monitors antimicrobial resistance among foodborne enteric bacteria, right?

A Yes.

Q And Campylobacter is included in that, right?

A Yes.

Q And Salmonella and E. coli and ~~Chagilla~~ Shigella, right?

A Yes.

Q And you are one of the designers of NARMS, right?

A Yes.

Q And you designed it along with Dr. Tollefson and Dr. Fedorka-Cray, am I right?

A We design -- in broad sense, yes, I would -- but in terms of designing the animal -- the human side that we at CDC monitor, Dr. Cray and Dr. Tollefson have less design contribution. It certainly was not solely my design.

So in terms of developing the concept of the system, yes, it was a tripartite design that represents the USDA, FDA and CDC together designed it, which the three scientists that you mentioned had a leading role but certainly not the only role in designing it.

Q And your role focused on the human part of NARMS. Am I right?

A In the beginning, that is correct, although we have since evolved to a third arm of NARMS which includes retail food, which I have been involved as a consultant to help design that part, and that's actually FDA's arm. So I have had some contribution in that also. But in the human side, yes, my focus.

Q Okay. So the original design of NARMS before the retail arm was added, you were focused primarily on

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the human side.

A Yes.

Q And as it's evolved after 2001, you're getting involved in the retail side.

A Yes.

Q And NARMS' activities are conducted within the framework of the FoodNet surveillance. Is that right?

A That's not entirely precise. NARMS is actually nationwide, and NARMS' surveillance is in all state health departments. In NARMS we do surveillance for those organisms that you mentioned, Salmonella, et cetera, and we also have Campylobacter surveillance within NARMS and the Campylobacter surveillance of NARMS is done within those 10 health departments that are the FoodNet health departments.

So if your question is NARMS ~~Campyl~~ Campylobacter surveillance, is it done within the context of FoodNet, the answer is yes. NARMS surveillance is larger.

Q Okay. Thank you. And FoodNet is different than NARMS, isn't it?

A Yes. A different name. I mean, different in many ways.

Q They put out separate annual reports, right?

A Yes.

Q So in a given year we may see a 1999 FoodNet report and a 1999 NARMS report, right?

A Yes. Our there are staff at CDC that's common to both systems and can go back, so there's much synergy between the two and much additional activity that they both focus on.

Q Would it be fair to say that they're interrelated?

A Yes.

Q Now, we mentioned incidence earlier. In fact, your testimony discusses Campylobacter incidence, doesn't it?

A Yes.

Q And in that framework of your testimony, incidence is reported in terms of 100,000 cases per year.

A Yes.

Q Now, Baytril was approved in 1996, wasn't it?

A Yes.

Q And the overall estimated incidence of

Campylobacter infections has fallen from 24.7 infections per 100,000 persons in 1997 to 15.4 infections per 100,000 in the United States in 2000, hasn't it?

A I'm not sure that that's the precise numbers. We use as baseline in FoodNet 1996. In my testimony, when I talked about change I talked about baseline 1996 and I believe my testimony talks about the change through 2001, not 1997 through 2000.

I guess my testimony -- so in the FoodNet reports, we talk about the change in the incidence from 1996 through 2001. In my testimony, as I tried to look specifically to the con -- to the interrelationship between NARMS and FoodNet, I talked about the change between 1997 and 2001, although in our FoodNet reports we talked about 1996 as really the baseline of FoodNet.

Q Dr. Angulo, I've got to agree with Judge Davidson. You're reading too much into the question.

MS. ZUCKERMAN: Objection, your Honor.

JUDGE DAVIDSON: Well, it's -- you know, you can explain the answer after you give it, but try and concentrate on the question. I know his questions are

not always that succinct because they ramble on a little bit sometimes, like the use of double negatives, but anyhow --

MR. KRAUSS: I'm not in any way trying to do that --

JUDGE DAVIDSON: I know you're not, but it makes it more difficult. And all witnesses, including, I assume, witnesses representing -- that you bring up will be very cautious not to say something that will hurt their case, so they're always trying to make sure they're not admitting something they shouldn't.

But if the questions are a little bit more direct and simpler, then maybe the answers will be the same way.

MR. KRAUSS: Okay.

JUDGE DAVIDSON: All right.

BY MR. KRAUSS:

Q Dr. Angulo, will you turn to page 4 of your testimony, line 43 through page 5, line 3? Have you had a chance to review that?

A Yes.

Q I'm going to ask my question again, hopefully

without any double negatives, and see if we can get an answer.

My question is the overall estimated incidence of culture-confirmed cases of Campylobacter infections has fallen from 24.7 infections per 100,000 in 1997 to 15.4 infections per 100,000 in 2000, hasn't it?

A No. Did you say 15.4? I'm sorry.

Q Yes. 15.4.

A Yes. That's correct.

Q Thank you. Now, you correctly stated that you actually go on to 2001 so let me ask that, too.

Referring now to page 5, lines 5 to 13, and in particular line 8, let me ask you this. The overall estimated incidence of culture-confirmed cases of Campylobacter infections has fallen from 24.7 infections per 100,000 in 1997 to 13.8 infections per 100,000 in 2001, hasn't it?

A Yes.

Q Let me turn your attention to paragraph 7 of your testimony.

JUDGE DAVIDSON: What page is that on?

MR. KRAUSS: Yes, your Honor. Page 3 is where

it starts, on the bottom.

JUDGE DAVIDSON: Thank you.

BY MR. KRAUSS:

Q Now, this paragraph relates to the representativeness of FoodNet and NARMS, doesn't it?

A Yes.

Q And NARMS gets its isolates from state health departments participating in FoodNet, right, for Campylobacter?

A In large part, yes.

Q I think your problem with my question is I didn't specify human NARMS, correct?

A There are currently 10 participating sites in FoodNet and therefore in NARMS Campylobacter. One of the 10 is just in its pilot phase; that's New Mexico. There are 9 other states. Of those 9 other states, one of those states, Georgia, does not send their isolates to their state health department. They send it directly to us.

So in 8 of the 9 states, yes, we receive the isolates from the state public health laboratory. One, we receive it directly from clinical laboratories and

it does not come through the state health department laboratory.

Q Okay. The state health departments that participated in FoodNet were not chosen to be representative of the United States population, were they?

A No. Well, for the first 9, that's correct. The tenth site was chosen specifically for geographic representation, New Mexico.

Q When was that added?

A That was added in 2002.

Q And NOOH in this case was filed on October 31, 2000, wasn't it? You don't know?

A I assume.

