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Risk of drug resistance in repeat gram-negative infections among patients with multiple hospitalizations

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Abstract

Purpose—Drug resistance in gram-negative bacterial hospital-acquired infections (GNB HAIs) has become ubiquitous in recent years. Patients who experience multiple hospitalizations are at high risk of developing repeat GNB HAIs. This study aims to evaluate the relationship between repeat GNB HAIs and antibiotic susceptibility patterns.

Methods—Using electronic medical records from three hospitals, 4053 patients were identified with at least one HAI caused by *K. pneumoniae* or *P. aeruginosa* over multiple hospitalizations in a 9-year period. Modified Poisson regression was used to evaluate the risk of drug resistance with increasing number of prior susceptible infections. Drug resistance was defined as resistant to carbapenems for *K. pneumoniae* and resistant to levofloxacin for *P. aeruginosa*.

Results—In patients with repeat infections, almost 15% of consecutive infections changed from susceptible to drug-resistant. Patients with *K. pneumoniae* infections had a 1.14 times increased risk of acquiring a drug-resistant HAI with each prior HAI, after adjusting for potential confounders and antibiotic use prior to infection. Patients with *P. aeruginosa* infections had a 1.23 times increased risk of a drug-resistant infection with each prior *P. aeruginosa* HAI.

Conclusions—Prevention of repeat infections in high healthcare utilizers may be important in reducing drug resistance in this population.

Keywords

Gram-negative infection; Hospital-acquired infection; Repeat infection; Drug resistance

1. Introduction

Rising rates of drug resistance in gram-negative bacteria (GNB) have threatened the gains made in reducing hospital-acquired infections (HAIs) around the world [1,2]. Patients who develop drug-resistant HAIs are at greater risk for longer hospital stays, complications, and mortality [3–5]. Prevention of infections caused by GNB including *K. pneumoniae* and *P. aeruginosa*, are particularly critical due to the limited treatment options. In early 2017, the

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World Health Organization declared that *P. aeruginosa* and *Enterobacteriaceae*, in particular extended-spectrum β -lactamase (ESBL) producing *K. pneumoniae*, were priority pathogens that urgently required new antibiotic development due to widespread multi-drug resistance [6].

Patients with multiple hospital admissions are a vulnerable group with high risk of HAIs [7-9]. These patients are exposed repeatedly to the hospital environment, specifically to intensive care units (ICUs), where the combination of compromised immune systems, empiric antibiotic therapy and medical devices creates the ideal haven for drug-resistant infections. These high-risk patients may experience repeat infections by the same organism, potentially resulting in an increased likelihood of developing a drug-resistant infection.

Repeat infections can lead to drug resistance through several mechanisms such as inappropriate antibiotic therapy, biofilms, and persister cells [10-12]. A number of studies have focused on repeat infections due to pathogens such as *Escherichia coli* and *Staphylococcus aureus* [13-15]. The few studies that have examined repeat GNB infections have primarily aimed at identifying risk factors for recurrence and less on antibiotic resistance patterns in the repeat infections [16-18]; changes in antibiotic susceptibility with repeat GNB HAIs has been largely overlooked. We recently reviewed peer-reviewed literature published between 2000 and 2015 and found only seven studies that examined changes in drug resistance in GNB HAIs [19-25]. Although one recently published study described an association between multidrug resistance and history of GNB bloodstream infections [26], the primary objective of the study was to measure costs associated with multidrug resistance rather than to focus on recurrent infections.

The aim of this study was to evaluate the association between repeat GNB HAIs and antibiotic susceptibility patterns in chronically ill patients who have repeated hospitalizations. It is hypothesized that as the number of infections by the same organism increases, there is a greater likelihood of developing a drug-resistant infection with that same organism.

2. Methods

2.1. Sample and setting

Electronic medical record (EMR) data were obtained from a clinical data warehouse, the development of which has been described in Apte et al. [27], which includes information from patient administrative records, clinical and medication records, laboratory and antibiotic susceptibility reports from blood, urine, respiratory, and wound cultures, and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes from admission and discharge. The data were part of a large healthcare system in New York City, which consisted of a community hospital and two tertiary care hospitals. The three hospitals had over 713,700 discharges of adult patients between 2006 and 2014 and 3.6% of patient discharges experienced at least one HAI. The database was developed as part of a federally funded project, "Health Information Technology to Reduce Healthcare- Associated Infections" (National Institute of Nursing

Research, R01NR010822) and was approved by the institutional review boards of the study sites.

