has tracked cipro resistance in isolates from retail chicken and saw for a long time an increase there as well. Just in recent years there's maybe some hope that this is starting to go down, so we'll be tracking that carefully.

The next story I wanted to tell you about is about resistance in non-typhoidal *Salmonella*. And here we're looking at resistance to ceftriaxone, which is a third-generation cephalosporin, and nalidixic acid, which is a quinolone of the same class as ciprofloxacin. So, again, the two drugs that are used most commonly to treat serious human infections.

Again, this is a slide with good news and bad news, the bad news being that, back in the mid-1990s, there was essentially no resistance to either of these agents and both of them have emerged and have persisted, but thankfully, they've persisted at fairly low levels, about 2% to 3%. And so this is a particular bug-drug combination that we track very closely every year. In 2012 FDA prohibited certain off-label cephalosporin uses in major food animals, and we will be eager to see the impact that this has. There's hope that it will actually decrease the ceftriaxone resistance substantially.

This slide shows resistance to ceftiofur in *Salmonella* Heidelberg from Canada. *Salmonella* Heidelberg is a serotype of *Salmonella* that tends to have high rates of resistance to ceftriaxone. And ceftiofur is an antibiotic that's very similar to ceftriaxone. When the use of ceftiofur for injection of eggs was withdrawn, you see that the resistance to ceftriaxone plummeted.

The last story that I'm going to mention is about *Salmonella* Heidelberg. And I just told you that ceftriaxone resistance varies quite a lot between different *Salmonella* serotypes. Heidelberg is a serotype that has tended to have a lot of ceftriaxone resistance. It's a serotype that's associated with poultry. It's been in the news in the past year, associated with a large outbreak -- as the cause of a large outbreak associated with chicken.

And what we see in NARMS, looking at the human data, which is shown here in the yellow bars, is that the percent resistance, the percent of isolates with resistance to ceftriaxone has been around 20% over the last several years. One year it was lower, but in general around 20%. And ceftriaxone-resistant isolates have been isolated from ground turkey, here in the blue; from chickens, here in the red. Don't pay too much attention to this zero here in the green. This gets to the point that Dr. McDermott was making earlier about the small number of isolates that are available from the retail foods and the difficulty that that poses in digging deeply into trends.

So I've been talking about our routine surveillance in NARMS. NARMS at CDC has also had an initiative to improve the availability of antibiotic resistance data in outbreaks. Since 2012 we've been testing more outbreak isolates, and we've been testing them faster, and our goal is to aim for real-time testing and reporting. And this has a number of benefits.

First of all, for multi-state outbreaks where CDC coordinates

the investigation, it helps with the prioritization of which clusters -- there are many that are being followed at any given time -- the prioritization of those that do have resistant infections, because those, we know, may be more severe. Looking at the resistance patterns can also give the investigators important clues about what food might be causing the outbreak, which can help solve the outbreak faster and stop it more quickly.

We're also trying to get isolates as quickly as possible from the single-state or local outbreaks and conducting active outreach to states to get those in as quickly as possible and to test them as quickly as possible.

And then we're linking the NARMS surveillance data, the resistance data to the outbreak surveillance data so that we can see which resistance patterns are going with which foods for food source attribution.

We're also reporting NARMS data with our outbreak web postings for all multi-state outbreaks that are posted by CDC. So this data is being made available to the public as soon as it's available.

So, just to sum up, CDC is addressing the challenge of resistant foodborne infections by promoting prevention both of resistant infections and of all infections -- if you prevent all *Salmonella* infections, you'll prevent resistant infections as well, by tracking resistance -- and the antibiotic resistance initiative that Dr. Solomon mentioned includes, as an important point, increasing the testing of *Salmonella* in NARMS from every 20th isolate to every isolate so that we would know, as soon as an outbreak is detected,

whether it's a resistant outbreak and also so that we would have much more ability to look into the details of resistance patterns in different parts of the country and different subgroups of the population, making that information more available faster, refining estimates of the health impact of resistance -- you'll hear talks about these later today and tomorrow -- using real-time resistance data in outbreak investigations, as I've been talking about, and then refining our knowledge of the sources of resistance and the mechanisms of resistance so that we can understand how better to control it.

So thank you for listening. I'd be happy to try to answer any questions.

(Applause.)

DR. SCOTT: Morgan Scott, Texas A&M University.

This actually is a question also for Dr. Solomon. I believe he had a slide that showed much higher prevalence of resistance or partial resistance to the quinolone, the fluoroquinolones, in *Salmonella*. I was quite shocked by it. I'm asking, did he include the Typhi and the Paratyphi in that graph? Because yours show much lower levels. And, again, for some of us who are cautiously optimistic that levels of quinolone resistance in animal agriculture or animal agriculture-attributed *Salmonella* has stayed low, I was kind of shocked by his graph.

DR. MAHON: I think his graph actually just had a typo on it. That was actually Typhi resistant, *Salmonella* Typhi only. So the quinolone --

the resistance data that I showed were for the non-typhoidal *Salmonella*. And so yeah, I would be very alarmed also if it was those levels for non-typhoidal *Salmonella*, but thankfully they're not.

MR. ROACH: This is Steve Roach with Food Animal Concerns Trust.

This is more just a comment. You stated that there were four enteric pathogens that were on the list, but clearly *E. coli* is an enteric organism that causes disease when it escapes a gut. And sometimes it is an enteric pathogen. And *Clostridium* is another one that are enteric. And I bring this up primarily because we don't generally think of these as foodborne pathogens, but there is growing evidence that there can be food animal sources of these and that they all could potentially be transmitted for food.

And I think, as we get more of the whole genome sequencing and more information about -- we kind of say anything we find on animals is a commensal *E. coli* unless it's causing them a toxigenic one. And really we don't know whether it's commensal or it's a potential pathogenic one. And particularly when we think of your -- I was looking at the threat report. It kind of ignores six to eight million *E. coli* urinary tract infections, many of which are also resistant.

So I think I would encourage you to kind of think beyond *Salmonella* and *Campylobacter* as the bugs that we're not primarily

concerned about from foodborne sources.

Thank you.

DR. MAHON: Yeah, it's an excellent comment. We're also very concerned about urinary tract infections and the role of food sources in resistant urinary tract infections. It's something that has not fallen into the bucket of NARMS, but we very much would like to -- both ourselves and for others to be working on improving our knowledge of the full burden, which would definitely include syndromes and pathogens beyond what I've discussed.

Okay, thank you.

(Applause.)

DR. ESTEBAN: So good morning. It's still a good morning.

I'd like to introduce our next speaker, Dr. Hill. He's a Scientific Advisor for the Food Safety Inspection Service laboratory services. In part of that, he was the Lab Director for the Eastern Laboratory in Athens, Georgia, and he did that for 13 years before we captured him, a scientific advisor. Joe received his doctor of veterinary medicine degree and Ph.D. in veterinary pathology at the University of Georgia College of Veterinary Medicine, and he's board certified by the American College of Veterinary Pathology.

Joe.

DR. HILL: Thank you.

Okay, I'm going to talk to you a little bit about how USDA uses

NARMS data, but I'm going to give it to you from the FSIS perspective or at least with an FSIS slant to it. So, if I'm going to give it to you with an FSIS slant, obviously I'm going to tell you a little bit about FSIS and some of the work that we're doing.

But, again, FSIS is responsible for meat, poultry, and processed egg products, making sure they're safe, wholesome, and correctly labeled. And FSIS has approximately 10,000 personnel and 7,500 of those are actually out in the field. They're either working in the plants or they're working in the laboratories. And FSIS oversees or regulates approximately 100 billion pounds of meat, poultry, and processed egg product production every year, and processing.

Let me give to you a little bit about our org structure. There are couple of departments within FSIS that are most aligned with NARMS, and that would be our Office of Field Operations, where we not only have our recall management staff, but then that's also where the inspectors and veterinarians are that collect our samples that are sent to the labs that we do our testing, and this data that we generate is used by NARMS. And then the other one would be the Office of Public Health Science, and that's where our scientists and headquarters are involved with outbreaks and epidemiology, but then the labs also fall under the Office of Public Health Science.

And FSIS began their participation in NARMS back in 1997. And, initially, all we did was isolate the samples and then we walked them

upstairs or shipped them across the U.S. from one of our other labs, and we shared them with our ARS partners in the BEAR group right in the Russell Research Center. And these isolates came from our HACCP verification samples. And then Paula Cray's group did the rest of the further characterization of those.

But then, as Pat mentioned, back in March of last year, 2013, we actually started collaborating with FDA to isolate pathogens and commensals from cecal content. And the first year, what we would do is we would isolate the organism, we would extract the organisms, and we would ship those to FDA NARMS, and they would do the further characterization. But then, starting this past January, we not only extract the organisms in our laboratory, but then we also do the further characterization of those. And then, as I mentioned again, now all of these isolates are further characterized in our Eastern Lab in Athens, Georgia, and we do -- for *Salmonella* we do molecular serotyping, we do the PFGE, and we do the antimicrobial susceptibility testing.

Another thing that we've started to get involved in, you know, right now, for all of the FSIS-related animal ARMS analyses, those are performed by our Eastern Laboratory. And we get this data real time. So, within a week, 10 days of isolating a *Salmonella* or a *Campy* from a HACCP sample, we will know the PFGE, we'll obviously know the molecular serotyping, and we'll know the antimicrobial susceptibility pattern for that

you know, why all of a sudden did this one crop up, and what makes it so special? This is a real learning opportunity to take that organism and break it apart and find out where it came from, why it could live through the chemical interventions that take place at the plant. Why is it so virulent? Why is it resistant to many serotypes or patterns of it are so resistant to antibiotics?

We had the same thing with other *Salmonellas* in the past, and we made changes. And sometimes those went away or at least the prevalence went down. You know, like Newport. Newport and cattle was a problem a while back. Did the processes that we put in place, did the policy changes, was that what made it go away or did the organism change?

Everybody knows this, but antimicrobial resistance is a serious health threat to both animals and humans. And again --

(Alarm.)

DR. HILL: I set the alarm off.

But it's a challenge that requires a One Health approach. And while USDA and FSIS is not the lead agency with respect to regulating antimicrobial drug use, it's a part of the solution, and it's up to us to help address this challenge, too. And FSIS has collaborated with other USDA agencies to develop an action plan that's comprehensive. It takes on an integrated approach for future surveillance, research, development, and education and outreach.

One of the things that USDA did is, back in 2012, they

sponsored a USDA antibiotic resistance workshop, and there were many agencies there, FDA, CDC, NIH, many employees from throughout USDA. Stakeholder groups were there. And the objectives -- you've seen these earlier today, but to review current antibiotic use and resistance monitoring; to review management practices; to review alternatives to the use of antibiotics. And then the stakeholders actually identified three categories of data deficits, and that was how are antibiotics -- how do you really find out how antibiotics are used on the farm and then come up with resistance measures? They wanted to know about ecologic assessments. And then they also wanted to know about the economic impact assessments, because taking drugs away does have some economic impacts.

So some data gaps that FSIS is interested in right now -- and we're looking into it -- is what makes -- is there a difference between a pan-susceptible *Salmonella* and a multi-drug resistant *Salmonella*? We know there is, but is one more susceptible to thermal inactivation? What's the difference in the infectious dose required to cause disease? Are there other risk factors associated with pre- and post-harvest management strategies that causes the MDR one to survive and surpass the pan-susceptible one? What are some pre-harvest and post-harvest intervention strategies?

So FSIS has research priorities, and we have a huge list of research wants and needs, and we work with our ARS sister agency and we go through this. And they're always great to collaborate with. They're willing to

do the research that we need done. And then this research, this list of research that we need, it goes through a vetting process. FSIS prioritizes it, and it goes through our governance process. And then once we have the top 20 or top 100, or whatever it is, research needs, then we communicate that. We not only communicate it to ARS, but we put that list on our website, our webpage, so folks in academia and other places can see the type of research that we're interested in.

And now I'll touch just a little bit on some of the ongoing work and collaboration. We've requested ARS to look at the susceptibility of a couple of outbreak-associated strains -- Heidelberg, obviously, and Hadar -- in some poultry products and how they respond to heat, pressure, and acid. And then another collaboration that we'll start within the next year -- again, this will be with ARS, and they will be using a lot of our *Salmonella* isolates -- is they will be looking at chemical interventions and how does that alter the organism. Does it select for more virulent *Salmonella* or *Campy*? Does it select for organisms that are more likely to be multi-drug resistant?

And then NARMS partners are conducting all types of research, you know, epidemiological, microbiological research studies. Some of them look at risk factors, clinical outcomes, subsets of bacteria that have specific resistance patterns. And, again, we're interested in the basic science of this.

And another thing that we're interested in, because we're doing a lot of the actual testing now, is we collaborate with our partners to

come up with new methods for isolation and typing of organisms. And then, obviously, we use NARMS data for outbreak investigations, such as a couple of high-profile ones, such as the Heidelberg and the Hadar investigations.

And then the last point I'll make is a current interest that we have. We found that we're seeing more ceftiofur in our National Residue Program samples for the last year or year and a half. So I know that ceftiofur resistance had actually been dropping over the years, I think, in most species other than swine. So now would be good to go back and look and see if we see a parallel increase in ceftiofur resistance if we keep seeing these ceftiofur residues. What we would really like to do is set up a program where we could take the same animal as it arrives at slaughter and we would not only test for residues, but we would also isolate for pathogens and then do the antimicrobial susceptibility testing on that particular animal or that flock that came through.

And then the other thing that we would -- that's a current interest to us is to evaluate changes to organisms along various steps in processing, because a few weeks ago we heard some of the preliminary results from on-farm testing, and sometimes what you would hear these researchers talk about is, if you look at an organism on the farm, it's here. If you look at it in lairage or right after it gets off the truck, you know, it's changed here. If we do a carcass swab, then what we find is the data might be here. But if we go to the poultry parts or pork parts in final packaging, the

data that we're coming up with might be different from what we saw way back on the farm.

Thank you for your attention, and I'll be glad to answer any questions.

(Applause.)

MS. SMITH DeWAAL: Good morning.

DR. HILL: Good morning.

MS. SMITH DeWAAL: Caroline Smith DeWaal with the Center for Science in the Public Interest.

Dr. Hill, I remember the day I spent with you down at Athens while you showed me the labs, and Paula Cray showed me the ABR resistance sampling method they were using. So really, really informative. So I hate to ask you a hard question.

DR. HILL: Oh, I'll make Emilio answer it.

(Laughter.)

MS. SMITH DeWAAL: Excellent, excellent. Always good when you have backup.

So the issue -- and it's really a broader question and it's kind of following the morning of discussions -- is while NARMS may be doing really great work, the reality is we have seen some very large outbreaks linked to ABR pathogens, *Salmonella* Heidelberg being the best example most recently. But these are outbreaks that are entirely predictable at this point. We know

they're going to happen again. And I'd very much like to know what you at FSIS are doing. You mentioned you're working with APHIS and ARS, which is terrific. What are you learning that's telling you, from these examples of outbreaks, what we need to do differently?

And I don't mean to put you on the spot, because really CDC and Emilio and others could probably weigh in as well. But thank you, Dr, Hill.

DR. HILL: Thank you. Well, you know, again I go back to the great collaboration that we've had. But I think, in the past, FSIS has been more -- and again, this is from Joe Hill's perspective because I know, in headquarters, that we've had scientists that have been very, very much involved in NARMS and know much more than I do, since I've only been working with NARMS for about a year or a year and a half. So I think we're still learning, I really do.

And, again, this is Joe Hill's perspective, but maybe for years we were looking for trends and maybe making small changes and then looking at trends again to see if it had an impact, rather than a holistic approach of this is the big problem and we need to -- you can't trend on real-time data, but having real-time data to be able to look at it, I think, is going to be a big help. And if we had this real-time data that's shared with a broad audience, I mean, there's going to be people that are a lot smarter than Joe Hill or Emilio to make decisions. So maybe that's the answer. But for folks that have been involved with NARMS longer than me, I'll be glad to -- I'm sure they can

answer better.

DR. ESTEBAN: If I can add something to Joe's statement. For many years since we started working on this in 1996, we made significant progress in all pathogens, *Salmonella* included. But it's only recently, the last few years, that we've hit this flat line with *Salmonella*, but we just can't seem to move it down.

FSIS last year announced a big change in -- another initiative where we are addressing specifically some of *Salmonella* in all of our slaughter classes, that together with our taking over, if you will, the analysis of the isolates to do it real time, those two things. And the third thing that we've done recently is the poultry slaughter rule that will allow us to do more at the plant to improve the quality of the product coming out of the establishment.

So I think these three things -- and as Joe said, we're still learning. But if we continue to move along these three things, you will see an effect real soon. Just what effect, I don't know. But all of this effort has to pay off somehow on the other side.

DR. MAHON: Barbara Mahon.