Q If the FoodNet catchment area -- do you understand what I mean by that, Dr. Angulo?

A Yes.

Q If the FoodNet catchment area is representative of the United States population, it would be by coincidence and not by design, isn't that right?

A I don't believe that's true.

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Q Well, you just testified that they weren't chosen to be representative.

A No. When the resources were provided to develop the CDC's emerging infections program, which FoodNet is the core element of, when the emerging infections program was designed, it was purposely designed to achieve a coverage of the U.S. population of about 10 percent because of the judgment that when you have 10 percent of a total, you were -- even though the sites are not drawn because of -- randomly drawn geographically, with a 10 percent collection of all the data within a total, you will reflect the representationess.

So it was a conscious decision to have 10 sites to generate a high enough population to achieve representation of the U.S. But you are correct in saying when the awards were given it was not based upon where they were geographically or upon -- so -- your question has two answers.

Q Let me re-ask it. The state health departments that participate in FoodNet were not chosen to be representative of the U.S. population, were they?

A The fact that there are 10 that were chosen -- that number 10 was chosen because -- to make them representative but the individual state that was chosen was not chosen to be representative of the country.

Q Prior to 2002, the state health departments that participate in FoodNet were not chosen to be representative of the U.S. population, were they?

MS. ZUCKERMAN: Objection, your Honor. Asked and answered several times.

JUDGE DAVIDSON: I think we have a problem here because of the use of the word "coincidence," which you used in your first question, because I'm pretty sure that's what Dr. Angulo was objecting to, and because, when you talk about representation, based on what I've heard the witness testify, there's a difference between statistical representation and geographic representation and your question doesn't narrow it down enough for him to distinguish that. Okay?

MR. KRAUSS: Thank you, your Honor.

THE WITNESS: Your Honor.

JUDGE DAVIDSON: Go ahead.

THE WITNESS: Your question -- if you say was an individual state chosen to be representative, I could give an answer but when we're talking about the plurality of all the states, they were all chosen as a group, the composite of all the states would become representative of the country.

JUDGE DAVIDSON: Okay. Let him answer. Go ahead.

BY MR. KRAUSS:

Q I'm sorry, Dr. Angulo. I was looking at your testimony, page 4, lines 2 through 5 where you say the selection of these participating state health departments was not chosen specifically to be representative of the United States population.

Is that true in your testimony?

A That's true that the individual selection of each state was not chosen to be representative.

Q And they were chosen based upon responses to requests for proposals, right?

A Yes.

Q Now, at some point, CDC set out to compare the population residing in the FoodNet surveillance area to

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the population residing in the United States, didn't it?

A Yes.

Q And that was undertaken by ~~Hard Net~~ Hardnett? Do you know that name?

A Yes.

MR. KRAUSS: May I approach, your Honor?

JUDGE DAVIDSON: Certainly.

BY MR. KRAUSS:

Q Dr. Angulo, I'm handing you what's been marked as Government's Exhibit 769. Take a look at that, please.

This is a poster, isn't it, poster presentation?

A Yes.

Q And it's the presentation or ~~site~~ cite referenced in your testimony for paragraph 7, reference number one on page 4, is that right?

A Yes.

Q And you're co-author of this study, aren't you?

A Senior author.

Q Senior author. In relying on this study in your testimony, your testimony states using 1996 United States Census Bureau data and community health status indicator project data, we performed a demographic comparison between the population in the FoodNet surveillance area in the United States on the basis of age, gender, race, urban residence, population density and percent at or below poverty.

Is that right?

A Yes.

Q And you draw a conclusion based on this study, don't you, that these data -- this is on page 4, lines 24 to 26 -- these data support the generalizability of FoodNet data to the United States population for the purpose of understanding the epidemiology of foodborne illness. Is that right?

A Yes.

Q And in that testimony your reference is G-769, right?

A Yes.

Q Now, if you'd look at G-769 under conclusions on the left-hand side, it says the generalizability of

the 1996 FoodNet data, then it goes on, and then it says almost verbatim to your testimony, these data support the generalizability of FoodNet data to the United States population for the purpose of understanding the epidemiology of foodborne illness. Isn't that right?

A Yes.

Q And the data that G-769 is referring to is the 1996 FoodNet data, am I right?

A Yes.

Q Because G-769 evaluates the comparability of the FoodNet population as it existed in 1996 to the United States population as it existed in 1996, isn't that right?

A I believe -- yes.

Q So this is relating to the original FoodNet sites as comprised in 1996, this Exhibit G-769 that you're relying on.

A Yes. I believe so, although my testimony is not solely based on obviously this reference. We've done --

Q It's the only reference you give, isn't it,

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Dr. Angulo? References to paragraph 7, one, ~~HardNet~~ Hardnett. Isn't that right?

MS. ZUCKERMAN: Objection, your Honor. The testimony speaks for itself and in fact, he does have two citations.

JUDGE DAVIDSON: All right. I'll sustain the objection.

I've given you a lot of leeway. You've asked the witness, Mr. Krauss, to repeat what's already in his testimony and then you ask him to go to another section and repeat what's written in the thing and then I never hear a question that that's a foundation for. You're just putting stuff on the record that's already there.

Now, I'm waiting for you to get to the question that's going to devastate the witness with all this, because you've set this up as this is what he said and how right or wrong he is or the changes, but I haven't heard it.

So, I mean, come on. Get to the point if you're going to do it.

MR. KRAUSS: Thank you, your Honor. I'll get

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to the point.

BY MR. KRAUSS:

Q The ~~Hard Net~~ Hardnett paper compares the original FoodNet sites to the population in 1996, right?

A Yes. It's a poster, not a paper.

Q The poster. Can you point to anywhere in your testimony that discloses that the conclusion you reach about the generalizability of FoodNet data is limited to the original 1996 FoodNet population?

A I'm sorry. Could you repeat the question?

Q Your written direct testimony is talking about the generalizability of FoodNet data in general to the United States population and you refer to a study that refers to the 1996 FoodNet population compared to the U.S. population in 1996, that it's the original FoodNet site.

A Yes.

Q Your testimony doesn't say that the study is limited to the original FoodNet sites, does it?

MS. ZUCKERMAN: Objection, your Honor. The testimony speaks for itself.

JUDGE DAVIDSON: Well, I'll let him answer.

THE WITNESS: I'm confused --

MR. KRAUSS: Well, let me --

JUDGE DAVIDSON: No, let him answer. He wants to say something.

