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The impact of COVID -19 on antibiotic prescribing in primary care in England: evaluation and risk prediction of appropriateness of type and repeat prescribing

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Abstract

Background

This study aimed to predict risks of potentially inappropriate antibiotic type and repeat prescribing and assess changes during COVID-19.

Methods

With the approval of NHS England, we used OpenSAFELY platform to access the TPP SystmOne electronic health record (EHR) system and selected patients prescribed antibiotics from 2019 to 2021. Multinomial logistic regression models predicted patient's probability of receiving inappropriate antibiotic type or repeat antibiotic course for each common infection.

Results

The population included 9.1 million patients with 29.2 million antibiotic prescriptions. 29.1% of prescriptions were identified as repeat prescribing. Those with same day incident infection coded in the EHR had considerably lower rates of repeat prescribing (18.0%) and 8.6% had potentially inappropriate type. No major changes in the rates of repeat antibiotic prescribing during COVID-19 were found. In the 10 risk prediction models, good levels of calibration and moderate levels of discrimination were found.

Conclusions

Our study found no evidence of changes in level of inappropriate or repeat antibiotic prescribing after the start of COVID-19. Repeat antibiotic prescribing was frequent and varied according to regional and patient characteristics. There is a need for treatment guidelines to be developed around antibiotic failure and clinicians provided with individualised patient information.

Keywords

Antibiotics; infection; COVID-19 pandemic; antibiotic stewardship; primary care

Introduction

In the UK, over 70% of antibiotic prescriptions are given in primary care(1). Antimicrobial resistance (AMR) is a major public health problem which is exacerbated by overuse of antibiotics. AMR is a worldwide concern, posing a serious threat to global health and placing a large economic burden on healthcare systems (2). Coronavirus disease (COVID-19) is an infectious respiratory disease caused by the SARS-CoV-2 virus. By May 2022, more than 500 million people have been infected by COVID-19 and more than 6 million deaths were reported worldwide (3). As both COVID-19 and bacterial pneumonia share similar clinical features, the COVID-19 pandemic has challenged the normal facilitation of antimicrobial stewardship programmes and challenged the use of antimicrobials in clinical practice (4).

In the UK's five-year national action plan, the target is to reduce human antimicrobial use by 15% by 2024, including a 25% reduction in community antibiotic use from the 2013 baseline (5). In order to help achieve this, better understanding of current antibiotic prescribing patterns following the pandemic is needed. National guidelines for England on infections in primary care have been published by National Institute for Health and Care Excellence (NICE) and Public Health England (PHE) (6,7). However, implementation of the national guidelines in primary care in the UK has not been satisfactory, with one study noting rate of potentially inappropriate type prescribing rates of 67.3% for otitis externa and 38.7% for upper respiratory tract infection (URTI) (8). Repeating prescribing involves the renewal of short-term antibiotic prescriptions for acute issues that exist beyond a single course of treatment. It may be related to the general practices (GPs)'s prescribing habits, or additional

infections that occurred over a certain period of time. Reducing repeat antibiotic prescribing was identified as part of ways to deal with the AMR, and it is suggesting that 30% of antibiotic prescriptions were classified as repeats (9,10). The reasons for antibiotic prescribing may not always be well documented, with up to half of antibiotic prescriptions unrelated to any specific diagnostic medical code recorded (11). Except for urinary tract infections (UTI) (where an initial antibiotic can be substituted after the results of urine culture), NICE guidelines mainly focus on initial treatment pathways for acute incident infections rather than on pathways for patients returning when the initial antibiotic treatment may not have been effective (7).

The aims of this study were (i) to identify whether repeat prescribing of antibiotics for specific infection in primary care has changed after the start of the COVID-19 pandemic and (ii) to create risk prediction model to predict the probability of receiving an appropriate, inappropriate, or repeat prescription for each infection.

Methods

Data Source

Primary care electronic health records (EHRs) managed by the GP software provider TPP were assessed securely through OpenSAFELY-TPP, a platform created to address urgent COVID-19 research questions (https://opensafely.org). OpenSAFELY provides a secure software interface that allows near real-time analysis of pseudonymised primary care patient records in England within the TPP highly secure data environment, avoiding the need to transfer large volumes of potentially disclosable pseudonymous patient data off-site. The database includes coded diagnoses, medications, and physiological parameters but

no free text. All analysis code is shared openly for review and re-use under MIT open license (https://github.com/opensafely/amr-uom-brit). To avoid the patient being potentially re-identified, detailed pseudonymised patient data can therefore not be shared. Further details on information governance can be found in Supplementary material.

Study population

This study had access to data between 1 January 2019 and 31 December 2021, one year prior to the COVID-19 pandemic and 21 months after the introduction of national lockdown restrictions in the UK on 23 March 2020. The study population included all patients aged 4 years or older who were registered with a general practice between 1st January 2019 and 31st December 2021, had at least one year of registration before 1st January 2019, and were prescribed at least one antibiotic during the study period. Two cohorts were identified: antibiotic user cohort included the overall study population of antibiotic users, infection coded cohort only included those with an antibiotic prescription and same day infection records.

There were two outcomes of interest in this study, potentially inappropriate antibiotic type for an infection and repeat antibiotic prescribing. The index date for a prescription was set to the date the antibiotic prescription was issued. Based on the active drug substance, 79 unique antibiotic types were identified as listed in the British National Formulary (BNF) chapter 5.1 (Antibacterial Drugs), except for BNF5.1.9 (Antituberculosis drugs) and BNF5.1.10 (Antileprotic drugs). Potentially inappropriate antibiotic types were those that deviated from recommended guidelines for the recorded infection. To identify potentially inappropriate antibiotic choices for incident infections the most recent NICE and PHE guidelines (last update: 11 March 2022, no major changes in the last five years) were used.

(6,7) The classification is shown in Table S1. Repeat antibiotic prescribing was defined as the issuance of any additional antibiotic prescription to the same patient within 30 days of the index date. This included all antibiotics prescribed during the 30-day time window for the individual patient.

The following infections were identified based on the diagnostic SNOMED CT codes in the EHRs(12): UTI, lower respiratory tract infection (LRTI) and URTI, sinusitis, otitis externa, otitis media, asthma, cold, Chronic obstructive pulmonary disease (COPD), cough, sore throat, pneumonia and renal. URTIs were defined as a coded infection in upper respiratory tract infection except for cough, sore throat, and pneumonia. A full list of the SNOMED CT codes used in this study can be found at www.opencodelists.org. Antibiotic prescriptions without an infection record on the same date were defined as "uncoded". The prescription with a same day infection record was defined as "coded". Each coded prescription record was classified into incident or prevalent based on the infection record. Incident event was defined as a record with no infection recorded in the 90 days before, and no antibiotic prescription in the 30 days before the index date. Prevalent events were the remaining records. As the first national lockdown occurred on 23rd, March 2020, the duration from 1st, March 2020 to 1st, April 2020 was used for highlighting the start of the COVID-19 pandemic (Supplementary Figure 1).