Just a few thoughts from the CDC point of view. There are two things I'd like to tell you about. So one is that the initiative that Dr. Solomon and I have both talked about, to test all *Salmonella* in real time so that we know, as soon as an outbreak is detected, whether it's resistant or not, that

also allows us to get to the people who have those *Salmonella* infections and find out what they've eaten, what they've been exposed to, what they've done, what they've petted, what sort of animals they've been in contact with, when their memory is still fresh.

We know from a long history of investigating outbreaks and tracking foodborne infections that solving outbreaks is the best way to find out what sources are actually making people sick. When people have an illness that isn't part of an outbreak, they could have gotten it from anywhere and there's really no way to figure that out. But when an outbreak occurs, it offers the chance to see what did a group of people have in common and to actually pinpoint the source. And then we can learn about what went wrong, how those people got sick. You know, if it was meat, how -- you know, where the meat came from, how it was processed, how it was developed, and so forth.

So I think that the initiative to test all *Salmonella* in real time offers a huge promise for decreasing not only resistant outbreaks but actually all resistant infections. And if you go to Dr. Solomon's website, there's actually a target of decreasing multi-drug resistant *Salmonella* by 25% by 2020. And I think that this is a really realistic way of going about that.

The other thing I'd like to just --

(Off microphone comment.)

DR. MAHON: I'll come back to you.

The other thing I just want to mention is -- and Dr. Tauxe has been involved in many of these discussions over the last year -- several months -- with producers, poultry producers, for instance -- I think that there are changes coming from within the industry as a result of their seeing these outbreaks, understanding that antibiotic resistance is something that people are paying a lot of attention to now and that I think they want to pay more attention to it. I think that it may be that the people that they're selling to want them to pay more attention to it. I think that can also drive change.

MS. SMITH DeWAAL: Yeah. And thank you very much to the three of you for responding. My real question is really going to root cause. If you look at this from a consumer perspective, we may have a lot of really good research data, but we may also be losing the war. I mean, we have a really good example of an outbreak that's current. And you mentioned, Dr. Hill, the collaboration and discussions with APHIS.

What's our root cause analysis? Do you have it yet? Is it coming? Why in that particular outbreak did we have so much resistant *Salmonella*, different resistance profiles, when the company claims it's not really using any?

DR. TAUXE: I'm happy to comment just in a general way. This is Rob Tauxe.

The two recent, rather agonizing and prolonged outbreaks associated with Foster Farms, I think, illustrate why I feel some cautious

optimism. The first one was two years ago, and it was in the Northwest. It was associated with one particular processing plant, the one that we just finally decided was likely to be over a week ago. That lasted longer than a year and was with their three main California plants. And in both cases the particular patterns that were involved, some were resistant. In the most recent one there were seven different patterns, and virtually all of them had a degree of resistance that was sometimes present. But those patterns were internally present. They were on the parts, they were in the factory, and they were very clearly coming in from the live animals.

And the fact is that working with FSIS and really a prolonged effort on the part of the company brought the counts down both on the chicken and in the people, to the point that those patterns are now very rare. The one in the Northwest is gone. It hasn't occurred in Washington State this year. And the ones on the West Coast from the more recent outbreak are now very low, they're very low as a result of changes in in-plant production. They're focusing on cleaning up the parts and changes on the live side that I think are still going on, and there's more to be done and there's more to be learned.

So the new policy of when an antimicrobial-resistant strain comes out of a meat sample or a cecal sample, letting the company know immediately you've got a problem is perhaps, to me, the most dramatic change of all because the context in which that will be received should be one

of great energy and interest and concern.

UNIDENTIFIED SPEAKER: Yeah. Actually my question sort of goes back to this root cause problem because -- you know, at least from talking to some people at FSIS, there is some understanding that potentially the root cause of some of these strains, both the Hadar in the turkey and the Heidelberg, probably came from primary breeders at least somewhere further up the chain. And we don't really have very good surveillance systems, at least in terms of the companies maybe doing some sampling. But I think that's a part of the problem that we're probably missing.

And, again, talking to the people I spoke to at FSIS, it's also beyond any authority of anyone that we really don't have -- APHIS has animal health authorities. FSIS has food safety authorities. But we really don't have anyone that has authorities to say to the breeders, something you're doing there is causing a food safety problem down the line.

But I would just think, you know, how can we actually -- and I think there's a lot of antibiotic use on that, as opposed to some of the -- you can raise a broiler chicken or a meat chicken in a house for the 42 days pretty easily without antibiotics. But the ones that you have to be breeding, that's actually probably where we're using more antibiotic use in the poultry region as well. And, also, there is some evidence that that is actually where your source point -- at least one of them -- and then it goes through the whole system and that's why you have these really big outbreaks that last for a long

time, because they're going from the breeders to a bunch of houses and then it's hard to clean it up.

So it's a comment, but it is also kind of a question. How do we address that problem?

DR. HILL: Yeah, it's very pertinent because I know -- you know, we have the National Poultry Improvement Plan, and that was started many, many years ago to control Pullorum and other serotypes of *Salmonella* that were harmful to the birds. But over time it grew, that now I think CDC and FSIS is really interested in sitting down at the table with the board of NPIP and saying, are you interested in adding other serotypes of *Salmonella*, like Heidelberg, to try to eradicate that and control that at the parent flock?

DR. BASU: This is Pat Basu with FSIS. And I'm going to put my neck out and then make some comments.

To answer the last question about working together and getting these things done, we have two documents that you can look at on the webpage, FSIS' website. We have two MOUs we have finally signed. One is with CDC and one is with APHIS, and both are for root cause analysis, where this is a partnership with CDC. We have already trained people to go to a plant and look at -- finding out the root cause analysis of different outbreaks that the plant is facing, recalls, et cetera. And we've already put it into effect, so we have people at the sites and working with us.

With APHIS, we signed MOU and we just finished the training

for the APHIS people, like Bruce over here. And we haven't implemented it out in the field yet, but we plan to, and that will be following, like similar for any outbreaks in the plant where APHIS will go and take over, with being invited by the producers, to look at helping the producer. And again by invitation only they will look at it and follow through and try to identify what the root cause is.

So these are already published on the website, and you can look it up. And I can answer more questions if you have any.

DR. HILL: Thanks, Pat.

DR. ESTEBAN: Thank you, Pat.

Thank you, Joe.

DR. HILL: Thank you.

(Applause.)

DR. ESTEBAN: I'd like to introduce our next speaker, Regan Rickert-Hartman. She's an epidemiologist with the National Antimicrobial Resistance Monitoring System at CDC. Ms. Rickert-Hartman has served as a coordinator for the NARMS program at CDC since 2007. Her work focuses on surveillance and epidemiology of antimicrobial resistance among human enteric infections. More recently she has been nominated to serve as a member of the World Health Organization's advisory group on integrated surveillance of antimicrobial resistance.

Regan, it's all yours.

MS. RICKERT-HARTMAN: Thank you.

So I think I'm the first person, I guess, to say good afternoon to you. And I'm sure everybody's hungry, so this is a tough spot to be in.

So my talk today is going to focus on how the NARMS program at CDC conducts surveillance of antibiotic resistance in human enteric infections. And this is going to be somewhat of an extension off of Dr. Mahon's presentation that you saw two presentations ago, and also to help set the stage for Dr. Whichard, who will be presenting right after lunch on some of the data management that we're currently involved with at CDC.

So, as you already heard this morning, the NARMS program is an interagency collaboration among CDC, FDA, and USDA, and it's a great example of agencies working together, leveraging their unique expertise to protect the public. The three agencies collaborate to track and prevent antibiotic-resistant intestinal infections, and each one of these agencies receives and tests isolates for antibiotic resistance.

NARMS at CDC began in 1996 and focuses on testing isolates from humans. Currently, CDC NARMS partners with 54 state and local health departments. There are two NARMS teams at CDC that work very closely together. The first team, on the left, led by Dr. Barbara Mahon, is within the Enteric Diseases Epidemiology Branch and focuses on data collection and management, annual report generation, research on the epidemiology of resistant infections, and trends of resistance. The team on the right, led by

Dr. Jean Whichard in the Enteric Diseases Laboratory Branch, focuses on receiving and testing isolates for antibiotic resistance, working closely with NARMS state partners on the preparation and shipment of isolates to CDC and research on mechanisms of resistance.

So I think Pat showed this slide previously. This is a slide that shows the NARMS human isolate sampling and how it expanded over the years. So we began in 1996 with 14 sites and then we expanded the number of sites to 17 in 1999 and then to 28 in 2002. Our last expansion was in 2003 when the CDC NARMS program became a nationwide surveillance system that included all 50 states and four local health departments. Starting in 2003, all 54 NARMS sites were forwarding in samples of isolates they received from clinical laboratories to CDC NARMS for antibiotic resistance testing.

So what isolates do NARMS sites send to CDC for testing? You've heard a little bit about this already this morning, and I'll try to go into a little more detail for you.

This slide lists the pathogens that are being tested, the year testing began for each pathogen, and the current sampling scheme. You'll notice that in addition to pathogens commonly transmitted through food, like *Salmonella*, *E. coli*, and *Campylobacter*, CDC NARMS also tests *Shigella* and Typhi, which helps to give a more comprehensive view of the major enteric bacterial infections that affect humans.

So, for example, CDC NARMS sites are currently sending every

20th non-typhoidal *Salmonella*, *E. coli* O157:H7, and *Shigella* that they receive at their state laboratory, as well as all *Salmonella* Typhi and *Vibrio* other than *Vibrio cholerae*. NARMS also receives and tests *Campylobacter* isolates, but *Campylobacter* isolates are only submitted to CDC NARMS by the 10 FoodNet sites.

So just quickly for those of you who are not familiar with FoodNet, FoodNet is a collaboration among CDC, 10 state and local health departments, USDA's Food Safety and Inspection Service, and FDA. And FoodNet conducts active surveillance for laboratory confirmed infections with nine pathogens transmitted commonly through food. And combining the total number of isolates from all of these pathogens, on average, CDC NARMS is testing approximately 5,000 isolates per year.

In addition to the routine surveillance just described, CDC NARMS also tests isolates from outbreaks, in order to characterize antibiotic-resistant pathogens isolated from patients in outbreaks. NARMS routinely tests isolates from outbreaks of *Salmonella*, *Shigella*, and *E. coli* infections. If isolates are found to be resistant, the outbreak will be prioritized and enhanced testing may occur.

Also additional resources have allowed for increased testing. For example, in 2013, NARMS tested over 600 outbreak isolates, which is a substantial increase since 2004, which was the first year that NARMS began testing outbreak isolates.

CDC NARMS has expanded outbreak isolate testing to help solve and stop more outbreaks, because we know that NARMS can aid outbreak investigations. First, outbreak isolate testing may help with hypothesis generation. One great example of this is multi-drug resistant *Salmonella* serotype Newport. We have found that multi-drug resistance, when seen in this particular *Salmonella* serotype, is commonly associated with cattle, and associations like this may help the outbreak response group at CDC determine the source of an outbreak more quickly. The good news is that in the early 2000s, changes in dairy farm practices slowed the spread of MDR *Salmonella* Newport.

Also we can determine the difference between foods causing resistant infections versus foods causing susceptible infections. And you'll have the opportunity to see a presentation on this analysis during tomorrow's epidemiology session.

NARMS outbreak testing results are also now routinely included in CDC outbreak website postings. The postings include information about the total number of outbreak isolates tested by NARMS, the drugs that the isolates are resistant to, and additional details about the clinical relevance of the resistance patterns.

The antibiotics that are used for NARMS testing differ depending on the bacterium. There's a standard panel for each bacterium that consists of several agents -- excuse me -- that consist of agents from

several Clinical and Laboratory Standards Institute, or what we refer to as CLSI, classes.

For example, in the column on the far left of the table there's a list of seven classes of drugs tested for *Campylobacter*. The next column displays the antibiotics that fall under each one of those classes. And the four columns to the right show the interpretation and is displayed as susceptible, intermediate, or resistant. Most NARMS testing is done by broth microdilution, which is the gold standard for antibiotic resistance testing, because it gives the most accurate, reliable, and consistent results.

So this figure shows the distribution of MICs, and it's a visual aid for the interpretation of MIC values. The MIC values are listed on the bottom, and the three categories used to interpret MICs are shaded in color. Green indicates the susceptible range, the orange area displays decreased susceptibility or what we refer to as intermediate, and the red, resistant.

So, for example, the isolate shown here was tested and found to have an MIC of eight, which falls in the susceptible range. However, we see that it is different from most of the other isolates that were tested; 95.9% of the isolates were shown to have "susceptible" at a lower MIC. Although the majority of the isolates fall into the susceptible category, looking at the data in this format helps us to see potential shifts in the MIC distribution, and this is one way that the NARMS program can monitor emerging resistance.

This slide -- excuse me. When you pool all of the NARMS

surveillance and testing activities into a timeline, what you will find is that the isolate submissions are ongoing and that the states are sending isolates, along with epidemiologic data that accompany those isolates, to NARMS on a quarterly basis. Also the isolate submission deadline is in early April of the subsequent year. So, for example, all 2013 isolates were due to NARMS by April of 2014. This allows most testing to be complete by the fall of the subsequent year, at which time analysis and report generation begins. The analysis and report generation takes approximately four months and currently we are testing up all -- finishing up testing for all 2013 isolates and plan to start report generation for our 2013 report this fall. So you can expect to see our 2013 report published and available by early next year.

This slide shows the cover of the CDC NARMS 2012 annual report that was published earlier this year, which includes over 100 pages and more than 50 tables of data. It is a detailed technical report that includes sections called "What is New" and also a "Highlights" section as well as a two-page summary.

The two-page summary is meant for audiences such as the general public or possibly policymakers, since the summary is short and focuses on findings related to medically important resistance. The report includes all of the pathogens tested as part of the CDC NARMS program and the resistance results for individual antibiotics as well as combinations of drugs or what we refer to as multi-drug resistant, or MDR.

For audiences such as researchers and academia, we include annual resistance percentages for the past 10 years and a trend analysis that compares the current surveillance year to a five-year baseline. So, as you can see, we have developed this report to serve multiple audiences.

Here is an example of the figure you will see in the CDC NARMS annual report. And this is an important figure, so I'd like to take some time reviewing it with you.

The figure shows changes in resistance in the current surveillance year, which in this example is 2012, to the average percentage of resistance during the first years that CDC NARMS conducted nationwide surveillance, which was 2003 to 2007. There are different pathogens listed below and medically important drugs or combinations of drugs for those pathogens.

So, for example, here is non-typhoidal *Salmonella,* and listed below are important drugs and combinations of drugs that we are paying close attention to. The vertical lines above each one show whether there has been a significant change in the current surveillance year compared to what we have seen in the past. If a vertical line crosses over the horizontal line, there has been no significant change. However, if the vertical line is completely above or completely below the horizontal line, this indicates that there has been a significant change.

So for the 2012 report, you will see that a significant increase

has been detected in four pathogen-drug combinations and also a decrease has occurred in three others. And all of the methods and results for this figure are described in the Highlights section of our annual report.

Another type of figure that you will see in the annual report looks like this. This example shows a summary of resistance for *Salmonella* serotype Heidelberg. You will see that all of the antibiotics tested for *Salmonella* are listed on the left and the proportion of isolates found to be resistant to each drug in blue. The light gray is indicative of the proportion of susceptible isolates, and if there are any that fall into the intermediate category, that will be shown in dark gray.

And one thing that we have found that's been extremely beneficial at CDC is working with our communications staff. They help us to publish a short list of key findings along with the annual report. This way, NARMS stakeholders can easily and quickly identify areas of concern as well as trends that we would describe as moving in the right direction. If you go to our website and click on our annual report, you will see this box under what we call "Key Trends." From here you can click on any of these to see additional details.

So, for example, if you click on the arrow next to "Right Direction," a pane opens that will give you additional details on resistance that is decreasing. One of the examples of this is that multi-drug resistance among *Salmonella* has declined over the past 10 years from 12% to 9%. This

information is derived from a figure in our annual report that I described to you previously, shown here on the right, where the two vertical lines for multi-drug resistance among *Salmonella* completely fall below the horizontal line, depicting a decrease in resistance.

Some areas of concern include resistance to ciprofloxacin. You've heard this a little bit this morning and saw a slide on it. Dr. Mahon showed this. It's remained at about 25%. We've seen this resistance hovering between 20% and 25%, even though in 2005 the FDA withdrew the use of these drugs in poultry. The good news here, however, is that the resistance is not continuing to increase like it was prior to the withdrawal. We know that once resistance appears, it can persist even without further antibiotic exposure. NARMS played an essential role in this success by tracking the problem, helping to point to sources, and showing the impact of actions taken to control it.

Also we are concerned about ciprofloxacin and azithromycin resistance among *Shigella*, because both of these drugs are important for the treatment of severe infections.

