BMJ Open

Impact of the COVID-19 pandemic on prescription coverage of immune mediated inflammatory disorders: A time series analysis (Jan 2019 to Oct 2020) using the English Prescribing Dataset.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051936
Article Type:	Original research
Date Submitted by the Author:	30-May-2022
Complete List of Authors:	Barrett, Ravina; University of Brighton, School of Pharmacy and Biomolecular Sciences; University of Portsmouth Faculty of Science, School of Pharmacy and Biomedical Sciences Barrett, Rob; University of Portsmouth Lin, Sharon; University of Southampton, Faculty of Health Sciences Culliford, David; University of Southampton, Faculty of Medicine Fraser, Simon; University of Southampton, Faculty of Medicine Edwards, Christopher; University Hospital Southampton NHS Foundation Trust, Rheumatology
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, COVID-19, EPIDEMIOLOGY, GASTROENTEROLOGY, GERIATRIC MEDICINE, Rheumatology < INTERNAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Impact of the COVID-19 pandemic on prescription coverage of immune mediated inflammatory disorders: A time series analysis (Jan 2019 to Oct 2020) using the English Prescribing Dataset.

Short title (40 characters): English DMARDs study.

Author:

1. corresponding author Mrs. Ravina Barrett (https://orcid.org/0000-0003-0004-2131) MPharm, FHEA, MSc Finance, Author affiliations and information:
    a. Senior Lecturer in Pharmacy Practice, School of Pharmacy and Biomolecular Sciences, Cockcroft Building, University of Brighton, Moulsecoomb, Brighton, BN2 4GJ. +44(0)1273643986, R.Barrett2@Brighton.ac.uk
    b. Visiting Researcher in Pharmacy Practice, University of Portsmouth, School of Pharmacy and Biomedical Sciences, St Michael's Building, White Swan Road, Portsmouth, PO1 2DT, ravina.barrett@port.ac.uk .
2. Mr. Robert Barrett, MBA, MCSE, MCSA, MCP, ITIL, Prince 2 rob-barrett@outlook.com ; https://orcid.org/0000-0003-3402-3377 Affiliations not disclosed.
3. Dr. Sharon X Lin; research fellow at The School of Primary Care and Population Sciences, Faculty of Medicine, Southampton General Hospital, SO16 6YD, X.Lin@soton.ac.uk
4. Dr. David Culliford, Principal Medical Statistician, NIHR Applied Research Collaboration Wessex, Faculty of Environmental and Life Sciences, University of Southampton, Southampton General Hospital (Room AA71, MP11), Southampton SO16 6YD, Tel + 44 (0) 23 8120 3374, d.j.culliford@soton.ac.uk
5. Dr. Simon Fraser BM. MSc, DM, DRCOG, DCH, MRCGP. Dip, FHEA, MFPH, FFPH. Associate Professor of Public Health; School of Primary Care and Population Sciences, Faculty of Medicine, Southampton General Hospital, SO16 6YD, Tel: 023 81206138 (https://orcid.org/) S.Fraser@soton.ac.uk.
6. Professor Christopher Edwards BSc, MBBS, MD, FRCP, Consultant Rheumatologist, University Hospital Southampton NHS Foundation Trust, Honorary Chair of Clinical Rheumatology, Professor in Rheumatology, Faculty of Medicine, University of Southampton, Associate Director, Southampton NIHR Wellcome Trust Clinical Research Facility, cedwards@soton.ac.uk

Word count (excluding abstract, references, tables, and figures):

Introduction.	607
Materials and methods.	785
Results.	1470
Discussion.	891
Total	3753

Supplementary Table 1 - ARIMA Syntax (Mar20-1) Jan 19 to Jan 21
Supplementary Table 2 - Sensitivity analysis (Mar20-1) Jan 19 to Jan 21
Supplementary Table 3 - RECORD checklist
Supplementary Table 4 - Quantity & Cost
Supplementary Table 5 - Region
Supplementary Table 6 - Methotrexate Quantity

Abstract (251/300)

Objective:

To examine the effect of the pandemic on prescription statistics for rheumatoid arthritis patients in England.

Design:

Interrupted time series analysis.

Setting:

the English Prescribing Dataset.

Main Outcome Measures:

the proportion of prescriptions that have been issued over a continuous 22-month period, 14 months before the pandemic and eight months after.

Results:

Since the March-lockdown, fluctuations in monthly volumes are observed. The Mann-Whitney two-tailed test for hydroxychloroquine (test statistics 84, standard error 14.652, standardised test statistic 1.911, p-value = 0.059) over the study period. There was evidence of a step change for hydroxychloroquine (p-value 0.027) and azathioprine (p-value 0.018), which was statistically significant after March 2020. There was also a change in linearity of the regression slope after March 2020, which was statistically significant for azathioprine (p-value 0.050). Hydroxychloroquine statistics also show interesting patterns against President Trump's proclamations and are presented as an infographic. The actual cost of medicines have gone up - Mann-Whitney U test for hydroxychloroquine (p-value < 0.001), azathioprine (p-value < 0.001), methotrexate (p-value < 0.001) and leflunomide (p-value = 0.004) which shows significant price changes after March 2020. We present data on regional distribution of prescriptions.

Conclusions:

A worrying change in trend is observed for all medicines that were studied. The trend overall is downwards which raises concerns for the longer term care of rheumatoid arthritis patients. We know that not taking medication is likely to result in increased morbidity and mortality in this patient group. Extra effort may be needed to help these patients.

Keywords.

COVID-19; severe acute respiratory syndrome coronavirus 2. COVID-19/SARS-CoV-2 Pandemic; Disparities, rheumatoid arthritis, medicines, pharmacy services, prescriptions

What is already known on this topic.

Anecdotal evidence from the UK suggests that there may be a inconsistent picture of patient care and medication taking. Abualfadl et al. have conducted a large-scale Egyptian study (N=1037), suggesting difficulties faced by rheumatoid arthritis patients in obtaining their medications with subsequent changes in their disease status.

What this study adds.

For the first time, we present real-world data analysis from England that suggests that rheumatoid arthritis prescription statistics are deteriorating. There was an increased use of hydroxychloroquine in March and April 2020, but we are particularly concerned with the statistically significant reduction in azathioprine use. Similarly, sulfasalazine shows a downward trend, though not statistically significant, this impacts a much larger number of patients because of its high use.

Introduction.

In England, all people above the age of 60 years, receive prescription medications free of charge through universal care provisions. The National Health Service (NHS) has been publicly funded since 1948 and reimburses primary-care contractors (e.g. GPs, pharmacies, dentists, etc.) through central and local budgets. Consequently, NHS datasets provide a valuable and accurate insight into current practice and the ongoing management of many chronic long term conditions.

Disease-modifying anti-rheumatic drugs (DMARD) are the mainstay for the treatment of many painful conditions of the joints which often include rheumatoid arthritis and related arthritic conditions (e.g. Rheumatoid arthritis, Psoriatic arthritis, Systemic lupus erythematosus, Spondyloarthritis). Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that primarily targets synovial joints, resulting in pain and functional limitations. It is the most common inflammatory arthritis, and a significant cause of morbidity and mortality. From the primary care perspective, early recognition of this disease, along with its extra-articular manifestations, can lead to faster time to treatment and better health outcomes, in addition to preserved joint functionality.

DMARDs are also used in chronic conditions of the bowels (e.g. Crohn's disease, ulcerated colitis, diverticulitis) as well as for anti-rejection therapy when organ transplants or grafts have been used as they supress the autoimmune destruction. These medicines are important because they provide a lifeline towards functional mobility and improves the quality of life for patients by relieving their pain as well as retarding disease progression. Other medicines include alkylating agents (e.g. cyclophosphamide), Janus kinase (JAK) inhibitors (e.g. Baricitinib), Phosphodiesterase type-4 (PDE4) inhibitor (e.g. apremilast) and Tumor Necrosis Factor (TNF) - alpha inhibitor (e.g. Adalimumab or Humira®, Etanercept or Enbrel®) are used for RA.

These medicines are usually taken as chronic long-term medications for the management of such relapsing-remitting autoimmune conditions. Their consistent use provides optimal pain relief and their mechanisms of action mean long-term use dampens the inflammatory cascade response. Collectively, this reduces pain, reduces the inflammatory mediators that recruit towards ongoing inflammatory cascades and arrests the autoimmune response. These medications, if not taken properly, can cause loss of disease control and progressing joint destruction with resultant loss of mobility, poorer mental health and diminished quality of life.

Given increasing life expectancies worldwide, the number of elderly people with RA is growing.[1] Comorbidities in elderly patients with RA often include cardiovascular disease, cancer, infections, venous and arterial insufficiency amongst others.[1] From a public health perspective, people with RA have been found to be significantly more likely to have reduced their work hours or stopped working; they are more likely to have lost their job or to have retired early; and are 3 times more likely to have had a reduction in household family income than either individuals with osteoarthritis (OA) or those without arthritis.[2–6] In this way, the economic effects of RA are staggering and emphasize the importance of early recognition and treatment.[7] A study from Egypt suggests that patients with RA faced remarkable difficulty to obtain their medications with subsequent change in their disease status.[8]

The COVID-19 pandemic has meant that many patients in the middle to elderly age category who may suffer from arthritis like conditions may be at higher risk of contracting the virus because of their advanced age, comorbidities and their dampened immune function. Normal care for patients has been affected, as reflected in urgently developed pandemic-guidelines.[9] We also know that there have been supply shortages across the United Kingdom (UK)[10], Europe and many parts of the world before [11–13] the pandemic and after for many medications during the pandemic (e.g. ibuprofen

and paracetamol). The European Medicines Agency (EMA) acknowledges shortage of etanercept (Enbrel®) in pre-filled pens and syringes.[14] Study objective was to examine the effect of the pandemic on prescription statistics for rheumatoid arthritis patients in England.

