ORIGINAL ARTICLE

Querying Automated Antibiotic Susceptibility Testing Instruments: A Novel Population-Based Active Surveillance Method for Multidrug-Resistant Gram-Negative Bacilli

Jessica Reno, MPH;[1,2,3] Calista Schenck, MLS(ASCP);[1,2,3] Janine Scott, MPH;[1,2,3] Leigh Ann Clark, MPH;[1,2,3] Yun F. (Wayne) Wang, MD, PhD;[2,4,5] Susan Ray, MD;[1,2,3,4,5] Paula Snippes Vagnone, MT(ASCP);[6] Jesse T. Jacob, MD[2,5]

OBJECTIVE. To describe the implementation of a population-based surveillance system for multidrug-resistant gram-negative bacilli (MDR-GNB).

DESIGN. Population-based active surveillance by the Georgia Emerging Infections Program.

SETTING. Metropolitan Atlanta, starting November 2010.

PATIENTS. Residents with MDR-GNB isolated from urine or a normally sterile site culture.

METHODS. Surveillance was implemented in 3 phases: (1) surveying laboratory antibiotic susceptibility testing practices, (2) piloting surveillance to estimate the proportion of GNB that were MDR, and (3) maintaining ongoing active surveillance for carbapenem-nonsusceptible Enterobacteriaceae and *Acinetobacter baumannii* using the 2010 Clinical and Laboratory Standards Institute (CLSI) breakpoints. Pilot surveillance required developing and installing queries for GNB on the 3 types of automated testing instruments (ATIs), such as MicroScan, in Atlanta's clinical laboratories. Ongoing surveillance included establishing a process to extract data from ATIs consistently, review charts, manage data, and provide feedback to laboratories.

RESULTS. Output from laboratory information systems typically used for surveillance would not reliably capture the CLSI breakpoints, but queries developed for the 3 ATIs did. In November 2010, 0.9% of Enterobacteriaceae isolates and 35.7% of *A. baumannii* isolates from 21 laboratories were carbapenem nonsusceptible. Over a 5-month period, 82 Enterobacteriaceae and 59 *A. baumannii* were identified as carbapenem nonsusceptible.

CONCLUSIONS. Directly querying ATIs, a novel method of active surveillance for MDR-GNB, proved to be a reliable, sustainable, and accurate method that required moderate initial investment and modest maintenance. Ongoing surveillance is critical to assess the burden of and changes in MDR-GNB to inform prevention efforts.

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Multidrug-resistant gram-negative bacilli (MDR-GNB) infections, particularly Enterobacteriaceae and *Acinetobacter* species resistant to carbapenems, are an emerging problem in the United States.[1] These pathogens cause both community-acquired and healthcare-associated infections, may spread their plasmid-encoded resistance genes rapidly or persist in the environment, and can have a high mortality with severe infections.[2-10] Current estimates of MDR-GNB are based on passive voluntary surveillance systems and are limited because they often calculate proportion (not a rate) of antibiotic sensitivity and reflect trends from large academic medical centers.[11,12] There is a need for a population-based active surveillance system to assess the burden and changes in trends of MDR-GNB infections.

Laboratory information systems are typically used by population-based active surveillance programs to identify patients with a given pathogen (eg, *Staphylococcus aureus*), sometimes with resistance to a single antibiotic of interest (eg, methicillin). However, MDR-GNB isolates belong to multiple genera and have various susceptibility breakpoints to different antibiotics. Additionally, recent changes in the carbapenem and cephalosporin susceptibility breakpoints for Enterobacteriaceae were adopted by the Clinical and Laboratory Standards Institute (CLSI), but implementation of these recommendations has been incomplete.

In 2010, the Centers for Disease Control and Prevention's (CDC's) Emerging Infections Program (EIP) piloted the Multi-Site Resistant Gram-Negative Bacilli Surveillance Ini-

Affiliations: 1. Atlanta Research and Education Foundation, Decatur, Georgia; 2. Georgia Emerging Infections Program, Decatur, Georgia; 3. Atlanta Veterans Affairs Medical Center, Decatur, Georgia; 4. Grady Memorial Hospital, Atlanta, Georgia; 5. Emory University School of Medicine, Atlanta, Georgia; 6. Minnesota Department of Health, St. Paul, Minnesota.

