Antimicrobial resistance prevalence and rates of hospitalization with septicemia in the diagnosis in adults in different US states

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Abstract

Background: Rates of hospitalization with sepsis and septicemia in the US have risen significantly during the last two decades, and changes in diagnostic practices don't fully explain that rise. Antibiotic resistance may contribute to the rates of sepsis/septicemia hospitalization through lack of clearance of bacterial infections following antibiotic treatment during different stages of infection. At the same time, there is limited information about the relation between prevalence of resistance to various antibiotics in different bacteria and rates of hospitalizations with sepsis and septicemia.

Methods: For different age groups of adults (18-49y,50-64y,65-74y,75-84y,85+y) and combinations of antibiotics/bacteria, we evaluated associations between state-specific average annual rates of hospitalizations with septicemia (ICD-9 codes 038.xx present on the discharge diagnosis) in a given age group reported to the Healthcare Cost and Utilization Project (HCUP) between 2011-2012, and state-specific prevalence (percentage) of resistant samples for a given combination of antibiotics/bacteria among catheter-associated urinary tract infections in the CDC Antibiotic Resistance Patient Safety Atlas data between 2011-2014.

Results: Prevalence of resistance to fluoroquinolones in *E. coli* had the strongest association with septicemia hospitalization rates for adults aged over 50y. A number of positive correlations between prevalence of resistance for different combinations of antibiotics/bacteria and septicemia hospitalization rates in adults were also found.

Conclusions: Our findings about the relation between prevalence of resistance to commonly prescribed antibiotics, particularly fluoroquinolones, and rates of septicemia hospitalization in US adults stress the need for enhancing antibiotic stewardship in different settings, especially for fluoroquinolones, preventing acquisition of antibiotic-resistant bacteria, and new antibiotics.

Introduction

Rates of hospitalization with septicemia or sepsis, as well as associated mortality and monetary costs, have been rising rapidly during the past decades in the US [1-4]. While changes in diagnostic practices have contributed to the rise in the rates of hospitalization with septicemia/sepsis in the diagnosis [5,6], those changes cannot fully explain that rise in hospitalization rates, particularly prior to 2010 [7]. Antibiotic resistance may also contribute to septicemia/sepsis hospitalization rates. The relation between infections with antibiotic-resistant bacteria and survival for sepsis, including the effect of initially appropriate antibiotic therapy (IAAT) is suggested by a number of studies [8,9]. However, less is known about the relation between prevalence of antibiotic resistance and rates of hospitalization with septicemia. Antimicrobial resistance and use can contribute to the volume of hospitalizations associated with bacterial infections, including sepsis, through several mechanisms. Importantly, antibiotic resistance can facilitate the progression to a severe disease state when infections not cleared by antibiotics prescribed during both the outpatient and the inpatient treatment eventually devolve into sepsis. For example, antibiotic resistance in Enterobacteriaceae, including fluoroquinolone resistance in *Escherichia coli* was found to be associated with a more severe presentation in urinary tract infections [10,11]. Antibiotic use and resistance can also contribute to the overall increase in the prevalence of bacterial infections associated with certain pathogens (e.g. fluoroquinolone use and MRSA infections [12-15]), with those infections subsequently leading to severe illness episodes, including sepsis (e.g. [12-19]). We note that the relation between prevalence of antimicrobial resistance and rates of hospitalization with sepsis can be affected by a number of factors such as antibiotic prescription practices, which may change with time [20,21], and patterns of resistance to different antimicrobials, including cross-resistance [22,23]. This study represents a step towards demonstrating the relationship between prevalence of resistance and rates of hospitalization for septicemia/sepsis in the context of population-level data in the US. Here, we examine associations between state-specific prevalence of antibiotic resistance for different combinations of antibiotics/bacteria in hospitalized elderly and non-elderly adults documented in the US CDC National Healthcare Safety Network (NHSN) Antibiotic Resistance Patient Safety Atlas [24,25], and state-specific rates of hospitalization with septicemia(ICD-9 codes 038.xx present on the discharge diagnosis) in different age groups of adults recorded in the Healthcare Cost and Utilization Project (HCUP) data [26]. In the Discussion section, we draw a comparison between the practices of antibiotic use and their effect on the rates of hospitalization associated with bacterial infections in the US vs. the UK.

Methods

Hospitalizations with septicemia

We used weekly data between 2011-2012 on counts of hospitalizations with a septicemia diagnosis (both primary and contributing, [*ICD-9*] codes 038.xx) from the State Inpatient Databases of the Healthcare Cost and Utilization Project (HCUP), maintained by the Agency for Healthcare Research and Quality (AHRQ) through an active collaboration [26]. We will henceforth call these hospitalizations septicemia hospitalizations, even though some of them may involve low levels of bloodstream bacterial infection. This database contains hospital discharges from community hospitals in participating states. Forty-two states reported septicemia hospitalization data between 2011-2012 for each of the five adult age subgroups included in our analyses: (18-49y, 50-64y, 65-74y, 75-84y, 85+y). Those states are Alaska, Arkansas, Arizona, California, Colorado, Connecticut, Florida, Georgia, Hawaii, Iowa, Illinois, Indiana, Kansas, Kentucky, Louisiana, Massachusetts, Maryland, Minnesota, Missouri, Montana, North Carolina, North Dakota, Nebraska, New Jersey, New Mexico, Nevada, New York, Ohio, Oklahoma, Oregon, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Virginia, Vermont, Washington, Wisconsin, West Virginia, Wyoming. *Average annual* septicemia hospitalization rates between 2011-2012 per 100,000 individuals in each age group/state were then calculated from the septicemia hospitalization data and population estimates, obtained by linear interpolation of the annual, July 1 population estimates in [27].

