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MAJOR ARTICLE

Epidemiology of Antimicrobial Resistance Among Blood and Respiratory Specimens in the United States Using Genotypic Analysis From a Cloud-Based Population Surveillance Network

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Background. Antimicrobial resistance (AMR) surveillance is critical in informing strategies for infection control in slowing the spread of resistant organisms and for antimicrobial stewardship in the care of patients. However, significant challenges exist in timely and comprehensive AMR surveillance.

Methods. Using BioFire Pneumonia and Blood Culture 2 Panels data from BioFire Syndromic Trends (Trend), a cloud-based population surveillance network, we described the detection rate of AMR among a US cohort. Data were included from 2019 to 2021 for Gram-positive and -negative organisms and their related AMR genomic-resistant determinants as well as for detections of *Candida auris*. Regional and between panel AMR detection rate differences were compared. In addition, AMR codetections and detection rate per organism were evaluated for Gram-negative organisms.

Results. A total of 26 912 tests were performed, primarily in the Midwest. Overall, AMR detection rate was highest in the South and more common for respiratory specimens than blood. methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* detection rates were 34.9% and 15.9%, respectively, whereas AMR for Gram-negative organisms was lower with 7.0% CTX-M and 2.9% carbapenemases. In addition, 10 *mcr-1* and 4 *C auris* detections were observed. For Gram-negative organisms, *Klebsiella pneumoniae* and *Escherichia coli* were most likely to be detected with an AMR gene, and of Gram-negative organisms, *K pneumoniae* was most often associated with 2 or more AMR genes.

Conclusions. Our study provides important in-depth evaluation of the epidemiology of AMR among respiratory and blood specimens for Gram-positive and -negative organism in the United States. The Trend surveillance network allows for near real-time surveillance of AMR.

Keywords. antimicrobial resistance; healthcare epidemiology; surveillance.

The burden of antimicrobial resistance (AMR) cannot be overstated: 4.95 million people globally are estimated to die annually from AMR-associated complications [1]. This estimate exceeds the mortality from both human immunodeficiency virus and malaria. Moreover, current estimates from the Centers for Disease Control and Prevention (CDC) reflected the annual economic burden in the United States at $4.6 billion every year [2]. To address these issues, among other actions, the CDC has developed a list of drug-resistant organisms to target for detection and tracking in the CDC Threat Report 2019, including but not limited to carbapenem-resistant Enterobacteriaceae (CRE) and extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae [3].

Current tracking of AMR is limited by a variety of challenges: collection resource constraints that can lack real-time actionability, privacy concerns around data operability, and variation in AMR classification approaches [4, 5]. These limitations often translate into challenges for informing local tools (eg, clinical pathways), regional epidemiology, and national public health responses [5–7]. Moreover, although phenotypic AMR (eg, CRE) is often tracked, the genotypic epidemiology of AMR is not well elucidated, particularly for species-specific distributions of resistance and codetections of resistance [7]. bioMérieux has developed BioFire Syndromic Trends (Trend), a cloud-based population surveillance network with near real-time tracking of detections among BioFire Panels

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including those with AMR targets [8]. The Trend may allow for near real-time detection and tracking of AMR at the local, regional, and national level.

The objective of this study was to evaluate the epidemiology of AMR determinants from respiratory and blood specimens, using genotypic analysis of data collected by Trend from the BioFire Pneumonia Panel and the BioFire Blood Culture Identification 2 Panel, respectively, and to demonstrate proof-of-concept of the AMR capabilities of the surveillance network.

METHODS

Patient Consent

The data from Syndromic Trends used in this study are deidentified according to HIPAA (Health Insurance Portability and Accountability Act of 1996) standards. In addition, BioFire enters into a Data Use Agreement with each institution to protect against reidentification of any individual and to control the use of the data. Therefore, patient consent was neither required nor applicable due to the nature of this study.

