Levels of prescribing for four major antibiotic classes and rates of septicemia hospitalization in different US states

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Abstract

Background: Rates of sepsis/septicemia hospitalization in the US have risen significantly during recent years, and antibiotic resistance and use may contribute to those rates through various mechanisms.

Methods: We used multivariate Poisson regression to relate state-specific rates of outpatient prescribing overall for four antibiotic classes: fluoroquinolones, penicillins, macrolides, and cephalosporins between 2011-2012 to state-specific counts of hospitalizations with septicemia (ICD-9 codes 038.xx present anywhere on discharge diagnosis) in each of the following age groups of adults: (18-49y, 50-64y, 65-74y, 75-84y, 85+y) reported to the Healthcare Cost and Utilization Project (HCUP) between 2011-2012, adjusting for median household income and population density.

Results: The regression coefficients were positive for the rates of prescribing of fluoroquinolones, penicillins, as well as cephalosporins in the analysis for adults aged 18-49y, and negative for macrolides, and cephalosporins in the analyses for adults aged 50+y.

Conclusions: Antibiotic stewardship, particularly for fluoroquinolones, as well as penicillins could be beneficial for reducing the rates of sepsis hospitalization. Negative estimates in the regression analyses suggest that the relative share of the use of different antibiotics in the treatment of various syndromes may affect the rates of sepsis hospitalization. Further studies of those issues are needed to inform antibiotic prescribing guidelines.

Introduction

Rates of hospitalization with septicemia, sepsis, associated mortality and monetary costs have been rising rapidly during the past decades in the US [1-4]. While changes in diagnostic practices 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 and use may also contribute to the increase in/magnitude of septicemia/sepsis hospitalization rates [8]. The relation between infections with antibiotic-resistant bacteria and survival for sepsis, including the effect of initially appropriate antibiotic therapy (IIAT) is suggested by a number of studies, e.g. [9,10]. However, less is known about the relation between levels of antibiotic use, as well as prevalence of antibiotic resistance and rates of hospitalization with septicemia/sepsis. Antimicrobial use and resistance 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* (*E. coli*) was found to be associated with a more severe presentation in urinary tract infections [11,12]. Additionally, prevalence of fluoroquinolone resistance in *E. coli* was strongly correlated with rates of septicemia hospitalization in different US states for adults aged 50+y [8]. Antibiotic use and resistance can also contribute to the overall increase in the prevalence of bacterial infections associated with certain pathogens (e.g. the relation between fluoroquinolone use and MRSA infections [13-16]), with those infections subsequently leading to severe illness episodes, including sepsis (e.g. [13-20]).

Earlier work has shown a relationship, including spatial correlations between the rates of antibiotic consumption and antibiotic resistance, e.g. [21-23]. At the same time, there is limited information on the relationship between the levels of prescribing for different antibiotic types/classes, and rates of sepsis hospitalization. Moreover, that relationship may be context-specific and affected by various factors such as the use of other

antimicrobials and prevalence of cross-resistance, e.g. [24,25], local patterns of transmission/acquisition of antibiotic-resistant infections, demographic differences, etc. This study examines the relationship between the rates of prescribing for different antibiotic classes and rates of hospitalization for septicemia/sepsis for population-level data in the US. We use a regression framework to relate the state-specific rates of outpatient prescribing of fluoroquinolones, penicillins, macrolides, and cephalosporins in the US CDC Antibiotic Resistance Patient Safety Atlas data [26] to 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 [27]. We hope that such analyses can lead to further study of the contribution of different antibiotics to the rates of sepsis hospitalization, including the utility of antibiotic stewardship and shift in prescribing from some antibiotics to others in the treatment of certain syndromes for reducing the levels of sepsis hospitalization in the US.

Methods

Data

We used data between 2011-2012 on counts of hospitalization with a septicemia diagnosis (both primary and contributing, [*ICD-9*] codes 038.xx on the discharge diagnosis) 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 [27]. We will henceforth call these hospitalizations septicemia hospitalizations, even though some of them may involve low levels of bloodstream bacterial infection. The database [27] 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 groups utilized 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, Louisianna, 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.

We extracted data on the annual state-specific per capita rates of outpatient prescribing for four classes of antibiotics: fluoroquinolones, penicillins, macrolides, and cephalosporins in 2011 and 2012 from the US CDC Antibiotic Resistance Patient Safety Atlas [26]. Average annual state-specific outpatient prescribing rates (per 1,000

residents) for each class of antibiotics between 2011-2012 were then estimated as the average for the corresponding rates in 2011 and 2012.

