FTS-CDC-PHPPO

February 23, 2005
12:12 p.m. CST

Coordinator — Good afternoon and thank you for standing by. All participants will be able to listen only until the question and answer session of today's conference call. Today's call is being recorded. If anyone has any objections you may disconnect at this time. Now I will turn the call over to your first speaker for today. Ms. Labaar, you may begin.

C. Labaar — Good day. Welcome to our teleconference. Detecting Antimicrobial Resistance, A Partnership of Public Health Labs and CDC. My name is Christine Labaar and I am the State Training Coordinator at the Vermont Department of Health Laboratory in Burlington, Vermont. After the program, each participant needs to register and complete an evaluation form. Documenting your participation helps us continue to bring high quality training programs in a variety of formats. To do this just go to http://www.phppo.cdc.gov//phtnonline/ the password is DETECTING.

When you have completed the registration and evaluation form, you will be able to print your CEU certificate. You have until March 23rd to complete this process. These instructions are in your original confirmation letter and the general handout. They were also e-mailed to each site representative this morning. If time permits, the end of the program will be opened up for questions. You are on a listen-only line. We cannot hear you; you can only hear us.

Welcome and thank you for joining us. We have over 40 sites from across the United States listening to this teleconference. Today's speaker is Dr. Roberta Carey. After two decades as Director of Clinical Microbiology, Dr. Carey joined CDC to oversee diagnostic microbiology antieffectives, environmental microbiology and epidemiology section. It is my pleasure to introduce to you and to welcome our speaker, Dr. Roberta Carey.

R. Carey Thank you, Christine, and thanks to everyone out there today who's joining our teleconference. As was mentioned, I'm usually on the other side of the coin sending isolates from our hospital laboratory to my state and local public health labs for help. Now I'm at the other end on the receiving end with a little bit of a different perspective. So, today I hope I can marry the two: one, to give you an update about the clinical and public

health importance of the resistant microorganisms that we are inundated with; and two, to try and see how you and I can link together to do a better job, to have better PR so that we can serve not only our own federal and state organizations, but to have a greater presence with clinical labs because I think there's a great amount of synergy that we can have to do a better job.

My first slide shares with you the objectives for our time today and again, really focusing on the importance of these resistant microorganisms and to learn what are the ones that are the most important to monitor from both the local as well as the national level. I want to acquaint you with some of the pitfalls and susceptibility testing recognizing that many of you do different susceptibility methods but probably not all of you do as many as the diagnostic labs. Therefore, many of the trials and tribulations that clinical labs encounter and look to you for some help.

It's important for us to share the requirements for getting organisms from the state to CDC in the appropriate format with the appropriate paperwork. I cannot over estimate how important that is to facilitate the correct work and the speed with which we can act once everything's in place and certainly make sure that the public health labs and the CDC are partnering

well to communicate and to work together for the best public image we can have.

On my next slide, which is probably the most colorful of the group, I just kind of bring you into the wonderful world of the new super bugs. On the right hand side there's a page displaying everything from Neisseria to Staphylococci and micro bacteria. This article actually ran in *Time Magazine* almost ten years ago and it's really not gone out of date, unfortunately, because I think our super bugs have just gotten more super. Of course, in the microbiology world, we tend to give them all fancy code names. I think if somebody from another discipline every listened to a microbiologist talk, obviously, they would need their secret decoder ring because we talk about ESBLs and VREs etc. and everything's got alphabet letters.

Probably one of the earliest resistance organisms that we focused on were MDRTB or multiple drug resistant tuberculosis. That's not going to be a topic for us today, but that certainly made a huge impact in the public health arena as this organism acquired resistance to the key drug that we needed to treat it. The VRE or vancomycin resistant enterococcus, I can remember back in 1988 when I had an organism that we had found in one

of our patients. We had identified it as an enterococcus, and enterococcus faecium and yet when we did the susceptibilities it looked resistant to vancomycin, something we had never seen before. So, of course we pulled out every identification mechanism we had in the laboratory, conventional as well as kits, and it still kept telling me it was an enterococcus faecium.

We did the susceptibility by multiple methods and it always came out vanc resistant. So, I sent it to Dr. Dick Faclum here at CDC back in 1988 and I said, Dick, either we have really screwed up in our ID, our susceptibility or we have the bug from hell. He wrote back, you have the bug from hell. So it really goes on that these organisms that we attribute these wonderful alphabet letters such as the multiple drug resistant strep pneumo or ESBLs that we're going to talk about today or even the more popular VISA or vancomycin intermediate staph aureus, have totally surrounded our world and have become a huge focus in the diagnostic lab.

On the next slide maybe we can explain a little bit more of why are we seeing this resistance. Why are we seeing more resistance? I think it's very important to see that these organisms are really reacting to the environment where we are living.

