Article:

Nomamiukor, BO, Horner, C, Kirby, A et al. (1 more author) (2015) Living conditions are associated with increased antibiotic resistance in community isolates of Escherichia coli. Journal of Antimicrobial Chemotherapy, 70 (11). 3154 - 3158. ISSN 0305-7453

https://doi.org/10.1093/jac/dkv229

Title: Living conditions are associated with increased antibiotic resistance in community isolates of *Escherichia coli*.

Running title: Living conditions are associated with increased antibiotic resistance of *E. coli*.

Article type: Brief report

Authors: Brenda O Nomamiukor[1], Carolyne Horner[2], Andrew Kirby[1*] and Gareth J Hughes[3]

[1]Old Medical School, Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust, UK

[2]Old Medical School, Leeds General Infirmary, Public Health England - Leeds, UK

[3]Academic Unit of Public Health, Leeds Institute of Health Sciences, University of Leeds, UK.

[*]Corresponding author. Tel: +44 113 233 9239; E-mail: a.kirby@leeds.ac.uk

Keywords: antibiotic resistance, deprivation, epidemiology, modelling.

Synopsis

Objectives: To measure the associations between domains of deprivation and antibiotic resistance of *Escherichia coli*.

Methods: Routine surveillance data for antibiotic susceptibility of *E. coli* isolates were obtained from urine specimens taken from patients presenting to health care practitioners based in the community in Leeds and Bradford with suspected urinary tract infection in 2010–2012. Eight antibiotics were included in the analyses. Postcodes were linked to lower super output areas (average populations of 1500). The 2010 Indices of Deprivation were used as neighbourhood characteristics for each lower super output area. Multilevel logistic regression models were used to estimate the independent effect of structural components on the odds of resistance to each antibiotic.

Results: Residence in the most deprived areas compared to the least deprived areas with respect to living conditions was associated with increased odds of antibiotic resistance for all eight antibiotics analysed. The magnitude of these associations included: an odds ratio of 2.04 (95% confidence interval [CI]: 1.03- 3.07) for cefalexin, 2.16 (95% CI: 1.16–4.05) for ciprofloxacin, 2.47 (95% CI: 1.08-5.66) for nitrofurantoin, and 1.33 (95% CI: 1.07–1.75) for trimethoprim.

Conclusions: Social deprivation in the form of living conditions is associated with increased antibiotic resistance for *E. coli*. This evidence suggests there is a need for further individual-level studies to explore the potential mechanism for these associations.

Introduction

Antibiotic resistance is associated with reduced efficacy of antibiotic treatment, which translates into an estimated 25,000 extra deaths annually within Europe.[1] The distribution of antibiotic resistance between countries is not equal.[2] The reasons for this are not causally proven, but inter-country variation in resistance rates have been associated with income inequality and antibiotic consumption.[2] In addition, policies at the national level relating to the control of antibiotic consumption, and in Europe, the density of general practitioners and their remuneration method, have been suggested to influence rates of antibiotic resistance.[3,4] National-level analyses, however, do not explain the intra-country distribution of antibiotic resistance , nor the mechanisms that may give rise to antibiotic resistance.

Studies investigating intra-country distribution of resistance have used antibiotic consumption as a surrogate marker for antibiotic resistance. A study of Swedish children identified that parental educational level, parents being born outside Sweden, environmental exposure to smoking, economic stress, and parent reported access to personal support were associated with increased antibiotic consumption.[5] In England and Scotland, antibiotic prescribing by general practitioners has been related to social deprivation.[6,7] In the USA, antibiotic consumption has been shown to be associated with population rates of obese persons, children ≤2 years of age, prescribers per capita, and females.[8] In general, increasing social deprivation, which includes measures relating to income; education, skills and training; living environment; barriers to housing and services and health and disability, is associated with increased antibiotic consumption, but there is also evidence that increasing antibiotic consumption may be related to increased per capita income.[9,10]

Whilst there is evidence to link increasing social deprivation to increasing antibiotic consumption, associations between social deprivation and antibiotic resistance have not been determined. This retrospective secondary data analysis used the antimicrobial susceptibilities of *Escherichia coli* isolates derived from urine samples and neighbourhood characteristics to determine whether components of social deprivation were associated with increased rates of antibiotic resistance.

