

Safety of reducing antibiotic prescribing in primary care: a mixed-methods study

Martin C Gulliford,^{1,2*} Judith Charlton,¹
Olga Boiko,¹ Joanne R Winter,^{1,2}
Emma Rezel-Potts,^{1,2} Xiaohui Sun,¹
Caroline Burgess,¹ Lisa McDermott,¹
Catey Bunce,^{1,2} James Shearer,¹ Vasa Curcin,¹
Robin Fox,³ Alastair D Hay,⁴ Paul Little,⁵
Michael V Moore⁵ and Mark Ashworth¹

¹School of Population Health and Environmental Sciences, King's College London, London, UK

²National Institute for Health Research Biomedical Research Centre, Guy's and St Thomas' NHS Foundation Trust, London, UK

³Bicester Health Centre, Bicester, UK

⁴Centre for Academic Primary Care, Bristol Medical School, University of Bristol, Bristol, UK

⁵Primary Care Research Group, University of Southampton, Southampton, UK

*Corresponding author martin.gulliford@kcl.ac.uk

Declared competing interests of authors: Michael V Moore reports grants from the National Institute for Health Research (NIHR) during the conduct of the study (awards 13/88/13 and 09/127/19). Paul Little was a board member for the NIHR School for Primary Care Research and was the programme director of the NIHR Programme Grants for Applied Research programme and a member of the NIHR Journals Library Editorial Group from September 2012 to September 2018.

Published May 2021

DOI: 10.3310/hsdr09090

Scientific summary

Reducing primary care antibiotic prescribing

Health Services and Delivery Research 2021; Vol. 9: No. 9

DOI: 10.3310/hsdr09090

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Increasing antimicrobial resistance has motivated efforts to reduce unnecessary and inappropriate antibiotic prescribing in primary care. At the same time, diagnoses of serious bacterial infections have been increasing, contributing to concerns that reduced antibiotic prescribing might sometimes compromise patient safety.

Objectives

This research asked whether or not it is safe to reduce antibiotic prescribing in primary care. Is there a risk that serious bacterial infections might be more frequent if antibiotics are prescribed less often? If so, what is the safest way for the NHS to promote the reduction of antibiotic prescribing in primary care?

The specific objectives were to:

- conduct an epidemiological study to estimate the risks of a range of safety outcomes relevant to policies for reducing overall antibiotic utilisation in primary care
- construct a decision-analytic model that will compare the consequences for safety outcomes of prescribing or not prescribing antibiotics and identify groups in which antibiotic prescribing can be more safely reduced
- engage with members of the public, patients and clinicians to understand their views and values in developing candidate indicators of safe antibiotic prescribing reduction and implement these indicators into general practices.

Methods

Study design

This was a mixed-methods study and included interviews with patients and professionals, which informed epidemiological analysis and modelling, using electronic health records.

Ethics

The protocol for the study was approved by the Clinical Practice Research Datalink Independent Scientific Advisory Committee (protocol 18-041R) and the London – Hampstead NHS Research Ethics Committee 18/LO/1874.

Qualitative study

We conducted a qualitative study in two English regions (one urban metropolitan area and one town in rural England). Patients who had recently consulted for infections were recruited. The information power approach was used to determine the number of participants and yielded a sample of 31 participants. The sample included 24 women; 19 participants were aged ≥ 60 years, 11 participants had urinary infections and 16 participants had respiratory infections. We also recruited 30 primary care prescribers from 10 general practices: 23 general practitioners, five nurse prescribers and two pharmacists. Semistructured interviews were conducted and informed by topic guides for each respondent group. Thematic analysis of the interview data was conducted.

Data sources

We conducted a population-based cohort study in the UK Clinical Practice Research Datalink, employing data from 2002 to 2017. We analysed antibiotic prescribing for a random sample of registered patients from the Clinical Practice Research Datalink GOLD database. We included 671,830 individual participants from 706 general practices who contributed person-time between 2002 and 2017. In a methodological substudy, we compared antibiotic prescribing for random samples of registered patients in the Clinical Practice Research Datalink GOLD and Clinical Practice Research Datalink Aurum databases. Clinical Practice Research Datalink GOLD practices use the Vision[®] practice system, whereas Clinical Practice Research Datalink Aurum practices use the EMIS[®] practice system. Incident cases of serious bacterial infection were evaluated in the entire registered population of the same 706 general practices in Clinical Practice Research Datalink GOLD from 2002 to 2017, with the Clinical Practice Research Datalink denominator providing the person-time at risk. We analysed the data from 378 general practices in England from the Clinical Practice Research Datalink GOLD database from 2002 to 2017, with 36,209,676 patient-years of follow-up with linked Hospital Episode Statistics and Office for National Statistics mortality registrations.

