

Antibiotic Resistance Patterns and Association With the Influenza Season in the United States: A Multicenter Evaluation Reveals Surprising Associations Between Influenza Season and Resistance in Gram-Negative Pathogens

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Background. Viral infections are often treated with empiric antibiotics due to suspected bacterial coinfections, leading to antibiotic overuse. We aimed to describe antibiotic resistance (ABR) trends and their association with the influenza season in ambulatory and inpatient settings in the United States.

Methods. We used the BD Insights Research Database to evaluate antibiotic susceptibility profiles in 30-day nonduplicate bacterial isolates collected from patients >17 years old at 257 US healthcare institutions from 2011 to 2019. We investigated ABR in Gram-positive (*Staphylococcus aureus* and *Streptococcus pneumoniae*) and Gram-negative (Enterobacterales [ENT], *Pseudomonas aeruginosa* [PSA], and *Acinetobacter baumannii* spp [ACB]) bacteria expressed as the proportion of isolates not susceptible ([NS], intermediate or resistant) and resistance per 100 admissions (inpatients only). Antibiotics included carbapenems (Carb), fluoroquinolones (FQ), macrolides, penicillin, extended-spectrum cephalosporins (ESC), and methicillin. Generalized estimating equations models were used to evaluate monthly trends in ABR outcomes and associations with community influenza rates.

Results. We identified 8 250 860 nonduplicate pathogens, including 154 841 Gram-negative Carb-NS, 1 502 796 Gram-negative FQ-NS, 498 012 methicillin-resistant *S aureus* (MRSA), and 44 131 NS *S pneumoniae*. All *S pneumoniae* rates per 100 admissions (macrolide-, penicillin-, and ESC-NS) were associated with influenza rates. Respiratory, but not nonrespiratory, MRSA was also associated with influenza. For Gram-negative pathogens, influenza rates were associated with the percentage of FQ-NS ENT, FQ-NS PSA, and Carb-NS ACB.

Conclusions. Our study showed expected increases in rates of ABR Gram-positive and identified small but surprising increases in ABR Gram-negative pathogens associated with influenza activity. These insights may help inform antimicrobial stewardship initiatives.

Keywords. antibiotic resistance; hospitals; influenza; seasonality; United States.

Yearly influenza season invokes an interplay of many different respiratory viruses, including metapneumovirus and respiratory syncytial virus, which may incite secondary bacterial infections, particularly in patients at high risk due to structural lung disease, chronic conditions such as diabetes, or an immunocompromised state [1–4]. In addition, influenza infection may directly facilitate bacterial infections due to increased bacterial

adherence, influenza-associated immunosuppression, and other mechanisms [3, 5]. Across various studies, approximately 11% to 35% of patients with laboratory-confirmed influenza have a bacterial coinfection [6], and patients with influenza and bacterial coinfections who develop community-acquired pneumonia (CAP) have more severe disease and higher mortality rates than CAP patients without coinfections [7]. Even in the absence of bacterial coinfection, many patients with respiratory conditions receive empiric treatment with antibiotics. In one study, 41% of ambulatory patients treated with empiric antibiotics due to respiratory symptoms did not have a diagnosis for which antibiotics were indicated [8]. The higher rates of both bacterial infections and antibiotic use during influenza seasons are thought to play a role in seasonal antibiotic resistance (ABR), particularly in respiratory isolates [9].