A subset of data containing records of all adult inpatients (≥ 18 years) discharged between January 1, 2006 to December 31, 2014 was used for this study. Patients who were hospitalized two or more times during the study period and had at least one HAI caused by *K. pneumoniae* or *P. aeruginosa* were included in our analyses. HAIs due to *K. pneumoniae* and *P. aeruginosa* were selected because of the epidemiologic importance of these pathogens in acute care setting and there was sufficient sample size of patients with repeat infections with these organisms to provide adequate power to detect differences.

2.2. Data measures

An infection was considered to be an HAI if there was a positive culture with the organism on the third or later calendar day following hospital admission, the infection was not known to be incubating at the time of admission, and it met the criteria defined by the National Healthcare Safety Network of the Centers for Disease Control and Prevention [28]. In this study, repeat HAIs were defined as HAIs that met the above criteria and occurred at least 30 days after a previous hospital discharge. Exposure to repeat infections was defined as the count of HAIs (≥ 2) with the same causative organism across all hospitalizations in the study period. Patients were considered unexposed to repeat infections if they had ≥ 2 hospital visits but only one GNB HAI across all hospitalizations. In the case of multiple GNB infections with the same organism within the same hospitalization, only the first infection was included in the analyses to limit bias due to an unresolved initial infection.

The outcome measure was a binary variable denoting any antimicrobial-resistant infection versus an antimicrobial-susceptible infection for the last HAI caused by each organism. *K. pneumoniae* was considered to be drug resistant if it was not susceptible to imipenem or meropenem. *P. aeruginosa* was considered to be drug resistant if it was not susceptible to levofloxacin. Among exposed patients (those with ≥ 2 GNB HAIs), only the last HAI with the same organism was assessed for drug resistance. For unexposed patients (those with only one GNB HAI across all their hospitalizations), the one GNB HAI was assessed for drug resistance.

Variables assessed for potential confounding included age, sex, cumulative length of hospital stay prior to development of the last GNB HAI, number of total hospitalizations prior to the infection outcome, any stay in the intensive care unit (ICU), cumulative number of days in the ICU prior to the outcome infection, admission source from hospitalization with the outcome infection (clinic referral, non- health care point of origin (e.g., home), other health care facility, unknown), major procedures (operating room procedure, biopsy, dialysis, transplants), use of invasive medical devices (mechanical ventilator, feeding tube, cardiac catheter, vascular stent, CV/IV line), and co-infections (other GNB, other gram positive infection, other infection). Also, included in the dataset were change in the Charlson Comorbidity Index (CCI) [29] from first visit to the visit with the last infection as a proxy to measure change in health status across hospitalizations, comorbidities (chronic obstructive pulmonary disease, cystic fibrosis, diabetes, malignancies, renal failure, and liver disease) at

the last infection, insurance (Medicare, Medicaid, commercial, other), and antibiotic use across hospitalizations prior to the occurrence of the outcome infection.

Antibiotics were grouped as follows: penicillins, cephalosporins, carbapenems, monobactams, polymyxins, anti-*methicillin-resistant Staphylococcus aureus* (MRSA) agents (vancomycin, daptomycin, ceftaroline, linezolid), aminoglycosides, tetracyclines, macrolides, fluoroquinolones, and other (fosfomycin, nitrofurantoin, metronidazole, clindamycin).

2.3. Statistical analyses

Separate analyses were carried out for each organism, *K. pneumoniae* and *P. aeruginosa*. Bivariate analyses were conducted to identify any differences between exposed and unexposed patients using Student's *t*-tests, χ^2 tests, and Fishers exact tests, as appropriate. A modified Poisson regression model was used to analyze the relationship between repeat GNB HAIs and drug resistance. In our study population, 33.3% of patients with multiple hospitalizations and at least one GNB HAI of interest had a drug-resistant infection so the rare disease assumption was not valid. The Poisson model, modified through use of a generalized estimating equations (GEE) approach, was used to obtain unbiased robust standard errors for the relative risks [30,31].