THE WITNESS: I believe that this poster supports our conclusion that the data from FoodNet -- that you can generalize the data from FoodNet to the U.S. population in understanding the epidemiology of foodborne diseases. These are one of the data that support it. We have -- of course our population size has grown in half since that with addition of four additional sites.

We have done other analyses that allow us to evaluate the general -- the similarity between our sites and the non-sites and they all support the generalizability of the FoodNet data for purposes of understanding the epidemiology of foodborne diseases.

We acknowledge there's differences but we don't believe that those differences would prevent the generalizability of FoodNet data nationally in terms of the epidemiology of foodborne diseases.

BY MR. KRAUSS:

Q The FoodNet surveillance area changed from 1996 to 1997, didn't it?

A Not that by addition of a new state but by the states that existed, the five states that existed, they added some counties in 1997 and of course all the counties -- all the states in our -- all have had growth. But in terms of number of state health departments participating, it was the same number in '96 as it was in '97.

Q But there were more counties so the catchment area was bigger.

A Slightly larger.

Q So there were more people involved.

A Slightly more.

Q Your testimony doesn't provide any demographic comparison between 1997 Census data and the FoodNet population under surveillance in 1997, does it?

A No, it doesn't, but --

Q And --

JUDGE DAVIDSON: Let him -- he wants to add. But?

THE WITNESS: But it doesn't negate the general support of this -- to our conclusion that in fact the catchment area of FoodNet can -- in terms of understanding the epidemiology of foodborne diseases, what's occurring in FoodNet can be generalized in the nation.

This piece supports it, other pieces support it.

BY MR. KRAUSS:

Q G-769 relates to a 1996 FoodNet comparison to the United States population in 1996, right?

A Yes.

Q And then the FoodNet catchment area changed between 1996 and 1997. It got bigger, right?

A In small ways, yes. And we evaluated the change that occurred in '97 and we have the same -- it still supports the general notion. Every year that we add people to FoodNet, we evaluate the -- as you expect, we evaluate the contribution of the new populations to FoodNet to evaluate how they reflect the U.S. population.

And every year that we've expanded, we have

had the impression that, in terms of generalizing FoodNet data on the epidemiology of foodborne diseases, FoodNet is -- we're comfortable generalizing the data from FoodNet nationally.

Q Between 1996 and 1997 and then '97 to '98 and '99, 2000, 2001, every one of those years, the FoodNet catchment area got bigger, didn't it?

A That's correct. Sometimes bigger because of new states and sometimes bigger because in existing states, there's new counties. And even in one instance, a county no longer exists and forms two counties and got bigger, so there's subtle changes from year to year.

Q You haven't provided any testimony comparing the demographics between the FoodNet population in 2001 and the United States population in 2001, have you? Not in your testimony.

MS. ZUCKERMAN: Objection, your Honor. Mr. Krauss continues to ask the same question over and over again. The testimony that is written is not going to change over time. I think the witness has answered the question at least three or four times at this point.

JUDGE DAVIDSON: I'm not sure. I'm going to let him answer.

THE WITNESS: We support the conclusion that the FoodNet catchment area, in terms of understanding the epidemiology of foodborne diseases, the data from the FoodNet catchment area can be generalized to the U.S. population.

JUDGE DAVIDSON: That wasn't the question as I heard it.

THE WITNESS: Repeat the question, please?

BY MR. KRAUSS:

Q Your testimony doesn't provide any information on the demographic comparison between 2001 U.S. Census data and the 2001 FoodNet population that was under surveillance then, does it?

A No. My testimony doesn't include a lot of things.

JUDGE DAVIDSON: That's all right. Would this be a convenient place for you to break for a recess, Mr. Krauss?

MR. KRAUSS: Yes, your Honor. Thank you.

JUDGE DAVIDSON: All right. We'll take a 10-

BY MR. KRAUSS:

Q Now, Dr. Angulo, at the extreme risk of belaboring the point --

MR. KRAUSS: And I apologize, your Honor. I just have to make sure I understand this point about the demographics between FoodNet and the United States population.

BY MR. KRAUSS:

Q The FoodNet surveillance area increased from '96 to '97, right?

A Yes.

Q Did CDC do any kind of a written analysis of the demographics between the FoodNet surveillance area of 1997 and the United States population of 1997?

A Yes.

Q And was it published, like G-769 was?

A No.

Q When was it done?

A In 1997 when we -- every year that we change our -- we publish an annual report each year in FoodNet and in support of that report each year we evaluate how well we relate nationally. And in 1997, we did an

evaluation, I'm certain, of the catchment area of FoodNet versus the U.S. population.

Q You're certain of that. So if I looked in the 1997 FoodNet report, the annual report, there'd be a discussion of the representativeness?

A No. Would you -- because we do -- we don't publish everything we do in our annual report. There are many internal analyses that we are doing all the time and we don't put that -- we did not put that -- you are correct. We did not put that in the 1997 annual report of FoodNet.

Q Is there some kind of a formal document where that analysis is contained, between 1997 and '96?

A I -- we could look for it. This was 1997. I don't know if the document still exists. We could check people's e-mails or -- we've not been asked by Freedom of Information Act to provide that and we have not searched for it.

I don't know. I know it exists. I know that we did it and I don't know where it exists now and where it exists.

Q Now, the FoodNet surveillance area grew from

minute recess. And you don't have to stand up. I'm not going anywhere.

(A brief recess was taken.)

JUDGE DAVIDSON: On the record.

You had a 10-minute recess, I let it go to 15, and you're still not prompt coming back. I don't appreciate that. Next time I'll put a clock on it and we'll start promptly when I give you -- the 10 minutes are up, whether you're here or not.

And I don't appreciate people coming in the room and having conversation while I say "come to order." Once I say come to order, all conversation stops.

All right. I've already got the representation earlier in this hearing from Mr. Spiller that he's going to support any recommendation for a larger hearing room. If there's anybody from the Bayer Corporation here, I think they should tie their user fees to getting me a bigger hearing room.

(Laughter.)

JUDGE DAVIDSON: Go ahead, Mr. Krauss.

MR. KRAUSS: Thank you, your Honor.

'97 to '98, right, and was there a written analysis of a comparison between the demographics of the FoodNet population in 1998 and the United States population of 1998?

A Yes.

Q And was that published?

A No.

Q When was it done?

A In '98.

Q And it was not in the -- was that discussed in the 1998 annual report for FoodNet?

A I don't believe so. I mean, we'd probably -- I'm certain in 1998 there were important differences in FoodNet because we added two new state health departments and we therefore had a remarkable increase in the population and I'm sure that we report the change in the population between '97 and '98.