Age, sex, ethnicity and region were extracted yearly by the index date. We included Index of Multiple Deprivation (IMD) quintiles to represent the socioeconomic status, Charlson Comorbidity Index (CCI) to estimate a patients' overall health (13) and the number of antibiotics prescriptions received in the 365 days before the index date. IMD quintiles were based on seven aspects of deprivation: income, employment, health and disability,

education, barriers to housing and services, crime and living environment (14). CCIs were measured in the most recent 5 years before index date.

Statistical analysis

Descriptive statistics were used to summarise the baseline characteristics of the study population, including age, sex, ethnicity, and region. In antibiotic user cohort, the percentage of antibiotic prescriptions that were classified as repeat antibiotics percentage was calculated in each month to capture changes before and during the COVID-19 pandemic. This analysis was stratified by coded or uncoded infections in antibiotic user cohort. These measures were also calculated for same day incident/prevalent infection recorded in coded group (infection coded cohort). For the coded prescription records (infection coded cohort), the rates of repeat antibiotic prescribing were calculated stratified by age, sex and region.

Prediction model development followed the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) checklist (15). A multinomial logistic regression model was developed to predict the probability of receiving an appropriate antibiotic, a potentially inappropriate antibiotic type or repeat antibiotic course (16). In infection coded cohort, the models were developed separately for each infection type. Models were adjusted for predictors based on previous research, which identified risk factors for potentially inappropriate antibiotic type prescribing (8). The models were adjusted with a missing indicator for ethnicity and IMD to increase the accuracy and reduce bias (17). The continuous variable age was modelled with restricted cubic splines (5 knots) (18) to allow for a non-linear relationship. The models were developed and validated with a large sample size, so there was no need to use cross-validation or bootstrap validation(19). To validate the prediction model, the sub-cohorts

were randomly divided into development cohort (75%) and validation cohort (25%). To assess calibration, we implemented the nominal recalibration framework of van Hoorde et al (20). The most common measure of discrimination for binary outcome models is the C-statistic (18). An extension of the C-statistic to polytomous outcomes is the Polytomous discrimination index (PDI) (21). To evaluate the discrimination, we calculated the PDI, pairwise C-statistics for every pair of outcome categories, and "one-versus-rest" C-statistics for each outcome category (22,23).

Software and Reproducibility

If required use: Data management was performed using Python 3.8.2, with analysis carried out using R 4.0.2. Code for data management and analysis, as well as codelists, are archived online (https://github.com/opensafely/amr-uom-brit). The published output can be found online (https://jobs.opensafely.org/university-of-manchester/brit-antibiotic-research/service_eval_work/releases/).

Results

A total of 9,080,193 patients from 2536 general practices in England were included in antibiotic user cohort. They were prescribed a total of 29,226,183 antibiotic prescription records over the study period. As a patient might be observed multiple times, we randomly selected one observation per patient in each calendar year to summarise the study population demographics in Table 1. (For characteristics in overall period of antibiotic user cohort and 2 see Supplementary Table 2)

The overall percentage of repeat antibiotic prescribing in antibiotic user cohort was 29.1% (including all antibiotics irrespective of infection coding), where 23.2 million prescriptions were identified as uncoded, and 6.0 million records were coded. Figure 1A shows the trend of repeat antibiotic prescriptions for coded and uncoded infections. The repeat prescription rate for uncoded prescribing was 1.4 times of the coded antibiotics issued, with no change to this ratio over time. No major changes in the rates of repeat antibiotic prescribing over calendar time were found, but the rate in the uncoded group increased from 30.1% in Jan 2020 to 32.5% in Feb 2020 and remained high until Nov 2021. A clearer trend was observed in the coded group; the rates of repeat antibiotic prescribing increased from 21.1% in Jan 2020 to 25.0% in Apr 2020. For infection coded repeat antibiotic prescriptions (infection coded cohort) there were more incident consultations to prevalent consultations, with similar trends over time (Figure 1B). Figure 2(infection coded cohort) and Supplementary Figure 2(antibiotic user cohort) show the percentage of repeat antibiotic prescriptions as a percentage of total monthly antibiotic prescriptions stratified by age, sex, and region in the infection recorded cohort (infection coded cohort) and the antibiotic prescriptions cohort (antibiotic user cohort). In infection coded cohort, there was a sharp increase in repeat antibiotic prescribing at the beginning of the COVID-19 pandemic, but it returned to normal by April 2021. Patients over 65 years old had the highest repeat prescribing rate. We found that females tend to have a higher repeat prescribing rate, and patients from London received the lowest percentage of repeat antibiotics.

As shown in Supplementary Table S3A, UTIs accounted for 33.3% of antibiotic prescriptions, LRTIs 13.7%, Sore throat 12.7%, cough 6.3%, sinusitis 5.7% and otitis media 5.6%. There was also variation between infections in the percentage of prescribing of potentially

inappropriate antibiotic types and repeat prescribing (Supplementary Table S4). In Sinusitis, it was observed that 0.8% antibiotic prescription records were potentially inappropriate and repeat prescribing accounted for 16.8%. However, the rate of potentially inappropriate antibiotic prescriptions for otitis externa and URTI were much higher at 39.3% and 69.6% respectively. The most frequent antibiotic prescriptions which were identified as potentially inappropriate were Amoxicillin and Doxycycline for URTI and Amoxicillin and Co-amoxiclav for otitis externa (See Supplementary Table S3B).

Table 2 reports the odds ratios (ORs) of the predictors in the multinomial logistic regression model predicting appropriateness of antibiotic prescribing in infection coded cohort. A multinomial logistic regression model was then fit within subgroups of infection coded cohort, defined by infection type. Models were fit for the top 9 most common infection types. ORs for LRTI, Sore throat and Cough are provided in Table 2, others are shown in Supplementary Table S5. Age, region, incident event and prior antibiotic prescribing were identified as important predictors according to higher value of coefficients in the models. The predictor age modelled with restricted cubic splines was reported in Supplementary Figure S3.

The calibration in the overall model was very good (Figure 3), with near perfect agreement between the predicted and observed risks across the entire range of predicted risk. This is supported by a calibration slope of 0.006 for inappropriate versus appropriate and 0.001 for repeat versus appropriate. This is supported by a calibration intercept of 1.015 and 1.003, respectively (Supplementary Table S6). Calibration of LRTI, sore throat and cough models was also good, although the cough and LRTI models over predicted the risk of inappropriate

prescribing at the higher end of predicted risks (Figure 3). The calibration in the rest models were also very good (Supplementary Figure S4).

Table 3 shows the range in percentiles of predicted risks in the validation cohort. We found that COPD has the highest risk score in getting repeat prescriptions, with the range of 2.5 to 97.5th percentile was 1.1 to 4.0%. URTI has the highest probability in getting potentially inappropriate prescription, with the range of percentile from 49.2 to 80.4 %. Patients did vary in their predicted risk of inappropriate type and repeat prescription. For sore throat, the range of 2.5 to 97.5th percentile was 2.7 to 23.5% (inappropriate type) and 6.0 to 27.2% (repeat prescription). For otitis externa, these numbers were 25.9 to 63.9% and 8.5 to 37.1%, respectively.

