

Explaining variation in antibiotic prescribing between general practices in the UK

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Running title: Practice variation in antibiotic prescribing

Abstract

Objectives: Primary care practices in England differ in antibiotic prescribing rates, and, anecdotally, prescribers justify high prescribing rates based on their individual case mix. The aim of this paper was to explore to what extent factors such as patient comorbidities explain this variation in antibiotic prescribing.

Methods: Primary care consultation and prescribing data recorded in The Health Improvement Network (THIN) database in 2013 were used. Boosted regression trees (BRT) and negative binomial regression (NBR) models were used to evaluate associations between predictors and antibiotic prescribing rates. The following variables were considered as potential predictors: various infection-related consultation rates, proportions of patients with comorbidities, proportion of patients with inhaled/systemic corticosteroids or immunosuppressive drugs, and demographic traits.

Results: The median antibiotic prescribing rate was 65.6 (IQR 57.4-74.0) per 100 registered patients among 348 English practices. In the BRT model, consultation rates had the largest total relative influence on antibiotic prescribing rate (53.5%), followed by steroid and immunosuppressive drugs (31.6%) and comorbidities (12.2%). Only 21% of the deviance could be explained by a NRB model considering only comorbidities and age and gender, while 57% of the deviance could be explained by the model considering all variables.

Conclusions: The majority of practice-level variation in antibiotic prescribing cannot be explained by variation in prevalence of comorbidity. Factors such as high consultation rates for respiratory tract infections and high prescribing rates for corticosteroids could explain much of the variation, and as such may be considered in determining a practices potential to reduce prescribing.

Introduction

There is substantial variation in antibiotic prescribing rates between general practices.¹ Part of this variation may be due to medically legitimate reasons, such as differences in the prevalence of comorbidities or in the age and gender distributions of practices' catchment populations. For example, the National Institute for Health and Care Excellence (NICE) recommends avoiding antibiotic treatment for self-limiting respiratory tract infections (RTIs), except if the patient is at high risk of serious complications because of pre-existing comorbidity.² Hence, one would expect higher prescribing rates in practices with a relatively high number of patients with pre-existing comorbidity compared to practices with mainly healthy patients without comorbidities. Similarly, a practice with a high proportion of young children or elderly would be expected to have higher prescribing rates than a practice with mainly working-age adults.¹

On the other hand, a substantial fraction of antibiotic prescriptions in primary care are likely to be inappropriate (defined here as clinically unnecessary).^{3,4} Variation in the percentage of antibiotics that are prescribed unnecessarily, may also explain part of the between-practice variation in antibiotic prescribing rates. To date, it is unclear to what extent observed variation in prescribing between practices is due to legitimate medical reasons and how much can be explained by differences in the amount of inappropriate antibiotic prescribing.

In England, to account for differences in the age and gender profiles of patients that may explain legitimate variation between practices, comparisons of antibiotic prescribing rates are typically performed by evaluating antibiotic use per STAR-PU (Specific Therapeutic group Age-sex weighting Related Prescribing Units).⁵⁻⁷ In the case of antibiotics, STAR-PU weightings are based on the number of antibiotic prescriptions in 16 different age-gender categories (Table 1).⁶ Using STAR-PU as the denominator instead of the number of registered patients is intended to result in fairer comparisons between practices. However, it is at least questionable whether it is fair to make comparisons and judge practices based on STAR-PU while ignoring other differences in case-mix. Patient populations with equal STAR-PU denominators might differ in the prevalence of

comorbidities and consultation rates for various infections. These remaining differences might legitimately explain at least some between-practice variation in antibiotic prescribing.

In this study, we evaluated the extent to which differences in comorbidity prevalence, the use of certain drugs, demographics and consultation rates could explain variation in antibiotic prescribing, beyond differences already explained by STAR-PU. Better insight into the importance of these variables in determining antibiotic prescribing rates is needed to better inform policies around inappropriate antibiotic prescribing in primary care.^{8,9} If variation in antibiotic prescribing per STAR-PU cannot be explained by differences in the prevalence of comorbidities or markers of frailty, such as consultation rates, then one can more comfortably set a single prescribing reduction target for all practices. By contrast, if these factors do play an important role, one may avoid using the same target for all practices or develop an alternative way of expressing antibiotic use that accounts for additional predictors of antibiotic prescribing.

Methods

Ethics

The Health Improvement Network (THIN) data were used for this work. The data collection scheme for THIN is approved by the UK Multicentre Research Ethics Committee (reference number: 07H1102103). In accordance with this approval, the study protocol was reviewed and approved by an independent Scientific Review Committee (SRC) (reference numbers 16THIN071 and 16THIN071-A1).

Data

This cross-sectional study used data from the UK's THIN, a large primary care electronic medical record database covering more than 3.7million active patients (about 7% of the general UK population).^{10–13} We extracted THIN data from English practices meeting acceptable standard for research data collection and with complete data for the whole period between January 2013 and December 2013.

We identified all systemic antibiotic prescriptions (British National Formulary chapter 5.1, except antituberculosis drugs [5.1.9] and antileprotic drugs [5.1.10]¹⁴) among permanently registered patients. The number of patients registered in each gender-age category (Table 1) at each practice was determined by counting the number of permanently registered patients in each category of interest at 1 July 2013, thereby assuming a relatively stable number of patients throughout the year. The amount of STAR-PU per practice was subsequently estimated by multiplying the number of patients in each category by the relevant STAR-PU weights.