So we did talk about the enlargement and I'm sure that we compared the 1998 FoodNet catchment area to the U.S. population in just general terms. I'm sure we cited what the U.S. Census data was in 1998 also when we reported the FoodNet catchment population at

that time.

In terms of doing an analysis of demographic features, we did that but we did not include that in our annual report. We circulated amongst our partners and ourselves and as we do every time, we look at every annual report.

Q So the CDC --

A I --

Q Go ahead.

A The important thing is we go through this review all the time and we have been comfortable with our conclusion that data from FoodNet is generalizable to U.S. population specifically for understanding the epidemiology of foodborne disease and I know that we evaluate this every year.

And the fact that we have retained that confidence -- and not just us but our -- large partnership that FoodNet is, all of us have retained that confidence. That's why we never publish it because we don't -- our conclusion has never changed.

So the fact that we -- just because we don't publish it doesn't -- we would have published it had it

been remarkably different. We certainly would state it if we felt that we had somehow lost confidence that FoodNet was generalizable to the U.S. population.

Q See, you're saying that you're confident of it but the only evidence I see that's in the record about a comparison relates from '96 FoodNet catchment area to the '96 United States population and you testified that the FoodNet area has grown every year. You say you've done these written analyses. Nobody has seen them. We don't know what the proof is.

MS. ZUCKERMAN: Objection, your Honor. Is there a question? I didn't hear Mr. Krauss ask a question.

JUDGE DAVIDSON: Well, I did. Overruled.

THE WITNESS: Yes. FoodNet publishes in the Spring of every year a annual report for the previous year, as we did just recently publish a report of the incidence -- the changes in incidence in 2002 compared to baseline.

And when we publish that, we have all our partner -- as -- in part of the development process of thinking through what we're going to say each year, we

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bring all of our partners in, all 10 -- now 10 state health departments. We review the text and also we bring in the representatives from the USDA which includes food safety inspection service and also from FDA, Center for Veterinary Medicine and Center for Food Safety and Applied Nutrition.

They ~~call~~ all come in. We review drafts. We have much discussion and ~~venting~~ vetting of those drafts. Those drafts -- what we state in FoodNet gets cleared by CDC and by FDA and by the Secretary of the Department of Health and Human Services and by Food Safety Inspection Service and by 10 different state health departments all of whom see the conclusions of FoodNet, all of whom have a -- all of whom we've talked through the process and everybody has been in agreement that this is the best -- in terms of understanding the epidemiology of foodborne disease in the United States, FoodNet data could be generalized to the U.S. population.

So there's -- so there was much discussion of this and the fact that we continue to go forward, it's because all of us have retained the confidence that FoodNet data can be generalized nationwide in terms of

understanding the epidemiology of foodborne disease.

BY MR. KRAUSS:

Q So let me just make sure I have this right, Dr. Angulo. All these discussions go on within the CDC. You do written analyses, put out an annual report every year, but they don't put in the annual report every year a discussion on a comparison between the demographics of the United States population for that relevant year and the FoodNet catchment area for that relevant year.

Is that what your testimony is?

A In the FoodNet annual reports, we talk about the size of FoodNet and we talk about the changes in the trends and incidence for the FoodNet and we have confidence that that is the best -- that that is data sufficient to conclude the -- what's happening nationwide in terms of the incidence of foodborne diseases.

Now, in our annual reports of FoodNet, no, we don't do a detailed analysis. It would be redundant.

Q Well, you testified that such a written analysis is done but it doesn't get published. Is that

right?

A I guess what we do share to all partners is what is the -- in the Census data set, there are a limited number of variables available, race, ethnicity information, county of residence, ages, et cetera.

And we publish -- we compare all those demographic features that are in the U.S. Census data to all that -- those same variables in FoodNet and look at them and we continue to have the conclusion that there are -- while there are some differences, those differences are not sufficient that it would prevent us from generalizing the FoodNet data to the rest of the country in terms of understanding the epidemiology of foodborne diseases.

Q You do that I believe you testified every year, right?

A Right.

Q And is there a written analysis every year?

A There is certain data printouts, computer runs, discussion -- and we've published this FoodNet report for six years and we have nev -- in peer review medical journal. We've never received any question

from anybody saying this issue -- the issue that if -- I guess the issue that you raise, if it were pertinent enough, if it was compelling enough, I imagine then we could easily explain it in our next annual report.

We have never been -- no one has ever questioned the fact that FoodNet does not represent the country in terms of understanding the epidemiology of foodborne disease. Actually, quite the converse. In fact, there is much endorsement of FoodNet data that in fact FoodNet is the best available data to track the changes in the incidence of foodborne diseases in the United States.

And that endorsement has come from all partners, including the National Cattlemen's Beef Association, National Chicken Council, to consumer groups. They all endorse the FoodNet data and no one has criticized the FoodNet data in saying these issues that you raise about the non-representationess of FoodNet in terms of impact in an important way that would influence the understanding of the epidemiology of foodborne disease.

Q Is that true for Campylobacter surveillance,

too, Dr. Angulo?

A FoodNet's incidence of Campylobacter data, in my understanding, most groups are comfortable that there has been -- that FoodNet is the best national data on the incidence of foodborne diseases -- I'm sorry -- of Campylobacter and there's widespread consensus that in fact the incidence of Campylobacter is reflected in the FoodNet data.

I'm not aware of any much disagreement. And in fact, there's a decline in the incidence of foodborne diseases observed in FoodNet. I think -- we haven't received comments that people think it's the -- that that is not an accurate portrayal.

Q Let me move on, Dr. Angulo. You were just talking about FoodNet in general and the representativeness. Let me move on to NARMS and the surveillance of Campylobacter on the human part of NARMS, okay?

A Yes.

Q NARMS began testing for resistance -- Fluoroquinolone resistance in human Campylobacter isolates in 1997, didn't it?

A We began testing for Ciprofloxacin resistance in 1997.

Q And Ciprofloxacin is a Fluoroquinolone, isn't it?

A Yes, it is.

Q And when NARMS began testing human Campylobacter isolates, that was from laboratories in California, Connecticut, Georgia, Minnesota and Oregon, wasn't it?

A Yes.

Q That's what your testimony states?

A Yes.

Q But it wasn't the entire state of California, was it?

A No.

Q And it wasn't the --

A Sorry. It was not the entire state of California, yes. It was not the entire state of California.

Q And it did not cover the entire state of Connecticut, did it?