Materials and methods

Data and Resources

The 'English Prescribing Dataset' (EPD)[15] provided anonymised prescription data in England covered by Open Government Licence (OGL). The EPD comprises detailed information on community-issued prescriptions (not hospital) issued in England but dispensed across the UK (England, Wales, Scotland, Guernsey, Alderney, Jersey, and the Isle of Man). It holds detailed prescribing information at practice level, aggregated by British National Formulary (BNF) code e.g. 0105010E0AAABAB for 'Sulfasalazine 500mg gastro-resistant tablets' to maintain patient confidentiality. Therefore, each row of data does not represent individual patients or prescriptions. The data includes total quantity of unit-doses (e.g. tablets, prefilled insulin pens), and 'actual cost' for reimbursement.

The data excludes prescriptions issued outside England (Wales, Scotland, Guernsey, Alderney, Jersey, and the Isle of Man); items not dispensed, disallowed and those returned for further clarification; prescriptions prescribed and dispensed in prisons, hospitals and private prescriptions; items prescribed but not presented for dispensing or not submitted to NHS prescription services by the dispenser. This dataset included small (487 out of 2,555,396 rows) operational irregularities (e.g. 17 rows in Jan 2019 of 'unidentified practice data', 470 rows of 'NULL' chemical substance codes, where accurate BNF codes were given to permit extraction of the missing data). The study population represents English residents who were issued a prescription and had it dispensed.

Monthly-data from January 2019 to October 2020 were compared for sulfasalazine; hydroxychloroquine sulfate; azathioprine; methotrexate and leflunomide. Sodium aurothiomalate; Anakinra; Baricitinib; Apremilast; Infliximab; Golimumab; Etanercept; Certolizumab pegol abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, Rituximab, sarilumab, tocilizumab, tofacitinib, penicillamine and cyclophosphamide were excluded because they are marginally important (normally used under specialist care and are of small volumes, less than a 1000 units per month).

Formulations not normally be used in RA (E.g., Sulfasalazine suppositories) were excluded as well as all cutaneous products (e.g., creams, gels, medicated plasters, sprays, cutaneous solutions, transdermal patches, topical solutions). Hence, the data contains tablets, oral liquids and injectables (pre-filled syringes, ampoules, vials).

333,459,762 rows of data (99 gigabytes of data) were extracted using Structured Query Language (SQL). After excluding unnecessary rows, 8,186,699 relevant rows (2.6 gigabytes of data) were filtered. We imported 22 comma-separated values (CSV) file into a Microsoft SQL® server table labelled EPD. As each one was imported, it was validated and assigned an exact datatype (e.g., 'Total quantity' is a 'floating' data point, 'regional office name' is a textfield) to each field of data. We removed spaces, blanks, checked for wrong kinds of data (e.g., that text characters weren't in a numeric field or purely numeric characters in a textfield). We used Microsoft Visual Studio® to create and edit SQL Server Integration Services® (SSIS) packages that imported, validated and consolidated the data within an automated import routine. See 'Supplement Method' for details. Data were aggregated by month, chemical substance, regional office name and BNF code, to allow for human analysis. Detailed methods for the above steps have been previously published.[16]

The reliable, consistent EDP data allowed for direct monthly comparison. We did not conduct detailed population analysis, and these were assumed to be constant. Patient's diagnosis were unknown. Lockdown commenced on 23rd of March 2020, a second lockdown commenced on 5th November 2020.

Analysis

Analysis was carried out in Excel® v. 2007 and SPSS® v. 26. Results are presented as nominal values, descriptive statistics and Mann-Whitney U test. Interrupted time series (ITS) analysis was used to fit time trends[17] at 95% confidence level.

We employed a commonly used time series modelling framework (autoregressive integrated moving average, or ARIMA) to analyse the monthly total-quantity of prescription data. ARIMA is a flexible modelling construct, allowing lagged correlations and seasonal differences to be modelled, but we used only a simple model with no allowance for serial correlation nor seasonality, mainly due to the lack of data points after the interrupt time point. We had available 22 consecutive monthly data points with the interrupt time set at the 14th month (March 2020), and 14 data points before and eight data points after March 2020. We estimated the difference in prescription total-quantity as at March 2020, and also the difference in the linear trend (i.e. between the slopes of the lines) before and after the interrupt time point. The observed temporal trend in prescription total-quantity was explored visually in advance of performing the main time series analysis. See ARIMA Syntax in Supplementary Table 1. See Sensitivity Analysis in Supplementary Table 2. The RECORD Checklist[18] was used (Supplementary Table 3 - RECORD checklist).

Research ethics: research ethics permission was not sought for this study because it is an anonymized database study that does not identify any individual patient. This data set is covered by the open government licence such that permit the free analysis and reporting of such analysis.

Patient and Public Involvement: patients and members of the public were not involved in the study.

Results

Descriptive statistics can be visualised in Table 1 and Figure 1.

[Insert Figure 1 here]

Table 1 Descriptive statistics of the total quantities, presented in millions.

	Total Quantity		**Actual Cost (£)**	
	Mean	Standard Deviation	Mean	Standard Deviation
Sulfasalazine	9.280	0.422	0.628	0.039
Hydroxychloroquine sulfate	4.721	0.247	0.448	0.122
Azathioprine	4.505	0.202	0.273	0.123
Methotrexate	4.182	0.179	4.046	0.482
Leflunomide	0.550	0.025	0.111	0.009

By total quantities of anti-rheumatics' medicines

Since the March-lockdown, fluctuations in monthly volumes are observed. See Supplementary Table 4 for Fluctuating total quantities of anti-rheumatics' medicines in millions (Jan 2019 to Jan 2021) by quantity and associated price. The Mann-Whitney two-tailed test was most interesting for hydroxychloroquine quantity (test statistics 84, standard error 14.652, standardised test statistic 1.911, p-value = 0.059) over the study period.

By price of anti-rheumatics' medicines

Examining the actual cost of medicines shows variation. Mann-Whitney U test for prices of hydroxychloroquine (p-value < 0.001), azathioprine (p-value < 0.001), methotrexate (p-value <

0.001) and leflunomide (p-value = 0.004) reject the null hypothesis that the price-distribution is same before and after March 2020.

Interrupted Time Series (ARIMA Modelling)

Sulfasalazine; Hydroxychloroquine; Azathioprine; Methotrexate; and Leflunomide are the anti-rheumatics medicines most used by total quantity in the study period. ARIMA model can be visualised in Table 2 and Figure 2.

[Insert Figure 2 here]

None of the five medicines showed evidence of a significant difference in the linear trend for monthly prescription statistics before the chosen interrupt time-point (March 2020) when modelled without any seasonal, moving average or autoregressive components, see table 2.

Table 2 Estimated change in prescription volumes at March 2020 without auto-regression ARIMA (0,0,0), Confidence intervals (CI)

Estimated slope (per month) BEFORE March 2020	**Parameter Estimate**	**Standard Error**	**t-statistic**	**p-value**	**Lower CI**	**Upper CI**
Sulfasalazine-Model_1	5435	27256	0.199	0.844	-51247.9	62118.12
Hydroxychloroquine sulfate-Model_2	-10955	14016	-0.782	0.445	-40102.8	18192.08
Azathioprine-Model_3	-12052	11839	-1.018	0.322	-36671.8	12568.47
Methotrexate-Model_4	7966	11727	0.679	0.506	-16420.9	32353.89
Leflunomide-Model_5	561	1666	0.337	0.740	-2903.27	4025.521
Post vs Pre effect	**Parameter Estimate**	**Standard Error**	**t**	**p-value**		
Sulfasalazine-Model_1	2179999	1138801	1.914	0.072	-188267	4548266
Hydroxychloroquine sulfate-Model_2	1411431	585611	2.41	0.027	193586	2629275
Azathioprine-Model_3	1284202	494659	2.596	0.018	255502.6	2312902
Methotrexate-Model_4	477343	489993	0.974	0.343	-541652	1496339
Leflunomide-Model_5	72620	69605	1.043	0.311	-72131.2	217372.1
Estimated slope (per month) AFTER February 2020	**Parameter Estimate**	**Standard Error**	**t**	**p-value**		
Sulfasalazine-Model_1	-131622	69041	-1.906	0.073	-275201	11957.49
Hydroxychloroquine sulfate-Model_2	-61802	35503	-1.741	0.099	-135635	12031.47
Azathioprine-Model_3	-63144	29989	-2.106	0.050	-125509	-777.635
Methotrexate-Model_4	-25041	29706	-0.843	0.410	-86818.1	36736.81
Leflunomide-Model_5	-3808	4220	-0.902	0.379	-12583.3	4968.152

However, there was evidence of a step change for hydroxychloroquine (p-value 0.027) and azathioprine (p-value 0.018), which was statistically significant after March 2020. There was also a change in linearity of the regression slope after March 2020, which was statistically significant for azathioprine (p-value 0.050). Figure 2 presents the model depicting March 2020 as the point of intervention. It is easy to see the change in intercept and slope after the pandemic, especially for azathioprine.

It should be stressed that these p-values only represent a suggestion of an association between temporal change and total prescription quantities, since we are estimating several interrupted time

series models within a general hypothesis of temporal change, and any estimates of effect have not been adjusted for multiplicity.

Hydroxychloroquine statistics also show interesting patterns. Total prescription volumes were charted for hydroxychloroquine on a political timeline against President Trump's claims of safety and efficacy (see Figure 3). Unusually high volumes in March and April 2020 may be due to social networking effects, rather than evidence-based clinical practice.