First of all, there's a great overuse of antibiotics. Overuse in the sense that people go to their physicians and virtually demand an antibiotic thinking that's going to cure them of almost anything including a viral illness. Luckily, now we do have some antivirals for influenza and other viral diseases, but many times the cough, the runny nose, the fever that's going to last two or three days is of viral origin and prescribing an antibiotic only serves to wipe out or normal respiratory flora and create resistant microorganisms.

Under treating can be as bad as over treating. In many cases people stop taking their medication before the entire prescription has been completely taken. Even though it says take for ten days, if you feel better after five or six you stop taking that medicine or it doesn't seem as important to get that antibiotic into your child who didn't like it in the first place. The problem is if we only take our antibiotic for a few days, we wipe out the most susceptible microorganisms, but those with MICs or minimum inhibitory concentrations that are higher and require a more antimicrobial activity, they remain. So, what we have done is select out a more resistant population.

In underdeveloped countries we actually have a problem where the antimicrobials that are produced are certainly not under any form of FDA. Those antibiotics, for economic reasons, may actually be watered down or diluted and not have the full potency. So, once again, instead of treating with full strength antimicrobials, we're giving a weaker version, which allows microorganisms to last longer and become resistant.

Finally, I think you're all aware reading the newspapers or magazines that lots of antibiotics produced, in fact the bulk of antimicrobials produced does not go into humans for treatment, but actually goes into the livestock feed for healthy animals. They're not sick and being treated for an illness; instead, the antimicrobials in their feed helps them to grow larger and bring in a better price per pound. So, when this meet and other dairy products etc. chickens and so forth, reach our market, there's a lot of antimicrobial resistance in those foods.

I know back in 1985 we had an outbreak of milk that was contaminated unpasteurized into the pasteurized lines and the salmonella that was released all over Chicago at that point was resistant to ampicillin because the cows that had produced that milk had all been given antibiotics. So, when the physicians when to prescribe an antimicrobial, many times they

were trying to give ampicillin and it certainly wasn't working at all because these organisms were all resistant to the antibiotic. So, it does have a direct impact on how we create resistant microorganisms.

On the next slide we have to ask our question, how does this affect public health? One, resistant bacteria certainly are transmitted person-to-person and perpetuates the disease. We certainly see this in a hospital environment where there's nosocomial transmission of resistant microorganisms but it also happens in the community as well. Day care centers are notorious for spreading resistant pneumococci and other infections; nursing homes as well where care and the appropriate precautions are not always well taken. Infection control practices are not really foremost in their minds when they're caring for these patients. So, these resistant microorganisms can go through many institutional settings and we'll learn a little bit more about that with the staph.

The other problem certainly is that there's fewer and fewer antimicrobials left to use. Since 1998, only eight new agents have been approved. That's really a very small number when we consider all the new resistant mechanisms that we're finding in our old friends such as the staphylococci

and many new microorganisms. There's now gram negative that are resistant to virtually every antimicrobial on the market.

We've also seen that this resistance is now combined with very resistant and virulent microorganisms such as before when we had vancomycin resistant enterococci, we probably didn't worry half as much because the enterococci didn't have virulence factors that allowed them to cause disease in and of themselves. Many times the organism needed a catheter to get the organism into a vulnerable site or you need to have a debilitated host. But now we have staphylococci that has great virulence factors that allow as they get on the skin to cause an infection and now with the resistance mechanisms you can't treat them as easily.

Certainly we can't isolate ourselves in the world of public health just to the United States where over-the-counter antibiotics are freely used in many foreign countries, remember that that resistant microorganism is only one plane ride away from your world and mine so that it's very easy for transmission.

In the next few slides we're going to talk about some of the most key organisms that you should be aware of, the ones that we need to really

focus and hone in on because of the number of cases that we're seeing and also the seriousness of their resistance. The first one we're going to talk about is methicillin-resistant staph aureus. Of course when it's methicillin resistant, that name was coined from the very original antibiotic that was used back in the 1960s, but we know now that certainly methicillin resistant also means naphcillin, oxacillin, and dicloxacillin resistant as well. These penicillin aced resistant antibiotics that were created when staph aureus became resistant to penicillin now have lost their great effect as well.

We actually use oxacillin to predict resistance. We do that because it is a more stable antibiotic. In the past, many disk test, etc. had been used and it was really shown that the oxacillin held up much longer in our refrigerated conditions and during the testing in our incubators and if we had a drug that was falling apart or unstable, obviously you would be calling more things resistant than really were and that would be a very bad thing. When we do have an organism such as staph aureus that's oxacillin resistant then we know from clinical data that the cephalosporins and amphicillin sulbactam do not work as well clinically. So, when we find in vitro data saying oxacillin resistant no matter what our other results are,

we have to put a big R next to cephalosporin, such as cefazolin as well as amphicillin sulbactam.