Antibiotic resistance rates

We extracted data on the prevalence of antibiotic resistance for bacterial specimens collected from hospitalized patients in the US between 2011-2014 from the US CDC National Healthcare Safety Network (NHSN) Antibiotic Resistance Patient Safety Atlas [24,25]. Those data are stratified by age group (<1y,1-18y,19-64y,65+y), state, year, infection type (CAUTI/CLABSI/SSI, [24]), and combination of bacteria/antibiotics (31 combinations documented in [24]). Resistance prevalence varies by type of infection ([25]; Tables 6,7,9), making the combination of different types of infection into the analysis problematic. Moreover, for a given combination of bacteria/antibiotics, and a given type of infection, only a fraction of states reported the corresponding resistance pattern [24], with that fraction generally being highest for catheter-associated urinary tract infections (CAUTIs). For each combination of bacteria/antibiotics, age group of adults (19-64y or 65+y), and state that reported data on CAUTI samples between 2011-2014 for the given age group/combination of bacteria/antibiotics, the corresponding state-specific *prevalence of resistance* was defined as the percent of tested CAUTI samples collected between 2011-2014 for the given age group/state containing the corresponding bacteria that were resistant (or have

tested as either intermediate or resistant – see [24]) for the corresponding antibiotics. The four-year aggregation was done due to low yearly counts in a number of states.

Correlation analyses

For each age group of adults: (18-49y, 50-64y, 65-74y, 75-84y, 85+y), and a combination of bacteria/antibiotics, we have examined correlations, both linear (Pearson) and Spearman (Supporting Information), between the state-specific average annual septicemia hospitalization rates per 100,000 individuals in the given age group of adults between 2011-2012, and the state-specific prevalence of resistance in CAUTI samples (see the previous subsection) between 2011-2014 for the given combination of bacteria/antibiotics among the non-elderly or elderly adults correspondingly. We note that no septicemia hospitalization data beyond 2012 were available for this study.

Results

Figures 1-5 show the linear (Pearson) correlations between the state-specific prevalence (percentages) of antibiotic resistance for the different combinations of antibiotics/bacteria in the age-specific CAUTI samples in the CDC AR Atlas data [24] between 2011-14 and the state-specific average annual rates of hospitalizations between 2011-12 with septicemia in either the principal or secondary discharge diagnosis recorded in the HCUP data [26] per 100,000 individuals in the corresponding age group. For each age group, results are presented for those combinations of antibiotics/bacteria for which at least 10 states reported the corresponding data.

A large number of positive correlations between prevalence of antibiotic resistance and rates of septicemia hospitalization in different age groups of adults were found (Figures 1-5 and Supporting Information), with 66/69 of the point estimates for the studied correlations in adults aged over 65y being positive (Figures 1-3). A smaller number of negative point estimates for the correlations between prevalence of antibiotic resistance and rates of septicemia hospitalization were also found, particularly for adults aged under 65y (Figures 4-5). At the same time, none of these negative estimates reached statistical significance.

