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Infection-related complications after common infection in association with new antibiotic prescribing in primary care: retrospective cohort study using linked electronic health records

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ABSTRACT

Objective Determine the association of incident antibiotic prescribing levels for common infections with infection-related complications and hospitalisations by comparing high with low prescribing GP practices.

Design Retrospective cohort study.

Data source UK primary care records from the Clinical Practice Research Datalink (CPRD GOLD) and SAIL Databank (SAIL) linked with Hospital Episode Statistics (HES) data, including 546 CPRD, 346 CPRD-HES and 338 SAIL-HES practices.

Exposures Initial general practice visit for one of six common infections and the rate of antibiotic prescribing in each practice.

Main outcome measures Incidence of infection-related complications (as recorded in general practice) or infection-related hospital admission within 30 days after consultation for a common infection.

Results A practice with 10.4% higher antibiotic prescribing (the interquartile range (IQR)) was associated with a 5.7% lower rate of infection-related hospital admissions (95% Confidence Interval 3.3% to 8.0%). The association varied by infection with larger difference in hospital admission rate with lower respiratory tract infection (16.1%; 12.4% to 19.7%) and urinary tract infection (14.7%; 7.6% to 21.1%) and smaller difference in hospital admission rate for upper respiratory tract infection (6.5%; 3.5% to 9.5%) The association of antibiotic prescribing levels and hospital admission was largest in younger patients (8.6%; 4.0% to 13.0%) and smallest in the elderly (0.3%; -3.4% to 3.9%).

Conclusions There is an association between lower levels of practice level antibiotic prescribing and higher infection-related hospital admissions. Indiscriminately reducing antibiotic prescribing may lead to harm. Greater focus is needed to optimise antibiotic use by reducing inappropriate antibiotic prescribing and better targeting antibiotics to patients at high risk of infection-related complications.

ARTICLE SUMMARY

Strengths and limitations of this study

- Two large primary care databases with linked hospitalisation data were used to evaluate the difference in hospital admission after community acquired common infections comparing high with low prescribing GP practices.
- This analysis focusses on antibiotic prescribing at practice level with the emphasis on evaluating governmental guidance on reducing overall prescribing.
- Incidental antibiotic prescriptions were evaluated in this analysis and the results can only be interpreted in this context.
- No data was extracted on infection severity or symptom scores therefore no conclusions can be drawn on the appropriateness of antibiotics prescribed.

INTRODUCTION

Common infections, such as sore throat or sinusitis, are often self-limiting and usually get better without antibiotics; nevertheless, they are frequently prescribed [1,2]. Research regarding antimicrobial resistance (AMR) and antibiotic prescribing rates often focuses on reducing inappropriate prescribing to lower the threat of increasing antimicrobial resistance [3]. Antibiotic prescribing for common self-limiting infections is often seen as a target for reduction [3,4]. However, a proportion of common infections are caused by bacterial infections that may progress and antibiotics may reduce infection-related adverse outcomes.

The UK AMR national action plan for 2019-2024 continues on from the last AMR strategy (2013-2018) with updated aims and targets to address the continued problem of resistance. One aim is to optimise antibiotic use through stewardship programmes, including a 25% reduction in antibiotic use in the community from the 2013 baseline [5]. Antibiotic prescribing in primary care in England shows a declining trend (-13.2%) between 2013 and 2017, however, to reach desired reduction targets continued efforts are needed [3].

A small number of studies have analysed the relationship between antibiotic prescribing rates and adverse events in primary care. Petersen *et al.* [6] (2007) and Gulliford *et al*. [7] (2016) studied the relationship between antibiotic prescribing rates in primary care and complication in patients with common respiratory tract infections (RTIs). Both studies reported reductions in incidence of pneumonia, as recorded by the general practitioner (GP), with higher levels of antibiotic prescribing. However, these studies did not evaluate the association of prescribing rates with the rate of hospital admission after common infections in primary care.

Gharbi *et* al. (2019) reported that prescribing immediate antibiotics in primary care to elderly patients for urinary tract infection (UTI) was associated with a lower risk of bloodstream infection, hospital admission, and all-cause mortality compared with no antibiotics and deferred antibiotic prescribing [8]. However, antibiotic prescribing in primary care is known to increase the risk of resistant infections [9]. This highlights the challenge in balancing prescribing to reduce the risk of severe outcomes and limiting overall antibiotic consumption to slow the development of AMR.

The association between practice antibiotic prescribing rates and the rate of hospital admission after common infection when clearly separated from other infection-related complications managed in the community has not previously been studied. There is uncertainty with regards to the relationship between antibiotic prescribing levels and complications that can arise after various common infections. The objective of this study was to investigate the association between practice level antibiotic prescribing in primary care for multiple common infections and the rate of infection-related complications through comparison of high and low prescribing GP practices. These data provide insight into the role of antibiotic prescribing patterns in controlling the rate of adverse events.

METHOD:

Data sources

The Clinical Practice Research Datalink (CPRD GOLD [10]) and the Secure Anonymised Information Linkage Databank (SAIL [11]) were used in this study. CPRD is a UK primary care database with routinely collected electronic health records [10]. All patients registered with a participating general practice are anonymously included in the dataset. Data has been collected from 1987 and represents about 8% of the UK population. CPRD is broadly representative of the general UK population in terms of age, sex, and ethnicity [10]. The SAIL databank is a data repository of anonymised personal data collected for research from 75% of Welsh general practices [11]. Within SAIL, individual GP practices share anonymised patient-level clinical information on symptoms, diagnoses and prescribed treatment. As Welsh GP practices are included in both CPRD and SAIL they have been removed from CPRD to avoid replication.

For both data sources, all patient level data was aggregated up to practice level. The final CPRD dataset contained 546 GP practices of which 346 (located in England only), were linked with hospital admitted patient care data (Hospital Episode Statistics (HES)). The SAIL Databank included 338 GP practices, all linked to HES.

Selection and eligibility criteria:

The CPRD study population included patients with a consultation between 1st January 2000 and 30th June 2015; for SAIL, the time period was between 1st January 2000 and 31st December 2017. The study population included patients with an initial GP consultation and clinical READ code for a common infection. This was defined as the first incident consultation for a common infection within six months and without an antibiotic prescription in the previous one month. Six common infections were included: upper respiratory tract infection (URTI, cough or cold, sore throat), lower respiratory tract infection (LRTI), otitis externa, otitis media, sinusitis, and urinary tract infection (UTI).

Patients were eligible to be included if they were permanently registered at the GP practice, had a minimum of one year follow-up since data collection (except for children under one), and at least one record of an incident common infection. Male and females of any age were

eligible. Patients were not required to have an antibiotic prescribed at the time of visit for common infection. Patients with an infection-related complication or an infection-related hospital admission in the six months prior or on the day of consultation were excluded. The number of patients who received an antibiotic at the consultation was determined. The practice antibiotic prescribing rate was the percentage of consultations that resulted in an antibiotic prescription in the complete study period.

Exposure and outcomes:

Infection-related hospital admission was identified using the primary admission diagnosis using ICD-10 codes from the linked HES data. This outcome was evaluated using the CPRD-HES and SAIL-HES datasets. The second outcome evaluated was infection-related complications as recorded in the primary care records. Both outcomes were evaluated during the 30 days after the initial common infection consultation. This outcome was evaluated using the CPRD and SAIL datasets.

Person time at risk was calculated for the registered CPRD and SAIL population by counting the days without diagnosis of infection-related complications during the 30 day follow-up after the date of common infection. The rates of infection-related outcomes were calculated by dividing the number of events by the person time at risk (per 1000 person-month). The outcomes were identified based on pre-defined code lists. Compiled code lists are available on clinicalcodes.org [12]. The ICD-10 codes used were reviewed by clinical experts. Infection-related hospital admission includes codes for admission for sepsis, endocarditis, acute respiratory tract infection, or bacterial meningitis. Infection-related complications as recorded in the primary care records includes any revisit to the GP for infection-related complications such as pneumonia, sepsis, quinsy, mastoiditis, or meningitis in the 30 day follow-up period.

subsequent analyses.

Statistical analysis

Infection-related complications were modelled with negative binomial regression using practice level antibiotic prescribing as a predictor and the log of person time at risk as an offset. The unit of analysis is the practice. The analysis was adjusted with the scaled mean at practice level of age, vaccination against influenza, and hospital admission in the previous year. Additionally, the analysis was adjusted with the scaled proportion of each category at practice level of the following categorical characteristic: Sex, Charlson Comorbidity Index [13], body mass index (BMI), smoking status (never, currently, past, unknown), and socioeconomic status (SES, least deprived to most deprived). Linked Index of Multiple Deprivation (IMD) data in quintiles based on patient's residential postcode were available for both datasets. Census based IMD data measures deprivation at area-level based on domains, such as income, employment, health, housing, and general environment [14]. The proportion of socioeconomic status (SES) was derived from patients with linkage to IMD quintiles. Additionally, analyses using CPRD and CPRD-HES were adjusted with the mean at practice level of the number of GPs per 1000 consults and the patient transfer-out rate. No imputations or other adjustments were performed for missing characteristics in the covariates.

All variables were scaled with their associated interquartile range (IQR: 75th to 25th percentile) by dividing the original values by the IQR from the variable [15]. This creates a natural comparison between high and low prescribing GP practices. The antibiotic prescribing rate was modelled continuously. Because of the scaling the IQR becomes the unit that the effect size is expressed in. Both outcomes were compared against all common infections in the initial analysis. The association of each of the six common infections was then studied against both outcomes separately. The analyses were further stratified by gender and age categories: 0-17, 18-39, 40-59, 60-74, 75+ years old to evaluate the varied prescribing among these risk groups. The beta coefficient of the antibiotic prescribing rate was exponentiated and is presented as an incidence rate ratio (IRR). The effect estimates

from the CPRD and SAIL cohorts were combined using a meta-analysis method with inverse variance weighting and DerSimonian and Laird random effect models.

Absolute difference in antibiotic prescribing between high and low prescribing practices was calculated from the prescribing rates (25th and 75th percentiles) and mean events per practice. The absolute difference in infection-related complications between high and low prescribing was calculated using the complication rate and the IRR. The number needed to treat (NNT) with antibiotics to prevent one event of hospital admission was calculated by dividing the absolute difference in antibiotic prescribing by the absolute difference in complications. Forestplot [16], dplyr [17], and MASS [18] packages in R were used for the analysis. All analyses were performed using R-software version 3.4.1 (R Foundation for Statistical Computing; Vienna, Austria).

RESULTS

The study was based on a total of 19.6 million GP consultations for common infections. URTI was the most frequent common infection (CPRD: 9,646,774) followed by LRTI (CPRD: 2,288,616) and UTI (CPRD: 1,511,176). A total of 884 GP practices were included in the analysis (CPRD: 546; SAIL: 338) (Table 1). The mean age of the practice population was 38 years in CPRD and 30 years in SAIL. The majority of patients had no comorbidities recorded (Charlson score: 0). There were 25,721 cases of infection-related complications as recorded in primary care in CPRD and 15,192 cases in SAIL. The rate of these complications was 1.3 and 4.1 per 1000 person-months respectively. For infection-related hospital admission, the number of cases was 17,810 in CPRD-HES and 19,796 in SAIL-HES, with rates of 1.4 and 5.1 per 1000 person-months, respectively (Table 2). The majority of antibiotics were prescribed for LRTI, Sinusitis, and UTI (Table 3). Antibiotics were less likely to be prescribed for Otitis Externa. There was considerable variability between general practices in the percentages of patients prescribed an antibiotic. For URTI, 28.6% of the patients received an antibiotic at the 5th percentile practice and 66.4% at the 95th percentile practice. Summary

counts of infection-related hospital admission types from CPRD-HES are available in appendix 1, supplementary material.

Infection-related hospital admission

The incidence of infection-related hospital admission was found to be associated with the practice-level antibiotic prescribing rate (Figure 1). A 10.4% higher antibiotic prescribing rate (IQR) was associated with an IRR of 0. 943 (0.920 to 0.967), denoting a 5.7% lower infection-related hospital admission rate in the combined analysis. Results between CPRD-HES and SAIL-HES were comparable. In CPRD-HES, a 10.1% higher antibiotic prescribing rate was associated with an IRR of 0.959 (0.926 to 0.992), meaning a 4.1% lower hospital admission rate. For SAIL-HES, this was 7.2% (IRR: 0.928; 0.895 to 0.961) lower with the IQR of 10.7% higher antibiotic prescribing by GP practices.

The observed association varied by infection. The largest difference in the incidence of hospital admission for the combined analysis was observed in LRTI (IRR: 0.839; 16.1%), UTI (IRR: 0.853; 14.7%), and URTI (IRR: 0.935; 6.5%) (Figure 2). In patients with URTI, 14.9% (CPRD-HES) and 17.2% (SAIL-HES) higher antibiotic prescribing was associated with infection-related hospital admissions being lower by 7.7% (0.923; 0.879 to 0.969) and 5.6% (0.944; 0.905 to 0.984). LRTI was associated with a 14.2% (CPRD-HES, IRR: 0.858) and 18.2% (SAIL-HES, IRR: 0.818) lower incidence for hospital admission when antibiotic prescribing was higher by 8.7% and 15.1%. In patients who consulted their GP for UTI, the incidence of hospital admission was 10.5% (IRR: 0.895) lower with 7.6% higher antibiotic prescribing (CPRD-HES). In SAIL-HES, 12.0% higher antibiotic prescribing for UTI was associated with lower incidence by 16.8% (IRR: 0.832). Patients aged 18-39 years old had the greatest difference in incidence for hospital admission (CPRD-HES: 0.884 (IQR unit: 10.88)) amongst the age categories (figure 3).

The number needed to treat with antibiotics to prevent one patient from developing infection-related complications was calculated over the 30 day follow-up period. The number needed

to treat for patients with URTI at risk of hospital admission was 1164. For patients with LRTI and UTI the number needed to treat was 417 and 484 respectively.

GP-recorded infection-related complications

Higher levels of antibiotic prescribing by GP practices were associated with lower incidence of infection-related complication as recorded by the GP. The incidence of GP-recorded infection-related complications reduced by 16.9% (0.831; 0.791 to 0.873) and 9.0% (0.910; 0.866 to 0.954) with an increase in antibiotic prescribing of 10.4% and 10.6% for CPRD and SAIL respectively.

Evaluating the observed association by common infection separately found that URTI was associated with lower GP-recorded infection-related complications by 20.4% (0.803; 0.758 to 0.852) when antibiotic prescribing increased by 15.5% in CPRD. In SAIL, the observed reduction was 12.7% (0.873; 0.832 to 0.916) when antibiotic prescribing increased by 17.2%.

Antibiotic prescribing for LRTI being higher by 9.1% and 15.1% was associated with the incidence of GP-recorded infection-related complications being lower by 16.2% (IRR: 0.838) and 5.5% (IRR: 0.945) for CPRD and SAIL respectively. For UTI, the incidence of GP-recorded infection-related complications was similarly lowered across CPRD (12.7% (IQR unit: 8.01)) and SAIL (8.7% (IQR unit: 11.95)).

No effect modification by gender was observed in any of the datasets evaluated (Figure 3). The effect was more obvious in younger patients. Patients aged 0-17 had the greatest difference in GP-recorded infection-related complications in CPRD (22%; IRR: 0.780, IQR: 12.05). Patients aged 0-17 years and 40-59 showed similar differences for both datasets (Figure 3). Polynomials were fitted on a deciled antibiotic prescribing rate as a sensitivity analysis. First order polynomials best fitted the data and showed a downward linear trend from low to high prescribing (Supplementary material, appendix 2).

DISCUSSION

This study found that higher levels of incident antibiotic prescribing by practices were associated with lower rates of hospital admission and GP diagnosed infection-related complications. Lower rate of poor clinical outcomes with higher levels of antibiotic prescribing was more pronounced for URTI, LRTI, and UTI but had no association with poor outcomes for otitis media and otitis externa. A higher level of incident antibiotic prescribing in younger patients was associated with better clinical outcomes while no association was observed in patients over 40 years old.

This is the first study to use two large primary care databases with linked hospitalisation data to evaluate the difference in hospital admission after common infections comparing high with low prescribing GP practices. The focus of this analysis was at practice level with the emphasis on evaluating governmental guidance on reducing overall prescribing. The study population was restricted to new antibiotic prescribing in patients with newly developed common infections. Including patients with more complex clinical scenarios, like repeated antibiotic users, complicates the estimation of the effect of interest. Past consultations and potential treatment for a common infection may be associated with future consultations, treatment, and future outcomes of interest. This will lead to a problem when the outcome of interest cannot be related back to a single index visit and instead potentially to more than one visit. The results of this analysis can only be interpreted in the context of the incidental antibiotic user.

This practice level analysis possibly simplifies the relationship between antibiotic prescribing rate and infection-related complications by aggregating data up to practice level and ignoring diversity in patient characteristics within a practice. Some potential confounding at practice level may occur due to variation in patient population frailty even when characteristics have been accounted for at practice level [19]. Diagnoses are based on clinical coding both in primary and secondary care and potential misclassifications or misdiagnoses in the underlying data could have occurred. Differences in coding practices for common infections

among English GP practices has been evaluated previously and found to be problematic at times [4]. As no data were available on infection severity or symptom scores, no conclusions can be drawn on the appropriateness of antibiotics prescribed. This analysis was based on digital patient charts without access to free-text due to GDPR rules as this poses a possible patient identification risk. Digital patient charts are automatically generated and transferred to the database.

The incidence rates of the clinical outcomes were different between SAIL and CPRD, with higher rates in Wales. There has been a measles epidemic in Wales recently which may partly explain these differences. However, this remains speculative. Infections are often localised and infection rates differ between locations. In addition, the level of data available does not allow in-depth investigation into this difference. The NNTs presented are related to the 30 day follow-up window. They may appear large and initial clinical relevance uncertain. UK guidance for initiating statin use states those with a 10-year risk of 10-19% are eligible. Converting this 10-year risk to a 30 day estimated NNT gives a NNT of 1139 (10%) and 569 (19%). These NNTs are similar to those presented in this analysis and have led to a change in clinical practice and prescribing behaviour.

