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BRIEF REPORT

A Multicenter Evaluation of the US Prevalence and Regional Variation in Macrolide-Resistant *S. pneumoniae* in Ambulatory and Hospitalized Adult Patients in the United States

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Macrolide resistance was found in 39.5% of 3626 nonduplicate *Streptococcus pneumoniae* isolates from adult ambulatory and inpatient settings at 329 US hospitals (2018–2019). Macrolide resistance was significantly higher for respiratory vs blood isolates and ambulatory vs inpatient settings. Despite geographic variation, *S. pneumoniae* macrolide resistance was >25% in most regions.

Keywords. antibiotic resistance; community-acquired pneumonia; epidemiology; macrolides; *Streptococcus pneumoniae*.

Streptococcus pneumoniae remains a highly virulent pathogen [1, 2] despite reductions in invasive pneumococcal disease following the widespread implementation of pneumococcal conjugate vaccination [3, 4]. *S. pneumoniae* is the most common bacterial etiology for community-acquired pneumonia (CAP) [5, 6], a disease that results in over 1 million emergency department visits [7] and an estimated 700 000 to 1.5 million hospitalizations annually in the United States [8, 9]. The mortality rate for patients hospitalized with CAP is ~10% [10]; although the number of deaths has decreased with the advent of pneumococcal vaccination, the mortality rate has not [3]. Resistance to commonly used antibiotics has complicated the management of pneumococcal infections [11].

Because of the significant health care burden associated with *S. pneumoniae*, the US Centers for Disease Control and Prevention (CDC) designated drug-resistant *S. pneumoniae* a serious threat [12]. Macrolides have long been an important component of empiric CAP therapy, but increasing resistance has diminished effectiveness and prompted a change in American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines for CAP treatment. Although macrolide monotherapy is still considered an option for initial treatment of outpatients with suspected CAP and no comorbid conditions, the ATS/IDSA 2019 update specifies that this therapy should only be used if local pneumococcal resistance is <25% [11].

In 2018, the CDC Active Bacterial Core Surveillance (ABCs) reported a nationwide *S. pneumoniae* macrolide nonsusceptibility rate of 28.8% [13] based on isolates cultured from normally sterile sites, primarily blood. The ABCs' surveillance area includes 10 states; for some states, only a specific metropolitan region is included. Data from other surveillance programs may provide additional insights into nationwide resistance and resistance in *S. pneumoniae* isolated from respiratory cultures to complement the CDC findings.

We used microbiological laboratory data from a large US hospital database to determine the prevalence of macrolide-resistant *S. pneumoniae* isolated from blood or respiratory cultures in hospitalized and ambulatory patients throughout the United States.

METHODS

Study Design

This retrospective cohort study was based on de-identified microbiological results from adult patients with a positive *S. pneumoniae* blood or respiratory culture evaluated between October 2018 and September 2019 at 329 US facilities in the BD Insights Research Database (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) [14–16], which provides diverse geographic and demographic representation across the United States. Evaluations of geographic distribution were based on US Census geographic regions and zip code tabulation areas. The primary objective was to determine the proportion of *S. pneumoniae* isolates resistant to macrolides in blood and respiratory cultures.

The study data set was approved as a limited, de-identified data set for retrospective analysis and was exempted from patient consent by the New England Institutional Review Board (Wellesley, MA, USA).

Microbiology and Susceptibility Testing

Nonduplicate *S. pneumoniae* isolates, defined as the first isolate of a species from the same source per 30-day period, were obtained from blood or respiratory cultures. Isolates from each source were considered separately, and isolates from the same source within 30 days were included if they differed by >1 susceptibility result. Antimicrobial susceptibility test (AST) data were obtained from *S. pneumoniae*–positive cultures.

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Assessment of macrolide resistance was based on facility reports using commercial panels and local laboratory breakpoints. Resistance to any member of the class (azithromycin, clarithromycin, or erythromycin) was considered macrolide resistance.