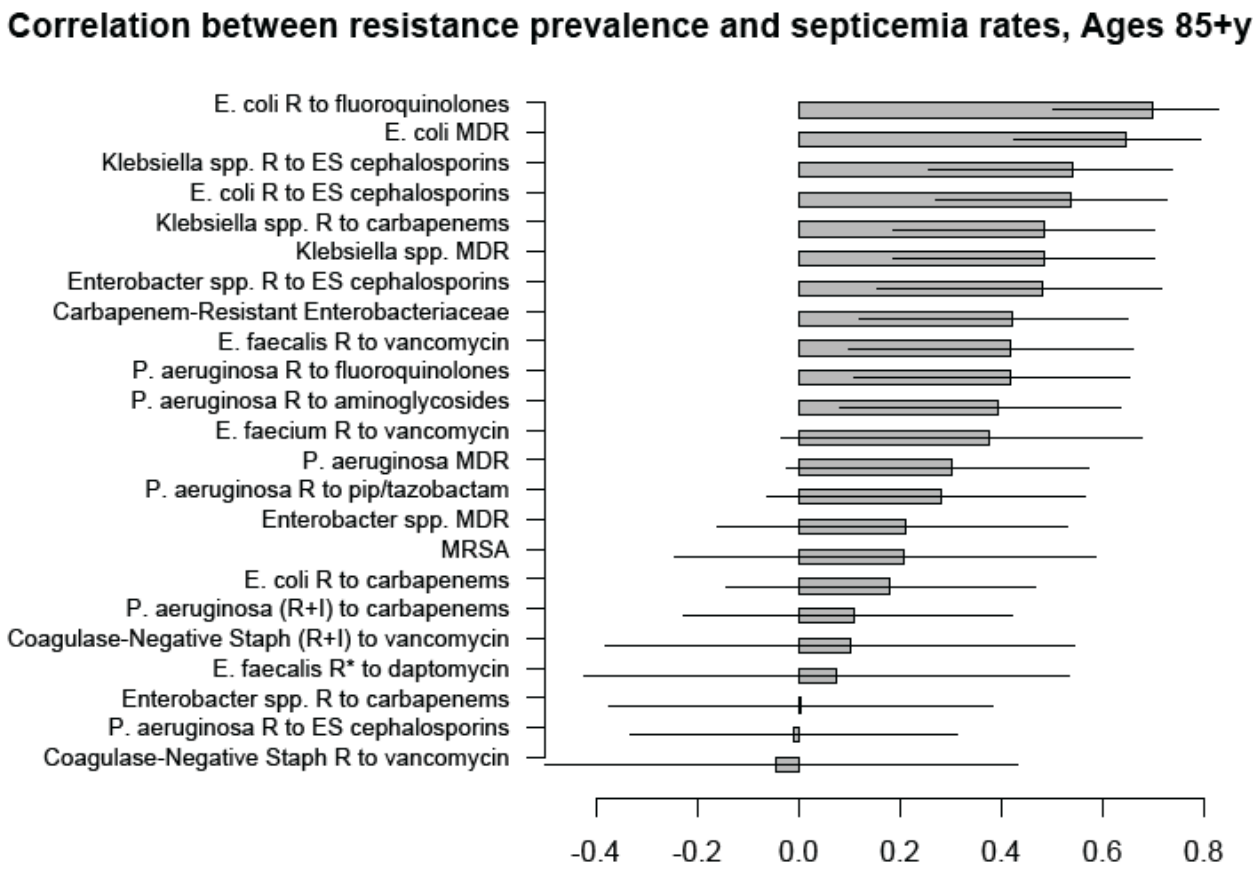

Figure 1: Correlation between state-specific prevalence (percentages) of resistance for different combinations of antibiotics/bacteria in CAUTI samples from hospitalized adults aged 65+y in the CDC AR Atlas data [24] between 2011-14 and state-specific average annual rates per 100,000 individuals aged 85+y of septicemia hospitalizations (principal or secondary diagnosis) recorded in the HCUP data [26].

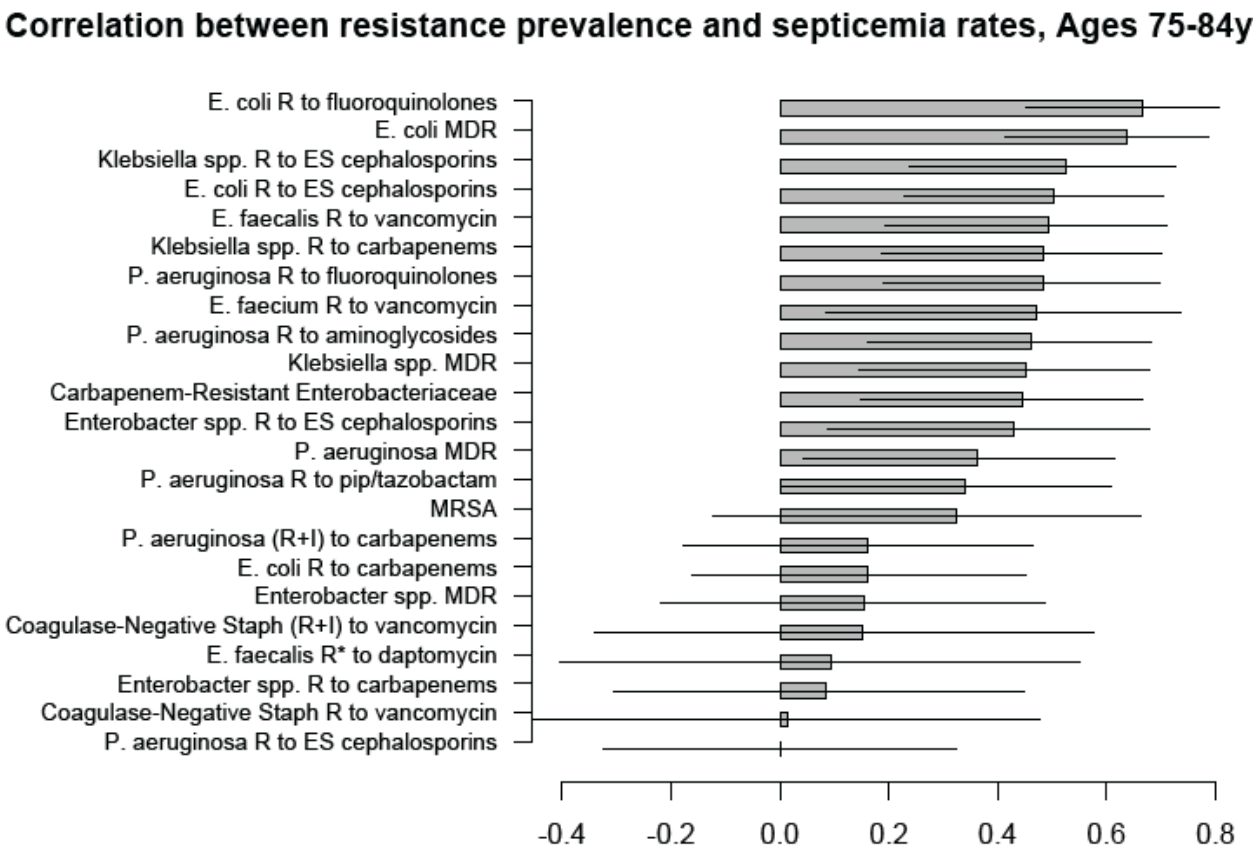

Figure 2: Correlation between state-specific prevalence (percentages) of resistance for different combinations of antibiotics/bacteria in CAUTI samples from hospitalized adults aged 65+y in the CDC AR Atlas data [24] between 2011-14 and state-specific average annual rates per 100,000 individuals aged 75-84y of septicemia hospitalizations (principal or secondary diagnosis) recorded in the HCUP data [26].