The problem with detecting resistance in staph aureus is that these organisms are not all the same; they're really a mix, sort of a color chart, if you will, of not just all one color but many shades of the same color. They're heterogeneous, which means that we have some that are very resistant and some that are less resistant and all kinds of in between. So because we have this mix, it is more difficult to detect resistance. Many times the conventional tests that laboratories use and that you use don't always give us the best answer. Now we're learning that maybe the best answer is a molecular test, but again, that's not accessible to many clinical laboratories or even in our public health arena.

The best test for resistance is to detect the gene that we know is associated with methacillin resistance and that's the mecA gene or we can actually look for its product, an altered penicillin binding protein PBP2a. Now, laboratories actually have a latex product that allows even a small laboratory to boil up some of this organism that they want to look at and then take a supernatant and test it with the PBP2 latex and if it reacts positively, we know that product, that altered penicillin binding protein

that then means resistance to the methacillin, oxacillin, etc. is present so that laboratories are getting a little bit better at doing this testing.

MRSA is an old story. You might say well why is she talking about this, but I think you'd have to have your head in the sand not to realize how MRSA is now a community acquired infection.

On that next slide you see the picture of a leg wound from an abrasion from a player who was playing football and had turf burns. The red of the turf burn obviously debreathes the skin and allows it to be very vulnerable for a future infection. The skin and soft tissue infections, even necrotizing pneumonia following influenza and sepsis are all occurring in the community setting with methacillin resistant staph aureus. Who are the people who we really have to watch for with these infections and make sure our physicians are very aware that this resistant staph aureus is now afoot in the community. We have seen these new strains, and they are not the same as our hospital strains that we've had had for years, in day care centers, in contact sports such as football and wrestling teams, people who have been put in jail and in prisons, men who have sex with men and IV drug abusers.

This new strain of MRSA has a very unique pulse feel gel electrophoresis type and it's called USA300. It also has a mec gene, which causes resistance, but the mec genes can be subdivided into five Roman numeral types. The community acquired has a mec type IV where your hospital strains have a mec type II. Also, the community MRSA carried the gene for a panton valentine leucocidin or PVL and maybe your public health laboratories have been asked to look for this particular gene for a toxin. This toxin has been associated with more virulent and devastating skin and soft tissue infections. It's not 100% of the community acquired strains have this, but a very high majority do have this toxin that we don't see as frequently in the hospital acquired infections. So, this toxin along with the resistance is making this really a very nasty pathogen.

Another concern is how are we going to treat this. If this is an outpatient you don't want to have to bring them into the hospital and give them vancomycin intravenously. There are people who receive their IV treatment at home, but if the physician can choose another antibiotic all the better. Clindamycin is an antimicrobial that is often susceptible; the organisms are susceptible to clindamycin. However, when routine testing is done either by a disk test or many of the automated susceptibility tests

hospitals use, clindamycin, if it's really resistant they can see that and a big R can go up on the patient's report.

However, clindamycin may appear susceptible in some of the tests but resistance can be induced after a few doses of the antibiotic has been given. That inducible resistance requires additional testing, something called the D-zone test where a disk of arithromycin and clindomycin are put in very close proximity to one another and you can actually see the blunting or the decrease zones of susceptibility around clindo if the arithromycin is inducing the resistance. If that happens, we know we have to call clindomycin resistance. So, it is very important because we don't want to take away this very useful antibiotic and therefore more antimicrobial testing needs to be done.

Staph aureus is spread whether it's regular old staph or the methacillin resistant through nasal colonization. We know that many of you have participated in studies where we have looked at the general population as part of the NHANES studies and looked at the nasal colonization. We do find that with regular staph that about 20% to 25% of our normal people carry staph in their noses. Luckily it's less than one percent for our MRSA, but this is truly a bug to watch.

On the next slide we're just moving our staph aureus from being bad to even worse. This is our VRSA or VISA as these are the vancomycin resistant staph aureus strains or vancomycin intermediate staph aureus. It wasn't until 2002 that truly vancomycin resistance staph aureus occurred. Before everything was really a vancomycin intermediate, intermediate based on the MIC that the organism had and how it fell in our break point. This is truly a public health issue since vancomycin is routinely used to treat MRSA in our hospitalized patients.

So far we only have three strains of VRSA: one from Michigan in 2002; one from Pennsylvania in 2002; and last year, 2004, in New York. Actually, we are working one up as we speak, which might be our fourth VRSA. Virtually every week we have strains sent in, that we'll talk about at the end of our time together, from the various state public health labs. For these VRSAs or vancomycin resistant staph aureus, it's very different than the VISA of how they are turning resistant. These staph aureus have actually had a close encounter with an enterococcus in the same part of the body where the vanA gene that's responsible fore resistance in our enterococci has actually been given to the staph aureus.