Those with weaker immune systems, the very young and very old, have an elevated susceptibility to infections which may increase their antibiotic use and risk of related complications [20]. Analysis performed by age group showed that higher levels of antibiotic prescribing were associated with reduced infection-related complications in younger patients. Higher levels of antibiotic prescribing were not associated with lower rates of infection-related complications in patients aged 60+ years. A possible hypothesis for this is that increased lifetime exposure and repeatedly using antibiotics could lower their effectiveness in reducing a patient's risk of complications. This observation should be considered and explored in further research. GPs may be more hesitant to withhold antibiotics from older patients to avoid under-treatment, leading to seeing a greater response in younger patients at higher prescribing rates.

Costelloe *et al.* (2010) found that patients who were prescribed an antibiotic for respiratory or urinary tract infections develop antibiotic resistance that was detectable for up to 12 months [9]. The more antibiotics prescribed, the higher the GP re-attendance rates for common infections and subsequently the larger the re-prescribing antibiotic rate becomes [21]. A randomised trial involving 34 general practices following the STAR educational programme saw reductions in overall levels of antibiotic prescribing in the intervention group [22]. Hospital admission for respiratory tract infections and complications increased by 1.9% in the intervention group, suggesting that reduced antibiotic prescribing may increase hospital admission. However, this result was not found to be statistically different and had limited statistical power.

UK initiatives have included the TARGET toolkit and the Quality Premium (QP) to reduce overall levels of antibiotic use [22–24]. The QP was introduced in April 2015 and provided a financial incentive to Clinical Commissioning Groups (CCGs) to reduce antibiotic prescribing rates. A significant 3% reduction in antibiotic prescribing rate was observed after this initiative was introduced, with greatest reduction in children [25]. Reducing antibiotic prescribing rates may be good for antibiotic resistance, but as shown here could potentially cause more infection-related complications. Antibiotic prescribing requires a careful balance; with each prescription to treat and reduce the risk of infection-related complications, the chance of developing resistant infections increases for individual patients and drives AMR risk for the wider community. With the current aim to reduce antibiotic prescribing in the community in the UK by 25% from the 2013 baseline, particular focus is required to understand individual patient risk, reducing inappropriate prescribing and monitor infection related complications. For patients with LRTI in primary care, Moore *et al*. [26] modelled a predictive value of the risk of patients developing serious outcomes including hospital admission. Such a direct approach, together with delayed prescribing strategies [27] are suggested to target prescribing to those most likely to develop complications and reduce overall prescribing.

A Cochrane review of 27 trials on antibiotics for sore throat found that antibiotics prevented complications (acute rheumatic fever, glomerulonephritis, otitis media, and sinusitis) in patients, but the rate of complications were so low the benefit of antibiotic prescribing may not always be clear [28]. Similarly another Cochrane review focused on antibiotics for acute otitis media in children found that serious complications, such as mastoiditis and meningitis, were rare [29]. Both reviews highlighted the inability to predict which patients are at risk of developing complications. Clinical tools such as the FeverPAIN score and Centor criteria are used to guide antibiotic treatment for acute sore throat. However, Little *et al*. (2013) concluded that clinical scores such as FeverPAIN were of limited value in predicting clinical complications [30].

In conclusion, lower levels of practice level antibiotic prescribing were associated with higher levels of infection-related complications and hospital admissions. Identifying and developing accurate clinical tools for predicting which patients are at risk of complications requires much needed further research. To improve patient outcomes and reduce the risk of avoidable complications, there is a need to target patients most likely to benefit from effective, safe prescribing, based on shared decision making.

NOTES

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Conflict of interest: All authors have completed the ICMJE uniform disclosure form and declare: BvB, VP, CM, DA, TvS report grants from the Department of Health and Social Care for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study protocol was approved by the Independent Scientific Advisory Committee for CPRD research [protocol number 16_153] and SAIL's Information Governance Protocol Review Panel [protocol number 0693]. We would like to acknowledge all the data providers who make anonymised data available for research.

Data sharing: Read codes used are published on Clinicalcodes.org. Electronic health records are, by definition, considered sensitive data in the UK by the Data Protection Act and cannot be shared via public deposition because of information governance restriction in place to protect patient confidentiality. Access to data is available only once approval has been obtained through the individual constituent entities controlling access to the data.

CPRD data can be requested via application to the Clinical Practice Research Datalink (www.cprd.com), and SAIL data are available by application to the Secure Anonymised Information Linkage Databank (https://saildatabank.com/).

Author contributor statement: BvB and TvS contributed to the idea and design of the study. TvS extracted the relevant data from the database. BvB analysed the data and drafted the paper. All authors contributed to drafts and critical revision and approved the final manuscript.

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TABLES

Table 1. Demographic and characteristics of the GP practices included in CPRD, CPRD-HES, and SAIL datasets. The CPRD dataset covers England, Scotland, and Northern Island. CPRD-HES covers England only. SAIL databank covers Wales only.

	CPRD n= 546	CPRD-HES linked n= 346	SAIL n= 338
Consultations			
Upper Respiratory Tract Infection (URTI)	9,646,774	5,698,611	1,956,752
Lower Respiratory Tract Infection (LRTI)	2,288,616	1,321,593	435,929
Otitis Externa	1,166,023	708,465	183,843
Otitis Media	864,791	529,946	215,495
Sinusitis	707,736	422,638	97,636
Urinary Tract Infection (UTI)	1,511,176	881,957	263,921
Age (mean, sd)	38.50 (3.86)	38.47 (3.72)	30.17 (7.11)
Sex female (%)	58.98	59.06	56.25
Charlson comorbidity index (CCI) (mean (%))			
None (0)	65.80	66.16	77.28
Low (1-2)	27.41	27.24	18.39
Medium (3-4)	5.10	4.97	3.24
High (5-6)	1.25	1.19	0.81
Very high (>7)	0.45	0.44	0.28
Region (count, %)			
North England	109 (20.0%)	83 (24.0%)	-
Midlands	120 (22.0%)	87 (25.1%)	-
South England	158 (28.9%)	124 (35.8%)	-
London	67 (12.3%)	52 (15.0%)	
Devolved Administrations (Northern Ireland and Scotland)	92 (16.8%)	-	-
Wales	-	-	338 (100%)
Socioeconomic status (mean (%))			
1 least deprived	13.29	20.98	23.77
2	14.25	22.49	21.36
3	12.49	19.71	21.17
4	12.47	19.68	17.65
5 most deprived	10.17	16.05	16.05
Missing data	37.32	1.09	-
Hospitalisation in previous year (mean (%))	0.02	0.02	0.03
GPs per 1000 consults (mean, sd)	3.54 (2.30)	3.52 (2.25)	NA

Footnote table 1. GP count per 1000 consults was not available in SAIL databank.

Table 2. Rates of infection-related complications and or hospital admission in the 30 days after GP visit for common infection. Hospital admission was identified from the linked HES data. GP-recorded infection-related complications were identified from the electronic health records, which included any revisit to the GP for complications after the initial consultation.

Infection-related complications	Number of cases (30 day follow-up)	Sum person-months (30 day follow-up)	Rate and 95% CI (per 1000 person-month)
Infection-related complication GP-recorded			
CPRD	25,721	19,220,606	1.34 (1.32 - 1.35)
SAIL	15,192	3,718,739	4.09 (4.02 - 4.15)
Hospital admission			
CPRD-HES linked	17,810	12,335,982	1.44 (1.42 - 1.47)
SAIL-HES	19,796	3,900,897	5.08 (5.00 - 5.15)

Table 2. Antibiotic prescribing rates for each common infection across practices included in CPRD (n= 546), CPRD-HES (n=346), and SAIL (n= 338). Rates are presented for six common infections. Proportion of consultations with antibiotics prescribed is presented with the mean percentage and the 5th through 95th percentile at practice level. The mean percentage of antibiotic prescribed in CPRD after a consultation for URTI was 46.1%.

	Mean % (sd)	5 %	25 %	50 %	75 %	95 %
Upper Respiratory Tract Infection (URTI); URTI, cough or cold, sore throat						
CPRD	46.14 (11.71)	28.59	38.25	45.14	53.73	66.36
CPRD-HES linked	43.74 (10.97)	28.88	38.17	45.15	53.09	63.97
SAIL	43.37 (12.07)	24.83	34.57	42.88	51.76	63.43
Lower Respiratory Tract Infection (LRTI); Excluding community acquired pneumonia						
CPRD	84.79 (8.89)	69.79	81.45	86.68	90.52	94.40
CPRD-HES linked	85.24 (8.03)	70.89	81.90	86.80	90.57	94.68
SAIL	78.11 (11.66)	55.47	71.56	80.45	86.69	93.17
Otitis Externa						
CPRD	26.33 (8.98)	15.34	20.00	24.55	31.00	42.70
CPRD-HES linked	26.52 (8.44)	15.34	20.13	25.16	31.37	41.57
SAIL	29.57 (10.65)	14.92	22.03	28.71	34.89	48.5
Otitis Media						
CPRD	78.10 (10.86)	58.35	73.05	80.27	86.09	91.57
CPRD-HES linked	78.27 (9.83)	59.20	73.35	79.51	85.81	91.30
SAIL	78.49 (11.81)	54.91	72.64	80.57	87.49	92.65
Sinusitis						
CPRD	84.97 (8.93)	67.89	82.48	87.13	90.29	94.43
CPRD-HES linked	85.75 (7.88)	70.07	83.20	87.60	90.63	94.57
SAIL	82.12 (9.91)	63.36	77.44	84.22	88.89	94.73
Urinary Tract Infection (UTI)						
CPRD	85.90 (7.39)	74.01	82.96	87.28	90.98	93.72
CPRD-HES linked	86.06 (6.40)	74.08	83.19	87.01	90.79	93.30
SAIL	81.50 (10.30)	61.46	76.70	84.66	88.65	93.18

Figures

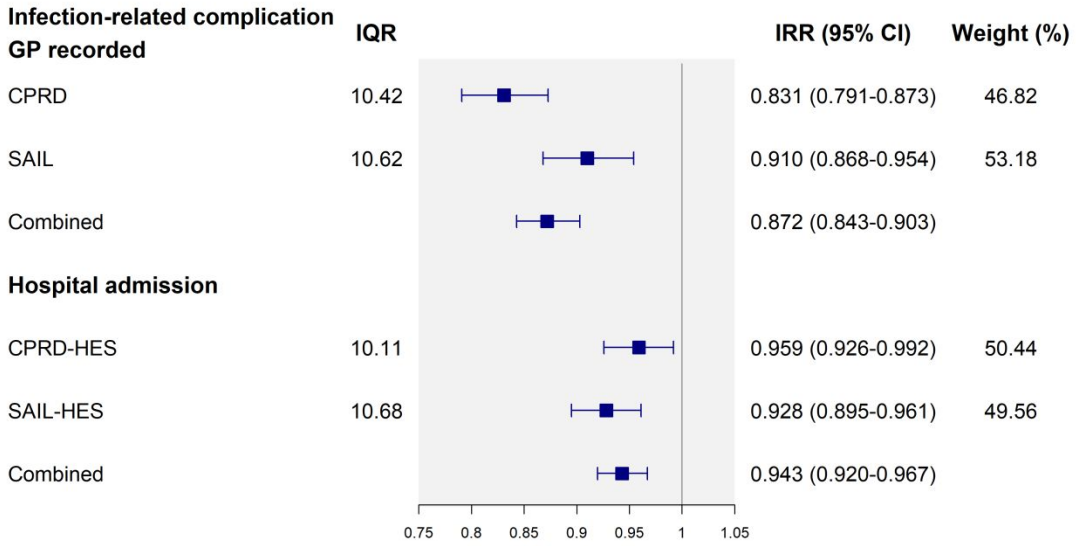


Figure 1. Incidence rate ratios (IRR) and 95% confidence interval (CI) of GP-recorded infection-related complications and hospital admissions comparing antibiotic prescribing at 75th to 25th percentile (IQR). Results are presented by data source. CPRD and SAIL effect estimates were combined using a fixed-effect meta-analysis method.

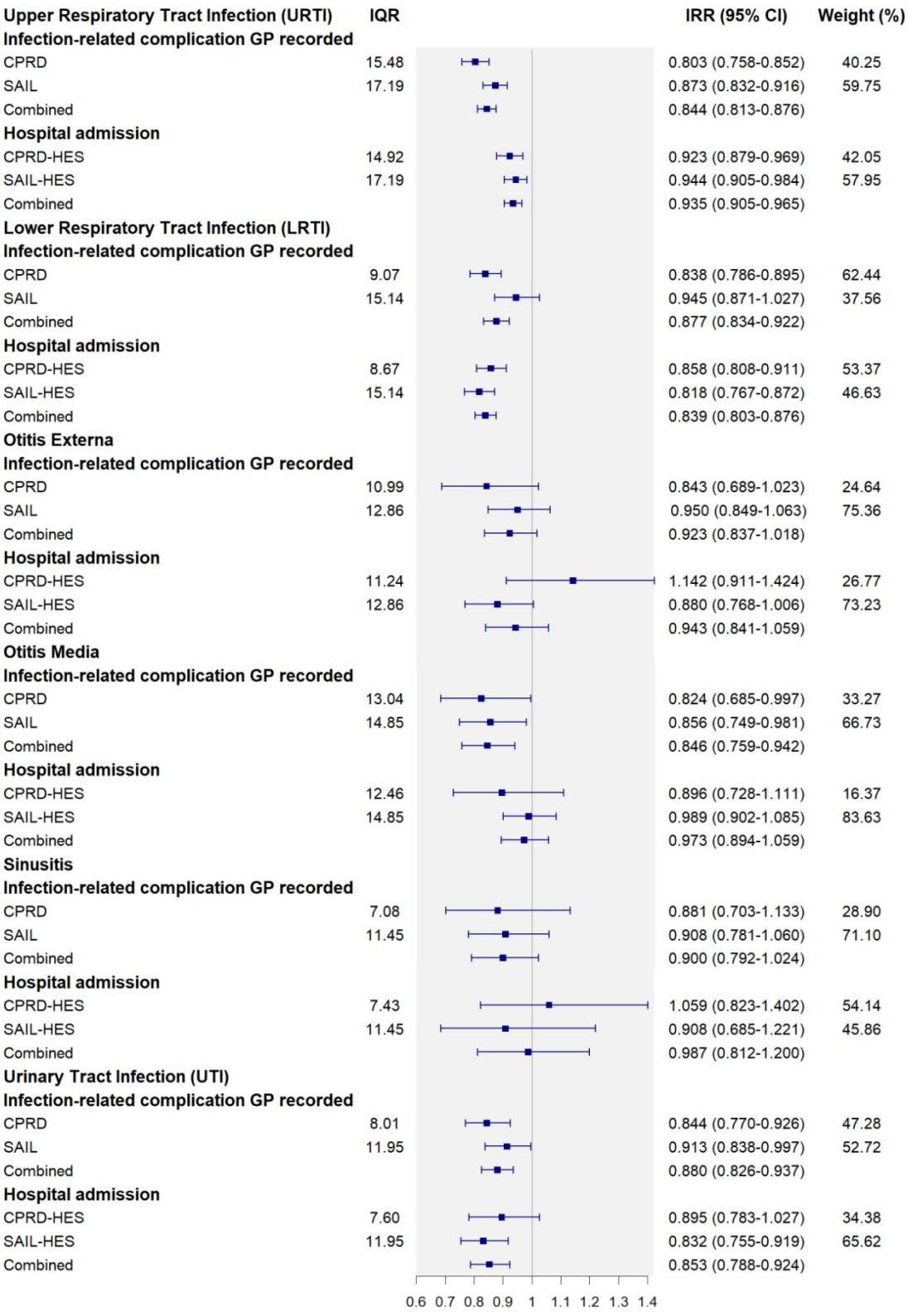


Figure 2. Effect estimates (IRRs and 95% CI) of GP-recorded infection-related complications and hospital admissions. Analyses compared antibiotic prescribing at 75th and 25th percentile (IQR) by 6 common infections. The IRR for hospital admission after a consultation for URTI in CPRD-HES was 0.923. This means for an 14.9% increase in antibiotic prescribing the rate of hospital admission is reduced by 7.7%.