Syndromic Trends

Data were acquired using BioFire Syndromic Trends, which deidentifies, combines, and exports BioFire panel run results from FilmArray instruments to a cloud-based database for near real-time surveillance [8]. These data are automatically aggregated into a cloud server for institutions who opt-in to contribute and allows for facility-level (eg, Supplementary Figure 1) and regional Web-view dashboards of detections to contributing users. The Trend only contains panel-run data, and no patient specific data are obtained.

BioFire Panel Data

All data was collected using the BioFire Pneumonia (PN Panel) and Blood Culture (BCID2 Panel) Panels. Both panels utilize multiplex polymerase chain reaction. Among bacteria with AMR targets, the PN Panel detects 10 typical bacteria (*Acinetobacter calcoaceticus-baumannii* complex, *Enterobacter cloacae* complex, *Escherichia coli*, *Klebsiella aerogenes*, *Klebsiella oxytoca*, *Klebsiella pneumoniae* group, *Proteus* spp, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Staphylococcus aureus*) with 7 corresponding antimicrobial resistance genes (*mecA/C* and MREJ, $bla_{\text{CTX-M}}$, bla_{KPC}, bla_{VIM}, $bla_{\text{OXA-48-like}}$, bla_{IMP}, bla_{NDM}). The BCID2 Panel detects 15 bacterial targets (*A calcoaceticus-baumannii* complex, *E cloacae*, *Enterococcus faecalis*, *Enterococcus faecium, Enterobacterales*, *E coli*, *K aerogenes*, *K oxytoca*, *K pneumoniae* group, *Proteus* spp, *P aeruginosa*, *Salmonella* spp, *S marcescens*, *S aureus*, *Staphylococcus epidermidis*) that can be associated with 10 corresponding antimicrobial resistance genes (*mecA/C* and MREJ, *vanA/B*, $bla_{\text{CTX-M}}$, bla_{KPC}, bla_{VIM}, $bla_{\text{OXA-48-like}}$, bla_{IMP}, bla_{NDM}, *mcr-1*). Information about the detection of specific AMR gene type targets (eg, CTX-M-15) may be found in the products' "Instructions for Use" documents [9, 10]. We also included *Candida auris* organism detections in our reporting given it is often multidrug resistant to the 3 classes of antifungals used for treatment and thus on the CDC Threat Report 2019 as 1 of 5 "Urgent Threats" [3]. Note that the BCID2 Panel does not test for presence of antifungal gene targets in *C auris*, but resistance is present in almost all isolates, and multidrug resistance is present in approximately 50% of isolates [11]. The PN Panel can be used with bronchoalveolar lavage-like samples or sputum-like samples, including endotracheal aspirates, whereas the BCID2 Panel is indicated for use among positive blood cultures [9, 10].

Analysis

Comparisons were made between AMR resistance gene detection rates and pathogen detections. Further analysis into subregions were performed to determine whether more localized differences existed. The Trend data for BioFire PN Panel and BCID2 Panel were collected from the date of panel initiation into the database until present (February 2019 through October 2021 and July 2020 through October 2021, respectively). The Trend data contributors are instructed to select and test specimens in accordance with the intended use of the panels [9, 10]. National calculations included aggregated data from all data-contributing US institutions. Subregion analyses were performed using the Midwest, the South, and the West census regions, which all contained 3 or more data-contributing institutions during the study period.

AMR Genes

In both PN and BCID2 Panels, AMR gene detections are only reported if a pathogen that can carry the gene is also detected. Supplementary Tables 1 and 2 describe the pathogens associated with each AMR gene. The AMR gene detection rate was defined as the percentage of detections in which an AMR gene was detected over the number of tests in which any pathogen that could be associated with the gene was detected. Overall and panel-specific regional detection rate values were calculated for each of the AMR genes as well as for the carbapenemase genes as a group. A χ^2 test was used to compare regional detection rates and also between-panel AMR gene detection rates for targets common between the 2 panels. For CTX-M and the grouped carbapenemase genes, which both are associated with numerous pathogens, the proportion of associated pathogen detections with the AMR gene was also investigated to determine which pathogen contributed most to AMR gene detection rates. Finally, to investigate which bacterial pathogens were involved in multi-AMR gene detections, the proportion of pathogen detections associated with zero, 1, and 2 or

more AMR genes was determined. All descriptive and statistical analyses were done using Python 3.8.

