



Antimicrobial resistance prevalence, rates of hospitalization with septicemia and rates of mortality with sepsis in adults in different US states [☆]

Edward Goldstein ^{a,*}, Derek R. MacFadden ^a, Zeynal Karaca ^b, Claudia A. Steiner ^{b,1}, Cecile Viboud ^c, Marc Lipsitch ^{a,d}

^a Center for Communicable Disease Dynamics, Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA 02115 USA

^b Agency for HealthCare Research and Quality, U.S. Department of Health & Human Services, Rockville, MD 20850 USA

^c Division of International Epidemiology and Population Studies, Fogarty International Center, National Institutes of Health, Bethesda, MD 20892 USA

^d Department of Immunology and Infectious Diseases, Harvard TH Chan School of Public Health, Boston, MA 02115 USA

ARTICLE INFO

Article history:

Received 18 September 2018

Accepted 2 March 2019

Editor: Geoffrey Coombs

Keywords:

Antibiotic resistance
sepsis
septicemia
mortality
fluoroquinolones
E. coli

ABSTRACT

Objectives: Rates of hospitalization with sepsis/septicemia and associated mortality in the US have risen significantly during the last two decades. Antibiotic resistance may contribute to the rates of sepsis-related outcomes through lack of clearance of bacterial infections following antibiotic treatment during different stages of infection. However, there is limited information about the relationship between prevalence of resistance to various antibiotics in different bacteria and rates of sepsis-related outcomes.

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 prevalence (percentage) of resistant samples for a given combination of antibiotics/bacteria among catheter-associated urinary tract infections (CAUTIs) in the CDC Antibiotic Resistance Patient Safety Atlas data between 2011–2014, and rates of hospitalization with septicemia (ICD-9 codes 038.xx present on the discharge diagnosis) reported to the Healthcare Cost and Utilization Project (HCUP), as well as rates of mortality with sepsis (ICD-10 codes A40–41.xx present on death certificate).

Results: Among the different combinations of antibiotics/bacteria, prevalence of resistance to fluoroquinolones in *Escherichia coli* had the strongest association with septicemia hospitalization rates for individuals aged over 50y, and with sepsis mortality rates for individuals aged 18–84y. There were several positive correlations between prevalence of resistance for different combinations of antibiotics/bacteria and septicemia hospitalization/sepsis mortality rates in adults.

Conclusions: These findings, and those from work on the relationship between antibiotic use and sepsis rates, support the association between use of/resistance to certain antibiotics and rates of sepsis-related outcomes, indicating the potential utility of antibiotic replacement.

© 2019 Elsevier B.V. and International Society of Chemotherapy. All rights reserved.

1. Introduction

Rates of hospitalization with septicemia (ICD-9 codes 038.xx) and associated mortality and monetary costs have risen rapidly during the last few decades in the US [1–4]. Although changes

in diagnostic practices have contributed to the rise in rates of hospitalization with septicemia/sepsis in the diagnosis [5,6], these changes cannot fully explain the increase in hospitalization rates, particularly prior to 2010 [7]. Indeed, trends in the rates of US hospitalizations with any diagnosis of sepsis between 2003 and 2009 closely resemble the trends in rates of hospitalizations that involved infection and the use of mechanical ventilation (Fig. 1 in [7]). Rates of hospitalization with severe sepsis in the US also increased quite rapidly between 2008 and 2012; the proportion of those hospitalizations with multiple organ failure also increased [8], which indicates the rise in hospitalizations was genuine.

Antibiotic resistance contributes to the rates of septicemia/sepsis hospitalization and associated mortality. Several

[☆] Competing interests: Dr. Lipsitch reports grants from NIH/NIGMS, during the conduct of the study; personal fees from Affinivax, personal fees from Merck, grants and personal fees from Pfizer, grants from PATH Vaccine Solutions, outside the submitted work. The other authors report no conflicts of interest.

* Corresponding author: ph: 1-650-922-2408, fax: 1-617-432-8077; address: 677 Huntington Ave, Kresge Room 506, Boston, MA 02115 USA.

E-mail address: egoldste@hsph.harvard.edu (E. Goldstein).

¹ Present address: Claudia A. Steiner, Institute for Health Research, Kaiser Permanente, Colorado, Denver, CO 80231 USA

Correlation between resistance prevalence and septicemia rates, Ages 85+y

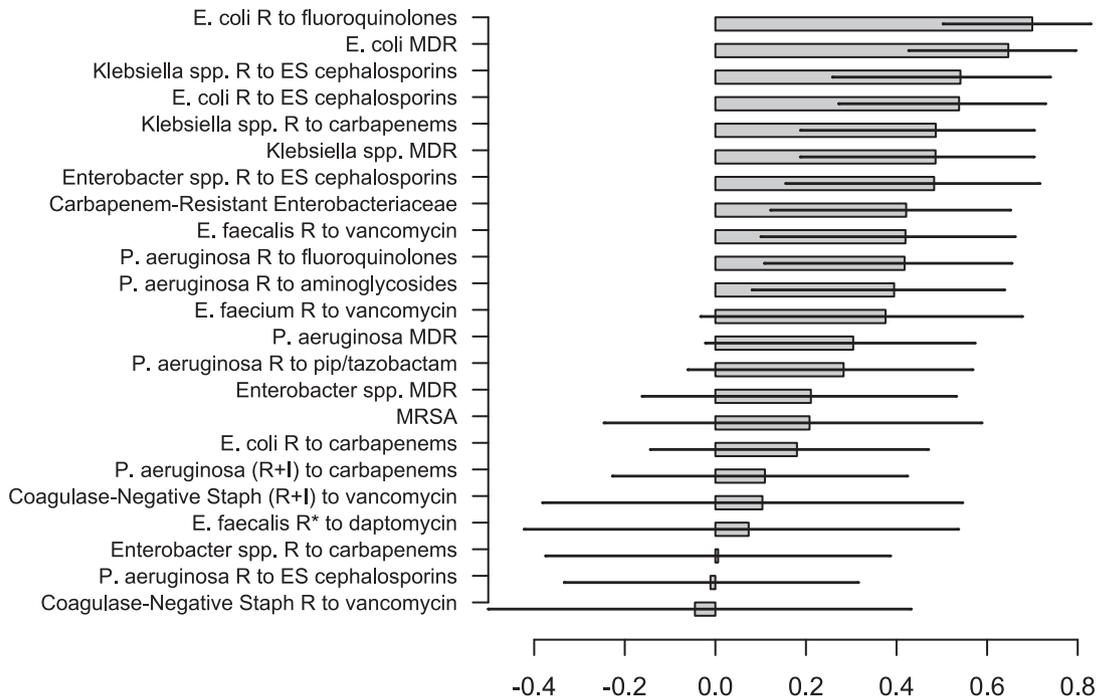


Fig. 1. Correlation between state-specific prevalence (percentages) of resistance for different combinations of antibiotics/bacteria in CAUTI samples from hospitalized individuals aged 65+y in the CDC Antibiotic Resistance Atlas data [21], 2011–14 and state-specific average annual rates per 100 000 individuals aged 85+y of septicemia hospitalizations (principal or secondary diagnosis) recorded in the HCUP data [22], 2011–12.

studies indicate a relationship between infections with antibiotic-resistant bacteria and survival for sepsis, including the effect of initially appropriate antibiotic therapy (IAAT) [9]. However, less is known about the relationship between prevalence of antibiotic resistance and rates of hospitalization with septicemia. Antimicrobial use and resistance can contribute to the volume of hospitalizations associated with bacterial infections, including septicemia and severe sepsis, through several mechanisms. Importantly, antibiotic resistance can facilitate progression to a severe disease state, when infections not cleared by antibiotics prescribed during outpatient and inpatient treatment eventually devolve into sepsis and associated lethal outcomes. More direct evidence for the relationship between antibiotic resistance and subsequent hospitalization with severe infections, including bacteremia/sepsis, is described in [10,11]. For example, prevalence of resistance to certain antimicrobials, including ciprofloxacin and trimethoprim, was found to be significantly higher in bacteremia outcomes associated with urinary tract infections (UTIs) than in the population of patients with UTIs in England [10], which indicates treatment failure is an important factor in UTI-associated bacteremia. Another study documented an association between trimethoprim resistance, trimethoprim use in UTI treatment and subsequent UTI-related bacteremia in England [12]. An association between amoxicillin use in England and prevalence of trimethoprim resistance (likely modulated by high rates of cross-resistance) has been shown [13]. The latter is an example of how use of/resistance to one antibiotic affects the prevalence of other resistance phenotypes, or pathogenic organisms. Further examples include the relationship between fluoroquinolone use/resistance and (i) methicillin-resistant staphylococcus aureus (MRSA) infections [14,15]; (ii) extended-spectrum beta-lactamase (ESBL)-producing infections [16,17]; and (iii) *Clostridium difficile* infections [18].