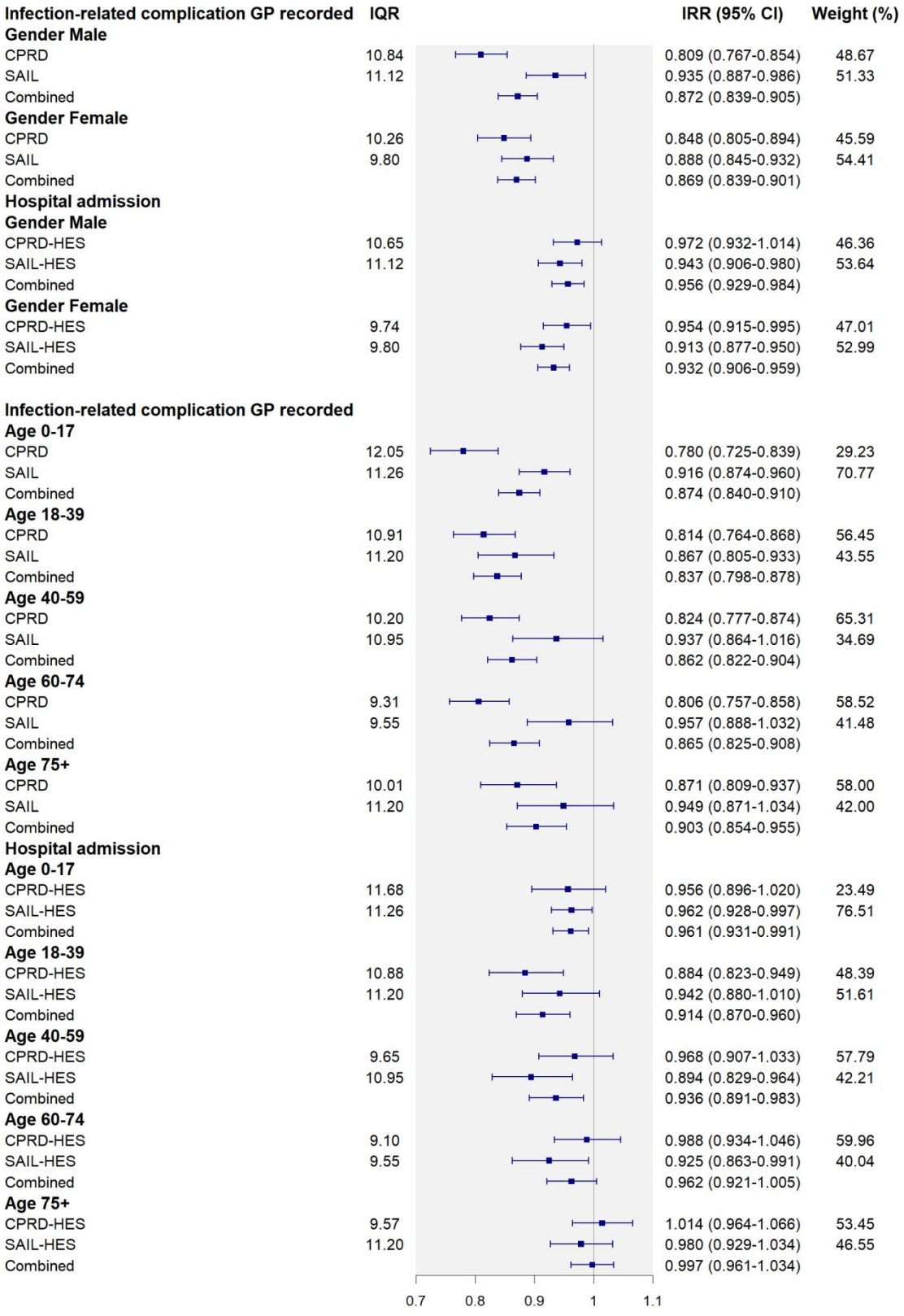
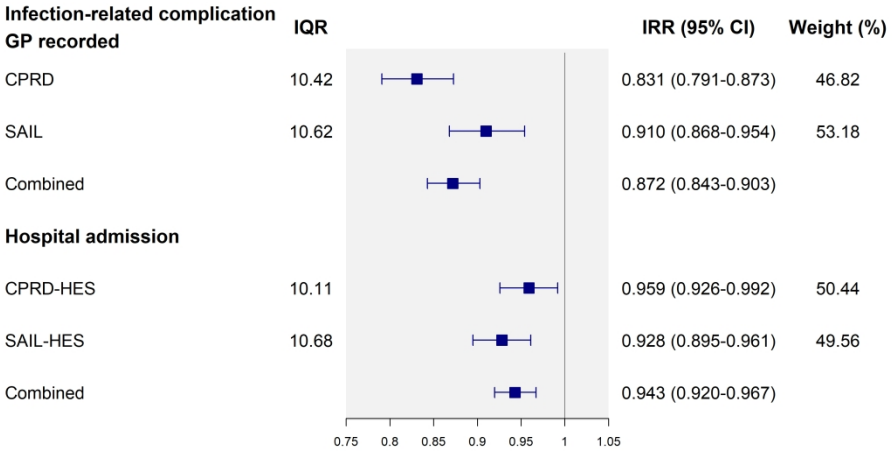


Figure 3. Association of GP-recorded infection-related complications and hospital admissions comparing practice antibiotic prescribing at 75th and 25th percentile (IQR) by gender and age groups. Weights are from fixed-effects analysis.



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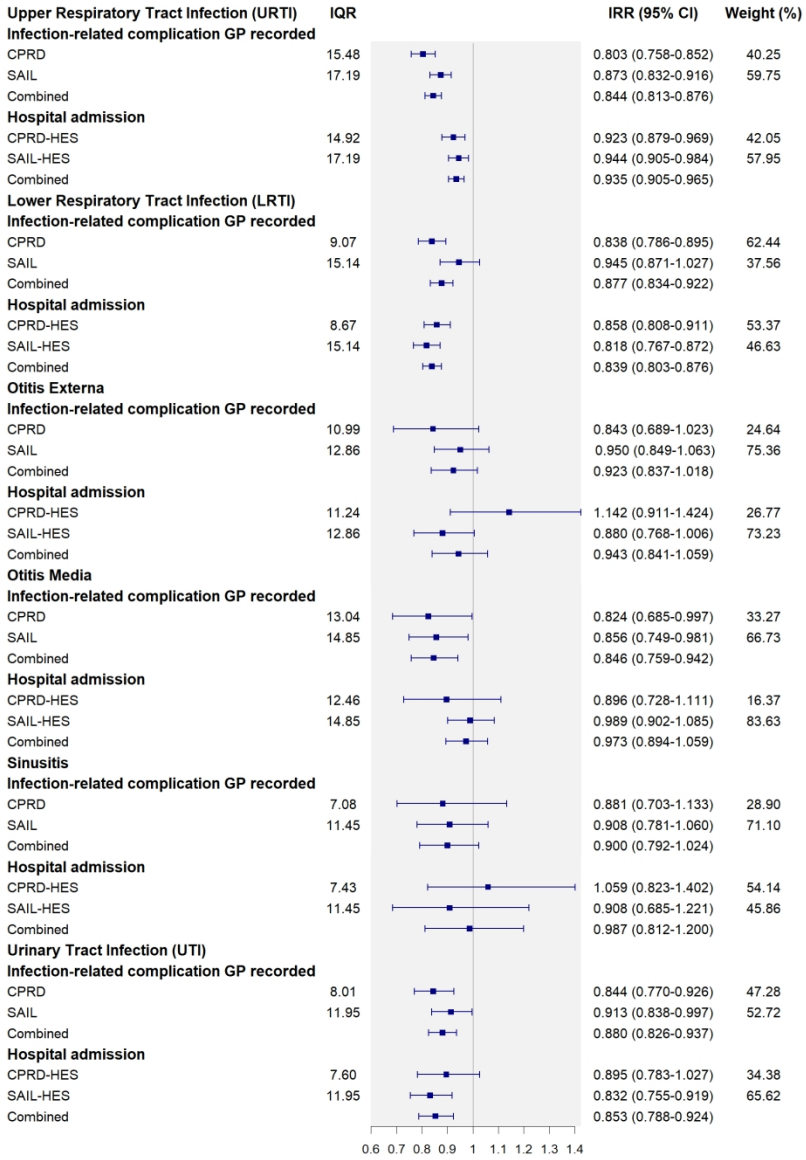

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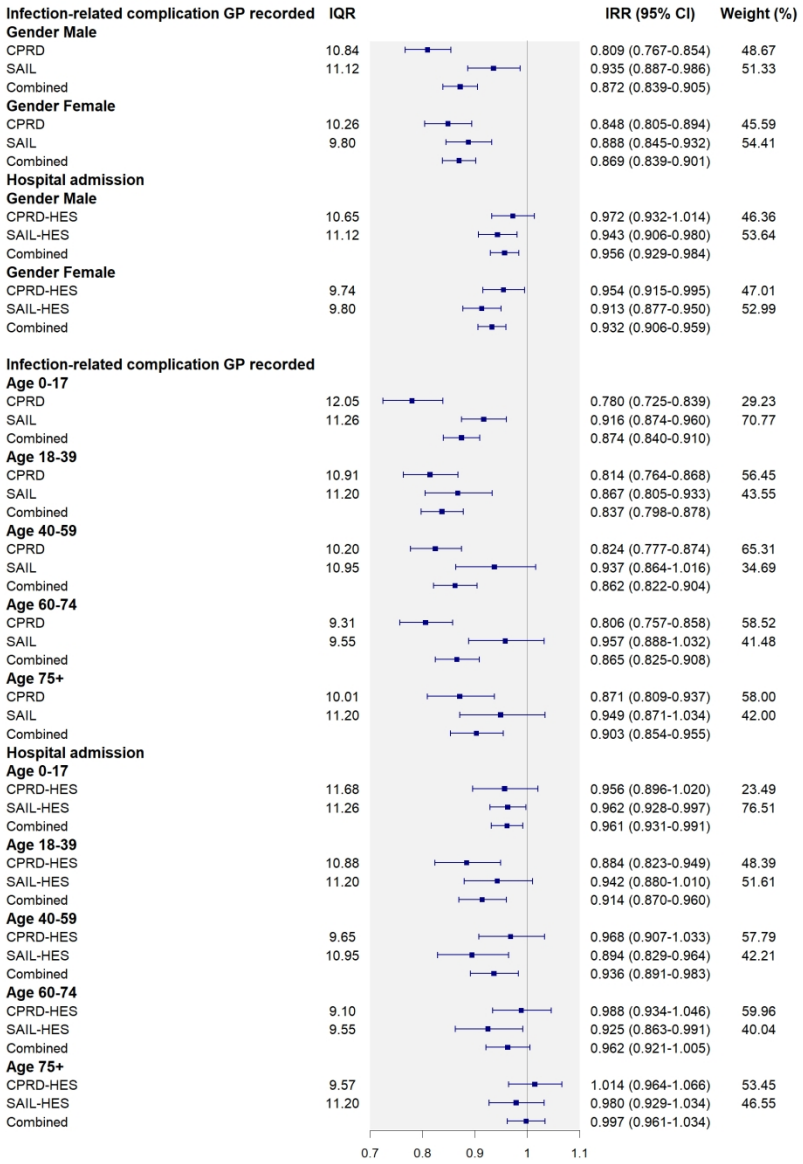

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330x457mm (150 x 150 DPI)

Supplementary Material

Appendix 1. Summary counts of infection-related hospital admission types as recorded as hospital admission codes in the primary care records.

Table S1. Summary counts of distribution of infection-related complications based on hospital admission codes in CPRD-HES. Table shows counts from CPRD-HES by sex and age for multiple infection-related complications.

CPRD-HES	All	Male	Female	Age 0-17	Age 18-39	Age 40-59	Age 60-74	Age 75+
Cough/Cold	103	60	43	96	<5	<5	<5	<5
LRTI/Pneumonia	13543	6026	7527	2515	877	1681	2418	6056
Otitis externa	67	29	38	12	18	16	10	10
Otitis media	432	223	209	236	64	64	47	18
Sinusitis	46	16	31	7	7	15	14	<5
Sore Throat	2000	1066	932	481	1085	357	58	17
URTI	695	375	319	509	47	42	36	62
UTI	112	39	73	<5	36	12	27	38
Sepsis	397	183	214	16	16	31	85	249
Meningitis	45	18	27	13	11	10	5	6
Infection-related complication, protocol defined	17810	8234	9580	3673	2226	2464	2890	6562
Any hospitalisation, not infection specific	77704	34050	43695	8196	7865	11990	18640	31030

Note 1: the sum of specific infections does not add up to sum of infection-related complications protocol defined due to a subset of patients having multiple infection-related complication admission codes. Note 2: the sum of Male and Female, and the sum of the age categories may not add up to the sum of 'All' due to some missingness in gender or year-of-birth registration in the patient's medical records.

Appendix 2. Sensitivity analysis of continuous antibiotic prescribing rate

A sensitivity analysis was performed to determine if treating the antibiotic prescribing rate continuously is justified. The rate of infection-related hospital admission and antibiotic prescribing rate was modelled with negative binomial regression. The antibiotic prescribing rate was decile ranked to create 10 equally sized subsections. These deciles were modelled in the exact same way as the main analyses presented in this paper. First, second, and third degree polynomials were fitted on the deciled antibiotic rate and evaluated against the IRRs for infection-related complication as recorded by the GP ('A', 'B', 'C') and for infection-related hospital admission ('D', 'E', 'F'). For both outcomes the first order polynomials were the preferred models. Figure S1 Plot A shows a strong linear trend for between low prescribing

at deciles 1 to 3 and high prescribing at deciles 8 to 10. Although the error bars of each point estimate overlap a downward linear trend is observable. Creating categories of the antibiotic prescribing rate may hide significant variability within each specific category. Treating the antibiotic prescribing rate continuously ensures that each GP practice is analysed separately against the outcomes of interest.

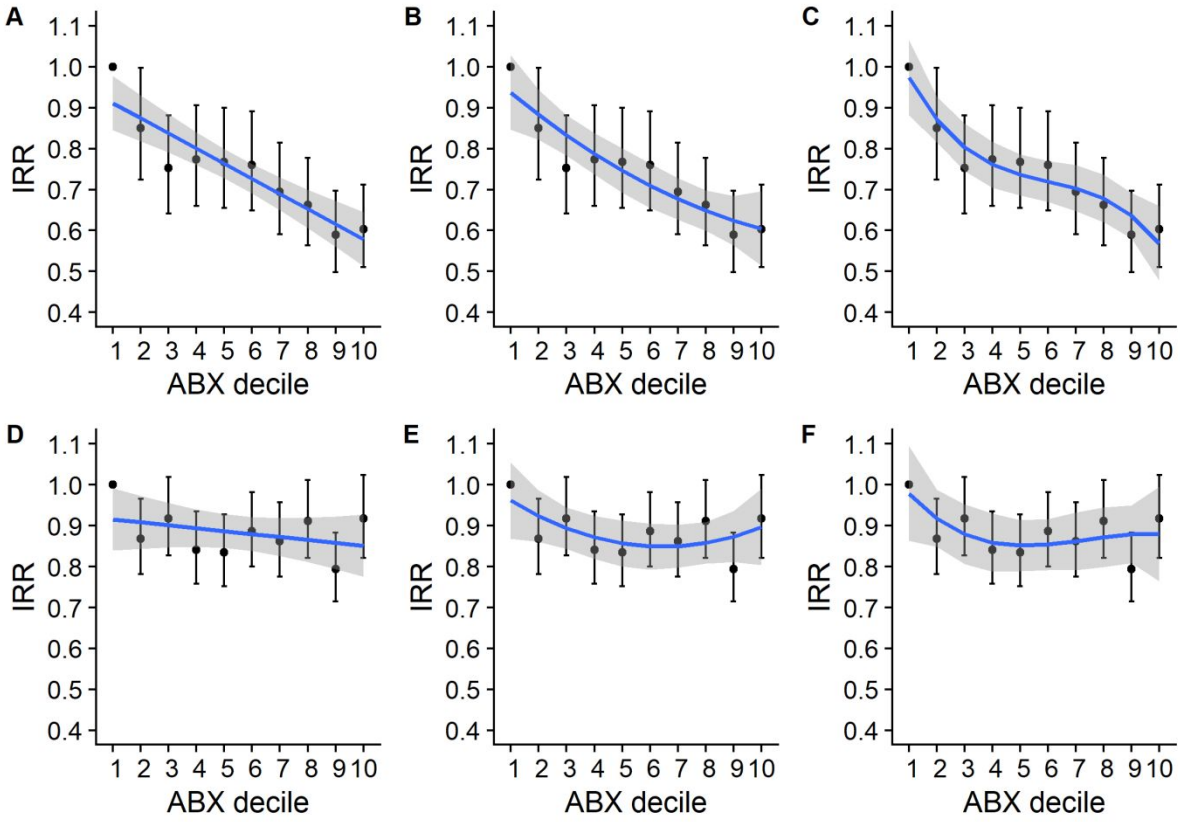

Figure s1. First (left), second (middle), and third (right) degree polynomials fitted on the deciled antibiotic prescribing rate. Plot A, B, and C model outcome infection-related complication as recorded by the GP. Plot D, E, and F model outcome infection-related hospital admission.

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Infection-related complications after common infection in association with new antibiotic prescribing in primary care: retrospective cohort study using linked electronic health records

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Keywords: Antibiotic prescription, hospitalisation, infection-related complications, common infection, primary care

Word count: 3786

ABSTRACT

Objective Determine the association of incident antibiotic prescribing levels for common infections with infection-related complications and hospitalisations by comparing high with low prescribing GP practices.

Design Retrospective cohort study.

Data source UK primary care records from the Clinical Practice Research Datalink (CPRD GOLD) and SAIL Databank (SAIL) linked with Hospital Episode Statistics (HES) data, including 546 CPRD, 346 CPRD-HES and 338 SAIL-HES practices.

Exposures Initial general practice visit for one of six common infections and the proportion of antibiotic prescribing in each practice.

Main outcome measures Incidence of infection-related complications (as recorded in general practice) or infection-related hospital admission within 30 days after consultation for a common infection.

Results A practice with 10.4% higher antibiotic prescribing (the interquartile range (IQR)) was associated with a 5.7% lower rate of infection-related hospital admissions (adjusted analysis, 95% Confidence Interval 3.3% to 8.0%). The association varied by infection with larger associations in hospital admissions with lower respiratory tract infection (16.1%; 12.4% to 19.7%) and urinary tract infection (14.7%; 7.6% to 21.1%) and smaller association in hospital admissions for upper respiratory tract infection (6.5%; 3.5% to 9.5%) The association of antibiotic prescribing levels and hospital admission was largest in patients aged 18-39 (8.6%; 4.0% to 13.0%) and smallest in the elderly aged 75+ (0.3%; -3.4% to 3.9%).

Conclusions There is an association between lower levels of practice level antibiotic prescribing and higher infection-related hospital admissions. Indiscriminately reducing antibiotic prescribing may lead to harm. Greater focus is needed to optimise antibiotic use by

reducing inappropriate antibiotic prescribing and better targeting antibiotics to patients at high risk of infection-related complications.

ARTICLE SUMMARY

Strengths and limitations of this study

- Two large primary care databases with linked hospitalisation data were used to evaluate the difference in hospital admission after community acquired common infections comparing high with low prescribing GP practices.
- This analysis focusses on antibiotic prescribing at practice level with the emphasis on evaluating governmental guidance on reducing overall prescribing.
- Incidental antibiotic prescriptions without details on local antibiotic resistance levels were evaluated in this analysis and the results can only be interpreted in this context.
- No data was extracted on infection severity or symptom scores therefore no conclusions can be drawn on the appropriateness of antibiotics prescribed.