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tiative (MuGSI) in Georgia and Minnesota to use a standard definition based on minimum inhibitory concentration (MIC) to inform infection prevention strategies. This report describes the design and implementation of this innovative active surveillance method in the metropolitan Atlanta area by the Georgia EIP in collaboration with the CDC and the Minnesota EIP.

METHODS

MuGSI was implemented by Georgia EIP staff in 3 phases: (1) determining the local laboratories' antibiotic susceptibility testing practices and capabilities for detecting MDR-GNB, (2) piloting surveillance to determine feasibility over the long term and to approximate the proportion of GNB that were MDR, and (3) initiating ongoing active surveillance for MDR-GNB in metropolitan Atlanta. A timeline is shown in Figure 1.

Phase 1: Laboratory Assessment (June 2010)

The EIP surveyed each clinical laboratory in the 20-county Atlanta Metropolitan Statistical Area (MSA; population in 2010: 5,128,159[13]) for automated testing instrument (ATI) manufacturer, model (eg, VITEK 2), and software version; the susceptibility panel used to test GNB isolates; any other methods used to test carbapenems or confirm susceptibility; and any methods used to detect organisms producing an extended-spectrum β-lactamase (ESBL) or carbapenemase. Surveys were repeated every 6 months during surveillance to ensure that the queries developed in phases 2 and 3 adequately captured changes in ATI panels or cards.

Phase 2: Pilot Surveillance (November 2010)

ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*, carbapenem-nonsusceptible *E. coli* and *K. pneumoniae*, and carbapenem-nonsusceptible *Acinetobacter baumannii* were targeted for the pilot using the 2010 CLSI breakpoints. ESBL positivity for *E. coli* and *K. pneumoniae* was defined as being intermediate or resistant to ceftriaxone (MIC more than or equal to 2 μg/mL), ceftazidime (MIC more than or equal to 8 μg/mL), or cefotaxime (MIC more than or equal to 2 μg/mL) or having a positive phenotypic test result for an ESBL. Carbapenem nonsusceptibility was defined as having a MIC for doripenem, imipenem, or meropenem above the breakpoint for sensitivity (more than 1 μg/mL for *E. coli* and *K. pneumoniae* and more than 4 μg/mL for *Acinetobacter baumannii*).[14] The 2010 CLSI breakpoints were used regardless of each laboratory's implementation of these new breakpoints, to improve sensitivity and sustainability of ongoing surveillance. No laboratory had the ability to test the ertapenem susceptibility breakpoint of 0.25 μg/mL, so this antibiotic was excluded from the case definition.

Pilot data included isolates of urine and invasive sources collected from MSA residents during the month of November 2010. For each of the 3 types of ATIs used by laboratories serving the MSA population, Georgia EIP staff developed 4 electronic queries to identify (1) all *E. coli*, *K. pneumoniae*, and *A. baumannii* isolates collected during the specified time period; (2) ESBL-producing *E. coli* and *K. pneumoniae* isolates; (3) carbapenem-nonsusceptible *E. coli* and *K. pneumoniae* isolates; and (4) carbapenem-nonsusceptible *A. bau-*