Weekly state-specific population estimates in each age group of adults were obtained by linear interpolation of the annual, July 1 population estimates in [28]. State-specific population in each age group between 2011-2012 was then estimated by averaging the corresponding weekly population estimates. Average population densities for the different states between 2011-2012 were obtained by dividing the average weekly population estimates between 2011-2012 by the state land area [29]. Data on median household income for the different US states between 2011-2012 were extracted from [30].

Regression model

For each age group of adults, we applied Poisson regression to relate the state-specific outpatient prescribing rates (per 1,000 state residents) for fluoroquinolones, penicillins, macrolides, and cephalosporins between 2011-2012 [26] to the state-specific counts of septicemia hospitalization in the given age group between 2011 and 2012 [27], adjusting for median household income and population density. Specifically, for each state s, let $H(s)$ be the state-specific septicemia hospitalization count in the given age group between 2011-2012, $P(s)$ be the state-specific population estimate in the given age group between 2011-2012 (used as an offset in the regression model), $A_i(s)$ $(i = 1,..,4)$ be the state-specific outpatient prescribing rates, per 1,000 state residents, for the four studied classes of antibiotics between 2011-2012, $I(s)$ be the median state-specific household income between 2011-2012, and $D(s)$ be the state-specific average population density between 2011-2012. Then

$$H(s) = \text{Poisson}(P(s) \cdot \exp(\beta_0 + \textstyle\sum_i \beta_i \cdot A_i(s) + \beta_5 \cdot I(s) + \beta_6 \cdot D(s))) \qquad (1)$$

Results

State-specific rates of outpatient prescribing of all antibiotics per 100,000 residents in [26] are correlated with the state-specific rates of septicemia hospitalization in each age group of adults in [27] (cor = 0.44 (95% CI (0.15,0.65)) for aged 18-49y, 0.51 (0.24,0.70) for aged 50-64y, 0.49 (0.21,0.69) for aged 65-74y, 0.41 (0.12,0.63) for aged 75-84y, and 0.3 (-0.01,0.55) for aged 85+y).

Partitioning the relationship between the rates of prescribing and rates of septicemia hospitalization by antibiotic class is challenging because of the positive correlations between the rates of use of different antimicrobial classes at the state level. Table 1 presents the correlations between the state-specific rates of outpatient prescribing for different classes of antibiotics: fluoroquinolones, penicillins, macrolides, and cephalosporins in [26]. All the correlations in Table 1 are high, with point estimates above 0.76 for each pair of classes of antibiotics.

	Fluoroquinolones	Penicillins	Macrolides	Cephalosporins
Fluoroquinolones	1	0.8 (0.66,0.89)	0.88 (0.79,0.94)	0.76 (0.59,0.86)
Penicillins	0.8 (0.66,0.89)	1	0.83 (0.7,0.91)	0.82 (0.69,0.9)
Macrolides	0.88 (0.79,0.94)	0.83 (0.7,0.91)	1	0.82 (0.68,0.9)
Cephalosporins	0.76 (0.59,0.86)	0.82 (0.69,0.9)	0.82 (0.68,0.9)	1

Table 1: Correlations between the state-specific rates of outpatient prescribing of fluoroquinolones, penicillins, macrolides, and cephalosporins in [26] between 2011-2012.

Table 2 presents the estimates (regression coefficients) for the multivariate Poisson regression model (eq. 1) that relates the state-specific rates of outpatient prescribing for the four studied classes of antibiotics between 2011-2012 [26], the median household income [29], and population density to the state-specific septicemia hospitalization counts in different age groups of adults between 2011-2012 [27]. The regression coefficients for the different antibiotic classes estimate the logarithm of the fold increase in septicemia hospitalization rates when the annual rate of outpatient prescribing of the corresponding antibiotic class (per 1,000 residents) increases by 1. The regression coefficients were positive for the rates of prescribing of fluoroquinolones, penicillins, as well as cephalosporins in the analysis for adults aged 18-49y. The regression coefficients were negative for macrolides, and cephalosporins in the analyses for adults aged over 50y – see more on this in the Discussion. The regression coefficients for fluoroquinolones were highest among the four studied antibiotic classes in all age groups. Population density was negatively associated with septicemia rates, while household income was positively associated with septicemia rates in adults aged over 50y, possibly as a result of differences in the practices for coding for septicemia – see Discussion.