Much of the current literature has evaluated changes in resistance patterns for the pathogen to which a vaccine is

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directed (eg, *Streptococcus pneumoniae* resistance and the pneumococcal vaccine) or more commonly isolated Gram-positive respiratory copathogens such as *Staphylococcus aureus*. However, there are minimal data on seasonal influences on resistance in nonrespiratory and Gram-negative pathogens. A previous study based on the BD Insights Research Database (Franklin Lakes, NJ) detected seasonal trends in ABR Gram-negative pathogens isolated from inpatients, but it did not explore possible associations with these patterns or evaluate seasonality in ambulatory patients [10]. Aggregated facility-level resistance trends may be of value in choosing empiric therapies for potential secondary bacterial coinfections, particularly if vaccines are championed further upstream to help mitigate the inciting viral infection. Insights on increased isolation of resistant pathogens associated with respiratory virus season may help spearhead vaccination campaigns, which are increasingly needed. Furthermore, epidemiological knowledge of resistant pathogens that peak during respiratory virus surges may help forewarn and inform infection prevention and control and antimicrobial stewardship programs. The goal of our study was to explore US trends in antibiotic-resistant respiratory and nonrespiratory bacteria and the relationship of these trends with influenza rates derived from facilities in the BD Insights Research Database, which includes approximately 13% of all-cause annual hospital admissions in the United States [11].

METHODS

Study Design

We conducted a retrospective, ecological analysis to evaluate possible associations between community influenza and ABR rates using real-world data collected between 2011 and 2019 from patients >17 years old at US acute healthcare institutions in the BD Insights Research Database. This database includes small and large acute healthcare facilities in urban and rural areas with geographical representation across the United States [10, 12, 13]. The outcomes of interest were the percentage of ABR pathogens for both inpatients and ambulatory patients and the rates of ABR pathogens per 100 admissions (inpatients only). Outcomes were analyzed by setting (ambulatory or inpatient) and source (respiratory vs nonrespiratory [urine, blood, skin/wound, intraabdominal, and other sites]). Geographic localization was based on US Department of Health and Human Services (HHS) regions. Associations between ABR bacteria and community influenza rates were evaluated as described below. The influenza status of individual patients with positive bacterial cultures was not assessed.

Patient Consent

Outcome studies using this retrospective, deidentified dataset were approved, and informed consent was waived by the New

England Institutional Review Board (Wellesley, MA; institutional review board no. 120180023).

Laboratory Analyses

Susceptibility results and pathogen identification were based on facility reports from healthcare facilities in the BD Insights Research Database. Microbiology results likely associated with surveillance or environmental cultures were excluded using previously described methodology [14].

Antibiotic resistance was based on a test result of resistance (for methicillin-resistant *S aureus* [MRSA]) or not susceptible ([NS] defined as intermediate or resistant) for specified pathogens and antibiotics as defined by local testing facilities. The following pathogen/antibiotic resistance patterns were assessed: (1) MRSA - *S aureus* with a test result of resistant to methicillin; (2) *S pneumoniae* - NS to macrolides, penicillin, or extended-spectrum cephalosporins (ESC); (3) Enterobacterales (ENT) and *Pseudomonas aeruginosa* (PSA) - NS to carbapenems (Carb) or fluoroquinolones (FQ); (4) *Acinetobacter baumannii* spp (AC) - NS to Carb; (5) *Stenotrophomonas maltophilia* - NS to FQ.

Influenza polymerase chain reaction and antigen laboratory data were used to determine facility-level influenza rates (positive results/100 tests). Although other respiratory viruses also display seasonal variations, influenza accounts for the majority of cases in adults [15] and was therefore chosen as the focus of respiratory virus evaluations.

Statistical Analysis

Influenza and ABR rates were calculated for each year-quarter Q1 2011 through Q4 2019 to best encapsulate the concept of a “season”. Sensitivity analyses were conducted at the monthly level(s) to test the extent of any potential misclassification, with year-quarters accurately capturing seasonal fluctuations in the influenza rate. Graphical representations were based on monthly levels to best highlight these seasonal trends.

Generalized estimating equations and logistic regression were used to evaluate the monthly trends for percentage of ABR isolates and the effect of the influenza season on ABR. Generalized linear mixed models were used to model the resistance rate per 100 admissions and explore associations between influenza and ABR rates. The time series data were viewed as repeated measures and acute healthcare facilities were modeled as random effect. These analyses were run separately by pathogen group while controlling for setting, source of isolates, and healthcare facility-level variables (region, bed size, and other characteristics). These analyses were then stratified by setting type and by source of isolates (respiratory vs nonrespiratory). The rates of ABR were graphically evaluated and superimposed to examine visual and statistical associations between the ABR time series and the influenza incidence time series. Results for the association between ABR

and influenza are presented as β coefficients reflecting the degree of change in antimicrobial resistance for every 1-unit change in the influenza rate. Positive coefficients reflect positive associations.