In validation cohort, 9 of 10 models had moderate levels of PDI (>0.40) in predicting repeat prescription except from Otitis media (Table 4). The PDI in predicting repeat prescription for the overall model was 0.53; the URTI model had the highest PDI of 0.53 and Otitis media had the lowest PDI of 0.38. All the models had moderate levels of PDI in predicting potentially inappropriate prescriptions. The sore throat model had the highest PDI of 0.51 and COPD model had the lowest PDI of 0.40. The overall model had a pairwise C-indexes in appropriate antibiotic types versus inappropriate antibiotic types of 0.59, indicating there was 59% chance for the model to predict the patient in the correct category from potentially inappropriate antibiotic types. The pairwise C-indexes of appropriate antibiotic types versus repeat prescribing was 0.68, and 0.69 for inappropriate versus repeat. The UTI model had the highest pairwise C-indexes for appropriate versus inappropriate (0.73) and otitis externa had the lowest but moderate pairwise C-indexes (0.60). We found the URTI

model had the highest pairwise C-indexes in appropriate versus repeat (0.71) and otitis externa had the lowest value (0.61). Sore throat and URTI had the highest pairwise C-indexes for inappropriate versus repeat (0.67) and sinusitis had the lowest value (0.57).

Discussion

This study found that repeat antibiotic prescribing was frequent, especially for those without coded infection in the EHR. The study found that the risk of potentially inappropriate types and repeat antibiotic prescribing was associated with patient characteristics and infection types. No major changes in antibiotic prescribing patterns (repeat and type) were found during the COVID-19 pandemic.

The study revealed that the effect of the pandemic on the frequency of repeating prescriptions and potentially inappropriate prescribing is temporary, displaying notable variations and fluctuations primarily between March 2020 and April 2021. This finding matches the fact that after the implementation of the national lockdown during the pandemic, there was a sharp decrease in consultations in primary care. While the national lockdown post-COVID-19 has had an impact on the way patients are consulted, with telephone consultations increasing by 270% in 2020 compared to 2019, and GPs facing greater clinical uncertainty when faced with telephone consultations, which could have posed a significant challenge to antibiotic prescription control (24).

A recent editorial by Krockow et al outlined possible clinical reasons for this repeat prescribing including ‘status quo bias’ (i.e., human tendency to maintain status quo) and

'decision inertia' (i.e., prefer decisions with cognitive effort) (9). A fundamental question is whether frequent repeat antibiotic prescribing, as routine in primary care, is actually effective and safe for the patient. There is limited evidence for the effectiveness of this practice while there are signals of risk of using antibiotics frequently over time. A review of culture study reported that use of an antibiotic is associated with an increased risk of patient's bacteria becoming resistant to the antibiotic (25). Previous epidemiological research has found that patients with history of more antibiotic prescribing has higher risks of infection-related complications (26). While confounding may explain these findings, there is increasing evidence of antibiotics adversely affecting microbiota (including in respiratory tract) and leading to a decreased ability of the host microbiota to defend against pathogenic microorganisms.(27,28). Krockow et al highlighted the importance of developing effective approaches including behavioural interventions to reduce repeat antibiotic prescribing (9).

In the UK, multiple implementations for controlling antimicrobial prescribing are supported by performance indicators, such as the Quality Outcomes Framework (QOF), which provides financial incentives(29). Also, there are data tools for practice-level summaries, such as OpenPrescribing(30). However, while these tools provide valuable insights, further interventions are needed to address inappropriate and repeat prescribing issues. For example, in the US, a study conducted in urgent care centres found that interventions such as staff and patient education, public commitment, and peer comparison effectively reduced inappropriate antibiotic prescribing rates (31). Similarly, a study that analysed antibiotic prescribing patterns across 18 European countries found significant variations in prescribing rates, influenced by clinicians' confidence in their prescribing decisions (32). To

address this variation, a knowledge support system that assists clinicians in making appropriate prescribing decisions is crucial.

This study found no updated guideline for URTI except for cough, sore throat and pneumonia. According to the treatment guidance supported by the previous study(8), providing Amoxicillin and Doxycycline should still be considered potentially inappropriate. This study found a substantial variation in repeat antibiotic prescribing between those with an infection recorded in the EHR and those without. This finding is consistent with another UK study which reported that most repeat antibiotic prescribing occurred without a specific coded infection.(33)One reason for higher repeat prescribing rates without infection codes may be prescribing for chronic conditions, which are typically not recorded at each follow-up prescription. However, the number of patients with conditions that require chronic antibiotic treatment is probably small. Another reason could be variability between GPs in how and they code into the EHR. Level of coding for common infections varied between 37.6 and 85.4% between GPs, although a 30-day window was used to assess coding (10). Hay outlined that diagnostic uncertainty could be a possible reason for lack of EHR coding as patients do not always present with neatly differentiated symptoms that lead to conclusive diagnosis. The use of provisional diagnostic codes (such as “suspected UTI”) should be promoted (34). The lack of EHR coding clearly complicates ongoing activities to reduce and optimise antibiotic prescribing. Individualised feedback to GPs on EHR coding and antibiotic prescribing may be needed to improve prescribing (34,35).

This study fitted overall model and separate models for each infection type, aiming to improve the prediction of calibration and discrimination. Except sinusitis and COPD performed poorly in predicting the inappropriate type of antibiotic, which is not

recommended in primary care. We found good calibration and moderate discrimination levels in the other eight risk prediction models. Our study found regional variation and patients in London were associated with lower risks in getting repeat antibiotic prescriptions. Another study evaluating hot- and cold-spots of antibiotic prescribing found lower rates in London and higher in Northern England, including more deprived areas. That study looked at correlations between neighbouring practices and hot-spots were those areas with stronger correlations in prescribing between practices (36). A qualitative study comparing high and low antibiotic prescribers highlighted the need to also consider supportive mechanisms, such as regular practice meetings, within the practice, and in the wider healthcare system (e.g., longer consultation times) (37). Also, GPs will need to be supported by guidelines that go beyond standard clinical conditions but also address the challenges as faced daily (such as repeat antibiotic prescribing. This may include the urgent development of computable treatment guidelines (38) and knowledge support systems during consultation that give individualised guidance (35).

Strengths and Limitations

To our knowledge, this is the largest study to investigate the impact of COVID-19 on the appropriateness of antibiotic prescribing. The main strengths of this paper include long follow-up, coverage of large geographical areas, and the ability to stratify by sex and geographic location. The current study adds a new contribution by highlighting the appropriateness of these prescriptions (type and repeated) and exploring predictors of potentially inappropriate choices to develop targeted and effective interventions to reduce unnecessary and inappropriate antibiotic prescribing. The model development process was

followed by TRIPOD Checklist, which provide detailed guidelines on reporting of studies developing, validating, or updating a prediction model (39).