	Aged 85+y	Aged 75-84y	Aged 65-74y	Aged 50-64y	Aged 18-49y
Fluoroquinolones	8.3 (7.9,8.7)	5 (4.7,5.4)	3.5 (3.2,3.9)	4.5 (4.1,4.8)	5.6 (5.2,6)
Penicillins	0.85 (0.64,1.1)	2.1 (1.9,2.3)	2.9 (2.7,3.1)	1.8 (1.6,2)	0.28 (0.06,0.51)
Macrolides	-1 (-1.3,-0.8)	-1.4 (-1.6,-1.2)	-1.7 (-1.9,-1.5)	-2.2 (-2.4,-2)	-2.8 (-3,-2.6)
Cephalosporins	-3.5 (-3.7,-3.2)	-1.7 (-1.9,-1.5)	-0.96 (-1.2,-0.75)	-0.3 (-0.5,-0.1)	1.1 (0.89,1.4)
Median household income	2.1 (2.1,2.2)	1.4 (1.4,1.5)	0.81 (0.75,0.88)	0.08 (0.02,0.15)	-0.14 (-0.22,-0.07)
Population density (per sq. mile)	-4.5 (-4.7,-4.3)	-3 (-3.2,-2.8)	-2.6 (-2.9,-2.4)	-2.3 (-2.5,-2.1)	-2.1 (-2.4,-1.8)

Table 2: Regression coefficients in eq. 1 (*multiplied by 1,000 for rates of antibiotic prescribing; multiplied by 100,000 for median household income; multiplied by 10,000 for population density*) for the different covariates in the model given by eq. 1 for different age groups. The coefficients for the different antibiotic classes estimate the logarithm of the fold increase in septicemia hospitalization rates when the annual rate of outpatient prescribing of the corresponding antibiotic class (per 1,000 residents) increases by 1.

Discussion

While antimicrobial use can contribute to the rates of hospitalization with septicemia and sepsis (see the Introduction), the strength of the relation between antibiotic prescribing rates and rates of septicemia/sepsis hospitalization may vary with antibiotic types/classes and depend on a number of factors including patterns of resistance to different antibiotics. In this study, we examine the relation between the rates of antibiotic prescribing and the rates of septicemia hospitalization in the US context. Univariate analysis shows an association between the state-level rate of outpatient prescribing of *any* antibiotics, and the rates of sepsis hospitalization in different age groups of adults. Moreover, there are strong correlations between he state-specific rates of prescribing for different classes of antibiotics. Multivariate analyses suggest the association between the state-level rate of outpatient prescribing of certain antibiotics, particularly fluoroquinolones, as well as penicillins and the rates of sepsis hospitalization in different age groups of adults. We note that earlier work has shown a relationship, including spatial

correlations between the rates of antibiotic consumption and antibiotic resistance, e.g. [21-23]. Our findings, to the extent that they reflect causal mechanisms, add an additional aspect to the potential value of outpatient antimicrobial stewardship. Similarly, the different associations found for different antibiotic classes in the multivariate analysis (Table 2) suggest that changing the choice of antibiotics for treating certain syndromes, perhaps to less often-prescribed antibiotic classes, may be beneficial for reducing the rates of sepsis hospitalization. Further studies of various related phenomena, including patterns of resistance to different antibiotics are needed to better understand the potential effect of antibiotic replacement on the rates of sepsis, as suggested in the next two paragraphs. We also note that US states with the lowest population density have some of the lowest rates of septicemia hospitalization, and population density was found to be negatively associated with rates of septicemia in the multivariate analysis. Finally, median household income was positively associated with septicemia hospitalization rates in adults aged over 50y. That association may partly reflect differences in coding practices for septicemia, particularly for older hospitalized adults – see also the penultimate paragraph of the Discussion.