We stratified the analyses by pathogen type and evaluated which pathogens were significantly associated with influenza rates, and whether these relationships varied by pathogen type (Gram negative vs Gram positive). By stratifying the analysis, we were able to assess the effect of other variables such as setting type and source of isolates on relationships between influenza season and ABR. All statistical analyses were conducted using R V 4.0.3 (R Core Team 2020) and the R geepack package. $P < .05$ was considered statistically significant.

RESULTS

A total of 257 acute healthcare facilities with 38 619 461 admissions contributed data to this study. Approximately 40% (39.3%) of healthcare facilities were in HHS Region 4 (South/Southeast) and 72% were in urban locations (Table 1). Between 2011 and 2019, we identified 8 250 860 confirmed 30-day nonduplicate pathogens and 3 510 459 influenza tests across 38 619 461

Table 1. Distribution of Study Healthcare Facilities

Characteristic	n	%
Overall	257	
HHS Region		
Region 1 (CT, ME, MA, NH, RI, VT)	14	5.5
Region 2 (NJ, NY)	3	1.2
Region 3 (DE, DC, MD, PA, VA, WV)	10	3.9
Region 4 (AL, FL, GA, KY, MS, NC, SC, TN)	101	39.3
Region 5 (IL, IN, MI, MN, OH, WI)	35	13.6
Region 6 (AR, LA, NM, OK, TX)	39	15.2
Region 7 (IA, KS, MO, NE)	16	6.2
Region 8 (CO, MT, ND, SD, UT, WY)	13	5.1
Region 9 (AZ, CA, HI, NV)	24	9.3
Region 10 (AK, ID, OR, WA)	2	0.8
Urban/Rural		
Urban	185	72.0
Rural	72	28.0
Teaching Status		
Nonteaching	217	84.4
Teaching	40	15.6
Bed Size		
< 100	74	28.8
100–300	99	38.5
> 300	84	32.7

Abbreviations: AL, Alabama; AR, Arizona; AK, Arkansas; CA, California; CO, Colorado; CT, Connecticut; DE, Delaware; DC, District of Columbia; FL, Florida; GA, Georgia; HHS, US Department of Health and Human Services; HI, Hawaii; IA, Iowa; ID, Idaho; IL, Illinois; IN, Indiana; KY, Kentucky; KS, Kansas; LA, Louisiana; MA, Massachusetts; MD, Maryland; ME, Maine; MI, Michigan; MN, Minnesota; MO, Missouri; MS, Mississippi; MT, Montana; NE, Nebraska; OH, Ohio; OK, Oklahoma; NC, North Carolina; ND, North Dakota; NH, New Hampshire; NJ, New Jersey; NM, New Mexico; NV, Nevada; NY, New York; OR, Oregon; PA, Pennsylvania; RI, Rhode Island; SC, South Carolina; SD, South Dakota; TN, Tennessee; TX, Texas; VA, Virginia; VT, Vermont; WA, Washington; WI, Wisconsin; WV, West Virginia; WY, Wyoming.

admissions (Supplementary Table 1). The most common pathogens were ENT (6 316 806 [76.6%]) and PSA (749 832 [9.1%]). Data on influenza rates (percent of positive tests) tracked well with influenza data from the Centers for Disease Control and Prevention [16] (Supplementary Figure 1).