We considered overall consultation rate as well as consultation rates for specific conditions, comorbidities, the use of certain prescription drugs and demographics as potential predictors of antibiotic prescribing rates. Consultation rates for the following common infection related conditions were considered: upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI), urinary tract infection (UTI), skin condition and acute otitis media (AOM).¹ URTI included sinusitis,

common cold/nasopharyngitis, sore throat, laryngitis/tracheitis and unspecific upper respiratory tract infections. LRTI included cough, exacerbations of chronic obstructive pulmonary disease (COPD), acute bronchitis, pneumonia and unspecific LRTI. UTI included both lower and upper urinary tract infections. Skin conditions included impetigo, cellulitis, boil/cyst/abscess and acne. Consultation rates were expressed as the number of consultations per 1000 registered patients.

Relevant comorbidities were based on the Read codes that indicate high-risk patients who qualify for the free seasonal influenza vaccination programme.^{15,16} The Read code classification represents a terminology used to code primary care electronic health records in the UK.¹⁷ The selected comorbidities were asthma, chronic kidney disease, chronic respiratory disease, chronic heart disease, diabetes, chronic liver disease, immunosuppression and chronic neurological disease.^{15,16} Of these considered comorbidities, GP-specific prevalences are publicly available at the national level for asthma, chronic kidney disease, chronic respiratory disease, chronic heart disease and diabetes via the Quality Outcomes Framework (QOF) indicators.¹⁸ Ideally one would use a model with variables that are all also publicly available on a general practice level. This would facilitate fair comparisons of antibiotic prescribing levels between practices not captured within THIN, accounting for those publicly available variables. The proportion of patients with the relevant comorbidities per practice was measured on 1 July 2013.

Besides these comorbidities, we also identified the proportion of patients within each practice that received at least two prescriptions of one of the following drugs in the 365 days before 1 July 2013: immunosuppressive drugs, inhaled corticosteroids and systemic corticosteroids. These drugs are considered as indicators for patients at risk for complications after (respiratory tract) infections.^{15,16}

Statistical analyses

The association between the potential predictor variables listed above and the number of antibiotic prescriptions per STAR-PU was analysed by general practice. We used two different methods: a

conventional negative binomial regression (NBR) model¹⁹ and a stochastic Poisson boosted regression tree (BRT) model.²⁰ The number of antibiotic prescriptions was modelled as the outcome with the natural logarithm of the number of STAR-PUs per practice as an offset.

Boosted regression trees

An advantage of the BRT model is that it can handle complex non-linear relationships with the outcome – almost all considered predictors were on a continuous scale – and its results can be intuitively understood, with results presented as the relative influence of each variable (i.e. predictor) and using partial dependence plots. The relative importance is a measure based on the number of times a variable is selected for splitting, weighted by the squared improvement to the model as a result of each split, and averaged over all trees.²⁰ The relative importance of all variables included in the model sum up to 100.^{20–22} The partial dependence plots show the effect of a variable on antibiotic prescribing rate per STAR-PU after accounting for the average effects of all other variables in the model. For this BRT model, all potential predictor variables were considered at once. We used a bagging fraction of 0.5 – making the model stochastic - and fixed the tree complexity to 1, because we were only interested in main effects and not in interactions between the predictor variables. We ran the stochastic BRT model 1000 times and averaged results over these runs. All BRT analyses were performed using the ‘gbm’ and ‘dismo’ package in R version 3.2.2.^{21,22}

Negative binomial regression model

We also evaluated associations between the predictor variables listed previously and the number of antibiotics per STAR-PU using NBR models. We built six different models, each with a different set of potential predictor variables. For each model, variables were selected for inclusion in the final model based on the Akaike Information Criterion (AIC). For model 1 we did not consider any potential predictors. For model 2 we considered comorbidities that are captured by the QOF indicators, i.e. asthma, chronic kidney disease, chronic respiratory disease, chronic heart disease and diabetes, and

demographics (the proportion of patients being male and the proportions aged <19 year and >64 year).¹⁸ For model 3, we additionally considered the proportion of patients having received at least two prescriptions of immunosuppressive drugs, inhaled corticosteroids or systemic corticosteroids.²³ For model 4, we also considered the proportion of patients with chronic liver disease, immunosuppressive diseases and chronic neurological disease (no QOF indicators). For model 5, we also considered the practice's consultation rate. Model 6 considered the same variables as model 5, but without any comorbidity.

Comparing countries within the UK

It has been suggested that variation in antibiotic prescribing rates in England could be mainly explained by geographical location of the practice, independent of practice and patient population characteristics.^{24,25} Although we had insufficient data to explore geographical variation within England, the THIN data allowed us to evaluate whether the country (England, Scotland, Wales or Northern Ireland) would explain much of the variation between practices. Since the STAR-PU weighting is based on England data only,⁵ we expressed for this analysis the antibiotic prescribing rate as the number of antibiotics per mid-year population. The analysis was performed in the same way as the previously described BRT model, except that the natural logarithm of the number of registered patients at 1 July 2013 was used as an offset.

Results

In total, 552 practices were included for analyses. Of those, 348 practices were located in England, 61 in Wales, 110 in Scotland and 33 in Northern Ireland. For the primary analysis, we focused on general practices from England. The characteristics of the 348 practices in England are shown in

Table 2. There was considerable variation in antibiotic prescribing rates, consultation rates, and the percentage of registered patients with relevant comorbidities.

Boosted regression trees

We used BRT to evaluate the relative importance of predictor variables in explaining between-practice variation in the number of antibiotic prescriptions per STAR-PU. The relative importance of each variable is shown in Figure 1. The cross-validation deviance of the full BRT model was 114.

