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The Path of More Resistance: a Comparison of National Healthcare Safety Network and Clinical Laboratory Standards Institute Criteria in Developing Cumulative Antimicrobial Susceptibility Test Reports and Institutional Antibiograms

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ABSTRACT In the absence of antimicrobial susceptibility data, the institutional antibiogram is a valuable tool to guide clinicians in the empirical treatment of infections. However, there is a misunderstanding about how best to prepare cumulative antimicrobial susceptibility testing reports (CASTRs) to guide empirical therapy (e.g., routine antibiogram) versus monitoring antimicrobial resistance, with the former following guidance from the Clinical and Laboratory Standards Institute (CLSI) and the latter from the Centers for Disease Control and Prevention's National Healthcare Safety Network (NHSN). These criteria vary markedly in their exclusion or inclusion of isolates cultured repeatedly from the same patient. We compared rates of nonsusceptibility (NS) using annual data from a large teaching health care system subset to isolates eligible by either NHSN criteria or CLSI criteria. For a panel of the three most prevalent Gram-negative pathogens in combination with clinically relevant antimicrobial agents (or priority pathogen-agent combinations [PPACs]), we found that the inclusion of duplicate isolates by NHSN criteria yielded higher NS rates than when CLSI criteria (for which duplicate isolates are not included) were applied. Patients with duplicate isolates may not be representative of antimicrobial resistance within a population. For this reason, users of CASTR data should carefully consider that the criteria used to generate these reports can impact resulting NS rates and, therefore, maintain the distinction between CASTRs created for different purposes.

KEYWORDS antibiogram, resistance, empiric, isolates, cumulative antimicrobial susceptibility test report, *Escherichia coli*, *Klebsiella*, *Pseudomonas aeruginosa*, antibiogram, antibiotic resistance, Clinical and Laboratory Standards Institute, inpatient, National Healthcare Safety Network, outpatient, stewardship

Clinicians frequently rely on institutional antimicrobial susceptibility reports, or "antibiograms"—a type of cumulative antimicrobial susceptibility test report (CASTR)—to initiate empirical treatment for their patients. One challenge with antibiogram preparation is the handling of duplicate isolates, or isolates of the same microbial species (with the same or different antimicrobial susceptibility profiles), cultured from different specimens (of the same or different type and source) collected from the same patient over an analysis period (1). While the effect of these duplicate isolates could

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skew antibiogram data toward either higher susceptibility or higher resistance (2), several groups have reported that duplicate isolates are more likely to be resistant than the initial isolate from a patient (2, 3) and that inclusion of duplicate isolates decreases susceptibility rates (4–12).

Several options to handle duplicate isolate data have been suggested. One approach is to generate antibiograms using the susceptibility profiles of only the last isolate cultured for each patient during an analysis period, while another is to include only the first isolate in a given analysis period (a process which may be automatically performed by some laboratory software). The Clinical and Laboratory Standards Institute (CLSI) presently recommends inclusion of only the first isolate of a given species cultured from a specimen of any source per patient per year (13). While the guidance from CLSI also recognizes alternative options for handling duplicate isolate data, it justifies the recommendation to include only the "first isolate per patient per calendar year" by noting that chronically ill patients with long hospital admissions would contribute repeat isolates that do not reflect a typical patient with initial infection (13), and without prior culture and susceptibility results, the cumulative antibiogram should guide empirical therapy for presumed infections (1). This guidance is currently used by University of California Los Angeles (UCLA) to generate annual antibiograms (14, 15).

The U.S. Centers for Disease Control and Prevention's National Healthcare Safety Network (NHSN) more recently released an Antimicrobial Use and Resistance Module, with requirements to standardize antimicrobial resistance event frequency data in a CASTR (16). In this module, isolates cultured from invasive sources (blood or cerebrospinal fluid [CSF]) are eligible if they were collected more than 14 days from the last isolate of that organism from a patient. For noninvasive sources (urine or lower respiratory specimen), the first isolate of an organism per calendar month per patient is eligible for inclusion in the module (16). Because the temporal criteria put forth by NHSN may include duplicate isolates that the CLSI criteria would not, we hypothesized that if users select the option to generate a CASTR using the NHSN criteria (16, 17), the result would be higher rates of nonsusceptibility (NS) relative to those prepared following CLSI criteria. Given that it may be challenging for clinical microbiology laboratories with limited bandwidth to generate multiple CASTRs and that the coexistence of multiple institutional CASTRs might complicate antimicrobial stewardship efforts, inflated rates of nonsusceptibility under an exclusively generated NHSN criteria may affect empirical therapy decisions.