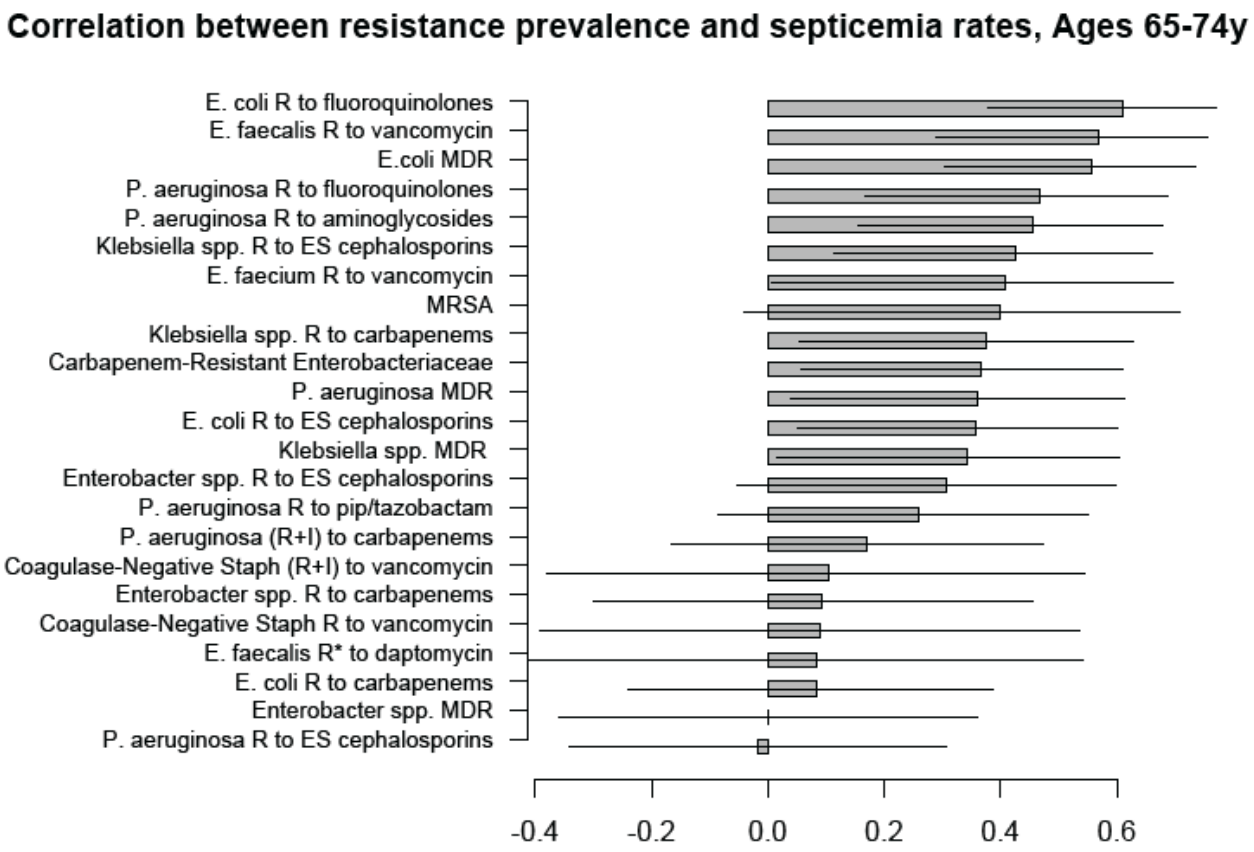

Figure 3: Correlation between state-specific prevalence (percentages) of resistance for different combinations of antibiotics/bacteria in CAUTI samples from hospitalized adults aged 65+y in the CDC AR Atlas data [24] between 2011-14 and state-specific average annual rates per 100,000 individuals aged 65-74y of septicemia hospitalizations (principal or secondary diagnosis) recorded in the HCUP data [26].