Lastly, *Salmonella* Heidelberg infections displaying resistance to a medically important drug, ceftriaxone, is of concern, especially given that this *Salmonella* serotype has been linked to recent outbreaks associated with poultry.

Another key trend in 2012 that falls under what we would say is

disturbing news is that quinolone resistance among *Salmonella* Typhi increased to 68%, which raises a concern that ciprofloxacin, a drug commonly used to treat typhoid fever, may not be as effective. This is a good example of an increase in resistance from sources outside of food animals, because *Salmonella* Typhi was only in humans.

NARMS data is also available to the public in the form of interactive graphs which allow the user the ability to visualize resistance percentages by year to the pathogens tested as part of CDC NARMS. Users can select the pathogen they are interested in seeing and the antibiotic that they would like to view. The data displays are available for everyone and can be found on the NARMS website. And I'll also share an example with you here.

So, if you all go onto the website, you will see a "Spotlight" section where the AR threats report that was mentioned several times already this morning can be found. Also our NARMS 2012 annual report can be found under the highlight section, and these interactive data displays.

So, if you click on the "interactive graphs," the first thing that you will see is a list of the six pathogens that CDC NARMS tests. You have the ability to choose any of the pathogens that you would like to view.

So, in this first example, "Non-typhoidal *Salmonella"* has been chosen. For non-typhoidal *Salmonella*, the user can choose "Overall" to view all serotypes or can view a few of the most commonly -- most common

serotypes individually. Excuse me. In this example, the "Overall" view has been selected. Also, on the far left, the user can choose the antibiotic class and the particular antibiotic within that class that they are interested in seeing. This particular graph shows ceftriaxone resistance among all non-typhoidal *Salmonella* tested from 1996 to 2012. Also included on this graph are the upper and lower confidence limits, indicated by the blue lines, and the total number of isolates tested by year at the bottom of the screen.

I also would just like to mention that the increase that you see there in the early 2000s was due to MDR Newport, which a couple people have talked about this morning, and also the small increase in 2009 was driven by serotype Heidelberg.

So some of the enhancements that have been implemented to the CDC NARMS surveillance over the past few years include a web-based surveillance system. And you'll get to see that after lunch. The first talk after lunch will go through that surveillance system for you. It was launched in 2012.

And with the new systems, the NARMS partners at the state and local level have been able to submit isolate details to CDC electronically. And this is a huge improvement over the way that we did it for the first 15 years, which was paper-based. They used to handwrite in paper log sheets submitted to us by mail. Then we would type everything in for them, have to go back and verify that what we typed was correct, and it took a long time to

get the isolates in and document all the details and then verify everything. This way the states can now just enter all of the information for the isolates to us electronically on their end and then they print out a paper log sheet from what they've entered and they can submit it with their isolates. So greater than 95% of the states were using this system within six months of deployment, and we've received very thought-positive feedback from them.

Also, as of last year, the states can now view and download resistance data for isolates that they submitted as soon as testing is complete at CDC, which is another big improvement for us. We have data forms that would have to be filled out and completed and submitted to us if any of the states wanted to see the susceptibility results to the isolates that they submitted. This way, once testing is complete at CDC, they can go into this electronic surveillance system and they can pull up the isolates they submitted to us and they can pull up all of the details of the testing. So no more data forms that they have to complete to get their data. And, again, you'll be able to see -- you'll have the opportunity to see the database and its functionality right after lunch.

So, also, the online interactive graphs that I just showed you were launched last year and have helped to communicate our results in a visual and easily understandable way.

And, in addition, the AR threats report is an enhancement of the use of NARMS surveillance data and it includes four enteric pathogens

monitored by NARMS.

And because NARMS is continually trying to improve the collection and dissemination of data for action, planned future enhancements for data availability include making data available even faster. And we are doing this by working closely with our information technology experts at CDC. Our goal is to be able to provide the public access to resistance results online on an isolate level and enable the public user the ability to download results for analysis directly from our website.

We are also currently building additional data visualization tools, and with these enhancements the public will be able to view and interpret NARMS data in a more timely fashion.

So, in closing, I would like to encourage everyone to visit our website where you can find information that CDC NARMS is currently spotlighting as well as information on several NARMS topics. And our website is listed here: www.cdc.gov/narms.

Thank you.

(Applause.)

DR. TAUXE: I think in the interest of time, the questions and discussions have been terrific, but we're a little behind schedule, and so if you could hold your questions until after the next two speakers are finished.

Our next speaker is Lieutenant Emily Crarey, an epidemiologist at the Center for Veterinary Medicine here at FDA, who now serves as a

epidemiologist in the NARMS retail program, liaison to the state public health laboratories.

Lieutenant Crarey.

LT CRAREY: Thank you. And good afternoon.

So I'm going to make it quick so that we can catch up, and I will skip a few slides. Today I'll be talking about the retail isolate surveillance and I will briefly go over the history of the retail meat program, talk in more detail about the retail sampling, since that was the main topic at our last public meeting, and finally show you some of the more recent retail isolate data.

So, as Pat mentioned earlier, the retail meat program started in 2002, shortly after the World Health Organization's Advisory Group on Integrated Surveillance had recommended that resistance be monitored from farm to fork with a three-pronged approach, including surveillance in food animals, retail sources, and clinical cases. As he also mentioned, we built this based on existing public health infrastructure, and the retail arm made use of the state public health laboratories that were part of the FoodNet program.

So, here, this is a slide that you'll probably see in everyone's presentations, but I just want to show you that we met the recommendations of WHO with a three-pronged approach, and all three arms are testing for *Salmonella* and *Campylobacter*, as well as in the animal and food isolates we're also testing for generic *E. coli* and *Enterococcus.*

Something that I do want to point out is that the food animal

species that are tested at USDA also correspond to the retail meats that are under surveillance. So for the chickens, we're testing the chickens with bone in/skin on, turkeys for ground turkey, cattle for ground beef, and swine we're testing pork chops.

So let's delve into this retail meat sampling scheme. There are two retail sampling objectives, and the first one is primarily that we'd like to detect the temporal changes in resistance; and, secondly, we want to determine the prevalence of antibiotic resistance in *Salmonella*, *Campylobacter*, *E. coli*, and *Enterococcus* in retail meats that are sold in the United States.

This is also a slide that Pat showed in his presentation. This is a great depiction that you can see how much we've grown from the very start of the retail program. In 2002 we started with five FoodNet sites, and as of January 2013, we currently have 14 retail meat study sites. And you can see those here highlighted in red. I also want to point out that currently, each of the 14 sites that we have, they collect the retail meat samples, and they isolate the target organisms from these samples. All the sites isolate for *Salmonella* and *Campylobacter*, but we only have four sites from the 14 that are testing for *E. coli* and *Enterococcus*. Those are Georgia, Maryland, Oregon, and Tennessee.

So let's look at the sampling locations. Over time, the retail sampling scheme has changed to incorporate some of the recommendations

that we received from the science review board. Prior to 2005, the grocery store locations were selected purely on convenience and sampling locations, now are based on a stratified random sampling scheme where each site will identify a minimum of three strata to sample from.

And these strata are designated by three-digit zip code areas. So I've selected California as an example because everyone is familiar with California. And here on the map you can see the red dots are the zip code areas that California has selected to sample from. They selected zip code areas that began with 941 and 945 to 948.

So once these areas are identified, the FDA then purchases a list of grocery stores within those zip code areas from a commercial entity called the Chain Store Guide. Next, we work with our partners at CDC, who stratify the list of stores into geographic quadrants, and they use a random number generated to randomly sample within each quadrant throughout the year. And, finally, once we have created these lists, each site is given five primary and five secondary grocery stores to sample from each month, as well as new sampling lists are provided on an annual basis.

So, here is an overview of the retail meat sampling scheme. In the blue boxes, these are activities that are done by the FDA and CDC. And then you'll see, in green, these are activities, surveillance activities, that are completed by the retail meat sites.

So each month, sites are required to visit five primary stores

where they collect two packages each of retail chicken, ground turkey, ground beef, and pork chops. And since we assume packages from the same lot can reflect cross-contamination that occurs in the slaughter plants and on the trucks that haul the animals to the slaughter plants, we require sites to sample two different brands. And when two different brands are not available, they've been instructed to select different establishment numbers and different sell-by dates. And, finally, secondary stores are visited when meat products meeting these criteria are not available.

So, since 2002, sites have been collecting 10 samples of each meat type, totaling 40 samples per month. You multiply this by the current 14 retail meat sites, and they sample throughout the entire year, which is 12 months, and this yields over 6,000 meat samples. So we do recognize that the number of samples has its limitations, and we do realize that it does yield too few isolates to make reasonable conclusions about short-term resistance trends. So we're currently looking into ways that we can increase the number of isolates and we want to do this through either expanding our sampling or revising the laboratory methods.

So, as you can see, the retail sampling scheme has its strengths and limitations. We've made significant improvements to the sampling by standardizing and randomizing the selection of the sampling locations as well as expanding the sites to have it be more geographically representative. But with any program, there is still room for improvement. Currently only 6% of

the population is represented by the postal codes that are selected by these sites, and we need more data and resources to really determine just how nationally representative the current catchment area is.

So here is a list of the data that each of our partnering sites collect. The items that are listed in red are currently not reported by the retail meat program. But we do find this data very helpful and interesting for other purposes, including research and epidemiological study questions.

Now for reporting. As with the human NARMS testing, all isolates are sent to the central location -- which in this case is the FDA Center for Veterinary Medicine -- for confirmatory identification, serotyping and speciation, antimicrobial susceptibility testing and other molecular workups, including whole genome sequencing and PFGE. Data from these tests are then reported annually by pathogen and source, and we produce those and make them publicly available to you all for your reading pleasure.

And here you can see the retail meat -- the cover of the retail meat 2012 report, which we expect to be released in the very near future.

And I just want to point out that the data that is in the coming slide should be considered preliminary until the 2012 report is officially released.

So let's take a look at the data. Here you can see how the retail meat program has grown over the years. In 2002 we sampled -- had about 2,500 samples, and that came from five sites. And you can see how we've

since doubled in 2012 to over 5,100 samples. And as I mentioned earlier, as of 2013, we've added three additional sites, and we have over 6,000 samples tested.

So here you see the *Salmonella* prevalence among the different retail sources. The majority of the *Salmonella* in the NARMS retail program is being isolated from poultry, which you can see here in the green and the purple lines, and over the years the prevalence has remained just over 20% -- just under 20%.

Here you see a different picture for *Campylobacter*. In the retail meat program, *Campy* is primarily isolated from retail chickens, which is in the purple line, and the *Campy* prevalence remains near 50%.

And so here we have the serotype distributions. So what we did was combine all the years and then we selected the top serotypes for retail chicken and ground turkey. And on the left you can see, for retail chicken, Typhimurium, Enteritidis, Heidelberg, and Kentucky were the top *Salmonella* serotypes in the NARMS program. And for ground turkey, it was Saintpaul, Heidelberg, Hadar, and *Salmonella* IIIa18:z4, z23:-.

So, over time, we can see how the serotype distributions have changed. And in retail chicken you can see -- for Typhimurium, which is in the blue, right here, and for Enteritidis, which is in red -- have increased over the years. Then, looking at Heidelberg, we can see that it was one of the top *Salmonella* serotypes in 2002 and has since decreased over time.

If you take a look at ground turkey in comparison, you can see that the same *Salmonella* Heidelberg is still continuing to decrease over time in ground turkey as well.

And, finally, *Salmonella* serotype IIIa18:z4, z23, which was first seen in the retail meat program in 2003, has become a top *Salmonella* serotype for ground turkey and seems to be increasing over time. Here you can see that, in 2012, it was the top *Salmonella* serotype.

So here's a figure from our latest report showing the antibiotic resistance in *Salmonella* isolates from poultry. First, let's highlight the really great news, which is that fluoroquinolones, like ciprofloxacin, which is seen here in the baby blue and is commonly used to treat *Salmonella* infections in the United States -- and it's practically 0% -- it's 0% from 2002 to 2012. And if you look in ground turkey, we can say that it is also at 0% as of 2012. So this is not a problem.

The not so great news, but still kind of good news, is that cephalosporin, ceftriaxone, which is seen here in the dark purple -- you can see the trend right here for retail chicken and here for ground turkey. It's also a critically important antibiotic for testing severe *Salmonella* infections in the U.S., and although it has had some increases in the past years, we do see in the most recent years that it is declining. So we are keeping a watch of this antimicrobial.

And since antibiotic resistance varies by serotype, it's really

important to note that overall changes in resistance in *Salmonella* may be a reflection of changes in resistance within the serotype, or it may be due to different serotype distributions, as well as it could be a combination of both. So to highlight this notion, we superimposed the Typhimurium prevalence in red so you can see how Typhimurium is driving the resistance seen in retail chickens.

Okay. And for ground turkey, we didn't superimpose any of the serotypes, just because ground turkey has a larger serotype distribution, and it's not exactly clear that there's any one particular serotype that's driving the antibiotic resistance in ground turkey.

And here we see a similar figure that we have also pulled from our 2012 report for *Campylobacter* species *jejuni* and for *Campy coli* from retail chickens. As you know, over 90% of the *Campy* that's isolated from the NARMS program is coming from the retail meats. So our reports focus on the *Campy* that is from retail chickens.

So I've highlighted here, in the blue boxes below, the macrolides over here on the left and the fluoroquinolones on the right, which are also used to treat human *Campylobacter* infections, and they're also authorized for use in food-producing animals. The good news is that macrolide resistance is very low at 1% or less for *jejuni* isolates, and it remains relatively level, here, for *Campy coli*.

Now, as you saw in some of our previous presentations, the

one from CDC, from Barbara, she highlighted how in September 2005 fluoroquinolone use was stopped in poultry. And here we can see that for quinolones, there just isn't a consistent decrease in the resistance. But, as Barbara mentioned, it remains level, and we have not seen large increases.

And the final thing that I want to point out in our data is the gentamicin resistance, which is in blue over here in the *Campy coli*. Prior to 2008, we didn't see any gentamicin resistance in *Campy coli*, but from 2007 to 2011, we saw a large spike in the gentamicin resistance. But since then, we have seen that it has decreased in 2012, and we briefly looked at our 2013 data, which also shows a continual decrease. And later in the afternoon, Dr. Shaohua Zhao will present more information on those gentamicin-resistant *Campy* isolates.

So, although we've come a long way from the start of the NARMS retail meat program, we continue to face new challenges and future needs. So, although we've added three new additional sites, we still need more isolates to make our sampling statistically robust.

And it's imperative that we become timelier in our reporting. As technologies improve and things become more real-time, we plan to make isolate-level data accessible as well as produce semiannual short reports, which Mike Grabenstein and Dr. Tate will speak more about those later.

And, next, there is a need for us to capture meaningful human and veterinary drug use data to better understand the risks that are

associated with their use, which Dr. Craig Lewis will discuss that in detail tomorrow.

And, finally, as all of us want to do, we want to better serve our public health mission through examining additional emerging hazards, but we want to do this without compromising our core monitoring functions.

And to finish, I just want to really thank our state public health laboratories that we partner with, because we wouldn't be able to complete the sampling or testing without their assistance, as well as the FDA/CVM NARMS working group, CDC, and USDA NARMS partners.

Thank you.

(Applause.)

DR. ESTEBAN: Thank you, Emily.

As Rob stated before, let's hold our questions until after we finish this morning's session.

I'd like to invite Joe Hill, whom I will not introduce again, to give us a presentation. And Joe, you're the only person standing between us and lunch.

DR. HILL: Okay, I'm going to get us out of here by one o'clock. So it's almost going to be like a data dump. But as I mentioned, FSIS has just recently become an active laboratory member of NARMS where we're generating data. So what I'm going to do is try to present to you some of this preliminary data.

So these are the sources of data that we're further characterizing right now. Obviously, we have our HACCP verification samples, our cecal samples. We have a program going on right now. It's called non-ready-to-eat poultry, but it's comminuted poultry or ground poultry. And we get a few isolates from our ready-to-eat products. We also get isolates from AMS school lunch program samples. We get them from baselines. We get them from for-cause testing. We get samples from state ag labs. And then past and future baselines have also been a good source of isolates for us.

This graph just sort of shows the growth of PFGE that we've performed and uploaded to PulseNet over the years. Starting back in 2006, we only had about 262 samples. This year we'll have over 8800 samples.

You know, again, starting in March of last year was when we started the NARMS cecal sample testing. So far, we have about over 7,000 samples. Just a couple of things I'll point out. It seems like the highest percent of *Salmonella* has been in swine. And then this is a little bit surprising, is the percent positives of *Campy* that we've seen in various animal classes of cattle.

I think the main thing that we're showing here is no -- if you look at cecal samples collected each month and isolations that we're seeing, there's no seasonality.

And if you look at the animal classes, at least the ones that we're getting a lot of isolates and we have pretty high numbers on, there's no

seasonality.