The good news is that after an event where someone has found this type of organism in a patient, when we go in and do surveillance of their contacts, of their family, of healthcare workers, etc. we have never seen any transmission of the three VRSAs to any of their contacts, so that's excellent. The VISAs do not have the vanA gene from an enterococci. Instead, they become more resistant or intermediate to the vancomycin and microbial by making a thicker cell wall where the antibiotic cannot penetrate and it actually behaves differently. All potential vancomycin resistant and vancomycin intermediate staph aureus, those with vancomycin's greater than four or if they grow on a vancomycin screening auger need to be sent to CDC for confirmation as soon as possible. That is really very important for the speed in detecting these and making sure that the patients put on appropriate antimicrobial drugs as well as infection control guideline practice.

On the next couple of slides I just show you some visual. This is from our New York isolate that we had this spring and this is a representation, a photograph, of the MIC panel that we actually make here at CDC. Going across in that very top row is my vancomycin and a microbial, the rows B through H have other antibiotics in the wells. On the far right side, number 12 well, has the most dilute concentration of vancomycin and if

you go all the way to your left, which is well A1, you see a little red arrow there that is actually indicating what the MIC is or the first well will receive no hint of growth of this staph aureus.

You can see where we get a very heavy dot on the right side where the organism is growing quite well an then we get a lighter and lighter white kind of haze showing the growth and in well two you can still see, at least on my picture, sort of a little cottony white growth. So the very first clear well was a vancomycin concentration of 128. The break points from NCCLS, which is now CLSI or Clinical Laboratory Standards Institute, that anything at 32 or greater is considered resistant. So you can see on the resistant panel this organism truly was a vancomycin resistant staph.

The next slide shows a Mueller Hinton … where a disk diffusion as well as an e-test has been placed. Again, this is our same microorganism showing that although it looks like there's a zone of inhibition around both the disk and our e-test, small colonies have invaded further in. As soon as you have these small colonies growing up to that disk, which is the usual 20 microgram disk or the vancomycin e-test, then the MIC was greater than 256. Lastly we show the picture of the plate of the brain heart infusion augers, which contains vancomycin at six micrograms per ml.

This is the auger that we're asking laboratories to use to help in confirming any of their automated results because our automation test, and it's not just one manufacturer, doesn't always pick up the vancomycin resistance of the staph aureus.

So, we have asked diagnostic labs in addition to running your routine testing to put a drop of the organism from a pipette or even streak with a swab onto the BHIB6 auger and look for growth. Here you can see on the left hand side there are two arrows, one with a very sort of dotted, spotted appearance and the other just totally opaque and confluent of the vancomycin resistant staph aureus and they can use their QC E. faecalis, the ATCC strain that they already use for this auger when they're working with VRE so that this organism can be detected multiple ways and you in the state public health laboratories, if you are able to, CDC would just be very happy to have some participation at the local level to screen for these vancomycin resistant staph aureus and we can talk a bit more about that.

The last slide I have here on the staph aureus is the algorithm for testing staph aureus with vancomycin and this is up on the CDC Web site, but if you have laboratories who are asking for more information and what they should do, I would refer them to this algorithm, which basically shows

what they should do if they are doing MIC testing to add that vancomycin screening plate that I showed you or if they're using disk diffusion testing and, as well, require that vancomycin screening plate and then depending on either the zone of inhibition that they get or the MIC, whether they should report it out of the vancomycin susceptible or whether it has the possibility of being a VISA or VRSA, in which case they need to check the purity, confirm the ID, retest it using a non-automated MIC method and make sure they save that isolate to send to you so that you can forward it to CDC if indeed it turns out to be vancomycin intermediate or resistant.

The next organism we're going to talk about is the VRE and that's our vancomycin resistant enterococci, primarily E. faecium and E. faecalis. This was a dangerous mix of already resistant microorganisms because the enterococci were already resistant to all the cephalosporins, trimethoprim-sulfamethoxazole as well as other antimicrobials. So now they acquired this resistance to vancomycin, which really made them a very difficult treatment modality. Enterococci are an important cause of nosocomial bactereias, many patients who have catheters get infected catheters and bacteremic with these organisms, surgical site infections and of course, urinary tract infections. They're spread in our healthcare environment as well as nursing homes on the hands of personnel.

The organism, once it is in the environment of the patient, can be just about anywhere. It's on the call buttons that the patient uses in the hospital environment, it's on the bed rails, it's on the sink handles, it's on the toilet seats, just about anyplace that patient can be and it really requires thorough disinfection with very strong agents after that patient is removed from that room. Luckily we do have new antibiotics such as linezolid or quinupristin/dalfopristin commonly called Synercid to treat with this. But several years ago, before these new drugs were released, virtually a patient with VRE was dead because there was no antimicrobial left to treat this organism.