[Insert Figure 3 here]

By location

Nomenclature for regional territories except London was modified in April 2020, making it difficult to make direct comparisons across regions before and after this period. However sufficient clarity is provided to permit the re-aggregation of the data (April -July 20) to allow for direct comparison (Northwest + North East and Yorkshire= North of England, Midlands = Midlands and East of England, South East + South West= South of England and London).

See Supplementary Table 5 for regional analysis by quantity and cost. Figure 4 summarises the regional prescription volumes.

[Insert Figure 4 here]

Some entries were unidentified by location. Regional descriptive statistics with (Mean, Std. Deviation) convention are presented: North England (6.677, 0.283), Midlands and East of England (7.577, 0.317), South England (6.487, 0.297), London (2.495, 0.126), unidentified (0.002, 0.001). No significant differences were found. Up-to-date population denominators are unavailable (these could have changed during the pandemic), so total quantity reflects differing prevalence in different regions.
More granular analysis was conducted to examine changes to Methotrexate Quantity (Supplementary Table 6) due to its crucial importance in the management and maintenance of disease remission. Research RECORD checklist (Supplementary Table 3) is also included.

Discussion

Our results are concerning and tell us that a significant number of patients may have not used their chronic long-term condition's medicines as they should have, for a variety of reasons. While we cannot be certain, the results of interrupted time series suggest the possibility of a causal relation between the pandemic and that changes to prescription volumes. Our analysis cannot rule out other possible causal explanatory factors, but our results are consistent with possibility that the pandemic may have directly contributed the changes we observe. This provides an early signal for potentially deteriorating medium to longer term health in this group of patients. The results demonstrate a statistically significant level of fluctuation for hydroxychloroquine and azathioprine. There are also worrying trend changes in Sulfasalazine, as it has high circulating volume (approximately 9 million doses per month).

The numbers we present are a fraction of the directly attributable costs of RA management. They do not cover the costs of complications, surgery and onward care including the health-burden borne by family or carers. Regional variations also mean that certain categories of patients are disproportionately affected, having further implications for health inequality.

Why do we use these medicines?

Clinical treatment is intended to relieve the symptoms of RA, achieve disease remission or low disease activity if remission cannot be achieved, and to improve the patient's ability to perform daily

activities. From a public health, primary care perspective, it is important for rheumatoid arthritis patients continue to get their medicines regularly and adhere to the treatment plans to ensure disease progression is as delayed as feasibly possible.

For the first time, we present data on prescription and regional variations during this pandemic for medicines licensed for the treatment of RA. These medicines also carry other licenced use (e.g., pain, Crohn's disease), so our analysis is more generalised for the patient populations we describe and is not specific to RA patients.

Adherence and the patient story

Adherence concerns and access to timely prescription refills may or may not occur for a variety of reasons including not being able to go to the doctor's surgery or pharmacies because of shielding or self-isolation during the pandemic. Also, many surgeries stopped seeing patient face-to-face and substituted these with digital services. The first point of patient contact was the 111 telephone triage services (run by allied professionals) which became overwhelmed.[19,20] Telephone triage may have substituted for the standard practice of a physical examination or annual review. In such events, patients may have had limited access to services, either because of not knowing how to access them digitally or failing to prioritise them.

While the pandemic has provided an opportunity for digital consultations and remote supervision, they have come with added uncertainty and anxiety for patients. Changes to routine has the potential for negative consequences on chronic long-term condition sufferers. Digital consultations have the potential to create a digital barriers to care. This may be especially problematic for elderly patients who suffer from RA and can be frail or infirm because of their condition as well as the immunosuppressant's (e.g., DMARDs) that they use. As a result, there may be instances across the country where patients have inadequate disease control, where underlying complications may escalate.

Strengths and weaknesses

There are several strengths and limitations to this observational study. For the first time, we report the impact on prescription volumes of medicines licenced for RA in England during a global pandemic. Strengths of this study include being evidence-based on real world data. One of the strengths of ITS studies is that they are generally unaffected by typical confounding variables which remain fairly constant, such as population age distribution or socioeconomic status, as these only change relatively slowly over time. Nevertheless, ITS can be affected by time-varying confounders that change more rapidly.[21] Confirmed diagnoses or prescription indications as well as linked data were unavailable to us. While this analysis provides important insight, it can only be descriptive and further work is needed to explore the underlying reasons for the trends observed and the implications for patients.

Limitations pertain to the timeframe, completeness, and quality of the data. We have extracted government data however, they have not been independently verified as complete, accurate and subject to revision. The analysis is descriptive with no adjustments, for changes in population structure (age, disease prevalence, social deprivation scores) which could impact prescriptions between periods and within regions. Hospital statistics are not represented in our analysis.

Future studies

This study generates an early warning signal from real-world data on patients' lives. Future studies must consider the impact on patients' lives with respect to disease progression, including over the life course of this pandemic. It is important to consider subsequent periods and interval between lockdowns to fully assess the potential impact to patients. Future studies may also look to examine

statistics of routine safety blood tests to check for bone marrow suppression, if they have been done and at what frequency. Similarly, markers of disease progression should be examined.

Conclusion

A worrying change in trend is observed for all medicines that were studied. The trend overall is downwards which raises concerns for the longer-term care of rheumatoid arthritis patients. We know that not taking medication is likely to result in increased morbidity and mortality in this patient group. Extra effort may be needed to help these patients.

Acknowledgments.

We thank the NHS business services authority staff who helped with the several information requests.

Contributors:

Lead author conducted the literature search, study conception and design data analysis, statistical analysis and interpretation of data, manuscript preparation, editing and revision and submitted the final version of the paper. RB provided technical expertise with data extraction, cleaning, manipulation and data for final analysis. DC acted as the principal medical statistician on the study and was the statistical analysis lead. SL advised on statistical techniques. SF provided a public health perspective of the likely impact and considered ways to improve community public health. CE considered the clinical impact and consequences of our findings on this patient population.

Funding: no special funding was provided for the study.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf

and declare: no financial relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: Original data are available from https://www.nhsbsa.nhs.uk/prescription-data/prescribing-data/english-prescribing-data-epd No additional data available.

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

References

1. Boots AMH, Maier AB, Stinissen P, et al. The influence of ageing on the development and management of rheumatoid arthritis. *Nat Rev Rheumatol* 2013; 9: 604–613.

2. Gabriel SE, Crowson CS, Campion ME, et al. Indirect and nonmedical costs among people with rheumatoid arthritis and osteoarthritis compared with nonarthritic controls. *J Rheumatol* 1997; 24: 43–48.

3. Gabriel SE, Crowson CS, Campion ME, et al. Direct medical costs unique to people with arthritis. *J Rheumatol* 1997; 24: 719–725.

4. Cross MJ, March LM, Lapsley HM, et al. Patient self-efficacy and health locus of control: relationships with health status and arthritis-related expenditure. *Rheumatol Oxf Engl* 2006; 45: 92–96.

5. Callahan LF. The burden of rheumatoid arthritis: facts and figures. *J Rheumatol Suppl* 1998; 53: 8–12.

6. Yelin E. The costs of rheumatoid arthritis: absolute, incremental, and marginal estimates. *J Rheumatol Suppl* 1996; 44: 47–51.

7. Littlejohn EA, Monrad SU. Early Diagnosis and Treatment of Rheumatoid Arthritis. *Prim Care Clin Off Pract* 2018; 45: 237–255.

8. Abualfadl E, Ismail F, Shereef RRE, et al. Impact of COVID-19 pandemic on rheumatoid arthritis from a Multi-Centre patient-reported questionnaire survey: influence of gender, rural-urban gap and north-south gradient. *Rheumatol Int*. Epub ahead of print 1 November 2020. DOI: 10.1007/s00296-020-04736-9.

9. National Institute for Health and Care Excellence. COVID-19 rapid guideline: rheumatological autoimmune, inflammatory and metabolic bone disorders Guidance, https://www.nice.org.uk/guidance/ng167 (accessed 10 August 2020).

10. Hughes DA. Medicines Shortages in the United Kingdom. *Clin Pharmacol Ther* 2019; 106: 712–712.

11. Batista A, Miljković N, Polidori P, et al. Medicines shortages. *Eur J Hosp Pharm* 2019; 26: 290–291.

12. Miljković N, Gibbons N, Batista A, et al. Results of EAHP's 2018 Survey on Medicines Shortages. *Eur J Hosp Pharm Sci Pract* 2019; 26: 60–65.

13. Acosta A, Vanegas EP, Rovira J, et al. Medicine Shortages: Gaps Between Countries and Global Perspectives. *Front Pharmacol* 2019; 10: 763.

14. European Medicines Agency. Medicines - Shortages. *European Medicines Agency*, https://www.ema.europa.eu/en/medicines/ema_group_types/ema_document-supply_shortage/field_ema_shortage_status/1/field_ema_shortage_status/0 (accessed 10 August 2020).

15. English Prescribing Dataset (EPD) - Open Data Portal BETA, https://opendata.nhsbsa.net/dataset/english-prescribing-data-epd (accessed 25 April 2020).

16. Barrett R, Barrett R, Dhar K, et al. Gonadorelins adherence in prostate cancer: A time-series analysis of England's national prescriptions during the COVID-19 pandemic (from Jan 2019 to Oct 2020). *BJUI Compass*. Epub ahead of print 19 August 2021. DOI: 10.1002/bco2.101.

17. Cochrane Effective Practice and Organisation of Care (EPOC). Interrupted time series (ITS) analyses. EPOC Resources for review authors, epoc.cochrane.org/resources/epoc-specific-resources-review-authors (2017).

18. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015; 12: e1001885.