Patterns of resistance to different antibiotics modulate the relation between antibiotic prescribing and the rates of sepsis hospitalization. For example, in the UK, outpatient amoxicillin prescribing rates are high ([31], Figure 3.4), and amoxicillin use may contribute to the prevalence of trimethoprim resistance [22], with high prevalence of trimethoprim resistance in *E. coli*-associated urinary tract infections reported in [31]. Another antibiotic relevant to the growth in the rates of *E. coli*-associated bacteremia in England is amoxicillin-clavulanate (co-amoxiclav). 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 [32,33,20]. Amoxicillin-clavulanate (co-amoxiclav) prescribing in England increased significantly between 2006-2011 [34], and incidence of bacteremia with *E. coli* strains resistant to co-amoxiclav began to increase rapidly after 2006 ([35], Figure 4), with co-amoxiclav resistance in *E. coli*-associated bacteremia exceeding 40% in 2014 [31]. In the US, for urinary tract infections (UTIs), prevalence of fluoroquinolone and penicillin resistance in *E. coli* (which is a major source of UTIs) is notably higher than the prevalence of resistance to certain other antimicrobials, including some narrow spectrum antibiotics like nitrofurantoin [25]. Moreover, there is high prevalence of cross-resistance for different pairs of antibiotics in *E. coli*-associated UTIs [25,24]. Those findings from the UK and the US suggest that data on resistance patterns for different antibiotics in different bacteria contributing to various syndromes, such as [25,31,36] should be part of the considerations behind antibiotic prescribing guidelines. We note that recently FDA has recommended the restriction of fluoroquinolone use for certain conditions (such as uncomplicated urinary tract infections) due to potential adverse effects [37]. Those recommendations may have

benefits in terms of reducing the rates of certain severe bacterial infections (e.g. invasive MRSA infections, and *C. Difficile* infections) due to the role of fluoroquinolone use/resistance in those outcomes -- e.g. [13-16,20]. Such an effect would be consistent with the UK experience in the reduction of fluoroquinolone/cephalosporin prescribing starting around 2006 [16,20,33,38,8]. At the same time, more detailed guidelines specifying antibiotics recommended for fluoroquinolone replacement in the treatment of various syndromes should enhance the effect of the recommendations in [37]. We note the recent update in the UK prescribing guidelines for urinary tract infections (UTIs), with nitrofurantoin generally recommended as the first-line option [39].

There is uncertainty regarding the causal links behind some of the results found in our paper. Reverse causality associated with antibiotic treatment for sepsis is unlikely to have a significant contribution to our results because we are considering the relation between *outpatient* prescribing rates and septicemia hospitalizations. Prevalence of resistance to penicillins and fluoroquinolones for several key syndromes contributing to sepsis for which penicillins and fluoroquinolones are used as treatment agents is high [25], which agrees with our findings about the contribution of penicillin and fluoroquinolone prescribing to the rates of septicemia. Prevalence of cephalosporin resistance in Gram-negative infections is generally lower compared to the prevalence of penicillin and fluoroquinolone resistance [25], which might have contributed to the negative estimates for the coefficient for cephalosporin prescribing rates in older adults (Table 2). At the same time, prevalence of cephalosporin resistance and the frequency of extended-spectrum beta-lactamase (ESBL) production, including in Gram-negative bacteria is growing [40], and our results should not be interpreted as supporting an increase in cephalosporin prescribing. Finally, there is uncertainty about our results for macrolide prescribing. The negative estimates for the regression coefficients for the macrolide prescribing rates in Table 2 may partly be the result of confounding, possibly related to prescribing practices in different states. Indeed, macrolide use should potentially contribute to the rates of sepsis as macrolides are commonly prescribed for the treatment of certain syndromes that are major causes of sepsis, notably respiratory diseases, both chronic [41] and acute, including pneumonia [42]. On the other hand, macrolides are used relatively infrequently in the treatment of urinary tract and gastrointestinal infections. A UK study found that for a high proportion of Gram-negative bacteremia, the main foci of infection were either urinary tract or abdomen/biliary tract [43]. Such infections are expected to take some time to devolve into bacteremia, and failure of the initial antibiotic treatment is likely a contributing factor for progression to bacteremia, suggesting the importance of antibiotics prescribed for those infections. Overall, the potential benefits of antibiotic stewardship for fluoroquinolones, as well as for penicillins may be the most important findings of this paper, while the possibility of changing the rates of macrolide

prescribing and the consequences for both the rates and the severity of septicemia/sepsis hospitalizations require further investigation.

Our study has some additional limitations. While the HCUP data utilized in our study generally cover about 97% of all community hospitalizations in the US [27], state-specific variability in the proportion of septicemia hospitalizations that are covered by the HCUP data is possible. Diagnostic practices for septicemia vary by state. It is uncertain whether states with higher antibiotic prescribing rates have more inclusive criteria for a septicemia diagnosis (boosting the association between antibiotic prescribing rates and septicemia hospitalization rates), or vice versa. For example, California has low antibiotic prescribing rates [44] and apparently more inclusive criteria for a septicemia/sepsis diagnosis that translate into lower case fatality rates for such hospitalizations compared to the national average, e.g. [45]. On the other hand, some of the states with low antibiotic prescribing rates, possibly outside the Northeastern US [46], may have more strict criteria for a septicemia/sepsis diagnosis compared to the national average. Data on antibiotic prescribing in the whole population [26] was used in the regression model for which the outcomes were age-specific counts of septicemia hospitalization [27]. We expect that those sources of noise/incompatibility should generally introduce noise into the regression model, reducing precision rather than creating spurious associations. Finally, there is uncertainty regarding the causal links behind some of the results in this paper, as explained in the previous paragraph.