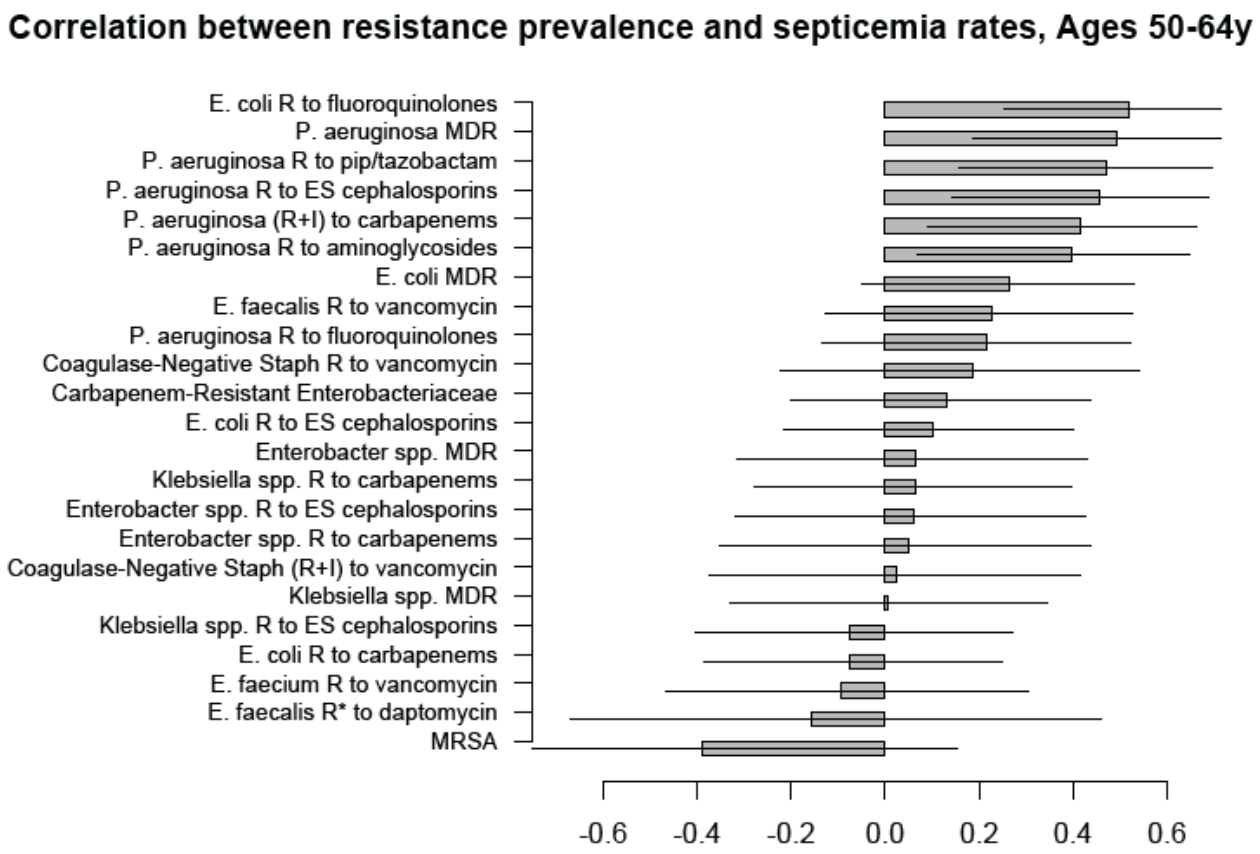

Figure 4: Correlation between state-specific prevalence (percentages) of resistance for different combinations of antibiotics/bacteria in CAUTI samples from hospitalized adults aged 19-64y in the CDC AR Atlas data [24] between 2011-14 and state-specific average annual rates per 100,000 individuals aged 50-64y of septicemia hospitalizations (principal or secondary diagnosis) recorded in the HCUP data [26].

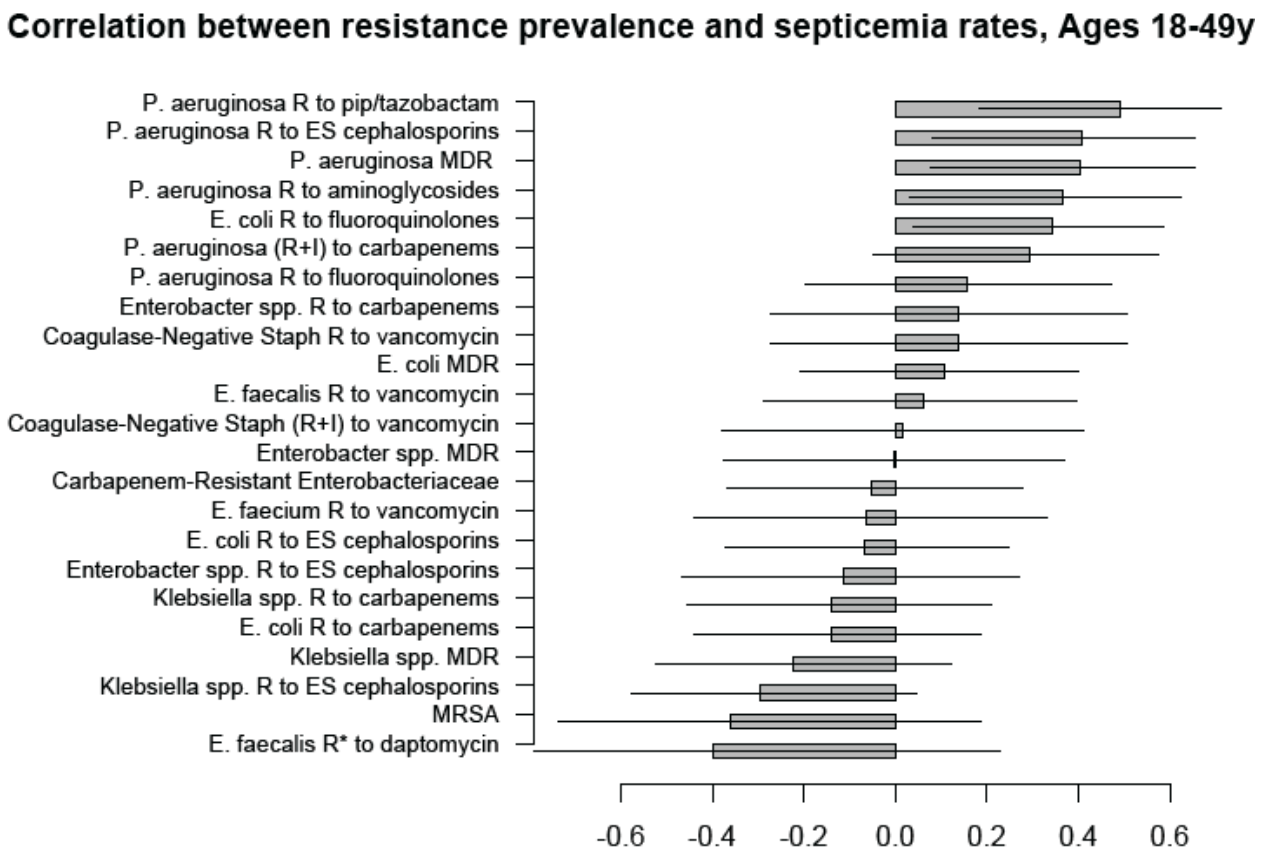

Figure 5: Correlation between state-specific prevalence (percentages) of resistance for different combinations of antibiotics/bacteria in CAUTI samples from hospitalized adults aged 19-64y in the CDC AR Atlas data [24] between 2011-14 and state-specific average annual rates per 100,000 individuals aged 18-49y of septicemia hospitalizations (principal or secondary diagnosis) recorded in the HCUP data [26].