19. Without more nurses, NHS 111 staff could be 'overwhelmed'. *Emerg Nurse* 2015; 23: 6–6.

20. Osamor K. I warned parliament that NHS 111 would never be able to cope. *The Guardian*, 23 April 2020, https://www.theguardian.com/commentisfree/2020/apr/23/nhs-111-crisis-coronavirus-pandemic (23 April 2020, accessed 9 June 2020).

21. Lopez Bernal J, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol* 2016; dyw098.

Figure 1 Box plot representing mean values before the pandemic and after its onset. Quantities are presented in absolute numbers.

Figure 2 ARIMA (0,0,0)(0,0,0) Prescription volumes for individual medicines (a)Sulfasalazine; (b)Hydroxychloroquine sulfate; (c)Azathioprine; (d)Methotrexate; (e)Leflunomide.

Figure 3 UK prescription quantities of hydroxychloroquine are presented in red-text within parenthesis in a political timeline, (President Trump vs. Hydroxychloroquine).

Figure 4 Monthly regional distribution (higher March and lower May 2020 quantities of RA medicines are presented in the callouts).

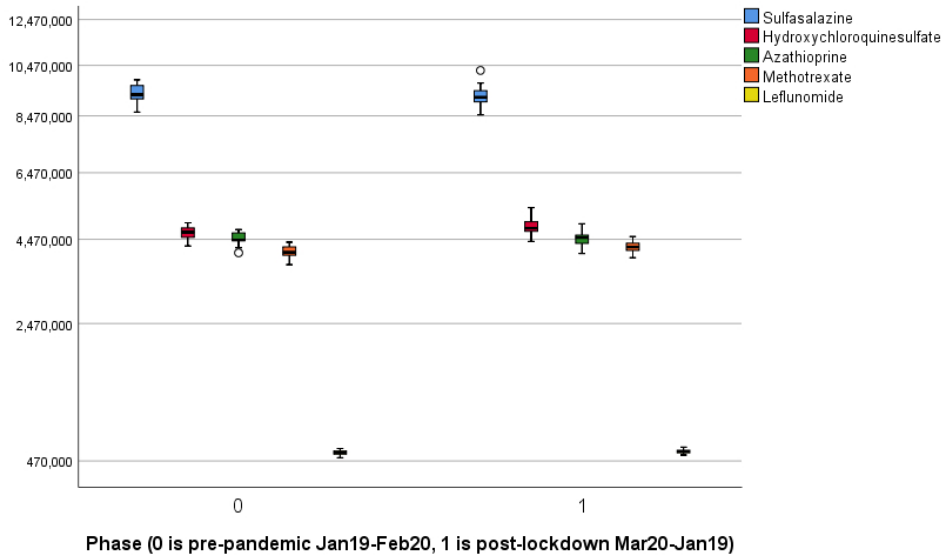

Figure 1 Box plot representing mean values before the pandemic and after its onset. Quantities are presented in absolute numbers.

300x176mm (72 x 72 DPI)

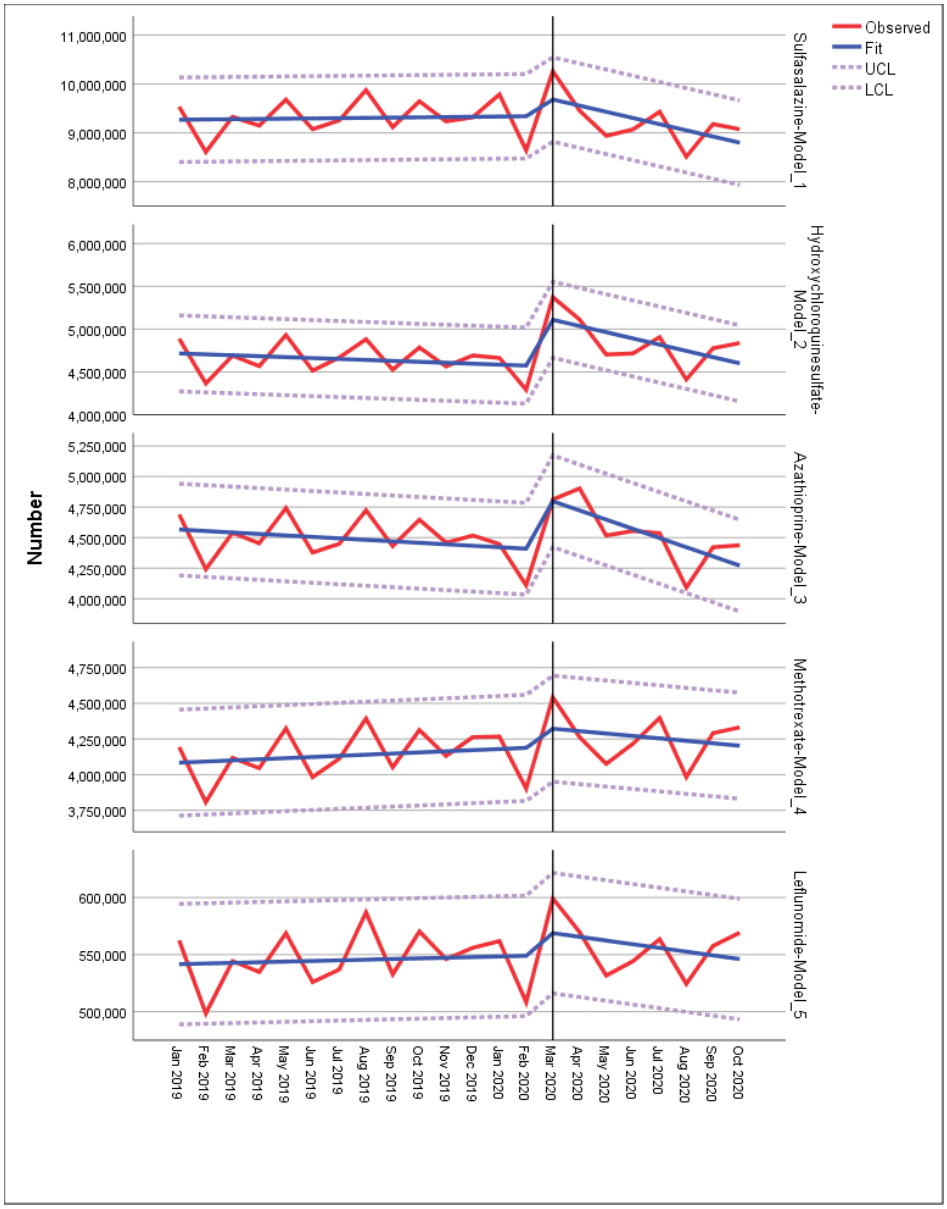

Figure 2 ARIMA (0,0,0)(0,0,0) Prescription volumes for individual medicines (a)Sulfasalazine; (b)Hydroxychloroquine sulfate; (c)Azathioprine; (d)Methotrexate; (e)Leflunomide.

272x347mm (72 x 72 DPI)

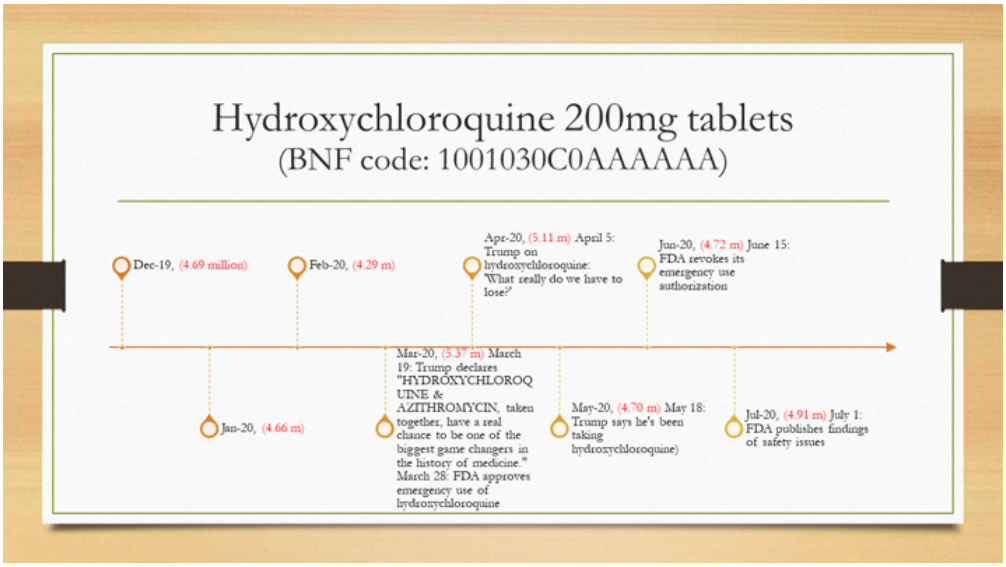

Figure 3 UK prescription quantities of hydroxychloroquine are presented in red-text within parenthesis in a political timeline, (President Trump vs. Hydroxychloroquine).