In related work [19,20], we studied the relationship between population-level prescribing of different antibiotic types/classes and rates of septicemia/bacteremia hospitalization and sepsis mortality, showing an association between the use of penicillins and (a) rates of septicemia hospitalizations and sepsis mortality in older US adults; and (b) rates of *Escherichia coli* and methicillin-sensitive staphylococcus aureus (MSSA) bacteremia in England. The current work represents another population-level study, examining the relationship between prevalence of resistance for different combinations of bacteria/antibiotics and rates of hospitalization with septicemia and mortality with sepsis in US adults. Specifically, 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 [21], and (a) state-specific rates of hospitalization with septicemia (ICD-9 codes 038.xx present on a discharge diagnosis) in different age groups of adults recorded in the Healthcare Cost and Utilization Project (HCUP) data [22]; and (b) state-specific rates of mortality with sepsis (ICD-10 codes A40–41.xx present on a death certificate) in different age groups of adults recorded in the US CDC Wonder data [23]. The aim of this work, and the analyses in [19,20], is to provide further evidence that use of/resistance to certain antibiotics is associated with sepsis-related outcomes.

2. Materials and Methods

2.1. Hospitalizations with septicemia and mortality with sepsis

We used weekly data between 2011 and 2012 on counts of hospitalizations with a septicemia discharge diagnosis (both primary and contributing, ICD-9 codes 038.xx) from the State In-

patient Databases of the HCUP, maintained by the Agency for Healthcare Research and Quality (AHRQ) through an active collaboration [22]. These hospitalizations will be referred to as 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 and 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, and Wyoming.

Data on annual state-specific mortality with sepsis (ICD-10 codes A40–A41.xx representing either the underlying or a contributing cause of death) for the 50 US states and District of Columbia between 2013 and 2014 for different age groups of adults (18–49y, 50–64y, 65–74y, 75–84y, 85+y) were extracted from the US CDC Wonder database [23]. Average annual septicemia hospitalization rates between 2011 and 2012, and average annual sepsis mortality rates between 2013 and 2014 per 100 000 individuals in each age group/state were then calculated from the septicemia hospitalization/sepsis mortality data and population estimates, taken to be the annual, July 1 population estimates in [24]. The ICD-9 code 038.xx (septicemia) has no exact analogue in the ICD-10 coding system; however, the majority of hospitalizations with septicemia have the 038.9 code (unspecified septicemia) on the discharge diagnosis. This code translates to A41.9 (sepsis, unspecified organism) in the ICD-10 coding system. The A41.9 code appears in the majority of deaths with sepsis (ICD-10 codes A40–41.xx listed on the death certificate).

Ethics statement: Aggregate hospitalization and mortality data were used in our analyses, with no informed consent from participants sought.

2.2. Antibiotic resistance prevalence

We extracted data on the prevalence of antibiotic resistance for bacterial specimens collected from hospitalized patients in the US between 2011 and 2014 from the US CDC NHSN Antibiotic Resistance Patient Safety Atlas (AR Atlas) [21]. These data are stratified by age group (<1y, 1–18y, 19–64y, 65+y), state, year, infection type (catheter-associated urinary tract infection [CAUTI]/central line-associated bloodstream infection [CLABSI]/surgical site infection [SSI], [21]), and combination of bacteria/antibiotics (31 combinations documented in [21]). Resistance prevalence in [21] varies by type of infection, 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 [21], with that fraction generally being highest for 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 percentage 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 [21]) for the corresponding antibiotics. The four-year aggregation was done due to low (or non-specified) yearly counts in several states.

2.3. 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 examined correlations, both linear (Pearson) and Spearman (Supporting Information), between (i) the state-specific average annual septicemia hospitalization rates per 100 000 individuals in the given age group of adults, 2011–2012; (ii) the state-specific average annual sepsis mortality rates per 100 000 individuals in the given age group of adults, 2013–2014 and the state-specific prevalence of resistance in CAUTI samples (see previous subsection), 2011–2014 for the given combination of bacteria/antibiotics among the non-elderly or elderly adults correspondingly. For each age group and sepsis-related outcome (septicemia hospitalizations or sepsis mortality), the above correlations were computed for those combinations of antibiotics/bacteria for which at least 10 states reported the corresponding data. There were no available septicemia hospitalization data beyond 2012 for this study, and the two most recent years (2013–2014) were used for the mortality data because of potential changes in coding for sepsis mortality on death certificates [25]. We also note that CAUTIs represent only a small fraction of all septicemia hospitalizations/subsequent sepsis mortality. Nonetheless, prevalence of resistance in CAUTI samples was used as a proxy for the statewide prevalence of resistance in different settings, under the premise that this source of noise should generally bias the correlation estimates towards the null, rather than create spurious associations.

3. Results

Figs. 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 Antibiotic Resistance Patient Safety Atlas (CDC AR Atlas) data [21], 2011–14 and the state-specific average annual rates of hospitalizations, 2011–12 with septicemia in either the principal or secondary discharge diagnosis recorded in the HCUP data [22] per 100 000 individuals in the corresponding age group. Figs. 6–10 present the linear correlations between the state-specific prevalence of antibiotic resistance [21] and rates of sepsis mortality [23], 2013–14 in different age groups of adults. All the correlations are presented for those combinations of antibiotics/bacteria and age group for which at least 10 states reported the corresponding data. More detailed results of the correlation analyses, including Spearman correlations between prevalence of resistance and rates of sepsis-related outcomes, are presented in the Supporting Information.

Many positive correlations were found between prevalence of antibiotic resistance and rates of septicemia hospitalization/sepsis mortality in different age groups of adults, particularly older adults (Figs. 1–10 and Supporting Information), with 66/69 point estimates for the studied correlations for hospitalization data in individuals aged over 65y and 69/75 point estimates for the studied correlations for mortality data in individuals aged over 65y being positive (Figs. 1–10). Although 99 of the positive estimates for the studied correlations reached nominal statistical significance (48 for hospitalizations and 51 for mortality, uncorrected for multiple comparisons), none of the negative estimates for the studied correlations were statistically significant.

Among the 23–25 combinations of antibiotics/bacteria in the CDC AR Atlas data [21] included in the analyses for the different age groups/sepsis-related outcomes (septicemia hospitalization or sepsis mortality), prevalence of resistance to fluoroquinolones in *E. coli* had the highest correlation with septicemia hospitalization rates in all age groups over 50y, and the highest correlation

Correlation between resistance prevalence and septicemia rates, Ages 75-84y

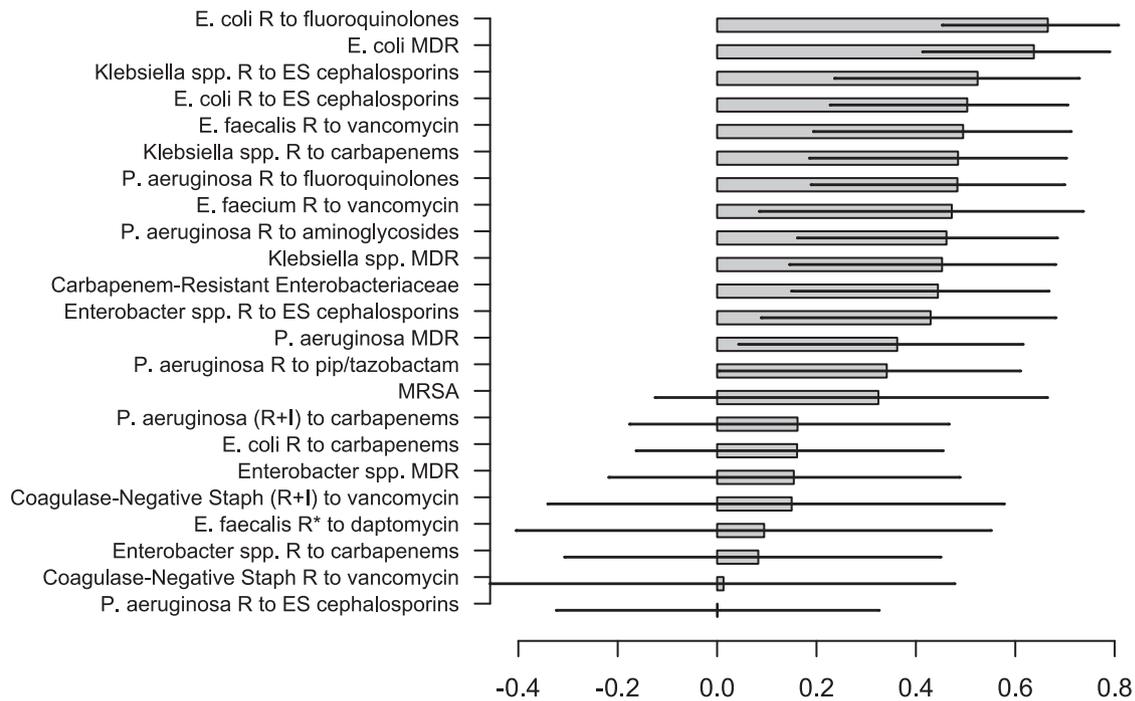


Fig. 2. Correlation between state-specific prevalence (percentages) of resistance for different combinations of antibiotics/bacteria in CAUTI samples from hospitalized individuals aged 65+y in the CDC Antibiotic Resistance Atlas data [21], 2011-14 and state-specific average annual rates per 100 000 individuals aged 75-84y of septicemia hospitalizations (principal or secondary diagnosis) recorded in the HCUP data [22], 2011-12.