Confounding was assessed though calculating the effect size of the β coefficient with and without inclusion of the potential confounders, those with a *p* value ≤ 0.05 in the bivariate analyses. Covariates that resulted in a 10% or greater change in the effect estimate were retained in the final model in addition to all antibiotic use. Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

3. Results

There were 2416 patients who had at least one *K. pneumoniae* HAI and 1637 who had at least one *P. aeruginosa* HAI across multiple hospitalizations between 2006 and 2014. Of the patients who acquired *K. pneumoniae*, 97 (4%) had repeat *K. pneumoniae* HAIs. Of the patients who acquired *P. aeruginosa*, 79 (4.8%) had repeat infections.

Table 1 summarizes the patient demographic, clinical, laboratory, and medication data based on whether they had repeat infections by the end of the study period. In the *K. pneumoniae* analysis, patients with two or more infections were younger, had more hospitalizations prior to last infection, spent a greater number of days in the hospital and in an ICU, more likely diagnosed with COPD, and more likely to have had an OR procedure, biopsy, or transplantation as compared to patients who only had one HAI caused by *K. pneumoniae*. Patients with repeat infections were also more likely to have experienced a feeding tube, mechanical ventilation, intubation, urinary catheterization and intravascular (IV) line as well as a greater number of days on all types of antibiotics as compared to unexposed patients.

Patients who had two or more *P. aeruginosa* infections compared to patients with only one infection were younger, had more hospitalizations, spent a greater number of days in the hospital and in an ICU, had a prior OR procedure, had a biopsy, underwent transplantation,

were exposed to invasive medical devices, and had a diagnosis of cystic fibrosis, and renal disease. These patients were also more likely to have taken all antibiotics, except penicillins, for a greater number of days compared to patients with one *P. aeruginosa* infection.

Patients who had one or more *K. pneumoniae* HAIs had a total of 2570 infections (Table 2). The majority of these were bloodstream infections (63%), followed by pneumonia (19%), urinary tract infections (15%), and surgical site infections (2.8%). However, 65% of surgical site infections were drug-resistant while only 35% of bloodstream pathogens were drug-resistant. For *P. aeruginosa*, there were a total of 1757 HAIs among all patients who had at least one infection. *P. aeruginosa* infections tended to be bloodstream (50%) or pneumonia (37%). Pneumonia caused by *P. aeruginosa* had the highest proportion of drug resistance (41%) as compared to other types of infection.

When changes in antibiotic susceptibility were evaluated (Fig. 1), there was minimal change in consecutive *K. pneumoniae* HAIs as 80% (n = 82) remained susceptible or resistant from the prior infection. Fifteen percent (n = 16) of paired *K. pneumoniae* infections had drug resistance in the second infection. In consecutive *P. aeruginosa* infections, a large proportion of infections remained resistant (44%) and 16% (n = 14) of second infections were drug-resistant.

Tables 3 and 4 summarize the crude and adjusted relative risks for drug-resistant infection for *K. pneumoniae* and *P. aeruginosa*, respectively. Poisson models with robust standard errors showed that a greater number of prior HAIs resulted in a higher likelihood of drug-resistant *K. pneumoniae* infection (Relative risk (RR): 1.14, 95% CI: 1.04–1.24) and a greater likelihood of a drug-resistant *P. aeruginosa* infection (RR: 1.23, 95% CI: 1.12–1.36) after adjusting for other confounders and antibiotic use. Mechanical ventilation (RR: 1.39, 95% CI: 1.24–1.57) and admission from another healthcare facility (RR: 1.61, 95% CI: 1.02–1.32) were also associated with increased risk of *K. pneumoniae* infection after adjustment. In the *P. aeruginosa* model, cystic fibrosis (RR: 2.7, 95% CI: 1.88–2.73) was associated with drug-resistant infection.

4. Discussion and conclusions

In a population of patients with multiple hospitalizations, more repeat GNB HAIs were associated with higher risk of drug-resistant infection. To the best of our knowledge, this study is the first to describe the association between repeat GNB HAIs and drug resistance, taking into account prior antibiotic use. For each prior hospitalization with a *K. pneumoniae* HAI, there was a 14% increased risk of having a drug-resistant *K. pneumoniae* HAI in a subsequent hospitalization. For patients with repeat *P. aeruginosa* infections, the risk of drug resistance increased by 23% with each prior HAI with *P. aeruginosa*.