189x105mm (96 x 96 DPI)

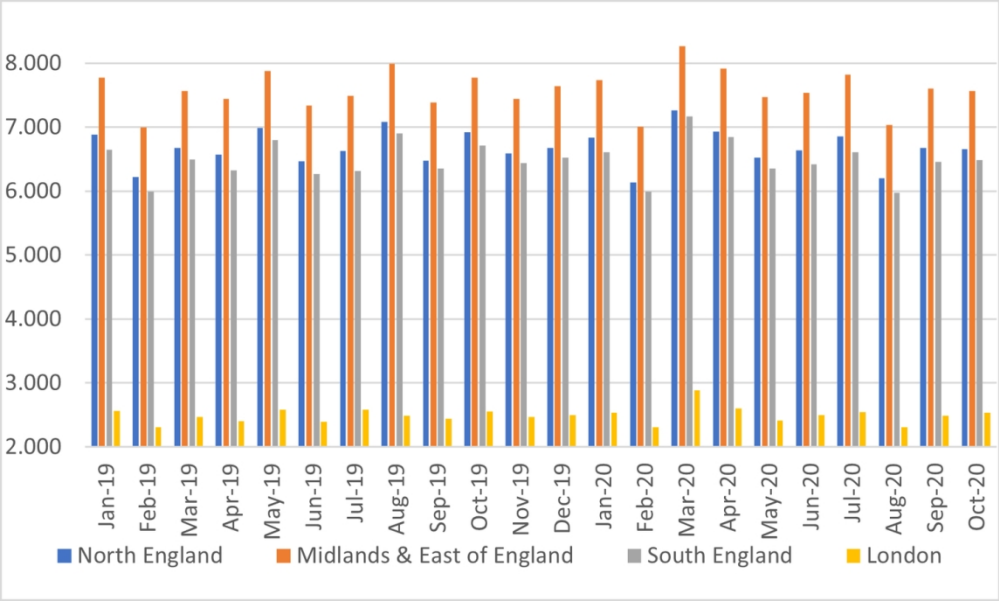

Figure 4 Monthly regional distribution (higher March and lower May 2020 quantities of RA medicines are presented in the callouts).

127x76mm (300 x 300 DPI)

Supplementary Table 1 - ARIMA Syntax (Mar20-1) Jan 19 to Jan 21

```
* Encoding: UTF-8.

DATASET ACTIVATE DataSet3.
PREDICT THRU END.
* Time Series Modeler.
TSMODEL
  /MODELSUMMARY  PRINT=[MODELFIT]
  /MODELSTATISTICS  DISPLAY=YES MODELFIT=[ SRSQUARE]
  /MODELDETAILS  PRINT=[ PARAMETERS]
  /SERIESPLOT OBSERVED FIT FORECASTCI FITCI
  /OUTPUTFILTER DISPLAY=ALLMODELS
  /SAVE  PREDICTED(Predicted) LCL(LCL) UCL(UCL)
  /AUXILIARY  CILEVEL=95 MAXACFLAGS=24
  /MISSING USERMISSING=EXCLUDE
  /MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
e
   INDEPENDENT=TimePeriod Phase Interact
    PREFIX='Model'
  /ARIMA AR=[1]  DIFF=0  MA=[0]
    TRANSFORM=NONE  CONSTANT=YES
  /AUTOOUTLIER DETECT=OFF.

PREDICT THRU END.
* Time Series Modeler.
TSMODEL
  /MODELSUMMARY  PRINT=[MODELFIT]
  /MODELSTATISTICS  DISPLAY=YES MODELFIT=[ SRSQUARE]
  /MODELDETAILS  PRINT=[ PARAMETERS]
  /SERIESPLOT OBSERVED FIT FORECASTCI FITCI
  /OUTPUTFILTER DISPLAY=ALLMODELS
  /SAVE  PREDICTED(Predicted) LCL(LCL) UCL(UCL)
  /AUXILIARY  CILEVEL=95 MAXACFLAGS=24
  /MISSING USERMISSING=EXCLUDE
  /MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
e
   INDEPENDENT=TimePeriod Phase Interact
    PREFIX='Model'
  /ARIMA AR=[0]  DIFF=1  MA=[0]
    TRANSFORM=NONE  CONSTANT=YES
  /AUTOOUTLIER DETECT=OFF.

PREDICT THRU END.
* Time Series Modeler.
TSMODEL
  /MODELSUMMARY  PRINT=[MODELFIT]
  /MODELSTATISTICS  DISPLAY=YES MODELFIT=[ SRSQUARE]
  /MODELDETAILS  PRINT=[ PARAMETERS]
  /SERIESPLOT OBSERVED FIT FORECASTCI FITCI
  /OUTPUTFILTER DISPLAY=ALLMODELS
  /AUXILIARY  CILEVEL=95 MAXACFLAGS=24
  /MISSING USERMISSING=EXCLUDE
```

```
  /MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
e
   INDEPENDENT=TimePeriod Phase Interact
    PREFIX='Model'
  /ARIMA AR=[0]  DIFF=0  MA=[1]
    TRANSFORM=NONE  CONSTANT=YES
  /AUTOOUTLIER DETECT=OFF.

PREDICT THRU END.
* Time Series Modeler.
TSMODEL
  /MODELSUMMARY  PRINT=[MODELFIT]
  /MODELSTATISTICS  DISPLAY=YES MODELFIT=[ SRSQUARE]
  /MODELDETAILS  PRINT=[ PARAMETERS]
  /SERIESPLOT OBSERVED FIT FORECASTCI FITCI
  /OUTPUTFILTER DISPLAY=ALLMODELS
  /AUXILIARY  CILEVEL=95 MAXACFLAGS=24
  /MISSING USERMISSING=EXCLUDE
  /MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
e
   INDEPENDENT=TimePeriod Phase Interact
    PREFIX='Model'
  /ARIMA AR=[0]  DIFF=0  MA=[0]
    TRANSFORM=LN  CONSTANT=YES
  /AUTOOUTLIER DETECT=OFF.
```

Supplementary Table 2 - Sensitivity analysis (Mar20-1) Jan 19 to Jan 21

ARIMA Model Parameters | ARIMA (March20+ is a '1') | Total Quantities
14 months (Jan-19 to Feb-20) before the COVID-19 first lockdown in England (23rd Mar-20) until 11 months after this date (Mar-20 to Jan-21).

ARIMA(0,0,0), No Transformation	TimePeriod (Before); Phase (Step); Interact (After)	Parameter Estimate	Standard Error	T-stat	P-value
Sulfasalazine-Model_1	TimePeriod	5435	28871	0.188	0.852
Sulfasalazine-Model_1	Phase	659017	875894	0.752	0.46
Sulfasalazine-Model_1	Interact	-38151	50570	-0.754	0.459
Hydroxychloroquinesulfate-Model_2	TimePeriod	-10955	14336	-0.764	0.453
Hydroxychloroquinesulfate-Model_2	Phase	814729	434936	1.873	0.075
Hydroxychloroquinesulfate-Model_2	Interact	-24392	25111	-0.971	0.342
Azathioprine-Model_3	TimePeriod	-12052	12273	-0.982	0.337
Azathioprine-Model_3	Phase	786705	372342	2.113	0.047
Azathioprine-Model_3	Interact	-31340	21497	-1.458	0.16
Methotrexate-Model_4	TimePeriod	7966	11836	0.673	0.508
Methotrexate-Model_4	Phase	249614	359099	0.695	0.495
Methotrexate-Model_4	Interact	-10634	20733	-0.513	0.613
Leflunomide-Model_5	TimePeriod	561	1662	0.338	0.739
Leflunomide-Model_5	Phase	30388	50436	0.603	0.553
Leflunomide-Model_5	Interact	-1188	2912	-0.408	0.687

ARIMA(0,0,0) Natural Logarithm, No Transformation	TimePeriod (Before); Phase (Step); Interact (After)	Parameter Estimate	Standard Error	T-stat	P-value
Sulfasalazine-Model_1	TimePeriod	0.001	0.003	0.179	0.86
Sulfasalazine-Model_1	Phase	0.067	0.094	0.707	0.488
Sulfasalazine-Model_1	Interact	-0.004	0.005	-0.715	0.483
Hydroxychloroquinesulfate-Model_2	TimePeriod	-0.002	0.003	-0.778	0.445
Hydroxychloroquinesulfate-Model_2	Phase	0.163	0.092	1.776	0.09
Hydroxychloroquinesulfate-Model_2	Interact	-0.005	0.005	-0.887	0.385
Azathioprine-Model_3	TimePeriod	-0.003	0.003	-0.986	0.335
Azathioprine-Model_3	Phase	0.171	0.084	2.046	0.053
Azathioprine-Model_3	Interact	-0.007	0.005	-1.404	0.175
Methotrexate-Model_4	TimePeriod	0.002	0.003	0.687	0.499
Methotrexate-Model_4	Phase	0.059	0.086	0.687	0.5
Methotrexate-Model_4	Interact	-0.003	0.005	-0.512	0.614
Leflunomide-Model_5	TimePeriod	0.001	0.003	0.348	0.731
Leflunomide-Model_5	Phase	0.054	0.092	0.584	0.565
Leflunomide-Model_5	Interact	-0.002	0.005	-0.396	0.696

ARIMA(1,0,0), AR	TimePeriod (Before); Phase (Step); Interact (After)	Parameter Estimate	Standard Erro	T-stat	P-value
Sulfasalazine-Model_1	TimePeriod	19759	20233	0.977	0.34
Sulfasalazine-Model_1	Phase	417103	614888	0.678	0.505
Sulfasalazine-Model_1	Interact	-37930	34973	-1.085	0.291
Hydroxychloroquinesulfate-Model_2	TimePeriod	-5175	11041	-0.469	0.644
Hydroxychloroquinesulfate-Model_2	Phase	700712	335790	2.087	0.05
Hydroxychloroquinesulfate-Model_2	Interact	-23233	19100	-1.216	0.238
Azathioprine-Model_3	TimePeriod	-9123	10465	-0.872	0.394
Azathioprine-Model_3	Phase	738472	317473	2.326	0.031
Azathioprine-Model_3	Interact	-31213	18041	-1.73	0.099
Methotrexate-Model_4	TimePeriod	14064	7165	1.963	0.064
Methotrexate-Model_4	Phase	86932	218834	0.397	0.695
Methotrexate-Model_4	Interact	-7128	12399	-0.575	0.572
Leflunomide-Model_5	TimePeriod	1432	1106	1.295	0.21
Leflunomide-Model_5	Phase	11071	33718	0.328	0.746
Leflunomide-Model_5	Interact	-882	1912	-0.461	0.649

the coefficient for 'time' gives us the slope of the regression line pre-intervention
the coefficient for 'phase' gives us the change in intercept
the coefficient for 'interact' gives us the change in slope pre and post intervention