What we need to be aware and I'm going to show you on the next two slides is the proper identification before we go off on the deep end and call everything a vancomycin resistant enterococcis. On my next slide that shows biochemical tests to identify enterococci, we have common tests that are used to pull up an enterococcis. On the far right you see a little filter paper disk with a cherry red color. This is a spot PYR or pyrrolidinyl beta naphylamide that laboratories use very quickly. It only takes about two minutes once you rub the organism on and add the cinnamaldahyde indicator and basically with the right morphology and

this cherry red color, a laboratory is going to send that out as an enterococcis.

Back in the other days when we could maybe spend more time or an overnight incubation, you see a bile esculin plate, the top of which is black from the bile esculin being hydrolyzed by enterococci, the bottom is clear because that organism on the bottom is not an enterococcis and we have the growth in salt, 6.5% salt. The tube that's yellow on the left is positive; no change with no growth in the other tube is a negative. But this only gets us in to calling it an enterococci. We need to go further when we have a vancomycin resistant organism because not all enterococci are truly vanomycin resistant enterococci that we worry about in the infection control arena.

On the next page you can see there are additional tests that we need to do to detect the species with intrinsic vancomycin resistance. We know that some of our enterococci were born resistant to vancomycin. The good news is for these organisms that are more commonly found in the environment, they cannot transmit that resistance with their vanC gene versus the vanA and B gene to other microorganisms. The way we can tell if we have these other intrinsically resistant vancomycin resistant

enterococci is by doing two quick tests: one a botility test that you see on your right with a dye indicator on the tube on the left that shows a nice red color with an organism has mottled out to the ends and traveled out; we can see that by the color. Also, they can be pigmented, and the best way to see pigment is just taking a swab of the colony and you can see the swab at the top is much more yellow that the swab on the bottom and it's that bright yellow color, at least a post-it note yellow color, that makes it a positive. These enterococcus casseliflavus, which are both mottle and pigmented or enterococcus gallinarum that is mottled but not pigmented help us pull this away from the usual E. faecalis and E. faecium because they are not VRE and the infection control guidelines for resistant organisms would not be in place.

The next organism, which we're going to make sure we don't forget, is our pneumococci. On that slide you can see with the gram stain that is actually a spinal fluid from one of my patients who had penicillin resistant pneumococci that have developed over the years. For the longest time, penicillin was the appropriate drug du jour for this microorganism and now this organism is not just penicillin resistant but has turned into a multiple drug resistant MDR, strep pneumo as well.

The next slide shows how trends in our pheumococcal resistance are seen and this is just one institution which was my past institution, which was a large medical center in suburban Chicago, where you have red bars showing the non-susceptible, which means intermediate and resistant rates and in the yellow bars intermediate or resistant isolates for the third generation of cephalosporin such as ceftriaxone or cefataxime and those are the big work horse drugs that hospitals would give for anyone coming in that looks septic or had meningitis.

You can see from back from 1992, 1993 where my penicillin and non-susceptible was only a 12% up to 2001 where it was at 44% and my more recent data from 2002 and 2003 are showing pretty close to 44% to 48% depending on the year. Likewise it wasn't until 1994 and 1995 that any resistance would seem, with the third generation of cephalosporins they were sort of that protected drug that could be used empirically with confidence but now you see about 25% of our isolates are not susceptible any longer to the concentrations that would be used for meningitis.

The next slide on multiple drug resistance strep pneumo is to remind us that it's not just resistance to penicillin and the third generation cephalosporins but also to many of the drugs that are being orally for otitis

media for sinusitis and pneumonia and so these resistant organisms are definitely out there and they're spreading, day care centers just being a wonderful place for these children who have a colonization in their nasal pharyngeal area to have these organisms spread. But there's good news, there's a new polysaccharide vaccine conjugate vaccine that encompasses seven of the most common cerotypes of pneumococci seen in these children. Now we're noticing in the early years of the vaccine that it's not only protecting them from the otitis media; it's also protecting them from more severe diseases such as meningitis and it's also protecting the adults around them, basically a herd immunity. So, hopefully the pneumococci will follow the same path that our haemophilus influenza type B did in disappearing as a major player in our patients.

The next few slides that I'm going to go over fairly quickly are going to be focusing on our gram-negative, our extended spectrum beta lactamase producers, or ESBLs on that next slide, have the capability of destroying all penicillins, all cephalosporins and as aztreonam. Unfortunately when the gene is acquired for this ESBL right next to it are the genes for aminoglycocide resistance such as gentamicin and tobramycin as well as resistance to trimethoprim sulfa. So we're losing multiple classes of antibiotics. Why is this important? Well, basically we know that there

have been very high failure rates of patients who were treated with cephalosporins who have these microorganisms; their mortality rate is higher.