Campylobacter, pretty much the same. If you look at the ones that have a high level of isolation for *Campy*, they're pretty uniform across the calendar.

And don't pay a lot of attention to this one, but again, for our HACCP samples, which is finished product -- you know, that's either a carcass that we swab or it's ground product -- we started actually doing the in-house testing in October of '13, and this is the number of isolates that we have so far. Cecal samples that we actually started testing in-house, we started in January. So a very small number. And then the last year. This is the number of samples that we have data on from FDA.

The main thing about this slide is that, obviously, from cecal samples and from HACCP samples, we have -- we generate a lot of isolates. But here are two programs, like the comminuted poultry, where we're generating a lot of isolates in a short period of time. And then this is our for-cause Heidelberg study that's been going on for several months now, and you can see that we've generated a lot of isolates. Now, this information is useful to us. It would not be a benefit to upload this to the NARMS integrated database because it would skew the results.

Salmonella serotypes. This is just a list that tells you the top 5 -- I mean the top 10 -- whether it's from HACCP samples or from cecal samples, and they match pretty closely. There are some that we're seeing in

HACCP that maybe we haven't seen in cecal samples so far, so they don't necessarily correlate well with what the most common serotypes are in PulseNet.

The most common serotypes in cattle. If you look at our cecal samples that we've done so far with FDA, those match pretty well. HACCP is a little different. There's one thing, that we haven't seen any Dublin in cecal samples so far, but it's been fairly common in our HACCP samples. And Dublin has been one of the more common serotypes in cattle over the years, and it's been one that has had some resistance issues.

For chicken serotypes, Kentucky wins again on all three.

Turkeys. Pretty diverse in a population or serotype at this time, but again, we have very small numbers.

Swine. Whether it's the cecal samples that we're looking at or the ones FDA is looking at, those correlate well. For the last couple of years we really haven't had any HACCP swine carcass rinses.

PFGE patterns are diverse and not the top pattern seen in PulseNet. If there's any commonality, it's probably more with our HACCP isolates than with the cecal isolates.

And then if we start looking at percent resistance, the main resistance is for streptomycin, sulfamethoxazole, and tetracycline. And this just sort of breaks it out to whether it's HACCP or cecal. And I think, through most of these slides that you'll see, that we have a little more percent

resistance with our HACCP samples than we do with cecal samples.

This is just a really busy slide, but the main thing I wanted to point out in cattle, streptomycin and tetracycline have the highest percent resistance.

Swine. More with the tetracycline.

Chicken. Streptomycin and tetracycline.

And then I think the interesting one is turkeys, where resistance has maybe been a problem compared with other animal classes, and you see that there are several -- whether it's HACCP samples or cecal samples, there's pretty high resistance to various antibiotics.

This slide shows *Salmonella* isolates for cecal samples, and 89% of all the isolates that we've had so far will fall under those seven resistance profiles. And then 70% are pan-susceptible. You have about 2.4% that seem to be resistant to a lot of organisms. Now, those are cecal samples.

If we look at HACCP samples, 87% fall under these seven resistance profiles. A little less are pan-susceptible, only 56.4%. And then, again, we have about 2.7% of the HACCP *Salmonella* isolates that are resistant to several antibiotics.

If you look at *Campylobacter* with our HACCP samples, it may be a little bit more percent are *jejuni*s compared with cecal samples, where we see a few more *colis.*

Looking at cecal samples, we're not seeing any *jejuni*, so far, in

turkeys, but we see *coli*. For HACCP samples, it's a different story. We do see *jejuni* and we see *coli*. And then if we look at the *Campylobacter* resistance, again, a lot of tetracycline. There's some nalidixic acid and cipro that you have upward of 30% resistance. If you compare the species, they're pretty consistent, although maybe with nalidixic acid and cipro, *jejuni* is showing a little more resistance.

I'll skip over that one. Those are just folks in the lab that are involved with NARMS work now and will answer questions at lunch.

(Laughter.)

(Applause.)

DR. TAUXE: Actually, I think let's take -- there may be some questions. Let's take just a few minutes. But we're going to then stop for lunch and gather here in the room again at exactly two o'clock.

Are there any questions for any of the three previous speakers?

DR. SCOTT: I have a quick question. Morgan Scott, Texas A&M. A question for Regan.

Do you keep a firewall between this outbreak mandate that you now have in the CDC NARMS and the reports that are typically based on the 1 in 20 *Salmonella*? So your annual reports aren't going to start including those outbreak isolates, I hope.

MS. RICKERT-HARTMAN: Did you say, do we keep a firewall?

DR. SCOTT: Well, yeah. They're not going into the trend

reporting, are they?

MS. RICKERT-HARTMAN: So they're not right now. We actually had an appendix in our last -- 2011 annual report. That described all of the outbreaks that we had done testing for up until that point. And then we had decided, at CDC, that we would like the opportunity to present the current analysis that includes up through 2012 in a peer-reviewed journal before we publish it again in our annual report. So that's our plan. So it will still be published and found, but we're planning to submit that to a peer-reviewed journal first.

DR. SCOTT: But you won't mix them in and report them as part of a trend?

MS. RICKERT-HARTMAN: No, no.

DR. SCOTT: Good.

MS. RICKERT-HARTMAN: No, no.

DR. TAUXE: Are there any other questions?

(No response.)

DR. TAUXE: No. Okay.

DR. TATE: Okay. Well, I wanted to thank everybody for attending this morning's session, and I just wanted to remind you that there is a food cart out here for you to purchase food items. Only if you have a name badge that has your picture on it can you leave this area, and even with that, you need an FDA escort. So just try to remain in this area. But if you

need to go out or would like to go out, please get an FDA escort. And we will see you at 2:00.

(Whereupon, at 1:00 p.m., a lunch recess was taken.)

AFTERNOON SESSION

(2:01 p.m.)

MS. RICKERT-HARTMAN: Welcome back, everybody. We're going to go ahead and get started for the afternoon session.

So this session is entitled "Improvements in Data Acquisition, Analysis, and Reporting." And our first presenter is Dr. Jean Whichard, who is the team lead of the National Antimicrobial Resistance Surveillance Team at CDC. She received her doctor of veterinary medicine and Ph.D. from the Virginia-Maryland Regional College of Veterinary Medicine, and after receiving her degrees, Dr. Whichard joined the CDC, and her work currently focuses on antibiotic resistance.

DR. WHICHARD: Okay, there you go. Here we are. Welcome to the afternoon session. We're going to talk about data management, databases, web graphs, improving our timeliness, coordination, and reporting. And right now you're probably asking yourself, what a nut. Stick around. Go to the farmers market over there and buy some vegetables. Go out for ice cream. Maybe run back and try the carrot cake.

So let's look at the four core activities that NARMS conducts, and we can see that effective data management and presentation are at the heart of everything we do. I mean, we're really trying to get data for action, data out there quickly, data in a usable form. If we want to monitor trends in antimicrobial resistance, we better have the data structured in a way that

facilitates looking at resistance over time. If we want to be able to share those data in a timely fashion, we need them portable for analysis, they need to be structured for accessibility, portability, and distribution.

So you're first going to hear a little bit from me about how we've approached data management and presentation for one of the three arms of the so-called NARMS beast. And then you'll hear from Michael Grabenstein and Claudine Kabera about the bigger-picture dataset that much of what we collect fits into, and then from Heather Tate about the culmination of data reporting for animals, retail meats, and the overarching executive reporting processes for the subset of bacteria that span all of the NARMS partners.

So we'll talk a little bit about what information goes into our dataset, what data goes out and how, and some things that we hope to do in the future.

So we collect three basic types of data. We collect data about the people who are infected with the bacteria we're studying, a little bit of information about the bacteria, some identification data, and also this minimum inhibitory concentration data. These are the numbers that we measure. We expose the bacteria of interest to doubling dilutions of the drugs, and then we actually get that minimum concentration necessary to prevent growth. I love it when the definition actually exists in the term itself. And we do that in a 96-well format with one of these Sensititre plates such as

you see on the bottom here.

And we do this on a lot of bacteria. In calendar year 2012, the NARMS human surveillance received over 5,000. You see quite a big proportion of these is the non-typhoidal *Salmonella*, but we're also doing typhoidal as well as *Shigella* isolates and non-cholera *Vibrio* and a whole lot of *Campylobacter*. Despite our efforts to reduce our sampling scheme, we still continue to get 1,500 or 1,600 a year.

And we're getting a lot more into the outbreak realm of things. You'll see a whole lot of non-typhoidal *Salmonella* coming in in calendar year 2012. But we also got a little into the *Vibrio cholerae*, the outbreak in Haiti and doing some comparisons there. So just to give you a profile and give you a sense of how big our sampling is.

And to understand how far we've come in our data management, I need to tell you a little bit about where we came from. We came from a paper-based system that was in place as late as 2012. Hard-copy log sheets coming from the NARMS state participants, we would bring them to NARMS CDC. Regan's crew would enter them in. In many cases the states already had this data electronically, and it really seemed a lot more tragic, as we went, to be having this data just have to be copied, transcribed, and then read again and entered in. It was duplicative. It didn't capitalize on data that was already available in electronic form. In the very early years of NARMS, it went into separate SAS databases for each calendar year, and our reporting

depended on annual cleaning and closeout processes. And that's cumbersome. That's a cumbersome way to deal with data, particularly if you want something available in real time. We knew that we had some growing to do.

So the first step was to standardize our data structure across the years, and we took all of those little SAS datasets and rolled them up into a standard format, NARMS data, into a SQL server with a Microsoft Access front end. It was relational, it served us very well, but it was strictly for in-house purposes. We knew we needed a secure way to communicate with our NARMS participating sites. You know, based on our 2007 external review of our program, how are we going to get this data out in a more usable form and communicate in more efficient ways?

So to communicate with the state partners, we built a secure web application that our state participants interact with. We also interact with it. So we do our quality checks, and we do our own data entries, and even the laboratory data comes in through a secure web application through this big CDC firewall. It looks like a scary thing, doesn't it? It's a big old firewall. I think it's even bigger than the drawing seems to indicate here. So you do your authentication, and then you interact with the web application, and it all goes back into this data that's stored in SQL servers behind the scenes.

Some key features that we developed include electronic entry

of information by the states that are submitting the data. They're able to generate a packing slip of those -- information about those bacteria they're about to send us, because to send it through the mail, they still need some information to put in the box for couriers and for IATA regulations.

Isolate accessioning tools. So we've got some tools on our end to be able to bring the bacteria in to say, as a condition of this specimen, the way it needs to be, we can hold, we can reject, we can accept. And we also have automated processes for importing and validating the laboratory results.

Epidemiology and laboratory quality checks and approval functions. You know, the epidemiologists look to see, does it look like all the patients are a certain age or sex? You know, maybe you need to call a state and say, are you sure that's accurate, because we might need to update something? On the laboratory side, we're looking for weird combinations of resistance that might indicate something novel or they might indicate that the test needs to be rerun.

We have some pushbutton graphics now out of the live data that produce the graphics and tables that you see in our annual report. And we finally have portable isolate-level data that's accessible to the states and what we're using and aiming to use for a variety of reporting methods.

So let's take a look at what the state sees. I'll show you behind the scenes, okay? So the state gets to log in at this landing page. They have a

means to put in their e-mail address and their password and that's where they log in. Once they do that, they have the ability to enter information about the isolates that they're going to submit to us. They've got two ways of doing that, the sort of à la carte individual isolates if they've got a small number to enter, and we also have ability for them to pull isolate data in from lists.

This just gives you an idea of the types of fields that we're asking for. We're getting the individual submitting site's identification number; the genus and species; in some cases serotype of the bacteria they're submitting; a little bit about the collection data, specimen source, whether it's blood, stool, otherwise; and then we like to get their age and sex, if they're able to provide that. They have an ability to save anew and add isolates to that list. Again, it's sort of like the small-plate order as opposed to the combo dinner.

But for states that already have their data in a laboratory information management system, they can pull that into an Excel file or a couple of other different electronic formats and actually map the fields from their dataset over to the target fields that we're looking for in NARMS. For instance, they would say their Alabama ID number maps to our site isolate ID number. That way they don't have to do a lot of manipulations with their source file. They can just bring over what they need. They can actually save those mappings if they're going to have a similar file the next quarter when

they want to submit their isolates. So they have that little save mapping function.

In the view from the CDC side, you'll see that we can import our susceptibility data. Either the Sensititre comes in the form of a SVN export file, but we can also capture E-test data, disk diffusion data, that sort of stuff. Again, if you've got an electronic list, we can find a way to pull it in. We also do some identification. For instance, we confirm species of *Campylobacter*. So, again, this is a means for us to interact through the firewall with authentication, to be able to upload sets of data to the SQL servers behind the scenes.

You'll also see on the CDC side this approval tab right here. And this is, again, our quality assurance step where we can look at the information that the states put in and say, does that need to be updated, or do we need to retest some isolates for closeout?

I'm going to step back out of these weeds a little bit, just to orient us to where we are. So now we've got some information about the patients who were sick, some information about the bacterial identification data, and also the antimicrobial susceptibility data. It goes into this preliminary data pool and then those quality assurance steps -- now we have that approved dataset.

And now we can move on to reporting. And these are some of the existing reporting mechanisms that we have and also a few planned ones.

So the beautiful thing is that now we can get isolate-level data back to our submitting states just as soon as it's approved. So no more of this annual silo of data that we've got to carve out a few weeks to clean it up and then put it out. We really wanted to reduce the barriers to getting data out in a timely fashion. This is the same dataset that then goes into our annual surveillance report and then our FDA-integrated database executive report, also what feeds the graphics for our public-facing webpage.

And Regan already alluded to some of our linkage efforts and also the planned public download via the public-facing webpage. That's still in the works. I'm not going to make any promises of timing, but that's certainly our goal, is to get this data not only out to the submitting states, but all of our other reporting needs, including some more timely public access to the data.

So let's look a little bit at the information the states get back. So they go back to their same landing page. After they do their authentication, they're going to see a listing of all of the isolates that they've put onto their log sheets. You know, some of the things might be in progress. Some things might have been submitted. If it's been submitted, they can drill in there and see what's been received, whether it's been accepted, whether some tubes were held or rejected for some reason.

And then they can go to the view test results. And it's that same sort of entry screen, or very similar to the entry screen for the isolates,

where they can either search for a specific isolate number that they submitted to us and hit the search, or they can do an advanced search and they can look either over a date range or they can look for a given genus-species-serotype combination for that dat range. And here's a really neat thing. They can get the data back out through a list as well.

But let's show you first what they see when they're viewing those results sort of à la carte. If they're looking at an individual isolate's results, they'll see all the drugs that we tested, they'll see the version of the Sensititre plate that we used to test that isolate, and they'll see their minimum inhibitory concentration results and also the conclusion, whether that MIC of four amikacin means it's susceptible, intermediate, or resistant. It will have the susceptible and the limits of the susceptible and the resistant range for them to know where their MIC falls in terms of those limits. And we also give some information at the bottom that tells them where we got those breakpoints. Was it a Clinical Laboratory Standards Institute breakpoint? Was it a European Committee on Antimicrobial Susceptibility Testing breakpoint? So they have some context. They know where these things are coming from.

But they can also download those results by a list. Here we just have a list for state *Salmonella* Infantis. And then they can get all of those data that they already put in, all of those accompanying data about the patient and the bacteria that they sent, and then they can get in, in table

form, all of those results. You may wonder what AMI and AMP and ATM mean, but there's also a data dictionary in the O tab so they know the meaning of some of those kind of geeky database terms for the fields that we've collected.

So I think we're doing pretty well in terms of the state reporting. Let's see about our public-facing webpage. Now, Regan has already helped you drill down to some of those web graphics that we're producing, so I'll just try to hit a few highlights here quickly.

So you can choose your bug. You can choose the bacteria that you want to look at, the resistance over time. And here I just chose *Salmonella* Newport on a whim. This is something that certainly shows the rise and fall of resistance. Here we're looking at ceftriaxone resistance. And, again, we have those confidence intervals on the data, using the Paulson-Camp-Pratt approximation to the Clopper-Pearson exact method. And if I didn't sound like a microbiologist then, just try to pretend to be an epidemiologist. And I may have pulled the wool over your eyes. But yeah, just something to give you a sense of the certainty or uncertainty of those point estimates.

So you see we had quite a rise in *Salmonella* Newport. It was resistant to ceftriaxone in the late '90s. That's about the time I came to CDC, and it just really hit like wildfire, and we were calling people and saying, are you sending any extra *Salmonella* Newport in your boxes, because we're

seeing an increase in the submissions of Newport and an increase in this resistance and it was pretty huge. Thankfully, it's going down.