RESULTS

From 2019 through 2021, 26 912 tests were performed and collected by Trend (Supplementary Table 3), the majority occurring in the Midwest and with BCID2. National AMR gene detection rates are shown in Table 1. In the United States, the *mecA/C* and MREJ detection combination used to identify methicillin-resistant *S aureus* (MRSA) was the most common AMR gene with an average detection rate of 34.9%. The average *vanA/B* detection rate was 15.9%, followed by CTX-M (7.0%) and carbapenemases (2.9%). The gene *mcr-1* was detected 10 times over the course of the study investigation, 6 detections occurring from 3 sites in the Midwest and the remainder in the West and Northeast. Similarly, emerging pathogen *C auris* was detected 4 times (of 16 119 BCID2 Panel tests).

Regional AMR gene detection rate values for CTX-M, carbapenemases, MRSA, and vancomycin-resistant *Enterococcus* (VRE) are shown in Figure 1. For all AMR gene groups investigated, the highest detection rate was present in the South. Furthermore, although CTX-M detection rate was not significantly different between panel types in any region, carbapenemase detection rate was higher in pneumonia tests (national average: 5.7%) than in bloodstream infection (BSI) tests (national average: 1.7%), particularly in the Midwest (Supplementary Table 4). The MRSA detection rate differed between panel types in the West and the South but not in the Midwest.

Table 1. National AMR Gene Detection Rates

AMR Gene	Pneumonia Panel	BCID2 Panel	Combined
CTX-M	159/2279 (7.0%)	286/4163 (6.9%)	445/6392 (7.0%)
IMP	9/2279 (0.4%)	7/4163 (0.2%)	16/6392 (0.3%)
KPC	45/2279 (2.0%)	18/4163 (0.4%)	63/6392 (1.0%)
NDM	8/2279 (0.4%)	10/4163 (0.2%)	18/6392 (0.3%)
VIM	17/2279 (0.7%)	17/4163 (0.4%)	34/6392 (0.5%)
OXA-48-like	7/1503 (0.5%)	8/3519 (0.2%)	15/5022 (0.3%)
mcr-1	N/A	10/3243 (0.3%)	10/3243 (0.3%)
mecA/C and MREJ	619/1753 (35.3%)	715/2069 (34.6%)	1334/3822 (34.9%)
vanA/B	N/A	111/696 (15.9%)	111/696 (15.9%)
mecA/C	N/A	2276/3380 (67.3%)	2276/3380 (67.3%)

Abbreviations: AMR, antimicrobial resistance; IMP, imipenemase; KPC, *K pneumoniae* carbapenemase; N/A, not applicable; NDM, New Delhi metallo-beta-lactamase; VIM, Verona integron-encoded metallo-β-lactamase.

NOTE. For BCID2, *mecA/C* is restricted to coagulase-negative *Staphylococcus* spp, whereas the combination of *mecA/C* and MREJ is restricted to for *Staphylococcus aureus*.