We know that these ESBL producing organisms are big infection control problem. Once we detect it, because it takes a while to detect, many times that patient has already transmitted the organism to his roommate or has been carried on the hands of the healthcare worker. The organisms we're concerned about here are E. coli, klebsiella and proteus morales, very common in our hospital and communities. Now we even see it in salmonella. The drug of choice for treatments are big league, big time antibiotics such as imipenem, which luckily, they still remain susceptible to.

On the next slide I just show you the different methods that we use to detect these ESBLs. Basically, it's relying on an MIC that's greater than two for many of our cephalosporins or a change in our disk diffusion zone sizes. But it's not enough just to see a higher MIC. All testing for ESBLs requires a confirmatory test before we give it that designation. So the way we do that is performing a test with the antimicrobial in question, usually a cephalosporin such as cephtazadine and clavulanic acid that's been

coupled with that drug. If we can lower the MIC more than threefold or we can make the zone of inhibition look better by five millimeters, that confirms it.

In the schematic drawing on this slide you can see that there are two pictures, one of cephtazadine alone and the little disk in white is showing that it has a 14 millimeter zone of inhibition using the diameter of the gray area. However, if we couple that drug, ceptazadine with clavulanic, the clavulanic or betalactinase inhibitor actually reverses the effect of that ESBL. Now my zone of inhibition is much longer, wider and we're up to 20 millimeters. If we subtract 14 from 20, we have six millimeters or five millimeters or greater confirming that that is indeed an ESBL. The important part is that if we find that this is an ESB,L we have to override all the results for our cephalosporins from susceptible to resistant otherwise the physician will use one of these and the patient will not do well.

Making things a little bit crazier on the next slide we have something called an amp-C betalactimase and this is you might imagine it like an ESBL gone even worse. Basically we can see this in the same organisms as E. coli and klebsiella. These enzymes are going to eat up the same

antimicrobials as before with one addition. They're also going to hydrolyze the cephamycins or cephoxatin and cephatican and those are different than the cephalosporins. So now this organism has gone through even more antimicrobials, but luckily for us right now imipenem is still susceptible. However, with the amp-C betalactimasis we have no standardized method for detecting and confirming these in the laboratory and so most laboratories are not reporting these out to their infection control practitioners and getting these patients on the appropriate infection control guidelines, which is contact precautions, so this is a real issue.

My last slide talking about organisms are the MDR gram-negative rods. This is something you're going to be seeing more and more of. For many of you who might be in New York and Baltimore, we know that acinetobacter baumaninii, which is a small gram-negative that likes to live in water environments much like pseudomonas, that we're seeing that this organism is resistant to all routinely used and tested antibiotics. An additional problem is our klebsiella have turned resistant to the imipenem that we just spoke about a few minutes ago and although this is very rare right now, once these klebsiella strains are resistant to all the cephalosporins as well as imipenem, there really is no treatment for these patients.

With our pseudomonas aeruginosa, which is always thought to have been the bad organism, we see that our percentage of isolates from 1993 that were resistant to three classes of antibiotics has grown from 4% to now to 14% in 2002. This does have an impact on how well our patients survive these infections. Inappropriate empiric therapy given to patients who have these very resistant microorganisms, but of course until the testing is done, the physician does not know that they have these bad microorganisms that they give an empiric antibiotic that they hope will work but when this organism is resistant to those empiric antimicrobials, the mortality rate is significantly higher. In this study, 38.4% mortality rates compared to 27.4% if the patient at least had an organism susceptible to one active antimicrobial. So, these organisms, these gram-negative rods will be on your radar screen. They will be on the radar screen of everyone in the hospital environment as well as other institutions.

So, how do laboratories that are looking at our patients, looking at our patient's isolates, detect resistance? Certainly large laboratories use high-volume automated testing. They use these to get an identification and a susceptibility test and there's many methods out there. These allow very rapid reporting and are labor-saving, but in some cases sacrifice accuracy

and they certainly limit the flexibility of antibiotics that you can test because everything's prepackaged in a card or in a panel. So when the physician wants a new antimicrobial tested, that just may not be available to them.

This diffusion that I know many of you do is technically simple, however, it is very cumbersome and it is slower to get a result. We can move our antimicrobials around substituting one disk for the other, but it still needs to go overnight. The e-test, which is really a combination of getting an MIC via a diffusion method works very well. However, it is labor intensive putting those strips down if you're going to do many antimicrobial and it's costly at $2.50 a strip. So, there are many methods, but maybe none quite ideal.

