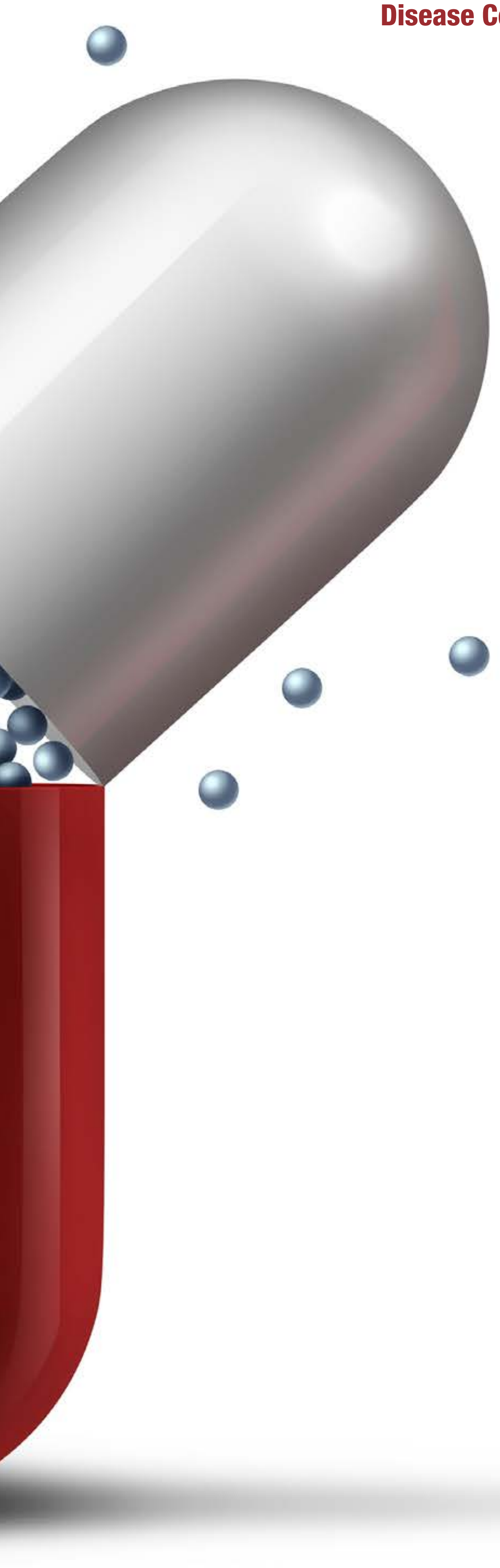
THE AR LAB NETWORK

A Game-changer in the Fight Against Antibiotic Resistance

by **Nancy Maddox**, MPH, writer

Arkansas resident Tamika Capone traveled to Tijuana last October for low-cost bariatric surgery and came home with a superbug—VIM-producing carbapenem-resistant Pseudomonas aeruginosa (VIM-CRPA), an organism the US Centers for Disease Control and Prevention (CDC) considers a serious health threat.



Arianna Allgood and Erica Terrell read AST plates.
Photo: TDH DLS

As quoted in *The Washington Post*, her Little Rock physician said "I've not yet had a patient with zero [treatment] options, but this is as close as I've had."

Capone started on a course of colistin—a last-resort antibiotic that can trigger kidney and nerve damage—but stopped treatment after her face and tongue went numb. Now, as *The Post* reports, she has an infected hole at the abdominal incision site, and it won't heal and "hurts a lot." If the highly drug-resistant bacterium enters her bloodstream, the infection could well be fatal.

Welcome to a world without antibiotics.