We could look at another drug. We could pick, for instance, tetracycline. If you go over here to this left side, you can either pick new serotypes or you can pick different drugs you want to look at. If we indeed look at tetracycline, you'll see that curve looks the same. And that just illustrates how the ceftriaxone resistance determinant and the tetracycline resistance determinant all travel on the same plasmid. So, if you've got one, you've got the other. So these curves look very similar, and so we see the same trend downward with the tetracycline resistance that we did with the ceftriaxone.

So, if we choose another one, we can pick maybe a human-specific bug, the sampling that we do strictly at CDC. And we see *Shigella*. I guess there's a little bit of good news there. We've had a fall in ampicillin resistance, although 30% is still nothing necessarily to cheer about. We're also looking at azithromycin very closely and *Shigella*. And for this one you can pick specific species, whether you want to look at *flexneri*, where we tend to see more multi-drug resistance, or *sonnei*. And, again, you can see the same drugs. These are the same drugs that we test for *Salmonella*. And we've seen that blip on the radar when it comes to ciprofloxacin resistance in *Shigella*.

I think I managed to pick some of the examples in the "of

concern" or "wrong direction," I guess, from your talk earlier, Regan.

And if we look at an example like *Salmonella* Typhi, we can see the rise of nalidixic acid resistance, which correlates very well with decreased susceptibility to ciprofloxacin. And we've even got some of those examples in *Salmonella* Typhi where they have both mutations in the quinolone resistance determining region, for the molecular biologists in the audience. There has also been a change in breakpoint for the typhoidal *Salmonella*, that we were able to bring some data to CLSI, and they revisited those breakpoints for invasive *Salmonella* serotypes.

So that's just some of the value addedness. And also the really good thing about having the data structured in the way we do, because then we can retro-apply new breakpoints if they're updated.

So how are we doing? Should we check our report card? I don't know. I was reading the strategic plan and feeling pretty good about how we're improving data management and in essence reducing the barriers to getting data out in a timely fashion, doing this quality check as we go and releasing the data as they're available to the states that are kind enough to pack the boxes of isolates and submit things to us. We're building all of our reporting needs based on those approved -- those quality checked isolates.

And now we're just trying to figure out what increments are going to be most appropriate to roll into our public-facing graphs and downloads and all. There are still opportunities to do better. Right now our

graphing tools depend on us making an Excel table of the data, making an actual summary of those data, instead of just feeding the live dataset into a graphing function. So those are some of the things that Regan and I and several other people at CDC are trying to find some more efficient tools for getting that data in a form that can be graphed on the fly.

So, with that, I will leave you to the others to talk about the grander scheme of things and the bigger NARMS umbrella and how this all fits into the executive reporting.

(Applause.)

MS. RICKERT-HARTMAN: We have time for a question or two, if there are any questions.

(No response.)

MS. RICKERT-HARTMAN: Okay. Thanks, Jean.

So the next presentation will be co-presented by Michael Grabenstein and Claudine Kabera.

Mr. Grabenstein is a regulatory information specialist with the FDA. He received his bachelor's degree in chemistry from the University of South Florida in 1997 and currently works as a data manager for the FDA arm of the NARMS program. Prior to his role at FDA, he worked at CDC managing antimicrobial resistance data collected through the Gonococcal Isolate Surveillance Project.

MR. GRABENSTEIN: Hi. Today I'll talk about the NARMS

interagency database and the FDA data for public access. I'll be talking about an update of the IDB status/progress made since the last public meeting, examples of the IDB reporting through business objects, adding genetic testing data to the IDB, and providing isolate-level FDA NARMS data on the web.

So for our initial goals for the NARMS IDB project, the first goal was to consolidate data from the NARMS program's three arms, the human, animal, and retail meat; also to enable the rapid production of consolidated data tables and graphs for the annual NARMS Executive Report; to enable the NARMS epidemiologists to explore the data to identify baseline searcher trends, et cetera; and to enable the FDA regulators to use our NARMS data to support risk assessments and other evaluations of animal drugs and new animal drug applications.

So here's a diagram of the IDB as it existed at the time of the last public meeting. Shortly before that, I was hired. So we added the internal FDA database analyst, and I created an Access database, which I used to gather the three parts of the data to assemble them, in order to hand them to the contractor so that they could be uploaded into our IDB.

I'll talk a little bit about the IDB. Shortly after the last public meeting, the IDB went online, and we were able to generate a can of reports for business objects. And I'll show some of those. Here's an example of showing some ceftriaxone resistance with *Salmonella* Heidelberg. This is a

table and a graph that are mirrored exactly in the Executive Report. And here's another diagram also from the Executive Report that was generated by the IDB. So antimicrobial susceptibility for non-typhoidal *Salmonella*. The table goes on and on and on, but this gives an example.

Now, with the IDB, ad hoc users can create a database for isolate-level data to really create any type of table or graph that they would like to see. They can select from the choices here on the left. They can pick different resistance flags, all the way down to isolate-level data really. And then, once they move these items over into the resolved object section, then they can have the report generated and they can select different years, select different genus, species.

Okay. Now, currently, for our current year we have a new data upload process. I worked hard to remove the contractor from the process so that we can upload data more often. So now I assemble the data myself and then I create the tables that go into the IDB. This saves us quite a bit of money, and like I said, it allows us to load the data much more often since we don't have to allot funds for this process.

We also have been able to add an additional storage for genetic data and the ability to add other susceptibility data for studies that are not built into the NARMS canned reports.

Here are some examples of some of the genetic data fields that we've added. Currently, the IDB doesn't have the data yet, but it has the

tables built, so we're ready to add this data into it.

And then, for the future, we hope to be linking data visualization software, like Tableau, directly to the IDB so that customized graphs can be pulled from this. And Claudine will be talking more about Tableau's functions.

For 2015, our goal is to upload the genomic data associated with NARMS isolates; to assist with data submissions so that contributing labs can send data to FDA for uploading as often as once a month; to enable assembly of the interim data before generating annual surveillance reports; and to apply new epidemiological tools for analyzing and communicating data, just like Claudine will talk about, and also to provide Business Object reports to support updates to the next Executive Report. There will be some changes, so we'll want to change some of these canned reports that we have.

Now, we have a desire to release data to the public, and certainly HHS is eager to follow the White House directive making research data more freely available to the public. And if you want to find more, you can go to data.gov. But if you go to the website, you'll see the FDA section and it's called "Open FDA."

Currently, security restraints prevent us from providing direct access to the IDB for users outside of NARMS, just for the public. But our solution to this is to post the FDA NARMS data to our website in a downloadable format. At this time we're thinking about an Excel

spreadsheet. So the data will be available after the NARMS reports have been published. The NARMS data will be downloadable as an Excel spreadsheet. And then there will also be a data dictionary that will be available, which will explain each of the fields that are there in the downloadable spreadsheet.

Here's an example of the spreadsheet. The data has been flattened to where each row is actually an isolate-level piece of data. So you'll see sample ID, genus, whether there's growth, species, serotype, depending on each isolate; state, month, year, meat type; if the meat is cut, ground; dates associated with it; organic indicator if it was collected; and then also more information about it and then rows of the actual MIC data; the sign for the data, the value that's like AMC relates to an antibiotic. So it would be the sign, then the value of the antibiotic, and then the AMC SIR. The S, I, and R would be sensitive, intermediate, and resistant to the antibiotic.

And that's all I have. On to Claudine to continue talking. Thanks.

(Applause.)

MS. RICKERT-HARTMAN: Ms. Kabera is an epidemiologist with the National Antimicrobial Resistance Monitoring System at FDA's Center for Veterinary Medicine. Claudine's work includes creation of the NARMS Executive Report and assisting with the coordination of activities related to

NARMS retail meat and food animal surveillance. She received her M.P.H. degree from Loma Linda University.

MS. KABERA: Good afternoon. So going off a bit of what Jean talked about in terms of interactive displays that we'll be looking at at NARMS and also going off what Mike mentioned in terms of Tableau, I'm going to give you a brief presentation of where we've been in terms of the interactive displays that we've used in NARMS and where we hope to go in the future.

So, as a brief introduction, NARMS has been around since 1996, so we've accumulated a great deal of data. And one of the things that we often talk about is how best to communicate this data to our stakeholders so that the data is in a manageable format and it also could be helpful for them to understand better what we're seeing on our end and communicate that information a little better. And one of the things that was considered looking at was interactive displays. And we've begun using displays in our 2008 and in 2009 NARMS reports. That was in 2011. And initially we started off by showing our resistance-level information for *Salmonella* and *Campylobacter* using the Xcelsius interactive graphs.

For the 2010 NARMS report, we added *Salmonella* serotype-level information, and we specifically focused on the *Salmonella* data that was serotype information relating to the top five *Salmonella* serotypes known to cause human illness. And as you can see, here I've included a copy of what the graphs look like, and I can also show you briefly, before I move on to

show you where we're thinking about going next in terms of our interactive displays.

I don't know if it's going to load. Since this seems to be taking a bit of time -- oh, wait. No, there it is.

Currently, in our NARMS reports, we include these interactive displays that, as Jean has shown you, allow you to look at specific drug-bug combinations and also look at specific sources. So in case you want to look at ceftriaxone resistance in humans -- say, chicken breasts and chickens and then you could also -- it has the added feature of scaling it so you can look at it specifically to the percent resistance and you can more easily see the results of the resistance information.

So this tool has allowed us, in the past, to really show the resistance information and communicate it better with our stakeholders. However -- sorry, it's not moving. There we go -- we've had some -- Xcelsius has some nice pros where it creates nice user-friendly interactive displays, and it allows us to use the displays either in our PowerPoint presentation or on the website. And it's easier to embed this information onto either CDC or NARMS or FDA websites.

It has some limitations, one being that it's only compatible with Excel. So you're limited to using a single Excel sheet to fit as much of our NARMS data into one sheet and then manipulate it on that sheet in a summarized format before importing it into this database and then continue

manipulation in the database to make the software more interactive before you can put it online. And that's really viewer intensive and it can take -- I know, in working with it, it's taken me months, sometimes, to create a singular interactive display. So that was one of the limitations of the software, another being that it's not compatible with anything past Microsoft 2007. Once we got Microsoft 2010, we found that that particular software was not at all compatible with anything -- with our Excel program.

And another limitation to the software is that it's limited to the amount of data you can fit in a singular Excel worksheet. So, if you have more data than that, you won't be able to house it, and you would have start removing years from your resistance trends, which we were hesitant to do since we wanted the stakeholders to have access to as much information as we can give them -- provide them.

So in looking at the limitations, we decided to look at several different softwares, and we honed in on Tableau. And while there are other competitors currently on the market -- one being Spotfire, which has been used previously by CVM; another one being Palantir, which I think is being used in surveillance programs at CDC -- we worked with our CVM IT contractors and after doing some product comparison decided that Tableau seemed to be the best fit for our needs in terms of the NARMS data.

So, briefly, I want to touch on what Tableau -- the different versions Tableau offers its users before I show you the pros to it and also

some visualization examples.

So Tableau offers a public version, which allows you essentially to upload for free interactive displays and also share them online. It offers you a public premium option, which enables you to secure some of your data so you don't share everything. So you have a little more control over your data. And then the version -- one of the versions we have at CVM is a desktop option, which allows a single user to sit to work with the software and create different visualization displays.

It also offers a server option which allows you to share whatever you create -- interactive displays you create -- to several users that you choose. And the nice thing about this is that if you are sharing the data and it is preliminary, you can actually -- you can limit how much manipulation they can do on their own in terms of your data.

And then there's also a large-scale, which has an unlimited number of users and you essentially have your own server and so you can create an infinite amount of visualizations and you can share as many as you want with your -- with stakeholders and with other partners.

So there are some limitations, but there are a lot of pros to this particular software. One is that it's easy to use and that you can connect to the data directly. So previously we had to create summarized data before we could import it into Xcelsius and use it. But with this, you can take the raw data from an Access database or a SQL server or an Oracle database and you

can upload it directly into the software, and then it automatically generates the variables for you, so then you can start manipulating it right away. And the nice thing about it is you can create a live connection. So, if you do have -- if you have corrections in the data or you have new data to add, you just hit a refresh button, and it automatically includes that new data into your existing displays.

And another nice thing about it is that it can handle very large datasets. So our NARMS dataset is ideal for this particular software. And you can also extract any analysis. So, if you create new variables within the actual software, you can extract that analysis into an Excel file and then upload it into another software as you need.

One of the limitations of this software, however, is that it can only be published on the Tableau server, unless you have a Tableau enterprise license. And also when you export the interactive graphs as an Excel or PDF or PowerPoint, they are static. So they don't allow you to do the same interactive visualization that Xcelsius does. However, you can publish on the Tableau server and then have the interactive display. And since we're intending to make our data more publicly available, I don't think that will be much of a hindrance.

So in the middle I included a brief visual showing the different types of interactive displays you can create. So you can do geographic data, you can do tabular data. You know, you can do bar graphs, scatter plots. It's

almost limitless in the things you can do with this particular software.

I included in this example the NARMS *Campylobacter* data that we have through 2011. And this is our first attempt at using this to show our NARMS data. We're hoping to get it on our website so we can share it with our partners and stakeholders.

And one of the things -- sorry, I think I went a little too far. Sorry, a little too far. So one of the nice things about this, that I like over the Xcelsius graphs, is it allows you to individually graph the different sources. And so when you say you want to look at a specific trend, say, ciprofloxacin resistance across the two species of *Campylobacter* and then the three sources, you can look at specifically each individual line and you can add lines as you go. And it gives you an individual idea of what the different trends are, which I think is really useful when we're trying to interpret what's going on in terms of the trends.

So one of the things -- I will have to say that I've been using this software for about a year, so I'm still pretty much a novice at this, and I hope to learn more and we hope that as we learn more, we can provide better visualization for our partners and our stakeholders. And to that point we have some ideas of how we can present the data in the future, one being creating a geographic map of our data. Say you want to look at the different stores that we're sampling and looking at the prevalence by a given a state, we can go ahead and map that into the software. And if you wanted to delve

farther into the data, we can include that map again here and then look at specific resistance trends and then add the data so you can actually have the percent resistance in a table format. So I'm hoping, as I learn, I can actually start creating these and providing it to our stakeholders.

Additionally, one of the ideas we also had was looking at the MIC shifts over time, so creating bar graphs similar to this, but with our MIC data and comparing it to our resistance trends over the years and then looking at the percent, the different MIC distributions, meaning susceptible versus intermediate versus resistant populations; and then also including here the bacteria, the sources, you know, maybe the years and months so you can look at things across the years, and it will give you more of a wealth of data in a singular tabular format that people can use and really delve into the data on their own and really experience the different possibilities that this software can offer us. And I think it's a good way to move forward in the future in terms of how we use our interactive displays for NARMS.

So, in summary, Tableau, I think, is a better alternative to Xcelsius. It's easier to use. It's compatible for multiple databases. It has a lot of dynamic displays you can use. It can handle a large dataset and you can -- the nice thing is you can connect directly to the data, so there's no need to create any additional work for our epidemiologists. And, hopefully, as we gain a better understanding of the software, we can hope to provide stakeholders more novel ways of experiencing the data.

Thank you.

(Applause.)

MS. RICKERT-HARTMAN: Any questions for Claudine or Michael?

(No response.)

MS. RICKERT-HARTMAN: Heather Tate is our next presenter. Dr. Tate is an epidemiologist for the NARMS program at FDA. She came to FDA in 2008 as a FDA Commissioner's Fellow. Her work focuses on epidemiological research of antimicrobial-resistant foodborne bacteria and reporting of NARMS data. She earned her doctorate in biomedical science from New York University and a master's degree in epidemiology from the Harvard School of Public Health.

DR. TATE: All right. So I'm going to talk about the new integrated NARMS report, also known currently as the Executive Report, and also FDA's plans to do interim *Salmonella* reporting.

So our Executive Reports have been published since 2003. And there's a very nice array of all of the reports that we've published. We most recently published our 2011 Executive Report yesterday. And the Executive Reports summarize data from all three agencies in a single report. Typically, they're published with a lag time of about two years. Obviously, yesterday's publication of the 2011 report was a little bit different, but typically, they're published with a lag time of two years.

And the reports are comprised of three main components. There are data analyses which make up the meat of this PDF report. There are also the interactive data displays. And Claudine just talked about the Tableau software that we're using to do that. And then there's also a five-page -- approximately five-page summary of key findings that we also incorporate into this PDF report.

And the pathogens we report on in the Executive Report are *Salmonella* -- and the data come from all three agencies. *Campylobacter* as well, come from all three NARMS-participating agencies. And then we also provide summarized data on generic or non-serotyped *E. coli*. And the data for *E. coli* come from just the retail and food animal arms of NARMS.

So the process for creating the NARMS Executive Report is as follows. FDA sends an Excel spreadsheet template to each agency. Summarized data are entered into the Excel spreadsheet and returned to FDA. Each agency maintains its own database, and agencies historically did not have access to each other's raw data. But as Michael Grabenstein presented in his presentation, this has now changed with the advent of the interagency database.