After averaging over 1000 runs, the variables with the largest relative influence were URTI consultation rates (18.7%), LRTI consultation rates (18.2%), percentage of patients receiving at least two prescriptions of systemic steroids (13.7%), and the percentage of patients receiving at least two prescriptions of inhaled steroids (12.6%). When summing the relative influences of all consultation rates, drugs and comorbidities, consultation rates had the largest total relative influence (49.9%), followed by steroid and immunosuppressive drugs (27.6%) and comorbidities (16.8%). The effect of the six predictor variables with the largest relative influence were plotted using partial dependence plots (Figure 2). As can be seen from these plots, the most important variables have a positive association with the number of antibiotics per STAR-PU. The skin consultation rates and percentage of patients with liver disease seem to have a negative association with the number of antibiotics per STAR-PU.

Negative binomial regression models

We also evaluated associations between the predictor variables and the number of antibiotics per STAR-PU using NBR models. The variables included in the final six models, their fit compared to the null model (model 1) are shown in Table 3. As indicated by lower AICs and more explained deviance, models 5 and 6 (which both include consultation rate) provide the best fit to the data. The small difference in percentage reduction in deviance between these models indicates that, accounting for other variables, the importance of comorbidities in explaining differences in antibiotic prescribing

rates per STAR-PU is limited. This is in line with the results of the BRT model where antibiotic prescribing rates per STAR-PU were mainly explained by consultation rates and the percentage of patients receiving at least two prescriptions of steroids or immunosuppressive drugs. The BRT model gave also similar predictions as the full NBR model (model 5) as shown in Figure 3. While model 2 – allowing publicly available comorbidities and demographics into the model – explained 17% of the deviance, only 11% of the deviance was explained by a model considering only publicly available comorbidities.

Comparing countries within the UK

Noticeable differences in the crude median antibiotic prescribing rates per 100 registered patients were observed between countries in the UK: 65.6 (IQR 57.4 – 74.0) in England; 70.0 (IQR 58.0 – 79.1) in Scotland; 77.1 (IQR 68.5 – 86.5) in Wales; and 90.2 (IQR 76.1 – 103.9) in Northern Ireland. Country was an important predictor of antibiotic prescribing rates in the BRT model (Figures 4 and 5). Variables that had an even stronger influence than country were the percentage of patients receiving at least two prescriptions of inhaled steroids or systemic steroids and the URTI consultation rate. The LRTI consultation rate and the percentage of patients with coronary heart disease were also among the 6 most influential predictors (Figure 4).

Discussion

Between-practice variation in age- and gender-weighted antibiotic prescribing rates could be partly explained by differences in consultation rates for various infectious conditions and the percentage of patients receiving inhaled and systemic steroids, as well as other factors to a lesser degree. Although patients with comorbidities are more likely to receive antibiotics,²⁶ both the BRT model and the more traditional NBR model indicated that comorbidities had much lower explanatory power. Even the most extensive NBR model, considering consultations rates, comorbidities, steroid and immunosuppressive use and demographics could not explain 47% of the total deviance, suggesting that a considerable amount of the between-practice variation is caused by other factors, such as inappropriate prescribing.³

It is important to consider whether differences in consultation rates and prescribing rates for inhaled and systemic steroids reflect legitimate medical reasons for variation in antibiotic prescribing rates. If they do, policies to reduce prescribing should take into account these factors. However, if these variables do not represent legitimate medical reasons for variation in antibiotic prescribing, they can safely be ignored. Apparent differences in consultation rates can have several causes. First, incidences of infection are known to vary by region, partly due to variation in behavioural, demographic, socioeconomic, health characteristics of the population in different areas.^{27–32} Variation in the incidence of infections can be considered as a legitimate reason for variation in antibiotic prescribing. Second, differences in health-care seeking behaviour may affect consultation rates. Some prescribers might attract patients who seek care for even mild cases of disease. If a proportion of these patients, who may be less frequently if ever seen in other practices, still receive an antibiotic because of diagnostic uncertainty and/or to meet patients' needs within a short consultation,^{33,34} higher prescribing rates would be observed at practices with a patient population with higher health-care seeking behaviour. This type of variation in health-care seeking behaviour may not be considered a legitimate reason for variation in antibiotic prescribing. In fact, high antibiotic prescribing rates might actually result in higher consultation rates and medicalisation of

self-limiting infections.^{35,36} Third, differences in diagnostic coding behaviour might contribute to apparent differences in consultation rates. It is well-known that there is variation in coding behaviour of practices, with a substantial proportion of visits having either no Read code at all, or only uninformative Read codes like 'had a chat with patient'.^{1,37-39} While overall consultation rates are not influenced by poor coding, some general practitioners may be more likely to document a relevant Read code when prescribing an antibiotic. Hence, infection-related consultation rates may be artificially high in high-prescribing practices. This type of bias, if present, is clearly not a legitimate reason for variation between antibiotic prescribing rates.

Likewise, differences in the percentage of patients receiving inhaled and systemic steroids may be explained by different underlying causes. First, some practices may truly have a higher number of severely ill patients that require more systemic and/or inhaled steroid prescriptions than other practices. Second, higher use of inhaled and/or systemic steroids may reflect that certain practices are more liberal with prescribing medication in general, be it antibiotics or steroids. Among adults presenting in primary care with sore throat and lower respiratory tract infection, both not requiring immediate antibiotics, oral corticosteroids appeared to be ineffective in two recent randomized controlled trials.^{40,41} Hence, liberal use of corticosteroids to treat respiratory tract infections does not represent best practice. The first but not the second of these causes can be considered as a legitimate reason for varying antibiotic prescribing rates.

This study has several strengths. First, it uses data from a large, representative sample of UK general practices.¹¹ To our knowledge, this is the first study evaluating whether variation in antibiotic prescribing rates between general practices can be explained by differences in consultation rates, the percentage of patients receiving immunosuppressive drugs, inhaled or systemic steroids; and the percentage of patients with comorbidities. Moreover, this is the first study showing substantial differences in antibiotic prescribing rates between countries within the UK. We used two different methodologies - boosted regression trees²⁰ and negative binomial

regression¹⁹ – that both resulted in similar conclusions, thereby strengthening confidence in our results.