On the next slide, I just share with you some of the pitfalls in the current susceptibility testing and this is the reasons why a hospital laboratory may be sending you some isolates to look at. One, automation that is widely used may overcall methacillin resistant staph aureus and this certainly is not good because we have to spend a lot more on infection control and a lot more worry with our patients and those patients might need to be on an IV antimicrobial versus an oral one. We know that automation may not

detect a vencomycin resistant staph aureus. Both the Pennsylvania strain and the New York strain were not easily detected by many of the automated instruments that are using, hence CDC recommended that an additional test such as that BHI with bank auger be used.

Automation cannot detect the inducible resistance with clindomycin, so laboratories who are using automation have to drop back and do a disk test to find that resistance. Now, you might say well this diffusion will do it all, but it won't. It doesn't effectively detect all vencomycin resistant enterococci and it doesn't find the VISAs. ESBL detection as we just spoke about requires confirmatory testing, which many little laboratories are unable to do or don't understand. Lastly, it's not just what we do or how we do it, but what do we do with those results. There's certainly pitfalls in interpreting some of the results we get such as for pheumococcal antibiotics we have different break points for the cephalosporins depending if it's a meningitis isolate or whether it's coming from a case of pneumonia or sinusitis so that the laboratory may not correctly use the right break point.

What can the public health labs do? Well, first of all, you are in line to be a great resource to the smaller clinical labs. You can disseminate some

accurate advice even if you yourself are not doing the testing holding workshops, having a newsletter, sharing Web sites with them that can give them advice is really appreciated by the smaller laboratory that may not have anyone other than their pathologist, who's really not in tune to this problem. If possible, you could perform reference testing to confirm unusual results and that to confirm a vancomycin resistant staph aureus by doing an e-test or when the people think they have a vancomycin resistant strep pneumo, which is usually due to a contamination problem. If you could weed those out at the local level, you could give them an answer back so much sooner and build those relationships with the clinical labs.

It's important if you can gather data to track resistance in your state so that when someone calls and says, gee, I have a resistant X and you can say well we've never seen that, why don't you send us the isolate or send it to us and we'll send to CDC to confirm. So, gathering data for your area even if you can't perform that testing yourself is very important. As many states and public health groups are establishing their own statewide antibiogram so that they know how resistant the phneumococci are in their state or how much vancomycin resistant enterococci they're seeing etc. and that may help them apply for additional funds.

So, how can public health labs be a good partner with CDC? I know that everyone is extremely busy, but when the isolate bugs have to travel to CDC, sending the information with the isolate is so incredibly important. The patient demographics: is this an adult or a child? The specimen sort: we need to know if this is a blood or a spinal fluid isolate versus is this out of a wound with 12 other things? Many of you have done some studies on the isolates before they get sent to CDC and you note that that the organism grows best under a certain condition: a lower temperature or it requires CO2 or it needs a special media. That information is just critical. Any biochemical reactions that you have done are very welcome. It is important for you to give your best guess so it goes to the right lab. If you just put gram-negative rod on there, that thing is going to travel all over CDC before it gets to the right place. Having your contact name and phone number at your public health laboratory is great.

On the next slide I've just shown the dash form, which is probably very familiar to you, with a few red highlights of what was just spoken about. One there's an arrow showing in the upper left hand corner where you can denote whether this is part of an outbreak or not. We can put the microbiologist name and phone number meaning your microbiologist, your public health laboratory person so that when CDC has a question,

we're not calling all over and getting transferred and not getting to the right person. Likewise, if you can put the phone number of the submitting lab or the doctor or some contact person, again if we can't get to you or we need to ask more medically related questions about that patient, we can call direct. So, those are very key.

On the next slide the laboratory exam requested of course is important so that we don't do too much or too little. I have circled specific agent suspected is your best guess. No one's going to grade you if it turns out that this is some weird enterobacter and you thought it was a E. coli, but at least we'll know it's going to go to the right laboratory. That will probably save at least two weeks in getting answers back to you and then to your constituents.

The source of the specimen is a must. CDC's resources are becoming more and more limited and higher priority is certainly going to be given to a blood or spinal fluid isolate versus a wound. In some cases we're getting things such as an anerobe from a sputum where an anerobe is a part of the normal flora and we're not even going to do the test. But we need to know where did this isolate come from. If your submitting lab

doesn't give that then you need to get back to them. Again, where it says submitted on, tell us what auger or temperature or atmosphere is best.

Lastly, the last for slide shows that any biochemical reactions that you can staple to the form, hand write, anything that you've ever done is important to us. Any testing that you have will help us accelerate what we can do and also if we get a different reaction we can share that with you and hopefully explain why.