Antibiotic Resistance in Gram-Positive and Gram-Negative Pathogens

Analyses of Gram-positive pathogens revealed that slightly over half of *S aureus* isolates tested (498 012 of 989 796 [50.3%]) were MRSA. High levels of ABR were also observed in the 74 554 *S pneumoniae* isolates tested: 28 421 (38.1%) were NS to macrolides, 13 240 (17.8%) were NS to penicillin, and 2470 (3.3%) were NS to ESC (Table 2).

Respiratory sources accounted for 10.7% of *S aureus* isolates and approximately half (46.3%) of *S pneumoniae* isolates. The ABR rates in respiratory isolates were slightly higher than in nonrespiratory isolates (Table 2). We also observed higher ABR rates for inpatients versus ambulatory patients for MRSA but not for *S pneumoniae*. With respect to seasonal trends, percentages of MRSA showed little variation across quarters. The highest rates of ABR in *S pneumoniae* were recorded in Q3 for all 3 of the antibiotic classes evaluated.

For Gram-negative pathogens, the majority of isolates tested were ENT (6 316 806 of 7 186 510 [87.9%]). Although not analyzed in this study, previous analyses with this database indicate that approximately 56% of ENT inpatient isolates in our database are *Escherichia coli*, followed by *Klebsiella pneumoniae* and *Proteus mirabilis* [13]. Overall, 154 841 (2.2%) of Gram-negative pathogens were Carb-NS and 1 502 796 (20.9%) were FQ-NS (Table 3). As observed for Gram-positive pathogens, ABR rates were higher in respiratory versus nonrespiratory isolates. However, only 5.3% of Gram-negative isolates had a respiratory source (2.6% of ENT, 23.1% of PSA, 25.8% of ACB, and 47.4% of *S maltophilia*). The ABR rates were higher for inpatients versus ambulatory patients for all pathogens and antibiotics evaluated. The percentages of resistant isolates were generally highest in Q1 with the exception of Carb-NS ENT, which was highest in Q4.

Multivariate Association Between Influenza and Antibiotic Resistance Rates

Respiratory MRSA rates per 100 admissions were statistically associated with influenza rates, but overall rates of MRSA (both respiratory and nonrespiratory sources) were not (Table 4). The rate per 100 admissions of ABR *S pneumoniae* showed significant associations with influenza rates for both respiratory isolates and overall isolates for all 3 antibiotic classes evaluated (macrolide-, penicillin-, and ESC-NS) (Table 4 and Figure 1). Macrolide-NS *S pneumoniae* had the strongest association (β coefficient of 0.464 overall and 0.253 for respiratory isolates; $P < .001$ for both associations). Associations between percentage of resistant Gram-positive pathogens and influenza rates were not observed.

Table 2. Distribution of Gram-Positive Antibiotic-resistant Pathogens by Setting, Culture Source, and Quarter

Characteristic	<i>Staphylococcus aureus</i>		<i>Streptococcus pneumoniae</i>			
	Tested	MRSA (%)	Tested	Macrolide-NS (%)	Penicillin-NS (%)	ESC-NS (%)
Overall	989 796	498 012 (50.3%)	74 554	28 421 (38.1%)	13 240 (17.8%)	2470 (3.3%)
Setting						
Ambulatory	501 644	236 435 (47.1%)	25 666	10 303 (40.1%)	4993 (19.5%)	959 (3.7%)
Inpatient	488 152	261 577 (53.6%)	48 888	18 118 (37.1%)	8247 (16.9%)	1511 (3.1%)
Culture Source						
Respiratory	106 170	56 691 (53.4%)	34 554	15 384 (44.5%)	7437 (21.5%)	1373 (4.0%)
Nonrespiratory	883 626	441 321 (49.7%)	40 000	13 037 (31.2%)	5803 (17.5%)	1097 (3.1%)
Quarter						
Q1	230 928	116 857 (50.6%)	24 286	9328 (38.4%)	4271 (17.6%)	825 (3.4%)
Q2	239 865	121 466 (50.6%)	18 190	6871 (37.8%)	3224 (17.7%)	579 (3.2%)
Q3	266 029	133 085 (50.0%)	11 764	4587 (39.0%)	2300 (19.6%)	451 (3.8%)
Q4	252 974	126 604 (50.1%)	20 314	7635 (37.6%)	3445 (17.0%)	615 (3.0%)

Abbreviations: ESC, extended-spectrum cephalosporins; MRSA, methicillin-resistant *S aureus*; NS, not susceptible.