So this process outlined here was what we used to create the 2011 report, but moving forward, we expect to rely more on the interagency database, which again can create these canned reports and hopefully speed up the time to create the Executive Report.

So for those of you who aren't familiar with the report -- but I'm sure most of you are -- *Salmonella* reporting is reported as resistance levels among all non-typhoidal *Salmonella* and within each of the top five human-source *Salmonella* serotypes that are also recovered from food animals. And so, typically, these are the top five serotypes that we report on in the Executive Report. And for *Campylobacter*, we split the reporting into susceptibility among *Campylobacter jejuni* and *coli*, as those are the predominant species recovered from humans.

So the data that we present in the NARMS report, we present it in several different permutations. And this is one of the most common tables that you'll see in the report, is a resistance by year table. And we have a table like this for all non-typhoidal *Salmonella*, for each of the *Salmonella* serotypes, for each of the *Campylobacter* species, and also for *E. coli*. And then we also have tables like this that not only show resistance over years for each individual drug, but we also have a table that shows resistance over years for multi-drug resistant patterns.

And then this is probably the second-most common table in our reports, the MIC distribution table. And we have, again, one for each of the genera in our NARMS Executive Report.

And then we also have some specialized reporting. So we focus on drugs that are commonly used to treat severe infections in humans. And for *Salmonella*, those drugs we focus on are cephalosporins and

fluoroquinolones. And so we will present the top serotypes that are resistant to ceftriaxone and nalidixic acid, and we use tables like this to do that. And then we also will show trends for both ceftriaxone resistance and nalidixic acid resistance among all non-typhoidal *Salmonella* and also ceftriaxone resistance trends in four of the top five serotypes and nalidixic acid resistance trends in *Salmonella* Enteritidis, and we'll do that usually with these graphical displays.

And I just wanted to point out that historically we have monitored nalidixic acid resistance as a sentinel for fluoroquinolone resistance. However, with CLSI lowering the breakpoint for ciprofloxacin in their 2013 document, moving forward we're going to begin highlighting ciprofloxacin susceptibility instead of nalidixic acid resistance.

And so then again, we're highlighting drugs that are commonly used to treat severe infections, and for *Campylobacter* those would be ciprofloxacin and erythromycin. And so, again, we graphically display the resistance trends for those drugs. And monitoring for ciprofloxacin resistance is also important to us as we're trying to follow the results following the withdrawal of fluoroquinolone for use in poultry in 2005.

So those previous tables I just showed you are tables that we've actually had in our reports since we first created it in 2003, and we've made a number of enhancements to the Executive Report over the past few years.

Beginning with the 2008 report, we began to incorporate tables that present the number of isolates resistant by class and agent among the most common serotypes for each source. And that type of table is shown here. And then also in 2008, we began to incorporate a table on multi-drug resistant *Salmonella*, *Campylobacter coli,* and *Campylobacter jejuni*.

In 2009 we began to incorporate the summary of the data in the Executive Report. Since 2009 we've made improvements in that summary. In 2010 we made some improvements. In 2011 we've also made some improvements into how we actually discuss what data is presented in the reports.

And then with the 2011 Executive Report, we also included an MIC distribution table for other beta-lactams, and this was included to show what isolates might be displaying phenotypes that are indicative of extended spectrum beta-lactamase expression.

And then we've also made a number of enhancements to our interactive data displays. And Claudine went through those in detail, so I'm not going to show anything for them. But in 2010, we did offer users the ability to view resistance levels by *Salmonella* serotype. And then with the 2011 report -- and, again, those Tableau graphs have not been made public yet. We're still working on formatting them. But with the Tableau graphs, we are adding some additional multi-drug resistance graphs. And also, as Claudine presented, users now have more control over graphing options.

So now the problems with the current report are, obviously, it's very data dense. I showed you several types of tables that are in our report, and if you multiply those by 20, you get our report. So it's very data dense, and it's hard for those without science backgrounds to understand what they're looking at. Also, there's no link to risk management in our report. We briefly touch on policy decisions that have been made in our executive summary, but we really don't go into depth about the policy decisions or public health interventions that have resulted from the NARMS findings.

And then our summary does describe increases and decreases in resistance for important bacteria-drug combinations, but we really don't explain those increases or decreases, and we don't discuss what we think may be driving those increases or decreases. And this leaves the door wide open for misinterpretation of NARMS data.

So, as Mike presented in his talk, we are making strides to give the data -- sorry -- release the data to the public, isolate-level data to the public. So then creation of these tables becomes less necessary. But what becomes extremely essential is making sure that the data are explained and that CDC, FDA, and USDA's thinking on resistance trends is described.

So then the goal of our new report is that we create one that is less dense and more focused, more digestible to consumers of the data, less likely to be misunderstood or misinterpreted, and also increases the ratio of plain language to technical language.

Here's our project plan for the new Executive Report. And we actually already have gone through a number of these steps. As you can see, we began this project last year. In December, we finished reviewing exemplary reports from other agencies and countries, and we also reviewed feedback that we've received from various stakeholders over the years, feedback on our Executive Reports. And then earlier this year we prioritized the needs for the report based on that feedback. We determined the best layout of the report, we finalized the template, and now we're in the process of receiving data and creating the report. And we expect that the report will undergo several rounds of review between the fall of this year and winter of next year. And so our plan is to release the new NARMS Executive Report for publication by spring of next year. And these are highlighted in red, just to show those are the steps we've completed so far.

Just to give you a little bit more detail on the exemplary reports we did review, we reviewed the antimicrobial resistance report from the Netherlands, the MARAN report. We also looked at the CIPARS report coming out of Canada. We looked at the Swedish antimicrobial resistance and antimicrobial use report, Swedres-Svarm. And then we also looked at the European Union's EFSA antimicrobial resistance report. And then, of course, we looked at DANMAP, the antimicrobial resistance report coming out of Denmark, which many consider to be the gold standard for antimicrobial resistance reporting. And we also looked at CDC's *Salmonella* surveillance

report.

The feedback that we've received over the years on our Executive Reports have come from several stakeholders. I think we've received comments from all of the spokes of the stakeholder wheel, including consumer protection groups, representatives from drug industry, animal health, academia, and public health.

And so with all of that information combined, our research, and also the feedback that we've received over the years, we came up with the following decisions on the new features to include in the new report.

Number one. The new report will now be called the "Integrated NARMS Report." We're doing away with the term "Executive Report." We feel that "integrated" reflects the integrated nature of the program a little better.

Also the new report is going to contain extensive background on the organisms tested, *Salmonella* serotypes, why resistance is a public health concern. We will describe measures of resistance and drug classes that are important to human and animal health.

And then what is currently in the report, the data tables that are currently in the Executive Report and the interactive displays, they will essentially comprise the appendices for this new report. So they will be very narrative heavy.

And we plan to describe resistance levels using defined terms

such as high, moderate, and low.

I do want to note that the criteria used for these terms -- that we will use for these terms will not be the same criteria that our Office of New Animal Drug Evaluations uses to assess the effectiveness of animal drugs.

We're also going to highlight NARMS research and other important information such as epidemiological cutoff values and susceptible dose-dependent values, et cetera.

And we're going to use a better-defined baseline so that we can compare that given reporting year to historical years. And then we can also use this baseline to compare across sources.

We're going to incorporate additional resistance data from *Salmonella* serotypes that are common to food animals. So, traditionally, we have not reported specific antimicrobial resistance data for serotypes such as *Salmonella* Kentucky, *Salmonella* Derby, serotypes that are not prevalent in the human population, but we're going to do that with this new report.

We're also going to incorporate multiple data sources that will provide context to the story in the report. So we're going to provide food animal and human demographic data, retail meat production data, and we'll also be providing outbreak information, the information that Regan had referred to that is already in the reports, and will be published in peer-reviewed journals. That will also be incorporated into the new report.

The report will provide additional guidance for readers. We will provide better visualizations by integrating graphics that describe the NARMS program and highlight key findings.

And the initial report, which again is going to come out in spring of 2015, is going to combine 2012 and 2013 data so we can catch up on our reporting.

And the new report is going to also include *Enterococcus* data from the retail and food animal arms. And the new report is also going to include the cecal data from the new food animal sampling program, which began in 2013.

And this is my final slide, just quickly. We recognize again that the lag in reporting has been an issue. And so in order to make data more timely for users, in the near future, FDA does plan to release summarized retail meat data at a semiannual rate. And these will be abbreviated reports. They won't have the narrative to go along with them. It will be data only, and that's because the time intervals for these will be too short for us to make any conclusions about what we're seeing for trends. And so these reports are going to be data only, coming out at a semiannual rate, and the data we'll include will be *Salmonella* prevalence by source and state, prevalence by source and month, resistance to clinically important drugs, and also multi-drug resistance.

That's it. Any questions?

(Applause.)

MS. RICKERT-HARTMAN: Questions for Dr. Tate?

Tom. Thank you.

DR. SHRYOCK: I have a question. So one of the things that NARMS traditionally has had to work somewhat against is we have animal isolates -- now we have carcass or some of the more recent cecal data isolates, which are one pool, and then have obviously those retail meat pieces, which is another pool, and then the human isolates, another pool. They're all independent. They are not connected in any epidemiologic way, in terms of spatial relationship, time, et cetera, and maybe on a year basis, that sort of thing.

So in terms of the misinterpretation when all the graphs are easy to manipulate and you might have *Salmonella* and the serotype and all the rest -- it looks like it's in A, B, and C --there might still not really be a link. And maybe that's for the attribution section that's coming up here. But I'm just wondering how that would be addressed in terms of helping to educate the reader of the new simplified report that's going to be coming out next year.

DR. TATE: Right. Yeah, we obviously will have to have some text providing disclaimers as to the sources of the data and how they differ and what kind of assumptions can be made when looking at the data in aggregate form.

MS. RICKERT-HARTMAN: Nkuchia.

DR. MIKANTHA: One other thing that may be good to consider is trying to ask the stakeholders for feedback on the new report and also for yourself to monitor how much the report is being used.

I think the current report is good because, since it's scientific data, it's quite hard to try to have it solve every one. So it will make it also a document that's more accessible to the general public, where I see you also have people who want it for scientific reasons.

So the other thing may be to explain the limitations and say these are the limitations, this is why we can only provide you these data.

DR. TATE: Yeah. And that's the challenge, that's been the challenge this whole time, in trying to develop a template for the new report, is understanding that there are those with highly scientific backgrounds that are reading the report. But then there are also the laypersons that will read the report and try to grasp what information they can. So how do we merge all of that together and make it a report that everyone can read? And so that does continue to be a challenge, and we haven't written any of the text yet, but I imagine that is going to be the biggest hurdle to jump.

MS. SMITH DeWAAL: Caroline Smith DeWaal.

There is a recent CDC report that uses, like, smiley faces and little flat lines and little frowns, but I'm not suggesting you go there. However, we heard this morning, I think, from Pat McDermott that you may

be shifting from susceptible, intermediate, and resistant -- like, maybe that's the smiley face, the flat line, and the frown -- to wild type and the other non-wild type.

So could you elaborate a little bit on that and how we can interpret that to the public, not using smiley faces, but as something that is a way to communicate to the public that wild type is actually good and the non-wild type is the other type?

Thanks.

DR. TATE: Yeah. And, Pat or Jean, feel free to jump in here, because that's conversation we've had also internally, is how do we present wild type versus non-wild type, when people have been used to us talking about susceptible versus resistant? And the door is still open as to how we're going to do that. We've thought about maybe just again adding another disclaimer to the report, saying that when we present wild type, you should interpret that as being susceptible, even though that's biologically not technically correct or -- yeah, the door is still open as to how we're going to address that.

(Off microphone comment.)

DR. TATE: Yes, correct. And Maria, the expert, is jumping up to answer.

DR. KARLSSON: No, I was just going to say that I will be covering this in my presentation later today. I will be talking about clinical

breakpoints and ECOFFs and the difference between them. So we will get there and we can discuss more.

Thanks.

MS. RICKERT-HARTMAN: Thank you, Heather.

(Applause.)

MS. RICKERT-HARTMAN: So it looks like we have a break scheduled in here, just a quick 10-minute break. So let's take our break, and we'll meet back here at 20 after 3:00 for the last session.

(Off the record.)

(On the record.)

DR. McDERMOTT: Hello, everyone. Can we please take our seats and resume the afternoon session, please?

I quickly would like to introduce this afternoon's moderator, Dr. Ruby Singh, a friend and colleague at FDA. Dr. Singh received her Ph.D. in microbiology from the University of Maryland, Baltimore, and a B.S. in neuroscience from the University of Maryland at College Park. She's a Senior Regulatory Reviewer/Scientist in the Division of Human Food Safety in CVM's Office of New Animal Drug Evaluation, and has a long interest in this topic and a solid understanding of the regulatory side of it, including the international policy cooperation. So Ruby is going to moderate the session this afternoon and introduce our first speaker.

DR. SINGH: Thanks, Pat.

So it's a pleasure to be moderating this afternoon's session on international collaborations. And it's been a fantastic day so far, full of very, very good talks, and it's my pleasure to moderate the final session. We have three fantastic speakers lined up.

So, without further ado, it's a pleasure to introduce Dr. Steve Solomon, who is currently Director of the Office of Antimicrobial Resistance in the Division of Healthcare Quality Promotion at the National Center for Emerging and Zoonotic Infectious Diseases in CDC. Dr. Solomon currently serves as the co-chair of the federal Interagency Task Force on Antimicrobial Resistance, and he's had several senior positions at CDC developing, conducting, and directing collaborative research and demonstrating programs that are too numerous to mention.

Dr. Solomon.

DR. SOLOMON: Thanks, Ruby.

I already had my time this morning, so I'll be relatively quick. I don't want to take you into too deep a dive on this, but I do want to make a couple of points about international issues and global AR.

This is, by the way, our new logo. You can weigh in on that. We had it designed in-house. It didn't cost the government any money. It's clearly a graphical design. I really like it. The only thing I worry about is they say children in the United States have a very poor grasp of geography, and I'm always worried some kid will see this and say, gee, Ireland's right off the coast

of Massachusetts. I can probably see it from Cape Cod.

(Laughter.)

DR. SOLOMON: Let's talk a little about the background and the history of TATFAR quickly and then talk a little bit about some of the recommendations that pertain specifically to what we're talking about here at this meeting.

TATFAR was established following a summit meeting that occurred in 2009 between the U.S. and the European Union. That meeting largely was around a variety of economic issues. But as one part of a very broad agenda at that summit meeting, there was a declaration -- a treaty, really, signed, urging both the U.S. and the European Union to get together on the issue of antimicrobial resistance viewed as a global problem and an international threat to health.

Now, since that has happened, as many of you know, there has been really a tremendous amount of activity, certainly in the United States, but globally as well. Steve Ostroff, when he spoke this morning, mentioned what's going on in England. There was recently an announcement from David Cameron, the prime minister there. We have had in the United States great support, not just through TATFAR, which I'll talk about in a minute, but also from a number of individual countries in the EU, not only England but also Sweden and the Netherlands.

There has been a tremendous increase in interest around the

world and that, as Steve also mentioned this morning, was reflected in the fact that at the World Health Assembly, which occurred just this last May in Geneva, the World Health Assembly voted on a new resolution on antimicrobial resistance and the development of a global action plan to address antibiotic resistance as a global health threat. And that is tied in with what you also may have heard about the global health security agenda, which has been talked about and about which there will be another meeting of health ministers here in the United States in Washington -- as a matter of fact, next month. And that will be aligned. So there's just been an explosion of interest and real commitment, not just in the United States but around the world.

But TATFAR was there five years ago. At that summit meeting, it was determined that three major areas of collaboration were identified, and those were the appropriate therapeutic use of antimicrobial drugs in both the medical and the veterinary communities, a focus on prevention of drug-resistant infections, and strategies to improve the pipeline of new antibacterial drugs for use in human medicine.

Just to give you just a little bit more background, the actual TATFAR is composed of 18 members. Nine are from the United States, nine are from the European Union. During these first few years of TATFAR, membership within the United States has been within the Department of Health and Human Services, from FDA, CDC, NIH, as well as the Office of

Global Affairs in the Department of Health and Human Services. And, in fact, the co-chairs of the entire TATFAR, one is the DHHS Assistant Secretary for Global Affairs, who is now Ambassador Jimmy Kolker, and the Director of Public Health for the European Commission. The acronym for that group, which is in French, is DG SANCO. So they actually co-chair, and then there are 16 other members evenly split between the U.S. and the EU. For the first couple of years, the management was housed at the European CDC in Stockholm. We took that over at CDC in Atlanta earlier this year.

I've gone through that.

The specific objectives of the partnership are to increase the mutual understanding, on both sides of the Atlantic, on activities and programs related to antimicrobial resistance, to promote a dialogue on what we can do together to learn from each other and to talk about problem solving and, importantly, to promote information exchange in a very rapidly developing and evolving area of public health.