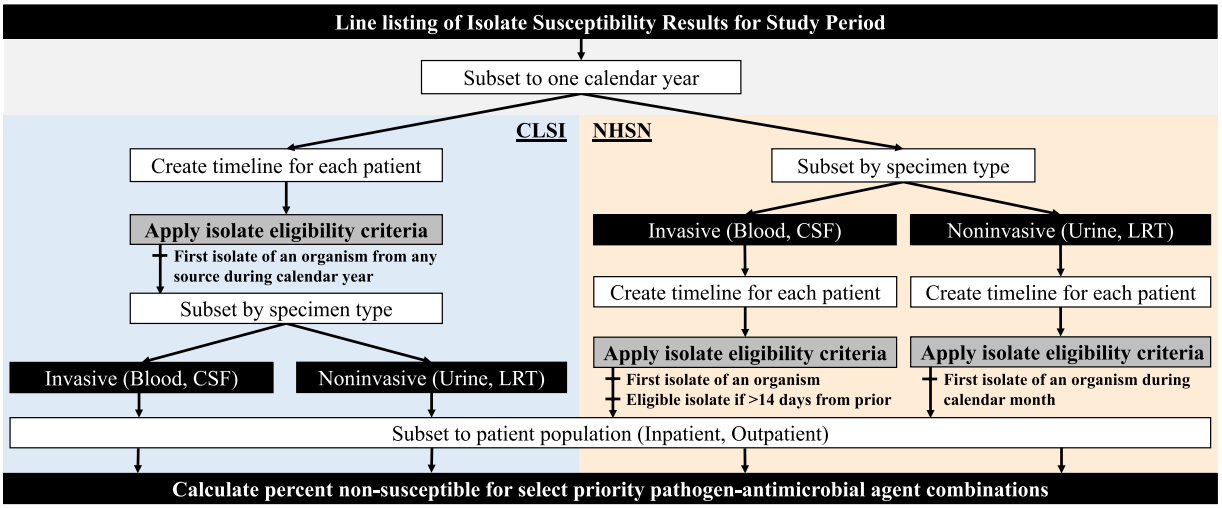
Here, we use data from a high-volume clinical microbiology laboratory at a large, academic health care system between 2018 and 2020 to investigate the correlation between duplicate isolates and higher NS rates for combinations of priority pathogens and antimicrobial agents of clinical relevance (priority pathogen-agent combinations [PPACs]) and the effect of CLSI and NHSN criteria on resulting antibiogram data.

MATERIALS AND METHODS

This study was performed at UCLA—a large, academic system with two acute care hospitals and over 100 outpatient clinics for primary and specialty care, servicing approximately 600,000 unique patients per year. A line listing of all validated susceptibility results (based on the CLSI M100 29th edition from 2018 to 2019 and the 30th edition from 2019 to 2020 [14, 15]) for isolates derived from culture-positive specimens processed by the UCLA Clinical Microbiology Laboratory between January 2018 and January 2020 was generated by the WHONET 2019 Laboratory Information System after UCLA Institutional Review Board approval (IRB 20-000025). Data were concatenated and stratified by year (2018, 2019) and by specimen collection in an inpatient or outpatient setting. Per NHSN guidelines, specimens collected in a hospital emergency department or 24-h observation unit were designated as outpatient, while data from outpatient clinics were excluded.

To compare the output of the CASTR generation methods, two antibiograms were generated using either the NHSN or the CLSI criteria (Fig. 1A). Importantly, NHSN requires only the reporting and grouping of select invasive (blood, cerebrospinal fluid) and noninvasive (urine, lower respiratory) specimen types. To generate the NHSN-eligible isolate list, the listing of all isolates was first categorized as invasive or noninvasive specimen types listed by NHSN and then subject to the NHSN criteria for inclusion of duplicate isolates. To generate the CLSI-eligible isolate list, the CLSI criteria (first isolate of a given organism from any specimen source per patient annually) were applied for all specimen types and then categorized to include only the select invasive or noninvasive specimen types listed by NHSN so that a direct comparison could be made between the two CASTRs. From the CLSI-eligible and NHSN-eligible isolate lists, NS rates were calculated as the proportion of isolates with resistant, intermediate, or

A



B

Antimicrobial Agent	Antimicrobial Class	*Escherichia coli*	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*
Ertapenem	Carbapenem	●	●	
Meropenem	Carbapenem			●
Ceftriaxone	Cephalosporin	●	●	
Cefepime	Cephalosporin			●
Ceftolozane/Tazobactam	b-lactam/b-lactamase inhibitor			●
Piperacillin/Tazobactam	b-lactam/b-lactamase inhibitor	●	●	●
Amikacin	Aminoglycoside			●
Gentamicin	Aminoglycoside	●	●	
Tobramycin	Aminoglycoside			●
Ciprofloxacin	Fluoroquinolone	●	●	●
Trimethoprim/Sulfamethoxazole	Folate synthesis inhibitor	●	●	
Nitrofurantoin (Urine Only)	Nitrofuran	●	●	

FIG 1 Visual algorithm for generating CLSI- and NHSN-eligible isolate lists for comparison of resulting cumulative antimicrobial susceptibility test reports (CASTRs). (A) Computational workflow to apply isolate eligibility criteria for inclusion in either CLSI or NHSN CASTRs. CLSI, Clinical and Laboratory Standards Institute Criteria; NHSN, National Healthcare Safety Network Criteria; LRT, lower respiratory specimen. (B) Selected priority pathogen-agent combinations (PPACs) of clinical relevance; circles indicate a PPAC analyzed. Note that nitrofurantoin susceptibility is only tested for isolates originating from urine specimens. Colors represent the class of antibiotic as defined by NHSN.

nonsusceptible interpretations in the total population of isolates as described in the 2019 NHSN Antimicrobial Resistance Module (16). As recommended by CLSI (13), confidence intervals (95%) for these rates were calculated using the Agresti-Coull method. Chi-squared tests were used to test the difference between NS rates. A P value of <0.05 was considered significant.

Our analysis focused on highly prevalent, priority pathogens with clinically relevant antimicrobial agent combinations (PPACs), determined by members of the antimicrobial stewardship program. Calculation of percent NS was not performed if either isolate list had fewer than 30 results for a given PPAC in a given year. Combined results of all isolates that would be eligible in either the 2018 or 2019 annual antibiograms were included to provide sufficient sample sizes for comparison of all PPACs. All data preparation and statistical analysis were conducted in R 4.0.1.