Associations were observed between the percentage of ABR Gram-negative pathogens and influenza rates but not between ABR rates per 100 admissions and influenza rates (Table 4 and Figure 1). The influenza rate was significantly associated with the percentages of FQ-NS ENT (β coefficient of 0.041; $P < .001$), FQ-NS PSA (β coefficient of 0.039; $P = .015$), and Carb-NS ACB (β coefficient of 0.205; $P < .001$). Associations were observed for both respiratory and nonrespiratory sources for Carb-NS ACB and FQ-NS ENT, but only for respiratory FQ-NS PSA (Table 4). An association for FQ-NS ENT was observed in both ambulatory patients and inpatients, whereas associations for Carb-NS ACB and FQ-NS PSA were observed in inpatients only.

DISCUSSION

Our study, based on a large nationwide database, demonstrates clear seasonality to ABR that follows trends in influenza rates after controlling for setting, source of isolates, and healthcare

facility characteristics. These associations do not imply causality, because the causes of ABR are multifactorial [11]. However, they provide important insights into ABR trends that may help health systems strategically allocate resources, including vaccination drives and antimicrobial stewardship initiatives [17]. We have also documented associations between influenza rates and increased inpatient antibiotic use for key antibiotic classes used to treat respiratory infections, including macrolides, ESC, and FQ (unpublished observations, KC Yu et al., 2022). Together, these studies provide insights into both bacterial pathogen transmission and antibiotic use at the hospital level that may be appropriate for targeted interventions and for informing policies that facilitate reduced ABR.

In Gram-positive pathogens, we identified significant associations between influenza rates and the rate per 100 admissions for drug-resistant *S pneumoniae* and respiratory MRSA. *Staphylococcus aureus* and *S pneumoniae* are the most common causes of secondary bacterial infections associated with influenza [6]. Antibiotic resistance in these key respiratory

Table 3. Distribution of Gram-Negative Antibiotic-Resistant Pathogens by Setting, Culture Source, and Quarter

Characteristic	Enterobacteriales			<i>Pseudomonas aeruginosa</i>			<i>Acinetobacter</i> spp		<i>Stenotrophomonas maltophilia</i>	
	Tested	Carb-NS (%)	FQ-NS (%)	Tested	Carb-NS (%)	FQ-NS (%)	Tested	Carb-NS (%)	Tested	FQ-NS (%)
Overall	6 316 806	43 272 (0.7%)	1 310 150 (20.7%)	749 382	96 961 (12.9%)	183 956 (24.6%)	48 172	14 608 (30.3%)	72 150	8690 (12.0%)
Setting										
Ambulatory	4 040 147	15 837 (0.4%)	750 020 (18.5%)	329 996	31 159 (9.4%)	73 309 (22.2%)	16 808	2616 (15.6%)	25 471	2932 (11.5%)
Inpatient	2 276 659	27 435 (1.2%)	560 130 (24.6%)	419 386	65 802 (15.7%)	110 647 (26.4%)	31 364	11 992 (38.2%)	46 679	5758 (12.3%)
Culture source										
Respiratory	165 252	6319 (3.8%)	34 438 (20.8%)	173 086	40 459 (23.4%)	54 696 (31.6%)	12 420	5670 (45.7%)	34 224	4562 (13.3%)
Nonrespiratory	6 151 554	36 953 (1.2%)	1 275 712 (20.1%)	576 296	56 502 (9.9%)	129 260 (18.8%)	35 752	8938 (26.0%)	37 926	4128 (10.4%)
Quarter										
Q1	1 437 289	9661 (0.7%)	311 796 (21.6%)	172 887	23 040 (13.3%)	44 119 (25.6%)	10 671	3674 (34.4%)	16 407	2046 (12.5%)
Q2	1 521 108	10 517 (0.7%)	320 811 (21.2%)	177 877	23 521 (13.2%)	44 966 (25.2%)	11 452	3 627 (31.7%)	17 314	2108 (12.2%)
Q3	1 697 602	11 514 (0.7%)	338 012 (19.9%)	200 624	25 214 (12.6%)	47 774 (23.8%)	13 666	3661 (26.8%)	19 261	2223 (11.5%)
Q4	1 660 807	11 580 (0.7%)	339 531 (20.5)	197 994	25 214 (12.7%)	47 097 (23.8%)	12 383	3646 (29.4%)	19 168	2313 (12.1%)