A In 1997, it did not cover the entire state of

Connecticut. Yes.

Q And it did not cover the entire state of Georgia, did it?

A In 1997, yes.

Q So in 1997, the only two states that were fully participating was Minnesota and Oregon, isn't that right, where the entire state was covered?

A No, that's not true. It was only Minnesota in 1997 that --

Q Oh. So there was only one state.

A So re-ask your question, please?

Q My question -- I thought there were two states that were fully participating but I take it Oregon was not fully participating in 1997. Is that right?

A Would you define the term fully participating?

Q Where the entire state was being represented in sending their isolates to CDC for Fluoroquinolone resistance testing.

A If you mean to imply that all clinical laboratories within the state were sending their isolates to the state health departments, only Minnesota was following that design.

Q In 1997?

A In 1997.

Q Now, within the surveillance system for Campylobacter resistance, can you explain for me, please, how an isolate would get from a patient who has Campylobacteriosis through the chain to get to CDC for resistance testing?

A And would you like that in general or specific states? What year would you like it to be in that state? Because there were variations.

Q It varies from year to year, doesn't it?

A It changed in some years but once it changed it did not vary again. But yes, there were some changes over time in some states.

Q Why don't we start at the beginning and tell me when they first started to conduct surveillance for human -- in the human population for resistance -- Fluoroquinolone resistance in Campylobacter, how those specimens -- those isolates would have gotten from the patient to CDC for resistance testing?

A So a patient would become ill with a Campylobacter infection, would seek medical attention.

The physician would gather a specimen, usually a stool sample of Campylobacter. The physician would order a specimen; someone else might collect it.

But nonetheless a specimen would be collected, submitted to a clinical diagnostic laboratory. The diagnostic laboratory would isolate the Campylobacter. Then the isolate resides at the clinical laboratory and then from there we have two models with the NARMS Campylobacter surveillance.

We have a Sentinel Clinical Laboratory model where that clinical laboratory submits its isolates -- that Sentinel Clinical Laboratory submits its isolates to CDC, sometimes passing through the state health department but essentially all the isolates selected by that clinic -- that Sentinel Clinical Laboratory are forwarded to CDC either directly or through the state health department. That's one model.

We have another model --

Q I'm sorry. Let me just interrupt. Is this second model still applicable to 1997?

A Would you mind if I answered the question and then I'd be glad to tell you who follows what models

when, because it can -- but that model applied to some states in 1997, Sentinel Clinical Laboratory model applied in some states in 1997 but different -- but not all the states in '97 follow that model today.

Q So what you just described was the Sentinel Clinical Laboratory model.

A Yes.

Q And then there's a second model.

A Yes.

Q When was the second model first used?

A Would you like to explain the second model? That was the pending question I haven't answered.

Q If it was being used in 1997, yes, because my original question was tell me how it was done in '97.

A No. Your original question, which perhaps we might want to -- was if a person has Campylobacteriosis, how does the isolate get to CDC. And I was describing how that was occurring.

I don't believe you asked --

Q Well, you told me it changed over the years and it changes from state to state so I said let's start at the beginning.

A Right. And I was doing that.

Q Right. So we're at 1997, at the beginning, right?

JUDGE DAVIDSON: Let's not quibble. Let him answer in his own way and if you have additional information you want -- you can answer.

MR. KRAUSS: Thank you, your Honor.

THE WITNESS: I've described how a patient that has Campylobacter seeks care, has specimens gathered and it goes to a clinical laboratory and one model is a Sentinel Clinical Laboratory model.

The other model is within a geographic area all the clinical laboratories or almost all of the clinical laboratories -- all but a very few -- so essentially all of the clinical laboratories within a geographic area, they all submit the isolates to a collection and then from that collection an isolate is selected that's forwarded to CDC or there's a slight modification.

They might submit that collection to CDC and CDC selects the isolate. But nonetheless, the isolate that is tested is from a collection of isolates pulled

together from all or almost all clinical laboratories within a geographic area. That's the second model.

BY MR. KRAUSS:

Q And when you say a geographical area, that wouldn't encompass more than one state, would it?

A No, it would not encompass more than one state.

Q Okay. In the first model, the Sentinel Clinical Laboratory model, where are the isolates initially speciated?

A Well, they may -- clinical laboratories -- well, we've surveyed all of the Sentinel Clinical Laboratories and they are not, as of today -- they are not speciating the Campylobacter but they may wish to speciate Campylobacter for their own purposes but we don't use that data.

So where are they speciated for the data that we use for the NARMS report? They are speciated at CDC.

Q I'm sorry, Dr. Angulo. I've got to make sure I'm making a clear record. Hopefully the Judge will appreciate this, too.

Let's just talk about 1997. In 1997, the Sentinel Clinical Laboratory model was being used in some places, right?

A Yes.

Q And in 1997, where were the isolates speciated initially? And did it vary by state or --

A In the Sentinel Clinical model, the data that we used for speciation is -- we'd speciate the isolates at CDC. I can't say -- I do not know whether then in '97 any of those clinical laboratories speciated -- they may have initially speciated isolates. That's their prerogative. We don't use that data. We'd never ask for that data.

It wouldn't influence -- what we do know -- we have done a survey of these Sentinel Clinical Laboratories and we do know that they do not select their isolate based upon a screening test like speciation or susceptibility testing or anything else. They send us the isolate -- maybe they speciate it but it doesn't influence what they send to us and we do the confirmatory speciation in our laboratory.

Q I'm sorry. I don't want to keep saying about

what you've done now and what's being done now. I want to stick to 1997, the first year, so that we have a clear record. Do you understand?

A Yes.

Q In 1997, what states were following the Sentinel Clinical Laboratory model?

A Georgia, California, Oregon and Connecticut.

Q For those states following that model, the Sentinel Clinical Laboratory model, where were the Campylobacter isolates initially speciated?

JUDGE DAVIDSON: He doesn't know. He said so before. He said they may speciate it themselves but CDC doesn't use those. So if CDC doesn't use it, how would he know where it was initially speciated? I mean, it's in his testimony already. You've asked it before.

Now, there may be some difference between -- I thought he was talking about 1997 because you said model number one in your last question. And then you said you don't think he was talking about '97 so you asked it again.

Now, let's move on.

MR. KRAUSS: All right. Thank you, your Honor.

BY MR. KRAUSS:

Q For states that followed the geographical area model, were there any in 1997?

A Yes.

Q Okay.

A I wouldn't call it -- well, that's a new term.

Q What did you call it? You said some of it is by geographical area.