RESULTS

A total of 26,343 and 27,189 specimen of any type and all collection locations were collected in 2018 and 2019, respectively, of which 9,303 (35.3%) and 9,404 (34.5%) were collected in eligible inpatient or outpatient locations for this analysis each year, respectively. During 2018, the 9,303 culture-positive specimens were collected in eligible locations from

TABLE 1 Demographic characteristics of patients[a]

Parameter	All patients (total no. = 11,528)		Patients contributing PPAC isolates (total no. = 6,593)	
	No.	% of total	No.	% of total
Age at collection date (years)				
≤21	1,199	10.4	610	9.3
22–39	1,786	15.5	986	15.0
40–59	2,598	22.5	1,374	20.8
60–79	3,777	32.8	2,150	32.6
≥80	2,168	18.8	1,473	22.3
Sex				
Male	5,076	44.0	2,282	34.6
Female	6,450	56.0	4,310	65.4
Unspecified	2	0.0	1	0.0
No. of specimen collected per patient in calendar year				
1	8,299	72.0	5,183	78.6
2–4	2,735	23.7	1,266	19.2
≥5	494	4.3	144	2.2

[a]Summary of patients contributing to study sample and specimen processed by the UCLA Clinical Microbiology Laboratory in 2018 and 2019 from eligible collection locations. Patients and specimen populations were significantly different (chi-squared $P < 0.01$) between the overall sample and the PPAC subset across all displayed characteristics. "Patient" indicates data based on unique medical record numbers for which a culture-positive specimen was processed in 2018 or 2019 (data for patients from which culture-negative specimen were obtained are not included). "Specimens" are clinical samples from which one or more isolates of distinct microbial species were grown.

6,126 patients; these specimens grew 10,940 isolates of 243 different microbial species. Similarly, in 2019, 9,404 culture-positive specimens were collected in eligible locations from 6,230 patients, from which 11,162 isolates of 246 different microbial species were identified. The combination of 2018 and 2019 data yielded 22,102 isolates for subsequent analysis (Tables 1 and 2). Gram-negative bacteria were the most prevalent organisms isolated (Table 2), and of these, the three most common species were *Escherichia coli*, present in 5,510 (24.9%) of all isolates from 2018 and 2019, followed by *Pseudomonas aeruginosa* with 2,307 (10.4%) isolates and *Klebsiella pneumoniae* with 1,872 (8.5%) isolates. Subsequent analysis focuses on the isolates of these organisms with susceptibility data available for agents included as PPACs (Fig. 1B); this yields a total of 9,669 isolates, or 43.7% of all 22,102 isolates. The demographics of patients contributing PPAC isolates was similar to the population contributing all isolates (Table 1).

When the CLSI criteria were applied to all 9,669 PPAC isolates, we observed a total of 7,693 CLSI-eligible isolates from all specimen types, but for comparison to NHSN-eligible isolates, this was then limited to 6,680 CLSI-eligible isolates from specimen types included in the NHSN CASTR. When the NHSN criteria were applied, 7,669 NHSN-eligible isolates were identified; of these, 989 were duplicate isolates not eligible by CLSI criteria (Fig. 2A).

When NS rates for PPACs were calculated relative to the duplicate isolate collected per patient in a calendar year, we observed higher NS rates in subsequent duplicate isolates (Fig. 2B) that would be captured by NHSN but not CLSI criteria.

Analysis of isolates from inpatients. We expected that patients with longer lengths of stay contribute more duplicate isolates and that the inclusion of duplicate isolates by NHSN criteria would skew the CASTR toward higher NS rates.

Before applying CLSI or NHSN criteria, we observed that almost all patients (2,966 of 3,157, 94.0%) with lengths of stay under 2 weeks had only one specimen collected from which an isolate was cultured, and fewer than 1% contributed 3 or more isolates. In contrast, duplicate cultures were increasingly prevalent among patients with longer lengths of stay (Fig. 3A); three or more isolates were contributed by 15.4% of patients with

TABLE 2 Collection characteristics of isolates[a]

Parameter	All specimen (total no. = 18,706); all isolates (total no. = 22,102)		PPAC specimen (total no. = 9,222); PPAC isolates (total no. = 9,669)	
	No.	% of total isolates	No.	% of total isolates
Specimen type				
Urine	8,529	38.6	5,670	58.6
Lower respiratory	4,463	20.2	1,783	18.4
Blood	3,445	15.6	872	9.0
Cerebrospinal fluid	76	0.3	10	0.1
Other	5,589	25.3	1,334	13.8
Organism				
Escherichia coli	5,510	24.9	5,500	56.9
Pseudomonas aeruginosa	2,307	10.4	2,303	23.8
Staphylococcus aureus	2,236	10.1		
Klebsiella pneumoniae	1,872	8.5	1,866	19.3
Other	10,177	46.0		
Collection location				
Inpatient	13,451	60.9	4,918	50.9
Outpatient	8,651	39.1	4,751	49.1

[a]Summary of patients contributing to study sample and specimen processed by the UCLA Clinical Microbiology Laboratory in 2018 and 2019 from eligible collection locations. Patients and specimen populations were significantly different (chi-squared $P < 0.01$) between the overall sample and the PPAC subset across all displayed characteristics. "Isolates" represent the culture of a single microbial species from a single patient specimen; isolates are designated as originating from an inpatient or an outpatient based on the collection location of the specimen from which the isolate was grown and by the type of specimen from which the isolate was grown (e.g., blood, urine, etc.). The top four most frequently cultured organism species are listed.

lengths of stay between 2 weeks and 1 month, 25.2% of patients with lengths of stay between 31 and 60 days, and 59.1% of patients with lengths of stay >60 days. Isolates cultured from specimens collected later in admission had higher NS rates than those obtained earlier, both for all pathogen-agent combinations and for PPACs (Fig. 3B).