Materials and methods

Antibiotic resistance data

Antimicrobial resistance surveillance data was collected from 2,778 urinary *E. coli i*solates collected from patients presenting to health care practitioners based in the community (Leeds and Bradford (UK)) during 2010–2012.[11] Isolates were therefore derived from patients resident in their own homes and community based health care institutions e.g. residential care facilities, but excludes hospitalised patients. Data associated with isolates did not include identifiable patient level data, we cannot therefore confirm all isolates are patient-unique. Resistance to eight antibiotics was considered: ampicillin, amoxicillin-clavulanic acid, cefalexin, ceftazidime, cefuroxime, ciprofloxacin, nitrofurantoin, trimethoprim. This use of pseudo-anonymised data removed the need for ethical consent. Approval for the use of the data was obtained from the Information Governance team at Leeds Teaching Hospitals NHS Trust.

Neighbourhood-level data

Patients postcodes were linked to neighbourhood deprivation scores via lower super output areas (LSOA; census derived small areas (neighbourhoods) with an average population of 1,500 persons) using GeoConvert (www.geoconvert.mimas.ac.uk). So each postcode corresponds to a neighbourhood level LSOA, and each neighbourhood level LSOA has a neighbourhood level deprivation score. The deprivation scores for each LSOA were obtained from the 2010 Indices of Deprivation.[12] This dataset assigns a deprivation scores to each LSOA, reporting on five deprivation domains which were considered independently. The five domains are: income; education, skills and training; living environment; barriers to housing and services; health and disability (See appendix A for further detail on the components of the domains). Quintiles were created for each of the five deprivation domains (within the dataset) and used for analysis. LSOA were grouped according to rural or urban setting based on Rural/Urban Area Classification (RUAC).[13] Population density (persons per hectare) based on the 2010 census was obtained from the Office for National Statistics (https://geoportal.statistics.gov.uk).

Statistical analysis

Multilevel logistic regression analysis was used to estimate the independent effect of structural components on the odds of a patient having a resistant bacterial infection. We considered structural components to be neighbourhood characteristics that exist above the level of individuals. A separate model was developed for each of the eight antibiotics using a defined model building strategy. We used a four stage model building strategy, at each stage testing for the statistical appropriateness of the more complex model: Model 1: single level model (individual); Model 2: inclusion of LSOA as a second level and consideration of significant variance at the second level; Model 3: fixed effects at individual-level (age, sex, year, season) and consideration of the predictive power of each effect; Model 4: fixed effects at LSOA-level (RUAC, population density, five deprivation domains) followed by backwards removal of predictors with an associated P-value >0.05 (one-by-one, starting with the least significant and with re-assessment of significance following removal of each variable). All changes in model fit were assessed through likelihood ratio tests. Overall fit of the final model was assessed using the Hosmer-Lemeshow goodness of fit summary statistic.[14] All statistical analysis was undertaken with Stata v12.1 (StataCorp 2009).

Results

Single variable associations with resistance for each antibiotic are shown in Supplementary Table 1. All eight final multilevel models represented a significantly good overall fit ($P<0.05$) with the inclusion of LSOA as a second level supported by significant variance at that level (all $P<0.05$). Increasing age was a significant predictor of increased resistance for all eight antibiotics; male sex was associated with significantly increased odds for ampicillin and nitrofurantoin resistance (Supplementary Table 2). Increasing population density was associated with increased odds of resistance to amoxicillin-clavulanic acid, cefalexin, cefuroxime, nitrofurantoin, and trimethoprim but the rural/urban nature of LSOA was not associated with resistance for any antibiotic (Supplementary Table 2).

Only two deprivation domains remained significant predictors of antibiotic resistance in the final multivariable models: living conditions (all eight antibiotics) and education, skills and training (cefuroxime, nitrofurantoin) (Figure 1; Supplementary Table 3). One or two quintiles of living conditions were associated with significantly increased odds of resistance for each antibiotic; in each case, the quintile with the worst living conditions had the highest odds ratio compared to the quintile with the best living conditions (Figure 2). The magnitude of these associations varied from an odds ratio of 3.03 (1.27–7.17) for ceftazidime to 1.33 (1.07–1.75) for trimethoprim. Where overall rates of resistance were relatively low, the effects of living conditions on odds of resistance were greater (Figure 2).

Discussion

This study has demonstrated that relative neighbourhood deprivation is associated with antibiotic resistance. In particular, we have identified that being in the most deprived quintile of the population with respect to living environment, across all eight antibiotics studied, was associated with an increased risk of antibiotic resistance compared to living in the least deprived quintile. Whilst previous studies have related deprivation to antibiotic consumption as a proxy for antibiotic resistance, this study makes the association between neighbourhood deprivation and antibiotic resistance without relying on consumption as a proxy for resistance.