Correlation between resistance prevalence and septicemia rates, Ages 65-74y

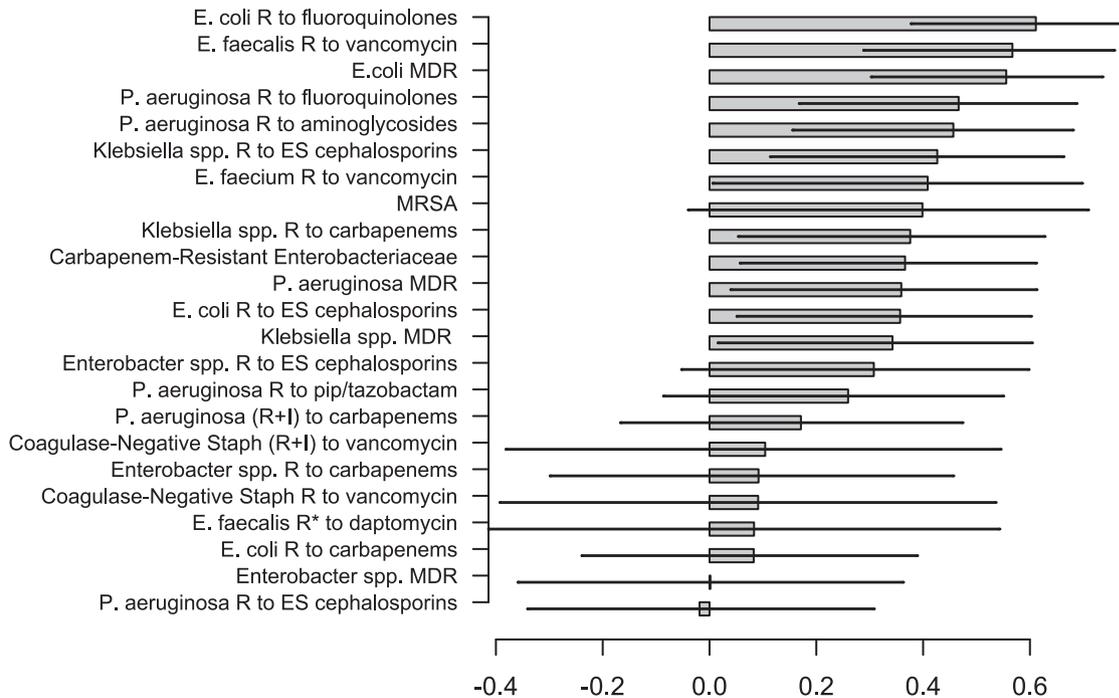


Fig. 3. Correlation between state-specific prevalence (percentages) of resistance for different combinations of antibiotics/bacteria in CAUTI samples from hospitalized individuals aged 65+y in the CDC Antibiotic Resistance Atlas data [21], 2011-14 and state-specific average annual rates per 100 000 individuals aged 65-74y of septicemia hospitalizations (principal or secondary diagnosis) recorded in the HCUP data [22], 2011-12.

Correlation between resistance prevalence and septicemia rates, Ages 50-64y

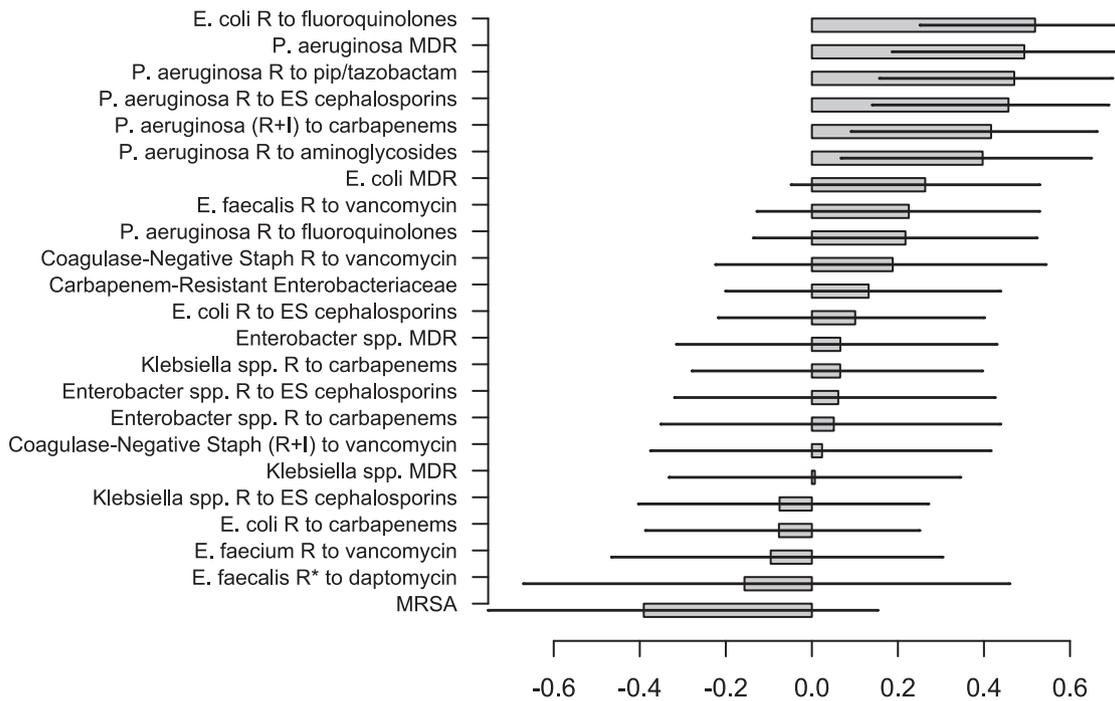


Fig. 4. Correlation between state-specific prevalence (percentages) of resistance for different combinations of antibiotics/bacteria in CAUTI samples from hospitalized individuals aged 19-64y in the CDC Antibiotic Resistance Atlas data [21], 2011-14 and state-specific average annual rates per 100 000 individuals aged 50-64y of septicemia hospitalizations (principal or secondary diagnosis) recorded in the HCUP data [22], 2011-12.

Correlation between resistance prevalence and septicemia rates, Ages 18-49y

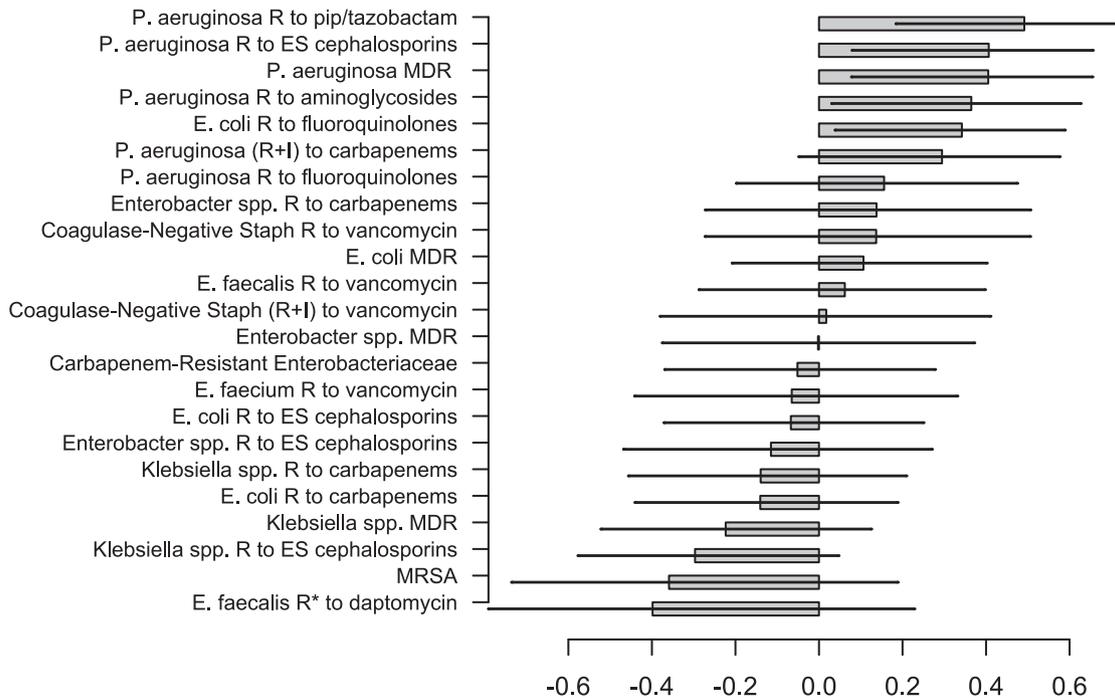


Fig. 5. Correlation between state-specific prevalence (percentages) of resistance for different combinations of antibiotics/bacteria in CAUTI samples from hospitalized individuals aged 19-64y in the CDC Antibiotic Resistance Atlas data [21], 2011-14 and state-specific average annual rates per 100 000 individuals aged 18-49y of septicemia hospitalizations (principal or secondary diagnosis) recorded in the HCUP data [22], 2011-12.