Abbreviations: Carb, carbapenem; FQ, fluoroquinolones; NS, not susceptible.

Table 4. Summary of Multivariate Regression Analyses^a for the Association Between ABR and Influenza Rates by Source and Setting

ABR	β Coefficient (PValue)				
	Overall	Source		Setting	
		Respiratory	Nonrespiratory	Ambulatory	Inpatient
Gram-Positive ABR per 100 Admissions					
MRSA	0.060 (0.615)	0.066 (0.028)	-0.087 (0.065)	NA	NA
Macrolide-NS <i>Streptococcus pneumoniae</i>	0.464 (<0.001)	0.253 (<0.001)	0.068 (0.376)	NA	NA
Penicillin-NS <i>S pneumoniae</i>	0.062 (0.011)	0.056 (0.046)	0.044 (0.103)	NA	NA
ESC-NS <i>S pneumoniae</i>	0.033 (0.036)	0.032 (0.012)	0.018 (0.073)	NA	NA
Gram-Negative ABR Percent NS					
FQ-NS ENT	0.041 (<0.001)	0.130 (<0.001)	0.031 (0.030)	0.018 (0.043)	0.048 (<0.001)
FQ-NS PSA	0.039 (0.015)	0.022 (0.036)	0.020 (0.087)	0.032 (0.172)	0.044 (0.015)
Carb-NS ACB	0.205 (<0.001)	0.379 (<0.001)	0.134 (0.040)	0.123 (0.077)	0.255 (<0.001)

Abbreviations: ABR antibiotic resistance; ACB, *Acinetobacter* spp; Carb, carbapenem; ENT, Enterobacterales; ESC, extended-spectrum cephalosporin; FQ, fluoroquinolone; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable; NS, not susceptible; PSA, *Pseudomonas aeruginosa*.

^aData were adjusted for region, teaching status, urban/rural location, bed size, and season.

NOTE: Statistically significant findings are shown in bold.

