J Antimicrob Chemother 2019; **74**: 3379–3383
doi:10.1093/jac/dkz312 Advance Access publication 17 July 2019

Journal of Antimicrobial Chemotherapy

Broad-spectrum antibiotic use in Europe: more evidence of cultural influences on prescribing behaviour

Michael A. Borg[1,2]* and Liberato Camilleri[1]

[1]*University of Malta, Msida, Malta;* [2]*Mater Dei Hospital, Msida, Malta*

*Corresponding author. Department of Infection Prevention & Control, Mater Dei Hospital, Msida, Malta. Tel: +356 2545 4528; Fax: +356 2545 7474; E-mail: michael.a.borg@gov.mt

Received 9 April 2019; returned 10 May 2019; revised 13 May 2019; accepted 21 June 2019

Objectives: Sociocultural factors have been hypothesized as important drivers of inappropriate antibiotic prescribing in European ambulatory care. This study sought to assess whether they can also explain the reported variation in broad-spectrum antibiotic (Br-Ab) use among EU/European Economic Area (EEA) countries.

Methods: Correlation and regression analysis were performed, using the bootstrap method, between Br-Ab ratios reported from 28 EU countries by the ECDC, and national Hofstede cultural dimensions and control of corruption (CoC) scores.

Results: Significant bootstrapping correlation coefficients were identified between Br-Ab ratios and the dimension of uncertainty avoidance (UAI) as well as CoC. However, following both bootstrapping multiple regression and generalized linear modelling, only UAI was retained as the sole predictor. A logarithmic model explained 58.6% of the variation in European Br-Ab variability solely using national UAI scores ($P<0.001$).

Conclusions: Br-Ab prescribing appears to be driven by the level of UAI within the country. Any interventions aimed at reducing Br-Ab in high-consuming EU/EEA countries need to address this cultural perception to maximize their chances of success.

Introduction

The importance of social and behavioural factors in antibiotic prescribing has been belatedly recognized.[1] Cultural determinants have arguably provided the most plausible explanation for the variation in antibiotic consumption levels between countries of the EU and European Economic Area (EEA),[2] as well as in practices that are either anathema to basic medical principles (prescribing of antibiotics for colds, influenza and sore throat),[3] or which are incompatible with irrefutable scientific evidence (excessively prolonged surgical prophylaxis).[4] These studies have utilized the anthropological model developed by Geert Hofstede, which proposes that national cultures vary along consistent, fundamental dimensions (Table 1).[5] The behavioural constructs of power distance (PDI), masculinity (MAS) and uncertainty avoidance (UAI) appear to be particularly relevant.[6] More recently, an association between antibiotic use in Europe and levels of corruption has also been suggested.[7]

It has long been reported that a significant variability exists in broad-spectrum antibiotic (Br-Ab) use between EU/EEA countries.[8] Narrow-spectrum formulations, especially penicillin V, are predominantly used in Scandinavia for the treatment of respiratory infections whereas doctors in southern and eastern European countries generally prescribe antimicrobials with a far wider spectrum of activity for the same conditions. This variability is important because Br-Abs are known to be potent disrupters of the human microbiome, especially within the large intestine, which can result in the proliferation of resistant mutants.[9] No plausible explanation has been provided for this geographical disparity. Indeed, Br-Ab prescribing decisions in high-consuming countries are often at odds with local antimicrobial resistance (AMR) epidemiology.[10] We therefore sought to investigate whether Hofstede's cultural dimensions can also explain the differences in Br-Ab use within EU/EEA countries.