There are also limitations to the use of EHR coded data to infer prescribing in this study. Firstly, the prescribing data is limited by the quality of the coding. This study was unable to differentiate the context of the clinical episodes (e.g., symptom severity or testing that may have resulted in a specific prescribing decisions), meaning that some repeat or potentially inappropriate prescriptions may have been clinically justified. However, repeat prescribing can occur for chronic conditions, such as COPD, where these repeat prescriptions are more likely to be appropriate. Although there is a lack of guidelines for repeat prescribing for acute conditions, repeat prescribing can occur because the previous antibiotic did not work, leading to repeat consultations by the patient. For this reason, we limited our analysis to repeat or appropriateness of immediate prescriptions (within 30 days) of a recorded acute infection (40).

To ensure consistency in research, definitions of inappropriate prescribing are based on the latest versions of NICE and PHE guidelines. For example, although NICE guidelines highlight that URTIs and coughs are usually self-limiting and do not need antibiotic treatment, for patients with a high risk of systemic discomfort or complication they recommended antibiotics. This study used the most recent guidelines to define appropriateness. However, a comparison of guidelines over the last five year shows there was very little change, except for co-amoxiclav was recommended according to the latest guideline for otitis media but not included in 2019. This study could only follow the guideline and distinguish between the type of prescription recommended as appropriate and those with deviation from the guideline, as potentially inappropriate (6,7). Although the previous study found that

frequent antibiotic exposure may increase the risk of infection-related complications, the gap between repeat prescribing and hospitalisation due to adverse events remains unclear(26). Therefore, future studies need to explore the above in more detail to provide more detailed evidence to develop guidance for clinical decision-making for antibiotic prescribing.

In conclusion, our study found no evidence of major changes in level of inappropriate or repeat antibiotic prescribing after the start of COVID-19. Repeat antibiotic prescribing was frequent and variable according to regional and patient characteristics. There is a need for treatment guidelines to be developed around antibiotic failure and for clinicians to have information about the risks of a patient returning (i.e., treatment failure). The lack of evidence of effectiveness of repeat antibiotic prescribing and developing signals of risks may indicate the need for targeting repeat prescribing as a priority for optimising antibiotic prescribing.

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Contributions

Conceptualisation: TvS, DA, KH, BMK, VP, AP; Methodology: XZ, VP, AP, YY, AF, JM, PI; Formal analysis: XZ, VP, AP, YY, AF; Diagnostic codelists: TvS; Software: BG, BMK, AM, SCJB; Writing – original draft: XZ; Writing – revising, review and editing: all authors. All read and approved the final manuscript. TvS is the guarantor for the article, and accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Information governance and ethical approval

NHS England is the data controller for OpenSAFELY-TPP; TPP is the data processor; all study authors using OpenSAFELY have the approval of NHS England. This implementation of OpenSAFELY is hosted within the TPP environment which is accredited to the ISO 27001 information security standard and is NHS IG Toolkit compliant(41);

Patient data has been pseudonymised for analysis and linkage using industry standard cryptographic hashing techniques; all pseudonymised datasets transmitted for linkage onto OpenSAFELY are encrypted; access to the platform is via a virtual private network (VPN) connection, restricted to a small group of researchers; the researchers hold contracts with NHS England and only access the platform to initiate database queries and statistical models; all database activity is logged; only aggregate statistical outputs leave the platform environment following best practice for anonymisation of results such as statistical disclosure control for low cell counts(42).

The OpenSAFELY research platform adheres to the obligations of the UK General Data Protection Regulation (GDPR) and the Data Protection Act 2018. In March 2020, the Secretary of State for

Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 (COPI) to require organisations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak and incidents of exposure; this sets aside the requirement for patient consent(43). This was extended in July 2022 for the NHS England OpenSAFELY COVID-19 research platform(44). In some cases of data sharing, the common law duty of confidence is met using, for example, patient consent or support from the Health Research Authority Confidentiality Advisory Group(45).

Taken together, these provide the legal bases to link patient datasets on the OpenSAFELY platform. GP practices, from which the primary care data are obtained, are required to share relevant health information to support the public health response to the pandemic, and have been informed of the OpenSAFELY analytics platform. This study was approved by the Health Research Authority and NHS Research Ethics Committee [REC reference 21/SC/0287].

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Tables and Figures

Table 1. Characteristics of overall study population stratified by calendar year

	Year	2019		2020		2021	
	Unique patients	4982376		4299652		4403305	
	Unique practices	2530		2535		2534	
		n	**%**	**n**	**%**	**n**	**%**
Age	<16	575946	11.6	419003	9.7	450262	10.2
	16-44	1564642	31.4	1394528	32.4	1479049	33.6
	45-64	1325126	26.6	1159199	27.0	1171856	26.6
	65+	1516662	30.4	1326922	30.9	1302138	29.6
Sex	Female	3089849	62.0	2733005	63.6	2803687	63.7
	Male	1892527	38.0	1566647	36.4	1599618	36.3
Region	East of England	1199503	24.1	1023776	23.8	1047364	23.8
	East Midlands	872797	17.5	746376	17.4	762505	17.3
	London	234554	4.7	204646	4.8	211870	4.8
	North East	252477	5.1	213661	5.0	211219	4.8
	North West	473981	9.5	416240	9.7	433661	9.9
	South East	316575	6.4	277278	6.5	277384	6.3

	South West	663924	13.3	588611	13.7	592280	13.5
	West Midlands	206014	4.1	177080	4.1	182260	4.1
	Yorkshire and The Humber	758471	15.2	648597	15.1	681451	15.5
Ethnicity	White	3641108	73.1	3199537	74.4	3249715	73.8
	Mixed	53224	1.1	47169	1.1	51907	1.2
	Asian	260559	5.2	217098	5.0	233130	5.3
	Black	65820	1.3	58144	1.4	61135	1.4
	Others	77632	1.6	66748	1.6	70754	1.6
	Unknown	884033	17.7	710956	16.5	736664	16.7
Charlson	zero	3292390	66.1	2806965	65.3	2910691	66.1
Comorbidity	low	1324667	26.6	1165222	27.1	1178500	26.8
Index*	medium	282716	5.7	251880	5.9	241898	5.5
	high	59942	1.2	53897	1.3	50862	1.2
	very high	22661	0.5	21688	0.5	21354	0.5
IMD quintile	1(least deprived)	1026362	20.6	887444	20.6	915880	20.8
	2	979407	19.7	843490	19.6	863943	19.6
	3	1032189	20.7	889252	20.7	904995	20.6
	4	963906	19.3	827185	19.2	838035	19.0
	5(most deprived)	881238	17.7	752927	17.5	758000	17.2
	Unknown	99274	2.0	99354	2.3	122452	2.8

Abbreviation: IMD, Index of Multiple Deprivation

*CCI, Charlson Comorbidities Index, calculated based on 17 weighted conditions, including Myocardial infarct, Congestive heart failure, Peripheral vascular disease, Cerebrovascular disease, Dementia, Chronic pulmonary disease, Connective tissue disease, Ulcer disease, Mild liver disease, Diabetes, Hemiplegia, Moderate or severe renal disease, diabetes with complications, any malignancy (including leukaemia and lymphoma), Moderate or severe liver disease, Metastatic solid tumour, AIDS.