We then applied the NHSN and CLSI inclusion criteria to inpatient isolates to compare CASTR data. The NHSN criteria yielded higher NS rates than CLSI criteria for all 21 PPACs evaluated (Fig. 4; see also Table S1 in the supplemental material). This increase in NS rate was significant for several of the PPACs; for example, of 1,725 *P. aeruginosa* isolates from inpatients, 741 (43.0%) were eligible by CLSI criteria and 985 (57.1%) by NHSN criteria. Of the CLSI-eligible isolates tested against piperacillin-tazobactam, 206

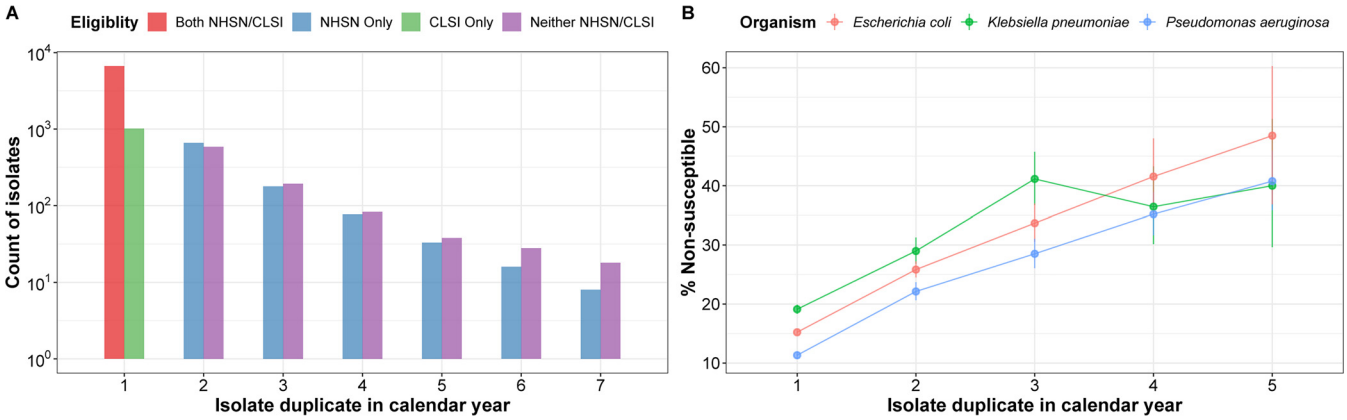


FIG 2 Duplicate isolates are eligible by NHSN but not CLSI and exhibit higher nonsusceptibility rates. (A) Effect of inclusion criteria on isolates of select priority pathogens processed in 2018 and 2019. Isolates were assessed for their inclusion under the CLSI criteria (green), NHSN criteria (blue), both criteria (red), or neither CLSI nor NHSN criteria (purple). Number of isolates falling into each category are shown (in log scale) relative to the isolate duplicate number for a given patient in a calendar year. Of note, CLSI-only eligible isolates represent specimen types not included by NHSN. (B) Correlation of nonsusceptibility (NS) rates with duplicate isolates obtained in a calendar year for select priority pathogens. NS rate was calculated for select priority Gram-negative organism (*E. coli*, red; *K. pneumoniae*, green; *P. aeruginosa*, blue) isolates from invasive or noninvasive sources against selected antimicrobial agents (Fig. 1B) relative to the isolate duplicate number for a given patient in a calendar year. Error bars represent 95% confidence interval calculated by the Agresti-Coull method. CLSI, Clinical and Laboratory Standards Institute criteria; NHSN, National Healthcare Safety Network criteria.

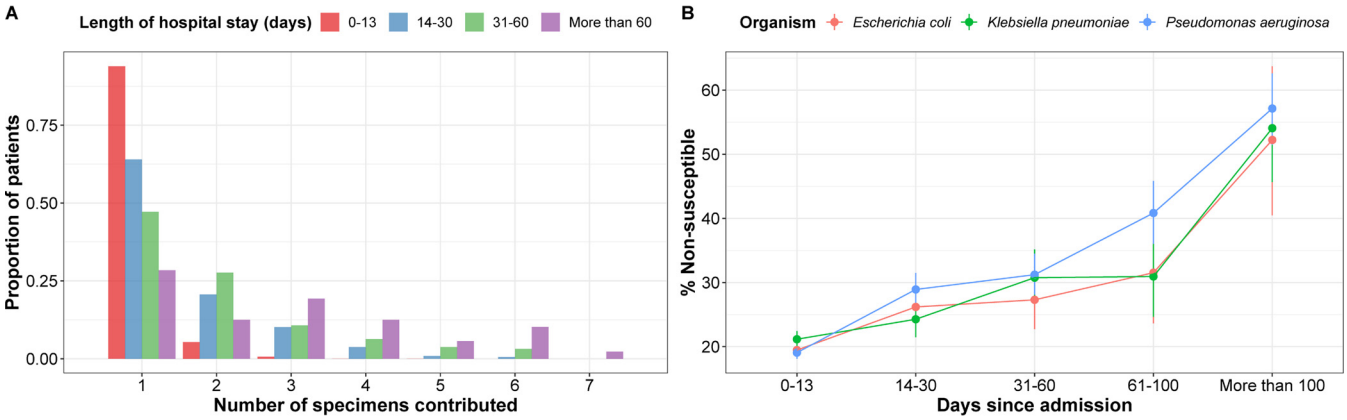


FIG 3 Inpatients with longer lengths of stay contribute more duplicate isolates, and isolates from later in admission have higher nonsusceptibility rates. (A) Distribution of duplicate isolates contributed by inpatients stratified by length of hospital stay; 0 to 13 days (red), 14 to 30 days (blue), 31 to 60 days (green), and more than 60 days (purple). (B) Correlation of nonsusceptibility rates with length of hospital stay for select priority pathogen-agent combinations as listed in Fig. 1B.