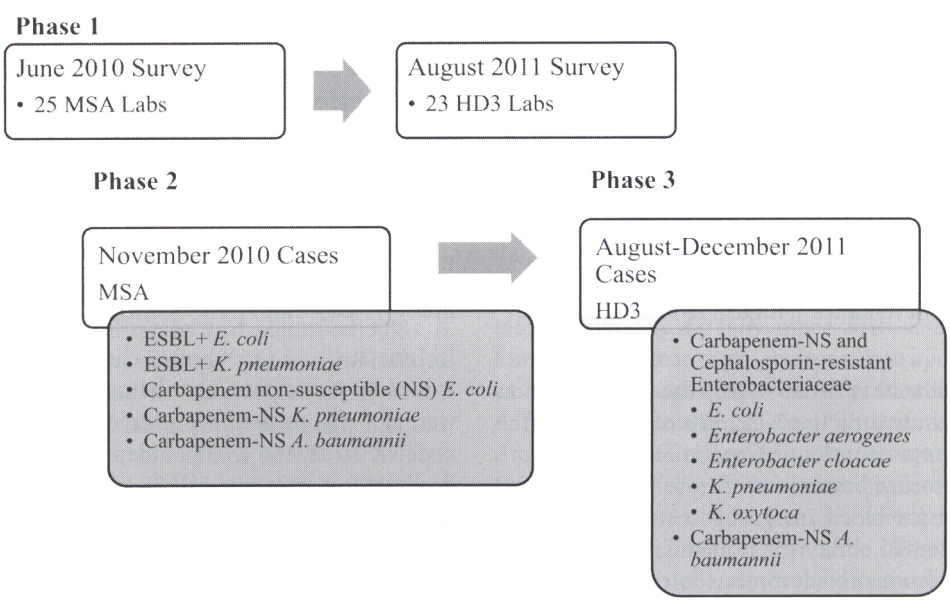


FIGURE 1. Timeline of the Multi-Site Resistant Gram-Negative Bacilli Surveillance Initiative in Georgia. The 20-county Atlanta Metropolitan Statistical Area (MSA) includes Barrow, Bartow, Carroll, Cherokee, Clayton, Cobb, Coweta, DeKalb, Douglas, Fayette, Forsyth, Fulton, Gwinnett, Henry, Newton, Paulding, Pickens, Rockdale, Spalding, and Walton Counties. The 8-county Georgia Health District 3 (HD3) includes Clayton, Cobb, DeKalb, Douglas, Fulton, Gwinnett, Newton, and Rockdale Counties. ESBL, extended-spectrum β-lactamase.

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TABLE 1. Automated Testing Instrument Susceptibility Testing Parameters for Clinical Laboratories Serving Georgia Health District 3 during August–December 2011

Antibiotics tested	No. (%) of laboratories (n = 23)	Proportion of laboratories able to test Enterobacteriaceae for the 2010 CLSI susceptibility breakpoints for these antibiotics
Cephalosporins		
Cefotaxime, ceftazidime, and ceftriaxone	16 (70)	3/16[a]
Ceftazidime and ceftriaxone	6 (26)	6/6
Ceftriaxone only	1 (4)	1/1
Carbapenems		
Imipenem and meropenem	11 (48)	9/11
Imipenem only	8 (35)	2/8
Doripenem and imipenem	3 (13)	3/3
Doripenem and meropenem	1 (4)	1/1

NOTE. CLSI, Clinical and Laboratory Standards Institute.

[a] The ceftriaxone breakpoint was the only antibiotic breakpoint the other 13 laboratories were not able to test.

mannii isolates. Parameters of each query included date of culture collection, organism name, antibiotics in the case definition, and MIC breakpoints. Georgia EIP staff then excluded cases occurring in persons living outside MSA and isolates collected from nonsterile sites (other than urine) by obtaining medical records with the assistance of healthcare facility personnel.

An incident case was defined as the first eligible isolate of each organism collected from a patient in 30 days. The Georgia EIP also quantified all *E. coli*, *K. pneumoniae*, and *A. baumannii* isolates collected from normally sterile sites and urine to estimate the proportion of GNB isolates that were MDR. Patient residence was not collected for this denominator because of the high volume of specimens.

Not all laboratories were able to test the CLSI breakpoints for carbapenem nonsusceptibility. Therefore, the proportion of GNB that were MDR was calculated in 2 ways. First, overall nonsusceptibility was calculated using the results from all laboratories able to provide denominator information for all GNBs of interest. A second, more accurate estimate was calculated by also excluding laboratories that were not able to test the 2010 CLSI susceptibility breakpoints from both the numerator and the denominator.