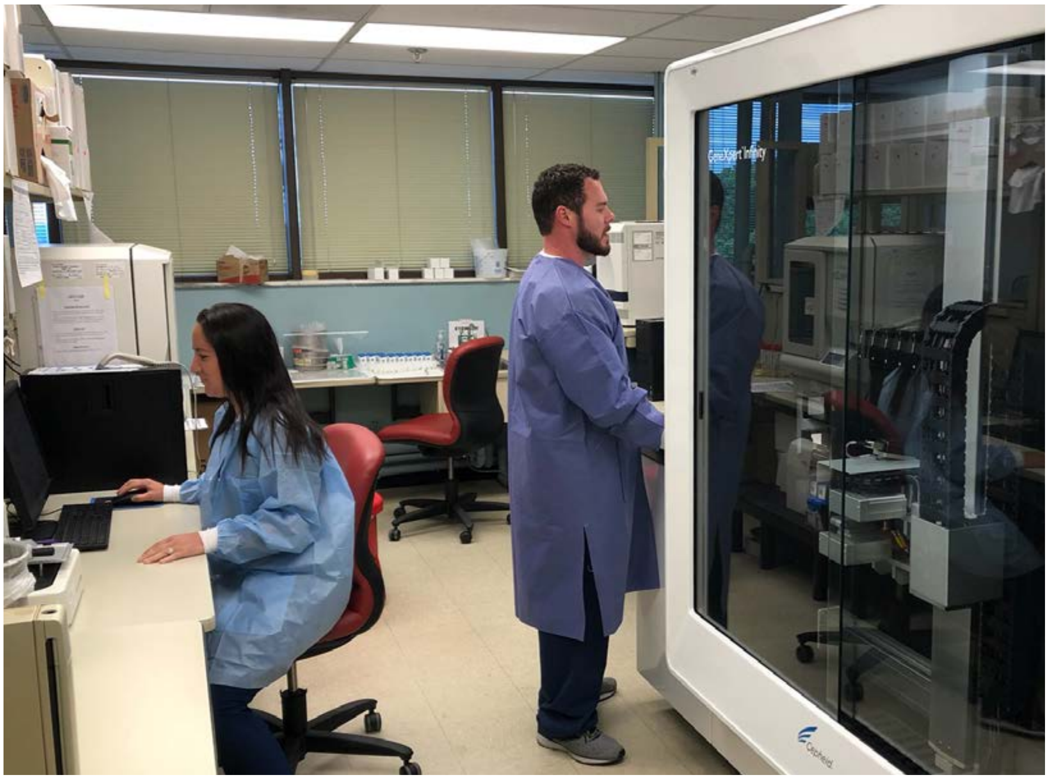
Although VIM-CRPA is uncommon in the United States—86 cases were reported to CDC through 2017—Capone's experience is a preview of what will certainly happen if our antibiotic pharmacopoeia becomes irrelevant.

Given the global rise of drug-resistant pathogens over the past few decades, some physicians and scientists warn of a possible *antibiotic apocalypse*—a scary, post-antibiotic era. Marion Kainer, MD, MPH, an infectious disease expert who directs the Healthcare-associated Infections and Antimicrobial Resistance Program at the Tennessee Department of Health (TDH), said such a fate "is definitely a valid threat." She said, "We have patients who have untreatable organisms right now. This is not something that's in the future. Fortunately, in the US it is still relatively rare."

A $160 million CDC effort now aims to keep antibiotic resistance rare. And the keystone of this effort is the Antibiotic Resistance Laboratory Network (AR Lab Network). Established in 2016, the AR Lab Network comprises public health laboratories in 50 states, five cities and Puerto Rico, including seven regional laboratories with advanced testing capabilities and the National Tuberculosis Molecular Surveillance Center overseen by the Michigan Department of Health and Human Services.

It was the AR Lab Network that generated the data linking Capone to a handful of other CRPA-infected patients who received healthcare in Tijuana. According to *The Post*, eight of these patients, including Capone, had surgery at the same hospital. Thanks to the AR Lab Network's scientific work, CDC issued a travel alert with recommendations for patients who had invasive medical procedures in Tijuana and for clinicians who might treat CRPA-infected individuals. The agency also contacted Mexican health authorities, who pinned the outbreak on poor infection control practices and temporarily closed Tijuana's Grand View Hospital.

As of April 20, 2019, the VIM-CRPA outbreak associated with Grand View Hospital appears to be over. But without the AR Lab Network, it might never have been detected.



Tennessee microbiologists Michelle Therrien and Justin Simpson process carbapenem-resistant Enterobacteriaceae specimens. Photo: TDH DLS

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>
> *Michael Craig, MPP*

“Whenever and wherever you use antibiotics, resistance is going to follow”

The problem of antibiotic resistance (AR) has been decades in the making. James “Albert” Burks, IV, MLS(ASCP), RN, who oversees carbapenem-resistance testing at the TDH Division of Laboratory Services explained that antibiotic research and development “slacked off” beginning in the mid-1980s, when an array of potent antibacterial agents was readily available. At the same time, he said, physicians began prescribing antibiotics for conditions like sinus infections, now known to be mostly viral and unresponsive to antibacterial drugs.