(27.8%) were classified as NS. However, of the NHSN-eligible isolates, 319 (32.4%) were classified as NS, yielding significantly different NS rates ($P = 0.04$). *P. aeruginosa* with ceftolozane-tazobactam and meropenem also had significantly different NS rates obtained by CLSI and NHSN criteria (Table S1).

Analysis of isolates from outpatients. Of the 22,102 isolates from specimen collected in all eligible locations in 2018 and 2019, 8,651 (39.1%) were collected during patient encounters at settings defined as outpatient by NHSN (emergency department, pediatric emergency department, and 24-h observation unit).

After applying the NHSN and CLSI inclusion criteria to these outpatient isolates, we again observed higher NS rates for nearly all (19 of 21) PPACs (Fig. 5; see also Table S2 in the supplemental material) with the NHSN criteria, relative to CLSI. Statistically significant differences in NS rate between NHSN and CLSI were noted for *E. coli*

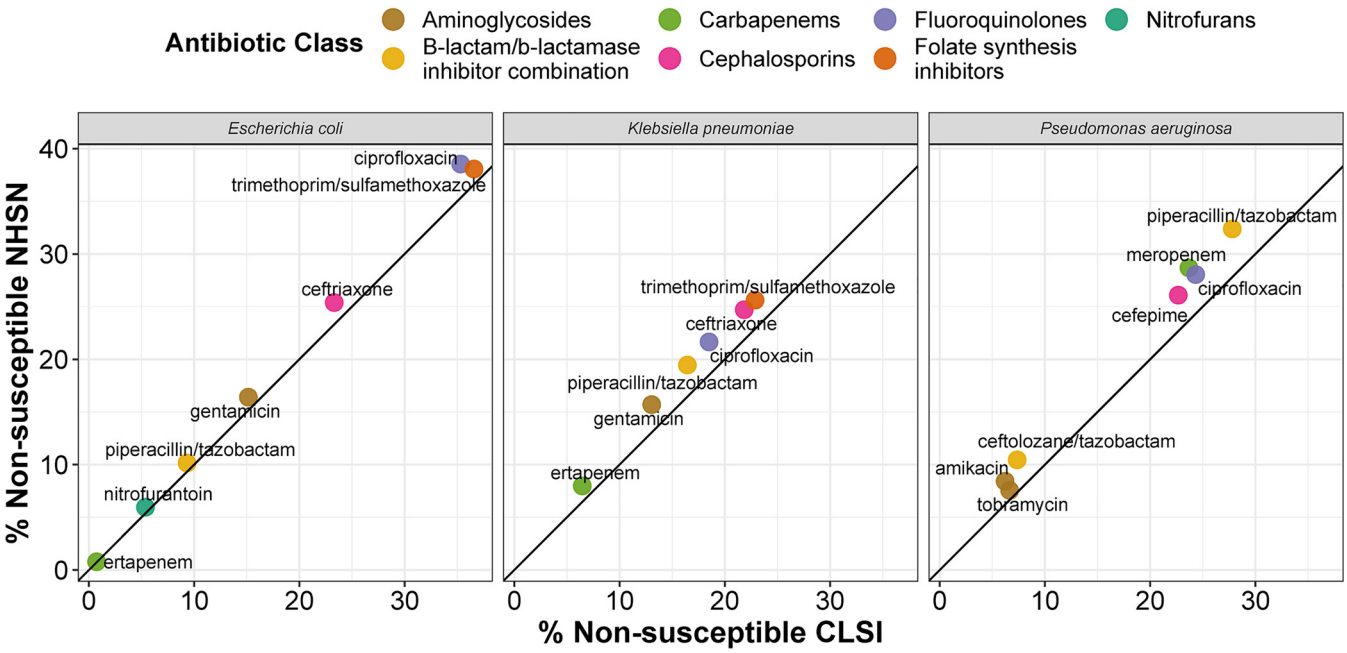


FIG 4 Comparison of CLSI and NHSN nonsusceptibility (NS) rates in isolates from inpatients in 2018 and 2019. Dots represent priority pathogen-agent combinations plotted relative to CLSI NS rate (*x* axis) and NHSN NS rate (*y* axis), colored by antibiotic class, and labeled with the specific agent. The diagonal line represents the line of equivalence, where CLSI and NHSN NS rates are equal. Each panel represents a priority organism, *E. coli*, *K. pneumoniae*, and *P. aeruginosa* (the *K. pneumoniae* NS rates for nitrofurantoin under CLSI and NHSN criteria, respectively, are 66.4% and 68.1%; data not shown). CLSI, Clinical and Laboratory Standards Institute; NHSN, National Healthcare Safety Network; NS, nonsusceptibility.