A Okay.

Q What would you call the model followed by the states that don't follow the Sentinel Clinical Laboratory model?

A I would call it the model that is not the Sentinel Clinical Laboratory model.

(Laughter.)

BY MR. KRAUSS:

Q Thank you. In that non-Sentinel model, how -- when and where are the isolates speciated initially?

A In 1997, the only state that did that model was Minnesota and I presume that they did some -- that

they do speciation or did some speciation initially but that did not influence the isolates they sent to us nor have I ever seen that data nor have we ever used that data, so I can't say with -- I don't know if they were speciated in Minnesota.

And I don't know if they were -- in time -- by the term initially, if you mean by the date when they were speciated, I don't know if Minnesota ended up speciating their isolates that they sent to us time line before we did, but I know for certain that the isolates that Minnesota sent to us did not influence -- was not influenced by testing that they did like speciation.

They randomly selected an isolate, sent it to us. We eventually got around to speciating it. We, in our NARMS report, used the speciation from our laboratory. Perhaps in the time line of things, Minnesota may have speciated the isolates initially before us but we never used that data, never was sent to us. I'm not familiar with that data.

Q So for Campylobacter for the human NARMS program, CDC does not receive isolates that are

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identified as a jejuni or ~~E. coli~~ coli specifically from any of the participating state health departments. Is that your testimony?

A When they send the isolates forward, they might report -- they may put Campylobacter jejuni on the isolate slip -- I'm sorry -- on the isolate log or we have linked FoodNet and NARMS together, because every Campylobacter case in NARMS is in FoodNet, and maybe through the electronic reporting of FoodNet they have reported this case to us as jejuni.

But we don't use that data that's been reported to us by a state. We do all the speciation ourselves. So perhaps they are reporting the species to us but we do not use that data.

Q But here is --

A In NARMS. Excuse me.

Q Here is the question. The lab gets in a sample and they want to find out what enteric bacteria may be in there so they have to go through an isolation procedure, right? Am I right on that?

A Now, we're talking a clinical laboratory, not public health?

Q Sure. Yes.

A Yes. The specimens.

Q That's in the chain of events going from sick person to CDC for resistance testing.

A Right.

Q A sample is taken. They want to find out what enteric bacteria are in there. There's a process that they use to isolate the bacteria, right?

A At clinical diagnostic labs, yes.

Q Okay.

A Isolate from a stool specimen or other specimen.

Q Right. And if in that -- and then once they see that there's some bacteria growing, they have to figure out what it is, don't they?

A Yes.

Q Whether it's a Campylobacter or a Salmonella or something else, right?

A Yes.

Q And once they -- how do they determine that it's a Campylobacter versus a Salmonella?

A Well, the Campylobacter is growing on a

special plate where it's highly likely whatever is growing on that plate, especially in the growth conditions of the clinical laboratory, that only Campylobacter will be growing.

Salmonella will not grow -- well, maybe it grows -- but will not grow well in the conditions that Campylobacter grows in. It has to go in a special incubator with special oxygen environments. So they have a Campylobacter plate, they see Campylobacter on it or isolates on it, presumed Campylobacter.

Q And that plate -- would that have auger on it or agar?

A Yes.

Q And agar that's used for Campylobacter, under the CDC protocol for isolating Campylobacter, does that have antibiotics in it?

A The CDC isolate -- we don't have a protocol that directs the clinical laboratories in either model, Sentinel Clinical Laboratories or the non-Sentinel Clinical Laboratories -- those clinical diagnostic labs, we don't direct them how to isolate Campylobacter. We just inform them to do routine

laboratory procedures to isolate them.

In routine laboratory procedures to isolate Campylobacter, there is antibiotics in that agar and it's -- but it is not an antibiotic that would have an influence on the selection of Ciprofloxacin resistant Campylobacter. The antibiotics that are there are a cephalosporin that help with the selection of Campylobacter, all Campylobacter, Fluoroquinolone resistant and Fluoroquinolone susceptible.

So there are some antibiotics -- there is an antibiotic in most routine Campylobacter isolation media but it would not influence the selection of a resistant isolate.

Q And you're aware, aren't you, that there are some differing opinions on whether the antibiotics in the agar will influence the selection of Fluoroquinolone resistant Campylobacter in the scientific community?

A That's a general question.

Q Right. Are you aware that --

A Are you talking specifically about the antibiotic that we know is used routinely in

Campylobacter isolates, the cephalosporin? There is no disagreement in the scientific community that I'm aware of.

Certainly I could state that our laboratory, which is the National Campylobacter Reference Laboratory, is confident that the antibi -- that labs routinely put in Campylobacter agar for isolation that cephalosporin would not influence the selection of Fluoroquinolone resistance.

Now, there's other antibiotics and there's some controversy about using other antibiotics in agar, none of which -- we have no evidence anybody is doing and how those other antibiotics may influence resistance.

Q Okay. In the process that we're talking about here -- so now this clinical lab has used whatever method it chooses -- CDC doesn't tell it how to sample and isolate Campylobacter, right?

A Well, that's not a precisely correct question, either, because all clinical laboratories in the United States, in order to receive reimbursement from the U.S. government, must be CLIA-certified laboratories,

Clinical Laboratory Improvement Act, which has government's oversight onto whether they follow those procedures.

And in order to be CLIA-certified, you will have to follow standard isolation procedures for isolating Campylobacter. So there is a branch of CDC that does actually participate with state health departments that ensure clinical laboratories follow standard procedure for isolation.

But that's not in the NARMS system. That's just standard laboratory practices that clinical laboratories get evaluated on.

Q Okay. So the labs are, as far as you know, following the same procedure when they isolate the Campylobacter initially? This CLIA procedure that you testified to.

A Right. Correct. In our Sentinel Clinical Laboratories -- we have surveyed the Sentinel Clinical Laboratories and we know what they have done and did do and they are following CLIA-certified procedures for the isolation of Campylobacter.

Q Okay. Once the clinical laboratory determines

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that they have a Campylobacter, what do they do next? They got the plate, they do what you just testified about regarding the agar and they know they have a Campylobacter. What do they do next in the NARMS system?

A They -- well, they don't know it's a Campylobacter. It's a presumed Campylobacter growth on this plate and they confirm Campylobacter and then forward the isolate to -- directly to CDC or to state labs, depending on which is their model.

Q How do they confirm Campylobacter?