Correlation between resistance prevalence and sepsis mortality, Ages 85+y

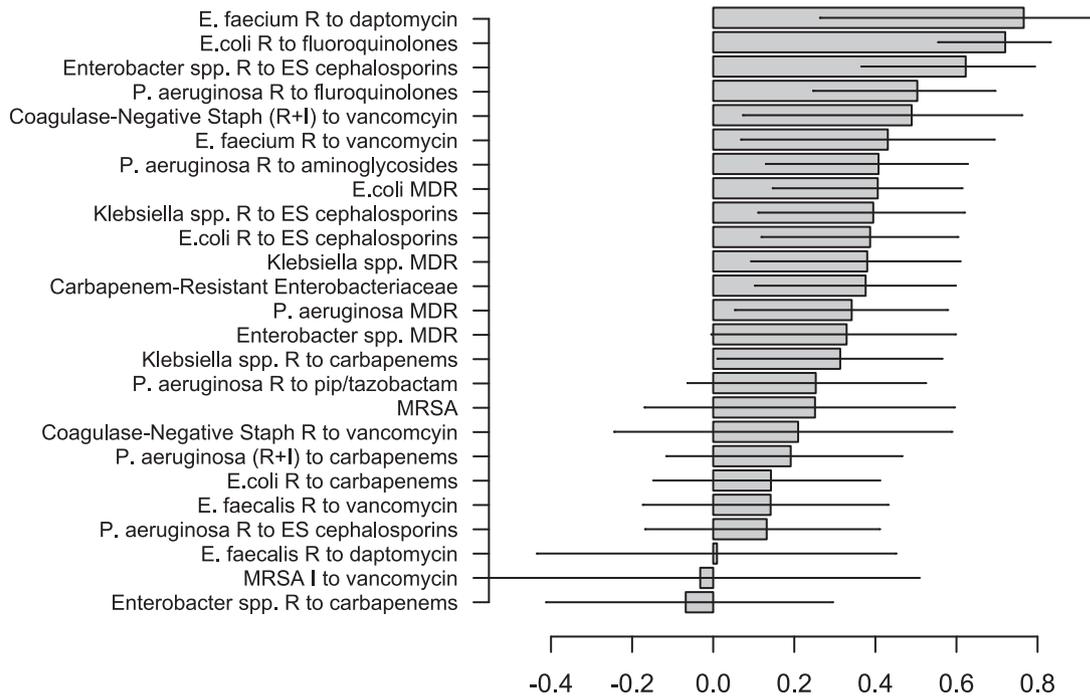


Fig. 6. Correlation between state-specific prevalence (percentages) of resistance for different combinations of antibiotics/bacteria in CAUTI samples from hospitalized individuals aged 65+y in the CDC Antibiotic Resistance Atlas data [21], 2011-14 and state-specific average annual rates per 100 000 individuals aged 85+y of mortality with sepsis listed on the death certificate, 2013-14 [23].

Correlation between resistance prevalence and sepsis mortality, Ages 75-84y

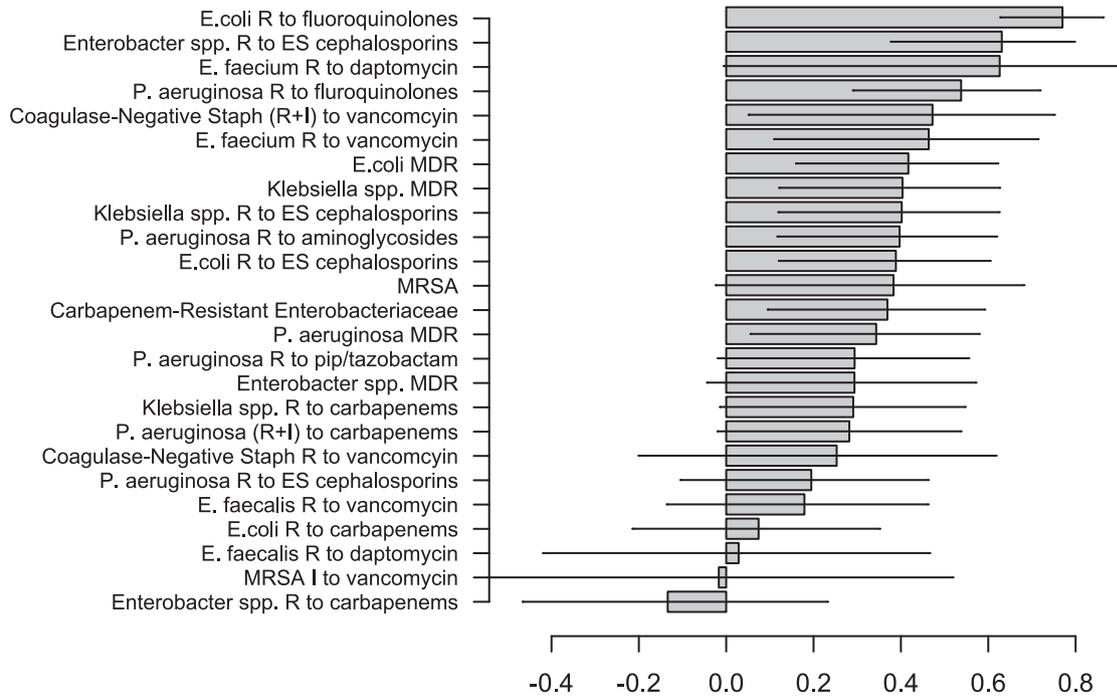


Fig. 7. Correlation between state-specific prevalence (percentages) of resistance for different combinations of antibiotics/bacteria in CAUTI samples from hospitalized individuals aged 65+y in the CDC Antibiotic Resistance Atlas data [21], 2011-14 and state-specific average annual rates per 100 000 individuals aged 75-84y of mortality with sepsis listed on the death certificate, 2013-14 [23].

Correlation between resistance prevalence and sepsis mortality, Ages 65-74y

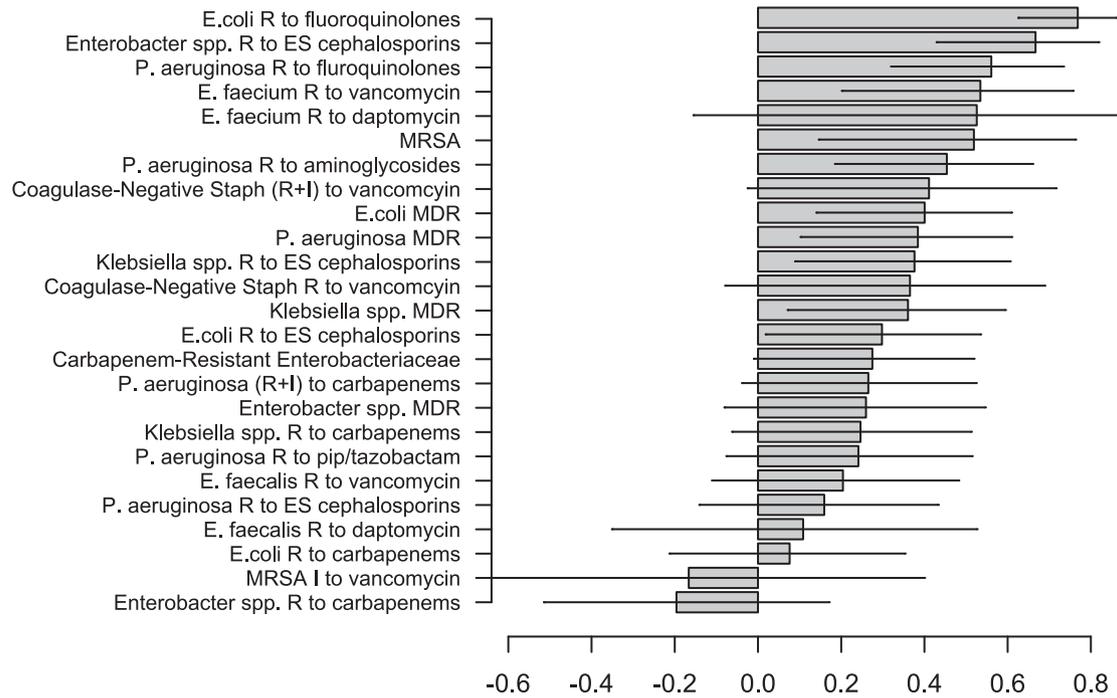


Fig. 8. Correlation between state-specific prevalence (percentages) of resistance for different combinations of antibiotics/bacteria in CAUTI samples from hospitalized individuals aged 65+y in the CDC Antibiotic Resistance Atlas data [21], 2011-14 and state-specific average annual rates per 100 000 individuals aged 65-74y of mortality with sepsis listed on the death certificate, 2013-14 [23].