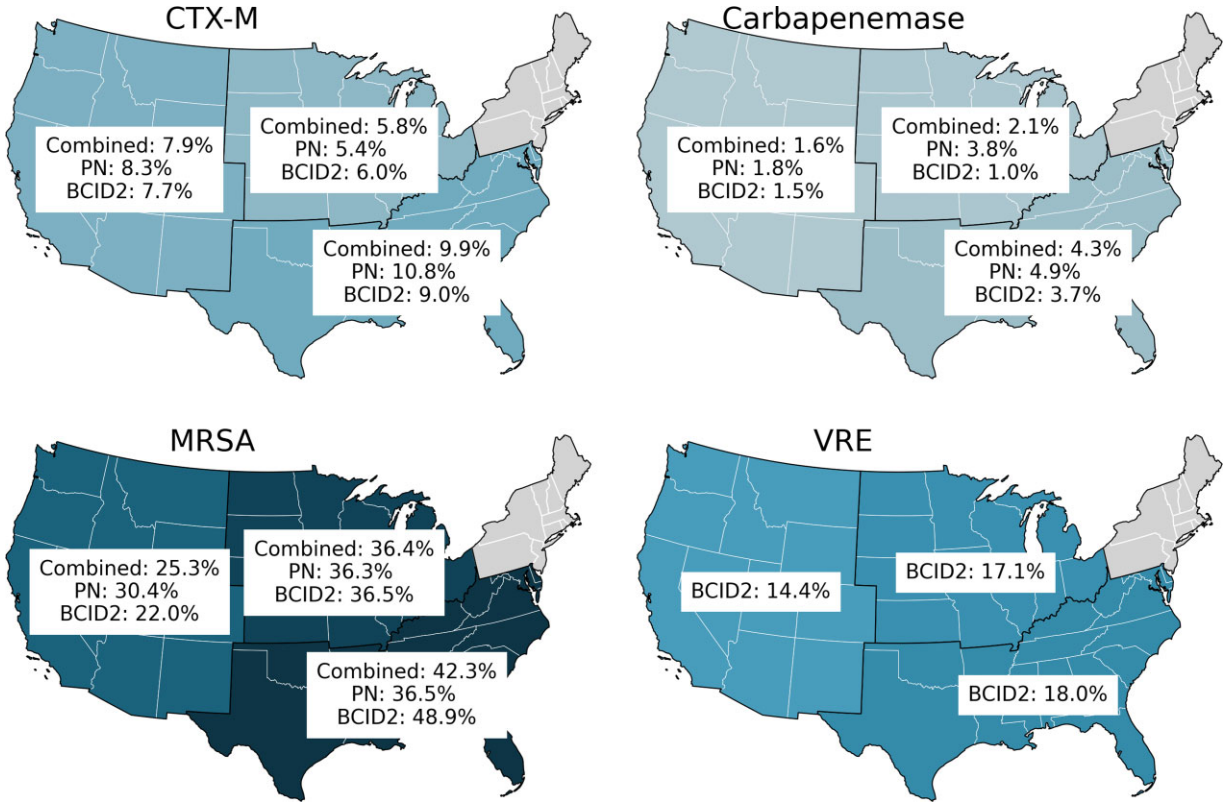

Figure 1. Detection rates of genotypic antimicrobial resistance detections per region overall and stratified by syndromic testing type. MRSA, methicillin-resistant *Staphylococcus aureus*; PN, BioFire Pneumonia; VRE, vancomycin-resistant *Enterococcus*.

The Gram-negative bacterial species most associated with CTX-M and carbapenemases were also investigated as percent detections per region (Figure 2, Supplementary Tables 5 and 6). *Escherichia coli* and *K pneumoniae* were among the most detected bacteria with CTX-M in all regions for both panels. *Pseudomonas aeruginosa* and *A calcoaceticus-baumanniii* complex had the third most common detections for CTX-M with the PN Panel and BCID2 Panel, respectively. Finally, *K pneumoniae* was the most detected of the carbapenemase organisms, followed by *E coli*.

Most Gram-negative bacteria were not associated with multiple AMR gene detections (Figure 3). For both pneumonia and BSI patients, *K pneumoniae* and *E coli* were most likely to be detected with an AMR gene, whereas *K pneumoniae* was also the pathogen most likely to be detected with 2 or more AMR genes. CTX-M was predominantly negatively correlated to carbapenemase gene codetections across organisms as were carbapenemase codetections (Supplementary Figure 2). However, there was a high positive correlation with the codetection of *K pneumoniae* carbapenemase (KPC) and OXA-48-like carbapenemase genes among *E coli*. It is notable that among the *mcr-1* detections, 4 CTX-M and 3 NDM codetections occurred.