Table 2. Adjusted ORs for potentially inappropriate and repeat antibiotic prescribing based on multinomial regression models for overall/LRTI/Sore throat/Cough

Predictor	[a]Overall		LRTI		Sore throat		Cough	
	OR (95% CI)		OR (95% CI)		OR (95% CI)		OR (95% CI)	
	[b]Inappropriate	[c]Repeat	Inappropriate	Repeat	Inappropriate	Repeat	Inappropriate	Repeat
[d]Age								
10	1.17 (1.15-1.19)	0.73 (0.71-0.74)	1.33 (1.31-1.34)	0.62 (0.60-0.64)	0.78 (0.75-0.80)	0.90 (0.88-0.91)	1.74 (1.71-1.75)	0.66 (0.62-0.69)
20	0.95 (0.94-0.976)	0.78 (0.77-0.80)	1.22 (1.21-1.24)	0.73 (0.71-0.75)	0.49 (0.47-0.51)	0.90 (0.89-0.92)	1.44 (1.41-1.45)	0.77 (0.75-0.80)
30	0.88 (0.86-0.89)	0.87 (0.85-0.90)	1.12 (1.10-1.15)	0.86 (0.84-0.88)	0.63 (0.61-0.66)	0.96 (0.94-0.99)	1.19 (1.15-1.22)	0.88 (0.85-0.89)
50	1.15 (1.13-1.17)	1.17 (1.15-1.19)	0.88 (0.85-0.91)	1.15 (1.11-1.17)	1.47 (1.45-1.50)	1.15 (1.14-1.18)	0.86 (0.84-0.90)	1.12 (1.10-1.15)
60	1.10 (1.08-1.11)	1.34 (1.33-1.36)	0.85 (0.84-0.87)	1.29 (1.24-1.31)	2.08 (2.07-2.11)	1.38 (1.35-1.41)	0.83 (0.81-0.86)	1.23 (1.21-1.26)
70	1.03 (1.01-1.05)	1.48 (1.46-1.50)	0.95 (0.94-0.97)	1.40 (1.37-1.42)	2.92 (2.88-2.95)	1.68 (1.65-1.71)	0.93 (0.91-0.97)	1.31 (1.28-1.35)
80	1.04 (1.01-1.07)	1.58 (1.56-1.60)	1.07 (1.04-1.10)	1.41 (1.39-1.44)	4.09 (4.01-4.18)	2.05 (2.01-2.11)	0.96 (0.95-0.99)	1.36 (1.34-1.41)
Sex								

Male	1.34 (1.33,1.35)	0.97 (0.96,0.97)	0.74 (0.68,0.79)	0.91 (0.9,0.92)	1.03 (1.01,1.05)	0.88 (0.86,0.89)	0.94 (0.91,0.98)	0.91 (0.9,0.93)
Ethnicity								
Mixed	1.06 (1.03,1.09)	0.92 (0.9,0.95)	1.13 (0.84,1.51)	0.88 (0.82,0.94)	1.10 (1.02,1.18)	0.90 (0.84,0.96)	1.02 (0.86,1.21)	0.88 (0.8,0.98)
Asian	1.53 (1.51,1.55)	0.87 (0.86,0.88)	0.79 (0.68,0.92)	0.78 (0.76,0.8)	1.70 (1.64,1.76)	1.01 (0.98,1.05)	1.12 (1.04,1.21)	0.82 (0.78,0.86)
Black	1.21 (1.17,1.24)	0.75 (0.73,0.77)	1.25 (0.96,1.64)	0.69 (0.65,0.74)	1.04 (0.97,1.12)	0.79 (0.74,0.86)	1.09 (0.94,1.26)	0.74 (0.68,0.82)
Other	1.15 (1.12,1.19)	0.89 (0.87,0.91)	0.96 (0.71,1.28)	0.85 (0.8,0.91)	1.08 (1.01,1.15)	0.89 (0.83,0.95)	1.12 (0.97,1.29)	0.93 (0.85,1.01)
Region								
East Midlands	0.83 (0.82,0.84)	1.01 (1,1.02)	0.84 (0.76,0.93)	1.03 (1.01,1.05)	0.52 (0.5,0.54)	0.87 (0.85,0.9)	1.11 (1.05,1.17)	1.03 (1,1.06)
London	1.51 (1.49,1.54)	0.93 (0.91,0.94)	1.22 (1.02,1.46)	0.80 (0.77,0.84)	1.38 (1.32,1.43)	0.96 (0.92,1.01)	1.10 (1.01,1.19)	0.84 (0.8,0.88)
North East	0.71 (0.7,0.72)	0.89 (0.88,0.91)	0.83 (0.71,0.97)	0.95 (0.93,0.98)	0.51 (0.48,0.54)	0.79 (0.75,0.82)	0.87 (0.8,0.96)	0.91 (0.87,0.95)
North West	0.73 (0.72,0.74)	0.99 (0.98,1)	0.81 (0.71,0.91)	1.02 (0.99,1.04)	0.48 (0.46,0.5)	0.86 (0.84,0.89)	0.98 (0.91,1.05)	0.97 (0.94,1.01)
South East	0.78	1.00	0.91	1.02	0.89	0.95	0.89	0.98

	(0.77,0.79)	(0.99,1.01)	(0.78,1.06)	(0.99,1.05)	(0.85,0.93)	(0.91,0.98)	(0.81,0.96)	(0.94,1.03)
South West	0.71	1.02	0.75	1.04	0.78	0.98	0.78	0.99
	(0.7,0.72)	(1.01,1.03)	(0.66,0.86)	(1.01,1.06)	(0.75,0.8)	(0.95,1.01)	(0.72,0.84)	(0.96,1.02)
West Midlands	0.98	0.95	1.10	0.91	0.94	0.92	0.99	0.89
	(0.96,0.99)	(0.94,0.96)	(0.94,1.28)	(0.88,0.94)	(0.9,0.98)	(0.89,0.96)	(0.9,1.09)	(0.85,0.93)
Yorkshire and The Humber	0.88	0.97	0.85	0.98	0.50	0.85	0.85	0.96
	(0.87,0.89)	(0.96,0.98)	(0.76,0.94)	(0.96,1)	(0.49,0.52)	(0.83,0.88)	(0.8,0.91)	(0.93,0.99)
Charlson Comorbidity Index								
low	1.07	1.12	0.97	1.13	1.22	1.21	0.92	1.13
	(1.06,1.08)	(1.11,1.12)	(0.9,1.04)	(1.11,1.14)	(1.19,1.25)	(1.19,1.24)	(0.88,0.96)	(1.11,1.16)
medium	1.09	1.19	1.05	1.18	1.33	1.36	1.05	1.23
	(1.07,1.11)	(1.17,1.2)	(0.93,1.19)	(1.16,1.21)	(1.24,1.43)	(1.27,1.45)	(0.98,1.13)	(1.19,1.28)
high	1.17	1.23	1.01	1.21	1.27	1.29	1.17	1.29
	(1.13,1.21)	(1.21,1.26)	(0.79,1.29)	(1.16,1.27)	(1.08,1.49)	(1.11,1.51)	(1.02,1.34)	(1.21,1.38)
very high	1.14	1.34	1.21	1.26	1.48	1.51	1.18	1.42
	(1.08,1.21)	(1.3,1.38)	(0.83,1.76)	(1.18,1.35)	(1.15,1.91)	(1.18,1.92)	(0.95,1.47)	(1.28,1.58)
IMD quintile								
2	1.00	1.02	1.11	1.03	0.97	1.04	1.04	1.02
	(0.98,1.01)	(1.01,1.03)	(1.01,1.23)	(1.01,1.05)	(0.95,1)	(1.01,1.06)	(0.98,1.1)	(0.99,1.05)
3	0.93	1.04	1.15	1.07	0.87	1.08	1.02	1.01