Methods

For the purpose of the study, information on Br-Ab use in community care within the EU/EEA was sourced from the publicly available antimicrobial consumption database of ESAC-Net, a surveillance network coordinated by the ECDC (https://ecdc.europa.eu/en/antimicrobial-consumption/surveillance-and-disease-data/database). One of the quality indicators reported by this database is the broad-spectrum index (BrSI). It calculates the average ratio of consumption of broad-spectrum penicillins, cephalosporins and macrolides (except erythromycin) against consumption of narrow-

Table 1. Hofstede cultural dimensions, adapted from Hofstede *et al.*[5]

Power distance (PDI)	Indicates how hierarchy and power distribution are organized within society. In high PDI cultures, less powerful members accept and expect that power is distributed unequally.
Uncertainty avoidance (UAI)	Indicates the extent to which a society tolerates uncertainty and ambiguity. In high UAI cultures, individuals feel discomfort and stress in unstructured situations that are novel, unknown or different from usual.
Individualism (IDV)	Refers to the integration of individuals within society. In high IDV cultures, people tend to value independence and form loose groups, in contrast to tight inter-dependent groups of collectivist societies.
Masculinity (MAS)	Refers to the distribution of roles within society. In masculine cultures, ego needs, assertiveness, targets and success are emphasized, whereas feminine cultures focus on caring for the weak and quality of life.
Long-term orientation (LTO)	Reflects long-term pragmatic versus short-term normative attitudes. Cultures scoring high on LTO show a pragmatic emphasis on future rewards and adaptation to changing circumstances.
Indulgence (IVR)	Reflects societies that encourage people to enjoy life and have fun as opposed to societies where restraint is emphasized.

spectrum penicillins, cephalosporins and macrolides (erythromycin) per country. BrSI ratios for the years 2015, 2016 and 2017 were extracted from the ECDC database. Countries unable to provide separate community data (Cyprus, Romania) were excluded from the analysis. In order to reduce possible inter-year reporting variability, the BrSI for each country was averaged for the three study years. Scores for PDI, MAS, UAI, individualism (IDV), long-term orientation (LTO) and indulgence (IVR) were collated from Hofstede's publicly available resource (https://www.hofstede-insights.com/product/compare-countries). Control of corruption (CoC) indices were extracted from the World Bank Worldwide Governance Indicators (https://datacatalog.worldbank.org/dataset/worldwide-governance-indicators).

The respective data per country were input into Excel (Microsoft Excel 2016, Microsoft Corp.) for preliminary evaluation and averaging of BrSI ratios. The bootstrapping method was used to obtain robust individual estimates of correlation and regression coefficients within the BrSI dataset. This method was chosen because of the small sample size (28 countries) and violation of certain assumptions, including normality and homoscedasticity. Correlation coefficients were computed to separately assess the strength of the relationship between the BrSI ratios and each of the six Hofstede cultural dimensions and CoC scores. Multiple bootstrapped regression analysis as well as generalized linear modelling were then used to analyse all the predictors collectively, in order to take into account their mutual effect. Analyses were performed using Statistical Package for the Social Sciences, Version 25 (SPSS Inc., Chicago, IL, USA) assuming a 0.05 level of significance.

Results

The average BrSI country ratio for the years 2015 to 2017 ranged from 0.18 in Norway to 245 in Greece and Italy (Figure 1). The bootstrapping 95% CI of the correlation coefficients between BrSI and each cultural score as well as with the CoC index showed significant, positive correlation with UAI (95% CI=0.337 to 0.771) and negative correlation with CoC (95% CI=−0.692 to −0.192). At the same time, UAI was significantly negatively associated with CoC (95% CI=−0.799 to −0.424). Following bootstrapped multiple regression analysis, only UAI was retained as a significant predictor in the model fit. Repeating the analysis using a generalized linear model yielded the same outcome, with UAI again being the sole predictor (95% CI=−0.0014 to −0.0004). Regression analysis of UAI, after logarithmic transformation of BrSI to address the skewness and satisfy normality assumptions, yielded a model with R^2=0.586 and P<0.001 (Figure 2).