Phase 3: Ongoing Surveillance (August 2011–December 2011)

For ongoing surveillance of MDR-GNB, the case definition was adjusted to include only the 3,752,180 residents[13] of the 8 metropolitan Atlanta counties of Georgia Health District 3 (HD3) based on resource limitations of travel and staff time, to add new organisms based on group consensus of their prevalence and potential ability for transmission (the entire *A. calcoaceticus–A. baumannii* complex, *Enterobacter aerogenes*, *Enterobacter cloacae*, and *Klebsiella oxytoca*), and to include only carbapenem-nonsusceptible Enterobacteriaceae resistant to all tested third-generation cephalosporins (cefotaxime MIC more than or equal to 4 μg/mL, ceftriaxone MIC more than or equal to 4 μg/mL, and ceftazidime MIC more than or equal to 16 μg/mL). ESBL-producing Enterobacteriaceae isolates not meeting the above carbapenem and cephalosporin susceptibility criteria were not included, to focus surveillance efforts on the most clinically important emerging MDR organisms.

After queries were modified to fit the revised case definition, laboratories submitted monthly or quarterly reports of all eligible isolates, and each patient's demographic, clinical, and outcome information was obtained by reviewing the patients' medical records with the assistance of healthcare facility records personnel. Cases were categorized as hospital onset (initially cultured after the third day of hospital admission), healthcare-associated community onset (initially cultured before the third day of hospital admission with an existing indwelling device or one of the following healthcare-associated events in the year prior: hospitalization, surgery, dialysis, or residence in a long-term care facility), or community associated (initially cultured before the third day of hospital admission with no indwelling device or history of the aforementioned healthcare-associated events).

RESULTS

Phase 1: Laboratory Assessment

In June 2010, 25 (86%) of 29 clinical laboratories in the MSA agreed to participate. Two laboratories at pediatric hospitals were not eligible pending additional approval by institutional review boards, and 2 large independent reference laboratories declined to participate. All 25 laboratories preferentially used ATIs and not manual methods to test antibiotic susceptibilities of GNB isolates. MicroScan (Siemens; n = 14) and VITEK (bioMérieux; n = 10) were the 2 most commonly used ATIs, and 1 laboratory used Phoenix (BD). Two laboratories with VITEK ATIs were using prior software versions that could not search for specimens by antibiotic MIC. In these cases, laboratory staff assisted with creating customized

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TABLE 2. Proportion of Urine and Normally Sterile Specimens Collected from Atlanta Metropolitan Statistical Area Residents That Were Carbapenem Nonsusceptible in November 2010

Species	Carbapenem nonsusceptible	Total	% carbapenem nonsusceptibility	Eligible laboratories
Accurate resistance: results from laboratories with accurate denominators and the ability to test November 2010 breakpoints				
Enterobacteriaceae	13	1,723	0.75	13
Acinetobacter	10	28	35.71	21
Overall resistance: results from laboratories with accurate denominators but not necessarily the ability to test November 2010 breakpoints				
Enterobacteriaceae	34	3,881	0.88	21
Acinetobacter	10	28	35.71	21

local queries using either the laboratory information system or third-party software.

In November 2010, all of the laboratories tested either imipenem or meropenem, with 13 (52%) of 25 testing both, 11 (44%) of 25 testing only imipenem, and 1 (4%) of 25 testing only meropenem. No laboratory performed doripenem susceptibilities. The lowest MIC of carbapenems tested at some laboratories (8/25 [32%]) was 8 μg/mL, but the majority of laboratories were able to accurately apply the 2010 CLSI carbapenem-susceptibility breakpoints. Of the 22 laboratories responding to a survey of manual testing methods, all tested for ESBL production, and only 8 (36%) routinely used the modified Hodge test as recommended by contemporary CLSI standards.

In August 2011, 23 (92%) of 25 laboratories serving HD3 participated in a follow-up survey. Eight (35%) were not able to test the 2010 CLSI carbapenem-susceptibility breakpoints for Enterobacteriaceae (Table 1). These laboratories were able to ensure complete case identification only for *Acinetobacter* isolates because the lowest carbapenem dilution tested was 8 μg/mL. Thirteen laboratories (57%) were not able to test the lower 2010 CLSI ceftriaxone-susceptibility breakpoint for Enterobacteriaceae, so isolates from these laboratories were required to be nonsusceptible to the other tested cephalosporins (ceftazidime and/or cefotaxime) to be included.