Correlation between resistance prevalence and sepsis mortality, Ages 50-64y

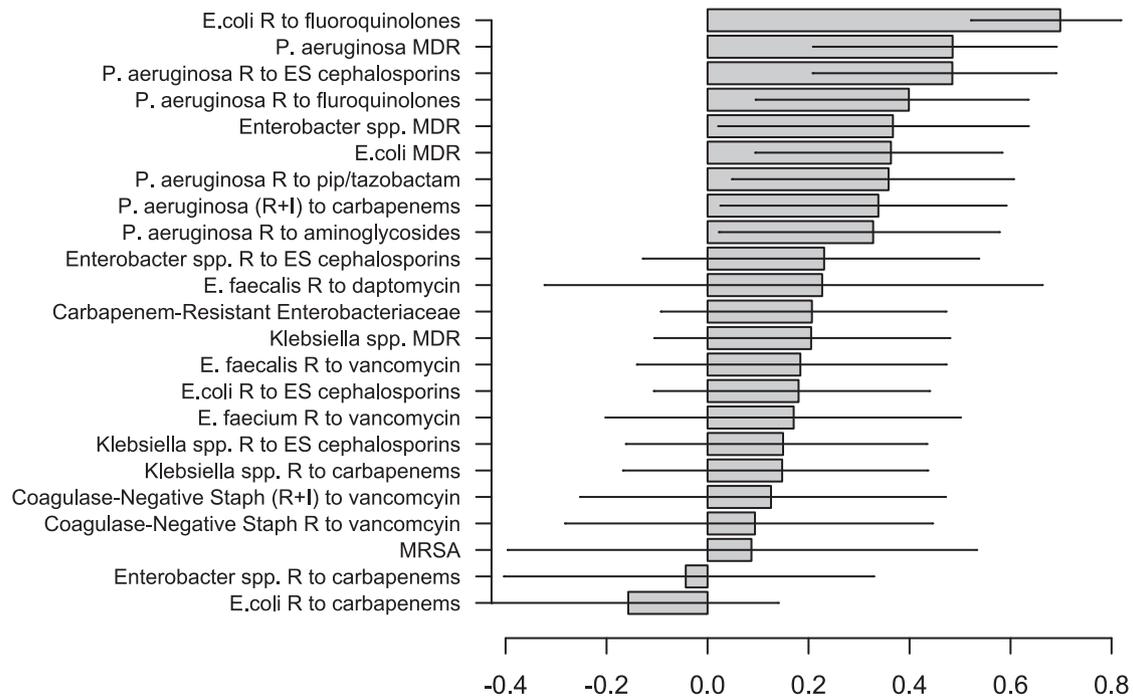


Fig. 9. Correlation between state-specific prevalence (percentages) of resistance for different combinations of antibiotics/bacteria in CAUTI samples from hospitalized individuals aged 19-64y in the CDC Antibiotic Resistance Atlas data [21], 2011-14 and state-specific average annual rates per 100 000 individuals aged 50-64y of mortality with sepsis listed on the death certificate, 2013-14 [23].

Correlation between resistance prevalence and sepsis mortality, Ages 18-49y

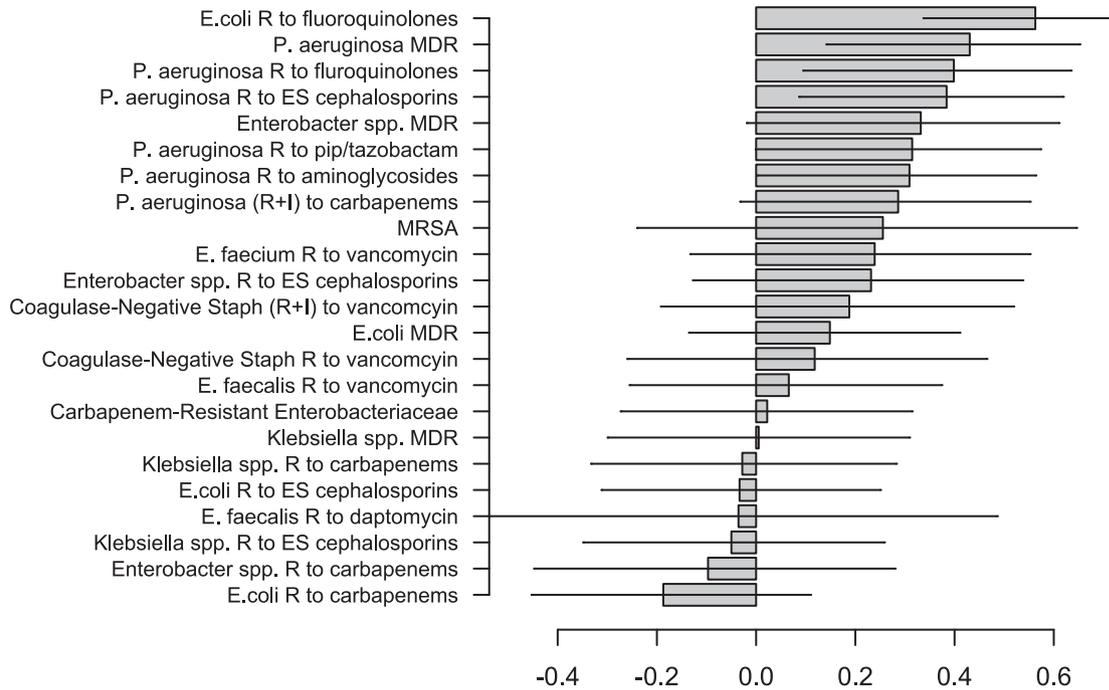


Fig. 10. Correlation between state-specific prevalence (percentages) of resistance for different combinations of antibiotics/bacteria in CAUTI samples from hospitalized individuals aged 19-64y in the CDC Antibiotic Resistance Atlas data [21], 2011-14 and state-specific average annual rates per 100 000 individuals aged 18-49y of mortality with sepsis listed on the death certificate, 2013-14 [23].

with sepsis mortality in all age groups under 85y (Figs. 1-10). 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 [17,26,27]. There are no data on prevalence of resistance to penicillins (except for methicillin) in [21]. Fig. 11 plots the state-specific prevalence of resistance to fluoroquinolones in *E. coli* isolated in the CAUTI samples in the CDC AR Atlas data [21] in hospitalized individuals aged 65+ years, 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 HCUP database [22], 2011-2012 for the 42 states included in our analyses (Methods). Fig. 12 plots the state-specific prevalence of resistance to fluoroquinolones in *E. coli* isolated in the CAUTI samples in individuals aged 65+y vs. rates of sepsis mortality in individuals aged 75-84y. Figs. 11 and 12 indicate a strong correlation between prevalence of resistance and rates of septicemia/sepsis-related outcomes (Cor=0.70, 95% confidence interval [CI] (0.50,0.83) for hospitalizations; Cor=0.77(0.63,0.86) for mortality). There may be substantial differences in diagnostic practices for septicemia and coding practices for sepsis mortality between states [25]. Nonetheless, Figs. 11 and 12 indicate significant differences in state-specific septicemia hospitalization and sepsis mortality rates, and in the types of states that have low septicemia hospitalization/sepsis mortality rates compared with states that have high septicemia hospitalization/sepsis mortality rates (Discussion and Supporting Information).

There is uncertainty regarding the causal links contributing to several of the correlations presented in Figs. 1-10 – see Discussion and Supporting Information. Finer data are needed to better understand the causal nature of the correlations described in this paper.