INTRODUCTION

Common infections, such as sore throat or sinusitis, are often self-limiting and usually get better without antibiotics; nevertheless, they are frequently prescribed [1,2]. Research regarding antimicrobial resistance (AMR) and antibiotic prescribing rates often focuses on reducing inappropriate prescribing to lower the threat of increasing antimicrobial resistance [3]. Antibiotic prescribing for common self-limiting infections is often seen as a target for reduction [3,4]. However, a proportion of common infections are caused by bacterial infections that may progress and antibiotics may reduce infection-related adverse outcomes.

The UK AMR national action plan for 2019-2024 continues on from the last AMR strategy (2013-2018) with updated aims and targets to address the continued problem of resistance. One aim is to optimise antibiotic use through stewardship programmes, including a 25% reduction in antibiotic use in the community from the 2013 baseline [5]. Antibiotic prescribing

in primary care in England shows a declining trend (-13.2%) between 2013 and 2017, however, to reach desired reduction targets continued efforts are needed [3].

A small number of studies have analysed the relationship between antibiotic prescribing rates and adverse events in primary care. Petersen *et al.* [6] (2007) and Gulliford *et al*. [7] (2016) studied the relationship between antibiotic prescribing rates in primary care and complication in patients with common respiratory tract infections (RTIs). Both studies reported reductions in incidence of pneumonia, as recorded by the general practitioner (GP), with higher levels of antibiotic prescribing. However, these studies did not evaluate the association of prescribing rates with the rate of hospital admission after common infections in primary care.

Gharbi *et* al. (2019) reported that prescribing immediate antibiotics in primary care to elderly patients for urinary tract infection (UTI) was associated with a lower risk of bloodstream infection, hospital admission, and all-cause mortality compared with no antibiotics and deferred antibiotic prescribing [8]. However, antibiotic prescribing in primary care is known to increase the risk of resistant infections [9]. This highlights the challenge in balancing prescribing to reduce the risk of severe outcomes and limiting overall antibiotic consumption to slow the development of AMR.

The association between practice antibiotic prescribing rates and the rate of hospital admission after common infection when clearly separated from other infection-related complications managed in the community has not previously been studied. There is uncertainty with regards to the relationship between antibiotic prescribing levels and complications that can arise after various common infections. The objective of this study was to investigate the association between practice level antibiotic prescribing in primary care for multiple common infections and the rate of infection-related complications through comparison of high and low prescribing GP practices. These data provide insight into the role of antibiotic prescribing patterns in controlling the rate of adverse events.

METHOD:

Data sources

The Clinical Practice Research Datalink (CPRD GOLD [10]) and the Secure Anonymised Information Linkage Databank (SAIL [11]) were used in this study. CPRD is a UK primary care database with routinely collected electronic health records [10]. All patients registered with a participating general practice are anonymously included in the dataset. Data has been collected from 1987 and represents about 8% of the UK population. CPRD is broadly representative of the general UK population in terms of age, sex, and ethnicity [10]. The SAIL databank is a data repository of anonymised personal data collected for research from 75% of Welsh general practices [11]. Within SAIL, individual GP practices share anonymised patient-level clinical information on symptoms, diagnoses and prescribed treatment. As Welsh GP practices are included in both CPRD and SAIL they have been removed from CPRD to avoid replication.

For both data sources, all patient level data was aggregated up to practice level. The final CPRD dataset contained 546 GP practices of which 346 (located in England only), were linked with hospital admitted patient care data (Hospital Episode Statistics (HES)). The SAIL Databank included 338 GP practices, all linked to HES.

Selection and eligibility criteria:

The CPRD study population included patients with a consultation between 1st January 2000 and 30th June 2015; for SAIL, the time period was between 1st January 2000 and 31st December 2017. The study population included patients with an initial GP consultation and clinical Read code for a common infection. This was defined as the first incident consultation for a common infection within six months and without an antibiotic prescription in the previous one month. Six common infections were included: upper respiratory tract infection (URTI, cough or cold, sore throat), lower respiratory tract infection (LRTI), otitis externa, otitis media, sinusitis, and urinary tract infection (UTI).

Patients were eligible to be included if they were permanently registered at the GP practice, had a minimum of one year follow-up since data collection (except for children under one), and at least one record of an incident common infection. Male and females of any age were eligible. Patients were not required to have an antibiotic prescribed at the time of visit for common infection. Patients with an infection-related complication or an infection-related hospital admission in the six months prior or on the day of consultation were excluded.

Exposure and outcomes:

The number of patients who received an antibiotic at the consultation was determined. The practice antibiotic prescribing rate was the percentage of consultations that resulted in an antibiotic prescription in the complete study period.

Infection-related hospital admission was identified using the primary admission diagnosis using ICD-10 codes from the linked HES data. This outcome was evaluated using the CPRD-HES and SAIL-HES datasets. The second outcome evaluated was infection-related complications as recorded in the primary care records. Both outcomes were evaluated during the 30 days after the initial common infection consultation. In case of death or end of data collection within these 30 days, observations were censored. The outcomes were evaluated using the CPRD and SAIL datasets.

Person time at risk was calculated for the registered CPRD and SAIL population by counting the days without diagnosis of infection-related complications during the 30 day follow-up after the date of common infection. The rates of infection-related outcomes were calculated by dividing the number of events by the person time at risk (per 1000 person-month). The outcomes were identified based on pre-defined code lists. Compiled code lists are available on clinicalcodes.org [12]. The codes for outcomes and infections used were reviewed independently by two clinical epidemiologists. Infection-related hospital admission includes codes for admission such as for sepsis, endocarditis, acute respiratory tract infection, or bacterial meningitis. Infection-related complications as recorded in the primary care records

includes any revisit to the GP for infection-related complications such as pneumonia, sepsis, quinsy, mastoiditis, or meningitis in the 30 day follow-up period.

Confounders

The proportion of socioeconomic status (SES) was derived from patients with linkage to IMD quintiles. Linked Index of Multiple Deprivation (IMD) data in quintiles based on patient's residential postcode were available for both datasets. Census based IMD data measures deprivation at area-level based on domains, such as income, employment, health, housing, and general environment [13].

Statistical analysis

Infection-related complications were modelled with negative binomial regression using practice level antibiotic prescribing as a predictor and the log of person time at risk as an offset. The unit of analysis is the practice. The analysis was adjusted with the scaled mean at practice level of age, vaccination against influenza, and hospital admission in the previous year. Additionally, the analysis was adjusted with the scaled proportion of each category at practice level of the following categorical characteristic: Sex, Charlson Comorbidity Index [14], body mass index (BMI), smoking status (never, currently, past, unknown), and socioeconomic status (SES, least deprived to most deprived). Additionally, analyses using CPRD and CPRD-HES were adjusted with the mean at practice level of the number of GPs per 1000 consults, the patient transfer-out rate and region. No imputations or other adjustments were performed for missing characteristics in the covariates.

All variables were scaled with their associated interquartile range (IQR: 75th to 25th percentile) by dividing the original values by the IQR from the variable [15]. This creates a natural comparison between high and low prescribing GP practices. The antibiotic prescribing rate was modelled continuously. Because of the scaling the IQR becomes the unit that the effect size is expressed in. Both outcomes were compared against all common infections in the initial analysis. The association of each of the six common infections was

then studied against both outcomes separately. The analyses were further stratified by gender and age categories: 0-17, 18-39, 40-59, 60-74, 75+ years old to evaluate the varied prescribing among these risk groups. The beta coefficient of the antibiotic prescribing rate was exponentiated and is presented as an incidence rate ratio (IRR). The effect estimates from the CPRD and SAIL cohorts were combined using a meta-analysis method with inverse variance weighting and DerSimonian and Laird random effect models.

Absolute difference in antibiotic prescribing between high and low prescribing practices was calculated from the prescribing rates (25th and 75th percentiles) and mean events per practice. The absolute difference in infection-related complications between high and low prescribing was calculated using the complication rate and the IRR. The number needed to treat (NNT) with antibiotics to prevent one event of hospital admission was calculated by dividing the absolute difference in antibiotic prescribing by the absolute difference in complications. Forestplot [16], dplyr [17], and MASS [18] packages in R were used for the analysis. All analyses were performed using R-software version 3.4.1 (R Foundation for Statistical Computing; Vienna, Austria).

Patient and public involvement

No patients were involved in the study design and no patients were asked to consult on the outcomes or interpretation of the results. Results will be disseminated to relevant patient communities through news media and social media.

RESULTS

The study was based on a total of 19.6 million GP consultations for common infections. URTI was the most frequent common infection (CPRD: 9,646,774) followed by LRTI (CPRD: 2,288,616) and UTI (CPRD: 1,511,176). A total of 884 GP practices were included in the analysis (CPRD: 546; SAIL: 338) (Table 1). The mean age of the practice population was 38 years in CPRD and 30 years in SAIL. The majority of patients had no comorbidities recorded (Charlson score: 0). There were 25,721 cases of infection-related complications as recorded

in primary care in CPRD and 15,192 cases in SAIL. The rate of these complications was 1.3 and 4.1 per 1000 person-months respectively. For infection-related hospital admission, the number of cases was 17,810 in CPRD-HES and 19,796 in SAIL-HES, with rates of 1.4 and 5.1 per 1000 person-months, respectively (Table 2). The majority of antibiotics were prescribed for LRTI, Sinusitis, and UTI (Table 3). Antibiotics were less likely to be prescribed for Otitis Externa. There was considerable variability between general practices in the percentages of patients prescribed an antibiotic. For URTI, 28.6% of the patients received an antibiotic at the 5th percentile practice and 66.4% at the 95th percentile practice. Summary counts of infection-related hospital admission types from CPRD-HES are available in appendix 1, supplementary material.

Infection-related hospital admission

The incidence of infection-related hospital admission was found to be associated with the practice-level antibiotic prescribing rate (Figure 1). A 10.4% higher antibiotic prescribing rate (IQR) was associated with an IRR of 0.943 (0.920 to 0.967), denoting a 5.7% lower infection-related hospital admission rate in the combined analysis. Results between CPRD-HES and SAIL-HES were comparable. In CPRD-HES, a 10.1% higher antibiotic prescribing rate was associated with an IRR of 0.959 (0.926 to 0.992), meaning a 4.1% lower hospital admission rate. For SAIL-HES, this was 7.2% (IRR: 0.928; 0.895 to 0.961) lower with the IQR of 10.7% higher antibiotic prescribing by GP practices.

The observed association varied by infection. In the combined analysis, the largest association was observed in LRTI (IRR: 0.839(16.1%); 0.803 to 0.876), UTI (IRR: 0.853 (0.788 to 0.924); 14.7%), and URTI (IRR: 0.935 (0.905 to 0.965); 6.5%) (Figure 2). In patients with URTI, 14.9% (CPRD-HES) and 17.2% (SAIL-HES) higher antibiotic prescribing was associated with infection-related hospital admissions being lower by 7.7% (0.923; 0.879 to 0.969) and 5.6% (0.944; 0.905 to 0.984). LRTI was associated with a 14.2% (CPRD-HES, IRR: 0.858; 0.808 to 0.911) and 18.2% (SAIL-HES, IRR: 0.818; 0.767 to 0.872) lower incidence for hospital admission when antibiotic prescribing was higher by 8.7% and 15.1%.

In patients who consulted their GP for UTI, the incidence of hospital admission was 10.5% (IRR: 0.895 (0.783 to 1.027) lower with 7.6% higher antibiotic prescribing (CPRD-HES). In SAIL-HES, 12.0% higher antibiotic prescribing for UTI was associated with lower incidence by 16.8% (IRR: 0.832 (0.755 to 0.919)). Patients aged 18-39 years old had the largest association for hospital admission (CPRD-HES: 0.884 (0.823 to 0.949; IQR unit: 10.88)) amongst the age categories (figure 3).

The number needed to treat with antibiotics to prevent one patient from developing infection-related complications was calculated over the 30 day follow-up period. The number needed to treat for patients with URTI at risk of hospital admission was 1164. For patients with LRTI and UTI the number needed to treat was 417 and 484 respectively.

GP-recorded infection-related complications

Higher levels of antibiotic prescribing by GP practices were associated with lower incidence of infection-related complication as recorded by the GP. The incidence of GP-recorded infection-related complications reduced by 16.9% (0.831; 0.791 to 0.873) and 9.0% (0.910; 0.866 to 0.954) with an increase in antibiotic prescribing of 10.4% and 10.6% for CPRD and SAIL respectively.

Evaluating the observed association by common infection separately found that URTI was associated with lower GP-recorded infection-related complications by 20.4% (0.803; 0.758 to 0.852) when antibiotic prescribing increased by 15.5% in CPRD. In SAIL, the observed reduction was 12.7% (0.873; 0.832 to 0.916) when antibiotic prescribing increased by 17.2%.

Antibiotic prescribing for LRTI being higher by 9.1% and 15.1% was associated with the incidence of GP-recorded infection-related complications being lower by 16.2% (IRR: 0.838; 0.786 to 0.895) and 5.5% (IRR: 0.945; 0.871 to 1.027) for CPRD and SAIL respectively. For UTI, the incidence of GP-recorded infection-related complications was similarly lowered

across CPRD (15.6%; 0.844 (0.770 to 0.926) (IQR unit: 8.01)) and SAIL (8.7%; 0.913 (0.838 to 0.997) (IQR unit: 11.95)).

No effect modification by gender was observed in any of the datasets evaluated (Figure 3). The effect was more obvious in younger patients. Patients aged 0-17 had the largest association in GP-recorded infection-related complications in CPRD (22%; IRR: 0.780 (0.725 to 0.839); IQR: 12.05). Patients aged 0-17 years and 40-59 showed similar associations for both datasets (Figure 3). Polynomials were fitted on a deciled antibiotic prescribing rate as a sensitivity analysis. First order polynomials best fitted the data and showed a downward linear trend from low to high prescribing (Supplementary material, appendix 2). An inverse association was found in an additional sensitivity analysis which paired URTI and LRTI with plausible subsequent infection-related complications, such as pneumonia and hospital admission for LRTI (Supplementary material, appendix 3. In patients who consulted their GP for LRTI, the incidence of a hospital admission with LRTI was 18% (0.820 (0.765 - 0.879)) lower with 8.7% higher antibiotic prescribing (CPRD-HES).

DISCUSSION

This study found that higher levels of incident antibiotic prescribing by practices were associated with lower rates of hospital admission and GP diagnosed infection-related complications. Lower rate of poor clinical outcomes with higher levels of antibiotic prescribing was more pronounced for URTI, LRTI, and UTI but had no association with poor outcomes for otitis media and otitis externa. A higher level of incident antibiotic prescribing in younger patients was associated with better clinical outcomes while no association was observed in patients over 40 years old.

This is the first study to use two large primary care databases with linked hospitalisation data to evaluate the difference in hospital admission after common infections comparing high with low prescribing GP practices. The focus of this analysis was at practice level with the emphasis on evaluating governmental guidance on reducing overall prescribing. The study

population was restricted to new antibiotic prescribing in patients with newly developed common infections. Including patients with more complex clinical scenarios, like repeated antibiotic users, complicates the estimation of the effect of interest. Past consultations and potential treatment for a common infection may be associated with future consultations, treatment, and future outcomes of interest. This will lead to a problem when the outcome of interest cannot be related back to a single index visit and instead potentially to more than one visit. The results of this analysis can only be interpreted in the context of the incidental antibiotic user.

This practice level analysis possibly simplifies the relationship between antibiotic prescribing rate and infection-related complications by aggregating data up to practice level and ignoring diversity in patient characteristics within a practice. Some potential confounding at practice level may occur due to variation in patient population frailty even when characteristics have been accounted for at practice level [19]. In addition, although this analysis attempted to adjust for several available factors which might influence the association investigated. There remains a potential for additional residual confounding by non-adjusted for covariates.

Diagnoses are based on clinical coding both in primary and secondary care and potential misclassifications or misdiagnoses in the underlying data could have occurred. Differences in coding practices for common infections among English GP practices has been evaluated previously and found to be problematic at times [4]. As no data were available on infection severity or symptom scores, no conclusions can be drawn on the appropriateness of antibiotics prescribed. This analysis was based on digital patient charts without access to free-text due to GDPR rules as this poses a possible patient identification risk. Digital patient charts are automatically generated and transferred to the database. Individual patients were able to contribute multiple infection episodes, as long as the consultations were at least 6 months apart.

The incidence rates of the clinical outcomes were different between SAIL and CPRD, with higher rates in Wales. There has been a measles epidemic in Wales recently which may

partly explain these differences. However, this remains speculative. Infections are often localised and infection rates differ between locations. In addition, another possible explanation could be that this difference is due to coding behaviour. However, the level of data available does not allow in-depth investigation into this difference. The NNTs presented are related to the 30 day follow-up window. They may appear large and initial clinical relevance uncertain. UK guidance for initiating statin use states those with a 10-year risk of 10-19% are eligible. Converting this 10-year risk to a 30 day estimated NNT gives a NNT of 1139 (10%) and 569 (19%). These NNTs are similar to those presented in this analysis and have led to a change in clinical practice and prescribing behaviour.

Those with weaker immune systems, the very young and very old, have an elevated susceptibility to infections which may increase their antibiotic use and risk of related complications [20]. Analysis performed by age group showed that higher levels of antibiotic prescribing were associated with reduced infection-related complications in younger patients. Higher levels of antibiotic prescribing were not associated with lower rates of infection-related complications in patients aged 60+ years. A possible hypothesis for this is that increased lifetime exposure and repeatedly using antibiotics could lower their effectiveness in reducing a patient's risk of complications. Recent research reported reduced effectiveness of antibiotics with repeated use over several years [21]. A literature review by Costelloe *et al.* (2010) found that individuals who were prescribed an antibiotic for respiratory or urinary tract infections develop bacterial resistance that was detectable for up to 12 months [9]. Similar association has been reported recently for resistant blood stream infection after UTI prescribing [22]. However, further research is needed to assess any age effect in the effectiveness of antibiotics. Another reason may be that GPs may be more hesitant to withhold antibiotics from older patients to avoid under-treatment, leading to seeing a greater response in younger patients at higher prescribing rates.