The first mandate was a two-year commitment. The parties agreed -- from the period from the summit meeting in 2009 until early 2011 was preparing for this partnership, developing a list of 17 specific areas of focus and what are called recommendations for what the partners will do together divided into the three working groups that I outlined: improving antimicrobial use, preventing infections, and developing new antibacterial drugs. A group of implementers, specialists, subject matter experts was

identified for each of these 17 recommendations. And that was the content of the first report, which was released in 2011, is what are these 17 recommendations? What are we going to work on together?

This past April, we released a two-year update on that report. The essence of our conversations were that this had been so successful as a learning experience, as a dialogue between the U.S. and the EU, that everyone was determined to commit for another two years. So we're now committed for 2014 through 2016. We went over the 17 recommendations. Fifteen of the recommendations will continue. Two have been essentially completed in terms of what we need to get out of them, and one recommendation, which I'll talk about at the end, has been added.

So I want to talk about the three continuing recommendations and the one new recommendation which relate really to what we're talking about here. And the way these are set up, all of these are in the first focus area, which addresses the use of antimicrobial drugs in medical and veterinary communities.

The first issue was the need for common measures of antimicrobial use in veterinary medicine so that we can better compare information between the U.S. and the EU. So FDA, the European Food Safety Agency, and the European Medicines Agency agreed to collaborate on looking at how data is collected in these two areas to these parts of the world and think about how to do meaningful comparisons. That work has been going

on. None of this is easy. Again, you remember we talked, and really we've been talking all day, about how complex these issues are, how difficult they are. They're difficult from a scientific standpoint, and when you're dealing with not only two different governments, the U.S. and the EU, but remember, the European Union is composed of 28 sovereign countries, all of which do things a little bit differently themselves. So none of these things are easy.

But there has really been meaningful progress in these interactions in looking at and learning just what people are doing on both sides of the Atlantic, digging down, if you will, into the weeds, which is something new. I mean, that is one of the things that on both sides, as we had various TATFAR meetings, conference calls, people felt they were getting a lot of out of the interaction because they were digging much deeper and talking to experts, their counterparts in these other agencies, about details that they really didn't know before and hadn't plumbed into because this is such difficult stuff. So that work is ongoing. Those discussions are progressing. Trying to find these common areas is an ongoing effort. And, again, you've heard a lot of that during the day.

The second issue was methods for analyzing the risk of AMR in foodborne pathogens. And this is really focused on collaborating on implementation of the guidelines in the codex. And, again, the same three groups, FDA, EFSA, and the European Medicines Agency similarly are working together and again felt that they were getting a tremendous amount out of

these bilateral meetings and discussions and digging down really deep into the scientific exchange for how these issues are handled on both sides of the Atlantic, the kind of knowledge that's being gained, and trying to look for areas of comparability, understand the differences. Again, not easy to do, but very encouraging in terms of the way the participants feel about the progress that's being made.

And then, thirdly, of the continuing recommendations, methods to promote appropriate use of antimicrobial drugs. And, again, you've heard a lot of that discussion here on the U.S. side, and our colleagues are learning a lot from what we do in the United States because, again, there are rules that apply to the entire European Union. But then there are also ways that things are done across the 28 different countries in the EU. And so that kind of information exchange and how we actually address that is an ongoing conversation. And my colleague Beth Karp is going to talk a little bit more about AGISAR and related issues in the next talk.

So there was one new recommendation, so far, that's been added, and there may be others. But the one new one, I think, is very significant. And this was actually proposed by our European colleagues. The issue that they put on the table just this past December was that antibiotic use in animals can select for antimicrobial resistance that may represent a risk to man either through direct infection by resistant bacteria or by the transfer of resistant determinants to other bacteria. The problem is that we

need much better scientific information about that to understand how to address this issue. Part of what you've heard all day today -- and tomorrow -- around NARMS clearly is going to provide more insight into that.

But, in addition, the actual recommendation is to establish a joint working group of international subject matter experts to look specifically at knowledge gaps in our understanding of this process of -- if you remember the slide this morning, the left-hand side of the One Health slide -- really the One Health continuum of humans, animals, and the environment and how that impacts on human health. We need to understand the transmission to human beings of antimicrobial resistance arising as a result of the use of antimicrobial drugs in animals and on the development of effective intervention measures to prevent this transmission, including, as we've already discussed -- and I know I discussed with some of you the alternatives to using antimicrobial drugs.

And you see, one of the things that we're most pleased about is that joining us now in HHS are our colleagues from the U.S. Department of Agriculture. And, in fact, they have taken the lead in working with us on this recommendation. So that, I think, is a testament to the growth of TATFAR and our commitment to it both in the United States and overseas.

So let me stop there. It's 10 to 4:00. If you have any questions, I can answer them; otherwise, we'll get the rest of this session on the way.

(Applause.)

DR. SINGH: Any questions for Dr. Solomon?

(No response.)

DR. SINGH: All right. Then we'll continue with our second speaker.

It's a pleasure to introduce a former colleague from CVM, Dr. Beth Karp. Dr. Karp is now a Senior Veterinary Epidemiologist on the NARMS team at CDC. Dr. Karp has a doctor of veterinary medicine degree from Cornell University and a master's of public health degree from Johns Hopkins. She's also board certified in veterinary preventive medicine and epidemiology. Before joining the NARMS team at CDC four years ago, Dr. Karp worked at the Maryland Department of Health for five years and at the Center for Veterinary Medicine for nine years, serving as a coordinator for NARMS during her last three years at FDA.

DR. KARP: Thanks, Ruby.

DR. SINGH: Okay, Dr. Karp.

DR. KARP: Good afternoon, everyone. It's my pleasure to talk about the World Health Organization's Advisory Group on Integrated Surveillance of Antimicrobial Resistance and some of the other work that WHO is doing to address the problem of antimicrobial resistance, as well as how NARMS and the agencies involved in NARMS support these efforts.

After a brief introduction, I'll explain what AGISAR is and why it was formed. I'll then spend some time talking about three key AGISAR

activities and conclude with a description of other WHO activities related to antimicrobial resistance.

Antimicrobial resistance is a global problem that requires a global approach. There's extensive movement of people, animals, and foods around the world, which provides an opportunity for resistant bacteria to spread across international borders. As Dr. Solomon said earlier, it's there today, it's here tomorrow. Therefore, resistance in any country is a global concern. It is a problem which impacts both human and animal health.

To better understand the problem of resistance and effectively address it, we need global surveillance to detect the emergence and spread of resistance, international data sharing and harmonization so that data from different regions can be more easily compared, and we need international cooperation to limit the global spread of resistance.

WHO issued its first global report on antimicrobial resistance surveillance in April. In a news release announcing the report, Dr. Fukuda, the WHO Assistant Director-General for Health Security, stated, "Without urgent coordinated action by many stakeholders, the world is headed for a post-antibiotic era, in which common infections in minor injuries, which have been treatable for decades, can once again kill." I will touch upon some of the many actions that WHO is taking at the global level to address resistance.

Here are a few examples from NARMS that show how resistant *Salmonella* abroad impacts us in the U.S. The first example is quinolone-

resistant *Salmonella* Enteritidis. Tomorrow you'll hear Allison O'Donnell talk about quinolone-resistant *Salmonella* Enteritidis infections in the United States and how it is strongly associated with international travel. And Claudine Kabera from FDA will talk about resistant *Salmonella* Enteritidis in imported foods.

Another example is a recent detection by NARMS of a particular strain of *Salmonella* Kentucky, which is resistant to ciprofloxacin and other antimicrobials, in several people who traveled or who were visiting from Africa and Asia where the strain has emerged.

In several earlier studies, NARMS found resistant strains acquired abroad, including *Salmonella* with extended-spectrum beta-lactamases (ESBLs), *Salmonella* with plasmid-mediated quinolone resistance, and also typhoidal *Salmonella* with quinolone resistance, which is now common as we saw this morning.

Before AGISAR was established, WHO held a number of consultations and meetings on antimicrobial resistance in the food chain, as shown on this slide. Some were expert consultations and workshops held jointly by WHO and FAO, the Food and Agriculture Organization of the United Nations, and OIE, the World Organisation for Animal Health, which is an inter-governmental organization responsible for improving animal health worldwide.

Given growing concerns about antimicrobial resistance in the

food chain, in December of 2008 WHO established AGISAR, the Advisory Group on Integrated Surveillance of Antimicrobial Resistance, to support WHO efforts to minimize the public health impact of resistance associated with the use of antimicrobials in food animals. The advisory group provides expert advice to WHO on containing resistance associated with the use of antimicrobials in food animals and promoting integrated surveillance of antimicrobial resistance and antimicrobial usage.

I will now briefly take a moment to explain the term "integrated surveillance." WHO has defined integrated surveillance as a coordinated sampling and testing of bacteria from food animals, foods, and clinically ill humans, and the subsequent evaluation of resistance trends throughout the food chain using harmonized methods. NARMS is one of the oldest and largest integrated surveillance programs for resistance in the food chain.

I'll now talk briefly about AGISAR participant subcommittees in terms of reference. More than 30 experts with a broad range of backgrounds participate in AGISAR, including physicians, microbiologists, veterinarians, and epidemiologists. I think there are about four or five AGISAR participants in the room with us today. The advisory group includes participants from all six WHO regions and includes representatives from FAO, the Food and Agriculture Organization; OIE, the World Organisation for Animal Health; ECDC, the European Centre for Disease Control; and EFSA, the European Food

Safety Authority. Several NARMS scientists from CDC, FDA, and USDA have participated in AGISAR.

AGISAR has five different subcommittees: the antimicrobial resistance surveillance subcommittee, which Pat McDermott co-chairs; the antimicrobial usage monitoring subcommittee; capacity building and pilot projects; data management; and risk communication.

The terms of reference for AGISAR are to support WHO activities on containment of resistance from the food chain, including capacity-building activities related to integrated surveillance of resistance and usage data, selection of sentinel sites and the design of integrated surveillance pilot projects, update the WHO list of critically important antimicrobials for human medicine, and implement joint activities on resistance with WHO, FAO, and OIE. I'll describe each of the items highlighted in orange in more detail during the remainder of my talk.

I'll now spend a few minutes talking about three key AGISAR activities, which are to support WHO capacity-building activities, maintain and update the list of critically important antimicrobials for human medicine, and develop guidance on integrated surveillance of antimicrobial resistance. We'll first look at capacity-building activities.

WHO and AGISAR conduct a number of activities to help member countries develop the capacity to conduct antimicrobial resistance surveillance. This includes providing support for national surveillance

programs and pilot studies. Support was provided to Brazil in 2013 and to Mexico in 2014 for establishing national programs for integrated surveillance of antimicrobial resistance. Support was also provided to a number of countries in Africa, Asia, the Middle East, and Latin America to conduct pilot projects on resistance surveillance. The photo on the right is from an aquaculture pilot project in Vietnam.

In addition to providing support for AGISAR projects, NARMS staff have also worked directly with other countries on projects and investigations. NARMS epidemiologists have been working with the Republic of Georgia on a project on antimicrobial resistance in foodborne bacteria. And just a few weeks ago several NARMS scientists from CDC traveled to Kenya to investigate the emergence of ceftriaxone-resistant *Salmonella* Typhimurium.

WHO has collaborated with FAO, the Food and Agriculture Organization, in some field projects to strengthen national and regional capacities to monitor, regulate, and manage resistance in the food chain. FAO/WHO projects have been completed in Kenya and Cambodia, both with tangible outputs. National guidelines on prudent antimicrobial use in food animals were developed in both countries, and in Kenya a national cross-sectional antimicrobial resistance task force was established. The approaches taken to address resistance in Kenya and Cambodia in these projects are models that can be adapted for implementation in other countries. The

photo on the right is from the Kenya project, and the bottom of the slide is a report that was published about the project.

AGISAR also partners with GFN, the Global Foodborne Infections Network, for some capacity-building activities. GFN is a WHO-facilitated network of institutions and individuals committed to enhancing the capacity of countries to detect, control, and prevent foodborne and other enteric infections, promoting integrated laboratory surveillance and fostering collaboration among human health, veterinary food, and other relevant sectors. Both the FDA and CDC are represented on the steering committee of GFN.

GFN contributes to global efforts to contain resistance in foodborne pathogens in several ways. GFN collaborates with AGISAR on developing and teaching antimicrobial resistance training modules. Scientists from FDA and CDC have taught some of these training modules. Between 2011 and 2013, training was provided to more 200 microbiologists and epidemiologists from more than 60 countries.

GFN also has lab protocols for resistance testing as well as an external quality assurance program that includes antimicrobial resistance testing, which is led by a WHO Collaborating Centre in Denmark. And NARMS laboratories participate in this program.

We'll now talk about the second key activity of AGISAR, which is to maintain and update the list of critically important antimicrobials for

human medicine.

The list was first developed in 2005 in a WHO expert working group consultation. The list has been updated regularly, and since 2009, revisions have been made by AGISAR. AGISAR worked on updating the list this past year, and the fourth revision will be published soon. This list is intended to help preserve the effectiveness of antimicrobials. The public health and animal health professionals, practicing physicians and veterinarians, and other stakeholders can use the list as a reference when formulating and prioritizing risk assessment and risk management strategies for containing resistance due to the use of antimicrobials in humans and animals.

The document includes criteria that are used to rank antimicrobial agents as highly resistant -- I'm sorry -- critically important, highly important, and important. The agents in the critically important category are prioritized so that resources can be directed towards the agents for which risk management strategies are most urgently needed. The highest priority agents are the fluoroquinolones, third- and fourth-generation cephalosporins, macrolides, and glycopeptides.

The document also recommends that antimicrobial classes not currently used in food animals, such as carbapenems, and any new antimicrobials that are developed for human therapy should not be used in animals or plants.

This is a table from CDC's annual NARMS report that lists antimicrobial agents that are tested for *Salmonella*, *Campylobacter*, and *E. coli*. Most of the agents tested are classified as critically important, shown in red here, and the remainder are classified as highly important, according to the WHO list.

I did want to mention that OIE, the World Organisation for Animal Health, has a list of antimicrobial agents of veterinary importance. A 2013 update to the document includes specific recommendations on the use in animals of fluoroquinolones and third- and fourth-generation cephalosporins, which are considered critically important for human and animal health.

In addition to this document, OIE has developed standards on the prudent use of antimicrobials in terrestrial and aquatic animals and standards on monitoring antimicrobial use and resistance. Last year, OIE had the first global conference on the prudent use of antimicrobials in veterinary medicine.

The last key AGISAR activity I would like to discuss is the guidance document on integrated surveillance of antimicrobial resistance. The guidance was developed by AGISAR and published in November. It is an important output of the five-year strategic framework for AGISAR and was developed through a four-year consultative process. The guidance is intended to provide basic information that countries need to establish

programs for integrated surveillance of resistance, and it makes recommendations that facilitate international harmonization and data sharing. NARMS scientists from CDC, FDA, and USDA helped draft the guidance.

The guidance has seven sections. The first is on surveillance of resistance in foodborne bacteria and includes information on both sampling strategies and laboratory standards. Sections 2, 3, and 4 are on surveillance of antimicrobial use in humans and animals. Sections 5 and 6 are for managing data on antimicrobial resistance in use. And the last section is on how to effectively communicate risk. The fact that three of the seven sections in the guidance relate to antimicrobial use data reflects how important these data are, and I'd like to say a little bit more about this.

Antimicrobial use data are important for a number of reasons. They help us identify trends and regional differences in use, interpret transient resistance and assess associations between antimicrobial use and resistance, support risk analysis efforts, help us implement evidence-based strategies and policies for containing resistance, and evaluate the impact of judicious use efforts and changes in management practices. And tomorrow you'll hear Dr. Craig Lewis talk about efforts by FDA, USDA, and CDC to collect more data on antimicrobial use in food animals in the United States.

Now I'd like to briefly talk about some other WHO activities related to antimicrobial resistance, starting with WHONET.

WHONET is a free software package for managing and analyzing microbiology test results, including antimicrobial susceptibility data. It was developed by the WHO Collaborating Centre for surveillance of antimicrobial resistance in Boston. WHONET is currently in use in hospital, veterinary, and food laboratories in more than 110 countries, and it is available in 20 different languages. You can find more information about WHONET on the WHO website and also in the guidance document.

This slide shows some of the many recent WHO activities related to antimicrobial resistance. The focus of World Health Day in 2011 was antimicrobial resistance. The following year, in 2012, WHO issued a report on the evolving threat of antimicrobial resistance options for action. And in April, WHO published a global report on resistance surveillance that I'll talk more about.

As we heard from Dr. Solomon, at the World Health Assembly in May, a resolution on resistance was adopted. It urged governments to strengthen national actions and international collaborations to address resistance, and the resolution also called on WHO to lead the development of a draft global action plan. Just last month, WHO launched an online consultation on the draft global action plan, and the aim is to present a draft plan to the World Health Assembly next year.