The last slide is just the reminder to please check the purity. This is probably something that every public health lab can do before you send it forward. Too often everyone gets very excited that they have a very new resistant microorganism such as a vancomycin resistant staph aureus only to find out there's an enterococcus hiding under there or last week when we had a pseudomonas aeruginosa taking the trip with the staph. The state public health laboratories if you could sub it to a chocolate plate that will grow everything or a McConky plate to make sure there's not a gram-negative hiding or a Columbia nalidixic acid that selects for gram-positive just to make sure that you really have something pure because the laboratory that's submitting to you probably thought it was pure, but most

of the cases we have to say are not of a single organism and they're getting an unusual resistance pattern because it's mixed.

At the end of this slide I would just try to provide phone numbers because CDC is a maze, I admit it. After one year here, I'm still finding places to go and people to see. That it you have a particular question, CDC is very open to try and have you call and talk to us so that we can give you the best guidance before you send something through the FedEx or overnight. In many cases maybe we can stop it at your local level or give you some information that you can turnaround and use very quickly. I've give you the staph lab, a stress lab, anarobe lab, special bac-t which is just about everything else, all the non-fermentors and the … etc. that these are numbers that you can use to try and reach us so that we can be the best partners possible for public health. With that, I know I have gone a long time with stores, etc. and I suppose it is time for questions.

C. Labaar Dr. Carey, while we wait for that first question, I have one for you. If a public health lab had one susceptibility test they could do to detect resistance, what would that test be?

R. Carey I think right now the most important test public labs could do for the local constituents as well as helping CDC would be able to rule out or rule in vancomycin resistance staph aureus; one, to check the purity because many times, as I mentioned, it's not a single isolate that the local lab is getting these results. But because many of you are already doing an e-test or are familiar with that, the e-test has performed very well in ruling some of these out our saying that they might be vancomycin resistance staph aureus. It's not the end-all and be-all but if the public health labs could do that that would be terrific.

Coordinator Ma'am, there are no questions.

R. Carey I guess we've overwhelmed them with too many bugs and drugs, potentially. But hopefully people can refer to the handout and certainly there are fact sheets for all these organisms under the CDC Web site under drug resistance fact sheets where many of you can go and get a lot more information than I could provide in this 50-minute period with you.

Coordinator It looks like we do have one question from Wendy. Your line is open.

Wendy I think it's great that we have, now a list of phone numbers to contact labs, but can we get a list of names because we need a contact person in order to send isolates to down at CDC. Is that possible?

R. Carey The reason I didn't give you names is because there are multiple people in each of these laboratories and if it's a certain person's name, if they're away on vacation or gone somewhere, you may not get the attention as promptly as you would like. When you're sending isolates and so forth to the lab you can just put, as you saw, staph lab, strep lab, special bac-t, E. coli, that will help you get it to the right place. All the isolates, when they come to CDC, go to a building where the specimens are received and that's the dash area for specimen handling. They're going to look at that form and they're going to see what organism or where did you want to send it. So at least if your best guess is that this is probably a staph, put staph lab on there and that's it's probably some kind of staph species. If that turns out to be wrong and it's strep for example, then the staph lab will share it and take it over to the strep lab after initial testing. But I will say for gram-negative rods it's divided that we have … in one group and these non-fermentors in others and then the food borne, salmonella, shigella goes someplace else. The more information you can give for that it will get to the right laboratory sooner. So I deliberately did not put

people's names on there again, so somebody will pick up these numbers and get it to them. You can just call us the staph lab or strep lab and that works.

Wendy Okay, some of the isolates that we send though we have to require a contact person on our shipping list. Do you understand what I'm saying?

R. Carey Yes, I do, for the special goods and handling for that. I certainly understand. If you need a name, put mine on there because many of the things that you're going to send do end up in our laboratory for the staph and the gram-negative rods etc. and they will get to us or the appropriate lab but I understand for the regulation for transporting dangerous goods you do need a person that you're sending it to.

Coordinator There are no further questions.

C. Labaar If there are any further questions you can always send an e-mail to the following address: neoffice@nltn.org. I would like to remind all the participants listening in to our program to register and complete an evaluation form by March 23rd. The directions for this are on your confirmation letter and general handout. They were also e-mailed to each

site representative this morning. Documenting your participation helps us continue to bring high quality training programs in a variety of formats. When you have completed the registration and evaluation form you will be able to print your CEU certificate.

That concludes our program. Our next teleconference will be on March 16th and the topic is Verification Strategies for Implementation of Molecular Diagnostic Essays. The co-sponsors of today's program would like to thank our speaker, Dr. Roberta Carey. Thank you for joining us. I hope that all of you will consider joining us for future programs and that you will make the National Laboratory Training Network your choice for laboratory training. From the Vermont Health Laboratory in Burlington, Vermont, I'm Christine Labaar and thank you and goodbye.

Coordinator This will conclude today's conference call.