The more antibiotics prescribed, the higher the GP re-attendance rates for common infections and subsequently the larger the re-prescribing antibiotic rate becomes [23]. A

randomised trial involving 34 general practices following the STAR educational programme saw reductions in overall levels of antibiotic prescribing in the intervention group [24]. Hospital admission for respiratory tract infections and complications increased by 1.9% in the intervention group, suggesting that reduced antibiotic prescribing may increase hospital admission. However, this result was not found to be statistically different and had limited statistical power.

UK initiatives have included the TARGET toolkit and the Quality Premium (QP) to reduce overall levels of antibiotic use [24–26]. The QP was introduced in April 2015 and provided a financial incentive to Clinical Commissioning Groups (CCGs) to reduce antibiotic prescribing rates. A significant 3% reduction in antibiotic prescribing rate was observed after this initiative was introduced, with greatest reduction in children [27]. Reducing antibiotic prescribing rates may be good for antibiotic resistance, but as shown here could potentially cause more infection-related complications. Antibiotic prescribing requires a careful balance; with each prescription to treat and reduce the risk of infection-related complications, the chance of developing resistant infections increases for individual patients and drives AMR risk for the wider community. With the current aim to reduce antibiotic prescribing in the community in the UK by 25% from the 2013 baseline, particular focus is required to understand individual patient risk, reducing inappropriate prescribing and monitor infection related complications. For patients with LRTI in primary care, Moore *et al*. [28] modelled a predictive value of the risk of patients developing serious outcomes including hospital admission. Such a direct approach, together with delayed prescribing strategies [29] are suggested to target prescribing to those most likely to develop complications and reduce overall prescribing.

A Cochrane review of 27 trials on antibiotics for sore throat found that antibiotics prevented complications (acute rheumatic fever, glomerulonephritis, otitis media, and sinusitis) in patients, but the rate of complications were so low the benefit of antibiotic prescribing may not always be clear [30]. Similarly another Cochrane review focused on antibiotics for acute

otitis media in children found that serious complications, such as mastoiditis and meningitis, were rare [31]. Both reviews highlighted the inability to predict which patients are at risk of developing complications. Clinical tools such as the FeverPAIN score and Centor criteria are used to guide antibiotic treatment for acute sore throat. However, Little *et al*. (2013) concluded that clinical scores such as FeverPAIN were of limited value in predicting clinical complications [32].

In conclusion, lower levels of practice level antibiotic prescribing were associated with higher levels of infection-related complications and hospital admissions. Identifying and developing accurate clinical tools for predicting which patients are at risk of complications requires much needed further research. To improve patient outcomes and reduce the risk of avoidable complications, there is a need to target patients most likely to benefit from effective, safe prescribing, based on shared decision making.

NOTES

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Conflict of interest: All authors have completed the ICMJE uniform disclosure form and declare: BvB, VP, CM, DA, TvS report grants from the Department of Health and Social Care for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study is partly based on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency (MHRA). HES data is subject to Crown copyright (2018) protection, re-used with the permission of The Health, & Social Care Information Centre, all rights reserved. The data is provided by patients and collected by the NHS as part of their care and support. This study also used anonymised data held in the Secure Anonymised Information Linkage (SAIL) System, which is part of the national e-health records infrastructure for Wales. The interpretation and conclusions contained in this study are those of the authors alone, and not necessarily those of the SAIL, MHRA, NHSA, NHS or the Department of Health.

The study protocol was approved by the Independent Scientific Advisory Committee for CPRD research [protocol number 16_153] and SAIL's Information Governance Protocol Review Panel [protocol number 0693]. We would like to acknowledge all the data providers who make anonymised data available for research.

Data sharing: Read codes used are published on Clinicalcodes.org. Electronic health records are, by definition, considered sensitive data in the UK by the Data Protection Act and cannot be shared via public deposition because of information governance restriction in

place to protect patient confidentiality. Access to data is available only once approval has been obtained through the individual constituent entities controlling access to the data. CPRD data can be requested via application to the Clinical Practice Research Datalink (www.cprd.com), and SAIL data are available by application to the Secure Anonymised Information Linkage Databank (https://saildatabank.com/).

Author contributor statement: BvB and TvS contributed to the idea and design of the study. TvS extracted the relevant data from the databases. BvB analysed and interpreted the data with feedback from TvS and MS. BvB drafted the initial paper. VP, CM, MS, AW, WW, and DA contributed to drafts and critical revision for intellectual content. All authors approved the final manuscript.

Patient and public involvement: No patients were involved in the study design and no patients were asked to consult on the outcomes or interpretation of the results. Results will be disseminated to relevant patient communities through news media and social media.

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TABLES

Table 1. Demographic and characteristics of the GP practices included in CPRD, CPRD-HES, and SAIL datasets. The CPRD dataset covers England, Scotland, and Northern Island. CPRD-HES covers England only. SAIL databank covers Wales only.

	CPRD n= 546	CPRD-HES linked n= 346	SAIL n= 338
Consultations			
Upper Respiratory Tract Infection (URTI)	9,646,774	5,698,611	1,956,752
Lower Respiratory Tract Infection (LRTI)	2,288,616	1,321,593	435,929
Otitis Externa	1,166,023	708,465	183,843
Otitis Media	864,791	529,946	215,495
Sinusitis	707,736	422,638	97,636
Urinary Tract Infection (UTI)	1,511,176	881,957	263,921
Age (mean, sd)	38.50 (3.86)	38.47 (3.72)	30.17 (7.11)
Sex female (%)	58.98	59.06	56.25
Charlson comorbidity index (CCI) (mean (%))			
None (0)	65.80	66.16	77.28
Low (1-2)	27.41	27.24	18.39
Medium (3-4)	5.10	4.97	3.24
High (5-6)	1.25	1.19	0.81
Very high (>7)	0.45	0.44	0.28
Region (count, %)			
North England	109 (20.0%)	83 (24.0%)	-
Midlands	120 (22.0%)	87 (25.1%)	-
South England	158 (28.9%)	124 (35.8%)	-
London	67 (12.3%)	52 (15.0%)	
Devolved Administrations (Northern Ireland and Scotland)	92 (16.8%)	-	-
Wales	-	-	338 (100%)
Socioeconomic status (mean (%))			
1 least deprived	13.29	20.98	23.77
2	14.25	22.49	21.36
3	12.49	19.71	21.17
4	12.47	19.68	17.65
5 most deprived	10.17	16.05	16.05
Missing data	37.32	1.09	-
Hospitalisation in previous year (mean (%))	0.02	0.02	0.03
GPs per 1000 consults (mean, sd)	3.54 (2.30)	3.52 (2.25)	NA

Footnote table 1. GP count per 1000 consults was not available in SAIL databank.

Table 2. Rates of infection-related complications and or hospital admission in the 30 days after GP visit for common infection. Hospital admission was identified from the linked HES data. GP-recorded infection-related complications were identified from the electronic health records, which included any revisit to the GP for complications after the initial consultation.

Infection-related complications	Number of cases (30 day follow-up)	Sum person-months (30 day follow-up)	Rate and 95% CI (per 1000 person-month)
Infection-related complication GP-recorded			
CPRD	25,721	19,220,606	1.34 (1.32 - 1.35)
SAIL	15,192	3,718,739	4.09 (4.02 - 4.15)
Hospital admission			
CPRD-HES linked	17,810	12,335,982	1.44 (1.42 - 1.47)
SAIL-HES	19,796	3,900,897	5.08 (5.00 - 5.15)

Table 2. Antibiotic prescribing rates for each common infection across practices included in CPRD (n= 546), CPRD-HES (n=346), and SAIL (n= 338). Rates are presented for six common infections. Proportion of consultations with antibiotics prescribed is presented with the mean percentage and the 5th through 95th percentile at practice level. The mean percentage of antibiotic prescribed in CPRD after a consultation for URTI was 46.1%.

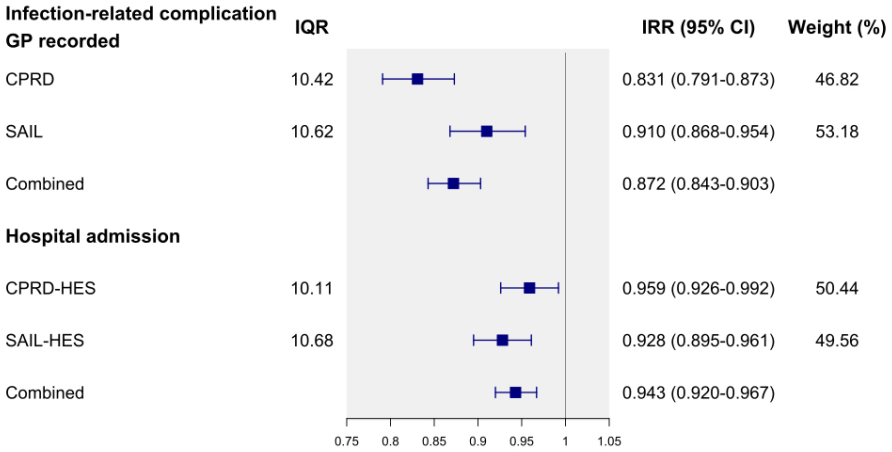
	Mean % (sd)	5 %	25 %	50 %	75 %	95 %
Upper Respiratory Tract Infection (URTI); URTI, cough or cold, sore throat						
CPRD	46.14 (11.71)	28.59	38.25	45.14	53.73	66.36
CPRD-HES linked	43.74 (10.97)	28.88	38.17	45.15	53.09	63.97
SAIL	43.37 (12.07)	24.83	34.57	42.88	51.76	63.43
Lower Respiratory Tract Infection (LRTI); Excluding community acquired pneumonia						
CPRD	84.79 (8.89)	69.79	81.45	86.68	90.52	94.40
CPRD-HES linked	85.24 (8.03)	70.89	81.90	86.80	90.57	94.68
SAIL	78.11 (11.66)	55.47	71.56	80.45	86.69	93.17
Otitis Externa						
CPRD	26.33 (8.98)	15.34	20.00	24.55	31.00	42.70
CPRD-HES linked	26.52 (8.44)	15.34	20.13	25.16	31.37	41.57
SAIL	29.57 (10.65)	14.92	22.03	28.71	34.89	48.5
Otitis Media						
CPRD	78.10 (10.86)	58.35	73.05	80.27	86.09	91.57
CPRD-HES linked	78.27 (9.83)	59.20	73.35	79.51	85.81	91.30
SAIL	78.49 (11.81)	54.91	72.64	80.57	87.49	92.65
Sinusitis						
CPRD	84.97 (8.93)	67.89	82.48	87.13	90.29	94.43
CPRD-HES linked	85.75 (7.88)	70.07	83.20	87.60	90.63	94.57
SAIL	82.12 (9.91)	63.36	77.44	84.22	88.89	94.73
Urinary Tract Infection (UTI)						
CPRD	85.90 (7.39)	74.01	82.96	87.28	90.98	93.72
CPRD-HES linked	86.06 (6.40)	74.08	83.19	87.01	90.79	93.30
SAIL	81.50 (10.30)	61.46	76.70	84.66	88.65	93.18

Figures

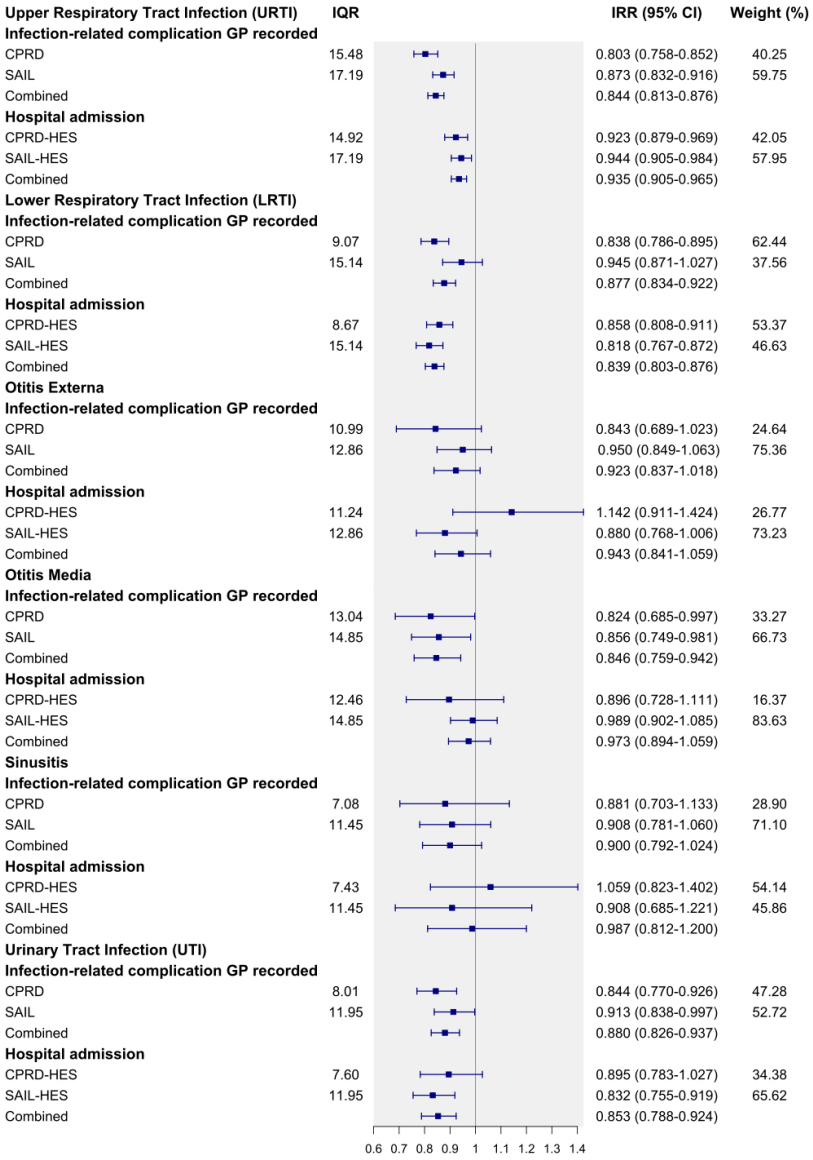
Figure 1. Incidence rate ratios (IRR) and 95% confidence interval (CI) of GP-recorded infection-related complications and hospital admissions comparing antibiotic prescribing at 75th to 25th percentile (IQR). Results are presented by data source. CPRD and SAIL effect estimates were combined using a fixed-effect meta-analysis method.

Figure 2. Effect estimates (IRRs and 95% CI) of GP-recorded infection-related complications and hospital admissions. Analyses compared antibiotic prescribing at 75th and 25th percentile (IQR) by 6 common infections. The IRR for hospital admission after a consultation for URTI in CPRD-HES was 0.923. This means for a 14.9% increase in antibiotic prescribing the rate of hospital admission is reduced by 7.7%.

Figure 3. Association of GP-recorded infection-related complications and hospital admissions comparing practice antibiotic prescribing at 75th and 25th percentile (IQR) by gender and age groups. Weights are from fixed-effects analysis.



Incidence rate ratios (IRR) and 95% confidence interval (CI) of GP-recorded infection-related complications and hospital admissions comparing antibiotic prescribing at 75th to 25th percentile (IQR). Results are presented by data source. CPRD and SAIL effect estimates were combined using a fixed-effect meta-analysis method.



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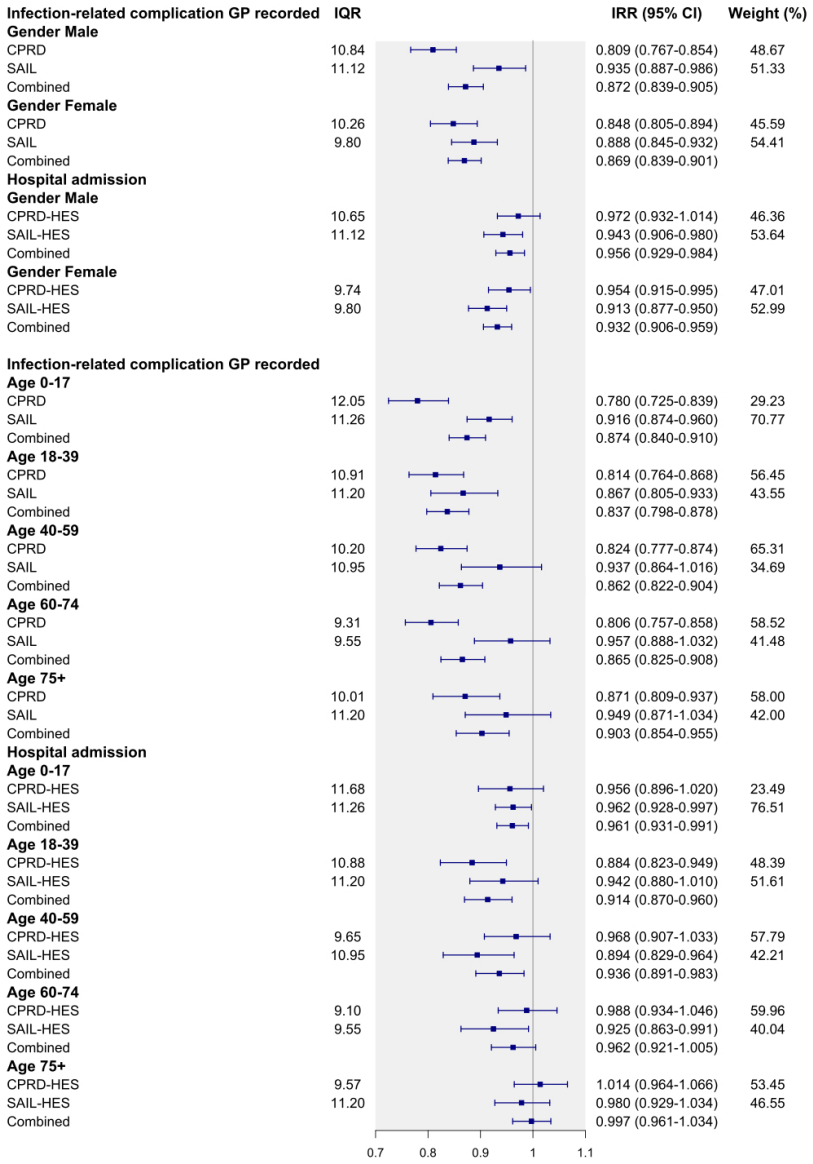

Association of GP-recorded infection-related complications and hospital admissions comparing practice antibiotic prescribing at 75th and 25th percentile (IQR) by gender and age groups. Weights are from fixed-effects analysis.