A Using CLIA-certified procedures for identification of Campylobacter which can be with biochemical tests or can be a commercially available biochemical test, an API strip. They also use -- I'm not a clinical microbiologist so I don't know the algorithm that's in the -- to reach the bottom of the algorithm that says yes, this is a Campylobacter but it can include looking at ~~grahms~~ Grams stain, et cetera.

We know what they do at all the laboratories. We have surveyed all the clinical laboratories that are Sentinel Clinical Laboratory at NARMS and they all

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follow a CLIA-certified approach for identifying Campylobacter but I couldn't explain with precision exactly what everybody is doing except for the conclusion that they are following a standard procedure.

Q Would speciation with nalidixic acid and cephalothin be a biochemical test like you just discussed? Would that be CLIA-certified?

A Before the emergence of Fluoroquinolone resistant Campylobacter, globally and in the United States you used to be able to identify non-Campylobacter ~~juni~~ jejuni, non-Campylobacter coli by screening with nalidixic acid because the only Campylobacter resistant to nalidixic acid would be non-jejuni, non-E. coli.

But because of the emergence of Fluoroquinolone resistant campylobacter to ~~juni~~ jejuni and coli so we can no longer -- or labs can no longer use nalidixic -- or when a lab try to speciate Campylobacter they can no longer use the nalidixic acid screening test as a method of speciation, which is why in our National Campylobacter Reference Laboratory we

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have gone to genetic-based tests to speciate.

Now, clinical laboratories largely would not speciate -- there's little incentive for a clinical diagnostic lab to speciate Campylobacter ~~isolate~~ isolates. So they probably would not have used a nalidixic acid screening test or its genetic -- ~~it's~~ its PCR-based alternative and so they probably would not, although perhaps they did. Maybe they have a research project or something.

But what I can say is that since NARMS started in '97, all the Sentinel Clinical Laboratories that participate in NARMS, none of them have chosen isolates to be forwarded to CDC based upon speciation.

They do not speciate before they select and if they had used the old method of speciation, which would be a nalidixic acid screen, or they used the new PCR-based method, regardless -- if they do any speciation, I'm not sure -- regardless, they don't -- those results do not influence what isolate they select to forward to CDC.

Q Now, at CDC, when CDC is doing its resistance testing for Fluoroquinolone resistance, for

Ciprofloxacin resistance in the Campylobacter isolates it receives, it uses the E test system for determining the minimum inhibitory concentration, doesn't it?

A Yes.

Q And at CDC, for the purposes of NARMS' susceptibility testing for Ciprofloxacin resistance, Ciprofloxacin resistance is defined as a Ciprofloxacin minimum inhibitory concentration of greater than or equal 4 micrograms per milliliter, isn't it?

A Yes. Is it not and the answer is -- sorry. Is it? Yes. The answer is yes to the question is that what we do. Yes.

Q Now, the fact that NARMS might find an isolate with a minimum inhibitory concentration of greater than or equal to 4 micrograms per milliliter in a Campylobacter, that doesn't necessarily indicate a loss of clinical effectiveness if the person with that isolate would have been treated with Ciprofloxacin, does it?

A Well, we have epidemiological evidence on the record that demonstrates that Fluoroquinolone resistant Campylobacter is associated with longer duration of

diarrhea and less effectiveness of Fluoroquinolone. So I think we have evidence on the record that shows in fact Fluoroquinolone -- I'm sorry -- Ciprofloxacin resistant Campylobacter is associated with a clinical con -- adverse clinical consequence.

Q Let me ask my question again. CDC does resistance testing. They characterize resistance as greater than or equal to 4 micrograms per milliliter, right?

A Yes.

Q The determination that -- that's for Ciprofloxacin resistance for Campylobacter, right?

A Yes.

Q The fact that NARMS makes that determination that it's "resistant" because it's got an MIC of greater than or equal to four milligrams per milliliter doesn't necessarily mean that there would be a loss of clinical effectiveness if the patient with that isolate had been treated with a Fluoroquinolone, does it?

A Again, I actually think it does because as also part of our record, we demonstrate that the MICs of Campylobacter, the MICs of the Ciprofloxacin

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resistance
~~resistant~~ that we observe in Campylobacter are in fact greater than 32, which is -- 32 is the highest concentration that we test.

And in fact, if you were to titrate out the minimum inhibitory concentrations to their full end point, they're going to be higher than 32 which I think most clinicians would agree that you will not achieve concentrations in the blood to kill that or inhibit that organism.

So I think most clinicians would judge that -- a matter of fact, I would think almost all clinicians would judge that a ~~MCI~~ MIC and Ciprofloxacin-resistant Campylobacter that's greater than 32, they would be subject to malpractice if they treated that patient with Fluoroquinolone. Clearly you would not choose to treat that patient with Fluoroquinolone.

Q You're not a clinician, are you?

A No, but --

Q And you're not a lawyer, are you, to tell us what would be malpractice or not?

A No. I'm certain -- CDC has published clinical guidelines on the treatment of patients with acute

gastroenteritis and in those guidelines it states that Fluoroquinolone is a drug of choice in adults to treat acute gastroenteritis and to look at the susceptibility results.

And if someone were to go against that, they would be against the clinical practice guidelines which there are litigation all the time against not following clinical --

Q Okay. We have evidence in the record on both sides of that issue and ultimately Judge Davidson will determine the facts so let me stop you there, if you don't mind, and get back to my question.

And I'm going to run the risk of getting a warning from Judge Davidson here, but I've got to --

JUDGE DAVIDSON: Well, don't bother.

BY MR. KRAUSS:

Q -- ask you about --

JUDGE DAVIDSON: Just don't ask the question and you won't have to run the risk.

MR. KRAUSS: Sorry, your Honor.

JUDGE DAVIDSON: You set yourself up.

MR. KRAUSS: Yes, your Honor. It's not the

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first time.

JUDGE DAVIDSON: Okay.

BY MR. KRAUSS:

Q You'll agree with me, won't you, that there's no national committee for clinical laboratory standards breakpoint that would indicate a loss of clinical effectiveness for the use of Ciprofloxacin to treat Campylobacter infections in humans? Right? That's true?

A Could you repeat that question?

Q There is not an established breakpoint that would indicate at what MIC concentration clinical effectiveness would be lost if somebody was treating a Campylobacter infection with Ciprofloxacin.

MS. ZUCKERMAN: Objection, your Honor. I believe that's joint stipulation --

JUDGE DAVIDSON: Sustained.

BY MR. KRAUSS:

Q Let me go back to my question. CDC does susceptibility testing of Campylobacter and they call something resistant if it is -- the MIC ~~or~~ for Ciprofloxacin for Campylobacter is greater than or

equal to 4 micrograms per milliliter, right?