Outcome measures

The qualitative study identified sepsis (including septicaemia) as the condition of greatest concern. The research also included localised bacterial infections, including bacterial infections of the central nervous system, bacterial infections of the cardiovascular system, kidney infections, lung abscess and empyema, mastoiditis, osteomyelitis, peritonsillar abscess and septic arthritis.

Exposures and covariates

All antibiotic prescriptions, subgroups of acute and repeat antibiotic prescriptions, and proportion of antibiotic prescriptions associated with specific-coded indications. Rates of infection consultations in primary care including subgroups of respiratory tract infections, skin infections and urinary tract infections. Age group, gender and frailty category were evaluated as modifiers of associations.

Statistical analysis

We analysed antibiotic prescribing and associated safety outcomes in primary care between 2002 and 2017. A hierarchical Poisson model was fitted, with counts of serious bacterial infections as the outcome. Estimates were adjusted for the fixed effects of gender, age group, fifth of deprivation at general practice level, comorbidity, region in the UK and calendar year. We evaluated whether or not there was evidence that the incidence rate might be higher at low antibiotic prescribing general practices.

Decision-analytic model

We constructed a decision tree to evaluate the probability of a serious bacterial infection following a common infection consultation in primary care. We used estimates from Clinical Practice Research Datalink data analysis to populate the decision tree with empirical estimates and employed Bayes' theorem to estimate the probability of a serious bacterial infection following an infection consultation if antibiotics were prescribed or not. We estimated the number needed to treat (i.e. the number of antibiotic prescriptions required to prevent one serious bacterial infection) as the reciprocal of the difference in probability with and without antibiotics. The model was first developed using peritonsillar abscess as an outcome; it was then applied to sepsis and then to other localised serious bacterial infections. We constructed a Shiny application (app) (RStudio, Boston, MA, USA) to present the results to prescribers in primary care as a series of interactive web pages. End-user feedback was obtained to inform the design of the Shiny app.

Patient and public involvement

Patient and public involvement informed all stages of the research of patient and public views. A patient and public involvement group was formed and included patients and service users recruited from the National Institute for Health Research (NIHR) Biomedical Research Centre at Guy's and

St Thomas' Hospitals (London, UK) and from general practices in south London. The group included seven patient and public involvement members: comprising five women and two men of diverse ages and ethnic origins. Most had experience of consulting infections and some had experience of antibiotic-resistant infections. Meetings were held at intervals during the project. Preliminary findings from the research were presented and members were invited to discuss emerging findings and themes, and comment on their relevance.

Results

Prescribers' perspectives of safe antibiotic prescribing

Primary care prescribers indicated that their decisions were grounded in clinical risk assessment; however, this was informed by different approaches to antibiotic use, with most leaning towards reduced prescribing. Prescribers' perceptions of risk included the consequences of both inappropriate prescribing and inappropriate withholding of antibiotics. Sepsis was viewed as the most concerning potential outcome of non-prescribing, leading to possible patient harm and potential litigation. Risks of antibiotic prescribing included antibiotic-resistant and *Clostridium difficile* infections, as well as side effects, such as rashes, that might lead to possible mislabelling as antibiotic allergy. Prescribers elicited patient preferences for use or avoidance of antibiotics to inform management strategies, which included educational advice, advice on self-management (including warning signs), use of delayed prescriptions and 'safety-netting' advice.

Patients' perspectives on safe antibiotic prescribing

The analysis of interviews with patients identified five themes: (1) beliefs, (2) expectations, (3) experiences of taking antibiotics, (4) experiences of antimicrobial resistance and side effects and (5) experiences of consultations. Patient accounts reflected improved public knowledge (i.e. antibiotics were perceived to be much-needed medicines that should be prescribed when appropriate). Patient experiences were nuanced and detailed with knowledge of antimicrobial resistance and side effects of antibiotics in the context of positive consultation experiences.