Discussion

Our study continues to highlight that antibiotic prescribing in EU/EEA countries appears to be strongly influenced by deep-rooted, socio-anthropological values. It is not surprising that, of all the cultural dimensions, UAI was the variable that showed a significant relationship with Br-Ab prescribing. This dimension estimates the extent to which a society tolerates uncertainty and ambiguity. High-UAI cultures often try to counteract the unease created by situations of uncertainty through adoption of dogmatic, bureaucratic or excessive measures, even where there is no evidence of cost-effectiveness or risk attenuation.[5] Community-associated infections present a challenge of ambiguity to the clinician, especially since laboratory diagnostic support is often unavailable.[11] In high-UAI countries, prescribing Br-Ab can be hypothesized to offer a means of assuaging that uncertainty. The CoC index was the only other factor that exhibited significant univariate correlation with BrSI. Various theories have been put forward to explain the link between corruption and inappropriate antibiotic use in Europe, including bribery and financial dependence of doctors on pharmaceutical firms.[7] The fact that corruption was ultimately found to be non-significant in our study suggests that the relationship is spurious, the result of the already-reported strong association between CoC and UAI.[12] We postulate that doctors in high-UAI countries opt for broader-spectrum formulations, not for nefarious reasons, but instinctively to lessen uncertainty and obtain a perceived reassurance that any possible pathogen would be covered 'just in case'![6]

The log regression model explained almost 60% of the variation in BrSI between EU/EEA countries solely from the UAI country score, which is a completely unrelated anthropological measurement. While correlation does not automatically infer causality, cultural determinants have now provided explanations for practically every aspect of inappropriate antibiotic prescribing in Europe.[5] Indeed, these behavioural drivers offer a far more plausible rationale to elucidate the heterogeneity of antibiotic quality indicators in the EU/EEA than any economic or structural factors.[13] Schein[14] has defined culture as 'a pattern of shared basic assumptions learned by a group as it solved its problems of external adaptation and internal integration'. Changing such a deep-rooted 'software of the mind'[5] is unlikely to be achieved using solely educational