We believe that despite those limitations, our findings indicate a possible causal association between the use different antibiotics, particularly fluoroquinolones, as well as penicillins, and the rates of sepsis hospitalization, suggesting the potential benefits of antibiotic stewardship. Our results also suggest that the relative share of the use of different antibiotics in the treatment of various syndromes may affect the rates of sepsis hospitalization, supporting the potential utility of replacement of some of the use of certain antibiotics, particularly fluoroquinolones, by administration of other antimicrobials. We hope that this population-level study would lead to further investigations of the relation between antibiotic prescribing practices and the rates of sepsis hospitalization in different contexts. Finally, we believe that a comprehensive, long-term approach for controlling the rates of severe outcomes associated with bacterial infections, including sepsis should include not only the adoption of appropriate antibiotic prescribing practices but also the introduction of new antibiotics [47].

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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. Available from: https://www.hcup-us.ahrq.gov/reports/statbriefs/sb122.pdf

[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. Available from: https://www.hcup-us.ahrq.gov/reports/statbriefs/sb225-Inpatient-US-Stays-Trends.pdf

[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.

[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. Available from: https://www.hcup-us.ahrq.gov/reports/statbriefs/sb204-Most-Expensive-Hospital-Conditions.jsp

[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

[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

[7] Walkey AJ, Lagu T, Lindenauer PK. Trends in sepsis and infection sources in the United States. A population-based study. Ann Am Thorac Soc. 2015;12(2):216-20

[8] Goldstein E, MacFadden D, Lipsitch M. Antimicrobial resistance and use, and rates of hospitalization associated with bacterial infections, including sepsis. ArXiv 2018. Available from: https://arxiv.org/abs/1803.07189

[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

[10] Zilberberg MD, Shorr AF, Micek ST, Vazquez-Guillamet C, Kollef MH. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: a retrospective cohort study. Crit Care. 2014;18(6):596

[11] Talan DA, Takhar SS, Krishnadasan A, Abrahamian FM, Mower WR, Moran GJ, et al. Fluoroquinolone-Resistant and Extended-Spectrum β-Lactamase-Producing Escherichia coli Infections in Patients with Pyelonephritis, United States. Emerg Infect Dis. 2016;22(9):1594–1603

[12] 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

[13] 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

[14] Weber SG, Gold HS, Hooper DC, Karchmer A, Carmeli Y. Fluoroquinolones and the risk for methicillin-resistant Staphylococcus aureus in hospitalized patients. Emerg Infect Dis. 2003;9: 1415 -22

[15] Bisognano C, Vaudaux P, Rohner P, Lew DP, Hooper DC. Induction of fibronectin-binding proteins and increased adhesion of quinolone-resistant *Staphylococcus aureus* by subinhibitory levels of ciprofloxacin. Antimicrob. Agents Chemother. 2000;44:1428–1437

[16] 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.

[17] Paterson DL. "Collateral Damage" from Cephalosporin or Quinolone Antibiotic Therapy. Clin Infect Dis. 2004;38 Suppl 4:S341-5

[18] Lautenbach E, Patel JB, Bilker WB, Edelstein PH, Fishman NO. Extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae: risk factors for infection and impact of resistance on outcomes. Clin Infect Dis. 2001;32:1162 -71

[19] Paterson DL, Mulazimoglu L, Casellas JM, et al. Epidemiology of ciprofloxacin resistance and its relationship to extended-spectrum β-lactamase production in Klebsiella pneumoniae isolates causing bacteremia. Clin Infect Dis. 2000;30:473-8

[20] 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):411-421

[21] Costelloe C , Metcalf C , Lovering A et al. Effects of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ 2010;340:c2096

[22] 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):1700-1707

[23] Bergman M, Huikko S, Huovinen P, Paakkari P, Seppälä H; Finnish Study Group for Antimicrobial Resistance (FiRe Network). Macrolide and azithromycin use are linked to increased macrolide resistance in Streptococcus pneumoniae. Antimicrob Agents Chemother. 2006;50(11):3646-50