Antibiotic utilisation in Clinical Practice Research Datalink GOLD

The age-standardised rate of prescribing of all antibiotics per 1000 patient-years increased from 2002 (male, $n = 423$; female, $n = 621$) to 2012 (male, $n = 530$; female, $n = 842$) before declining in 2017 (male, $n = 449$; female, $n = 753$). The median general practice had an antibiotic prescribing rate of 648 per 1000 patient-years, and the 95% range for different practices was 430–1038 antibiotic prescriptions per 1000 patient-years. Specific coded indications were recorded for 58% of antibiotic prescriptions at the median general practice and the 95% range at different general practices was 10% to 75%.

Antibiotic utilisation in Clinical Practice Research Datalink Aurum compared with Clinical Practice Research Datalink GOLD

In a methodological substudy to inform future research, analysis of data from English general practices in the Clinical Practice Research Datalink Aurum gave similar results to Clinical Practice Research Datalink GOLD data for England for the rate of antibiotic prescribing, the most frequently prescribed antibiotic products and the coding of infection consultations with antibiotics prescribed.

Serious bacterial infections in relation to general practice-level antibiotic prescribing

In 706 general practices in Clinical Practice Research Datalink GOLD, there were 139,759 first episodes of serious bacterial infection from 2002 to 2017. There was no evidence that serious bacterial infections were lower at general practices with higher total antibiotic prescribing. The adjusted rate ratio for 20% higher total antibiotic prescribing was 1.03 (95% confidence interval 1.00 to 1.06; $p = 0.074$). There was strong evidence that the recorded incidence of serious bacterial infections was higher at general practices that recorded specific indications for a higher proportion of antibiotic prescriptions (adjusted rate ratio for a 20% increase in coding proportion 1.24, 95% confidence interval 1.18 to 1.29; $p < 0.001$).

Antibiotic prescribing and risk of peritonsillar abscess

There were 11,007 patients with peritonsillar abscess, of whom 6996 (64%) consulted their general practitioner in the 30 days preceding peritonsillar abscess diagnosis, including 4243 (39%) consulting for respiratory tract infection. The probability of peritonsillar abscess following a respiratory tract infection consultation was greatest in men aged 15–24 years, with one peritonsillar abscess in 565 (95% uncertainty interval 527 to 605) respiratory tract infection consultations without antibiotics prescribed, but one peritonsillar abscess in 1139 (95% uncertainty interval 1044 to 1242) respiratory tract infection consultations if antibiotics were prescribed. One peritonsillar abscess might be avoided for every 1121 (95% uncertainty interval 975 to 1310) additional antibiotic prescriptions for men aged 15–24 years and 926 (95% uncertainty interval 814 to 1063) additional antibiotic prescriptions for men aged 25–34 years. The risk of peritonsillar abscess following respiratory tract infection consultation was lower at other ages and lower in women than in men.

Antibiotic prescribing and risk of sepsis

The probability of sepsis was lower if an antibiotic was prescribed at an infection consultation, but the number of antibiotic prescriptions required to prevent one episode of sepsis (i.e. the number needed to treat) decreased with age. At age 0–4 years, the number needed to treat was 29,773 (95% uncertainty interval 18,458 to 71,091) in boys and 27,014 (95% uncertainty interval 16,739 to 65,709) in girls. For those aged > 85 years, the number needed to treat was 262 (95% uncertainty interval 236 to 293) in men and 385 (95% uncertainty interval 352 to 421) in women. Frailty was associated with greater risk of sepsis and a smaller number needed to treat. For severely frail patients aged 55–64 years, the number needed to treat was 247 (95% uncertainty interval 156 to 459) for men and 343 (95% uncertainty interval 234 to 556) for women. At all ages, the probability of sepsis was greatest for urinary tract infection, followed by skin infection and respiratory tract infection. At age 65–74 years, the number needed to treat following respiratory tract infection was 1257 (95% uncertainty interval 1112 to 1434) for men and 2278 (95% uncertainty interval 1966 to 2686) for women; following skin infection it was 503 (95% uncertainty interval 398 to 646) for men and 784 (95% uncertainty interval 602 to 1051) for women; and following urinary tract infection it was 121 (95% uncertainty interval 102 to 145) for men and 284 (95% uncertainty interval 241 to 342) for women. The numbers needed to treat were generally smaller for the period 2014–17, when sepsis was diagnosed more frequently.