Deprivation indices can be derived using a number of domains, such as income and the living environment. This study suggests that living conditions are consistently associated with antibiotic resistance, after adjusting for other significant predictors within a multivariable analysis. The living environment deprivation index is composed of indoor living conditions (e.g. thermal comfort) and outdoor conditions (e.g. air quality). These factors are known to impact negatively on health and our findings may result indirectly from the adverse health impacts derived from a poor living environment.[15,16] For example, adverse health status may increase antibiotic use or healthcare utilisation, and so increase the selection and transmission of antibiotic resistant bacteria.

The absence of associations with income and health and disability were unexpected, but may be due to methodological limitations. We have been unable to adjust for individual-level income and health outcomes which may, in addition to the structural effects of the living environment, be associated with the risk of antibiotic resistance. We found increasing age to be associated with resistance, in keeping with previous reports and likely due to increased antibiotic consumption by older age groups.[17] Increased antibiotic resistance was significantly associated with increasing population density for five of the eight antibiotics studied. This association has been reported previously. [18] A possible explanation is that as population density increases, so does the transmission of antibiotic resistant strains

The effect of living environment on antibiotic resistance appears to be increased when the prevalence of resistance for a specific antibiotic is lower. The mechanism behind this is unclear, but this effect has also been seen at a national-level in relation to income.[2] A possible explanation is that sustained antibiotic consumption in a population over a period of time increases an individual's probability of contact with an already resistant organism, such that the potential for deprivation to contribute to the selection of antibiotic resistance within an individual is reduced.

This study supports existing evidence for the association between deprivation and increased rates of antibiotic resistance, suggesting that living conditions are strong predictors of increased antibiotic resistance rates. Further studies are required to explore this relationship by incorporating individual-level data with neighbourhood characteristics.

Funding: This work was supported by the Department of Microbiology at Leeds Teaching Hospitals NHS Trust.

Transparency declarations: Nil to declare.

References

1. ECDC/EMEA. The bacterial challenge: time to react, Joint Technical Report from ECDC and EMA. Stockholm, Sweden: European Centre for Disease Prevention and Control, 2009. http://ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=199
2. Kirby A, Herbert A. Correlations between Income Inequality and Antimicrobial Resistance. *PLoS ONE* 2013; **8**: e73115
3. Masiero G, Filippini M, Ferech M *et al*. Socioeconomic determinants of outpatient antibiotic use in Europe. Socioeconomic determinants of outpatient antibiotic use in Europe. *Int J Public Health* 2010; **55**: 469-78.
4. Ilić K, Jakovljević E, Skodrić-Trifunović V. Social-economic factors and irrational antibiotic use as reasons for antibiotic resistance of bacteria causing common childhood infections in primary healthcare. *Eur J Pediatr* 2012; **171**: 767-77.
5. Mangrio E, Wremp A, Moghaddassi M *et al*. Antibiotic use among 8-month-old children in Malmö, Sweden--in relation to child characteristics and parental sociodemographic, psychosocial and lifestyle factors. *BMC Pediatr* 2009; **9**: 31.
6. Curtis C, Marriott J. Is there an association between referral population deprivation and antibiotic prescribing in primary and secondary care? *Int J Pharm Pract* 2008; **16**: 217–222.
7. Covvey JR, Johnson BF, Elliott V *et al*. An association between socioeconomic deprivation and primary care antibiotic prescribing in Scotland. *J Antimicrob Chemother* 2014; **69**: 835-41.
8. Hicks LA, Bartoces MG, Roberts RM *et al*. US Outpatient Antibiotic Prescribing Variation According to Geography, Patient Population, and Provider Specialty in 2011. *Clin Infect Dis* 2015; pii: civ076.

9. Klein EY, Makowsky M, Orlando M *et al*. Influence of provider and urgent care density across different socioeconomic strata on outpatient antibiotic prescribing in the USA. *J Antimicrob Chemother* 2015; pii: dku563.
10. Nilsson P, Laurell MH. Impact of socioeconomic factors and antibiotic prescribing on penicillin- non-susceptible Streptococcus pneumoniae in the city of Malmö. *Scand J Infect Dis* 2005; **37**: 436-41.
11. Horner CS, Abberley N, Denton M *et al*. Surveillance of antibiotic susceptibility of Enterobacteriaceae isolated from urine samples collected from community patients in a large metropolitan area, 2010-2012. *Epidemiol Infect* 2014; **142**: 399-403.
12. McLennan D, Barnes H, Noble M, *et al*. The English Indices of Deprivation 2010. Department for Communities and Local Government, 2011. https://www.gov.uk/government/statistics/english-indices-of-deprivation-2010
13. Bibby, PR, Brindley PG. Urban and Rural Area Definitions for Policy Purposes in England and Wales: Methodology. Office for national statistics, 2013. https://www.gov.uk/government/statistics/2011-rural-urban-classification
14. Hosmer DW & Lemeshow S. *Applied Logistic Regression*. New York: John Wiley & Sons, 2001
15. Wilkinson P, Landon M, Armstrong B *et al*. Cold Comfort: The Social and Environmental Determinants of Excess Winter Deaths in England, 1986–96. Bristol: The Policy Press, 2001.
16. Mustafic H, Jabre P, Caussin C *et al*. Main air pollutants and myocardial infarction: a systematic review and meta-analysis. *JAMA* 2012; **307**: 713–21
17. McGregor JC, Elman MR, Bearden DT *et al*. Sex-and age-specific trends in antibiotic resistance patterns of *Escherichia coli* urinary isolates from outpatients. *BMC Fam Pract* 2013; **22**; 14:25.
18. Bruinsma N, Hutchinson JM, van den Bogaard AE *et al*. J Influence of population density on antibiotic resistance. *J Antimicrob Chemother* 2003; 51:385-90.