Supplementary Material

Appendix 1. Summary counts of infection-related hospital admission types as recorded as hospital admission codes in the primary care records.

Table S1. Summary counts of distribution of infection-related complications based on hospital admission codes in CPRD-HES. Table shows counts from CPRD-HES by sex and age for multiple infection-related complications.

CPRD-HES	All	Male	Female	Age 0-17	Age 18-39	Age 40-59	Age 60-74	Age 75+
Cough/Cold	103	60	43	96	<5	<5	<5	<5
LRTI/Pneumonia	13543	6026	7527	2515	877	1681	2418	6056
Otitis externa	67	29	38	12	18	16	10	10
Otitis media	432	223	209	236	64	64	47	18
Sinusitis	46	16	31	7	7	15	14	<5
Sore Throat	2000	1066	932	481	1085	357	58	17
URTI	695	375	319	509	47	42	36	62
UTI	112	39	73	<5	36	12	27	38
Sepsis	397	183	214	16	16	31	85	249
Meningitis	45	18	27	13	11	10	5	6
Infection-related complication, protocol defined	17810	8234	9580	3673	2226	2464	2890	6562
Any hospitalisation, not infection specific	77704	34050	43695	8196	7865	11990	18640	31030

Note 1: the sum of specific infections does not add up to sum of infection-related complications protocol defined due to a subset of patients having multiple infection-related complication admission codes. Note 2: the sum of Male and Female, and the sum of the age categories may not add up to the sum of 'All' due to some missingness in gender or year-of-birth registration in the patient's medical records.

Appendix 2. Sensitivity analysis of continuous antibiotic prescribing rate

A sensitivity analysis was performed to determine if treating the antibiotic prescribing rate continuously is justified. The rate of infection-related hospital admission and antibiotic prescribing rate was modelled with negative binomial regression. The antibiotic prescribing rate was decile ranked to create 10 equally sized subsections. These deciles were modelled in the exact same way as the main analyses presented in this paper. First, second, and third degree polynomials were fitted on the deciled antibiotic rate and evaluated against the IRRs for infection-related complication as recorded by the GP ('A', 'B', 'C') and for infection-related hospital admission ('D', 'E', 'F'). For both outcomes the first order polynomials were the preferred models. Figure S1 Plot A shows a strong linear trend for between low prescribing at deciles 1 to 3 and high prescribing at deciles 8 to 10. Although the error bars of each point estimate overlap a downward linear trend is observable. Creating categories of the antibiotic prescribing rate may hide significant variability within each specific category. Treating the antibiotic prescribing rate continuously ensures that each GP practice is analysed separately against the outcomes of interest.

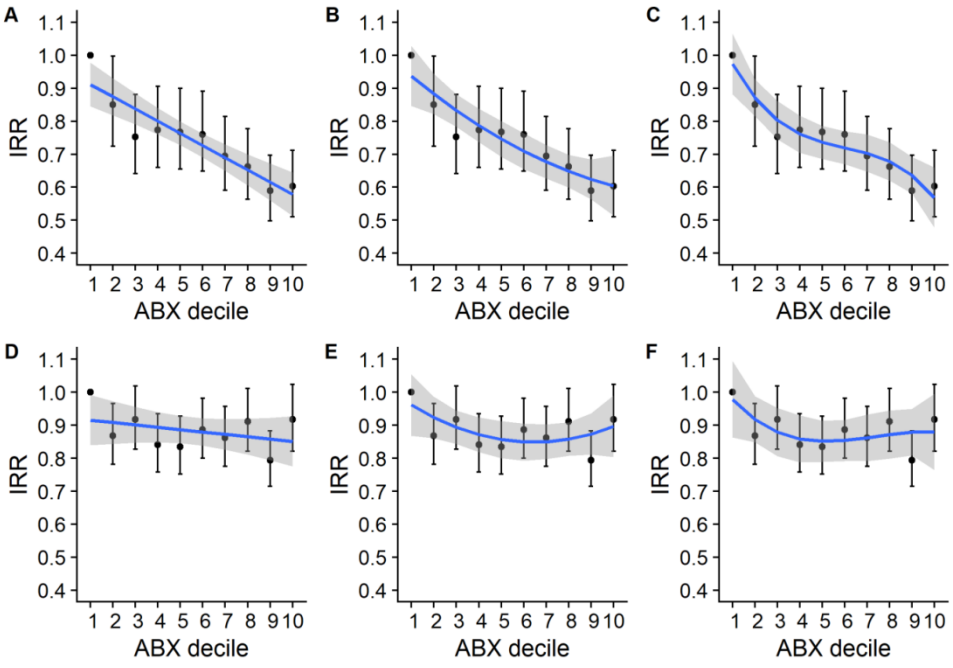

Figure s1. First (left), second (middle), and third (right) degree polynomials fitted on the deciled antibiotic prescribing rate. Plot A, B, and C model outcome infection-related complication as recorded by the GP. Plot D, E, and F model outcome infection-related hospital admission.

Appendix 3. Sensitivity analysis of paired infection-related complication with common infection

A sensitivity analysis was performed where antibiotic prescribing for URTI and for LRTI was linked with three adverse outcomes: 1) Pneumonia GP diagnosed (CPRD), 2) LRTI hospital admission (CPRD-HES), and 3) Pneumonia hospital admission (CPRD-HES).

Table S2. Adjusted IRRs from paired analysis of infection-related complications after a common infection with URTI or LRTI.

Common infection / infection-related complication	Adjusted IRR (95% CI)	IQR
URTI / Pneumonia (CPRD)	0.801 (0.743 - 0.864)	15.48
URTI / LRTI (CPRD-HES)	0.928 (0.868 - 0.992)	14.92
URTI / Pneumonia (CPRD-HES)	0.888 (0.805 - 0.978)	14.92
LRTI / Pneumonia (CPRD)	0.842 (0.787 - 0.902)	9.07
LRTI / LRTI (CPRD-HES)	0.820 (0.765 - 0.879)	8.67
LRTI / Pneumonia (CPRD-HES)	0.917 (0.834 - 1.011)	8.67

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	-
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9 + table 1
		(b) Indicate number of participants with missing data for each variable of interest	9 + table 1
		(c) Summarise follow-up time (eg, average and total amount)	9 + table 2
Outcome data	15*	Report numbers of outcome events or summary measures over time	9 + table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9 – 11 + Figure 1 – 3
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11- 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Infection-related complications after common infection in association with new antibiotic prescribing in primary care: retrospective cohort study using linked electronic health records

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Infection-related complications after common infection in association with new antibiotic prescribing in primary care: retrospective cohort study using linked electronic health records

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Keywords: Antibiotic prescription, hospitalisation, infection-related complications, common infection, primary care

Word count: 4073

ABSTRACT

Objective Determine the association of incident antibiotic prescribing levels for common infections with infection-related complications and hospitalisations by comparing high with low prescribing GP practices.

Design Retrospective cohort study.

Data source UK primary care records from the Clinical Practice Research Datalink (CPRD GOLD) and SAIL Databank (SAIL) linked with Hospital Episode Statistics (HES) data, including 546 CPRD, 346 CPRD-HES and 338 SAIL-HES practices.

Exposures Initial general practice visit for one of six common infections and the proportion of antibiotic prescribing in each practice.

Main outcome measures Incidence of infection-related complications (as recorded in general practice) or infection-related hospital admission within 30 days after consultation for a common infection.

Results A practice with 10.4% higher antibiotic prescribing (the interquartile range (IQR)) was associated with a 5.7% lower rate of infection-related hospital admissions (adjusted analysis, 95% Confidence Interval 3.3% to 8.0%). The association varied by infection with larger associations in hospital admissions with lower respiratory tract infection (16.1%; 12.4% to 19.7%) and urinary tract infection (14.7%; 7.6% to 21.1%) and smaller association in hospital admissions for upper respiratory tract infection (6.5%; 3.5% to 9.5%) The association of antibiotic prescribing levels and hospital admission was largest in patients aged 18-39 (8.6%; 4.0% to 13.0%) and smallest in the elderly aged 75+ (0.3%; -3.4% to 3.9%).

Conclusions There is an association between lower levels of practice level antibiotic prescribing and higher infection-related hospital admissions. Indiscriminately reducing antibiotic prescribing may lead to harm. Greater focus is needed to optimise antibiotic use by

reducing inappropriate antibiotic prescribing and better targeting antibiotics to patients at high risk of infection-related complications.

ARTICLE SUMMARY

Strengths and limitations of this study

- Two large primary care databases with linked hospitalisation data were used to evaluate the difference in hospital admission after community acquired common infections comparing high with low prescribing GP practices.
- This analysis focusses on antibiotic prescribing at practice level with the emphasis on evaluating governmental guidance on reducing overall prescribing.
- Incidental antibiotic prescriptions without details on local antibiotic resistance levels were evaluated in this analysis and the results can only be interpreted in this context.
- No data was extracted on infection severity or symptom scores therefore no conclusions can be drawn on the appropriateness of antibiotics prescribed.

INTRODUCTION

Common infections, such as sore throat or sinusitis, are often self-limiting and usually get better without antibiotics; nevertheless, they are frequently prescribed [1,2]. Research regarding antimicrobial resistance (AMR) and antibiotic prescribing rates often focuses on reducing inappropriate prescribing to lower the threat of increasing antimicrobial resistance [3]. Antibiotic prescribing for common self-limiting infections is often seen as a target for reduction [3,4]. However, a proportion of common infections are caused by bacterial infections that may progress and antibiotics may reduce infection-related adverse outcomes.

The UK AMR national action plan for 2019-2024 continues on from the last AMR strategy (2013-2018) with updated aims and targets to address the continued problem of resistance. One aim is to optimise antibiotic use through stewardship programmes, including a 25% reduction in antibiotic use in the community from the 2013 baseline [5]. Antibiotic prescribing

in primary care in England shows a declining trend (-13.2%) between 2013 and 2017, however, to reach desired reduction targets continued efforts are needed [3].

A small number of studies have analysed the relationship between antibiotic prescribing rates and adverse events in primary care. Petersen *et al.* [6] (2007) and Gulliford *et al*. [7] (2016) studied the relationship between antibiotic prescribing rates in primary care and complication in patients with common respiratory tract infections (RTIs). Both studies reported reductions in incidence of pneumonia, as recorded by the general practitioner (GP), with higher levels of antibiotic prescribing. However, these studies did not evaluate the association of prescribing rates with the rate of hospital admission after common infections in primary care.

Gharbi *et* al. (2019) reported that prescribing immediate antibiotics in primary care to elderly patients for urinary tract infection (UTI) was associated with a lower risk of bloodstream infection, hospital admission, and all-cause mortality compared with no antibiotics and deferred antibiotic prescribing [8]. However, antibiotic prescribing in primary care is known to increase the risk of resistant infections [9]. This highlights the challenge in balancing prescribing to reduce the risk of severe outcomes and limiting overall antibiotic consumption to slow the development of AMR.

The association between practice antibiotic prescribing rates and the rate of hospital admission after common infection when clearly separated from other infection-related complications managed in the community has not previously been studied. There is uncertainty with regards to the relationship between antibiotic prescribing levels and complications that can arise after various common infections. The objective of this study was to investigate the association between practice level antibiotic prescribing in primary care for multiple common infections and the rate of infection-related complications through comparison of high and low prescribing GP practices. These data provide insight into the role of antibiotic prescribing patterns in controlling the rate of adverse events.

METHOD:

Data sources

The Clinical Practice Research Datalink (CPRD GOLD [10]) and the Secure Anonymised Information Linkage Databank (SAIL [11]) were used in this study. CPRD is a UK primary care database with routinely collected electronic health records [10]. All patients registered with a participating general practice are anonymously included in the dataset. Data has been collected from 1987 and represents about 8% of the UK population. CPRD is broadly representative of the general UK population in terms of age, sex, and ethnicity [10]. The SAIL databank is a data repository of anonymised personal data collected for research from 75% of Welsh general practices [11]. Within SAIL, individual GP practices share anonymised patient-level clinical information on symptoms, diagnoses and prescribed treatment. As Welsh GP practices are included in both CPRD and SAIL they have been removed from CPRD to avoid replication.

For both data sources, all patient level data was aggregated up to practice level. The final CPRD dataset contained 546 GP practices of which 346 (located in England only), were linked with hospital admitted patient care data (Hospital Episode Statistics (HES)). The SAIL Databank included 338 GP practices, all linked to HES.

Selection and eligibility criteria:

The CPRD study population included patients with a consultation between 1st January 2000 and 30th June 2015; for SAIL, the time period was between 1st January 2000 and 31st December 2017. The study population included patients with an initial GP consultation and clinical Read code for a common infection. This was defined as the first incident consultation for a common infection within six months and without an antibiotic prescription in the previous one month. Six common infections were included: upper respiratory tract infection (URTI, cough or cold, sore throat), lower respiratory tract infection (LRTI), otitis externa, otitis media, sinusitis, and urinary tract infection (UTI).

Patients were eligible to be included if they were permanently registered at the GP practice, had a minimum of one year follow-up since data collection (except for children under one), and at least one record of an incident common infection. Male and females of any age were eligible. Patients were not required to have an antibiotic prescribed at the time of visit for common infection. Patients with an infection-related complication or an infection-related hospital admission in the six months prior or on the day of consultation were excluded. Individual patients were able to contribute multiple infection episodes, as long as the consultations were at least 6 months apart.

Exposure and outcomes:

The number of patients who received an antibiotic at the consultation was determined. The practice antibiotic prescribing rate was the percentage of consultations that resulted in an antibiotic prescription in the complete study period.

Infection-related hospital admission was identified using the primary admission diagnosis using ICD-10 codes from the linked HES data. This outcome was evaluated using the CPRD-HES and SAIL-HES datasets. The second outcome evaluated was infection-related complications as recorded in the primary care records identified from Read codes. Both outcomes were evaluated during the 30 days after the initial common infection consultation. In case of death or end of data collection within these 30 days, observations were censored. The outcomes were evaluated using the CPRD and SAIL datasets.

Person time at risk was calculated for the registered CPRD and SAIL population by counting the days without diagnosis of infection-related complications during the 30 day follow-up after the date of common infection. The rates of infection-related outcomes were calculated by dividing the number of events by the person time at risk (per 1000 person-month). The outcomes were identified based on pre-defined code lists. Compiled code lists are available on clinicalcodes.org [12], ICD-10 codes are available from van Staa *et al.* (2020)[13]. The codes for outcomes and infections used were reviewed independently by two clinical epidemiologists. Infection-related hospital admission includes codes for admission such as

for sepsis, endocarditis, acute respiratory tract infection, or bacterial meningitis. Infection-related complications as recorded in the primary care records includes any revisit to the GP for infection-related complications such as pneumonia, sepsis, quinsy, mastoiditis, or meningitis in the 30 day follow-up period. The same set of conditions were included in both outcomes.

Confounders

The analysis was adjusted with the scaled mean at practice level of age, vaccination against influenza, and hospital admission in the previous year. Additionally, the analysis was adjusted with the scaled proportion of each category at practice level of the following categorical characteristic: Sex, Charlson Comorbidity Index [14], body mass index (BMI), smoking status (never, currently, past, unknown), and socioeconomic status (SES, least deprived to most deprived). The proportion of socioeconomic status (SES) was derived from patients with linkage to IMD quintiles. Linked Index of Multiple Deprivation (IMD) data in quintiles based on patient's residential postcode were available for both datasets. Census based IMD data measures deprivation at area-level based on domains, such as income, employment, health, housing, and general environment [15].

Additionally, analyses using CPRD and CPRD-HES were adjusted with the mean at practice level of the number of GPs per 1000 consults, the patient transfer-out rate and region. No imputations or other adjustments were performed for missing characteristics in the covariates. Missing data was present for the following covariates; BMI (CPRD: 41.4%), Smoking status (CPRD: 30.4%), and socioeconomic status (CPRD: 37.3%).

Statistical analysis

Infection-related complications were modelled with negative binomial regression using practice level antibiotic prescribing as a predictor and the log of person time at risk as an offset. The unit of analysis is the practice. All variables were scaled with their associated interquartile range (IQR: 75th to 25th percentile) by dividing the original values by the IQR

from the variable [16]. This creates a natural comparison between high and low prescribing GP practices. The antibiotic prescribing rate was modelled continuously. Because of the scaling the IQR becomes the unit that the effect size is expressed in. Both outcomes were compared against all common infections in the initial analysis. Models were adjusted for missing data using a covariate specific missing data indicator. The association of each of the six common infections was then studied against both outcomes separately. The analyses were further stratified by gender and age categories: 0-17, 18-39, 40-59, 60-74, 75+ years old to evaluate the varied prescribing among these risk groups. The beta coefficient of the antibiotic prescribing rate was exponentiated and is presented as an incidence rate ratio (IRR). The effect estimates from the CPRD and SAIL cohorts were combined using a meta-analysis method with inverse variance weighting and DerSimonian and Laird random effect models.