If the coefficient for time is β1, for phase is β2 and for interact is β3 then the regression model is:

Therefore, pre intervention becomes:

Outcome = constant + β1time

Outcome= constant + β1time + β2 + β3interact = (constant + β2) + (β1 + β3) time
(as time and interact are the same post intervention)

ARIMA(0,1,0), Difference	TimePeriod (Before); Phase (Step); Interact (After)	Parameter Estimate	Standard Erro	T-stat	P-value
Sulfasalazine-Model_1	TimePeriod	-16503	54217	-0.304	0.764
Sulfasalazine-Model_1	Phase	446642	1491083	0.3	0.768
Sulfasalazine-Model_1	Interact	-5626	88335	-0.064	0.95
Hydroxychloroquinesulfate-Model_2	TimePeriod	-4262	29227	-0.146	0.886
Hydroxychloroquinesulfate-Model_2	Phase	712710	803796	0.887	0.386
Hydroxychloroquinesulfate-Model_2	Interact	-29016	47618	-0.609	0.549
Azathioprine-Model_3	TimePeriod	-6734	23232	-0.29	0.775
Azathioprine-Model_3	Phase	573262	638927	0.897	0.38
Azathioprine-Model_3	Interact	-21531	37851	-0.569	0.576
Methotrexate-Model_4	TimePeriod	-6809	23305	-0.292	0.773
Methotrexate-Model_4	Phase	439338	640948	0.685	0.501
Methotrexate-Model_4	Interact	-15532	37971	-0.409	0.687
Leflunomide-Model_5	TimePeriod	-753	3188	-0.236	0.816
Leflunomide-Model_5	Phase	58732	87689	0.67	0.511
Leflunomide-Model_5	Interact	-2093	5195	-0.403	0.691

Total Quantities
11 months after this date (Mar-20 to Jan-21).

ARIMA(0,0,1), MA	TimePeriod (Before); Phase (Step); Interact (After)	Parameter Estimate	Standard Erro	T-stat	P-value
Sulfasalazine-Model_1	TimePeriod	27834	9982	2.788	0.011
Sulfasalazine-Model_1	Phase	459301	421006	1.091	0.288
Sulfasalazine-Model_1	Interact	-50867	21544	-2.361	0.028
Hydroxychloroquinesulfate-Model_2	TimePeriod	1157	5185	0.223	0.826
Hydroxychloroquinesulfate-Model_2	Phase	637368	207951	3.065	0.006
Hydroxychloroquinesulfate-Model_2	Interact	-26929	10730	-2.51	0.021
Azathioprine-Model_3	TimePeriod	-2278	4740	-0.481	0.636
Azathioprine-Model_3	Phase	660176	167979	3.93	0.001
Azathioprine-Model_3	Interact	-34495	8907	-3.873	0.001
Methotrexate-Model_4	TimePeriod	18549	3714	4.994	0.00007
Methotrexate-Model_4	Phase	27587	116695	0.236	0.816
Methotrexate-Model_4	Interact	-8773	5851	-1.499	0.149
Leflunomide-Model_5	TimePeriod	2037	543	3.754	0.001
Leflunomide-Model_5	Phase	-1004	18464	-0.054	0.957
Leflunomide-Model_5	Interact	-931	985	-0.945	0.356

We considered monthly quantities in the time period defined by 14 months (Jan-19 to Feb-20) before the COVID-19 first lockdown in England (23rd Mar-20) until 11 months after this date (Mar-20 to Jan-21).

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title and abstract PG 1 Title and abstract PG 1 N/A
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			In Introduction section (pg 4-)
Objectives	3	State specific objectives, including any prespecified hypotheses			End of Introduction section (pg 5)
Methods					

Study Design	4	Present key elements of study design early in the paper			PG 5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			PG 5-6
Participants	6	*(a) Cohort study*- Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*- Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*- Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study*- For matched studies, give matching criteria and number of exposed and unexposed		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	PG 5-6 Pg 5 N/A

		Case-control study- For matched studies, give matching criteria and the number of controls per case			
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	PG 5-6, See Supplementary Table 3 - Quantity & Cost Supplementary Table 4 - Region Supplementary Table 5 - Methotrexate Quantity
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			PG 5-6, Pg 10, Original data are available from https://www.nhsbsa.nhs.uk/prescription-data/prescribing-data/english-prescribing-data-epd
Bias	9	Describe any efforts to address potential sources of bias			N/A
Study size	10	Explain how the study size was arrived at			PG 5

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			PG 5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study*- If applicable, explain how loss to follow-up was addressed *Case-control study*- If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*- If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			PG 5
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	PG 5

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	PG 5
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	None, N/A. Data Source.
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	N/A

Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study*- summarise follow-up time (*e.g.*, average and total amount)			Results, Table 1 PG 6
Outcome data	15	*Cohort study*- Report numbers of outcome events or summary measures over time *Case-control study*- Report numbers in each exposure			Results, Table 1 PG 6
		category, or summary measures of exposure *Cross-sectional study*- Report numbers of outcome events or summary measures			

Main results	16	(a) Give unadjusted estimates and, if applicable, confounder- adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (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			Pg 7-8 Supplementary Table 3 - Quantity & Cost Supplementary Table 4 - Region Supplementary Table 5 - Methotrexate Quantity
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			Pg 7-8, Supplementary Table 1 - ARIMA Syntax (Mar20-1) Jan 19 to Jan 21 Supplementary Table 2 - Sensitivity analysis (Mar20-1) Jan 19 to Jan 21
Discussion					
Key results	18	Summarise key results with reference to study objectives			PG 8

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	PG 9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			PG 9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results			PG 8-10
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			PG 10

Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Supplementary Table 1 - ARIMA Syntax (Mar20-1) Jan 19 to Jan 21 Supplementary Table 2 - Sensitivity analysis (Mar20-1) Jan 19 to Jan 21

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

Supplementary Table 4 - Quantity & Cost

Supplemental Results (Total Quantity)

CHEMICAL_SUBSTANCE	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Trend
Sulfasalazine	9.54	8.61	9.33	9.15	9.68	9.07	9.26	9.88	9.12	9.65	9.23	9.32	9.79	8.64	10.26	9.45	8.94	9.08	9.43	8.51	9.18	9.07	8.89	9.75	9.38	
Hydroxychloroquine sulfate	4.89	4.37	4.69	4.57	4.93	4.51	4.67	4.88	4.52	4.79	4.56	4.69	4.66	4.29	5.37	5.11	4.70	4.78	4.91	4.41	4.78	4.84	4.66	5.02	4.68	
Azathioprine	4.69	4.24	4.54	4.45	4.74	4.38	4.45	4.72	4.43	4.65	4.46	4.52	4.45	4.11	4.81	4.90	4.52	4.52	4.54	4.09	4.42	4.44	4.27	4.62	4.30	
Methotrexate	4.19	3.81	4.12	4.05	4.32	3.98	4.11	4.39	4.05	4.31	4.13	4.26	4.27	3.90	4.54	4.26	4.08	4.21	4.40	3.98	4.29	4.33	4.18	4.55	4.17	
Leflunomide	0.56	0.50	0.54	0.53	0.57	0.53	0.54	0.59	0.53	0.57	0.55	0.56	0.56	0.51	0.60	0.57	0.53	0.53	0.56	0.52	0.56	0.57	0.55	0.59	0.55	

Table 1 Total Quantity; Monthly Subtotal (in millions)

Supplemental Results (Actual Cost)

Medicine	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Trend
Sulfasalazine	0.62	0.56	0.61	0.60	0.64	0.60	0.60	0.66	0.61	0.64	0.62	0.62	0.65	0.58	0.68	0.61	0.57	0.60	0.70	0.64	0.69	0.69	0.73	0.82	0.81	
Hydroxychloroquine sulfate	0.30	0.27	0.29	0.28	0.39	0.49	0.45	0.45	0.38	0.37	0.35	0.36	0.54	0.50	0.62	0.77	0.55	0.49	0.51	0.46	0.50	0.54	0.53	0.56	0.57	
Azathioprine	0.19	0.17	0.18	0.20	0.21	0.19	0.20	0.23	0.21	0.22	0.21	0.22	0.32	0.20	0.56	0.59	0.47	0.43	0.27	0.24	0.26	0.24	0.23	0.24	0.25	
Methotrexate	3.27	3.12	3.45	3.43	3.73	3.52	3.75	4.01	3.85	4.15	4.02	4.21	4.29	3.96	4.70	4.47	4.26	4.04	4.67	4.33	4.65	4.68	4.56	4.94	4.63	
Leflunomide	0.12	0.10	0.11	0.11	0.12	0.11	0.11	0.13	0.12	0.12	0.12	0.12	0.12	0.11	0.12	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.09	0.10	0.09	

Table 2 Actual Cost; Monthly Subtotal (in £millions)