“Patients were taking [antibiotics] until they felt better when the lifecycle of the virus was complete; they weren’t taking the full regimen,” said Burks. Consequently, mildly drug-resistant pathogens were able to survive and evolve.

Outside the healthcare arena, antibiotics have also been overused in veterinary and agricultural settings. In fact, agricultural usage of antibiotics far exceeds their healthcare usage. Farmers administer the drugs not only to treat acute animal illness, but also to prevent illness and to enhance animal growth. According to one estimate, about 90% of pigs raised for food in the US get tetracyclines or similar drugs in their feed as a matter of course. And nearly all US dairy cows are given prophylactic, intramammary drug infusions—typically penicillins or other beta-lactam drugs—to prevent mastitis.

Antibiotics are also used as pesticides. The US Environmental Protection Agency, for example, is in the process of re-approving the use of streptomycin for wholesale spraying on apple, pear and nectarine trees to control citrus canker and citrus greening disease.

Global developments have exacerbated the problem. In 2010, India was the world’s largest consumer of antibiotics for human health, followed by China. According to researchers Ramanan Laxminarayan and Ranjit Roy Chaudhury, a perfect storm of poor public health systems, high rates of infectious disease, inexpensive antibiotics and rising incomes has led to the proliferation of resistant pathogens in many parts of the world and especially the BRICS countries—Brazil, Russia, India, China and South Africa. Increased demand for meat and poultry in places like India has fueled even greater agricultural antibiotic use.

Michael Craig, MPP, CDC’s senior advisor for AR, said, “Whenever and wherever you use antibiotics, resistance is going to follow.” He said, “We take for granted sometimes that antibiotics are really the scaffolding that makes surgical procedures possible, organ transplants possible, invasive disease treatments possible. All of those are risky, and people susceptible to infections are vulnerable. When antibiotics start to be ineffective, the risk-benefit profiles of those treatments change; doctors might not

Tennessee’s GC AR Lab Network Team (from l to r): Robin Rasnic, Arianna Allgood, Erica Terrell, Brielle Davis and Henrietta Hardin. Photo: TDH DLS recommend doing them if we can't treat any infections that might come up."

In 2014, the World Health Organization called AR "a problem so serious that it threatens the achievements of modern medicine."

Indeed, Craig said reservoirs of AR are now so great, it is no longer sufficient to simply stop misusing and overusing antibiotics: "Even if we have perfect antibiotic prescribing and use, AR would still be a problem, largely because of the transmission of [existing] resistant pathogens." These pathogens may colonize individuals who never become symptomatic. Or they may persist in animal hosts, in healthcare facilities or in the broader environment (for example, after being discharged in hospital waste).

Bacteria containing the AR gene NDM-1 have been found in water pools in New Delhi streets and in High Arctic soils in Norway's Svalbard archipelago, demonstrating just how widely dispersed the organisms are.

And because AR genes are often found on mobile genetic elements called plasmids, they can be transferred from one microorganism to another without any antibiotic exposure. So, for example, KPC—the most common AR gene found in carbapenemase-producing organisms (CPOs) in the US—may be transferred from *Klebsiella* to *Salmonella* to CRPA.

In 2013, CDC released an AR threat report listing 18 microbes, collectively responsible for more than two million illnesses and at least 23,000 deaths in the US each year. However, the report was written before the launch of the AR Lab Network, when data were less complete. Craig said an updated report due out later this year will note that, "as we expected, the burden of AR infections is more than we estimated previously; for some pathogens, significantly more."