Antibiotic prescribing and risk of other localised serious bacterial infections

In women aged 15–24 years, the number of antibiotic prescriptions estimated to prevent one kidney infection was 81 (95% uncertainty interval 72 to 90). In men, the probability of a kidney infection following a urinary tract infection consultation was greatest at age 45–54 years, with a number needed to treat of 186 (95% uncertainty interval 136 to 267). The number of antibiotic prescriptions required to prevent one episode of lung abscess or empyema was 8208 (95% uncertainty interval 5955 to 12,506) at age 55–64 years and 7588 (95% uncertainty interval 5419 to 11,763) at age 75–84 years. Septic arthritis and osteomyelitis were found to be most frequent after skin infections at older ages. In men aged 75–84 years, the number needed to treat was 2574 (95% uncertainty interval 1102 to 15,373) for osteomyelitis and 2204 (95% uncertainty interval 1329 to 4499) for septic arthritis.

Data linkage study

Analysis of linked records included 20,206 first episodes of sepsis from primary care records, 20,278 from Hospital Episode Statistics and 13,972 from Office for National Statistics. There were 4117 (20%) first Hospital Episode Statistics sepsis events and 2438 (17%) mortality records concurrent with incident primary care sepsis records. Linked data were included in the model for sepsis as a sensitivity analysis, but this had only a small effect on estimates because cases recorded in Hospital Episode Statistics alone were less likely to have had preceding primary care consultations.

A Shiny app for clinical risk assessment in primary care

We used Shiny software to incorporate these estimates into an app that presented data to general practitioners through interactive web pages that might be viewed during consultations. A preliminary qualitative study was conducted to obtain end-user feedback to inform the design of the app, including six general practitioners, four of whom were members of the study team. Further evaluation will be needed before this can be used in practice. Risks of serious bacterial infections were generally low, except for kidney infection following urinary tract infection in young women, peritonsillar abscess following respiratory infections in young adults and sepsis in older adults.

Strengths and limitations

Data were drawn from primary care electronic health records, but the research identified important deficiencies in data recording that could bias estimates. Data were analysed for a 16-year period, and changes over time in antibiotic prescribing and disease incidence may make estimates less transferable to future years. Comparisons between antibiotic- and non-antibiotic-treated episodes were non-randomised; consequently, estimates of the number needed to treat might be too large. Several of the outcomes studied were too infrequent to obtain precise estimates from analysis of Clinical Practice Research Datalink, even over a 16-year period.

Conclusions

Implications for health care

- The research found that antibiotic prescribing in primary care is decreasing, but the decline is most evident for prescriptions with clearly defined indications recorded. Incompletely coded prescriptions have not decreased. Improving the recording of infection episodes and antibiotic prescriptions is important for informing antimicrobial stewardship in primary care.
- Both antibiotic prescribing and the coding of prescriptions vary widely between general practices. The research did not find evidence that general practices with lower total antibiotic prescribing might have more frequent occurrence of serious bacterial infections. Serious bacterial infections were more frequently recorded at general practices with higher proportions of informatively coded infection consultations.
- Data from Vision general practices in Clinical Practice Research Datalink GOLD and EMIS practices in Clinical Practice Research Datalink Aurum provide similar antibiotic prescribing estimates and future research may be conducted in Clinical Practice Research Datalink Aurum.
- The research provided stratified estimates of risk that identify groups of patients and types of consultations in which antibiotic prescribing can be more safely reduced. We developed an interactive app that can be used to communicate these estimates to primary care prescribers. We found evidence that serious bacterial infection complications were generally less frequent if antibiotics were prescribed, but the possibility of benefit depended on the underlying frequency of the complication in the context of a particular patient's characteristics.
- The safety trade-offs associated with either use or non-use of antibiotics present difficulties, especially when prescribing decisions are inconsistent with patients' expectations. The research highlighted how patients' expectations are now more complex than earlier research reported, and exhibit tensions between adherence to antibiotics and consuming antibiotics in more reflexive, informed ways. Ensuring that present and future patients are better informed about both the potential benefits and harms of antibiotic use will contribute to future antimicrobial stewardship.