Supplementary Table 5 - Region

Total Quantity by region	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Trend
North West + North East and Yorkshire,	6.88	6.22	6.68	6.57	6.99	6.47	6.63	7.08	6.47	6.92	6.59	6.68	6.84	6.13	7.26	6.93	6.53	6.64	6.86	6.2	6.68	6.66	6.43	7.01	6.54	
Midlands + East of England,	7.77	7.	7.57	7.44	7.87	7.34	7.49	7.99	7.39	7.78	7.45	7.64	7.74	7.01	8.27	7.92	7.47	7.54	7.82	7.04	7.6	7.56	7.36	8.03	7.57	
South East + South West	6.65	6.	6.5	6.33	6.79	6.27	6.32	6.9	6.36	6.71	6.44	6.53	6.61	6.	7.17	6.84	6.35	6.42	6.61	5.98	6.46	6.49	6.35	6.88	6.5	
London	2.57	2.3	2.47	2.41	2.59	2.39	2.58	2.49	2.44	2.55	2.46	2.5	2.54	2.31	2.89	2.61	2.42	2.5	2.55	2.31	2.49	2.54	2.4	2.6	2.47	
UNIDENTIFIED	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.01	0.	
Monthly Subtotal	23.87	21.52	23.22	22.75	24.25	22.48	23.02	24.46	22.66	23.96	22.94	23.35	23.73	21.45	25.59	24.3	22.77	23.1	23.84	21.52	23.23	23.25	22.54	24.52	23.08	

Table 3 Total Quantity in millions by region

Actual Cost by region	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Trend		t-test (North vs. Total)
North West + North East and Yorkshire,	1.11	1.03	1.12	1.12	1.23	1.2	1.24	1.33	1.25	1.32	1.25	1.3	1.4	1.25	1.57	1.53	1.39	1.42	0.82	0.74	0.79	0.79	0.77	0.84	0.8		P-value	9.99E-35
Midlands + East of England,	1.49	1.41	1.56	1.55	1.7	1.64	1.73	1.84	1.76	1.9	1.83	1.92	2.06	1.88	2.3	2.29	2.09	2.15	2.19	2.01	2.17	2.17	2.16	2.31	2.23			
South East + South West	1.68	1.59	1.75	1.73	1.91	1.81	1.86	2.04	1.91	2.03	1.98	2.05	2.15	1.95	2.44	2.34	2.15	2.24	2.28	2.13	2.26	2.32	2.26	2.48	2.33			
London	0.22	0.2	0.22	0.22	0.25	0.26	0.27	0.26	0.25	0.27	0.25	0.26	0.31	0.27	0.38	0.38	0.31	0.32	0.31	0.29	0.31	0.32	0.31	0.33	0.33			
UNIDENTIFIED	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.			
Monthly Subtotal	4.51	4.23	4.64	4.62	5.09	4.91	5.11	5.47	5.17	5.51	5.32	5.53	5.91	5.35	6.69	6.54	5.95	6.13	5.6	5.17	5.54	5.59	5.5	5.96	5.68			

Table 4 Actual Cost in £millions by region

Supplementary Table 6 - Methotrexate Quantity (in millions)