Among the 23 combinations of antibiotics/bacteria in the CDC Atlas data [24] examined for each age group, resistance to fluoroquinolones in *E. coli* had the highest correlation with septicemia hospitalization rates in all age groups over 50y (Figures 1-4 and Supporting Information). Additionally, *E. coli* is a major source of Gram-negative septicemia in the US [1], and prevalence of resistance to fluoroquinolones in *E. coli* isolates in both urinary tract and bloodstream infections is high in the US [22,23,29,30]. Figure 6 plots the state-specific prevalence of resistance to fluoroquinolones in E*. coli* isolated in the CAUTI samples in the CDC AR Atlas data [24] in hospitalized adults aged 65+ years between 2011-2014 vs. state-specific average annual rates per 100,000 individuals aged 85+y of hospitalizations with septicemia in either the principal or secondary diagnosis recorded in the Healthcare Cost and Utilization Project (HCUP) database [26] between 2011-2012 for the 42 states included in our analyses (Methods). Figure 6 suggests significant variability in both the state-specific septicemia hospitalization rates and the prevalence of fluoroquinolone resistance in *E. coli*, as well as the strong correlation between the two (Cor=0.70, 95% CI(0.50,0.83)). We note that there may be substantial differences in diagnostic practices for septicemia between states. Nonetheless, Figure 6 suggests that there are significant

differences in the state-specific septicemia hospitalizations rates, as well as in the types of states that have low septicemia hospitalization rates compared to states that have high septicemia hospitalization rates (Discussion).