This study has also some limitations. As described above, some of the predictor variables may be markers of both legitimate as well as non-legitimate reasons of variation in antibiotic prescribing rates. In addition, variation in prescribing may be further explained by factors that were not readily available to us, such as markers of the severity of infections.^{42–45} We analysed only antibiotic items prescribed by the practice, which may artificially create differences between practices that tend to prescribe multiple shorter courses compared to practices that tend to prescribe one longer course for the same condition. Finally, ideally one would obtain a parsimonious good-fitting model using only variables that are publicly available for all practices. While between-practice variation in prescribing of inhaled and systemic steroids are readily available to identify practices that may legitimately have higher prescribing rates per STAR-PU - if assumed to be markers of more severely ill patients - this is unfortunately not possible for consultation rates using publicly available data.

In conclusion, the proportion of patients with comorbidities in a practice's patient population does not explain a substantial proportion of the variance in antibiotic prescribing rates, suggesting that practice-level prescribing targets do not necessarily have to account for levels of comorbidities.

Although we cannot exclude the possibility that consultation rates and use of inhaled and systemic steroids may be markers of (i) poor coding practice, (ii) a high propensity of prescribing drugs in general, or (iii) stronger health-care seeking behaviour, the predictive power of these variables indicates that one should be careful in setting the same practice-level antibiotic prescribing target for all practices, and that differences in these variables between practices may need to be taken into account. Further studies are needed to evaluate whether the explanatory power of consultation rates is mainly due to true differences in the incidence of infection or severity of infections, or e.g. due to differences in health-care seeking behaviour.

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References

1. Dolk FCK, Pouwels KB, Smith DRM *et al.* Antibiotics in English primary care: which antibiotics are prescribed and for which conditions? *J Antimicrob Chemother.* THIS SUPPLEMENT
2. Respiratory tract infections (self-limiting): prescribing antibiotics | Guidance and guidelines | NICE. 2008. <https://www.nice.org.uk/guidance/CG69>.
3. Smieszek T, Pouwels KB, Dolk FCK *et al.* Potential for reducing inappropriate antibiotic prescribing in English primary care. *J Antimicrob Chemother.* THIS SUPPLEMENT
4. Fleming-Dutra KE, Hersh AL, Shapiro DJ *et al.* Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010-2011. *JAMA* 2016; **315**: 1864–73.
5. Lloyd DCEF, Harris CM, Roberts DJ. Specific therapeutic group age-sex related prescribing units (STAR-PU): weightings for analysing general practices' prescribing in England. *BMJ* 1995; **311**: 991–4.
6. NHS Digital. 2009 and 2013 ASTRO-PU and STAR-PU weightings. 2014. <http://content.digital.nhs.uk/media/13654/Prescribing-Units-2013/xls/PrescribingUnits2013.xlsx>.
7. NHS Digital. Changes to ASTRO-PU and STAR-PU weightings: Questions and Answers (March 2014). 2014. http://content.digital.nhs.uk/media/13723/Prescribing-Units-2013-Briefing/pdf/Prescribing_Units_2013_Briefing.pdf.
8. NHS mandate 2017 to 2018 - GOV.UK. 2017. <https://www.gov.uk/government/publications/nhs-mandate-2017-to-2018>.
9. G7 2016 in Japan: PM press statement - GOV.UK. 2016. <https://www.gov.uk/government/speeches/g7-2016-in-japan-pm-press-statement>.
10. Bourke A, Dattani H, Robinson M. Feasibility study and methodology to create a quality-evaluated database of primary care data. *Inform Prim Care* 2004; **12**: 171–7.
11. Blak BT, Thompson M, Dattani H *et al.* Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care* 2011; **19**: 251–5.
12. IMS Health : THIN data. 2015. <http://csdmruk.cegedim.com/our-data/our-data.shtml>.
13. Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidemiol Drug Saf* 2009; **18**: 76–83.
14. OpenPrescribing. BNF section 5.1: Antibacterial Drugs. <https://openprescribing.net/bnf/0501/>.
15. Influenza: the green book, chapter 19 - GOV.UK. 2015. <https://www.gov.uk/government/publications/influenza-the-green-book-chapter-19>.

349 16. Seasonal influenza vaccination programme Read Codes used for payment. 2015.
350 [http://www.nhsemployers.org/~media/Employers/Documents/Primary%20care%20contracts/V%20and%20I/V%20and%20I%20Home%20Page/15-](http://www.nhsemployers.org/~media/Employers/Documents/Primary%20care%20contracts/V%20and%20I/V%20and%20I%20Home%20Page/15-16%20Seasonal%20flu%20at%20risk%20Read%20codes.xlsx)
351 [16%20Seasonal%20flu%20at%20risk%20Read%20codes.xlsx](http://www.nhsemployers.org/~media/Employers/Documents/Primary%20care%20contracts/V%20and%20I/V%20and%20I%20Home%20Page/15-16%20Seasonal%20flu%20at%20risk%20Read%20codes.xlsx).
352

353 17. NHS Digital. Read codes. 2016. <https://digital.nhs.uk/article/1104/Read-Codes>.

354 18. NHS Digital. Quality and Outcomes Framework (QOF) - 2013-14. 2014.
355 <https://digital.nhs.uk/catalogue/PUB15751>

356 19. Hilbe JM. *Negative Binomial Regression*. Cambridge: Cambridge University Press; 2011.
357 <http://ebooks.cambridge.org/ref/id/CBO9780511973420>.

358 20. Elith J, Leathwick JR, Hastie T. A working guide to boosted regression trees. *J Anim Ecol* 2008; **77**:
359 802–13.