The AR Lab Network—"A Game-changer"

Two years after the threat report came out, the Obama Administration released its National Action Plan for Combating Antibiotic-Resistant Bacteria. The so-called "CARB" plan directs federal agencies to "accelerate response to antibiotic resistance," including:

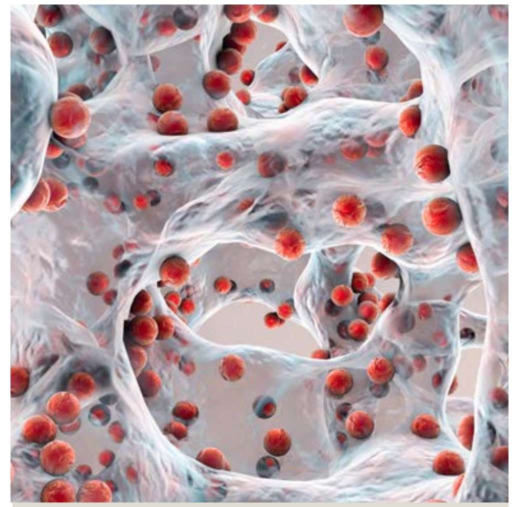
- Improving antibiotic stewardship in healthcare settings, including cutting antibiotic use by 50% in outpatient settings and 20% in inpatient settings by 2020
- Preventing the spread of AR threats
- Eliminating the sub-therapeutic use of medically important antibiotics in food animals
- Expanding surveillance for AR bacteria in people and animals
- Creating a regional public health laboratory network
- Establishing an AR specimen repository and genetic sequence database to facilitate development of new diagnostic tests and pathogen-specific treatments.

So far, Craig said, one of CDC's biggest AR achievements, "if not *the* biggest achievement," is the founding of the regional AR Lab Network.

All 56 AR Lab Network members perform basic testing, such as antibiotic susceptibility testing and detection of carbapenemases (enzymes that hydrolyze certain antibiotics) in Enterobacteriaceae and *Pseudomonas aeruginosa* isolates.

In addition, the seven regional AR Lab Network members perform molecular testing to detect colonization of CPOs in people potentially exposed by an index case; fungal susceptibility testing of *Candida* species; colonization screening for *Candida auris*; and detection and characterization of emerging threats, such as *mcr*-1, a bacterial gene that confers plasmid-mediated resistance to colistin (the drug-of-last-resort prescribed for Tamika Capone). AR Lab Network laboratories also provide isolates for the new CDC/FDA AR Isolate Bank and for federal whole genome sequencing projects.

The TDH Division of Laboratory Services—the state public health laboratory—is the Southeast Regional AR Lab Network Laboratory that provides core AR Lab Network testing for six states plus Puerto Rico, expanded drug susceptibility testing



URGENT THREATS

- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae
- Drug-resistant *Neisseria gonorrhoeae*

SERIOUS THREATS

- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida*
- Extended spectrum ß-lactamase producing Enterobacteriaceae
- Vancomycin-resistant *Enterococcus*
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant non-typhoidal *Salmonella*
- Drug-resistant *Salmonella* Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus*
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

CONCERNING THREATS

- Vancomycin-resistant *Staphylococcus aureus*
- Erythomycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

Source: CDC. *Antibiotic Resistance Threats in the United States, 2013* for 14 states plus Puerto Rico and surge capacity nationwide. In 2017-2018, the laboratory examined over 9,600 specimens for carbapenem resistance and detected or confirmed over 300 highly resistant *Acinetobacter* isolates, over 1,100 resistant *Pseudomonas* isolates and almost 3,500 carbapenem-resistant Enterobacteriaceae isolates.

Among other successes, Burks said his scientific team employed a new PCR method to identify three new AR gene groups in *Acinetobacter*. "The number of *Acinetobacter* specimens [we receive] seems to be holding steady," he said, "but resistance is surprisingly high—about 70% positive for one of the three genes Tennessee identified." But because there is no reliable pre-AR Lab Network assessment of carbapenem resistance in *Acinetobacter*, Burks said, "We don't know if the rate is increasing or if it was already that high."

Under the direction of Henrietta Hardin, MPA, MT(ASCP), the facility's general bacteriology manager, the Tennessee laboratory is also one of four regional AR Lab Network laboratories testing for resistance in *Neisseria gonorrhoeae* (the so-called GC AR Lab Network). The bacteriology team tests specimens from high-prevalence sites across the country that participate in CDC's Gonococcal Isolates Surveillance Program (GISP), enhanced GISP or Strengthening US Response to Resistant Gonorrhea program. Since the laboratory joined the GC AR Lab Network in spring 2017, it has analyzed over 5,500 isolates for susceptibility to seven antibiotics using agar dilution plates produced in-house. Overall, 7% of isolates have exhibited drug resistance.