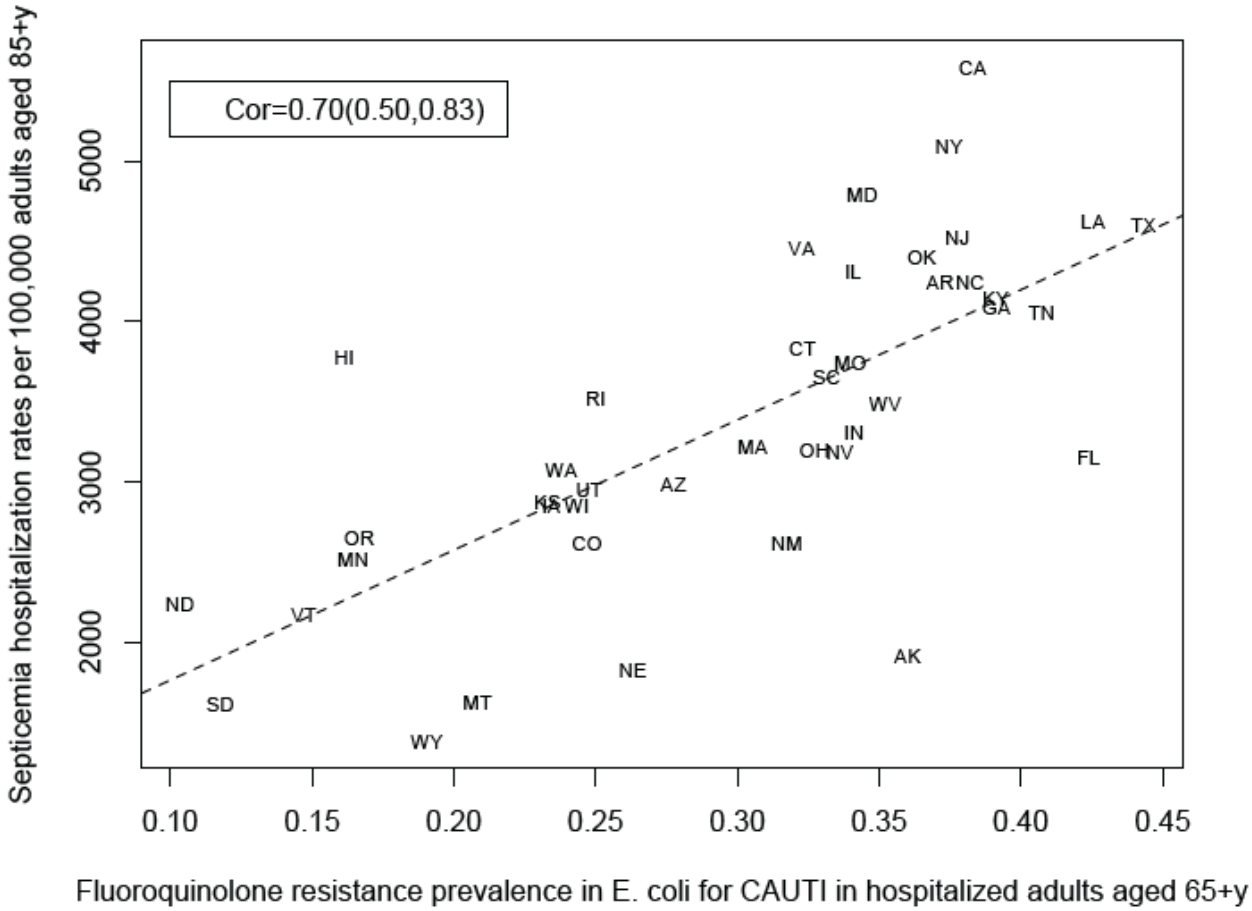

Figure 6 : State-specific prevalence (percentages) of resistance to fluoroquinolones in *E. coli* for CAUTI samples in hospitalized adults aged 65+y in the CDC AR Atlas data [24] between 2011-14 vs. state-specific average annual rates per 100,000 individuals aged 85+y of septicemia hospitalizations (principal or secondary diagnosis) recorded in the HCUP data [26] for the 42 states reporting septicemia hospitalization data between 2011-2012 (Methods).

We note that there is uncertainty regarding the causal links contributing to several of the correlations presented in Figures 1-5 – see also the 2nd paragraph of the Discussion, as well as the Supporting Information. Finer data are needed to better understand the causal nature of the correlations described in this paper.

Discussion

Rates of hospitalization with septicemia and sepsis in the diagnosis, and related mortality have risen significantly in last decades in the US [1-3], and that rise couldn't be fully explained by changes in diagnostic practices for sepsis [7]. Moreover, septicemia hospitalization rates vary a good deal by state (Supporting Information). In particular, states with the lowest septicemia hospitalization rates tend to be northern states with low population density, which may be suggestive of the differences in the rates of bacterial transmission between different states. Antimicrobial resistance can also contribute to the rates of hospitalization with septicemia (Introduction). The strength of the relation between prevalence of antibiotic resistance and rates of septicemia hospitalization depends on a number of factors, including patterns of antibiotic use and patterns of resistance to different antibiotics. In this study, we examine the relation between prevalence of antibiotic resistance and rates of septicemia hospitalization in the US context. For several age groups of adults, and a number of combinations of bacteria/antibiotics, we evaluate the correlations between the state-specific prevalence of resistance in catheter-associated urinary tract infection (CAUTI) samples in the CDC AR Safety Atlas data [24] and state-specific rates of hospitalizations with septicemia present in the discharge diagnosis in the HealthCare Cost and Utilization Project (HCUP) data [26]. Our results suggest that the state-specific prevalence of resistance to several antibiotics in different bacteria is positively correlated with the rates of hospitalization with septicemia in the diagnosis in different age groups of adults. For each subgroup of adults aged 50+y, the highest effect size found in our correlation analyses is for the prevalence of fluoroquinolone resistance in *E. coli* and rates of hospitalization with septicemia. Additionally, *E. coli* is the most common source of septicemia among the bacteria covered by the AR Atlas data [1,24], and prevalence of resistance to fluoroquinolones in *E. coli* isolates in both urinary tract and bloodstream infections is high in the US [22,23,29,30]. We note that the positive correlations found in our analyses can be affected by several factors including the pairwise correlation between the state-specific prevalence of resistance for different combinations of antibiotics/bacteria as discussed in the next paragraph.

A possible contributing factor to the correlations that we found is the association between state-specific prevalence of resistance for different pairs of combinations of antibiotics/bacteria. Section S2 of the Supporting Information presents those associations for a number of pairs of combinations of antibiotics/bacteria covered by the CDC Antibiotic Patient Safety Atlas [24]. Prevalence of resistance for certain combinations of antibiotics/bacteria not covered by the CDC Atlas data [24] could have also contributed to the correlations found in our analysis. For example, for *E. coli*-associated UTIs recorded in the Veterans Affairs data [23], prevalence of resistance to ampicillin/amoxicillin was higher than prevalence of resistance to fluoroquinolones, and prevalence of resistance to trimethoprim/sulfamethoxazole was also high. Additionally, significant associations between presence of resistance to different antibiotics in the samples in [23] were found. Thus the correlation between the prevalence of fluoroquinolone resistance in *E. coli* and rates of septicemia hospitalization found in this paper could have been affected not only by the contribution of fluoroquinolone resistance in *E. coli* to the rates of septicemia hospitalization, but also by (i) the contribution of resistance to other antibiotics in *E. coli*, including amoxicillin and

trimethoprim/sulfamethoxazole, (ii) the contribution of resistance to fluoroquinolones, and possibly other antibiotics in different bacteria that cause septicemia hospitalization. The overall conclusion supported by our findings is that resistance to different antibiotics in different bacteria (including drug resistance in *E. coli*) contributes to the rates of hospitalization for septicemia/sepsis in the US.