360 21. Elith J, Leathwick J. Boosted Regression Trees for ecological modeling. 2017. [https://cran.r-](https://cran.r-project.org/web/packages/dismo/vignettes/brt.pdf)
361 [project.org/web/packages/dismo/vignettes/brt.pdf](https://cran.r-project.org/web/packages/dismo/vignettes/brt.pdf).

362 22. Ridgeway G. Generalized Boosted Models: A guide to the gbm package. 2007.
363 <http://www.saedsayad.com/docs/gbm2.pdf>.

364 23. NHS Digital. Prescribing by GP practice. 2017. <http://content.digital.nhs.uk/gpprescribingdata>.

365 24. Wang KY, Seed P, Schofield P *et al*. Which practices are high antibiotic prescribers? A cross-
366 sectional analysis. *Br J Gen Pract* 2009; **59**: e315–20.

367 25. Ashiru-Oredope D, Sharland M, Charani E *et al*. Improving the quality of antibiotic prescribing in
368 the NHS by developing a new antimicrobial stewardship programme: start smart--then focus. *J*
369 *Antimicrob Chemother* 2012; **67** Suppl 1: i51–63.

370 26. Shallcross L, Beckley N, Rait G *et al*. Antibiotic prescribing frequency amongst patients in primary
371 care: a cohort study using electronic health records. *J Antimicrob Chemother* 2017; **72**: 1818–24.

372 27. Hughes G, Field N. The epidemiology of sexually transmitted infections in the UK: impact of
373 behavior, services and interventions. *Futur Microbiol* 2015; **10**: 35–51.

374 28. Donker T, Henderson KL, Hopkins KL *et al*. The relative importance of large problems far away
375 versus small problems closer to home: insights into limiting the spread of antimicrobial resistance in
376 England. *BMC Med* 2017; **15**: 86.

377 29. Tosas Auguet O, Betley JR, Stabler RA *et al*. Evidence for community transmission of community-
378 associated but not health-care-associated methicillin-resistant *Staphylococcus aureus* strains linked
379 to social and material deprivation: spatial analysis of cross-sectional data. *PLOS Med* 2016; **13**:
380 e1001944.

381 30. Deeny SR, van Kleef E, Bou-Antoun S *et al*. Seasonal changes in the incidence of *Escherichia coli*
382 bloodstream infection: variation with region and place of onset. *Clin Microbiol Infect* 2015; **21**: 924–
383 9.

384 31. See I, Wesson P, Gualandi N *et al.* Socioeconomic factors explain racial disparities in invasive
385 community-associated methicillin-resistant *Staphylococcus aureus* disease rates. *Clin Infect Dis* 2017;
386 **64**: 597–604.

387 32. *Public Health England. Quarterly analyses: mandatory MRSA, MSSA and E. coli bacteraemia and*
388 *C. difficile in England (up to October-December 2016)*. London; 2017.
389 [https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/597642/QEC_Mar](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/597642/QEC_March_2017.pdf)
390 [ch_2017.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/597642/QEC_March_2017.pdf).

391 33. Horwood J, Cabral C, Hay AD *et al.* Primary care clinician antibiotic prescribing decisions in
392 consultations for children with RTIs: a qualitative interview study. *Br J Gen Pract* 2016; **66**: e207–13.

393 34. Lucas PJ, Cabral C, Hay AD *et al.* A systematic review of parent and clinician views and
394 perceptions that influence prescribing decisions in relation to acute childhood infections in primary
395 care. *Scand J Prim Health Care* 2015; **33**: 11–20.

396 35. Little P, Gould C, Williamson I *et al.* Reattendance and complications in a randomised trial of
397 prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. *BMJ* 1997;
398 **315**: 350–2.

399 36. Ashworth M, Charlton J, Ballard K *et al.* Variations in antibiotic prescribing and consultation rates
400 for acute respiratory infection in UK general practices 1995-2000. *Br J Gen Pract* 2005; **55**: 603–8.

401 37. Francis NA, Hood K, Lyons R *et al.* Understanding flucloxacillin prescribing trends and treatment
402 non-response in UK primary care: a Clinical Practice Research Datalink (CPRD) study. *J Antimicrob*
403 *Chemother* 2016; **71**: 2037–46.

404 38. Petersen I, Gilbert R, Evans S *et al.* Oral antibiotic prescribing during pregnancy in primary care:
405 UK population-based study. *J Antimicrob Chemother* 2010; **65**: 2238–46.

406 39. James GDR, Petersen I, Nazareth I *et al.* Use of long-term antibiotic treatment in COPD patients
407 in the UK: a retrospective cohort study. *Prim Care Respir J* 2013; **22**: 271–7.

408 40. Hayward GN, Hay AD, Moore MV *et al.* Effect of oral dexamethasone without immediate
409 antibiotics vs placebo on acute sore throat in adults. *JAMA* 2017; **317**: 1535–43.

410 41. Hay AD, Little P, Harnden A *et al.* Effect of oral prednisolone on symptom duration and severity
411 in nonasthmatic adults with lower respiratory tract infection. *JAMA* 2017; **318**: 1–11.

412 42. Van den Bruel A, Aertgeerts B, Bruyninckx R *et al.* Signs and symptoms for diagnosis of serious
413 infections in children: a prospective study in primary care. *Br J Gen Pract* 2007; **57**: 538–46.

414 43. Hay AD, Redmond NM, Turnbull S *et al.* Development and internal validation of a clinical rule to
415 improve antibiotic use in children presenting to primary care with acute respiratory tract infection
416 and cough: a prognostic cohort study. *Lancet Respir Med* 2016; **4**: 902–10.