DISCUSSION

The CDC Threat Report 2019 Urgent and Serious Threats include, but are not limited to CRE, ESBL-producing Enterobacteriaceae, MRSA, VRE, and *C auris* [3]. We report on the epidemiology of these in the United States, notably observing a detection rate of 7.0% CTX-M and 2.9% carbapenemases (bla_{KPC}, bla_{VIM}, $bla_{OXA\text{-}48\text{-}like}$, bla_{IMP}, bla_{NDM}) among

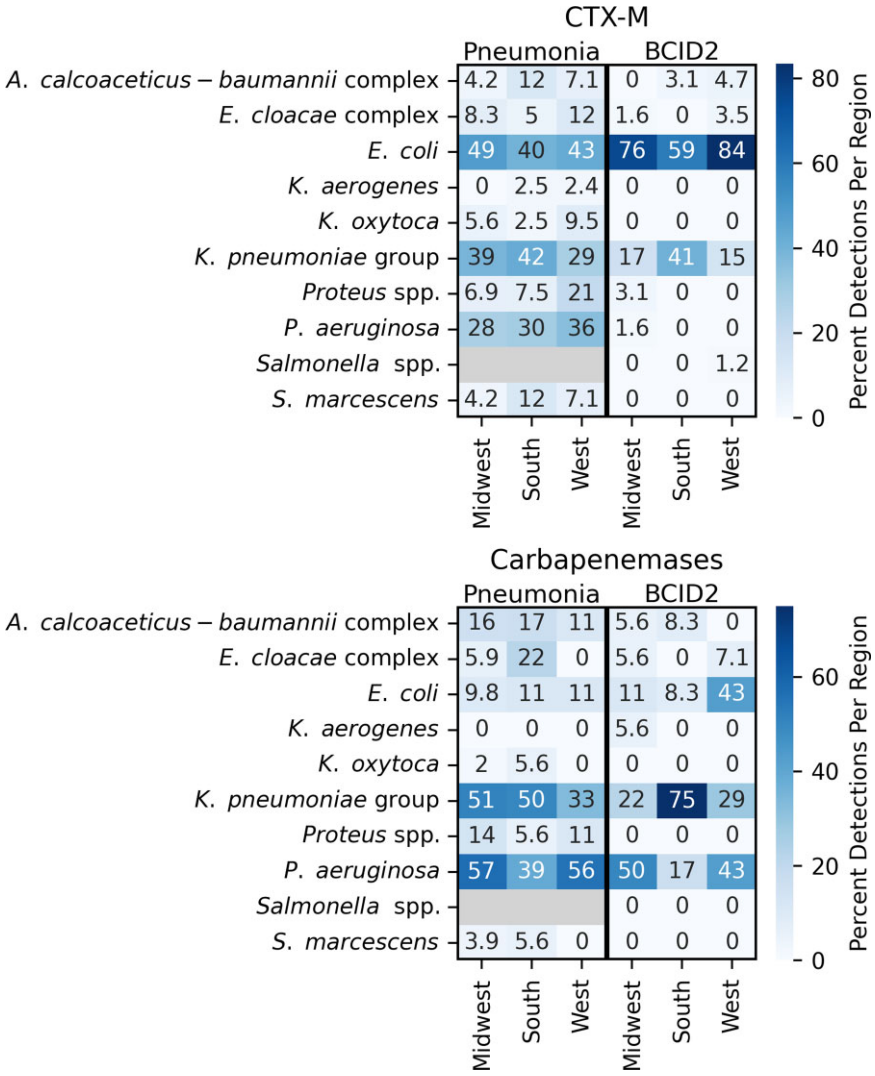

Figure 2. Most detected Gram-negative bacterial species among CTX-M and carbapenemase-related antimicrobial resistance gene positive testing. Gray coloring indicates that tests were not given to detect the pathogen. Columns may sum to greater than 100 due to the possibility of codetected pathogens.

