Safety of Reducing Antibiotic Prescribing In Primary Care. Mixed Methods Study

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Important

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 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 reduction of antibiotic prescribing in primary care?

The specific objectives were to:

1) Conduct an epidemiological study to estimate risks of a range of safety outcomes relevant to policies for reducing overall antibiotic utilisation in primary care;

2) construct a decision analytic model that will compare the consequences for safety outcomes of prescribing or not prescribing antibiotics and identify groups in whom antibiotic prescribing can be more safely reduced;

3) 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

Mixed methods study including 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 CPRD Independent Scientific Advisory Committee (ISAC 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 an urban metropolitan area and the other a town in rural England. Patients who recently consulted for infections were recruited. The information power approach was used to determine the number of participants, yielding a sample of 31 participants, including 24 women, 19 were aged ≥60 years, 11 had urinary and 16 had respiratory infections. We also recruited 30 primary care prescribers from 10 general practices, including 23 general practitioners, five nurse prescribers and two pharmacists. Semi-structured interviews were conducted 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 (CPRD) employing data for 2002 to 2017. We analysed antibiotic prescribing for a random sample of registered patients from the CPRD GOLD database. We included 671,830 individual participants from 706 general practices, who contributed person time between 2002 and 2017. In a methodological sub-study, we compared antibiotic prescribing for random samples of registered patients in the CPRD GOLD and CPRD Aurum databases. CPRD GOLD practices use the Vision practice system while CPRD 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 CPRD GOLD for the years 2002 to 2017 with the CPRD denominator providing the person time at risk. In 378 general practices in England from Clinical Practice Research Datalink (CPRD) GOLD database from 2002-2017 with 36 209 676 patient-years of follow-up, linked Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality registrations were also analysed.

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 (CNS); bacterial infections of the cardiovascular system (CVS); kidney infections; lung abscess and empyema; mastoiditis; osteomyelitis; peritonsillar abscess; and septic arthritis.

Exposures and covariates

All antibiotic prescriptions, sub-groups of acute and repeat antibiotic prescriptions, and proportion of antibiotic prescriptions associated with specific-coded indications. Rates of infection consultations in primary care including sub-groups 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 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 infections following common infections consultations in primary care. We used estimates from CPRD 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' (NNT), 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 app to present the results to prescribers in primary care as a series of interactive web-pages. End-used feedback was obtained to inform the design of the Shiny app.

Patient and Public Involvement

Patient and public involvement (PPI) informed all stages of the research of patient and public views. A PPI group was formed including patients and service users recruited from the NIHR Biomedical Research Centre at Guy's and St Thomas' Hospitals and from general practices in South London. The group included seven PPI members including five women and two men of diverse ages and ethnic origins. Most had experience of consulting with infections

and some also 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 on safe antibiotic prescribing

Primary care prescribers indicated that their decisions were grounded in clinical risk assessment, but 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 C. 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

Analysis of interviews with patients identified five themes: beliefs, expectations, experiences of taking antibiotic, experience of antimicrobial resistance and side-effects, and experiences of consultations. Patient accounts reflected improved public knowledge: antibiotics were perceived to be much-needed medicines that should be prescribed when appropriate. Patient experiences featured as nuanced and detailed with knowledge of AMR and side-effects of antibiotics in the context of positive consultation experiences.

Antibiotic utilisation in CPRD GOLD

The age-standardised rate of prescribing of all antibiotics per 1,000 patient-years increased from 2002 (male 423; female 621) to 2012 (male 530; female 842) before declining to 2017 (male 449; female 753). The median general practice had an antibiotic prescribing rate of 648 per 1,000 patient-years with 95% range for different practices of 430 to 1,038 antibiotic

prescriptions per 1,000 patient-years. Specific coded indications were recorded for 58% of antibiotic prescriptions at the median general practice, the 95% range at different general practices was from 10% to 75%.