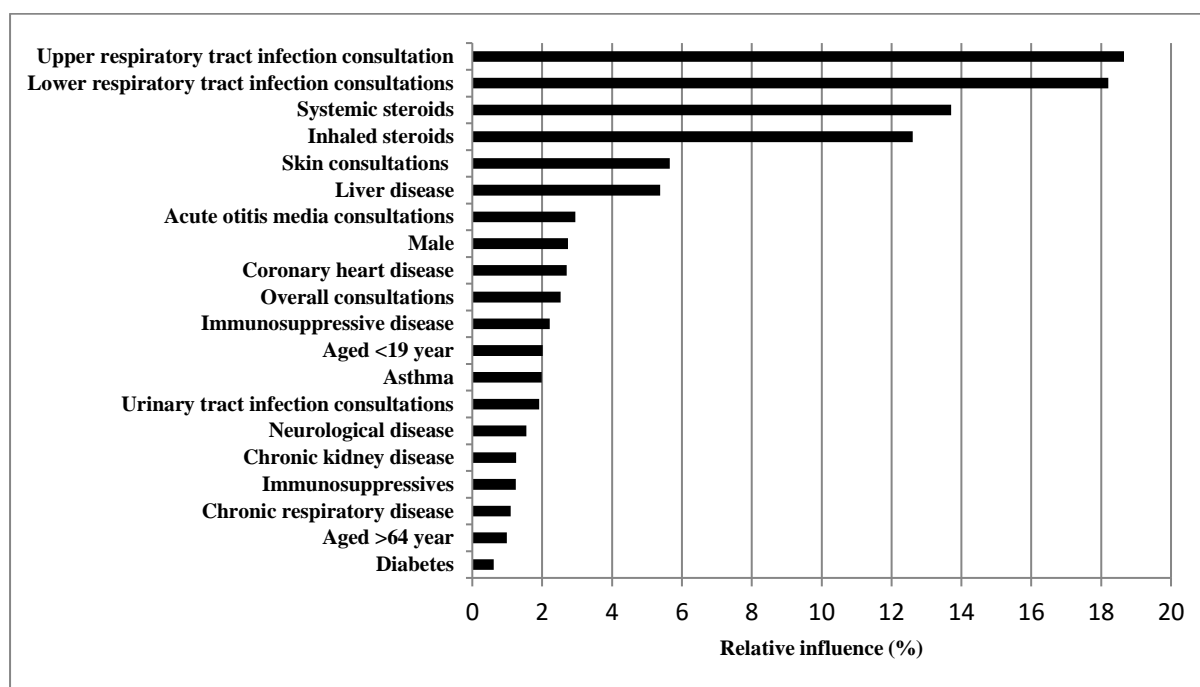
417 44. Huddy JR, Ni MZ, Barlow J *et al.* Point-of-care C reactive protein for the diagnosis of lower
418 respiratory tract infection in NHS primary care: a qualitative study of barriers and facilitators to
419 adoption. *BMJ Open* 2016; **6**: e009959.

420 45. Little P, Stuart B, Francis N *et al.* Effects of internet-based training on antibiotic prescribing rates
421 for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial.
422 *Lancet* 2013; **382**: 1175–82.

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427 **Figure 1.** Relative influence of the variables in the model predicting antibiotic prescriptions per STAR-
 428 PU in England. Variables are ranked from most important at the top to least important at the
 429 bottom, and the sum of the relative influence of all variables is 100.

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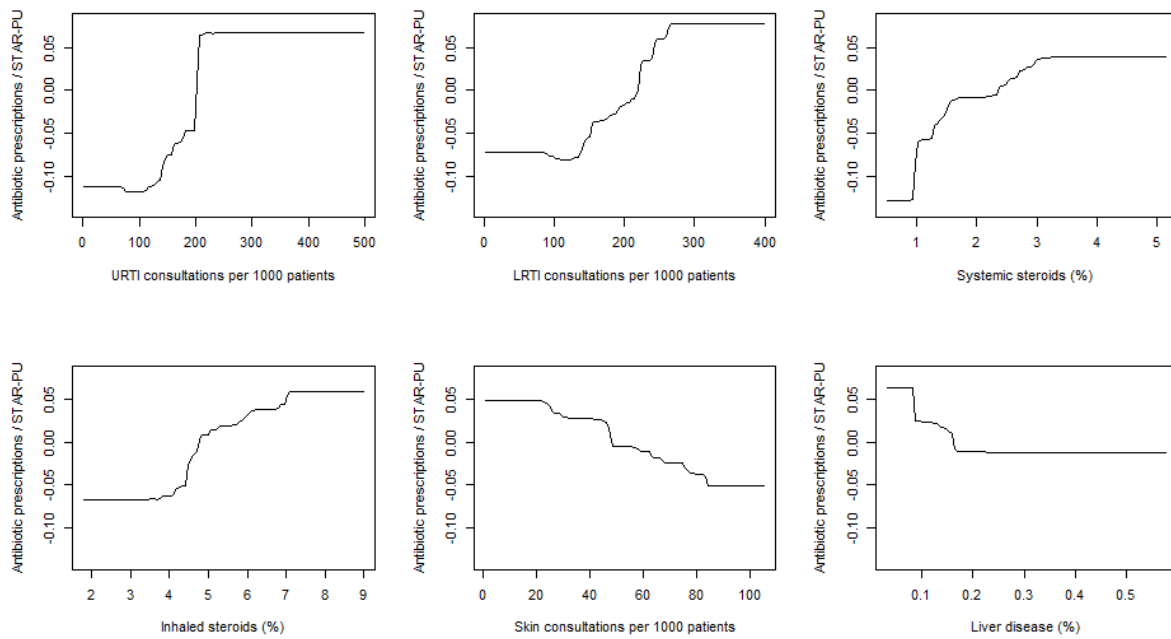


Figure 2. Partial dependence plots for the six most influential variables in the generalized boosted regression model assessing the association between predictors and antibiotic prescribing rates per STAR-PU in England. Y-axes are centred to have zero mean over the data distribution.