	(0.92,0.94)	(1.03,1.05)	(1.04,1.28)	(1.05,1.1)	(0.84,0.89)	(1.05,1.1)	(0.96,1.08)	(0.98,1.04)
4	0.91 (0.9,0.92)	1.05 (1.04,1.06)	1.17 (1.05,1.3)	1.08 (1.06,1.1)	0.79 (0.76,0.82)	1.08 (1.05,1.11)	1.10 (1.03,1.16)	1.02 (0.99,1.05)
5	0.91 (0.9,0.92)	1.06 (1.05,1.07)	1.17 (1.04,1.31)	1.08 (1.06,1.1)	0.75 (0.72,0.77)	1.09 (1.06,1.12)	1.12 (1.05,1.2)	1.04 (1,1.07)
Incident event								
prevalent	1.18 (1.17,1.19)	1.37 (1.36,1.38)	1.55 (1.43,1.67)	1.18 (1.16,1.2)	1.15 (1.12,1.18)	1.36 (1.33,1.39)	1.58 (1.51,1.65)	1.30 (1.27,1.33)
Antibiotics history								
1	0.96 (0.95,0.97)	1.10 (1.09,1.11)	1.24 (1.12,1.37)	1.13 (1.11,1.15)	1.07 (1.04,1.1)	1.21 (1.18,1.24)	1.17 (1.11,1.24)	1.08 (1.05,1.11)
2	0.98 (0.96,0.99)	1.32 (1.31,1.33)	1.54 (1.37,1.73)	1.35 (1.33,1.38)	1.13 (1.09,1.17)	1.51 (1.46,1.55)	1.45 (1.36,1.54)	1.36 (1.31,1.4)
3+	1.06 (1.05,1.07)	2.50 (2.49,2.52)	2.81 (2.55,3.09)	2.54 (2.5,2.59)	1.34 (1.3,1.38)	2.62 (2.56,2.69)	2.38 (2.25,2.51)	2.81 (2.74,2.89)

The reference groups are Age: 40 years old, Sex: Female, Ethnicity: White, Region: East of England, Charlson Comorbidity Index: Zero (Health), IMD quintile: 1(least deprived), Incident event: incident, Antibiotics history: 0(No)

[a]Overall: Overall model is a model included all ten types of infection records (Ordered by the number of records: UTI, LRTI, Sore throat, Cough, Sinusitis, Otitis media, URTI, Otitis externa, COPD, Pneumonia).

[b]Inappropriate: Potentially inappropriate antibiotic types deviated from recommended guidelines

[c]Repeat: Other antibiotics issues 30 days after the index date.

[d]Age ORs estimated based on the polynomials in the models.

Table 3. Distribution of predicted probabilities based on multinomial logistic models in validation cohorts stratified by infection (ordered by the number of records)

		Percentiles				
		2.5th	25th	50th	75th	97.5th
[a]Overall						
	[b]Inappropriate	0.052	0.066	0.078	0.096	0.160
	[c]Repeat	0.083	0.130	0.186	0.277	0.487
UTI						
	Inappropriate	0.006	0.016	0.027	0.044	0.090
	Repeat	0.124	0.180	0.247	0.375	0.524
LRTI						
	Inappropriate	0.002	0.004	0.005	0.007	0.014
	Repeat	0.081	0.149	0.198	0.268	0.448
Sore throat						
	Inappropriate	0.027	0.044	0.065	0.100	0.235
	Repeat	0.060	0.081	0.098	0.131	0.272
Cough						
	Inappropriate	0.020	0.028	0.038	0.052	0.088
	Repeat	0.075	0.131	0.173	0.271	0.438
Sinusitis						
	Inappropriate	0.003	0.004	0.006	0.010	0.020
	Repeat	0.083	0.118	0.143	0.192	0.353
Otitis media						
	Inappropriate	0.006	0.019	0.042	0.063	0.125

	Repeat	0.071	0.107	0.148	0.191	0.353
URTI						
	Inappropriate	0.492	0.657	0.720	0.755	0.804
	Repeat	0.060	0.098	0.137	0.192	0.401
Otitis externa						
	Inappropriate	0.259	0.330	0.381	0.427	0.639
	Repeat	0.085	0.129	0.159	0.205	0.371
COPD						
	Inappropriate	0.011	0.017	0.021	0.027	0.040
	Repeat	0.152	0.216	0.370	0.470	0.516

[a]Overall: Overall model is a model included all ten types of infection records (Ordered by the number of records: UTI, LRTI, Sore throat, Cough, Sinusitis, Otitis media, URTI, Otitis externa, COPD, Pneumonia).

[b]Inappropriate: Potentially inappropriate antibiotic types deviated from recommended guidelines

[c]Repeat: Other antibiotics issues 30 days after the index date.

Table 4. Discrimination in multinomial logistic regression models: pairwise c-indexes, 1-versus-rest c-indexes and polytomous discrimination indexes (PDI)

	Pairwise c-indexes			**1-versus-rest c-indexes**			**PDI**		
Model	**Comparison**	**[a]D**	**[b]V**	**Comparison**	**D**	**V**	**Comparison**	**D**	**V**
Overall	[c]A versus [d]I	0.59	0.59	A versus rest	0.64	0.64	A	0.44	0.44
	A versus [e]R	0.68	0.68	I versus rest	0.59	0.59	I	0.45	0.45
	I versus R	0.69	0.69	R versus rest	0.68	0.68	R	0.53	0.53
UTI	A versus I	0.73	0.73	A versus rest	0.68	0.68	A	0.55	0.55
	A versus R	0.67	0.68	I versus rest	0.69	0.69	I	0.50	0.50
	I versus R	0.61	0.61	R versus rest	0.67	0.67	R	0.41	0.41
LRTI	A versus I	0.68	0.66	A versus rest	0.66	0.66	A	0.48	0.47
	A versus R	0.66	0.67	I versus rest	0.65	0.64	I	0.45	0.44
	I versus R	0.62	0.61	R versus rest	0.66	0.67	R	0.42	0.43