Phase 2: Pilot Surveillance

Twenty-one of the 25 participating laboratories in the MSA provided denominators of all GNBs and identified 3,881 *E. coli* and *K. pneumoniae* isolates and 28 *A. baumannii* isolates. ESBL production was detected in 212 (5.5%) of all *E. coli* and *K. pneumoniae*. Using the overall resistance method, 0.88% of *E. coli* and *K. pneumoniae* but 35.7% of *A. baumannii* were carbapenem nonsusceptible (Table 2). Using the accurate resistance method, the proportion did not change for *A. baumannii* but decreased to 0.75% for *E. coli* and *K. pneumoniae*.

Two laboratories submitted incomplete carbapenem susceptibilities for *A. baumannii* isolates. For these laboratories, ertapenem was used to identify 7 *A. baumannii* as carbapenem nonsusceptible.

Phase 3: Ongoing Surveillance

Twenty-three of the 25 laboratories serving HD3 submitted reports of eligible MuGSI isolates collected from August 1, 2011, to December 31, 2011. The remaining 2 were independent reference laboratories that declined to participate. There were 141 incident MuGSI cases among HD3 residents, with the majority comprising *A. baumannii* ($n = 59$) and *K. pneumoniae* ($n = 57$) and found initially in urine ($n = 118$; Table 3). Four isolates of *K. pneumoniae* and 3 isolates of *A. baumannii* were isolated from both blood and urine on the first day of eligible culture collection.

Of the 136 cases with available medical records, 44 (32.4%) were hospital onset, 84 (61.8%) were healthcare-associated community onset, and 8 (5.9%) were community associated. Of the 136 cases with known outcome at hospital discharge (or 30 days for nonhospitalized patients), 11 (8.1%) died. Cases initially identified in urine only had a mortality of 5.7% ($n = 106$), whereas cases with initial isolation from normally sterile sites had a mortality of 16.7% ($n = 30$). Cases with *A. baumannii* isolates had a mortality of 12.5%, and cases with Enterobacteriaceae had a mortality of 5.0%. Cases hospitalized within 30 days of their incident culture had a mortality of 10.4%, and none of the nonhospitalized patients died.

DISCUSSION

The design and implementation of a novel strategy for active population surveillance of MDR-GNB can be successful and informative. During November 2010, less than 1% of 3,881 Enterobacteriaceae isolated from metropolitan Atlanta residents were carbapenem nonsusceptible, but at least 35.7% of *A. baumannii* were nonsusceptible. Previous studies in North America have found resistance to carbapenems ranging from 6% to 60% among *A. baumannii* isolates and from 6% to 15% among Enterobacteriaceae isolates.[11,12,15,16] The mortality of cases initially identified in urine (6%) may reflect underlying comorbidities and not the direct result of infection, and the issue merits further investigation. Among cases initially recovered from a sterile site, mortality was nearly tripled (17%), but it is still markedly lower than early reports of these organisms.[4,17-20] This may be due to the larger denom-

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TABLE 3. Incident Carbapenem-Nonsusceptible Species Isolated from Georgia Health District 3 Residents between August 1 and December 31, 2011, by Initial Culture Source

Source	*Escherichia coli*	*Enterobacter cloacae*	*Enterobacter aerogenes*	*Klebsiella pneumoniae*	*Klebsiella oxytoca*	Total Enterobacteriaceae	*Acinetobacter baumannii*	Total incident cultures
Urine	13	3	4	53	4	77	41	118
Blood	0	0	0	8	0	8	15	23
Peritoneal fluid	0	1	0	0	0	1	2	3
Pleural fluid	0	0	0	0	0	0	2	2
Joint/synovial fluid	0	0	0	0	0	0	1	1
Deep tissue	0	0	0	0	0	0	1	1
Total cases	13	4	4	57[a]	4	82	59[b]	...