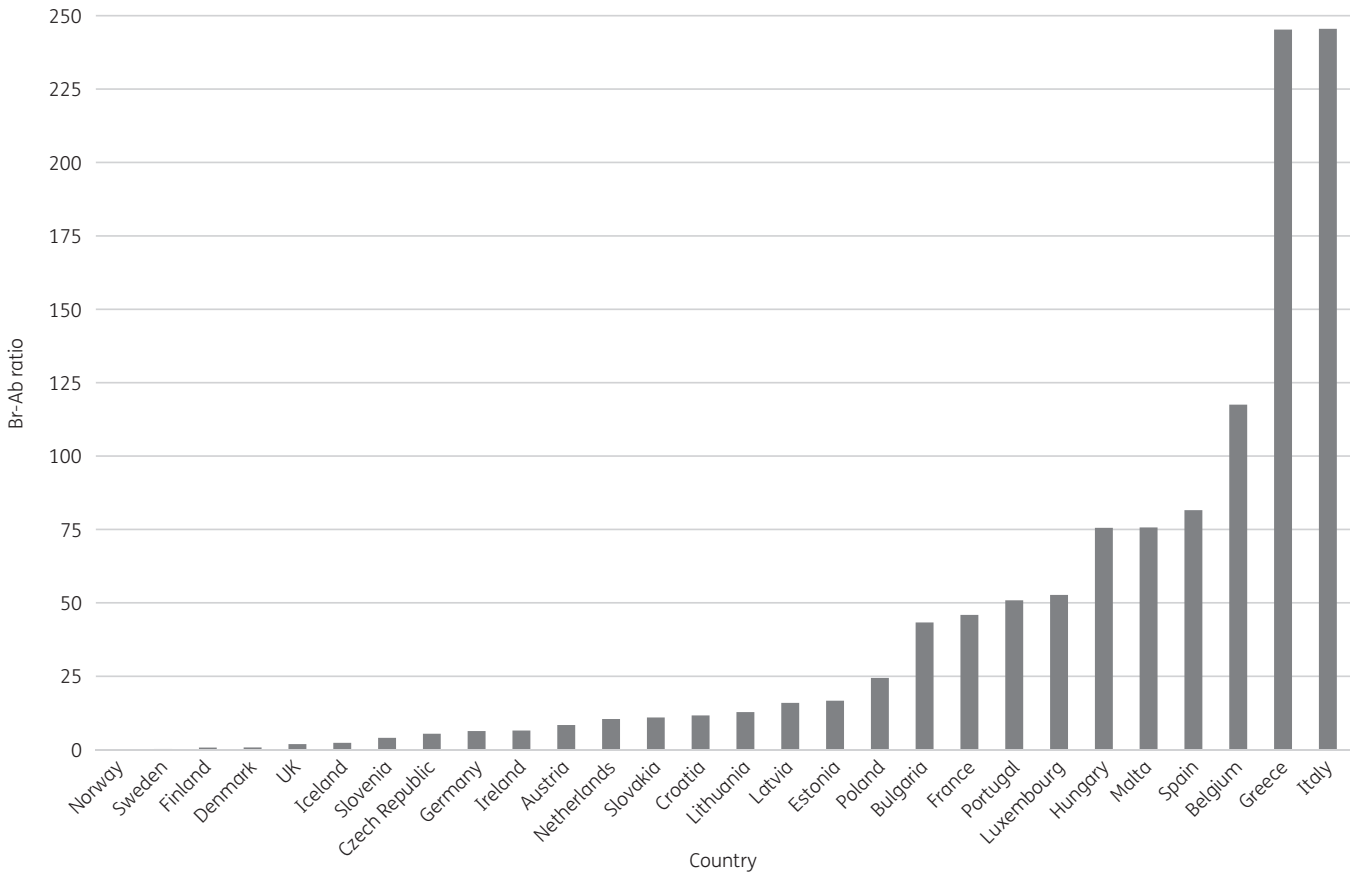

Figure 1. Br-Ab ratio for the 28 studied EU/EEA countries (source: ECDC) aggregated for the years 2015 to 2017.

interventions. Indeed, Schein[14] goes further in pointing out that 'human minds need cognitive stability and any challenge of a basic assumption will release anxiety and defensiveness'. The majority of publications describing successful antibiotic stewardship interventions tend to originate from North America, Australia, the British Isles and Scandinavia.[15] They are invariably underpinned by a strong adhocratic emphasis on multidisciplinary treatment guidelines.[16] Such an approach is congruent with their low UAI and PDI; a cultural combination that is found in no other countries worldwide.[5] However, attitudes to antibiotic guidelines are often very different among doctors within high-UAI and -PDI countries, who may widely view them as an infringement of their prescribing power and being less relevant than the perceived certainty of anecdotal personal experiences.[17]

Since countries with high Br-Ab prescribing also exhibit above-average AMR, it could be postulated that Br-Ab prescribing may be driven by a clinical need. Yet the highest consumption of quinolones occurs in countries where resistance within Gram-negative bacteria exceeds 25%, well beyond the safe threshold for empirical prescribing.[18] The same applies for broad-spectrum β-lactams and penicillin-resistant *Streptococcus pneumoniae*.[19] Above all, the hypothesis is not supported by the findings of AMR country visits carried out by the ECDC in recent years within high-prescribing EU/EEA countries.[20] A study of this specific focus will invariably have some limitations. Other factors not included in the model, such as population, geographic distribution, pharmaceutical availabilities and healthcare structures, could be relevant drivers of Br-Ab prescribing behaviour. However, studies that looked at the differences in antibiotic consumption between EU/EEA countries have failed to identify any such structural determinants.[13] Even if some confounding were to be a factor, the high correlation identified suggests that cultural determinants, which have been in existence for thousands of years, are likely major drivers behind the observed variation in the prescribing of Br-Abs within EU/EEA countries. It is therefore not surprising that antibiotic practices in many southern and eastern European countries remain a massive challenge, despite more than a decade of guideline development and awareness campaigns.[21,22]