This is the report that WHO published in April on the global surveillance of antimicrobial resistance. This graphic highlights some of the

information included in the report. The report was WHO's first attempt to obtain an accurate picture of the magnitude of resistance and the current state of surveillance globally. The report includes data from 114 countries for seven common bacteria that cause serious disease. These include three bacteria monitored by NARMS: non-typhoidal *Salmonella*, *E. coli*, and *Shigella*. The report describes how high levels of resistance are found through all regions of the world and how resistance has reached alarming levels in some areas. The report discusses health and economic impacts of resistance as well as major gaps in tracking it.

The report makes a clear case that strengthening global surveillance for antimicrobial resistance is critical, as it serves as a basis for informing global strategies to contain resistance, monitoring the effectiveness of public health interventions, and detecting new trends and threats.

Section 5 of the surveillance report focuses on resistance in food-producing animals in the food chain. This WHO slide summarizes some of the key points from Section 5.1 of the report. It describes how major gaps exist in surveillance and data sharing, emphasizes the importance of integrated surveillance and the need for global surveillance standards, and it describes the importance of a multi-sectoral approach to the problem.

There have been longstanding collaborations among WHO, OIE, and FAO. Recognizing a need for stronger collaboration, these organizations

established a formal alliance to enhance global coordination of activities that address health risks at the animal-human-ecosystem interface. Antimicrobial resistance was identified as one of three priority topics for joint action, because it is a complex problem that cannot be effectively addressed by one health sector alone, and it is both the human and animal health issue.

I wanted to briefly mention a publication from the WHO regional office for Europe, entitled "Tackling Antibiotic Resistance from a Food Safety Perspective in Europe." This is a very nice primer on antimicrobial resistance that explains the problem and options for prevention and containment of resistance in the food chain. It is primarily intended for policymakers and people working in public health, agriculture, food production, and veterinary sectors.

A few concluding comments. Antimicrobial resistance is a complex global problem that requires a multi-sectoral and global approach. Strengthening global surveillance of resistance is critical for addressing the problem.

WHO and other international organizations have prioritized addressing antimicrobial resistance, and WHO is currently developing a global action plan.

NARMS, one of the oldest and largest integrated surveillance programs monitoring resistance in the food chain, is working closely with international partners, including WHO, to help build international capacity for

monitoring resistance in the food chain through initiatives such as the Global Foodborne Infections Network and AGISAR.

We're also working with international partners to identify and investigate emerging resistance. We work particularly closely with our neighbors to the north, from CIPARS, the Canadian Integrated Program for Antimicrobial Resistance. We now have working groups, interagency working groups for both microbiology and epidemiology with CIPARS. NARMS is also working to harmonize resistance testing and reporting to facilitate international data sharing. And Dr. Maria Karlsson will talk more about that, about some of these efforts.

And with that, I will conclude my talk. Thank you.

(Applause.)

DR. SINGH: Thanks, Beth.

Are there any questions for Dr. Karp?

(No response.)

DR. SINGH: I have a question, yeah, just on the statement that you had about the recommendation for not allowing use of any new antimicrobials that are being developed for use in humans should not be developed for further use in animals. Is that also taking into consideration any outcomes of any risk management or risk assessment process?

DR. KARP: This was a broad statement that was in the critically important document, and it talks about the classes, I believe, the specific

wording, and it mentions carbapenems and two other classes specifically and then had that broader statement about new classes that are specifically developed for use in humans. So that's as much detail that's currently in the document.

DR. SINGH: Okay. All right, thank you. Great. Thanks, Dr. Karp.

So we'll move on to our third speaker, Dr. Maria Karlsson. Dr. Karlsson is a research microbiologist with the National Antimicrobial Resistance Surveillance Team at CDC. Her research interests include the characterization of antimicrobial drug-resistant bacteria, mechanisms of resistance, and studies of the biological cost of antimicrobial drug resistance. And Dr. Karlsson will be talking today about the NARMS breakpoint-setting studies and EUCAST synergies.

Thanks.

DR. KARLSSON: Thank you.

So the last talk of the day is going to be on breakpoint-setting studies and EUCAST synergies. However, I am going to start by talking a little bit about antimicrobial susceptibility testing in general, or AST for short.

So, as you know, AST may be performed for different purposes. The primary purpose is to help predict outcome of therapy, but it can also be used for epidemiological purposes, including monitoring resistance development, detection on new resistant variants, and for the comparison of

trends among geographic areas and healthcare facilities.

Currently, the most widely used testing methods include agar and broth dilution techniques and diffusion methods such as E-test and disk diffusion. However, in order to obtain consistent and comparable AST data, these methods have to be performed using standardized conditions. So this includes using a standardized concentration of the test bacteria, using standardized concentrations of the drug of interest. The testing has to be performed under consistent standardized conditions, and appropriate control isolates should be included to validate the accuracy of the test conditions.

Currently, a number of competent bodies provide instructions for performing AST, and some of these methodologies are being published both nationally and internationally. The major international contributors to AST today are the CLSI, the Clinical and Laboratory Standards Institute; and EUCAST, the European Committee on Antimicrobial Susceptibility Testing. However, there are also many organizations at the national level that make important contributions, such as the British, French, and German committees.

So, if we look closer at CLSI, it has separate standing subcommittees to consider AST in human and veterinary medicine. They publish standards and guidelines for AST, including interpretative criteria. Documents are produced by experts and working groups under the direction of a consensus committee. And the human AST subcommittee is composed of experts from regulatory and public health agencies, pharmaceutical and

diagnostic industry, clinical microbiology labs, academia, healthcare providers, and educators, et cetera. And you can find more information about this at their webpage.

EUCAST is a standing committee organized by ESCMID and the European CDC. And ESCMID stands for the European Society of Clinical Microbiology and Infectious Diseases. It's led by a steering committee, which also is the decision-making body, supported by a general committee with representatives from European and other countries, including Australia and the U.S. And the U.S. is represented by a national AST committee called USCAST.

EUCAST also publishes standards and guidelines for AST, including interpretative criteria. And EUCAST also functions as the breakpoint committee for the European Medicines Agency (EMA). And you can find information about EUCAST on their webpage, eucast.org.

When it comes to AST interpretative criteria, both CLSI and EUCAST define clinical breakpoints. However, although CLSI and EUCAST share a common definition of clinically susceptible and resistant, the way the breakpoints are presented differ. While CLSI defines resistance as greater than or equal to a certain concentration, EUCAST defines resistance as just greater than a certain concentration.

In addition, CLSI recently introduced a fourth category of clinical breakpoints called S-DD, susceptible dose-dependent breakpoints.

And as the name implies, these breakpoints are associated with the use of a specific optimized dose. EUCAST currently does not have an S-DD category. However, EUCAST defines a completely different set of interpretative criteria called epidemiological cutoffs, or ECOFFs or ECVs.

ECOFFs differ from clinical breakpoints, and this slide here shows you how. So while clinical breakpoints are intended to guide the therapy, ECOFFs do not take into consideration any data on dosages or clinical efficacy but are aimed at optimizing the phenotypic detection of isolates with acquired resistance.

Also, as you might know, several different datasets are required to establish a clinical breakpoint. You need the laboratory susceptibility data, you need clinical outcome data, and you need pharmacological properties of the drug, PK/PD data. This is in contrast to ECOFFs, which are completely based on the microbiological data, the susceptibility data.

Thus, the ECOFF distinguishes between organisms with and without phenotypically expressed resistance mechanisms. The ECOFF is expressed as wild type greater than -- less than or equal to a certain concentration, and it will categorize isolates as wild type or non-wild type. So there is no intermediate category when it comes to ECOFFs.

The ECOFF is based on the testing of large numbers of isolates from different institutions and areas to determine the MIC range of the wild-

type population. And the ECOFF is then defined as the highest MIC value of the susceptible wild-type population. ECOFFs have been determined for a large number of organisms and drugs, and you can find all of this information and the lists of ECOFFs at the EUCAST webpage.

ECOFFs, as I mentioned, are currently being used for sensitive detection or screening for resistance. They are also an important tool in the determination of clinical breakpoints where the ECOFF will sort of set the floor for the susceptibility breakpoint.

ECOFFs can also be used for surveillance of antimicrobial resistance when clinical breakpoints are not sensitive enough, if they have not been determined. And ECOFFs can also be used for harmonization purposes if clinical breakpoints differ between systems such as CLSI and EUCAST, or when breakpoints differ for humans and animals, for example.

This slide here is just to again illustrate the difference between clinical breakpoints and epidemiological cutoffs. And as you can see, an isolate defined as being non-wild type might still be classified as clinically susceptible.

Now I'm going to switch over and talk a little bit about NARMS involvement in CLSI and EUCAST and how our data can be used to inform clinical breakpoint and ECOFF setting. And I am going to start by talking about our involvement in CLSI. And since NARMS is the only nationwide source of information on resistance in intestinal infections, we think it's really

important to share our data with this organization to facilitate development of AST guidelines and interpretative criteria.

So since NARMS was initiated, NARMS researchers have been represented on various CLSI AST working groups. We have shared MIC data to support clinical breakpoint development and revisions. And these parts also included doing special studies where we performed disk diffusion to establish MIC disk correlates. And we have also contributed data for well-characterized resistant variants to CLSI. Finally, we have been involved in developing and optimizing AST assays and methodologies.

And these are three more recent examples where NARMS has contributed data for clinical breakpoint development. And I'm going to say a few words about each one of these.

So the first one is related to *Salmonella* and azithromycin. The CLSI human AST subcommittee recently developed clinical breakpoints for *Salmonella enterica* serovar Typhi and azithromycin. And here, the NARMS data played an integral role supporting the breakpoint determination. Clinical outcome versus MIC data were only available through studies performed in Asia, but in all of these studies, testing was performed with E-test, which is not an approved CLSI reference method. However, broth microdilution test results from NARMS supported the data from Asia, and through our collaboration with EUCAST, a similar ECOFF could be derived for both distributions using standardized statistical methods.

To further validate the E-test data, we investigated the correlation between E-test and broth microdilution, and work in our lab showed that E-test results were comparable to broth microdilution data.

Finally, NARMS performed disk diffusion testing on a number of *Salmonella* isolates to evaluate the correlation between zone diameters and MICs. And these data, along with the corresponding data from Asia, led the CLSI committee to approve a susceptibility breakpoint of 16 µg/mL for MIC testing and a breakpoint of 13 mm for disk diffusion testing for Typhi and azithromycin. And this decision was made in June this year, and these new breakpoints are going to appear in next year's version of CLSI Document M100.

NARMS has also made contributions toward the establishment and revision of fluoroquinolone breakpoints. NARMS researchers partnered with CDC epidemiologists to provide the laboratory and clinical data that led CLSI to revise the clinical criteria for resistance for ciprofloxacin and *Salmonella* a few years back. NARMS data also played an integral part in setting the MIC breakpoints for levofloxacin and ofloxacin, and we have performed special studies to suggest disk diffusion breakpoints for levofloxacin and ofloxacin as well. Finally, for this project we were able to provide MIC data for emerging resistant variants, which CLSI found incredibly valuable and useful.

When it comes to *Campylobacter*, NARMS researchers have

been greatly involved not only in breakpoint development but also in the development of standardized testing methodology. Although *Campylobacter* was first recognized as an important human pathogen in 1972, standardized susceptibility testing methods were not available until 2004 when NARMS researchers, in collaboration with other partners, published guidelines. One year later, NARMS followed up with a publication on broth microdilution testing guidelines for *Campy*, including quality control ranges for 14 antimicrobial agents.

Today, both CLSI and EUCAST provide guidance and interpretative criteria for *Campylobacter jejuni* and *coli*, and there are also guidelines available from national committees such as the British and French programs. In addition, EUCAST recently developed a disk diffusion method and clinical breakpoints for ciprofloxacin, erythromycin, and tetracycline.

The CLSI guidelines for *Campylobacter*, which can be found in CLSI Document M45, are currently undergoing revision. NARMS is represented on this working group, and we have also been highly involved in the development of a new CLSI disk diffusion method where breakpoints for erythromycin, ciprofloxacin, and tetracycline are being developed.

Finally, I'm going to say a few words about our work and our collaborations with EUCAST. So one important objective of NARMS is to work closely with international partners to harmonize antimicrobial resistance testing and reporting and to facilitate data sharing. And NARMS has, since

many years back, a very good relationship to EUCAST where we have shared data and performed collaborative projects.

NARMS recently contributed *Campylobacter* MIC data to help EUCAST update MIC distributions and ECOFFs. And we are currently working on a project looking at wild-type distributions of *Salmonella*, different *Salmonella* serotypes.

Another very successful collaboration with EUCAST was related to *Salmonella* and the detection of fluoroquinolone-resistant variants -- sometime ago, both fluoroquinolones. And CLSI identified limitations with using the ciprofloxacin and nalidixic acid disks to detect isolates with acquired fluoroquinolone resistance.

As a response to this, EUCAST and NARMS researchers performed a study where we evaluated 16 different quinolone and fluoroquinolone disks for their ability to detect resistant variants. And results from this investigation indicated that the pefloxacin 5 µg disk was the best candidate.

So we continued to investigate the performance of the pefloxacin disk assay by evaluating disks from different manufacturers, their performance on different media, and the inter-lab variation associated with the assay. And it turned out to be a very robust test that right now represents the best way of detecting *Salmonella* isolates with an acquired fluoroquinolone resistance mechanism. This pefloxacin screening assay has

already been implemented by EUCAST earlier this year, and it was approved by CLSI in June of this year, and it's going to appear in next year's M100 document.

So, to summarize, CLSI and EUCAST are the major international bodies establishing AST guidelines and interpretative criteria. Both CLSI and EUCAST define clinical breakpoints. In addition, EUCAST defines epidemiological cutoffs (ECOFFs), which are primarily used for surveillance purposes.

NARMS data are used to inform breakpoint-setting studies and revisions. The large nationwide collection of isolates, along with the molecular data on resistance mechanisms, make NARMS data valuable. NARMS will continue to work closely with international partners, like EUCAST, to facilitate data sharing, AST method development, and harmonization.

With that, I thank you for your attention and will be happy to try and answer any questions. Thank you.

(Applause.)

DR. SINGH: Thank you, Dr. Karlsson.

Are there any questions?

DR. SHRYOCK: Tom Shryock, Elanco.

Usually during the process of setting clinical breakpoints for CLSI, there is a presentation on clinical effectiveness and something on pharmacology. I was not able to attend the June CLSI AST subcommittee

meeting. Perhaps that was in the agenda minutes or meeting pre-reads. Would you be able to provide any insight into those two parameters that would be part of the triad that is used to derive clinical breakpoints?

DR. KARLSSON: Yes. So that is correct. So they usually consider three different sets of data, you know, the clinical outcome versus MIC data, the susceptibility data, and the PK/PD modeling data. So you're asking specifically about -- I'm sorry.

DR. SHRYOCK: The PK/PD data and clinical effectiveness data look like, on your scatter-gram up there, everything was pretty much in the susceptible box. There wasn't anything that you could even attribute to or would suggest that there was any resistance in any of the isolates there. So I'm just wondering how that actually was set when you look at clinical effectiveness and the pharmacology for the doses that were administered to the patients, because you'd have bloodstream infections, correct?

DR. KARLSSON: So you are referring to the azithromycin breakpoints, right?

DR. SHRYOCK: The new ones that were set there for azithromycin for *Salmonella*.

DR. KARLSSON: Yes, correct. Yes. So there are currently no PK/PD data available. I mean, optimally, you want to have all of these three datasets to establish a clinical breakpoint, but sometimes they are not available. For example, if we look at *Campylobacter*, that's the same thing

there. Clinical outcome data and PK/PD data are lacking. So then the breakpoints will be determined -- the susceptibility data will be the base for the decision. So for azithromycin, there were actually no PK/PD or modeling data available.

DR. SINGH: Any additional questions?

(No response.)

DR. SINGH: Okay. Thank you. And if you could just join me in giving our three speakers a round of applause. Thank you.

(Applause.)

DR. McDERMOTT: Well, thank you to all of our speakers and our moderators today, and thank you to our last afternoon speakers from CDC for giving us the gift of an early dismissal today. So I think it's always good to end a little early if you can.

I think, Heather, as far as returning to the hotel for those from out of town, is there a time --

DR. TATE: Five o'clock.

DR. McDERMOTT: Five o'clock. So the shuttle will be here at five o'clock to return those who came in on the shuttle this morning. And we will meet again tomorrow at 8:15 and do it again.

Thank you, everyone.

(Whereupon, at 4:34 p.m., the meeting was adjourned, to be reconvened on Thursday, August 13, 2014.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

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August 12, 2014

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Office of Foods and Veterinary Medicine, Center for Veterinary Medicine.

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CATHY BELKA

Official Reporter