Hardin said her team is now involved in setting susceptibility "breakpoints" for new drugs, like gentamicin, which will hopefully prove effective against some drug-resistant gonorrhea strains.

Within the state of Tennessee itself, Kainer said the biggest AR threat is "an oldie" that is making a comeback: methicillin-resistant Staphylococcus aureus (MRSA). She said, "We have seen very significant increases particularly among the younger population and more among females."

Between 2014 and 2018, the number of MRSA bloodstream infections reported by Tennessee hospitals jumped from 2,123 to 3,277—a 54% increase.

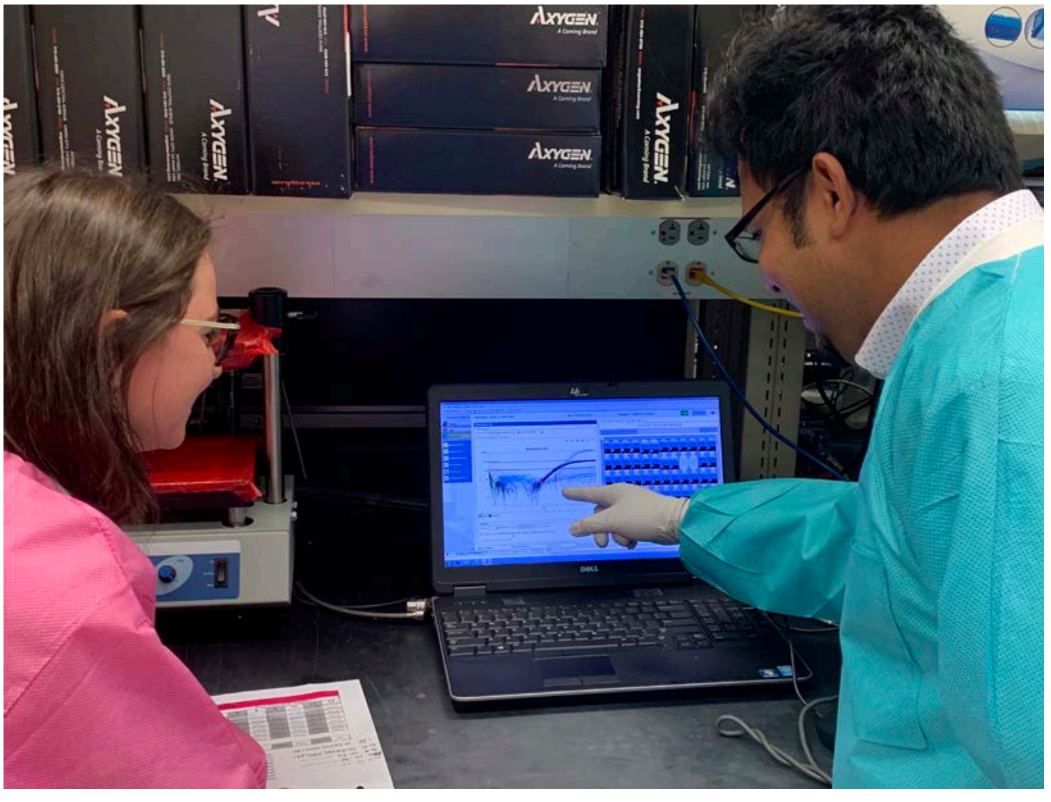
"The epidemiology of [MRSA transmission] is changing," said Kainer. "It's now likely to be driven by the opioid epidemic—users injecting with tainted needles, syringes or other paraphernalia. They often get these MRSA infections along with endocarditis. Those are very serious, very expensive, high-mortality conditions." In fact, one-year mortality for hospital-onset MRSA bloodstream infection in Tennessee runs about 50%.

On the flip side, Kainer said, CPOs carrying the KPC gene have become notably rarer in Tennessee. She said, "We attribute that to improved infection control and environmental cleaning in healthcare settings." And those improvements she attributes directly to CDC's stepped-up investment in AR control.