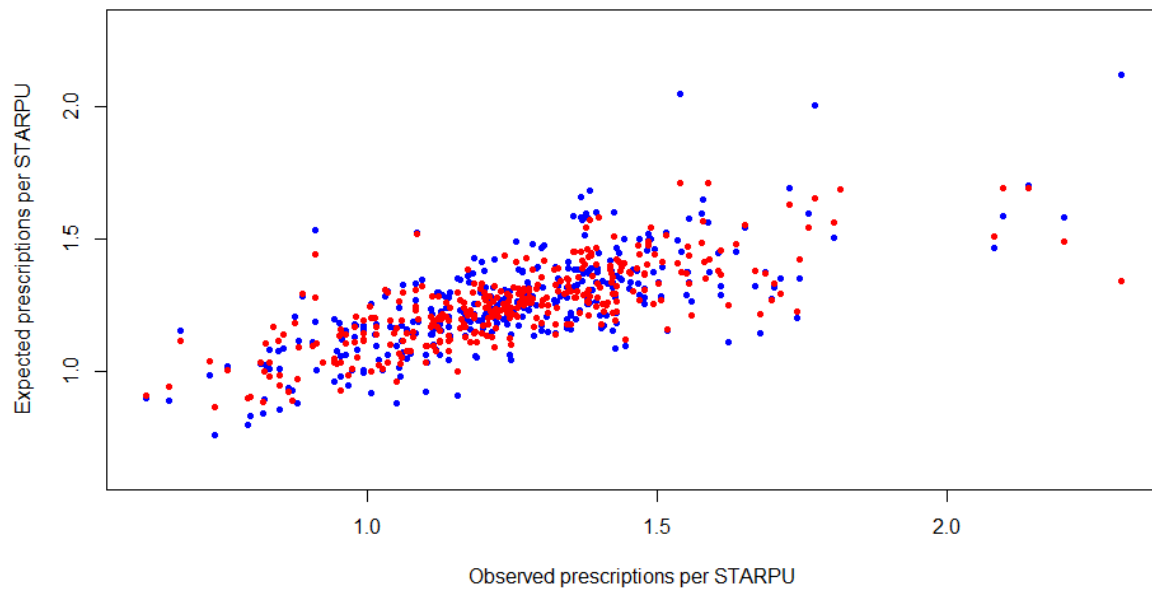


Figure 3. Observed versus expected antibiotic prescriptions per STAR-PU. Each dot represents an individual general practice. The red dots represent the boosted regression trees model and the blue dots represent the full negative binomial regression model (model 5).

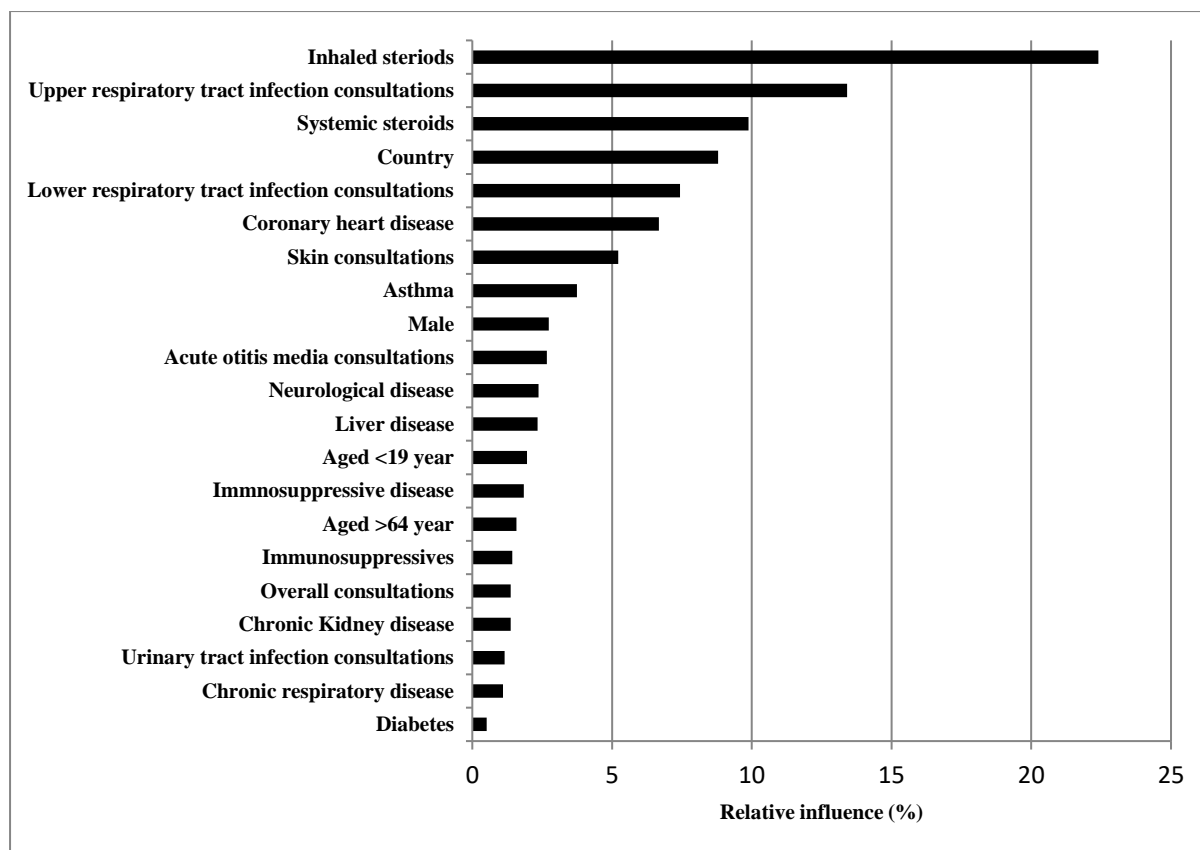


Figure 4. Relative influence of the variables in the model predicting antibiotic prescriptions per registered population in the UK. The sum of the relative influence of those variables is 100.