Antibiotic utilisation in CPRD Aurum compared with CPRD GOLD
In a methodological sub-study to inform future research, analysis of data from English general practices in CPRD Aurum gave similar results to CPRD 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 CPRD 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 (RR) 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, 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 6,996 (64%) consulted their GP in the 30 days preceding peritonsillar abscess diagnosis, including 4,243 (39%) consulting for RTI. The probability of peritonsillar abscess following an RTI consultation was greatest in men aged 15 to 24 years with one peritonsillar abscess in 565 (95% uncertainty interval 527 to 605) RTI consultations without antibiotics prescribed but one in 1,139 consultations (1,044 to 1,242) if antibiotics were prescribed. One peritonsillar abscess might be avoided for every 1,121 (975 to 1,310) additional antibiotic prescriptions for men aged 15 to 24 years and 926 (814 to 1,063) for men aged 25 to 34 years. The risk of peritonsillar abscess following RTI consultation was smaller at other ages and lower in women than 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 (NNT) decreased with age. At 0 to 4 years, the NNT was 29,773 (95% UI 18,458 to 71,091) in boys and 27,014 (16,739 to 65,709) in girls; over 85 years, NNT was 262 (236 to 293) in men and 385 (352 to 421) in women. Frailty was associated with greater risk of sepsis and lower NNT. For severely frail patients aged 55-64 years, the NNT was: men, 247 (156 to 459); women 343 (234 to 556). At all ages, the probability of sepsis was greatest for UTI, followed by skin infection followed by RTI. At 65-74 years, the NNT following RTI was, men: 1,257 (1,112 to 1,434); women, 2,278 (1,966 to 2,686); following skin infection, men: 503 (398 to 646), women: 784 (602 to 1,051); following UTI, men 121 (102 to 145), women, 284 (241 to 342). NNT values were generally smaller for the period 2014 to 2017 when sepsis was diagnosed more frequently.

Antibiotic prescribing and risk of other localised serious bacterial infections
In women aged 15 to 24 years, the number of antibiotic prescriptions estimated to prevent one kidney infection was 81 (72 to 90). In men, the probability of a kidney infection following a urinary tract infection consultation was greatest at 45 to 54 years, with a number needed to treat of 186 (136 to 267). The number of antibiotic prescriptions required to prevent one episode of lung abscess or empyema was 8,208 (5,955 to 12,506) at 55 to 64 years and 7,588 (5,419 to 11,763) at 75 to 84 years. Septic arthritis and osteomyelitis were found to be most frequent after skin infections at older ages. In men age 75 to 84, the number needed to treat was 2,574 (1,102 to 15,373) for osteomyelitis, and 2,204 (1,329 to 4,499) for septic arthritis.

Data linkage study
Analysis of linked records included 20,206 first episodes of sepsis from primary care records, 20,278 from HES and 13 972 from ONS. There were 4,117 (20%) first HES sepsis events and 2,438 (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 HES 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 GPs 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 UTI 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 sixteen-year period and changes over time in antibiotic prescribing and disease incidence may make estimates less transferable to future years. Comparisons between antibiotic treated and non-antibiotic treated episodes were non-randomised, consequently estimates of the number needed to treat might be too high. Several of the outcomes studied were too infrequent to obtain precise estimates from analysis of CPRD, even over a 16-year period.

Conclusions

Implications for healthcare

1. 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.

2. 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.

3. Data from Vision general practices in CPRD GOLD and EMIS practices in CPRD Aurum provide similar antibiotic prescribing estimates and future research may be conducted in CPRD Aurum.

3. 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.

4. 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
1. Measures are needed to improve the recording of infection episodes in primary care both when antibiotics are prescribed and when they are not. 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.

2. Estimates for antibiotic prescribing and infection recording were broadly similar in both CPRD GOLD and CPRD Aurum databases suggesting that future research on antimicrobial stewardship may be conducted using primary care data in CPRD Aurum.

3. 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.

4. 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.

5. 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 (GP/nurse/pharmacist), risk perceptions, and further research on the quality of prescribing information and safety-netting by clinicians.