Before the CARB plan and associated state funding, Kainer said, "We didn't have laboratory capacity for rapid [AR] detection and identification, and we didn't have the public health infrastructure on the epi and infection control side."

Today, a single case of CPO infection in a Tennessee hospital triggers laboratory testing to identify the infectious organism and AR gene, sometimes supplemented by more detailed characterization, such as whole genome sequencing. In addition, Kainer's staff assesses the facility's infection control practices—hand hygiene, environmental cleaning, use of personal protective equipment and the like—and collects rectal swabs from potentially exposed patients as part of a point prevalence survey to determine whether transmission has occurred. If laboratory testing shows CPO colonization in other patients, further recommendations are made.

"We continue these point prevalence surveys every two weeks until we get two consecutive rounds of negative transmission," said Kainer. "Having the laboratory capacity to process these colonization swabs is a huge thing. The whole aim here is timely data to allow us to take the appropriate infection control and public health actions. It's literally a game-changer."



Brittany O'Brien and Rokebul Anower review results from the real-time PCR developed for *Candida auris*. Photo: Wadsworth Center

The *Candida* team from the Wadsworth Center Mycology Laboratory. First row (from l to r): Yan Chun Zhu, Brittany O'Brien, Sudha Chaturvedi. Second row (from l to r): Mitchell Kaplan, Manuel Pazos, Jiali Liang, Rokebul Anower. Photo: Wadsworth Center

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Marion Kainer, MD, MPH

One organism so far undetected in Tennessee, but an emerging problem elsewhere in the US is antibiotic-resistant *Candida auris*.

"When CDC put out the original [AR] threats report in 2013, we didn't even mention this, because we didn't know about it," said Craig. "It seems to have emerged independently in multiple places around the world and then spread. We don't know yet how or why it emerged when it did."

Antibiotic-resistant *Candida auris* is known for its extreme hardiness in the environment; its ability to colonize the human gut, skin and bloodstream—and a mortality rate as high as 80%, depending on the strain and infection site.

The organism was first described in a Japanese patient in 2009 and first identified in New York state at the time of a multi-hospital outbreak in New York City (NYC) in 2016. According to the New York State Department of Health, it can now "probably be considered endemic within some parts of the healthcare system in Brooklyn and Queens."

As of May 31, 2019, the Wadsworth Center—the New York state public health laboratory and Northeast Regional AR Lab Network Laboratory—confirmed 334 clinical cases of drug-resistant *C. auris* among NYC residents, with infection almost exclusively limited to people with extensive healthcare needs, such as nursing home residents with chronic ventilator usage and people with multiple ICU admissions.

To speed detection of the organism during the outbreak, Wadsworth scientists moved from MALDI-TOF mass spectrometry testing—which requires culturing specimens over 4 to 14 days—to a rapid molecular assay developed in-house. The new assay provides results within one day of specimen receipt.

To date, the Wadsworth Center has screened over 17,000 surveillance specimens from the NYC area and detected drug-resistant *C. auris* on the skin of over 450 healthy individuals, 40 of whom went on to develop illness and are also included in the clinical case count. The Center's molecular assay has been adopted by CDC and several other AR Lab Network members.

"If we're not looking for it, it's going to disseminate"

Containing the threat posed by drug-resistant pathogens is an ongoing project. Kainer said jurisdictions can assist by making drug-resistant conditions reportable and requiring isolate submission; conducting tabletop exercises with laboratorians, hospital and nursing home risk managers, infection control nurses and other stakeholders across the healthcare system; and working with sentinel laboratories that serve high-risk populations, such as ventilated nursing home patients and "medical tourists" who have had healthcare abroad. "When you're doing [AR] surveillance, you want to be sure you're looking at the places where you expect to find it," she said.

Historically, said Craig, "Even in the US we haven't done as good a job as we should have to detect and respond to [AR pathogens]." He said, "With the AR Lab Network, now we have an infrastructure to do that, and I'm thankful and grateful for all the hard work laboratorians have put in to support the network; they are fundamental to its success."

Without laboratory data, Craig said, "there's really not a good understanding about what [drug-resistant] strains are developing, how they're emerging and what's likely to be transmitted locally and globally." He warned, "If we're not looking for it, it's going to disseminate secretly and quietly around the world." ■