4. Discussion

Rates of hospitalization with septicemia and sepsis in the diagnosis, and related mortality have risen significantly in the last few decades in the US [1-3,8]. This rise cannot be fully explained by changes in diagnostic practices for septicemia/sepsis [7,8]. Moreover, septicemia hospitalization rates and sepsis mortality rates vary by state (Supporting Information and [19,20]). Antimicrobial resistance is one of the factors that affects the rates of sepsis-related outcomes, particularly through lack of clearance of resistant infections following antibiotic treatment, with those infections subsequently progressing to septicemia/sepsis and lethal outcomes [9-11]. In this study, we examine the relation between prevalence of antibiotic resistance and rates of septicemia hospitalization and sepsis mortality in the US. For several age groups of adults, and a number of combinations of bacteria/antibiotics, we evaluated the correlations between state-specific prevalence of resistance in CAUTI samples in the CDC AR Atlas data [21] and (a) state-specific rates of hospitalizations with septicemia present in the discharge diagnosis in the HCUP data [22]; and (b) state-specific rates of mortality with sepsis recorded in the CDC Wonder data [23]. Our results indicate the state-specific prevalence of resistance to several antibiotics in different bacteria is positively correlated with rates of hospitalization with septicemia and mortality with sepsis in multiple age groups of adults. Among the different combinations of bacteria/antibiotics in the CDC AR Atlas data [21], prevalence of fluoroquinolone resistance in *E. coli* had the strongest correlation with the rates of hospitalization with septicemia in all age groups over 50y, and with the rates of mortality with sepsis in all age groups 18-84y. Additionally, *E. coli* is the most common source of septicemia among the bacteria covered by the CDC AR Atlas data [1], and prevalence of resistance to fluoroquinolones in *E. coli* isolates in both urinary tract and bloodstream infections is high in the

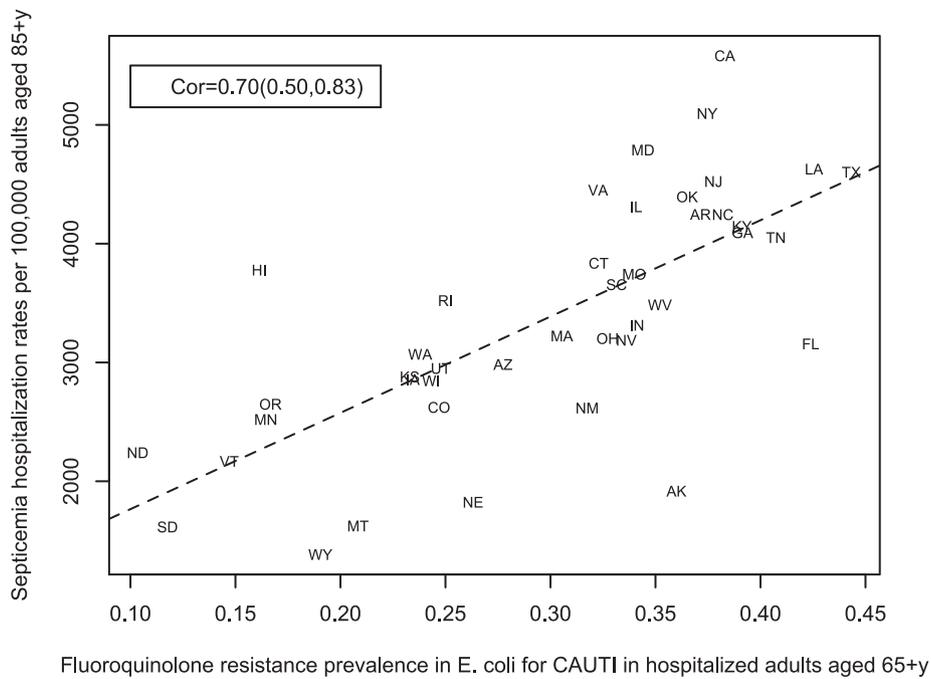


Fig. 11. State-specific prevalence (proportion) of resistance to fluoroquinolones in *E. coli* for CAUTI samples in hospitalized individuals aged 65+y in the CDC Antibiotic Resistance Atlas data [21], 2011–14 vs. state-specific average annual rates per 100 000 individuals aged 85+y of septicemia hospitalizations (principal or secondary diagnosis) recorded in the HCUP data [22], 2011–12 for the 42 states reporting septicemia hospitalization data (Methods).

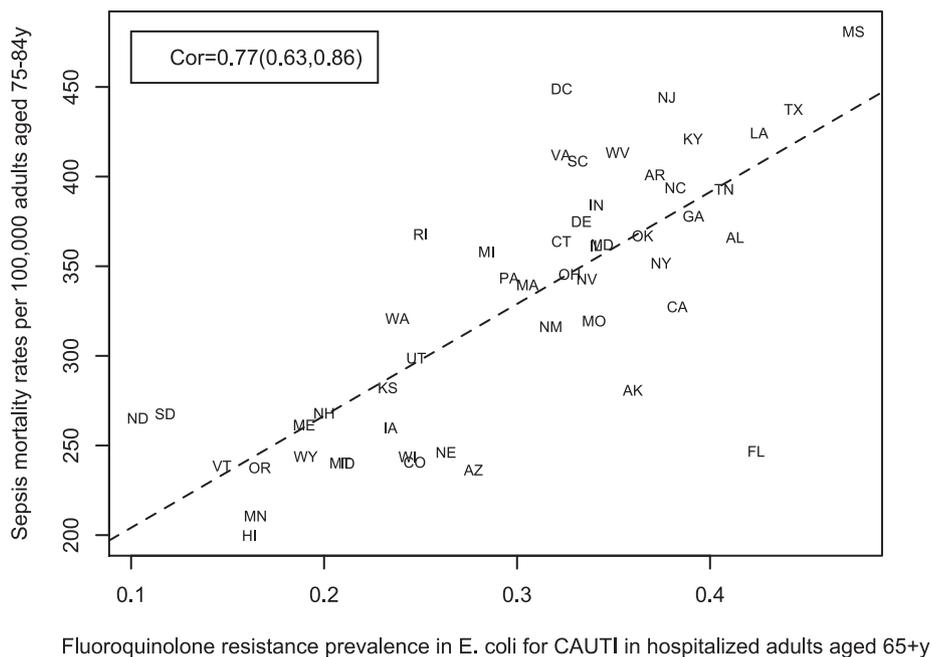


Fig. 12. State-specific prevalence (proportion) of resistance to fluoroquinolones in *E. coli* for CAUTI samples in hospitalized individuals aged 65+y in the CDC Antibiotic Resistance Atlas data [21], 2011–14 vs. state-specific average annual rates per 100 000 individuals aged 75–84y of sepsis mortality (underlying or contributing cause of death) recorded in the CDC Wonder data [23], 2013–14 for the 50 states + District of Columbia.

US [17,26,27]. There are no data on resistance to penicillins other than methicillin in [21], with use of penicillins found to be associated with rates of sepsis in older adults in our related work [19,20]. The results of this study, and those in [19,20], support the association between use of/resistance to certain antibiotics and rates of sepsis-related outcomes. Further work is needed to examine the potential utility of replacing certain antibiotics in the treatment of different syndromes on the rates of severe outcomes associated with bacterial infections, including septicemia/sepsis and related mortality.

A possible contributing factor to the various positive correlations found in this study (Figs. 1–10) is the association between state-specific prevalence of resistance for different pairs of combinations of antibiotics/bacteria. Section S3 of the Supporting Information presents those associations for several pairs of combinations of antibiotics/bacteria covered by the CDC AR Atlas [21]. Prevalence of resistance for certain combinations of antibiotics/bacteria not covered by the US CDC Atlas data [21] could have also contributed to the correlations found in our analysis. For example, for *E. coli*-associated UTIs recorded in Veterans Affairs data

[26], 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 were found between presence of resistance to different antibiotics in the samples in [17,26]. Thus, the correlation between the prevalence of fluoroquinolone resistance in *E. coli* and rates of septicemia hospitalization found in the current paper could have been affected by the contribution of fluoroquinolone resistance in *E. coli* to the rates of septicemia hospitalization, and also by (i) the contribution of resistance to other antibiotics in *E. coli*, including amoxicillin and trimethoprim/sulfamethoxazole, and (ii) the contribution of resistance to fluoroquinolones, and possibly other antibiotics in different bacteria that cause septicemia hospitalization. Our findings support the overall conclusion that resistance to different antibiotics in different bacteria (including drug resistance in *E. coli*) contributes to the rates of hospitalization for septicemia/sepsis mortality in the US, which resonates with the findings in [9–11,19,20].

The findings in this paper, and other work [9–11,19,20], lead to the question whether antibiotic stewardship and replacement of certain antibiotics could reduce 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 [14,15]. The drop in rates of MRSA bacteremia in England in 2006–2011 was sharper than the decline in rates of MRSA invasive disease in the US during the same period, particularly for community-associated infections (compare Figs. 1 and 3 in [28] with [29]). There has also been a high prevalence of fluoroquinolone (levofloxacin) non-susceptibility in community-associated MRSA isolates in the US in recent years [30]. For severe bacterial infections other than sepsis, reduction in fluoroquinolone and cephalosporin prescribing in England in 2006–2013 was associated with about a 75% reduction in the rates of *C. difficile* infections (and even greater reduction in rates of *C. difficile*-associated deaths) [18,28,31]. While rates of *C. difficile* infection in the US are much higher than in England [32], US rates of *C. difficile* infection have been decreasing in recent years [33], concomitant with the ongoing decrease in both inpatient fluoroquinolone use and the (fluoroquinolone-resistant) *C. difficile* epidemic strain NAP1/027 among persons aged ≥ 65 years [33]. Finally, levels of *E. coli* and *Klebsiella*-associated bacteremia continued to rise in England after 2006 while fluoroquinolone and cephalosporin use was declining [31,34]. Amoxicillin-clavulanate (AMC, or co-amoxiclav) prescribing in England increased significantly in 2006–2011 [35], and incidence of bacteremia with *E. coli* strains resistant to co-amoxiclav increased rapidly after 2006 ([36], Fig. 4), with co-amoxiclav resistance in *E. coli*-associated bacteremia exceeding 40% in 2014 [37]. Furthermore, prevalence of co-amoxiclav resistance in *E. coli*-associated bacteremia in England is more than twice the prevalence of co-amoxiclav resistance in *E. coli*-associated UTIs [37], which indicates the role of co-amoxiclav resistance in progressing to more severe outcomes resulting from *E. coli* infections. In 2017, the UK updated its prescribing guidelines for UTIs, with nitrofurantoin generally recommended as the first-line option ([37], p. 6). Recently, the US FDA has recommended the restriction of fluoroquinolone use for certain conditions (such as uncomplicated UTIs) due to potential adverse effects [38]. There were no recommendations in the FDA guidelines for antibiotics to replace fluoroquinolones [38]. Such recommendations are needed to optimize the effect of those guidelines on rates of severe outcomes associated with bacterial infections. For example, data for *E. coli*-associated UTIs in the US [26] indicate that prevalence of resistance varies significantly by antibiotic type, with the highest prevalence of resistance in [26] being for amoxicillin, ampicillin/beta-lactamase inhibitor and fluoroquinolones, with prevalence of