Our study is relevant because it suggests that interventions aimed at reducing Br-Ab prescribing in high-consuming EU/EEA countries cannot remain purely medical in nature but must address underlying cultural traits among the prescribers. An obvious approach would be to reduce the element of uncertainty in the diagnosis and treatment of community infections for both doctor and patient. Adoption of rapid antigen detection testing (RADT) by GPs in Spain, a country with high UAI, successfully reduced inappropriate prescribing.[23] Even so, antibiotics were still prescribed in more than 30% of cases with negative RADT results, supporting the pervasive effect of cultural drivers. Tacconelli and Pezzani[24] have proposed that the only way to improve prescribing practices

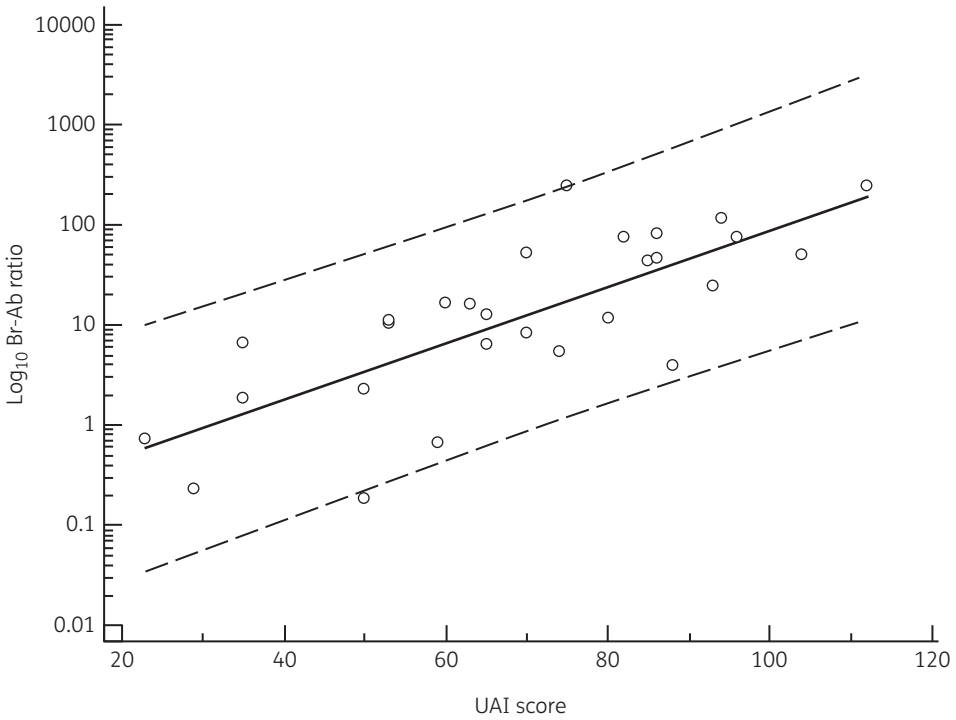

Figure 2. Scatter diagram of UAI scores and $\log_{10}$ Br-Ab ratios for studied EU/EAA countries with regression (continuous) and 95% prediction (broken) lines (R^2=0.586 and P<0.001).

in high-consuming European countries is through mandated targets and national consequences for suboptimal practices. If such initiatives can permeate down to prescriber level, the accountability element would introduce a new uncertainty factor in the equation that could displace the one created by the clinical situation. Well-designed behaviour change studies from high-UAI countries are sorely needed to inform more effective antibiotic stewardship programmes in these settings.

Acknowledgements

We would like to thank Dr Dominique Monnet (Head of Disease Programme Antimicrobial Resistance at the ECDC) for his helpful comments on the manuscript prior to submission.

Funding

This study was supported by internal funding.

Transparency declarations

None to declare.

References

1 Tonkin-Crine S, Walker AS, Butler CC. Contribution of behavioural science to antibiotic stewardship. *BMJ* 2015; **350**: h3413.

2 Deschepper R, Grigoryan L, Lundborg CS *et al*. Are cultural dimensions relevant for explaining cross-national differences in antibiotic use in Europe? *BMC Health Serv Res* 2008; **8**: 123.

3 Borg MA. National cultural dimensions as drivers of inappropriate ambulatory care consumption of antibiotics in Europe and their relevance to awareness campaigns. *J Antimicrob Chemother* 2012; **67**: 763–7.