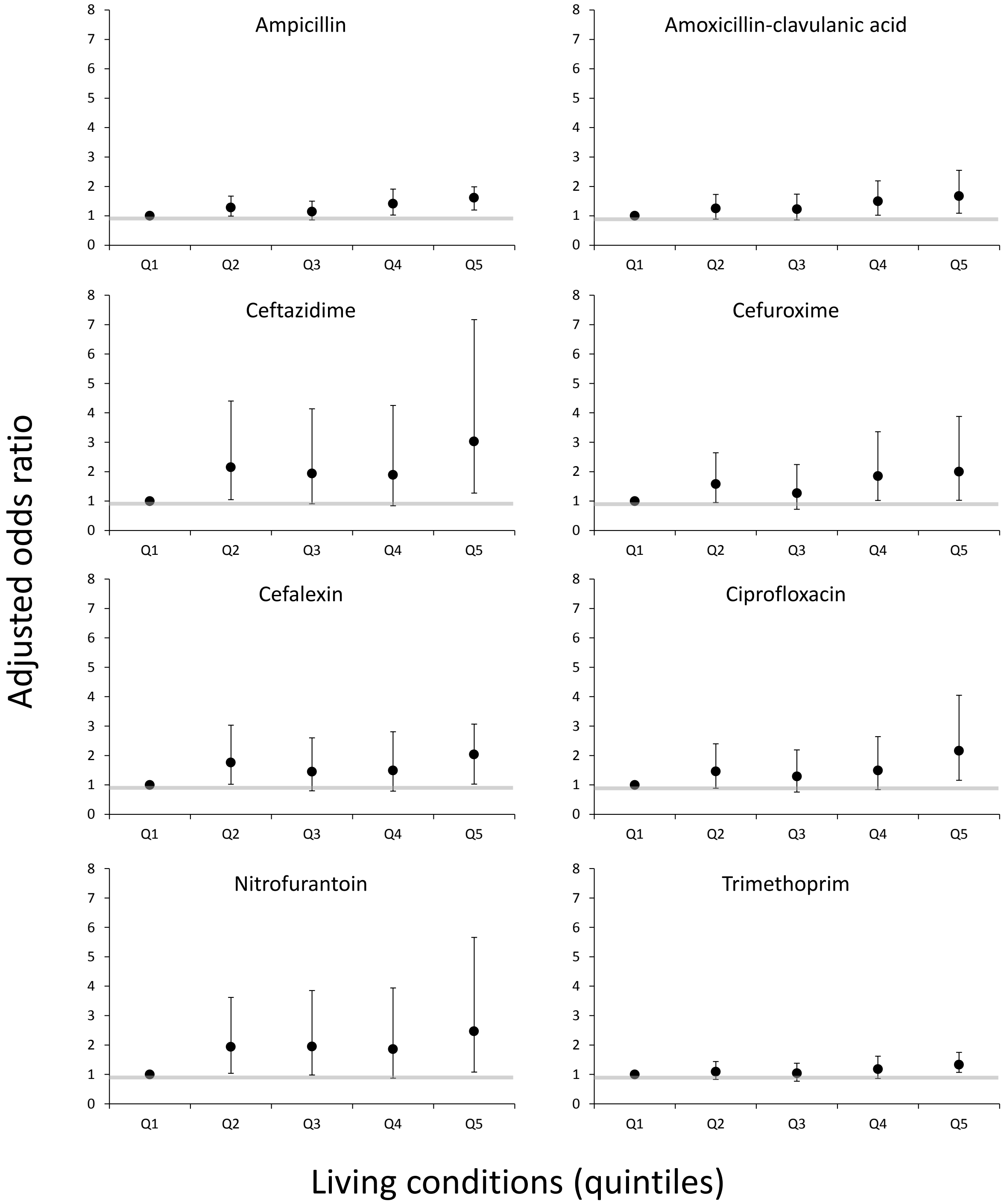

Figure 1. Associations between resistance of *E. coli* and neighbourhood living conditions for eight antibiotics. Quintile 1 (Q1) represents the least deprived living conditions and is used as the reference group, quintile 5 (Q5) the most deprived living conditions. Error bars show 95% confidence intervals of the adjusted odds ratio. Associations have been adjusted for age, sex, population density, rural/urban nature and education deprivation (cefuroxime, nitrofurantoin only).