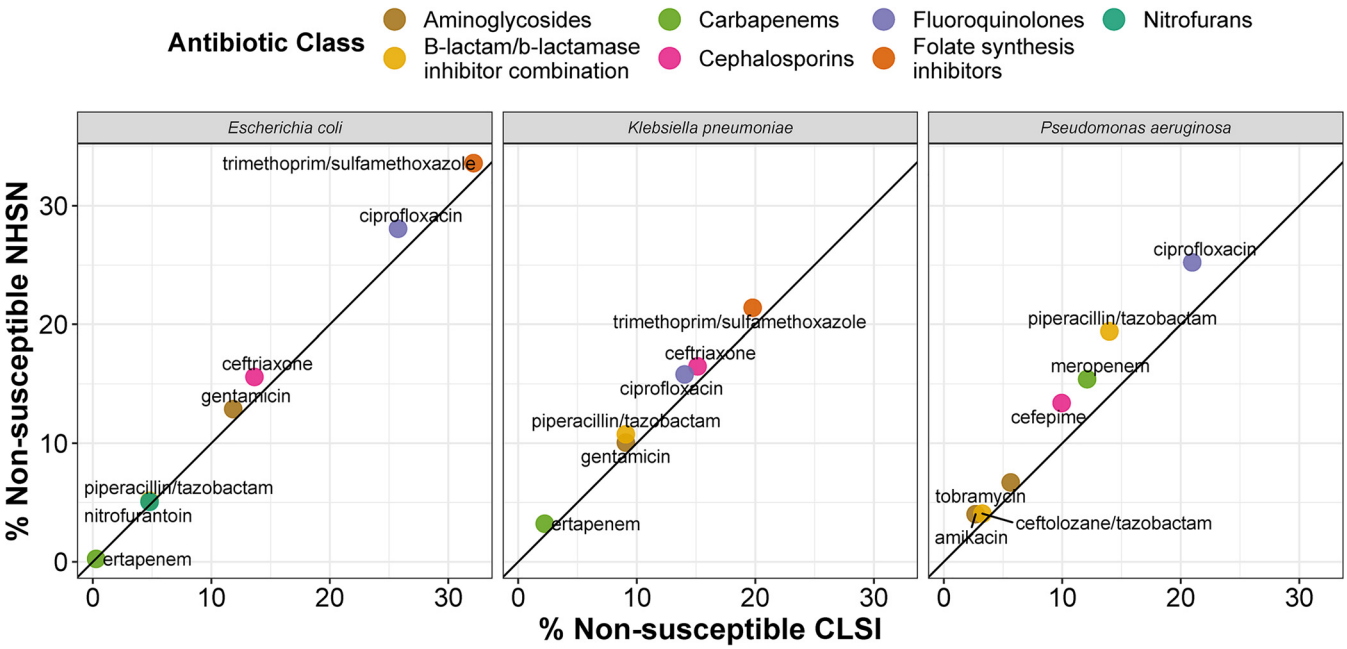


FIG 5 Comparison of CLSI and NHSN nonsusceptibility (NS) rates in isolates from outpatients in 2018 and 2019. Dots represent priority pathogen-agent combinations plotted relative to CLSI NS rate (*x* axis) and NHSN NS rate (*y* axis), colored by antibiotic class, and labeled with the specific agent. The diagonal line represents the line of equivalence, where CLSI and NHSN NS rates are equal. Each panel represents a priority organism, *E. coli*, *K. pneumoniae*, and *P. aeruginosa* (the *K. pneumoniae* NS rates for nitrofurantoin under CLSI and NHSN criteria, respectively, are 67.9% and 67.7%; data not shown). CLSI, Clinical and Laboratory Standards Institute; NHSN, National Healthcare Safety Network; NS, nonsusceptibility.

susceptibility to ceftriaxone and ciprofloxacin and for *P. aeruginosa* susceptibility to piperacillin-tazobactam.

Effect of temporal criteria for duplicate isolate exclusion on NS rates. The primary difference in the CLSI and NHSN criteria is the temporal parameter used to exclude duplicate isolates—for CLSI, one isolate per organism per patient per calendar year, and for NHSN, one isolate per organism per patient per 14-day interval (for invasive specimen) or calendar month (for noninvasive specimen). For PPACs with statistically significant differences in NS rate by the two criteria, we visualized the impact of this temporal exclusion criteria by changing the parameter by daily increments, determining eligible isolates, and recalculating the NS rate (Fig. 6).

For PPACs where significantly different NS rates were observed between NHSN and CLSI in either inpatients (*P. aeruginosa* with piperacillin-tazobactam, meropenem, and ceftolozane-tazobactam) or outpatients (*P. aeruginosa* with piperacillin-tazobactam and *E. coli* with ciprofloxacin and ceftriaxone), we observed maximum NS rates when every isolate was included (0-day temporal parameter for duplicate isolate exclusion), followed by a decline in NS rate as the temporal parameter increased and more duplicate isolates are excluded (Fig. 6). The 14-day parameter for invasive specimens and the 30-day parameter (e.g., calendar month) for noninvasive specimens under NHSN are displayed during the period with a high NS rate, after which the NS rate declines and appears to stabilize by day 180, at which point it is equivalent to the 365-day parameter recommended by CLSI criteria. For example, *P. aeruginosa* isolates from inpatients yielded piperacillin-tazobactam NS rates of 37.7%, 32.0%, 29.9%, 27.2%, and 26.5% for 0-, 14-, 30-, 180-, and 365-day temporal parameters, respectively.

As antibiograms are typically prepared by calendar year, we also conducted our analyses separately by individual calendar year and observed highly similar trends, albeit not statistically significant given the small sample size.