About 15% of consecutive infections went from antibiotic susceptible to resistant and 38% of consecutive *K. pneumoniae* infections and 44% of consecutive *P. aeruginosa* infections remained drug resistant. Because our definitions of drug resistance were carbapenems for *K. pneumoniae* and fluoroquinolones for *P. aeruginosa*, typically considered one of the last

lines of treatment for infections caused by these organisms, prevention of the first drug resistant infection is particularly important.

There are several limitations to this study. The use of electronic medical records from a single hospital system does not capture patient medical history from other facilities nor provide an in-depth background on the patient. Our data covered a relatively small time frame for many patients who may have had hospitalizations outside the time period studied. In addition, there was no genotyping data available so it was not possible to assess strain relatedness or confirm whether a repeat infection was indeed a new infection. However, in this study, we defined a repeat infection as a HAI occurring in a hospitalization at least 30 days after a prior hospital discharge, it is unlikely that the infection was an unresolved prior infection. Although the number of patients who had repeat HAIs with the same GNB was relatively small, power calculations confirmed that there was >80% power to detect a significant association between repeat infections due to *K. pneumoniae* or *P. aeruginosa* and drug resistance in this sample.

Using patient history over a nine-year period at three New York City hospitals, this study demonstrated the high threat of drug-resistant infections in patients with multiple admissions and repeat infections who may serve as a reservoir for drug-resistant infections in hospitals; hence, patients with history of GNB HAIs should be prioritized by infection control teams to prevent repeat infections and slow the spread of drug resistance in GNB HAIs.

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Fig. 1. Consecutive infections and antibiotic susceptibility in patients who had 2 or more HAIs, by organism and site.

Table 1

Descriptive statistics of study sample by exposure status.

	<i>K. pneumoniae</i>				<i>P. aeruginosa</i>			
	<u>One infection</u>		<u>Repeat infections</u>		<u>One infection</u>		<u>Repeat infections</u>	
	N = 2319	N = 97	N = 2319	N = 97	N = 1558	N = 79	N = 1558	N = 79
<i>Covariate</i>								
Age, mean (SD)	64.82 (17.04)	61.22 (17.47)			67.01 (17.12)	63.63 (18.66)		0.09
Female sex	1283 (55.33)	46 (47.42)			789 (50.64)	31 (39.24)		0.05
Prior hospitalizations, mean (SD)	2.78 (3.93)	6.79 (6.81)			2.62 (3.8)	6.73 (5.76)		<0.001
Total prior days in hospital, mean (SD)	56.58 (60.37)	145.05 (129.87)			56.64 (62.32)	135.47 (120.59)		<0.001
Total prior days in ICU, mean (SD)	10.72 (21.63)	28.54 (37.41)			14.23 (28.65)	28.42 (46.24)		<0.001
Drug resistance in last infection	822 (35.45)	55 (56.7)			427 (27.41)	46 (58.23)		<0.001
<i>Admission source</i>								
Clinic	658 (28.37)	24 (24.74)			448 (28.75)	17 (21.52)		0.03
Non-healthcare point of origin	773 (33.33)	23 (23.71)			482 (30.94)	29 (36.71)		
Other facility	303 (13.07)	12 (12.37)			232 (14.89)	5 (6.33)		
Other	585 (25.23)	38 (39.18)			396 (25.42)	28 (35.44)		
<i>Insurance</i>								
Medicare	1429 (61.62)	62 (63.92)			1040 (66.75)	59 (74.68)		0.42
Medicaid	400 (17.25)	20 (20.62)			244 (15.66)	11 (13.92)		
Commercial	459 (19.79)	14 (14.43)			260 (16.69)	9 (11.39)		
Other	31 (1.34)	1 (1.03)			14 (0.9)	0 (0)		
<i>Prior clinical history^a</i>								
Prior OR procedure	1123 (48.43)	62 (63.92)			839 (53.85)	52 (65.82)		0.04
Prior feeding tube	182 (7.85)	14 (14.43)			172 (11.04)	24 (30.38)		<0.001
Prior mechanical ventilation	571 (24.62)	39 (40.21)			505 (32.41)	38 (48.1)		<0.01
Prior biopsy	268 (11.56)	20 (20.62)			139 (8.92)	13 (16.46)		0.02
Prior intubation	473 (20.4)	36 (37.11)			410 (26.32)	33 (41.77)		<0.01
Prior cardiac catheter	399 (17.21)	20 (20.62)			227 (14.57)	15 (18.99)		0.28
Prior vascular stent	181 (7.81)	8 (8.25)			92 (5.91)	3 (3.8)		0.62
Prior transplant	168 (7.24)	17 (17.53)			103 (6.61)	9 (11.39)		0.10