Statistical Analysis

The data were analyzed descriptively. Macrolide resistance rates were compared by use of the chi-square test, with *P* values <.05 indicating statistical significance. All analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Nationwide *S. pneumoniae* Macrolide Resistance

Our primary analyses included 3626 *S. pneumoniae* isolates with AST results from blood (n = 1591; 43.9%) or respiratory (n = 2035; 56.1%) cultures collected from 329 US inpatient or ambulatory care facilities. The overall rate of macrolide resistance in *S. pneumoniae* isolates was 39.5% (Table 1). The resistance rate in respiratory isolates (47.3%) was significantly higher than the rate in blood isolates (29.6%; $P < .0001$). Isolates obtained from ambulatory settings had a significantly higher rate of macrolide resistance compared with isolates from inpatients (45.3% vs 37.8%; $P < .001$).

Geographic Differences in *S. pneumoniae* Macrolide Resistance

Statistically significant differences ($P < .0001$) were observed in macrolide resistance in different US Census regions (Table 1). The overall highest rate was observed in the West North Central region (54.2%), which also had the highest resistance rate in blood isolates (52.1%), followed by South Atlantic (48.0% overall), which had the highest resistance rate in respiratory isolates (60.8%). Regions with overall *S. pneumoniae* macrolide resistance rates <25% were Mountain (13.9%), New England (18.2%), and Pacific (18.3%). Even in these regions, however, the rates of macrolide resistance in respiratory isolates were ≥25% (33.3%, 25.0%, and 25.3%, respectively).

Analysis of geographic distribution by zip codes (Figure 1) identified subregional and within-state differences. For instance, California showed higher macrolide resistance in the southern part of the state, and Pennsylvania showed higher resistance rates in the western part of the state.

DISCUSSION

Our analyses of 3626 *S. pneumoniae* blood and respiratory isolates from US facilities reveal a high burden of macrolide resistance. Overall, 39% of *S. pneumoniae* isolates were resistant to macrolides; this rate increased to 47% for respiratory isolates. The rate of macrolide resistance was higher in ambulatory patients than in admitted patients, suggesting that outpatient macrolide resistance is common. Although geographic differences were observed, most regions had *S. pneumoniae* macrolide resistance rates that exceeded the 25% threshold for use of macrolide monotherapy as recommended by ATS/IDSA guidelines for outpatients with suspected CAP, and all regions had >25% macrolide resistance in *S. pneumoniae* respiratory isolates.

The overall *S. pneumoniae* macrolide resistance rates in our study are in line with rates from large-scale US or North American studies from previous years, including a 48.4% azithromycin resistance rate in 2014 [17], a 43.8% azithromycin nonsusceptibility rate in 2015–2016 [18], and a 46.6% erythromycin nonsusceptibility rate in 2016 [19]. The rate of resistance in blood isolates (29.6%) is similar to the 2018 rate reported by the CDC ABC surveillance system for isolates from sterile sites (28.8%). These data on the high rates of macrolide resistance may explain recent findings of high failure rates (21%)

Table 1. *S. pneumoniae* Macrolide Resistance Rates by Setting and US Census Region

		% Resistant (No. Tested)		
Setting or Region	No. of Facilities	Blood Isolates	Respiratory Isolates	All Isolates
Total	329[a]	29.6 (1591)	47.3 (2035)	39.5 (3626)
Inpatient	313	28.2 (1211)	45.2 (1587)	37.8 (2798)
Ambulatory	231	33.9 (380)	54.9 (448)	45.3 (828)
Census region (states)				
West North Central (IA, KS, MN, MO, ND, NE, SD)	12	52.1 (48)	55.0 (131)	54.2 (179)
South Atlantic (DE, DC, FL, GA, MD, NC, SC, VA, WV)	40	30.3 (145)	60.8 (199)	48.0 (344)
East South Central (AL, KY, MS, TN)	49	38.0 (229)	55.6 (252)	47.2 (481)
West South Central: (AR, LA, OK, TX)	71	35.6 (455)	48.5 (643)	43.2 (1098)
East North Central: (IL, IN, MI, OH, WI)	56	29.0 (217)	49.7 (320)	41.3 (537)
Middle Atlantic (NJ, NY, PA)	50	28.3 (191)	39.8 (236)	34.7 (427)
Pacific (AK, CA, OR, WA)	36	13.2 (257)	25.3 (190)	18.3 (447)
New England (CT, MA, ME, NH, RI, VT)	5	4.0 (25)	25.0 (52)	18.2 (77)
Mountain (AZ, CO, ID, MT, NM, NV, UT, WY)	10	4.2 (24)	33.3 (12)	13.9 (36)

[a]Facilities could provide both inpatient and ambulatory services.