Absolute difference in antibiotic prescribing between high and low prescribing practices was calculated from the prescribing rates (25th and 75th percentiles) and mean events per practice. The absolute difference in infection-related complications between high and low prescribing was calculated using the complication rate and the IRR. The number needed to treat (NNT) with antibiotics to prevent one event of hospital admission was calculated by dividing the absolute difference in antibiotic prescribing by the absolute difference in complications. Forestplot [17], dplyr [18], and MASS [19] packages in R were used for the analysis. All analyses were performed using R-software version 3.4.1 (R Foundation for Statistical Computing; Vienna, Austria).

Patient and public involvement

No patients were involved in the study design and no patients were asked to consult on the outcomes or interpretation of the results. Results will be disseminated to relevant patient communities through news media and social media.

RESULTS

The study was based on a total of 19.6 million GP consultations for common infections. URTI was the most frequent common infection (CPRD: 9,646,774) followed by LRTI (CPRD: 2,288,616) and UTI (CPRD: 1,511,176). A total of 884 GP practices were included in the analysis (CPRD: 546; SAIL: 338) (Table 1). The mean age of the practice population was 38 years in CPRD and 30 years in SAIL. The majority of patients had no comorbidities recorded (Charlson score: 0). There were 25,721 cases of infection-related complications as recorded in primary care in CPRD and 15,192 cases in SAIL. The rate of these complications was 1.3 and 4.1 per 1000 person-months respectively. For infection-related hospital admission, the number of cases was 17,810 in CPRD-HES and 19,796 in SAIL-HES, with rates of 1.4 and 5.1 per 1000 person-months, respectively (Table 2). The majority of antibiotics were prescribed for LRTI, Sinusitis, and UTI (Table 3). Antibiotics were less likely to be prescribed for Otitis Externa. There was considerable variability between general practices in the percentages of patients prescribed an antibiotic. For URTI, 28.6% of the patients received an antibiotic at the 5th percentile practice and 66.4% at the 95th percentile practice. Summary counts of infection-related hospital admission types from CPRD-HES are available in appendix 1, supplementary material.

Infection-related hospital admission

The incidence of infection-related hospital admission was found to be associated with the practice-level antibiotic prescribing rate (Figure 1). A 10.4% higher antibiotic prescribing rate (IQR) was associated with an IRR of 0.943 (0.920 to 0.967), denoting a 5.7% lower infection-related hospital admission rate in the combined analysis. Results between CPRD-HES and SAIL-HES were comparable. In CPRD-HES, a 10.1% higher antibiotic prescribing rate was associated with an IRR of 0.959 (0.926 to 0.992), meaning a 4.1% lower hospital admission rate. For SAIL-HES, this was 7.2% (IRR: 0.928; 0.895 to 0.961) lower with the IQR of 10.7% higher antibiotic prescribing by GP practices.

The observed association varied by infection. In the combined analysis, the largest association was observed in LRTI (IRR: 0.839(16.1%); 0.803 to 0.876), UTI (IRR: 0.853 (0.788 to 0.924); 14.7%), and URTI (IRR: 0.935 (0.905 to 0.965); 6.5%) (Figure 2). In patients with URTI, 14.9% (CPRD-HES) and 17.2% (SAIL-HES) higher antibiotic prescribing was associated with infection-related hospital admissions being lower by 7.7% (0.923; 0.879 to 0.969) and 5.6% (0.944; 0.905 to 0.984). LRTI was associated with a 14.2% (CPRD-HES, IRR: 0.858; 0.808 to 0.911) and 18.2% (SAIL-HES, IRR: 0.818; 0.767 to 0.872) lower incidence for hospital admission when antibiotic prescribing was higher by 8.7% and 15.1%. In patients who consulted their GP for UTI, the incidence of hospital admission was 10.5% (IRR: 0.895 (0.783 to 1.027) lower with 7.6% higher antibiotic prescribing (CPRD-HES). In SAIL-HES, 12.0% higher antibiotic prescribing for UTI was associated with lower incidence by 16.8% (IRR: 0.832 (0.755 to 0.919)). Patients aged 18-39 years old had the largest association for hospital admission (CPRD-HES: 0.884 (0.823 to 0.949; IQR unit: 10.88)) amongst the age categories (figure 3).

The number needed to treat with antibiotics to prevent one patient from developing infection-related complications was calculated over the 30 day follow-up period. The number needed to treat for patients with URTI at risk of hospital admission was 1164. For patients with LRTI and UTI the number needed to treat was 417 and 484 respectively.

GP-recorded infection-related complications

Higher levels of antibiotic prescribing by GP practices were associated with lower incidence of infection-related complication as recorded by the GP. The incidence of GP-recorded infection-related complications reduced by 16.9% (0.831; 0.791 to 0.873) and 9.0% (0.910; 0.866 to 0.954) with an increase in antibiotic prescribing of 10.4% and 10.6% for CPRD and SAIL respectively.

Evaluating the observed association by common infection separately found that URTI was associated with lower GP-recorded infection-related complications by 20.4% (0.803; 0.758 to 0.852) when antibiotic prescribing increased by 15.5% in CPRD. In SAIL, the observed

reduction was 12.7% (0.873; 0.832 to 0.916) when antibiotic prescribing increased by 17.2%.

Antibiotic prescribing for LRTI being higher by 9.1% and 15.1% was associated with the incidence of GP-recorded infection-related complications being lower by 16.2% (IRR: 0.838; 0.786 to 0.895) and 5.5% (IRR: 0.945; 0.871 to 1.027) for CPRD and SAIL respectively. For UTI, the incidence of GP-recorded infection-related complications was similarly lowered across CPRD (15.6%; 0.844 (0.770 to 0.926) (IQR unit: 8.01)) and SAIL (8.7%; 0.913 (0.838 to 0.997) (IQR unit: 11.95)).

No effect modification by gender was observed in any of the datasets evaluated (Figure 3). The effect was more obvious in younger patients. Patients aged 0-17 had the largest association in GP-recorded infection-related complications in CPRD (22%; IRR: 0.780 (0.725 to 0.839); IQR: 12.05). Patients aged 0-17 years and 40-59 showed similar associations for both datasets (Figure 3). Polynomials were fitted on a deciled antibiotic prescribing rate as a sensitivity analysis. First order polynomials best fitted the data and showed a downward linear trend from low to high prescribing (Supplementary material, appendix 2). An inverse association was found in an additional sensitivity analysis which paired URTI and LRTI with plausible subsequent infection-related complications, such as pneumonia and hospital admission for LRTI (Supplementary material, appendix 3. In patients who consulted their GP for LRTI, the incidence of a hospital admission with LRTI was 18% (0.820 (0.765 - 0.879)) lower with 8.7% higher antibiotic prescribing (CPRD-HES).

DISCUSSION

This study found that higher levels of incident antibiotic prescribing by practices were associated with lower rates of hospital admission and GP diagnosed infection-related complications. Lower rate of poor clinical outcomes with higher levels of antibiotic prescribing was more pronounced for URTI, LRTI, and UTI but had no association with poor outcomes for otitis media and otitis externa. A higher level of incident antibiotic prescribing in

younger patients was associated with better clinical outcomes while no association was observed in patients over 40 years old.

This is the first study to use two large primary care databases with linked hospitalisation data to evaluate the difference in hospital admission after common infections comparing high with low prescribing GP practices. The focus of this analysis was at practice level with the emphasis on evaluating governmental guidance on reducing overall prescribing. Practice level prescribing proportion as a standardised antibiotic measure allows for comparing the range of GP prescribing within and between datasets with similar inclusion criteria. Other standard measures, such as age- and sex-adjusted STAR-PU prescribing units, are available although the research question here specifically focussed on the reduction of overall antibiotic prescribing levels regardless of patient-mix within a practice. The study population was restricted to new antibiotic prescribing in patients with newly developed common infections. Including patients with more complex clinical scenarios, like repeated antibiotic users, complicates the estimation of the effect of interest. Past consultations and potential treatment for a common infection may be associated with future consultations, treatment, and future outcomes of interest. This will lead to a problem when the outcome of interest cannot be related back to a single index visit and instead potentially to more than one visit. The results of this analysis can only be interpreted in the context of the incidental antibiotic user.

This practice level analysis possibly simplifies the relationship between antibiotic prescribing rate and infection-related complications by aggregating data up to practice level and ignoring diversity in patient characteristics within a practice. Some potential confounding at practice level may occur due to variation in patient population frailty even when characteristics have been accounted for at practice level [20]. In addition, although this analysis attempted to adjust for several available factors which might influence the association investigated, missing data was present in some of the covariates. The analyses accounted for this by using a missing indicator and the presence of missing data in the covariates could have

influenced the estimates, although the large sample size and replication of the analysis in a second database (SAIL) gives weight to the interpretation of the results. There remains a potential for additional residual confounding by non-available covariates or other factors, such as quality of care, access to GPs and practices, and availability of consultations, all of which have been linked to deprivation [21,22]. However, without specific knowledge of a physician's prescribing preference relative to guidance, or qualitative data regarding patient care, it is not possible to evaluate the effects of these factors on the observed prescribing levels. Diagnoses are based on clinical coding both in primary and secondary care and potential misclassifications or misdiagnoses in the underlying data could have occurred. Differences in coding practices for common infections among English GP practices has been evaluated previously and found to be problematic at times [4]. As no data were available on infection severity or symptom scores, no conclusions can be drawn on the appropriateness of antibiotics prescribed. This analysis was based on digital patient charts without access to free-text due to GDPR rules as this poses a possible patient identification risk. Digital patient charts are automatically generated and transferred to the database. In addition, a small proportion of prescribing may be attributable to out of hours prescribing where coding of these consultation or prescriptions into the patient's record is performed afterwards and therefore subject to error and misclassification, potentially leading to an overestimation of the observed association.

The incidence rates of the clinical outcomes were different between SAIL and CPRD, with higher rates in Wales. There has been a measles epidemic in Wales recently which may partly explain these differences. However, this remains speculative. Infections are often localised and infection rates differ between locations. In addition, another possible explanation could be that this difference is due to coding behaviour. However, the level of data available does not allow in-depth investigation into this difference. The NNTs presented are related to the 30 day follow-up window. They may appear large and initial clinical relevance uncertain. UK guidance for initiating statin use states those with a 10-year risk of

10-19% are eligible. Converting this 10-year risk to a 30 day estimated NNT gives a NNT of 1139 (10%) and 569 (19%). These NNTs are similar to those presented in this analysis and have led to a change in clinical practice and prescribing behaviour.

Those with weaker immune systems, the very young and very old, have an elevated susceptibility to infections which may increase their antibiotic use and risk of related complications [23]. Analysis performed by age group showed that higher levels of antibiotic prescribing were associated with reduced infection-related complications in younger patients. Higher levels of antibiotic prescribing were not associated with lower rates of infection-related complications in patients aged 60+ years. A possible explanation for this is that increased lifetime exposure and repeated use of antibiotics could reduce antibiotic effectiveness, for example due to altered pharmacokinetics [24] . Recent research reported reduced effectiveness of antibiotics with repeated use over several years [13]. A literature review by Costelloe *et al.* (2010) found that individuals who were prescribed an antibiotic for respiratory or urinary tract infections develop bacterial resistance that was detectable for up to 12 months [9]. Similar association has been reported recently for resistant blood stream infection after UTI prescribing [25]. However, further research is needed to assess any age effect in the effectiveness of antibiotics. Another reason may be that GPs may be more hesitant to withhold antibiotics from older patients to avoid under-treatment, leading to seeing a greater response in younger patients at higher prescribing rates.

The more antibiotics prescribed, the higher the GP re-attendance rates for common infections and subsequently the larger the re-prescribing antibiotic rate becomes [26]. A randomised trial involving 34 general practices following the STAR educational programme saw reductions in overall levels of antibiotic prescribing in the intervention group [27]. Hospital admission for respiratory tract infections and complications increased by 1.9% in the intervention group, suggesting that reduced antibiotic prescribing may increase hospital admission. However, this result was not found to be statistically different and had limited statistical power.

UK initiatives have included the TARGET toolkit and the Quality Premium (QP) to reduce overall levels of antibiotic use [27–29]. The QP was introduced in April 2015 and provided a financial incentive to Clinical Commissioning Groups (CCGs) to reduce antibiotic prescribing rates. A significant 3% reduction in antibiotic prescribing rate was observed after this initiative was introduced, with greatest reduction in children [30]. Reducing antibiotic prescribing rates may be good for antibiotic resistance, but as shown here could potentially cause more infection-related complications. Antibiotic prescribing requires a careful balance; with each prescription to treat and reduce the risk of infection-related complications, the chance of developing resistant infections increases for individual patients and drives AMR risk for the wider community. With the current aim to reduce antibiotic prescribing in the community in the UK by 25% from the 2013 baseline, particular focus is required to understand individual patient risk, reducing inappropriate prescribing and monitor infection related complications. For patients with LRTI in primary care, Moore *et al*. [31] modelled a predictive value of the risk of patients developing serious outcomes including hospital admission. Such a direct approach, together with delayed prescribing strategies [32] are suggested to target prescribing to those most likely to develop complications and reduce overall prescribing.

A Cochrane review of 27 trials on antibiotics for sore throat found that antibiotics prevented complications (acute rheumatic fever, glomerulonephritis, otitis media, and sinusitis) in patients (NNT to benefit = 200), but the rate of complications were low (approximately 0.7%) the benefit of antibiotic prescribing may not always be clear [33]. Similarly another Cochrane review focused on antibiotics for acute otitis media in children found that serious complications, such as mastoiditis and meningitis, were rare (3/3000 children)[34]. Both reviews highlighted the inability to predict which patients are at risk of developing complications. Clinical tools such as the FeverPAIN score and Centor criteria are used to guide antibiotic treatment for acute sore throat. However, Little *et al*. (2013) concluded that

clinical scores such as FeverPAIN were of limited value in predicting clinical complications [35].

In conclusion, lower levels of practice level antibiotic prescribing were associated with higher levels of infection-related complications and hospital admissions. Identifying and developing accurate clinical tools for predicting which patients are at risk of complications requires much needed further research. To improve patient outcomes and reduce the risk of avoidable complications, there is a need to target patients most likely to benefit from effective, safe prescribing, based on shared decision making.

NOTES

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Conflict of interest: All authors have completed the ICMJE uniform disclosure form and declare: BvB, VP, CM, DA, TvS report grants from the Department of Health and Social Care for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study protocol was approved by the Independent Scientific Advisory Committee for CPRD research [protocol number 16_153] and SAIL's Information Governance Protocol Review Panel [protocol number 0693]. We would like to acknowledge all the data providers who make anonymised data available for research.

Data sharing: Read codes used are published on Clinicalcodes.org. Electronic health records are, by definition, considered sensitive data in the UK by the Data Protection Act and cannot be shared via public deposition because of information governance restriction in place to protect patient confidentiality. Access to data is available only once approval has been obtained through the individual constituent entities controlling access to the data.

CPRD data can be requested via application to the Clinical Practice Research Datalink (www.cprd.com), and SAIL data are available by application to the Secure Anonymised Information Linkage Databank (https://saildatabank.com/).

Author contributor statement: BvB and TvS contributed to the idea and design of the study. TvS extracted the relevant data from the databases. BvB analysed and interpreted the data with feedback from TvS and MS. BvB drafted the initial paper. VP, CM, MS, AW, WW, and DA contributed to drafts and critical revision for intellectual content. All authors approved the final manuscript.

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TABLES

Table 1. Demographic and characteristics of the GP practices included in CPRD, CPRD-HES, and SAIL datasets. The CPRD dataset covers England, Scotland, and Northern Island. CPRD-HES covers England only. SAIL databank covers Wales only.

	CPRD n= 546	CPRD-HES linked n= 346	SAIL n= 338
Consultations			
Upper Respiratory Tract Infection (URTI)	9,646,774	5,698,611	1,956,752
Lower Respiratory Tract Infection (LRTI)	2,288,616	1,321,593	435,929
Otitis Externa	1,166,023	708,465	183,843
Otitis Media	864,791	529,946	215,495
Sinusitis	707,736	422,638	97,636
Urinary Tract Infection (UTI)	1,511,176	881,957	263,921
Age (mean, sd)	38.50 (3.86)	38.47 (3.72)	30.17 (7.11)
Sex female (%)	58.98	59.06	56.25
Charlson comorbidity index (CCI) (mean (%))			
None (0)	65.80	66.16	77.28
Low (1-2)	27.41	27.24	18.39
Medium (3-4)	5.10	4.97	3.24
High (5-6)	1.25	1.19	0.81
Very high (>7)	0.45	0.44	0.28
Region (count, %)			
North England	109 (20.0%)	83 (24.0%)	-
Midlands	120 (22.0%)	87 (25.1%)	-
South England	158 (28.9%)	124 (35.8%)	-
London	67 (12.3%)	52 (15.0%)	
Devolved Administrations (Northern Ireland and Scotland)	92 (16.8%)	-	-
Wales	-	-	338 (100%)
Socioeconomic status (mean (%))			
1 least deprived	13.29	20.98	23.77
2	14.25	22.49	21.36
3	12.49	19.71	21.17
4	12.47	19.68	17.65
5 most deprived	10.17	16.05	16.05
Missing data	37.32	1.09	-
Hospitalisation in previous year (mean (%))	0.02	0.02	0.03
GPs per 1000 consults (mean, sd)	3.54 (2.30)	3.52 (2.25)	NA

Footnote table 1. GP count per 1000 consults was not available in SAIL databank.

Table 2. Rates of infection-related complications and or hospital admission in the 30 days after GP visit for common infection. Hospital admission was identified from the linked HES data. GP-recorded infection-related complications were identified from the electronic health records, which included any revisit to the GP for complications after the initial consultation.