	<i>K. pneumoniae</i>			<i>P. aeruginosa</i>		
	One infection	Repeat infections	p-Value	One infection	Repeat infections	p-Value
	N = 2319	N = 97		N = 1558	N = 79	
Prior urinary catheter	1837 (79.22)	90 (92.78)	0.001	1295 (83.12)	73 (92.41)	0.03
Prior CV or IV line	1220 (52.61)	76 (78.35)	<0.001	861 (55.26)	69 (87.34)	<0.001
<i>Chronic conditions</i>						
COPD	950 (40.97)	54 (55.67)	0.004	703 (45.12)	42 (53.16)	0.16
Cystic Fibrosis	77 (3.32)	2 (2.06)	0.769	75 (4.81)	11 (13.92)	<0.01
Diabetes	955 (41.18)	46 (47.42)	0.222	582 (37.36)	33 (41.77)	0.43
Renal disease	971 (41.87)	49 (50.52)	0.091	612 (39.28)	43 (54.43)	<0.01
Any malignancy	830 (35.79)	33 (34.02)	0.721	494 (31.71)	27 (34.18)	0.65
HIV/AIDS	56 (2.41)	4 (4.12)	0.302	36 (2.31)	3 (3.8)	0.43
Hypertension	1798 (77.53)	76 (78.35)	0.85	1197 (76.83)	59 (74.68)	0.66
Hypothyroidism	395 (17.03)	21 (21.65)	0.238	269 (17.27)	16 (20.25)	0.49
Change in CCI from 1st hospitalization to last hospitalization, mean (SD)	0.71 (2.27)	0.4 (2.23)	0.185	0.58 (2.07)	0.34 (2.12)	0.32
<i>Prior antibiotic use (days), mean (SD)</i>						
Penicillins	1.94 (7.6)	4.37 (10.35)	0.002	1.89 (8.82)	2.7 (6.47)	0.42
Cephalosporins	5.86 (15.16)	16.01 (24.08)	<0.001	9.94 (27.91)	21.77 (33.05)	<0.001
Carbapenems	3.83 (16.99)	12 (24.68)	<0.001	5.36 (27.51)	15.48 (29.28)	<0.01
Monobactams	1.02 (14.16)	3.87 (23.46)	0.061	1.17 (12.93)	8.85 (38.52)	<0.001
Polymyxins	0.81 (7.91)	5.32 (15.87)	<0.001	1.49 (11.34)	16.77 (54.78)	<0.001
Anti-MRSA agents	15.42 (38.56)	45.61 (53.75)	<0.001	20.05 (59.25)	56.05 (91.14)	<0.001
Aminoglycosides	2.82 (13.26)	8.84 (24.77)	<0.001	4.37 (15.44)	25.11 (49.52)	<0.001
Tetracyclines	1.16 (9.72)	5.16 (12.73)	<0.001	1.5 (15.55)	7.9 (33.63)	<0.01
Macrolides	2.27 (9.12)	10.55 (34.98)	<0.001	3.28 (11.91)	10.77 (40.47)	<0.001
Fluoroquinolones	2.85 (12.52)	6.35 (14.23)	0.007	3.15 (16.58)	13.44 (29.72)	<0.001
Other	6.07 (21.12)	16.61 (26.43)	<0.001	6.92 (20.99)	24.47 (53.31)	<0.001
Levofloxacin	2.83 (12.52)	6.35 (14.23)	0.007	3.12 (16.61)	13 (29.51)	<0.001
Meropenem/Imipenem	3.83 (16.99)	12 (24.68)	<0.001	5.36 (27.51)	15.48 (29.28)	<0.01

^a Prior history refers to any exposure across all hospitalizations in study time frame prior to the last GNB HAI.