[a] Four *K. pneumoniae* cases were initially identified by isolates from both blood and urine. These cases are counted in both source categories but are counted as only 1 case in the total.

[b] Three *A. baumannii* cases were initially identified by isolates from both blood and urine. These cases are counted in both source categories but are counted as only 1 case in the total.

inator than those of passive reporting systems and underscores the importance of active population-based surveillance.[11,12] There may also be substantial regional variation in the burden of antimicrobial resistance among MDR-GNB. Ongoing surveillance will more clearly define the scope of this problem, evaluate changes in trends, and inform prevention strategies. With increasing public interest in and awareness of the threat of antimicrobial resistance, these pathogens may increasingly become publicly reportable.

Defining and identifying these pathogens remains challenging because there are at least 3 ATIs, each with several permutations in both software version and the panels used across different laboratories that may change over time. There can be wide variation in the definition of carbapenem resistance, including variations in breakpoints (current compared with older CLSI breakpoints and current Food and Drug Administration [FDA] breakpoints and classification of "indeterminate" susceptibility), pathogens (Enterobacteriaceae vs *Acinetobacter* species), mechanisms of resistance (bla_{KPC} genotype compared with resistant phenotype), and antibiotics (number of carbapenems tested and adjudication of discordant results, inclusion versus exclusion of ertapenem). Consistency in definitions is critical to accurate surveillance, since the change in CLSI breakpoints caused reclassification of previously sensitive isolates into the nonsusceptible category and artificially increased observed rates,[21,22] although this may not lead to differences in outcomes.[23] The European Committee for Antimicrobial Susceptibility Testing guidelines released in 2011 decreased the breakpoints for carbapenems, but not to the same extent as the 2010 CLSI interpretive criteria, further complicating international comparisons.[24]

While running the queries was not time or labor intensive, data collection and validation required an ongoing resource investment for the EIP. Monthly reports, periodic surveys, confirmation of residency, and medical chart reviews represent a substantial time commitment. For individual clinical laboratories, resource utilization was minimal, and the queries could also be used to generate actionable clinical reports for infection control, hospital epidemiology, and administration.

This report likely underestimates the burden of MDR-GNB. Many laboratories could not test antibiotic dilutions low enough to detect the 2011 CLSI breakpoints, leading to incomplete case ascertainment—in part because manufacturers are regulated by FDA standards, which are currently discordant with CLSI breakpoints. This should be resolved quickly since it affects not only surveillance but also clinical decision making for individual patients. An artificial incidence increase is expected in the future as ATI manufacturers provide more sensitive and inclusive antibiotic panels, as partly occurred between phases 2 and 3. Additionally, engaging independent reference laboratories was challenging due to privacy concerns, since access to their database could not easily be geographically restricted. The state of Georgia's addition of healthcare-associated infections to the list of notifiable diseases from 2013 resulted in an ongoing dialogue to improve accuracy in capturing cases.

To provide useful feedback to local laboratories and infection preventionists, facility-specific reports including data from the facility's patients and all residents of HD3 have been provided to all participating facilities semiannually since July 2012. The Georgia EIP also assisted microbiologists and infection preventionists by developing and installing electronic alerts for ATI software that notify laboratory staff in real time of a potential isolate, resulting in an increase in the number of isolates submitted to the CDC via the EIP for testing, including polymerase chain reaction for carbapenemases and broth microdilution testing. These results were fed back to individual laboratories and infection preventionists and help to ensure that facilities are invested in ongoing, active surveillance for MuGSI cases and recognize their standing relative to other local institutions.

Directly querying ATIs requires some initial resource investment but subsequently provides a feasible, sustainable, and accurate method of surveillance for MDR-GNB compared with a laboratory information system or passive reporting system. This novel surveillance method may be leveraged to perform longitudinal multisite surveillance with

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different pathogen/antimicrobial combinations to evaluate future changes in breakpoints and for ongoing surveillance.

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Address correspondence to Jesse T. Jacob, MD, Orr Building 1020, 550 Peachtree Street NE, Atlanta, GA 30308 (jtjacob@emory.edu).

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