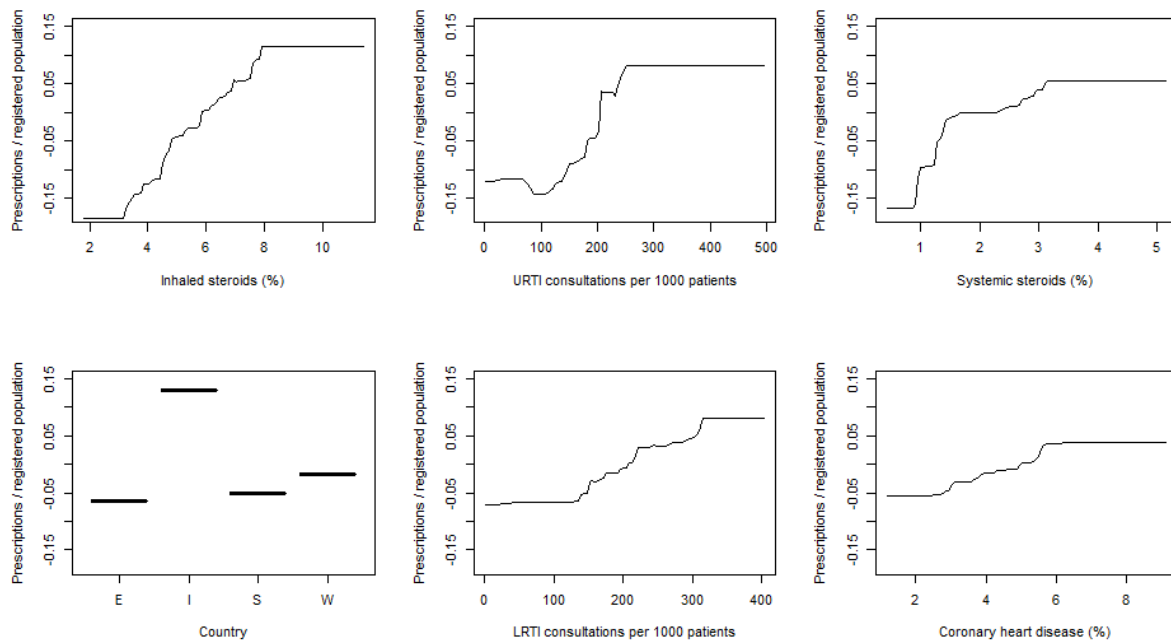


Figure 5. Partial dependence plots for the six most influential variables in the generalized boosted regression model assessing the association between predictors and antibiotic prescribing rates per registered population in the UK. Y-axes are centred to have zero mean over the data distribution. E=England; I= Northern Ireland; S= Scotland; W = Wales

Table 1. 2013 Item-based age-sex weighting for oral antibacterials (British National Formulary 5.1).

Age band (years)	Male	Female
0-4	0.8	0.8
5-14	0.3	0.4
15-24	0.3	0.6
25-34	0.2	0.6
35-44	0.3	0.6
45-54	0.3	0.6
55-64	0.4	0.7
65-74	0.7	1.0
75+	1.0	1.3

457 **Table 2.** Characteristics of English general practices included for analysis.
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Variable	Median (IQR)
Antibiotic prescriptions per 100 registered patients	65.6 (57.4-74.0)
Practice size, number of registered patients	7,879 (5,156-11,070)
% of patients with asthma	9.3 (7.7-10.8)
% of patients with chronic kidney disease	3.9 (2.6-4.9)
% of patients with diabetes	4.9 (4.1-5.6)
% of patients with chronic respiratory disease	3.0 (2.1-4.8)
% of patients with chronic heart disease	4.0 (3.2-4.8)
% of patients with immunosuppressive disease	0.9 (0.7-1.0)
% of patients with liver disease	0.2 (0.1-0.2)
% of patients with neurological disease	2.0 (1.6-2.4)
% of patients with at least 2 prescriptions of immunosuppressive drugs	0.2 (0.2-0.3)
% of patients with at least 2 prescriptions of systemic steroids	2.0 (1.4-2.5)
% of patients with at least 2 prescriptions of inhaled steroids	5.2 (4.6-6.1)
% of patients being male	49.4 (48.6-50.3)
% of patients aged <18 year	20.2 (18.2-21.8)
% of patient >64 year	18.2 (14.6 – 21.8)
URTI consultations / 1000 patients	139.0 (111.7 – 174.1)
LRTI consultations / 1000 patients	171.3 (140.7 – 213.2)
AOM consultations / 1000 patients	15.8 (11.2 – 21.5)
UTI consultations / 1000 patients	48.0 (32.2 – 63.1)
Skin consultations / 1000 patients	54.4 (43.8 – 63.7)
Overall consultations / patient	6.4 (5.3 – 7.5)

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462 AIC, Akaike information criterion; AOM, acute otitis media; CHD, chronic kidney disease; df, degrees of freedom; LRTI, lower respiratory tract infection; NA,
463 not applicable; rcs, restricted cubic splines; URTI, upper respiratory tract infection; UTI, urinary tract infection