resistance in [26] being notably lower for narrow spectrum antibiotics, such as nitrofurantoin.

Our study has some limitations. Various confounders could have affected the correlations found in our paper; e.g., some doctors may be more likely than others to assign a diagnosis of sepsis and prescribe antibiotics, particularly in the inpatient setting, creating an association between levels of antibiotic resistance and rates of sepsis. Our related work [19,20] indicates associations between outpatient use of certain antibiotics and rates of septicemia hospitalization and sepsis mortality, with those associations presumably being less affected by the practices for assigning a septicemia/sepsis diagnosis and inpatient antibiotic administration. The data in [21] 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, or penicillins other than methicillin). Although the HCUP data analysed in our study generally cover about 97% of all community hospitalizations in the US [22], state-specific variability in the proportion of septicemia hospitalizations covered by the HCUP data is possible. Additionally, diagnostic practices for septicemia vary by state. Moreover, we studied correlations between septicemia hospitalization rates, and sepsis mortality 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 [21], 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; we chose 2013–2014 to evaluate the average annual state-specific sepsis mortality rates due to temporal changes in coding practices for sepsis on death certificates [25]. Correspondingly, we studied correlations between the state-specific prevalence of antibiotic resistance, 2011–2014 and (a) septicemia hospitalization rates, 2011–2012; and (b) sepsis mortality rates, 2013–2014. These sources of noise/incompatibility should generally bias the correlation estimates towards the null, thus reducing precision rather than creating spurious associations.

5. Conclusions

Despite certain limitations, this study indicates a potentially important effect of prevalence of antibiotic resistance on rates of septicemia hospitalization and sepsis mortality in US adults. Our results support the need for: (i) examining replacement of certain antibiotics by others in the treatment of different syndromes to reduce rates of severe outcomes associated with bacterial infections; (ii) enhancing antibiotic stewardship (including use of fluoroquinolones) in inpatient and outpatient settings; and (iii) stepping up efforts to prevent acquisition of antibiotic-resistant bacteria (particularly *E. coli* in the elderly) [39]. The relationship between antibiotic use, antibiotic resistance and rates of severe bacterial infections, including sepsis, and associated mortality outcomes [9–12,19,20], plus the limited options for antibiotic replacement support the need for new antibiotics. This need may not be fulfilled by the current system of antibiotic development/production; additional incentives for antibacterial research and development are worth considering [40].

Acknowledgement

We would like to thank the HCUP Partner states that voluntarily provide their data to the project, and without whom this research would not be possible (<https://www.hcup-us.ahrq.gov/partners.jsp>).

Disclaimer

This study does not necessarily represent the views of the NIH or the US Government. An earlier version of the paper was posted on BioRxiv.

Funding

This work was supported by Award Number U54GM088558 from the National Institute Of General Medical Sciences (ML, EG), and by the in-house research program of the Division of International Epidemiology and Population Studies, The Fogarty International Center, US National Institutes of Health, funded in part by the Office of Pandemics and Emerging Threats at the United States Department of Health and Human Services (CV). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Competing Interests

Dr. Lipsitch reports grants from NIH/NIGMS, during the conduct of the study; personal fees from Affinivax, personal fees from Merck, grants and personal fees from Pfizer, grants from PATH Vaccine Solutions, outside the submitted work. The other authors report no conflicts of interest.

Ethical Approval

Aggregate hospitalization data were used in our analyses, with no informed consent from participants sought.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijantimicag.2019.03.004](https://doi.org/10.1016/j.ijantimicag.2019.03.004).