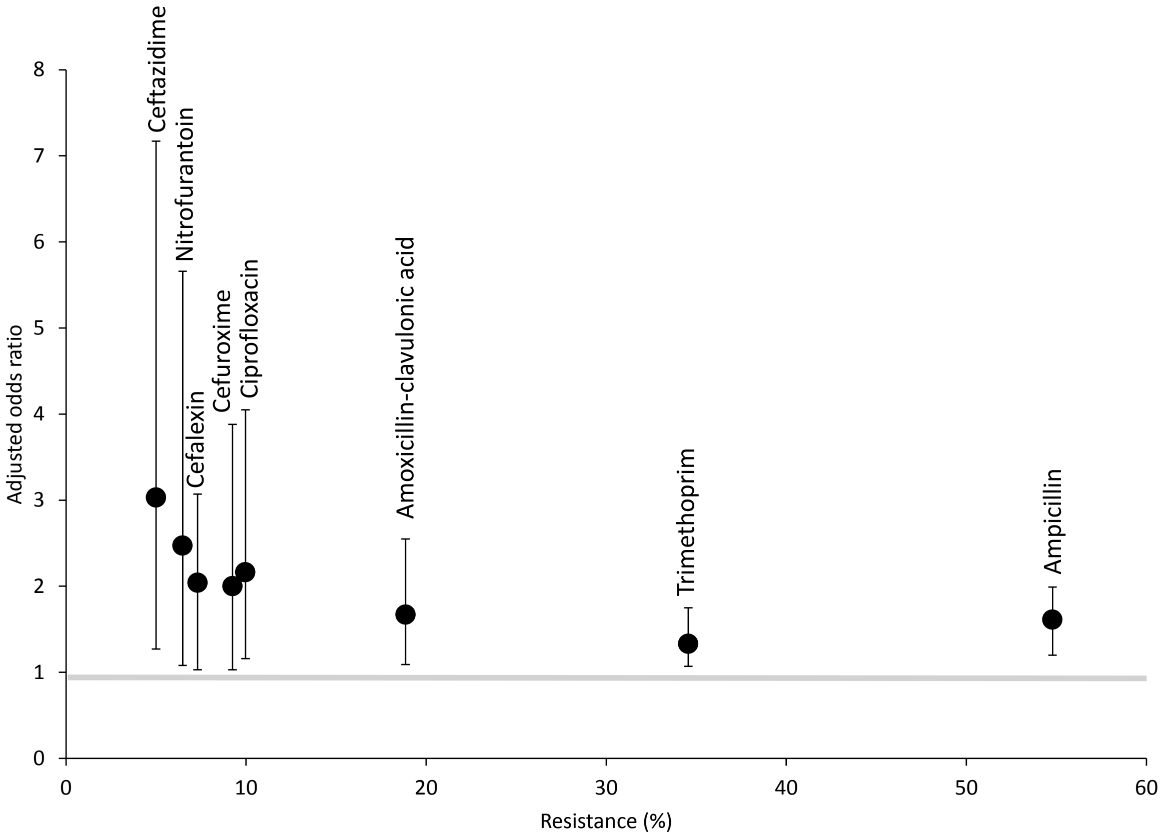

Figure 2. Correlation between levels of antibiotic resistance and magnitude of the association between living conditions and individual-level odds of resistance. Each datapoint represents a single antibiotic ranked according to percentages of resistant isolates within the dataset: ceftazidime (5.0%), nitrofurantoin (6.5%), cefalexin (7.3%), cefuroxime (9.3%), ciprofloxacin (10.0%), amoxicillin-clavulanic acid (18.9%), trimethoprim (34.6%) and ampicillin (54.8%). The odds ratio is the adjusted association between antibiotic resistance and living in the quintile of Leeds with the most deprived living conditions vs. the least deprived living conditions. Error bars show 95% confidence intervals of the adjusted odds ratio. Associations have been adjusted for age, sex, population density, rural/urban nature and education deprivation (cefuroxime, nitrofurantoin only).