Infection-related complications	Number of cases (30 day follow-up)	Sum person-months (30 day follow-up)	Rate and 95% CI (per 1000 person-month)
Infection-related complication GP-recorded			
CPRD	25,721	19,220,606	1.34 (1.32 - 1.35)
SAIL	15,192	3,718,739	4.09 (4.02 - 4.15)
Hospital admission			
CPRD-HES linked	17,810	12,335,982	1.44 (1.42 - 1.47)
SAIL-HES	19,796	3,900,897	5.08 (5.00 - 5.15)

Table 2. Antibiotic prescribing rates for each common infection across practices included in CPRD (n= 546), CPRD-HES (n=346), and SAIL (n= 338). Rates are presented for six common infections. Proportion of consultations with antibiotics prescribed is presented with the mean percentage and the 5th through 95th percentile at practice level. The mean percentage of antibiotic prescribed in CPRD after a consultation for URTI was 46.1%.

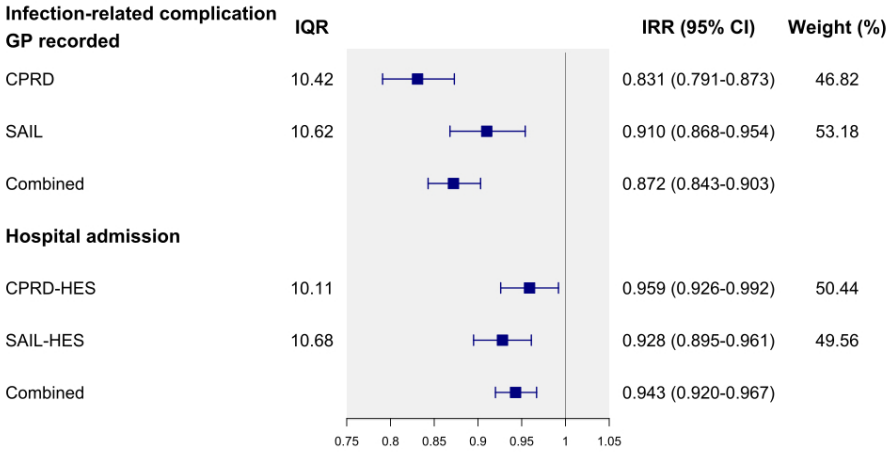
	Mean % (sd)	5 %	25 %	50 %	75 %	95 %
Upper Respiratory Tract Infection (URTI); URTI, cough or cold, sore throat						
CPRD	46.14 (11.71)	28.59	38.25	45.14	53.73	66.36
CPRD-HES linked	43.74 (10.97)	28.88	38.17	45.15	53.09	63.97
SAIL	43.37 (12.07)	24.83	34.57	42.88	51.76	63.43
Lower Respiratory Tract Infection (LRTI); Excluding community acquired pneumonia						
CPRD	84.79 (8.89)	69.79	81.45	86.68	90.52	94.40
CPRD-HES linked	85.24 (8.03)	70.89	81.90	86.80	90.57	94.68
SAIL	78.11 (11.66)	55.47	71.56	80.45	86.69	93.17
Otitis Externa						
CPRD	26.33 (8.98)	15.34	20.00	24.55	31.00	42.70
CPRD-HES linked	26.52 (8.44)	15.34	20.13	25.16	31.37	41.57
SAIL	29.57 (10.65)	14.92	22.03	28.71	34.89	48.5
Otitis Media						
CPRD	78.10 (10.86)	58.35	73.05	80.27	86.09	91.57
CPRD-HES linked	78.27 (9.83)	59.20	73.35	79.51	85.81	91.30
SAIL	78.49 (11.81)	54.91	72.64	80.57	87.49	92.65
Sinusitis						
CPRD	84.97 (8.93)	67.89	82.48	87.13	90.29	94.43
CPRD-HES linked	85.75 (7.88)	70.07	83.20	87.60	90.63	94.57
SAIL	82.12 (9.91)	63.36	77.44	84.22	88.89	94.73
Urinary Tract Infection (UTI)						
CPRD	85.90 (7.39)	74.01	82.96	87.28	90.98	93.72
CPRD-HES linked	86.06 (6.40)	74.08	83.19	87.01	90.79	93.30
SAIL	81.50 (10.30)	61.46	76.70	84.66	88.65	93.18

Figures

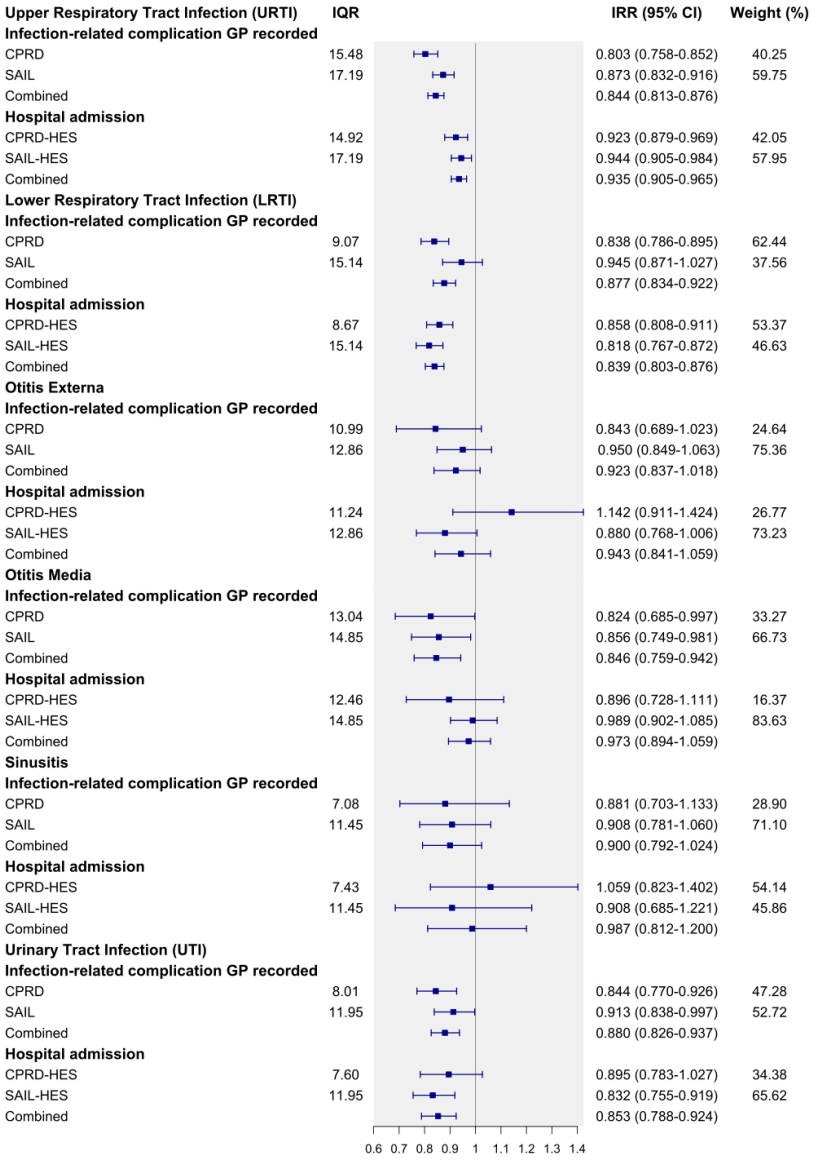
Figure 1. Incidence rate ratios (IRR) and 95% confidence interval (CI) of GP-recorded infection-related complications and hospital admissions comparing antibiotic prescribing at 75th to 25th percentile (IQR). Results are presented by data source. CPRD and SAIL effect estimates were combined using a fixed-effect meta-analysis method.

Figure 2. Effect estimates (IRRs and 95% CI) of GP-recorded infection-related complications and hospital admissions. Analyses compared antibiotic prescribing at 75th and 25th percentile (IQR) by 6 common infections. The IRR for hospital admission after a consultation for URTI in CPRD-HES was 0.923. This means for a 14.9% increase in antibiotic prescribing the rate of hospital admission is reduced by 7.7%.

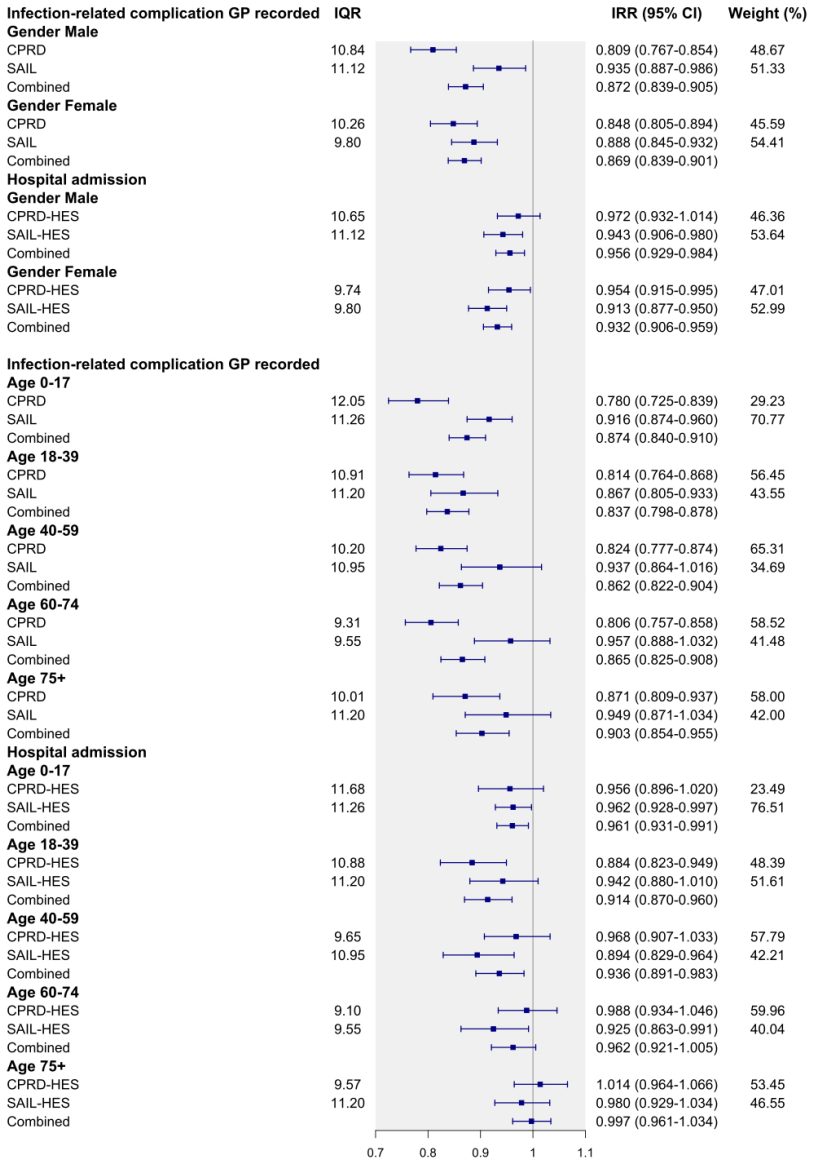
Figure 3. Association of GP-recorded infection-related complications and hospital admissions comparing practice antibiotic prescribing at 75th and 25th percentile (IQR) by gender and age groups. Weights are from fixed-effects analysis.



Incidence rate ratios (IRR) and 95% confidence interval (CI) of GP-recorded infection-related complications and hospital admissions comparing antibiotic prescribing at 75th to 25th percentile (IQR). Results are presented by data source. CPRD and SAIL effect estimates were combined using a fixed-effect meta-analysis method.



Effect estimates (IRRs and 95% CI) of GP-recorded infection-related complications and hospital admissions. Analyses compared antibiotic prescribing at 75th and 25th percentile (IQR) by 6 common infections. The IRR for hospital admission after a consultation for URTI in CPRD-HES was 0.923. This means for an 14.9% increase in antibiotic prescribing the rate of hospital admission is reduced by 7.7%.



Association of GP-recorded infection-related complications and hospital admissions comparing practice antibiotic prescribing at 75th and 25th percentile (IQR) by gender and age groups. Weights are from fixed-effects analysis.

Supplementary Material

Appendix 1. Summary counts of infection-related hospital admission types as recorded as hospital admission codes in the primary care records.

Table S1. Summary counts of distribution of infection-related complications based on hospital admission codes in CPRD-HES. Table shows counts from CPRD-HES by sex and age for multiple infection-related complications.

CPRD-HES	All	Male	Female	Age 0-17	Age 18-39	Age 40-59	Age 60-74	Age 75+
Cough/Cold	103	60	43	96	<5	<5	<5	<5
LRTI/Pneumonia	13543	6026	7527	2515	877	1681	2418	6056
Otitis externa	67	29	38	12	18	16	10	10
Otitis media	432	223	209	236	64	64	47	18
Sinusitis	46	16	31	7	7	15	14	<5
Sore Throat	2000	1066	932	481	1085	357	58	17
URTI	695	375	319	509	47	42	36	62
UTI	112	39	73	<5	36	12	27	38
Sepsis	397	183	214	16	16	31	85	249
Meningitis	45	18	27	13	11	10	5	6
Infection-related complication, protocol defined	17810	8234	9580	3673	2226	2464	2890	6562
Any hospitalisation, not infection specific	77704	34050	43695	8196	7865	11990	18640	31030

Note 1: the sum of specific infections does not add up to sum of infection-related complications protocol defined due to a subset of patients having multiple infection-related complication admission codes. Note 2: the sum of Male and Female, and the sum of the age categories may not add up to the sum of 'All' due to some missingness in gender or year-of-birth registration in the patient's medical records.

Appendix 2. Sensitivity analysis of continuous antibiotic prescribing rate

A sensitivity analysis was performed to determine if treating the antibiotic prescribing rate continuously is justified. The rate of infection-related hospital admission and antibiotic prescribing rate was modelled with negative binomial regression. The antibiotic prescribing rate was decile ranked to create 10 equally sized subsections. These deciles were modelled in the exact same way as the main analyses presented in this paper. First, second, and third degree polynomials were fitted on the deciled antibiotic rate and evaluated against the IRRs for infection-related complication as recorded by the GP ('A', 'B', 'C') and for infection-related hospital admission ('D', 'E', 'F'). For both outcomes the first order polynomials were the preferred models. Figure S1 Plot A shows a strong linear trend for between low prescribing at deciles 1 to 3 and high prescribing at deciles 8 to 10. Although the error bars of each point estimate overlap a downward linear trend is observable. Creating categories of the antibiotic prescribing rate may hide significant variability within each specific category. Treating the antibiotic prescribing rate continuously ensures that each GP practice is analysed separately against the outcomes of interest.

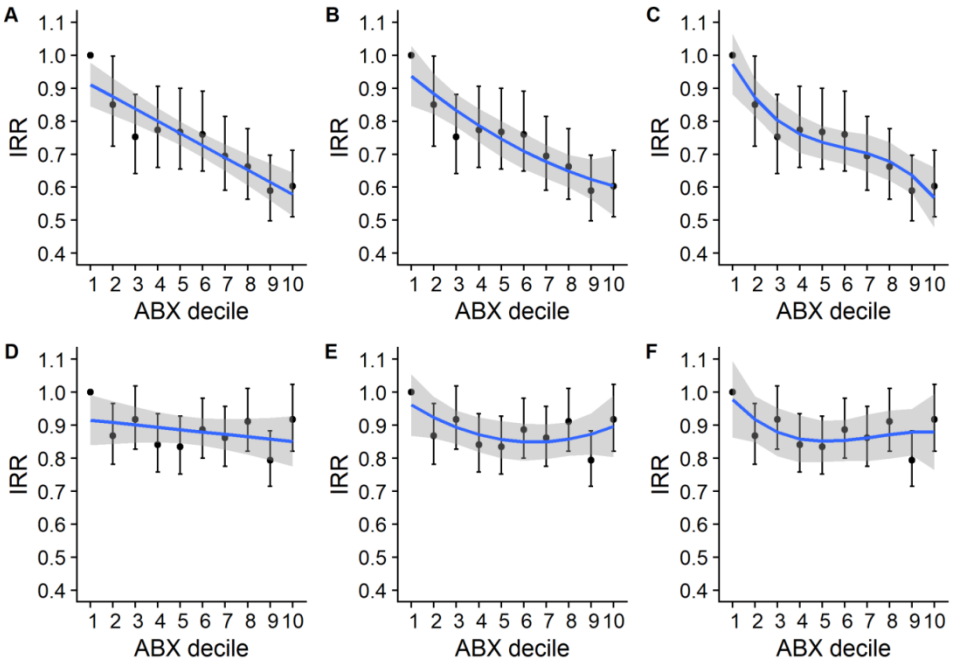


Figure s1. First (left), second (middle), and third (right) degree polynomials fitted on the deciled antibiotic prescribing rate. Plot A, B, and C model outcome infection-related complication as recorded by the GP. Plot D, E, and F model outcome infection-related hospital admission.

Appendix 3. Sensitivity analysis of paired infection-related complication with common infection

A sensitivity analysis was performed where antibiotic prescribing for URTI and for LRTI was linked with three adverse outcomes: 1) Pneumonia GP diagnosed (CPRD), 2) LRTI hospital admission (CPRD-HES), and 3) Pneumonia hospital admission (CPRD-HES).

Table S2. Adjusted IRRs from paired analysis of infection-related complications after a common infection with URTI or LRTI.

Common infection / infection-related complication	Adjusted IRR (95% CI)	IQR
URTI / Pneumonia (CPRD)	0.801 (0.743 - 0.864)	15.48
URTI / LRTI (CPRD-HES)	0.928 (0.868 - 0.992)	14.92
URTI / Pneumonia (CPRD-HES)	0.888 (0.805 - 0.978)	14.92
LRTI / Pneumonia (CPRD)	0.842 (0.787 - 0.902)	9.07
LRTI / LRTI (CPRD-HES)	0.820 (0.765 - 0.879)	8.67
LRTI / Pneumonia (CPRD-HES)	0.917 (0.834 - 1.011)	8.67

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	-
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9 + table 1
		(b) Indicate number of participants with missing data for each variable of interest	9 + table 1
		(c) Summarise follow-up time (eg, average and total amount)	9 + table 2
Outcome data	15*	Report numbers of outcome events or summary measures over time	9 + table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9 – 11 + Figure 1 – 3
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11- 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.