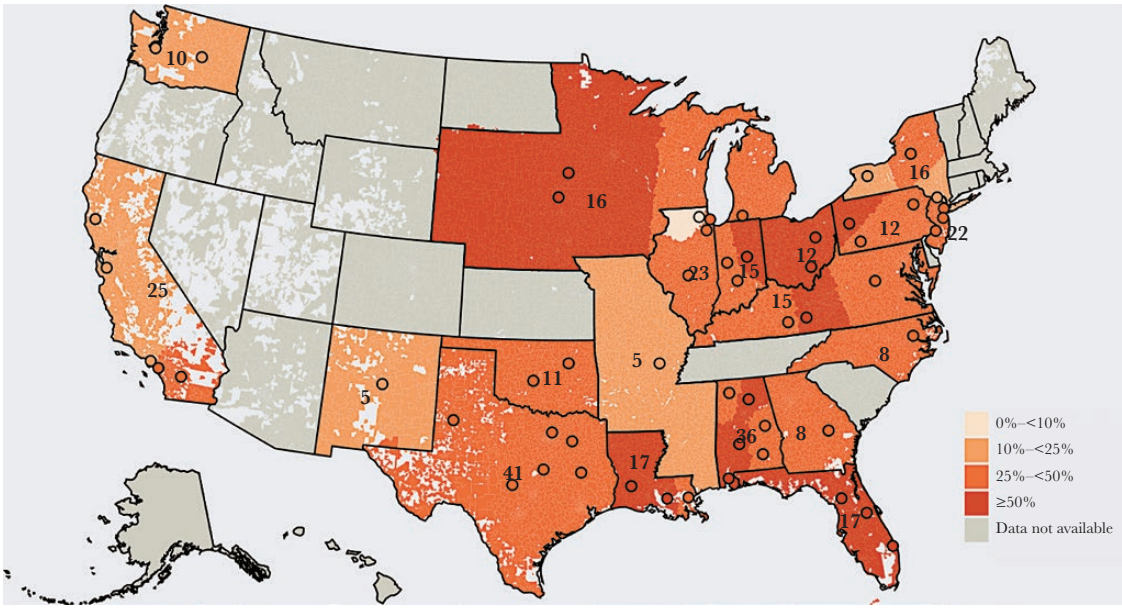

Figure 1. Geographic distribution of *S. pneumoniae* macrolide resistance rates by zip code. The data represent 3464 isolates collected from 314 facilities between October 2018 and September 2019.[a] Shaded circles show the geographic centroid for each geographic cluster, and numbers indicate the total number of included hospitals at the state level. [a]Facilities with <5 isolates were not included, which resulted in slight differences between the numbers shown here and in Table 1. Data were aggregated into geographic clusters of ≥5 hospitals from ≥2 integrated delivery networks; the geographic centroid for each cluster is represented by a shaded circle. Zip code tabulation areas were attributed a rate based on that area's proximity to the nearest cluster's geographic centroid. Within each state, the number of hospitals in each cluster is distributed equally, and the total number of hospitals at the state level is labeled on the map. Data for contiguous states each containing <5 hospitals were aggregated (IA, NE, SD, MN, WI, MI; KY, WV, MD, DC, VA; MS, AR, MO).

with macrolide monotherapy in outpatient CAP, resulting in increased mortality and health care costs [20].