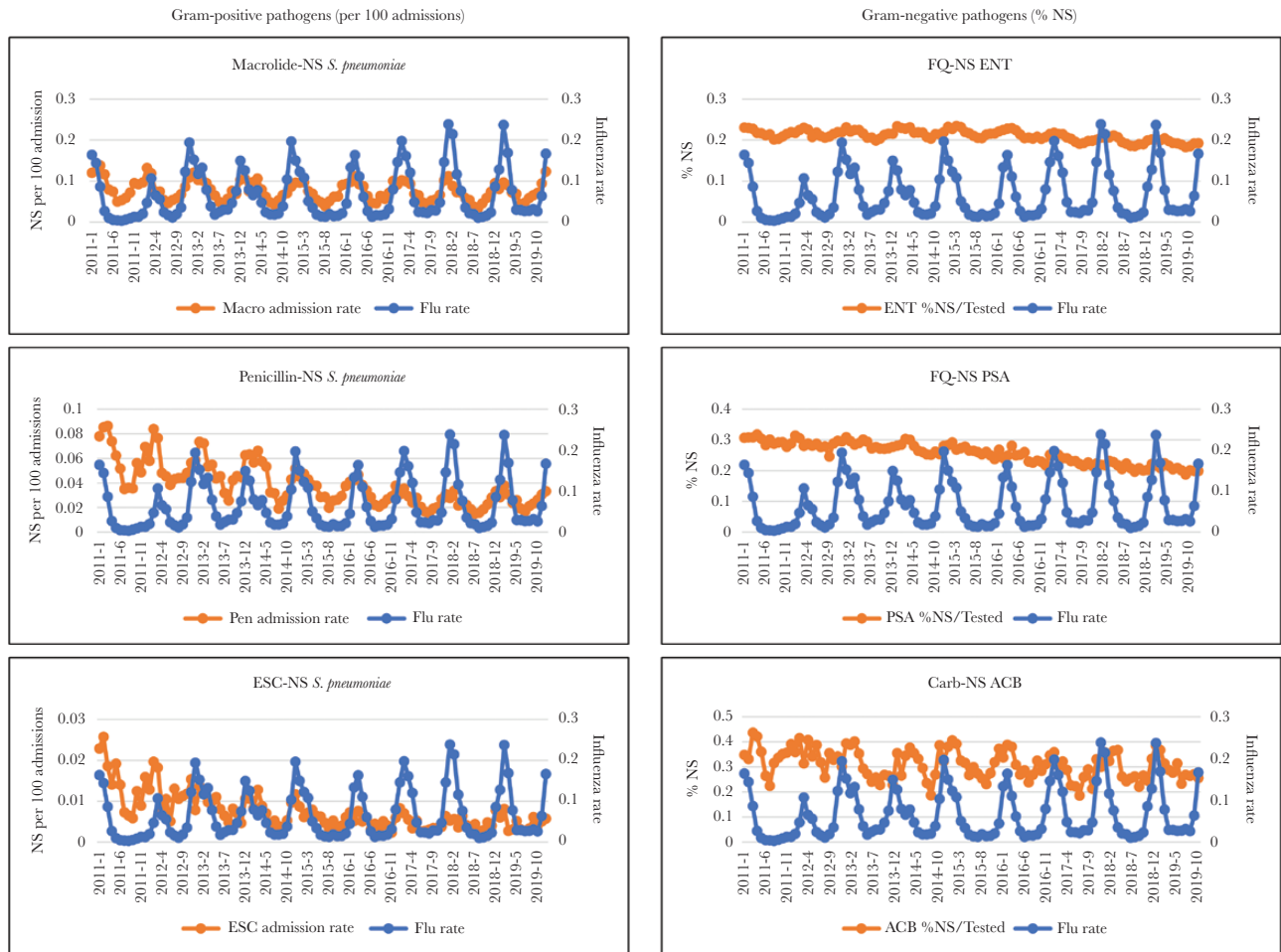


Figure 1. Significant associations between antibiotic resistance and influenza rates from 2011 to 2019. Influenza rate is expressed as positive tests per 100. ACB, *Acinetobacter* spp; Carb, carbapenem; ENT, Enterobacterales; ESC, extended-spectrum cephalosporin; FQ, fluoroquinolone; MRSA, methicillin-resistant *Staphylococcus aureus*; NS, not susceptible; PSA, *Pseudomonas aeruginosa*.

pathogens has the potential to complicate treatment of influenza coinfections, including CAP, and potentially impair patient outcomes [18]. An increased number of ABR admissions during influenza season may further increase the burden on hospitals. Based on β coefficients, a 20% increase in the rate of influenza would be associated with approximately 90 more patients with macrolide-NS pneumonias, 12 more patients with penicillin-NS *S pneumoniae*, and 7 more patients with ESC-NS *S pneumoniae* per 1000 admissions.