Sore throat	A versus I	0.70	0.70	A versus rest	0.65	0.65	A	0.49	0.49
	A versus R	0.64	0.64	I versus rest	0.69	0.69	I	0.51	0.51
	I versus R	0.67	0.67	R versus rest	0.63	0.63	R	0.44	0.44
Cough	A versus I	0.65	0.65	A versus rest	0.67	0.66	A	0.47	0.47
	A versus R	0.68	0.68	I versus rest	0.63	0.63	I	0.43	0.43
	I versus R	0.63	0.63	R versus rest	0.68	0.67	R	0.47	0.47
Sinusitis	A versus I	0.68	0.66	A versus rest	0.64	0.64	A	0.48	0.48
	A versus R	0.64	0.64	I versus rest	0.66	0.64	I	0.46	0.44
	I versus R	0.60	0.57	R versus rest	0.64	0.64	R	0.39	0.40
Otitis media	A versus I	0.72	0.72	A versus rest	0.67	0.66	A	0.54	0.54
	A versus R	0.65	0.65	I versus rest	0.67	0.70	I	0.49	0.49
	I versus R	0.61	0.61	R versus rest	0.64	0.70	R	0.38	0.38
URTI	A versus I	0.61	0.62	A versus rest	0.62	0.63	A	0.48	0.49
	A versus R	0.71	0.71	I versus rest	0.60	0.60	I	0.43	0.43
	I versus R	0.67	0.67	R versus rest	0.60	0.67	R	0.53	0.53
Otitis externa	A versus I	0.60	0.60	A versus rest	0.59	0.58	A	0.42	0.42
	A versus R	0.62	0.61	I versus rest	0.60	0.60	I	0.46	0.46
	I versus R	0.66	0.65	R versus rest	0.63	0.63	R	0.48	0.47
COPD	A versus I	0.64	0.63	A versus rest	0.66	0.66	A	0.49	0.48
	A versus R	0.66	0.66	I versus rest	0.60	0.58	I	0.41	0.40
	I versus R	0.58	0.59	R versus rest	0.66	0.66	R	0.43	0.43

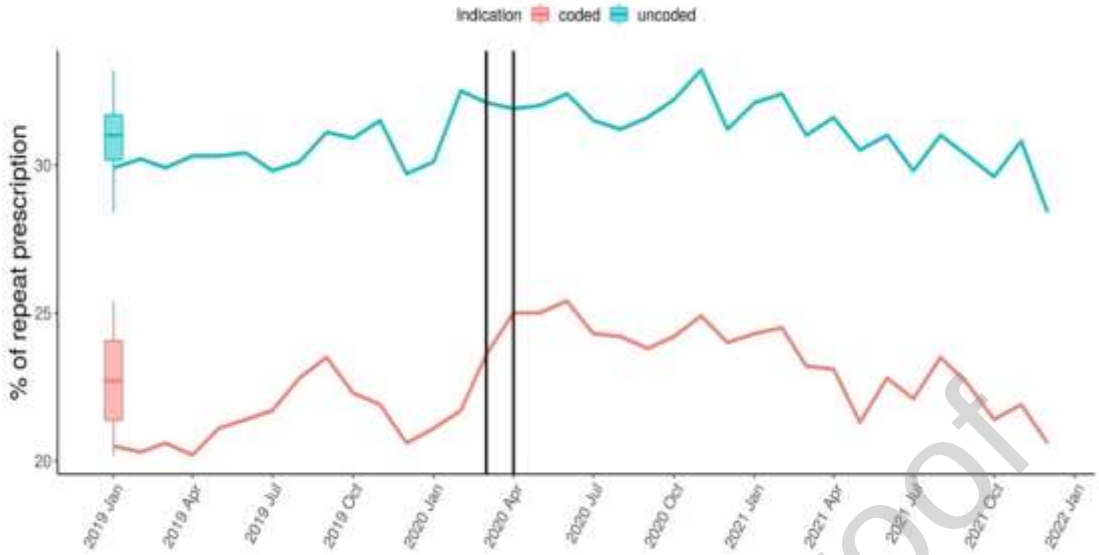
[a]D: development cohort (75%)

[b]V: validation cohort (25%)

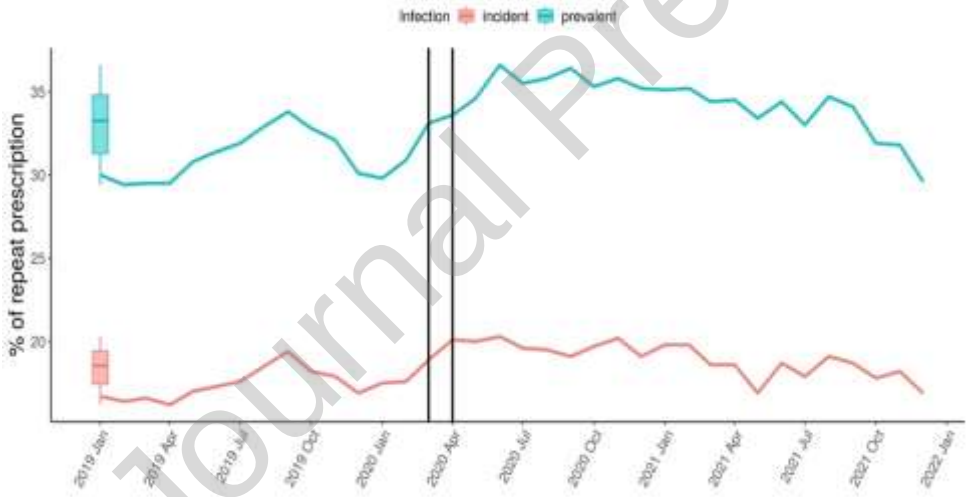
[c]A: the appropriate antibiotic was prescribed and no repeat antibiotic (30 days after the index date)

[d]I: Potentially inappropriate antibiotic types deviated from recommended guidelines

[e]R: Other antibiotics issues 30 days after the index date



A.



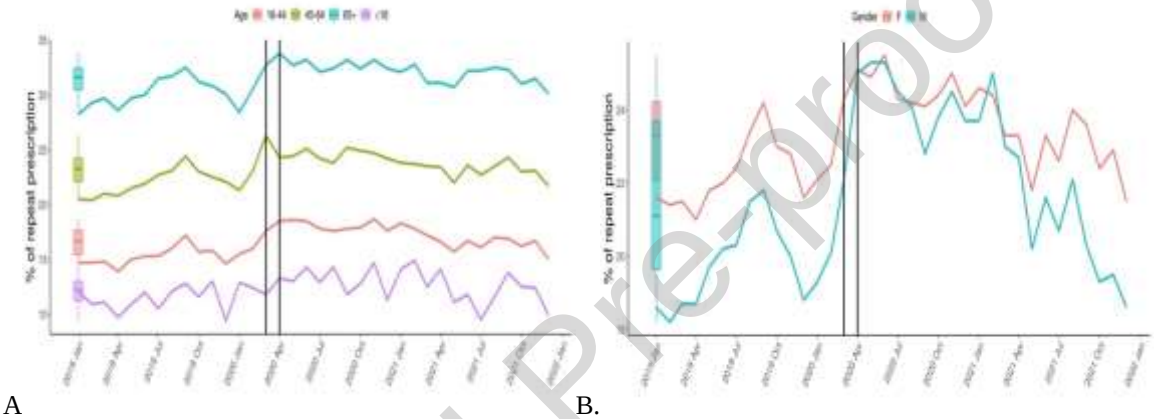
B.