Higher antimicrobial resistance rates in respiratory compared with blood cultures have been observed in previous studies of CAP, including studies focused solely on *S. pneumoniae* in CAP [21, 22] and a study of patients with pneumonia or other causes of respiratory failure associated with any bacterial pathogen [23]. These studies observed higher resistance rates for a broad range of CAP therapies in respiratory vs blood isolates [22, 23] as well as for nonpneumococcal pathogens, such as methicillin-resistant *Staphylococcus aureus* and gram-negative bacteria [23]. A recent study by Haessler et al. noted that patients with pneumonia/respiratory failure and positive respiratory cultures had different baseline characteristics from those with positive blood cultures, suggesting that resistance in isolates from different cultures sites is associated with distinct multifactorial risk factors or patient phenotypes [23]. We agree with these authors that the source of the isolate should be included in future prediction models of antibiotic resistance. In addition, in contrast to respiratory isolates, which are primarily identified in patients with CAP, blood culture isolation of pneumococcus can involve CAP, meningitis, or contiguous infections from patients with higher-risk comorbidities such as asplenia, HIV infection, or other immunocompromised states [24, 25]. These clinical situations would ideally also be delineated in future analyses to further assess risk factors for pneumococcal bacteremia, but were beyond the scope of the current study.

Our data support the need for ongoing surveillance of CAP epidemiology and resistance profiles. These efforts are particularly important given changes in azithromycin prescriptions during the coronavirus disease 2019 pandemic [26]. Current ATS/IDSA recommendations reserve urine antigen tests and blood/sputum cultures for patients with severe disease and those with empiric treatment or a history of methicillin-resistant *Staphylococcus aureus* (MRSA) or *P. aeruginosa* [11]. While the need for resource optimization is well taken, the prospect of reserving culture and urine antigen tests for patients with severe disease may hamper surveillance efforts and limit information on epidemiologic resistance patterns in patients with less severe disease, potentially impacting appropriate therapy. The risk of losing valuable culture data is further compounded by the increasing use of urine antigen testing. Without adequate AST data, future CAP guidelines may fall behind clinical needs and current resistance profiles, as seen with the advent of molecular diagnostics for gonorrhea, chlamydia, and *Mycoplasma genitalium* in sexually transmitted disease guidelines [27, 28]. We propose a balance of antimicrobial susceptibility results coupled with more convenient molecular diagnostics to optimize the guidance of appropriate empiric therapy, much like the Gonococcal Isolate Surveillance System enacted by the CDC for similar reasons [29].

In addition to macrolide monotherapy, other recommended empiric treatments for outpatients with suspected CAP include amoxicillin or doxycycline for patients with no comorbidities or risk factors for MRSA or *Pseudomonas aeruginosa*, and broader spectrum regimens (a respiratory fluoroquinolone or combination therapy with a beta-lactam plus macrolide or doxycycline) for patients with comorbidities or MRSA/*P. aeruginosa* risk factors [11]. Increasing resistance in nonvaccine pneumococcal serotypes [30–32] and potential adverse effects associated with fluoroquinolones, particularly in elderly patients [33], may limit the use of these therapies. New antibiotics for CAP may provide options for enhanced empiric therapy with reduced resistance [34]. In addition, antimicrobial stewardship programs in the outpatient setting have recently been supported by The Joint Commission [35] and may provide an infrastructure to counteract unnecessary macrolide use, which may help curtail macrolide resistance over time [36].

The limitations of our study include underrepresentation of certain geographic regions. The results represent culture-positive isolates and not confirmed invasive infections. Macrolide resistance was based on local microbiology practices at each facility and not standardized across facilities. Selection bias due to a higher likelihood of performing cultures in more severely ill patients is a potential issue for all microbiologic surveillance studies and may have increased estimates of resistance.

Our findings document the high rates of macrolide-resistant *S. pneumoniae* throughout the United States and suggest that, in most parts of the country, clinicians should consider alternatives to macrolide monotherapy as empiric therapy for suspected CAP. Ongoing surveillance efforts are required to track trends in resistance.

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Potential conflicts of interest. V.G. and K.C.Y. are employees of Becton, Dickinson & Company, which was contracted by Nabriva Therapeutics to conduct the study, and own stock in Becton, Dickinson & Company. J.S. and S.P.G. are employees of Nabriva and hold stock in Nabriva Therapeutics.

Patient consent. This study does not include factors necessitating patient consent. The study data set was approved as a limited, de-identified data set for retrospective analysis and was exempted from patient consent by the New England Institutional Review Board (Wellesley, MA, USA).

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