For Gram-negative pathogens, the percentage of Carb-NS ACB, FQ-NS ENT, and FQ-NS PSA were significantly associated with influenza rates. Based on β coefficients, a 20% increase in the rate of influenza would be associated with an approximately 1% increase in FQ-NS ENT and PSA isolates and a 4% increase in Carb-NS ACB isolates. This result is somewhat surprising because Gram-negative bacteria are less commonly involved in influenza coinfections [6]. Other studies that explored seasonality, but did not specifically evaluate associations with influenza rates, are consistent with our observations, including studies reporting increased ciprofloxacin and beta-lactam resistance in *E coli* during winter months compared with summer months [19, 20], and a previous study using our database that found higher rates of Carb-NS ACB in Q1 versus Q3 [10]. The associations we observed between Gram-negative resistance and influenza rates suggest that empiric antibiotic use associated with influenza season may have collateral effects on nonrespiratory pathogens and add corroborative evidence that potential bacterial pathogens of public health interest may be important targets for infection prevention practices in a post-COVID-19 era [21]. Given the association of these infections with poor outcomes and increased costs [22, 23], increases in ABR observed in our study can have meaningful impacts on healthcare systems.

Our study provides practical insights for healthcare facilities to incorporate into their stewardship policies and programs to help guide more appropriate antimicrobial selection in patients prone to respiratory infections based on season and severity of influenza rates in local communities. Information on resistant pathogens that peak during surge capacity of respiratory virus season may help forewarn infection prevention and control programs. Antimicrobial stewardship programs, which are now mandated by Centers for Medicare & Medicaid Services (CMS) as a Condition of Participation [24], can also be informed by these trends. The results from this aggregated facility-level analysis support the expansion of influenza vaccine coverage further upstream to help mitigate the inciting viral infection and thereby reduce secondary bacterial coinfections and antibiotic use [25–28]. We concur with the World Health Organization Action Framework on leveraging vaccines to reduce antibiotic use and prevent ABR [17] that vaccines and vaccination should be considered core components of stewardship policies and strategies.

Although some studies have reported a substantial lag time between increased antibiotic use during influenza season and ABR [29], other studies have shown an approximately 1-month lag period [19], which is more in line with the data reported here. A modeling study of seasonal antibiotic use suggested that due to a strong stabilizing force, resistance fluctuates in phase with usage [30].

A limitation of our study is that it did not include data after 2019 and therefore does not reflect significant changes in antibiotic treatment patterns in response to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) [31, 32], which may have also influenced ABR rates [33]. Future research will be required to evaluate the influence of pandemic alterations, including antibiotic prescribing, on ABR [34]. Earlier studies have shown that non-SARS-CoV-2 coronaviruses have a seasonality pattern similar to influenza [15]; additional research will be required to delineate whether SARS-CoV-2 will also ultimately have an influenza-like seasonality, which could further impact temporal trends in antibiotic use and ABR. It is possible that variations in local influenza vaccination rates may have affected the associations we observed. Additional respiratory viruses were not evaluated in this study, and they may also influence associations with ABR. Future evaluations of associations between other respiratory viruses and ABR should include the pediatric population because the majority of adenovirus, parainfluenza virus, and respiratory syncytial virus cases occur in children under the age of 18, a population that was not included in our study [15]. Further research is needed to explore potential associations between influenza rates and ABR at the individual level.

CONCLUSIONS

In conclusion, our study generates insights on the small but significant seasonal changes in Gram-negative resistance, particularly in the inpatient setting, and corroborates the increased occurrence of ABR Gram-positive respiratory pathogens during the influenza season. Our data may help inform targeted antimicrobial stewardship initiatives in preparation for and during influenza season and provide support for vaccination programs to decrease secondary bacterial coinfections and resulting antibiotic use, particularly in patients with chronic underlying conditions who are at risk of hospitalization during the influenza season.

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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Potential conflicts of interest. V. G., K. C. Y., and J. A. W. are employees of Becton, Dickinson & Company, which was contracted by Sanofi Pasteur to conduct the study. K. C. Y. and V. G. also own stock in Becton, Dickinson & Company. H. K. and A. A. are employees of Sanofi Pasteur and may hold shares and/or stock options in the company. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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