References

- [1] Elixhauser A, Friedman B, Stranges E. Septicemia in U.S. Hospitals, 2009: Statistical Brief #122. HealthCare Cost and Utilization Project (HCUP). Agency for Healthcare Research and Quality (AHRQ); 2011 <https://www.hcup-us.ahrq.gov/reports/statbriefs/sb122.pdf> [cited 1 August 2018].
- [2] McDermott KW, Elixhauser A, Sun R. Trends in Hospital Inpatient Stays in the United States, 2005–2014. Statistical Brief #225. HealthCare Cost and Utilization Project (HCUP). Agency for Healthcare Research and Quality (AHRQ); 2017 <https://www.hcup-us.ahrq.gov/reports/statbriefs/sb225-Inpatient-US-Stays-Trends.pdf> [cited 1 August 2018].
- [3] Iwashyna TJ, Cooke CR, Wunsch H, Kahn JM. Population burden of long-term survivorship after severe sepsis in older Americans. *J Am Geriatr Soc* 2012;60(6):1070–7. <https://doi.org/10.1111/j.1532-5415.2012.03989.x>.
- [4] Torio CM, Moore BJ. National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2013: Statistical Brief #204. HealthCare Cost and Utilization Project (HCUP). Agency for Healthcare Research and Quality (AHRQ); 2016 <https://www.hcup-us.ahrq.gov/reports/statbriefs/sb204-Most-Expensive-Hospital-Conditions.jsp> [cited 1 August 2018].
- [5] Rhee C, Murphy MV, Li L, Platt R, Klompas M. Comparison of trends in sepsis incidence and coding using administrative claims versus objective clinical data. *Clin Infect Dis* 2015;60(1):88–95. <https://doi.org/10.1093/cid/ciu750>.
- [6] Umscheid CA, Betesh J, VanZandbergen C, Hanish A, Tait G, Mikkelsen ME, et al. Development, implementation, and impact of an automated early warning and response system for sepsis. *J Hosp Med* 2015;10(1):26–31. <https://doi.org/10.1002/jhm.2259>.
- [7] Walkey AJ, Lagu T, Lindenaier PK. Trends in sepsis and infection sources in the United States. A population-based study. *Ann Am Thorac Soc* 2015;12(2):216–20. <https://doi.org/10.1513/AnnalsATS.201411-498BC>.
- [8] Stoller J, Halpin L, Weis M, Aplin B, Qu W, Georgescu C, et al. Epidemiology of severe sepsis: 2008–2012. *J Crit Care* 2016;31(1):58–62. <https://doi.org/10.1016/j.jcrc.2015.09.034>.
- [9] Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. *Antimicrob Agents Chemother* 2010;54(11):4851–63. <https://doi.org/10.1128/AAC.00627-10>.
- [10] Hawkey PM, Warren RE, Livermore DM, McNulty CAM, Enoch DA, Otter JA, et al. Treatment of infections caused by multidrug-resistant Gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party. *J Antimicrob Chemother* 2018;73(suppl_3):iii2–ii78. <https://doi.org/10.1093/jac/dky027>.
- [11] Lee YC, Hsiao CY, Hung MC, Hung SC, Wang HP, Huang YJ, et al. Bacteremic urinary tract infection caused by multidrug-resistant Enterobacteriaceae are associated with severe sepsis at admission: implication for empirical therapy. *Medicine (Baltimore)* 2016;95(20):e3694. <https://doi.org/0000000000003694>.
- [12] Lishman H, Costelloe C, Hopkins S, Johnson AP, Hope R, Guy R, et al. Exploring the relationship between primary care antibiotic prescribing for urinary tract infections, *Escherichia coli* bacteraemia incidence and antibiotic resistance: an ecological study. *Int J Antimicrob Agents* 2018;52(6):790–8. <https://doi.org/10.1016/j.ijantimicag.2018.08.013>.
- [13] Pouwels KB, Freeman R, Muller-Pebody B, Rooney G, Henderson KL, Robotham JV, et al. Association between use of different antibiotics and trimethoprim resistance: going beyond the obvious crude association. *J Antimicrob Chemother* 2018;73(6):1700–7. <https://doi.org/10.1093/jac/dky031>.
- [14] Tacconelli E, De Angelis G, Cataldo MA, Pozzi E, Cauda R. Does antibiotic exposure increase the risk of methicillin-resistant *Staphylococcus aureus* (MRSA) isolation? A systematic review and meta-analysis. *J Antimicrob Chemother* 2008;61(1):26–38. <https://doi.org/10.1093/jac/dkm416>.
- [15] Knight GM, Budd EL, Whitney L, Thornley A, Al-Ghusein H, Planche T, et al. Shift in dominant hospital-associated methicillin-resistant *Staphylococcus aureus* (HA-MRSA) clones over time. *J Antimicrob Chemother* 2012;67(10):2514–22. <https://doi.org/10.1093/jac/dks245>.
- [16] Wener KM, Schechner V, Gold HS, Wright SB, Carmeli Y. Treatment with fluoroquinolones or with beta-lactam-beta-lactamase inhibitor combinations is a risk factor for isolation of extended-spectrum-beta-lactamase-producing *Klebsiella* species in hospitalized patients. *Antimicrob Agents Chemother* 2010;54(5):2010–16. <https://doi.org/10.1128/AAC.01131-09>.
- [17] Bidell MR, Palchak M, Mohr J, Lodise TP. Fluoroquinolone and third-generation-cephalosporin resistance among hospitalized patients with urinary tract infections due to *Escherichia coli*: do rates vary by hospital characteristics and geographic region? *Antimicrob Agents Chemother* 2016;60(5):3170–3. <https://doi.org/10.1128/AAC.02505-15>.
- [18] Dingle KE, Didelot X, Quan TP, Eyre DW, Stoesser N, Golubchik T, et al. Effects of control interventions on *Clostridium difficile* infection in England: an observational study. *Lancet Infect Dis* 2017;17(4):411–21. [https://doi.org/10.1016/S1473-3099\(16\)30514-X](https://doi.org/10.1016/S1473-3099(16)30514-X).
- [19] Goldstein E, Olesen SW, Karaca Z, Steiner CA, Viboud C, Lipsitch M. Levels of outpatient prescribing for four major antibiotic classes and rates of septicemia hospitalization in different US states. *BioRxiv* 2018. <https://www.biorxiv.org/content/early/2018/12/13/404046> [cited 2 February 2019].
- [20] Goldstein E. Prescribing of different antibiotics, rates of bacteremia/septicemia and associated mortality in the US and England, and the utility of antibiotic replacement vs. reduction in prescribing. *BioRxiv* 2019. <https://www.biorxiv.org/content/10.1101/527101v3> [cited 15 February 2019].
- [21] Antibiotic Resistance Patient Safety Atlas. CDC National Healthcare Safety Network (NHSN) Antibiotic Resistance Data. <https://gis.cdc.gov/grasp/PSA/index.html> [cited 1 August 2018].
- [22] SID Database Documentation. Healthcare Cost and Utilization Project (HCUP). Rockville, MD: Agency for Healthcare Research and Quality; April 2017 <https://www.hcup-us.ahrq.gov/db/state/sidbdbdocumentation.jsp> [cited 1 August 2018].
- [23] US CDC Wonder. Multiple Cause of Death, 1999–2017 Request. <https://wonder.cdc.gov/mcd-icd10.html> [cited 1 February, 2019].
- [24] US Centers for Disease Control and Prevention. Bridged-Race Population Estimates, 1990–2016 data request (Accessed on Apr. 1, 2018). <https://wonder.cdc.gov/Bridged-Race-v2016.HTML> [cited 1 August 2018].
- [25] Ong P, Gambatese M, Begier E, Zimmerman R, Soto A, Madsen A. Effect of cause-of-death training on agreement between hospital discharge diagnoses and cause of death reported, inpatient hospital deaths, New York City, 2008–2010. *Prev Chronic Dis* 2015 Jan 15;12:E04. <https://doi.org/10.5888/pcd12.140299>.
- [26] Morrill HJ, Morton JB, Caffrey AR, Jiang L, Dosa D, Mermel LA, et al. Antimicrobial resistance of *Escherichia coli* urinary isolates in the Veterans Affairs Health Care System. *Antimicrob Agents Chemother* 2017;61(5). pii:e02236-16 <https://doi.org/10.1128/AAC.02236-16>.
- [27] Al-Hasan MN, Lahr BD, Eckel-Passow JE, Baddour LM. Antimicrobial resistance trends of *Escherichia coli* bloodstream isolates: a population-based study, 1998–2007. *J Antimicrob Chemother* 2009;64(1):169–74. <https://doi.org/10.1093/jac/dkp162>.
- [28] Public Health England Mandatory MRSA, MSSA and *E. coli* bacteraemia and *C. difficile* infection data 2015/16. Annual Epidemiological Commentary 2016. https://www.researchgate.net/profile/Simon_Thelwall/publication/305392637_Annual_Epidemiological_Commentary_Mandatory_MRSA_MSSA_and_E_coli_bacteraemia_and_C_difficile_infection_data_201516/links/578ccb6a08ae254b1de8610a/Annual-Epidemiological-Commentary-Mandatory-MRSA-MSSA-and-E-coli-bacteraemia-and-C-difficile-infection-data-2015-16.pdf [cited 1 August 2018].
- [29] Dantes R, Mu Y, Belflower R, Aragon D, Dumyati G, Harrison LH, et al. National burden of invasive methicillin-resistant *Staphylococcus aureus* infections, United States, 2011. *JAMA Intern Med* 2013;173(21):1970–8. <https://doi.org/10.1001/jamainternmed.2013.10423>.

- [30] Sader HS, Mendes RE, Jones RN, Flamm RK. Antimicrobial susceptibility patterns of community- and hospital-acquired methicillin-resistant *Staphylococcus aureus* from United States Hospitals: results from the AWARE Ceftazolinone Surveillance Program (2012–2014). *Diagn Microbiol Infect Dis* 2016;86(1):76–9. <https://doi.org/10.1016/j.diagmicrobio.2016.06.017>.
- [31] Public Health England. Thirty-day all-cause fatality subsequent to MRSA, MSSA and *E. coli* bacteraemia and *C. difficile* infection, 2016/17. March 2017. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/765014/HCAI_fatality_report_201718_v2.pdf [cited 1 August 2018]
- [32] King A, Mullish BH, Williams HRT, Aylin P. Comparative epidemiology of *Clostridium difficile* infection: England and the USA. *Int J Qual Health Care* 2017;29(6):785–91. <https://doi.org/10.1093/intqhc/mzx120>.
- [33] Guh AY, Mu Y, Baggs J, Winston LG, Bamberg W, Lyons C, et al. Trends in incidence of long-term-care facility onset *Clostridium difficile* infections in 10 US geographic locations during 2011–2015. *Am J Infect Control* 2018;46(7):840–2. <https://doi.org/10.1016/j.ajic.2017>.
- [34] Livermore DM, Hope R, Reynolds R, Blackburn R, Johnson AP, Woodford N. Declining cephalosporin and fluoroquinolone non-susceptibility among bloodstream Enterobacteriaceae from the UK: links to prescribing change? *J Antimicrob Chemother* 2013;68:2667–74. <https://doi.org/10.1093/jac/dkt212>.
- [35] Ashiru-Oredope D, Sharland M, Charani E, McNulty C, Cooke JARHAI Antimicrobial Stewardship Group. Improving the quality of antibiotic prescribing in the NHS by developing a new Antimicrobial Stewardship Programme: Start Smart—Then Focus. *J Antimicrob Chemother* 2012(67 Suppl 1):i51–63. <https://doi.org/10.1093/jac/dks202>.
- [36] Vihta KD, Stoesser N, Llewelyn M, Quan TP, Davies T, Fawcett NJ, et al. Trends over time in *Escherichia coli* bloodstream infections, urinary tract infections, and antibiotic susceptibilities in Oxfordshire, UK, 1998–2016: a study of electronic health records. *Lancet Infect Dis* 2018;18(10):1138–49. [https://doi.org/10.1016/S1473-3099\(18\)30353-0](https://doi.org/10.1016/S1473-3099(18)30353-0).
- [37] Public Health England. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR). Report 2017. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/656611/ESPAUR_report_2017.pdf [cited 1 August 2018]
- [38] US Food and Drug Administration. FDA updates warnings for fluoroquinolone antibiotics. July 2016. <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm513183.htm> [cited 1 August 2018]
- [39] Hsu D, Melzer M. Strategy to reduce *E. coli* bacteraemia based on cohort data from a London teaching hospital. *Postgrad Med J* 2018;94(1110):212–15. <https://doi.org/10.1136/postgradmedj-2017-135454>.
- [40] Árdal C, Baraldi E, Ciabuschi F, Outterson K, Rex JH, Piddock LJV, et al. To the G20: incentivising antibacterial research and development. *Lancet Infect Dis* 2017;17(8):799–801. [https://doi.org/10.1016/S1473-3099\(17\)30404-8](https://doi.org/10.1016/S1473-3099(17)30404-8).