4 Borg MA. Prolonged perioperative surgical prophylaxis within European hospitals: an exercise in uncertainty avoidance? *J Antimicrob Chemother* 2014; **69**: 1142–4.

5 Hofstede G, Hofstede GJ, Minkov M. *Cultures and Organizations: Software of the Mind*. New York, NY, USA: McGraw-Hill, 2010.

6 Touboul-Lundgren P, Jensen S, Drai J *et al*. Identification of cultural determinants of antibiotic use cited in primary care in Europe: a mixed research synthesis study of integrated design "Culture is all around us". *BMC Public Health* 2015; **15**: 908.

7 Rönnerstrand B, Lapuente V. Corruption and use of antibiotics in regions of Europe. *Health Policy* 2017; **121**: 250–6.

8 Cars O, Mölstad S, Melander A. Variation in antibiotic use in the European Union. *Lancet* 2001; **357**: 1851–3.

9 Francino MP. Antibiotics and the human gut microbiome: dysbioses and accumulation of resistances. *Front Microbiol* 2016; **6**: 1543.

10 McDonnell L, Armstrong D, Ashworth M *et al*. National disparities in the relationship between antimicrobial resistance and antimicrobial consumption in Europe: an observational study in 29 countries. *J Antimicrob Chemother* 2017; **72**: 3199–204.

11 Stanton N, Francis NA, Butler CC. Reducing uncertainty in managing respiratory tract infections in primary care. *Br J Gen Pract* 2010; **60**: e466–75.

12 Husted BW. Wealth, culture, and corruption. *J Int Bus Stud* 1999; **30**: 339–59.

13 Gaygısız Ü, Lajunen T, Gaygısız E. Socio-economic factors, cultural values, national personality and antibiotics use: a cross-cultural study among European countries. *J Infect Public Health* 2017; **10**: 755–60.

14 Schein EH. *Organizational Culture and Leadership*. San Francisco, CA, USA: Jossey Bass, 2017.

15 Tonkin-Crine SK, Tan PS, van Hecke O. Clinician-targeted interventions to influence antibiotic prescribing behaviour for acute respiratory infections in primary care: an overview of systematic reviews. *Cochrane Database Syst Rev* 2017; issue 9: CD012252.

16 Mölstad S, Löfmark S, Carlin K *et al*. Lessons learnt during 20 years of the Swedish strategic programme against antibiotic resistance. *Bull World Health Organ* 2017; **95**: 764–73.

17 Formoso G, Liberati A, Magrini N. Practice guidelines: useful and "participative" method? Survey of Italian physicians by professional setting. *Arch Intern Med* 2001; **161**: 2037–42.

18 ECDC, European Food Safety Authority, EMA. ECDC/EFSA/EMA first joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals. *EFSA J* 2015; **13**: 4006.

19 Bronzwaer SL, Cars O, Buchholz U *et al*. A European study on the relationship between antimicrobial use and antimicrobial resistance. *Emerg Infect Dis* 2002; **8**: 278–82.

20 Menichetti F, Falcone M, Lopalco P *et al*. The GISA call to action for the appropriate use of antimicrobials and the control of antimicrobial resistance in Italy. *Int J Antimicrob Agents* 2018; **52**: 127–34.

21 Finch R, Sharland M. 18 November and beyond: observations on the EU Antibiotic Awareness Day. *J Antimicrob Chemother* 2009; **63**: 633–5.

22 Humphreys G. Are antibiotics still "automatic" in France? *Bull World Health Organ* 2011; **89**: 8–9.

23 Llor C, Madurell J, Balagué-Corbella M *et al*. Impact on antibiotic prescription of rapid antigen detection testing in acute pharyngitis in adults: a randomised clinical trial. *Br J Gen Pract* 2011; **61**: e244–51.

24 Tacconelli E, Pezzani MD. Public health burden of antimicrobial resistance in Europe. *Lancet Infect Dis* 2019; **19**: 4–6.