Table 2

Number of total infections in study population, by body site.

	<u><i>K. pneumoniae</i></u>		<u><i>P. aeruginosa</i></u>	
	<u>N = 2570</u>		<u>N = 1757</u>	
	n	% resistant	n	% resistant
Urinary tract infection	373	36.73	122	23.77
Bloodstream infection	1627	34.54	878	23.80
Pneumonia	496	41.33	644	40.68
Surgical site infection	74	64.86	113	23.01

Table 3Crude and adjusted risk ratios of having a drug resistant *K. pneumoniae*.

	Crude		Adjusted^a	
	RR	95% CI	RR	95% CI
Number of infections	1.242	1.141–1.352	1.136	1.038–1.244
Prior biopsy	1.205	1.042–1.394	1.115	0.956–1.300
Prior transplant	1.311	1.112–1.546	1.116	0.939–1.326
Prior days in ICU	1.004	1.003–1.006	0.998	0.995–1.000
Prior mechanical ventilation	1.463	1.315–1.627	1.391	1.237–1.565
Admission source				
Non-healthcare point of origin	Ref		Ref	
Clinic	0.743	0.618–0.894	0.766	0.660–0.890
Other healthcare facility	1.138	0.963–1.344	1.161	1.021–1.320
Other	0.970	0.820–1.146	0.981	0.831–1.157
Prior antibiotic use (days)				
Penicillins	1.009	1.006–1.013	1.004	1.001–1.008
Cephalosporins	1.006	1.004–1.009	1.001	0.998–1.004
Carbapenems	1.006	1.004–1.008	1.003	1.000–1.005
Monobactams	1.002	1.001–1.003	0.999	0.997–1.002
Polymyxins	1.010	1.007–1.013	1.001	0.998–1.004
Anti-MRSA agents	1.003	1.002–1.004	0.999	0.997–1.001
Aminoglycosides	1.006	1.004–1.008	1.001	0.999–1.004
Tetracyclines	1.008	1.005–1.010	1.004	1.002–1.006
Macrolides	1.005	1.003–1.007	1.001	0.998–1.004
Fluoroquinolones	1.007	1.004–1.009	1.002	0.998–1.005
Other	1.004	1.002–1.006	1.004	1.001–1.006

^a Adjusted for all other potential confounders shown in table.

Table 4Crude and adjusted risk ratios of having a drug resistant *P. aeruginosa*.

	Crude		Adjusted^a	
	RR	95% CI	RR	95% CI
Number of infections	1.242	1.141–1.352	1.136	1.038–1.244
Prior biopsy	1.205	1.042–1.394	1.115	0.956–1.300
Prior transplant	1.311	1.112–1.546	1.116	0.939–1.326
Prior days in ICU	1.004	1.003–1.006	0.998	0.995–1.000
Prior mechanical ventilation	1.463	1.315–1.627	1.391	1.237–1.565
Admission source				
Non-healthcare point of origin	Ref		Ref	
Clinic	0.743	0.618–0.894	0.766	0.660–0.890
Other healthcare facility	1.138	0.963–1.344	1.161	1.021–1.320
Other	0.970	0.820–1.146	0.981	0.831–1.157
Prior antibiotic use (days)				
Penicillins	1.009	1.006–1.013	1.004	1.001–1.008
Cephalosporins	1.006	1.004–1.009	1.001	0.998–1.004
Carbapenems	1.006	1.004–1.008	1.003	1.000–1.005
Monobactams	1.002	1.001–1.003	0.999	0.997–1.002
Polymyxins	1.010	1.007–1.013	1.001	0.998–1.004
Anti-MRSA agents	1.003	1.002–1.004	0.999	0.997–1.001
Aminoglycosides	1.006	1.004–1.008	1.001	0.999–1.004
Tetracyclines	1.008	1.005–1.010	1.004	1.002–1.006
Macrolides	1.005	1.003–1.007	1.001	0.998–1.004
Fluoroquinolones	1.007	1.004–1.009	1.002	0.998–1.005
Other	1.004	1.002–1.006	1.004	1.001–1.006

^a Adjusted for all other potential confounders shown in table.