DISCUSSION

From this analysis, we found that NHSN criteria includes duplicate isolates that would not be included under CLSI criteria and that these duplicate isolates have higher

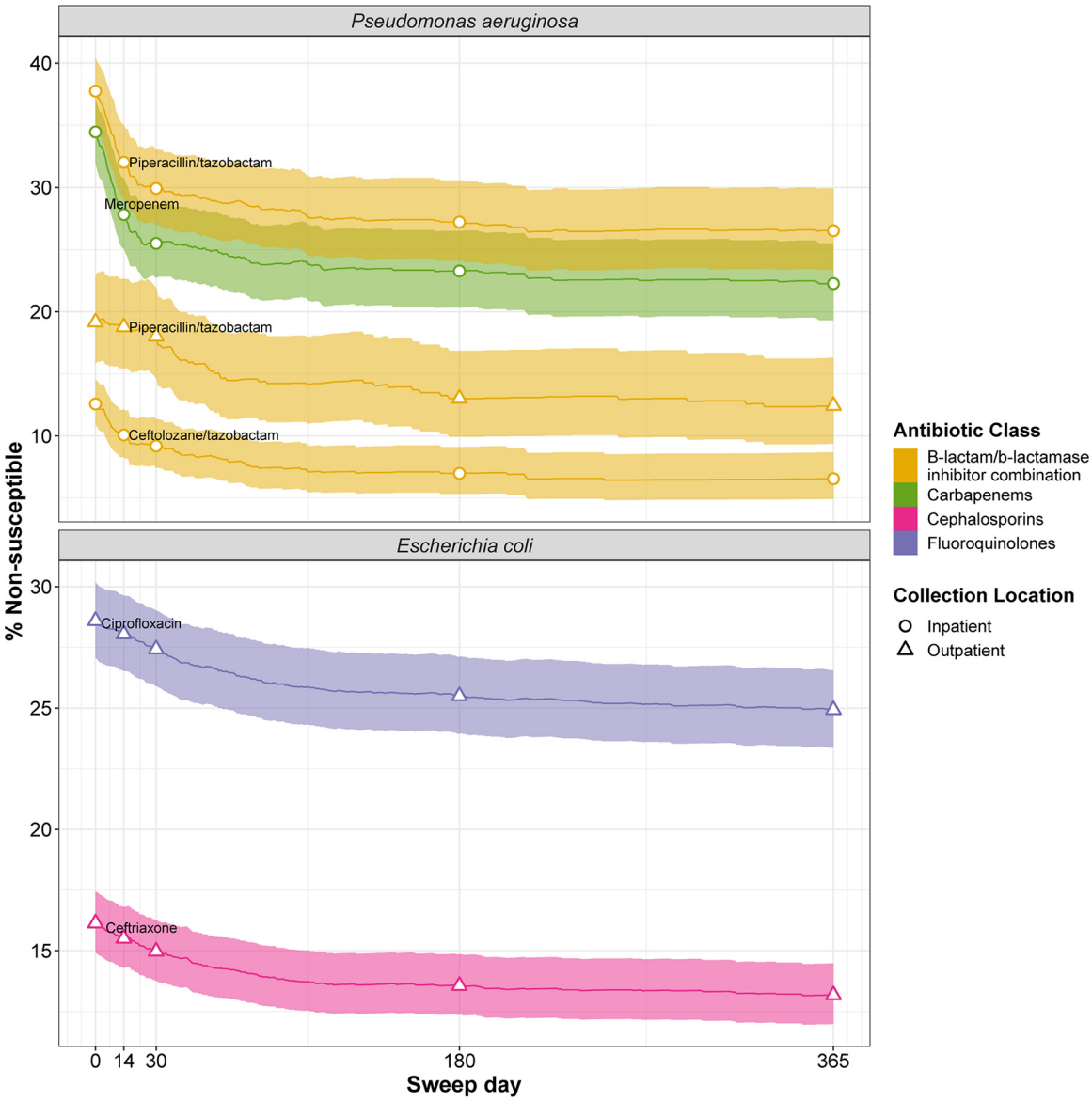


FIG 6 Effect of the temporal parameter for duplicate isolate inclusion on nonsusceptibility rates for priority pathogen-agent combinations with statistically significant differences between cumulative antimicrobial susceptibility test report (CASTR) preparation methods. Colored lines represent the NS rate calculated for a given pathogen-agent combination, as the temporal parameter used to determine inclusion of duplicate isolates is swept from 0 to 365 days. Shading represents the 95% confidence interval calculated by Agresti-Coull method. From left to right, white dots indicate the points where the temporal parameter is 0 days (for which all isolates included), 14 days (the NHSN criteria for invasive specimen), 30 days (the NHSN criteria for invasive specimen), 180 days, and 365 days (the CLSI criteria). CLSI, Clinical and Laboratory Standards Institute; NHSN, National Healthcare Safety Network; NS, nonsusceptibility.

rates of nonsusceptibility. As a result, we observed higher NS rates when using the NHSN criteria. These differences could impact antimicrobial use if used to guide empirical therapy.

Among inpatients, longer lengths of stay correlated with the collection of more specimens from which duplicate isolates were cultured, and NS rates were higher among duplicate isolates later in admission. This aligns with reports that longer admissions in an acute care hospital are associated with drug-resistant infections (such as carbapenem-resistant *Enterobacterales* [18]) due to increased exposure to antimicrobials, device utilization, illness severity, comorbidities and advanced age, and potential acquisition of drug-resistant organisms during hospitalization (19, 20). Inpatients with

unresolved infections due to treatment failure from drug resistance may be sampled repeatedly to monitor therapeutic progress and may remain hospitalized for a longer length of time secondary to treatment challenges. Inclusion of duplicate isolates from these patients under NHSN criteria may skew the resulting CASTR to higher NS rates than would be observed under CLSI criteria.

In the settings classified as outpatient by NHSN (the emergency department, pediatric emergency department, and 24-h observation unit), inclusion of duplicate isolates under NHSN criteria again yielded higher NS rates than those yielded by CLSI criteria. The majority of these duplicate isolates were cultured from urine specimens. While there is no "length of stay" equivalent for patients in these settings, chronic predisposing conditions or risk factors for recurrent urinary tract infection, such as geriatric patients with many comorbidities or younger patients with severe comorbidities, may prompt emergency department visits with frequent, repeat urine cultures. These patients may be more likely to have more frequent exposure to antibiotics and, therefore, higher risk for infection or colonization by multiple-drug-resistant organisms (21–26). This is consistent with the higher NS rates observed in the NHSN CASTR than in the CLSI antibiogram.