The findings in this paper, as well as other work, e.g. [10-19] lead to the question whether antibiotic stewardship and replacement of certain antibiotics by others could bring about a reduction in the rates of severe bacterial infections, including sepsis. Some evidence to that effect is provided by the reduction in fluoroquinolone and cephalosporin prescribing in the UK after 2006. Fluoroquinolone use and resistance was found to be associated with MRSA acquisition [12-15]. The drop in the rates of MRSA bacteremia in England between 2006-2011 was sharper than the decline in the rates of MRSA invasive disease in the US during the same period, particularly for the community-associated infections (compare Figures 1 and 3 in [31] with [32]). Moreover, rates of outpatient fluoroquinolone prescribing to US adults were stable between 2000-2010 [21], and stable in older adults between 2011-2014 [33]. Additionally, prevalence of fluoroquinolone (levofloxacin) non-susceptibility in community-associated MRSA isolates in the US in the recent years was high [34]. The discrepancy in the trends in outpatient fluoroquinolone prescribing in the US vs. UK may partly explain why the rates of community-associated invasive MRSA infections in the US were stable between 2005-2011 [32], while the rates of community-acquired MRSA bacteremia in the UK dropped by more than half after 2006 (Figures 1 and 3 in [31]). For severe bacterial infection other than sepsis, reduction in fluoroquinolone and cephalosporins prescribing in England between 2006-2013 was associated with about 75% reduction in the rates of *C. difficile* infections (and even greater reduction in the rates of *C. difficile*-associated deaths) [19,31,35]. In the US, rates of *C. difficile* infections continued to increase between 2006-2011 [36]. For the later time period, a recent US study reported a 17.5% decrease in the incidence rates of long-term-care onset *C. difficile* infection in 10 US sites between 2011-2015 (concomitant with the ongoing decrease in inpatient fluoroquinolone use [37,20]), which is an encouraging reversal of the earlier trends in the incidence of *C. Difficile* infection [36].

Recent FDA guidelines have recommended the restriction of fluoroquinolone use for certain conditions (such as uncomplicated urinary tract infections) due to potential adverse effects [38]. It remains to be seen what would be the effect of those recommendations on fluoroquinolone use, particularly in the outpatient setting, prevalence of fluoroquinolone resistance and the rates of associated severe outcomes. Moreover, that effect is potentially specific to an organism, and antibiotics used to replace fluoroquinolones. For example, levels of *E. coli* and *Klebsiella*-associated bacteremia were continuing to rise in England after 2006 while reduction in fluoroquinolone and cephalosporin use was taking place [39,31]. Amoxicillin-clavulanate (co-amoxiclav) prescribing in England increased significantly between 2006-2011 [40], and incidence of bacteremia with *E. coli* strains resistant to co-amoxiclav began to increase rapidly after 2006 ([41], Figure 4), with co-amoxiclav resistance in *E. coli*-associated bacteremia exceeding 40% in 2014 [42]. Furthermore,

prevalence of co-amoxiclav resistance in *E. coli*-associated bacteremia in England is more than twice as high as the prevalence of co-amoxiclav resistance in *E. coli*-associated UTIs [42], which is also suggestive of the role of co-amoxiclav resistance in progressing to the more severe outcomes resulting from *E. coli* infections. Data for *E. coli*-associated UTIs in the US [23] suggest that prevalence of resistance varies significantly by antibiotic type, with the highest prevalence of resistance in [23] being for amoxicillin, ampicillin/beta-lactamese inhibitor and fluoroquinolones, with prevalence of resistance in [23] being notably lower for narrow spectrum antibiotics such as nitrofurantoin. We also note the recent update in the UK prescribing guidelines for urinary tract infections (UTIs), with nitrofurantoin generally recommended as the first-line option [43]. The data in [23], as well as the experience from England support the notion that antibiotic prescribing guidelines that account for resistance patterns to different antibiotics for various types of bacterial infection are needed to better control the rates of sepsis and other severe bacterial infections.

Our study has some limitations. The data in [24] do not contain information on several bacteria that are important sources of septicemia (e.g. MSSA and Streptococci), and resistance to several types of antibiotics (e.g. macrolides and animopenicillins). No significant correlations between prevalence of MRSA among staphylococci, or prevalence of resistance to different antibiotics in MRSA and septicemia hospitalization rates were found, though this may partly stem from the fact that staphylococci are rarely found in urinary samples, with relatively few states reporting data on MRSA in CAUTI samples in [24] (Tables S12-S16 in the Supporting Information). While the HCUP data utilized in our study generally cover about 97% of all community hospitalizations in the US [26], state-specific variability in the proportion of septicemia hospitalizations that are covered by the HCUP data is possible. Additionally, diagnostic practices for septicemia vary by state. Moreover, we studied correlations between septicemia hospitalization rates in various subgroups of the elderly (e.g. aged 74-85y) and non-elderly adults and prevalence of antibiotic resistance in CAUTI samples from elderly (aged 65+y) or non-elderly (aged 19-64y) hospitalized adult patients correspondingly. Finally, data on antimicrobial resistance were available for the 2011-2014 period [24], with low counts/missing data for some combinations of bacteria/antibiotics in certain states during certain years; data on septicemia hospitalizations were available through the end of 2012. Correspondingly, we studied correlations between the state-specific prevalence of antibiotic resistance between 2011-2014 and septicemia hospitalization rates between 2011-2012. We expect that those sources of noise/incompatibility should generally bias the correlation estimates towards the null, reducing precision rather than creating spurious associations.

We believe that despite those limitations, our paper makes a contribution towards demonstrating the effect of the prevalence of resistance to commonly prescribed antibiotics on the rates of septicemia hospitalization in adults. Our results support the need for (i) enhancing antibiotic stewardship (including the use of fluoroquinolones [44]), both in the inpatient and the outpatient settings [45]; (ii) linking antibiotic prescription guidelines for various syndromes to data on the prevalence of antibiotic resistance; (iii) stepping up efforts for preventing acquisition of antibiotic-resistant bacteria (particularly *E. coli* in the elderly) [46,47]. Additionally, the relation between

antibiotic resistance as well as antibiotic use and the rates of bacterial infections, including sepsis [10-19], and the limited options for antibiotic replacement support the need for new antibiotics. This need may not be fulfilled through the current system of antibiotic development/production, and additional incentives for antibacterial research and development are worth considering [48].

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