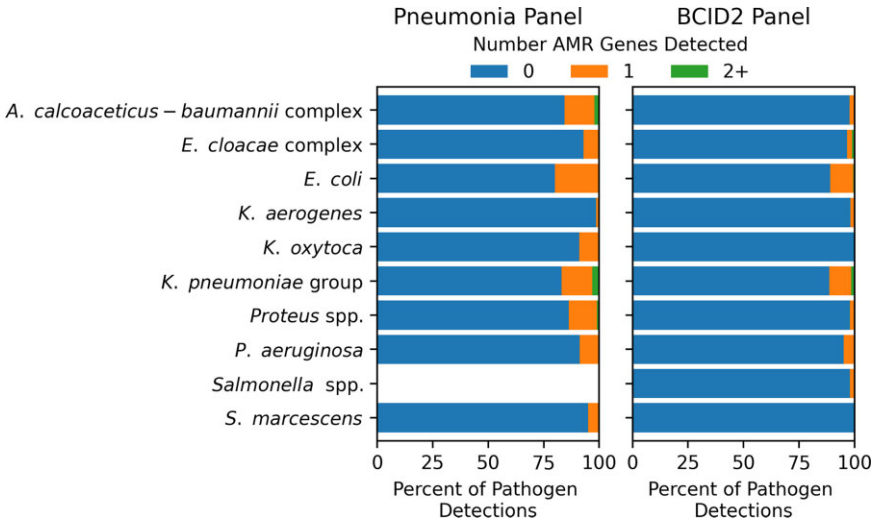

Figure 3. National proportion of bacterial detections broken down by number of antimicrobial resistance (AMR) gene detections. Empty bars indicate no detections.

Gram-negative organisms. Near real-time characterization of these resistance types is important for local guideline development and outbreak detection, regional benchmarking, and informing national public health initiatives. In addition, this study reflects the potential AMR capabilities of the genotypic surveillance network, which has important implications because proof-of-principle studies on molecular AMR surveillance has been identified as a priority by the World Health Organization's Global Antimicrobial Resistance Surveillance System (GLASS) program [12].

Nationally, we found AMR-resistant determinants that were overall nearly comparable proportions to US phenotypic resistance reported elsewhere [13–16]. Specifically, for blood and respiratory isolates, our data were consistent with national phenotypic data in reflecting higher proportions of resistance among respiratory specimens than blood cultures [14]. Moreover, our AMR-resistant determinants were very similar to other national explorations of Gram-negative genotypic resistance for $bla_{\text{CTX-M}}$ and carbapenemase genes among blood culture isolates, although ours reflected a more robust sample of testing compared with previous work [7]. Specifically, the previous reporting on carbapenemase genes among 4209 Gram-negative BSIs indicated 2% detection rate whereas we found 3.1% among our data, both reporting bla_{KPC} as the most common carbapenemase gene. Uniquely among our data, we reported 10 *mcr-1* detections, a plasmid-mediated gene resulting in colistin resistance, and 4 *C auris* detections, both groups reflecting important emerging resistance concerns [17, 18].

Among individual species, we found *K pneumonia* and *E coli* had the highest $bla_{\text{CTX-M}}$ detections with both respiratory and blood culture isolates, which is similar to a recent study evaluating the genomic-resistant determinants among blood culture isolates [7]. Similarly, we observed these species as predominant for carbapenemase gene detections. *Klebsiella pneumonia* was also noted to have predominance in carbapenemase gene detections in the aforementioned recent study, although conversely in that study, *A calcoaceticus-baumannii* complex carbapenemase detections were more common than those for *E coli.* More importantly, we observed 3 codetections of *mcr-1 and* bla_{NDM} in Enterobacteriaceae, a combination that is nearly pandrug resistant and an emerging concern [19]. These observations reinforce the need of near real-time surveillance to inform infection control practices to mitigate further spread of such isolates and resistance.

These data and the AMR surveillance system functionality have important implications on regional- and institutional-level actions. Knowledge of circulating carbapenemase family types can primarily support local hospital formulary decisions, clinical pathway development, and individual patient treatment decisions [20]. For example, meropenem-vaborbactam is active against class A carbapenemases, such as KPC, while not being active against class B metallo-β-lactamases. Moreover, for Gram-negative infections, genotypic information may be useful in supplementing phenotypic data [21, 22]. Regional AMR data may allow for individual hospitals to evaluate their detection rate of AMR against the region, identifying potential opportunities for antimicrobial stewardship and infection control initiatives [23]. Finally, in smaller hospitals with lower isolate frequencies, regional-level data may allow clinically relevant information for decision making such as formulary decisions and clinical pathway development [24].