[24] 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

[25] 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

[26] US CDC. Antibiotic Resistance Patient Safety Atlas. Outpatient Antibiotic Prescription Data (Accessed on Apr. 1, 2018). Available from: https://gis.cdc.gov/grasp/PSA/indexAU.html

[27] SID Database Documentation. Healthcare Cost and Utilization Project (HCUP). Agency for Healthcare Research and Quality, Rockville, MD. April 2017. (Accessed on Nov. 1, 2017). Available from: https://www.hcup-us.ahrq.gov/db/state/siddbdocumentation.jsp

[28] US Centers for Disease Control and Prevention. Bridged-Race Population Estimates, 1990-2016 data request (Accessed on Apr. 1, 2018). Available from: https://wonder.cdc.gov/Bridged-Race-v2016.HTML

[29] United States Census Bureau. United States Summary: 2010, Population and Housing Unit Counts, 2010 Census of Population and Housing. (2012) pp. V–2, 1 & 41 (Tables 1 & 18). (Accessed on Apr. 1, 2018). Available from: https://www.census.gov/prod/cen2010/cph-2-1.pdf

[30] United States Census Bureau. MEDIAN HOUSEHOLD INCOME (IN 2011 INFLATION-ADJUSTED DOLLARS) - United States -- States; and Puerto Rico: Households. 2011 American Community Survey 1-Year Estimates (2011). (Accessed on Apr. 1, 2018). Available from: https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?src=bkmk

[31] Public Health England. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR). Report 2017. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/656611/ESPAUR_report_2017.pdf

[32] 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;68:2667-2674.

[33] Public Health England. Mandatory MRSA, MSSA and *E. coli* bacteraemia and *C. difficile* infection data 2015/16. Annual Epidemiological Commentary. July 2016. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/535635/AEC_final.pdf

[34] Ashiru-Oredope D, Sharland M, Charani E, McNulty C, Cooke J; ARHAI 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 Jul;67 Suppl 1:i51-63

[35] Vihta KD, Stoesser N, Llewelyn M, Quan TP, Davies T, Fawcett NJ. Trends in Escherichia coli bloodstream infection, urinary tract infections and antibiotic susceptibilities in Oxfordshire, 1998-2016: an observational study. BioRxiv 2017. Available from: http://dx.doi.org/10.1101/223107

[36] Jenkins SG, Brown SD, Farrell DJ. Trends in antibacterial resistance among Streptococcus pneumoniae isolated in the USA: update from PROTEKT US Years 1-4. Ann Clin Microbiol Antimicrob. 2008;7:1

[37] US Food and Drug Administration. FDA updates warnings for fluoroquinolone antibiotics. July 2016. Available from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm513183.htm

[38] Johnson AP, Davies J, Guy R, Abernethy J, Sheridan E, et al. Mandatory surveillance of methicillin-resistant Staphylococcus aureus (MRSA) bacteraemia in England: the first 10 years. J Antimicrob Chemother. 2012;67(4):802-9

[39] Public Health England. Management and treatment of common infections Antibiotic guidance for primary care: For consultation and local adaptation. 2017. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/664740/Managing_common_infections_guidance_for_consultation_and_adaptation.pdf

[40] Park, SH. Third-generation cephalosporin resistance in gram-negative bacteria in the community: a growing public health concern. Korean J Intern Med. 2014;29(1):27-30

[41] Fitzpatrick JM, Biswas JS, Edgeworth JD, Islam J, Jenkins N, Judge R, et al. Gram-negative bacteraemia; a multi-centre prospective evaluation of empiric antibiotic therapy and outcome in English acute hospitals. Clin Microbiol Infect. 2016;22(3):244-51

[42] Suresh Babu K, Kastelik J, Morjaria JB. Role of long term antibiotics in chronic respiratory diseases. Respir Med. 2013;107(6):800-15.

[43] Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44 Suppl 2:S27-72

[43] Klein EY, Makowsky M, Orlando M, Hatna E, Braykov NP, Laxminarayan R. Influence of provider and urgent care density across different socioeconomic strata on outpatient antibiotic prescribing in the USA. J Antimicrob Chemother. 2015;70(5):1580-7

[45] Liu V, Escobar GJ, Greene JD, Soule J, Whippy A, Angus DC, et al. Hospital Deaths in Patients With Sepsis From 2 Independent Cohorts. JAMA. 2014;312(1):90-2.

[46] Wang HE, Devereaux RS, Yealy DM, Safford MM, Howard G. National variation in United States sepsis mortality: a descriptive study. Int J Health Geogr. 2010;9:9

[47] Årdal 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