Figure 1A. Monthly percentages of repeat antibiotic prescribing over calendar time. 1B. Monthly percentages of repeat antibiotic prescribing for all same day infection coded records over calendar time.

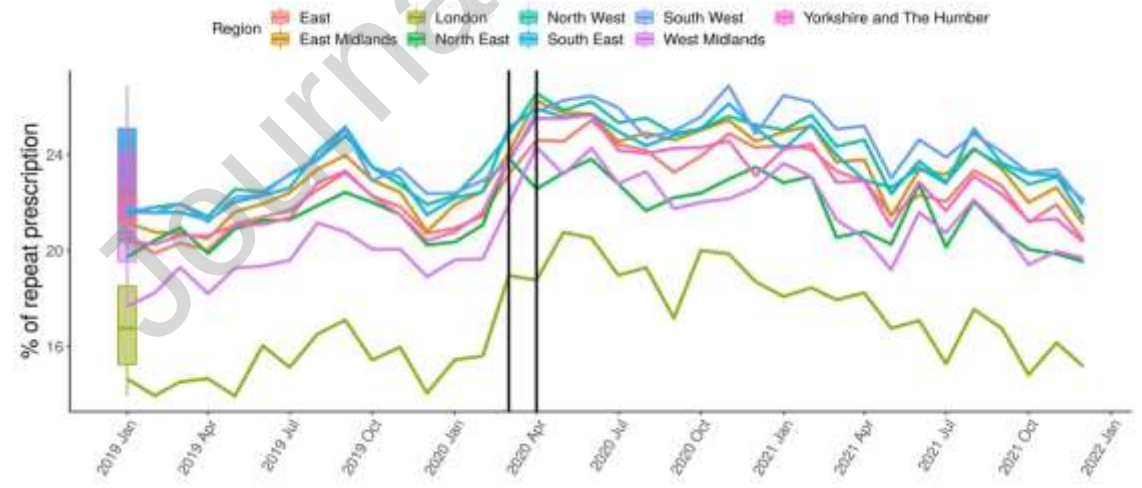
A. Numerator is the number of repeat antibiotic prescriptions, and the denominator is the number of all antibiotic prescriptions, stratified by same day coded or uncoded records for a specific infection record

(antibiotic user cohort). Boxplots represent the historical average (median and IQR) percentage of the repeat antibiotic prescribing from January 2019 to December 2021. Vertical solid lines indicate the start of COVID-19-related national restrictions (1st March 2020 to 31st March 2020).

B. Repeat prescribing stratified by incident infection (A record with no other infection recorded in the 90 days before, and no antibiotic prescription in the 30 days before the index date) or prevalent infection from the coded prescription cohort (infection coded cohort).



A B.



C.

Figure 2. Monthly percentages of repeat antibiotic prescribing over calendar time (stratified by age(A), sex(B) and region(C) in infection coded cohort)

The numerator is the number of repeat antibiotic prescriptions, and the denominator is the number of all antibiotic prescriptions. Boxplots represent the historical average (median and IQR) percentage of repeat

antibiotic prescribing. Vertical solid lines indicate the COVID-19-related national restriction started month (1st March 2020 to 31st March 2020).

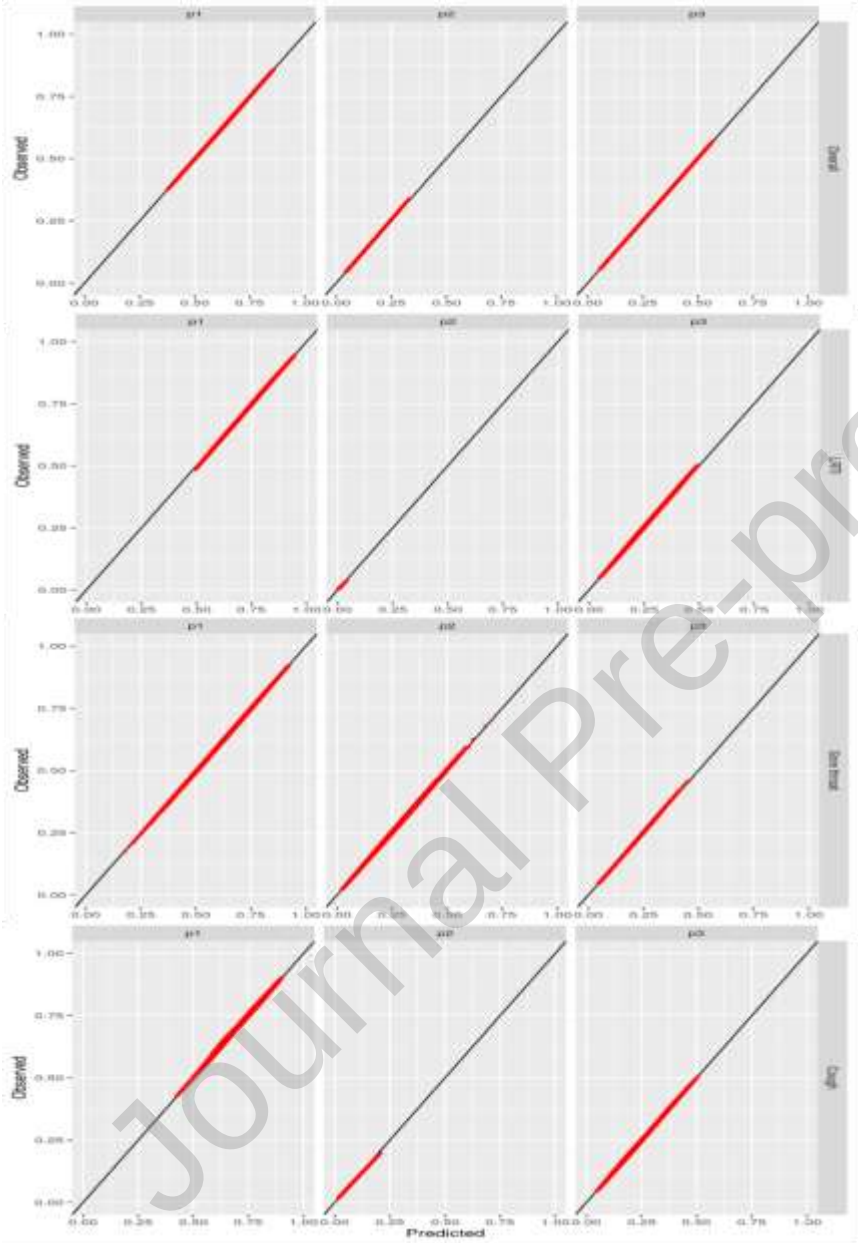


Figure 3. Parametric nominal calibration plot for Overall/LRTI/Sore throat/Cough models

Parametric nominal calibration plot showing observed probabilities (Y-axis) versus predicted probabilities (X-axis) for different outcome categories. The observed probabilities were calculated from the recalibration framework (see Equation S3). P1: the appropriate antibiotic was prescribed and no repeat antibiotic (30 days after the index date). P2: a potentially inappropriate antibiotic was prescribed with no repeat antibiotic. P3: other antibiotics issues 30 days after the index date. The plot was generated from the validation cohort.