Recommendations for research

- Measures are needed to improve the recording of infection episodes in primary care, both when antibiotics are prescribed and when antibiotics are not prescribed. Interventions should be developed and tested to improve the quality of infection recording in primary care electronic health records and ensure consistency of terminology and coding across primary and secondary care.

- Estimates for antibiotic prescribing and infection recording were broadly similar in both Clinical Practice Research Datalink GOLD and Clinical Practice Research Datalink Aurum databases, suggesting that future research on antimicrobial stewardship may be conducted using primary care data in Clinical Practice Research Datalink Aurum.
- The conditions identified as 'sepsis' may represent a range of disease severity, and further research is needed to refine the predictive accuracy of models of sepsis following primary care infection consultations.
- The app developed for this research should undergo further iterative development to incorporate antibiotic prescribing and coding information, drawn from individual patient data rather than the aggregate data presently utilised in existing information feedback strategies. This can then be employed as an antimicrobial stewardship tool and tested in a randomised controlled trial.
- Previous research into antibiotic prescribing practices in primary care may need to be updated to include the need to understand more about prescribing behaviour by professional background (e.g. general practitioner, nurse and pharmacist), risk perceptions and further research on the quality of prescribing information and safety-netting by clinicians.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Services and Delivery Research programme and will be published in full in *Health Services and Delivery Research*; Vol. 9, No. 9. See the NIHR Journals Library website for further project information.

Health Services and Delivery Research

ISSN 2050-4349 (Print)

ISSN 2050-4357 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HS&DR archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hsdr. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Services and Delivery Research* journal

Reports are published in *Health Services and Delivery Research* (HS&DR) if (1) they have resulted from work for the HS&DR programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

HS&DR programme

The HS&DR programme funds research to produce evidence to impact on the quality, accessibility and organisation of health and social care services. This includes evaluations of how the NHS and social care might improve delivery of services.

For more information about the HS&DR programme please visit the website at <https://www.nihr.ac.uk/explore-nihr/funding-programmes/health-services-and-delivery-research.htm>

This report

The research reported in this issue of the journal was funded by the HS&DR programme or one of its preceding programmes as project number 16/116/46. The contractual start date was in August 2018. The final report began editorial review in October 2020 and was accepted for publication in February 2021. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HS&DR editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HS&DR programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HS&DR programme or the Department of Health and Social Care.

© 2021 Gulliford *et al.* This work was produced by Gulliford *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This is an Open Access publication distributed under the terms of the Creative Commons Attribution CC BY 4.0 licence, which permits unrestricted use, distribution, reproduction and adaptation in any medium and for any purpose provided that it is properly attributed. See: <https://creativecommons.org/licenses/by/4.0/>. For attribution the title, original author(s), the publication source – NIHR Journals Library, and the DOI of the publication must be cited.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

NIHR Journals Library Editor-in-Chief

Professor Ken Stein Professor of Public Health, University of Exeter Medical School, UK

NIHR Journals Library Editors

Professor John Powell Chair of HTA and EME Editorial Board and Editor-in-Chief of HTA and EME journals. Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK, and Professor of Digital Health Care, Nuffield Department of Primary Care Health Sciences, University of Oxford, UK

Professor Andrée Le May Chair of NIHR Journals Library Editorial Group (HS&DR, PGfAR, PHR journals) and Editor-in-Chief of HS&DR, PGfAR, PHR journals

Professor Matthias Beck Professor of Management, Cork University Business School, Department of Management and Marketing, University College Cork, Ireland

Dr Tessa Crilly Director, Crystal Blue Consulting Ltd, UK

Dr Eugenia Cronin Senior Scientific Advisor, Wessex Institute, UK

Dr Peter Davidson Consultant Advisor, Wessex Institute, University of Southampton, UK

Ms Tara Lamont Senior Scientific Adviser (Evidence Use), Wessex Institute, University of Southampton, UK

Dr Catriona McDaid Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK

Professor William McGuire Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads Emeritus Professor of Wellbeing Research, University of Winchester, UK

Professor James Raftery Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts Professor of Child Health Research, UCL Great Ormond Street Institute of Child Health, UK

Professor Jonathan Ross Professor of Sexual Health and HIV, University Hospital Birmingham, UK

Professor Helen Snooks Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Professor Ken Stein Professor of Public Health, University of Exeter Medical School, UK

Professor Jim Thornton Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Please visit the website for a list of editors: www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: journals.library@nihr.ac.uk