The clinical value of an antibiogram is to guide empirical antimicrobial therapy until culture-directed antimicrobial therapy is possible (27). This is less relevant for inpatients with chronic infections or outpatients with recurrent infections because often in these cases the pathogen has been characterized by prior specimen culture and sensitivity testing; for these patients, clinicians can simply look at a patient's prior culture results to guide current therapy (28, 29). As others have reported, and as our data show, these patients contribute to a majority of duplicate isolates, which also have higher NS rates than initial isolates. Therefore, the susceptibilities of duplicate isolates from these patients would not reflect the community prevalence of resistance or the most likely susceptibility profile of a pathogen causing initial infection. Overestimated NS rates due to the inclusion of duplicate isolates may prompt the use of broader-spectrum or next-line antibiotics for empirical therapy, which may drive resistance to these agents and the use of more toxic or costly agents (30).

While empirical antimicrobial therapy selection is dependent on both pathogen and individual patient factors (e.g., presumed infection source, medical comorbidities, illness acuity, and goals of treatment) and institutions may have different guidance for best practice, we note instances where the difference between the NS rate from the NHSN CASTR and the CLSI antibiogram may affect treatment decisions at our institution. For example, in the treatment of *Pseudomonas aeruginosa* infection among inpatients on the bone marrow transplant service at our institution, infectious disease physicians would select cefepime as the first-line agent of choice based on the CLSI antibiogram data; however, piperacillin-tazobactam would be more attractive if the NHSN CASTR data are shown.

The effect of this difference may be heightened in outpatient clinic settings. Since the NHSN module only includes select outpatient locations (emergency department and 24-h observation unit), in our analysis, 39,400 isolates (82% of the outpatient total) that would have been from eligible outpatient locations by CLSI were excluded because they were not from eligible outpatient locations by NHSN. The NS rates for defined outpatient locations by NHSN may not be representative of NS rates in outpatient clinics and may be poorly suited to guide empirical treatment for infections in outpatient clinic settings (where the majority of antibiotics are prescribed [30]).

This work is subject to several limitations. First, characteristics of specific patient populations have been noted as factors that can influence antibiograms (9). This analysis represents a single health care system that may have a patient population or culture and antimicrobial susceptibility testing workflows distinct from other institutions. As a quaternary care center, our institution may provide medical services to more patients with chronic illness who are at high risk of developing recurrent infections. Our results suggest that the CLSI criteria for antibiogram generation would be less subject to the

variation in patient populations at different health care systems than the NHSN criteria. Additionally, due to the size of the UCLA health care system and the high throughput of the UCLA clinical microbiology laboratory, smaller institutions may not be able to detect significant differences in the NS rates obtained by each CASTR. However, if institutional antibiogram data will be used to measure and compare regional resistance rates in a population, consistency across institutional variation in patient population is critically important. Second, the NHSN criteria and CLSI criteria include different specimen types; we chose to limit the specimens included in CLSI criteria (any source) to the more restrictive subset included by NHSN criteria (only blood, cerebrospinal fluid, urine, lower respiratory tract). When CLSI criteria were applied to all specimens versus only the subset of NHSN-eligible specimen types, we observed similar NS results (see Fig. S1 in the supplemental material). This reduction in the number of eligible specimens may also affect the ability to detect statistically significant differences in CASTR data. Third, while antibiograms are typically prepared annually, to obtain adequate sample size, data from both 2018 and 2019 were combined for this analysis. Results were consistent and reproducible each year independently, and the combination of data from the 2-year span provided enough isolate measurements to observe significant differences between the two CASTR generation methods. Finally, this analysis was limited to PPACs deemed by the researchers as high priority for clinical practice and antimicrobial stewardship. These combinations are included in the priority pathogen-agent combinations defined by NHSN, but additional combinations not included in this analysis may also demonstrate significant differences based on the CASTR generation method used.

The inclusion of duplicate isolates may be useful for epidemiological purposes, but as our data have shown, a subpopulation of patients with frequent cultures may elevate nonsusceptibility rates that can affect broader empirical treatment recommendations. To overcome this, institutions might consider preparing multiple CASTRs with clearly distinguished functions—guiding empirical therapy versus monitoring trends in resistance for exclusively epidemiological purposes. That said, preparation of multiple CASTRs may be excessively taxing for clinical laboratories with limited bandwidth, and as a result, this practice may not be uniformly adopted. In addition, the coexistence of multiple CASTRs may require careful dissemination of each to specific stakeholders and additional training of users to understand the differences between the use of each or confuse providers and other relevant stakeholders to the detriment of patient care.

Our analysis highlights that institutional CASTRs generated using NHSN criteria may represent a "path of more resistance" relative to those generated by CLSI criteria. Clinical microbiology laboratorians, clinical providers, and antimicrobial stewardship policymakers should carefully consider the criteria used to generate CASTR data alongside the data itself when developing antimicrobial empirical treatment recommendations and maintain the distinction between CASTRs created for different purposes. Additionally, as data reported to NHSN may be reported publicly, the resulting susceptibility rates should be considered in the context of patient populations served by the health care institution, which may contribute duplicate isolates that impact the reported resistance by this CASTR generation method.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.2 MB.

SUPPLEMENTAL FILE 2, XLSX file, 0.02 MB.

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