A Yes.

Q Okay. Just because CDC calls it resistant at 4 micrograms per milliliter, that doesn't mean, does it, that there will be a loss of clinical effectiveness if that patient who has that Campylobacter in them would have been treated with Ciprofloxacin, does it?

MS. ZUCKERMAN: Objection, your Honor. Counsel has asked this question at least twice and Dr. Angulo has given a full answer each time.

JUDGE DAVIDSON: I'm going to sustain the objection, but primarily because I'm not happy with the way you're asking the question. Maybe I'm wrong, because I'm never in doubt, as I told you. But you're not giving him any parameters of what kind -- you know, the amount of dosage you're talking about and yet you're saying -- you have no indication that it would be effective or not effective.

And from what I'm understanding in his testimony, the witness has indicated that the dosage necessary to make it effective would be too high, in his opinion. Now, we understand there's disagreements

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on that but your question doesn't put any dosage on it so that's why I'm sustaining the objection. It's too broad.

BY MR. KRAUSS:

Q When NARMS does resistance testing of a Campylobacter isolate and determines that the MIC for Ciprofloxacin is greater than or equal to 4 micrograms per milliliter, that's no representation on the part of NARMS that that patient would have been treated perhaps with the standard dosage for Ciprofloxacin would have had ~~an effective~~ ineffective treatment, is it?

A I don't understand -- we -- that -- if someone has an MIC of Campylobacter that's more than 4 -- there are instances I've described that are actually more than 32 --

Q I'm talking about greater than or equal to 4. Don't change the question on us, okay? I'm talking about determination by NARMS that a Campylobacter has Ciprofloxacin resistance of greater than or equal to 4 micrograms per milliliter -- you with me so far?

A Yes.

Q That's not any kind of a representation or

indication by CDC that that patient would have had ineffective treatment if they were given a standard course of Ciprofloxacin, is it?

A No, it is and in fact it's used -- those results are used by our state health departments who publish guidelines for their practitioners in their states and they advise what antibiotics to treat with and they advise not to treat a person with Campylobacter if they have an MIC greater than 4 with Fluoroquinolones.

Q And so those guidelines that you just testified about are promulgated without there being a NCCLS breakpoint that would indicate a loss of clinical effectiveness for treating Campylobacter infections with Ciprofloxacin, right?

A Those guidelines are based --

Q Just answer yes or no.

JUDGE DAVIDSON: Just answer the question first.

THE WITNESS: Yes. There is no NCCLS breakpoint for Ciprofloxacin-resistant Campylobacter.

That does not negate the need to give advice

A Prior to this year, yes.

Q And it's been changed to every 20?

A The first of this year it changed to every twentieth Salmonella isolate.

Q And for E. coli, the participating sites select every fifth isolate?

A Prior to this year, yes.

Q And for Campylobacter it's the first isolate of a week. Isn't that right?

A It's one isolate a week, yes.

Q It's not necessarily the first one?

A The guidance to our state partners was to -- we set the -- we set baseline guidelines of how you would send the isolates to us. And if they have a -- if they set up their system as a Sentinel Clinical Laboratory system, it should be the first isolate isolated each week if they follow that model.

If they choose to follow a model of submitting isolates other than the Sentinel Clinical Laboratory, it wouldn't necessarily be the first isolate isolated every week. They would be drawing from a random collection of their isolates that they receive each

week which might in some -- some states may choose to select that based upon the first isolate isolated each week.

Q For Salmonella, which is every 10 isolates -- if you have a hundred in a lab in a week they would send 10, right?

A Yes.

Q And for Campylobacter, if they had a hundred in a week they'd send one, right, for resistance testing?

A Yes, but no clinical lab is going to -- it would be unlikely to have a hundred one week but --

JUDGE DAVIDSON: The answer is yes.

THE WITNESS: Yes.

JUDGE DAVIDSON: Okay. Come on. Didn't you ask the prior witness all these same questions?

MR. KRAUSS: Those two questions, yes, your Honor.

JUDGE DAVIDSON: I think you went further and I stopped you, but okay.

BY MR. KRAUSS:

Q Now, the sampling scheme for Campylobacter is

not population-based, is it?

A In some of our states, in fact, it is.

Q I'm talking about the national program.

A In total it is not population-based. Some states it is.

Q But overall --

A It is not.

Q For Campylobacter, you do not have a representative sample in NARMS, do you?

A I think we do have a representative sample in NARMS for Campylobacter.

Q Representative of what?

A Of Campylobacter in the country. I'm confident that the prevalence -- I'm confident that the Campylobacter that we receive approximates the Campylobacter in the country that reside at clinical laboratories.

Q Would you agree that for the Campylobacter Fluoroquinolone-resistant sampling through NARMS, that there are limitations in applying the percentage resistance that NARMS reports to the nation as a whole?

A Yes, there is limitations in all surveillance

systems.

Q Dr. Angulo, in your capacity as the chief of the FoodNet NARMS unit of the foodborne and diarrheal diseases branch at CDC, did you attend the NARMS annual scientific meeting held in November of 2002 in Hilton Head?

A Yes.

Q In that meeting, did you characterize the Campylobacter sampling program under -- for the NARMS surveillance system as artificial and not population-based?

A Would you like to break that in two questions?

Q Yes. Did you characterize it as artificial?

A No. I don't recall saying that.

Q Did you characterize it as not population-based?

A Yes, and I've so stated today.

Q At that same NARMS meeting, did you state that the Campylobacter resistance numbers that NARMS reports are not a prevalence?

A I don't recall saying -- I don't know the context of that. When I was saying that something was

not a prevalence, I was talking about the regression analysis and the prevalence that's observed in the ~~aggression~~ regression analysis in which there's an adjusted prevalence that's created through the -- adjust -- through the regression analysis.

So I don't recall the context of what -- of this and I don't recall precisely saying that.

Q Bayer had proposed a finding of fact to CVM that states that at the NARMS conference that we just talked about -- should be proposed finding of fact number 336 that you stated, "so and then Campylobacter is not population-based as was pointed out so I think that for all pathogens except Campylobacter we have a representative sample of culture-confirmed cases at the state level."

Now, CVM objected to that proposed finding of fact. My question to you is is it a fact that you said that?

MS. ZUCKERMAN: Objection, your Honor. CVM also objects to counsel's representation of the quotes from the NARMS meeting. There has been no authentication of the recording, of the transcription.