The potential capabilities of the Syndromic Trends surveillance network have been previously described elsewhere using BioFire Respiratory Panel testing data [8]. The Trend database allows for surveillance ability of syndromic testing within

"big data" capacity, which includes volume, speed of acquisition, diversity of information, and utility of data [25]. The existence of Trend and the proof-of-principle reflected in this report should facilitate other IVD manufacturers to develop similar AMR surveillance solutions with improved acceptance by their customers, thus facilitating improved international AMR surveillance. Moreover, specific exemptions (eg, follow-up studies on reportable infectious diseases) exist under HIPAA for public health agencies, such as local or state health departments and the CDC. Therefore, surveillance systems, such as Trend, have the potential to allow the facilitation of identification, acquisition, and testing of residual samples from potential outbreaks.

There are several limitations of the current study. There was no clinical adjudication of isolates. Still these isolates reflect an epidemiologic burden of resistance, which may be a transmittable source of infection [13]. In addition, the data may not be representative based on sampling variations driven by clinician determinations for testing (ie, blood culture ordering) or on local diagnostic use policy (ie, BioFire PN Panel). However, most facilities in the United States universally run rapid diagnostics, where present, for all positive blood cultures; therefore, these results are likely representative in this population, although there may be differences in availability or distribution of testing between settings (eg, rural vs urban centers) [4]. Moreover, it is worth noting these potential biases in local testing use variation with the evaluation of the data is an issue of any AMR study where not prospectively and systematically cultured via protocol. Likewise, we are unable to differentiate community-onset versus healthcare-associated infections that can have variation in burden of AMR [13]. Furthermore, based on current data privacy agreements and related data deidentification procedures, we are unable to identify specific hospital types or patient populations. Akin to other epidemiological literature, the Trend data likely reflect unique collected cultures, not unique patients [16, 26]. However, there is a particularly low probability of duplicates among Gram-negative BSI testing because prolonged bacteremia with Gram-negative BSIs is uncommon [7, 27, 28]. In contrast, for respiratory cases and testing repeats may occur as for example chronic lung disease patients on ventilation may have multiple respiratory cultures over time. The potential impact of these types or similar respiratory cases on the current data is unclear given the increasing awareness of diagnostic stewardship and policies limiting repeat testing on newer diagnostic technologies [29]. Our results do not reflect the phenotypic burden of AMR given that the testing evaluates the most common mechanisms of resistance, and, thus, our detection rate estimates are likely an underestimation of prevalence. In contrast, phenotypic evaluations of AMR burden are not without limitations. There is a lack of standardization with antibiotic susceptibility testing method surveillance, which also change over time due to adjustment in breakpoint standards, and often, facilities with lower breakpoints generally report higher rates of resistance [26, 30, 31]. Low frequency AMR detections reported herein should be interpreted with caution due to the potential of false positives that may occur with testing. Finally, there is a potential for biased estimates from Trend data, which have not been externally validated for the included panel data. However, the functionality of this network in supporting AMR monitoring is corroborated by previous studies of Trend data reflecting the utility in evaluating the epidemiology of foodborne illnesses when correlated to the CDC's FoodNet surveillance system, correlated to the CDC's FluView, in determining social distancing impact on nonsevere acute respiratory syndrome coronavirus 2 viruses, and validated against historical and in predicting Enterovirus D68 (EV-D68) outbreaks [8, 32–34]. Despite the reviewed limitations, we consider Trend data to yield important insights into the epidemiology of AMR resistance determinants that may assist in future clinical, operational, and public health research pursuits.

CONCLUSIONS

This study provided an in-depth understanding of the epidemiology of common AMR determinants from blood and respiratory specimens for Gram-positive and -negative organisms in the United States. Among AMR surveillance, CDC Urgent Threat organism *C auris* was low nationally whereas carbapenemase Enterobacteriaceae were more common, particularly in the South region. The Syndromic Trends surveillance network data on AMR has important implications on national public health initiatives as well as informing antimicrobial stewardship and infection control actions through regional- and institutional-level reporting.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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