BNF_DESCRIPTION	BNF_CODE	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21
Methotrexate 5mg/2ml solution for injection vials	1001030U0AAABAB	3.928	3.556	3.842	3.776	4.03	3.709	3.821	4.087	3.757	4.	3.828	3.948	3.949	3.608	4.195	3.934	3.763	3.89	4.059	3.67	3.958	3.993	3.851	4.191	3.84
Methotrexate 50mg/2ml solution for injection vials	1001030U0BEARBW	0.055	0.053	0.059	0.058	0.064	0.06	0.065	0.069	0.067	0.072	0.07	0.074	0.075	0.07	0.083	0.079	0.076	0.078	0.082	0.077	0.082	0.084	0.081	0.088	0.082
Methotrexate 1g/10ml solution for injection vials	1001030U0BEARBW	0.055	0.053	0.059	0.058	0.064	0.06	0.065	0.069	0.067	0.072	0.07	0.074	0.075	0.07	0.083	0.079	0.076	0.078	0.082	0.077	0.082	0.084	0.081	0.088	0.082
Methotrexate 20mg/0.8ml inj pre-filled syringes	1001030U0BEAWCB	0.037	0.036	0.041	0.04	0.044	0.042	0.045	0.048	0.048	0.051	0.05	0.054	0.053	0.049	0.06	0.056	0.054	0.056	0.06	0.055	0.06	0.06	0.059	0.064	0.06
Methotrexate 22.5mg/0.9ml inj pre-filled syringes	1001030U0BEAWCB	0.037	0.036	0.041	0.04	0.044	0.042	0.045	0.048	0.048	0.051	0.05	0.054	0.053	0.049	0.06	0.056	0.054	0.056	0.06	0.055	0.06	0.06	0.059	0.064	0.06
Methotrexate 25mg/1ml inj pre-filled syringes	1001030U0BEAXCC	0.036	0.035	0.04	0.04	0.043	0.04	0.044	0.046	0.044	0.049	0.045	0.048	0.048	0.046	0.054	0.052	0.049	0.052	0.054	0.051	0.054	0.056	0.053	0.058	0.055
Methotrexate 10mg/0.4ml inj pre-filled syringes	1001030U0BEAXCC	0.036	0.035	0.04	0.04	0.043	0.04	0.044	0.046	0.044	0.049	0.045	0.048	0.048	0.046	0.054	0.052	0.049	0.052	0.054	0.051	0.054	0.056	0.053	0.058	0.055
Methotrexate 7.5mg/0.3ml inj pre-filled syringes	1001030U0BEAZCE	0.016	0.017	0.018	0.017	0.02	0.019	0.02	0.021	0.021	0.022	0.022	0.022	0.023	0.021	0.025	0.023	0.023	0.023	0.024	0.022	0.024	0.024	0.023	0.025	0.024
Methotrexate 12.5mg/0.5ml inj pre-filled syringes	1001030U0BEAZCE	0.016	0.017	0.018	0.017	0.02	0.019	0.02	0.021	0.021	0.022	0.022	0.022	0.023	0.021	0.025	0.023	0.023	0.023	0.024	0.022	0.024	0.024	0.023	0.025	0.024
Methotrexate 15mg/0.6ml inj pre-filled syringes	1001030U0AAACAC	0.035	0.031	0.032	0.03	0.032	0.029	0.029	0.029	0.027	0.028	0.026	0.026	0.025	0.022	0.025	0.023	0.021	0.022	0.021	0.019	0.019	0.019	0.017	0.02	0.016
Methotrexate 17.5mg/0.7ml inj pre-filled syringes	1001030U0BEAQBV	0.01	0.009	0.01	0.011	0.011	0.011	0.011	0.013	0.012	0.012	0.013	0.013	0.013	0.012	0.015	0.014	0.013	0.014	0.014	0.013	0.015	0.015	0.014	0.016	0.015
Methotrexate 7.5mg/0.3ml inj pre-filled disposable	1001030U0BEAQBV	0.01	0.009	0.01	0.011	0.011	0.011	0.011	0.013	0.012	0.012	0.013	0.013	0.013	0.012	0.015	0.014	0.013	0.014	0.014	0.013	0.015	0.015	0.014	0.016	0.015
Methotrexate 10mg/0.4ml inj pre-filled disposable	1001030U0BEAYCD	0.008	0.009	0.009	0.009	0.01	0.009	0.01	0.01	0.01	0.011	0.011	0.011	0.011	0.011	0.013	0.012	0.011	0.012	0.013	0.012	0.013	0.013	0.013	0.014	0.013
Methotrexate 12.5mg/0.5ml inj pre-filled disposabl	1001030U0BEAYCD	0.008	0.009	0.009	0.009	0.01	0.009	0.01	0.01	0.01	0.011	0.011	0.011	0.011	0.011	0.013	0.012	0.011	0.012	0.013	0.012	0.013	0.013	0.013	0.014	0.013
Methotrexate 15mg/0.6ml inj pre-filled disposable	1001030U0BDAAAB	0.013	0.011	0.012	0.012	0.013	0.011	0.012	0.013	0.012	0.012	0.011	0.012	0.011	0.011	0.013	0.011	0.011	0.011	0.012	0.01	0.01	0.011	0.01	0.011	0.01
Methotrexate 17.5mg/0.7ml inj pre-filled disposabl	1001030U0BEASBX	0.005	0.005	0.006	0.006	0.007	0.006	0.006	0.007	0.006	0.007	0.007	0.007	0.008	0.007	0.009	0.009	0.008	0.008	0.009	0.008	0.009	0.009	0.009	0.009	0.009
Methotrexate 20mg/0.8ml inj pre-filled disposable	1001030U0BEASBX	0.005	0.005	0.006	0.006	0.007	0.006	0.006	0.007	0.006	0.007	0.007	0.007	0.008	0.007	0.009	0.009	0.008	0.008	0.009	0.008	0.009	0.009	0.009	0.009	0.009
Methotrexate 22.5mg/0.9ml inj pre-filled disposabl	1001030U0BEATBY	0.006	0.005	0.006	0.006	0.007	0.006	0.007	0.007	0.007	0.008	0.007	0.008	0.007	0.007	0.008	0.008	0.007	0.008	0.008	0.008	0.008	0.008	0.008	0.009	0.008
Methotrexate 25mg/1ml inj pre-filled disposable de	1001030U0BEATBY	0.006	0.005	0.006	0.006	0.007	0.006	0.007	0.007	0.007	0.008	0.007	0.008	0.007	0.007	0.008	0.008	0.007	0.008	0.008	0.008	0.008	0.008	0.008	0.009	0.008
Zlatal 20mg/0.8ml solution for injection pre-fille	1001030U0AABWBW	0.01	0.009	0.009	0.009	0.01	0.009	0.009	0.009	0.008	0.009	0.008	0.008	0.008	0.007	0.008	0.008	0.007	0.007	0.007	0.006	0.007	0.006	0.006	0.006	0.006
Zlatal 22.5mg/0.9ml inj pre-filled syringes	1001030U0AACCCC	0.006	0.006	0.006	0.006	0.006	0.006	0.006	0.006	0.005	0.006	0.005	0.006	0.005	0.005	0.006	0.005	0.005	0.005	0.005	0.004	0.005	0.004	0.004	0.004	0.004
Zlatal 25mg/1ml solution for injection pre-filled	1001030U0AACBCB	0.006	0.005	0.006	0.006	0.006	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.004	0.005	0.005	0.005	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.004
Zlatal 10mg/0.4ml solution for injection pre-fille	1001030U0AACFCF	0.003	0.003	0.003	0.002	0.002	0.002	0.002	0.002	0.003	0.002	0.003	0.002	0.003	0.003	0.003	0.002	0.003	0.003	0.003	0.002	0.002	0.003	0.003	0.003	0.003
Zlatal 7.5mg/0.3ml inj pre-filled syringes	0801030P0BFAFFS	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.002	0.001	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
Zlatal 12.5mg/0.5ml inj pre-filled syringes	0801030P0BFADFQ	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
Zlatal 15mg/0.6ml solution for injection pre-fille	1001030U0AACECE	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.002	0.003	0.003	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
Zlatal 17.5mg/0.7ml inj pre-filled syringes	0801030P0BFAHFU	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 7.5mg/0.3ml solution for injection pre-fi	1001030U0AABVBV	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.001	0.002	0.001	0.002	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 10mg/0.4ml solution for injection pre-fil	1001030U0AABHBH	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 12.5mg/0.5ml solution for injection pre-f	1001030U0AACDCD	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 15mg/0.6ml solution for injection pre-fil	1001030U0AABXBX	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 17.5mg/0.7ml solution for injection pre-f	1001030U0AABYBY	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 20mg/0.8ml solution for injection pre-fil	1001030U0AABGBG	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.001	0.	0.001	0.001	0.001	0.001	0.001
Nordimet 22.5mg/0.9ml solution for injection pre-f	0801030P0BFABFN	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.001	0.001	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 25mg/1ml solution for injection pre-fille	0801030P0AAFSFS	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Methotrexate 2.5mg tablets	1001030U0AAAEAE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.001	0.	0.	0.	0.	0.001	0.	0.	0.001	0.	0.	0.	0.	0.	0.	0.001
Methotrexate 10mg tablets	1001030U0BGAFBW	0.	0.	0.	0.	0.	0.	0.001	0.	0.	0.001	0.001	0.001	0.	0.	0.001	0.	0.	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Methotrexate 2.5mg/5ml oral liquid	1001030U0BEAVCA	0.	0.	0.	0.	0.	0.	0.	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.
Methotrexate 5mg/5ml oral liquid	1001030U0BEAVCA	0.	0.	0.	0.	0.	0.	0.	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.
Methotrexate 10mg/5ml oral liquid	0801030P0AAFUFU	0.	0.	0.	0.001	0.001	0.001	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.
Methotrexate 7.5mg/5ml oral liquid	0801030P0AAFQFQ	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.	0.001	0.	0.	0.001	0.	0.	0.	0.
Methotrexate 12.5mg/5ml oral liquid	1001030U0AABIBI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 15mg/5ml oral liquid	1001030U0AABFBF	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 20mg/2ml inj pre-filled syringes	0801030P0BFAEFR	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 15mg/1.5ml inj pre-filled syringes	1001030U0BGADCC	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 7.5mg/0.15ml inj pre-filled syringes	1001030U0BGAHCB	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 10mg/0.2ml inj pre-filled syringes	0801030P0AAFEFE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 15mg/0.3ml inj pre-filled syringes	0801030P0BFACFP	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 20mg/0.4ml inj pre-filled syringes	1001030U0AABKBK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 25mg/0.5ml inj pre-filled syringes	0801030P0AAFGFG	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 30mg/0.6ml inj pre-filled syringes	0801030P0AAFNFN	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 12.5mg/0.25ml inj pre-filled syringes	0801030P0BFAAFM	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 17.5mg/0.35ml inj pre-filled syringes	0801030P0AAFKFK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 22.5mg/0.45ml inj pre-filled syringes	1001030U0AABLBL	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 17.5mg/0.35ml inj pre-filled disposab	1001030U0BDABAC	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 20mg/0.4ml inj pre-filled disposable	0801030P0BFAGFT	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 22.5mg/0.45ml inj pre-filled disposab	1001030U0BGABCE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 7.5mg/0.15ml inj pre-filled disposabl	0801030P0AAFRFR	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 27.5mg/0.55ml inj pre-filled disposab	0801030P0BEAAFE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 30mg/0.6ml inj pre-filled disposable	0801030P0AAFPFP	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 25mg/0.5ml inj pre-filled disposable	1001030U0AABEBE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 15mg/0.3ml inj pre-filled disposable	0801030P0BEAGFK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 12.5mg/0.25ml inj pre-filled disposab	1001030U0BEAUBZ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 10mg/0.2ml inj pre-filled disposable	1001030U0BEAUBZ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 2mg/ml oral solution sugar free	0801030P0AAFHFH	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Maxtrex 2.5mg tablets	1001030U0BGAEBV	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Maxtrex 10mg tablets	1001030U0AABMBM	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 20mg/2ml solution for injection pre-fille	0801030P0AAFMFM	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 10mg/1ml solution for injection pre-fille	1001030U0BGACCD	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 15mg/1.5ml inj pre-filled syringes	0801030P0BEACFG	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 25mg/2.5ml inj pre-filled syringes	0801030P0AAFTFT	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 7.5mg/0.15ml inj pre-filled syringes	1001030U0AAAHAH	0.	0.	0.	0.	0.001	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 10mg/0.2ml inj pre-filled syringes	1001030U0BGAPBH	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 15mg/0.3ml inj pre-filled syringes	0801030P0AAFLFL	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 20mg/0.4ml inj pre-filled syringes	1001030U0BGAGBX	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 25mg/0.5ml inj pre-filled syringes	0801030P0AAFFFF	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 12.5mg/0.25ml inj pre-filled syringes	1001030U0BGAABY	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 17.5mg/0.35ml inj pre-filled syringes	0801030P0AAFIFI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 22.5mg/0.45ml inj pre-filled syringes	1001030U0BGARBI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 17.5mg/0.35ml inj pre-filled pens	1001030U0BGAMBG	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 17.5mg/0.35ml inj pre-filled pen	0801030P0AAFJFJ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 20mg/0.4ml inj pre-filled pens	1001030U0AACACA	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 20mg/0.4ml inj pre-filled pen	0801030P0BEADFH	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 22.5mg/0.45ml inj pre-filled pens	0801030P0BEAEFI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 22.5mg/0.45ml inj pre-filled pen	1001030U0AABZBZ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 7.5mg/0.15ml inj pre-filled pen	0801030P0BEAHFL	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 7.5mg/0.15ml inj pre-filled pens	1001030U0BEACBB	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 27.5mg/0.55ml inj pre-filled pens	1001030U0BGAQBM	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 27.5mg/0.55ml inj pre-filled pen	1001030U0BGAUBK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 30mg/0.6ml inj pre-filled pens	0801030P0BEABFF	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 30mg/0.6ml inj pre-filled pen	1001030U0BEAMBL	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 25mg/0.5ml inj pre-filled pens	0801030P0BEAFFJ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 25mg/0.5ml inj pre-filled pen	1001030U0BEAIBH	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 15mg/0.3ml inj pre-filled pen	1001030U0BEAGBF	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 15mg/0.3ml inj pre-filled pens	1001030U0BEAHBG	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 12.5mg/0.25ml inj pre-filled pens	1001030U0BEAJBI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 12.5mg/0.25ml inj pre-filled pen	1001030U0BEALBK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 10mg/0.2ml inj pre-filled pens	1001030U0BGAKBE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 10mg/0.2ml inj pre-filled pen	1001030U0BGANBL	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 7.5mg/0.15ml inj pre-filled injector	1001030U0BEADBC	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill10mg/0.2ml inj pre-filled injector	0801030P0AAAIAI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 12.5mg/0.25ml inj pre-filled injector	0801030P0AAANAN	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 15mg/0.3ml inj pre-filled injector	0801030P0AACKCK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 17.5mg/0.35ml inj pre-filled injector	1001030U0AAAFAF	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 20mg/0.4ml inj pre-filled injector	1001030U0AAAIAI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 22.5mg/0.45ml inj pre-filled injector	1001030U0AAAKAK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 25mg/0.5ml inj pre-filled injector	1001030U0AAARAR	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 27.5mg/0.55ml inj pre-filled injector	1001030U0AABABA	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 7.5mg/0.15ml inj pre-filled syringes	1001030U0AABCBC	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 10mg/0.2ml inj pre-filled syringes	1001030U0AABJBJ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 15mg/0.3ml inj pre-filled syringes	1001030U0BEABBA	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 17.5mg/0.35ml inj pre-filled syringes	1001030U0BEAEBD	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 20mg/0.4ml inj pre-filled syringes	1001030U0BEAFBE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 22.5mg/0.45ml inj pre-filled syringes	1001030U0BEANBM	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 25mg/0.5ml inj pre-filled syringes	1001030U0BGAIBZ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 12.5mg/0.25ml inj pre-filled syringes	1001030U0BGALBF	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
	Sum Total (Methotrexate)	4.368	3.977	4.306	4.232	4.529	4.177	4.321	4.615	4.267	4.546	4.357	4.502	4.508	4.125	4.81	4.516	4.318	4.47	4.661	4.229	4.557	4.6	4.438	4.829	4.439
	Sum of top ten rows (10010	4.253	3.868	4.187	4.116	4.402	4.061	4.197	4.484	4.143	4.415	4.228	4.37	4.374	4.001	4.662	4.378	4.187	4.332	4.52	4.098	4.416	4.459	4.299	4.68	4.299
	% Sum of top ten rows	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%

BMJ Open

Impact of the COVID-19 pandemic on prescription refill of immune mediated inflammatory disorders: A time series analysis (Jan 2019 to Jan 2021) using the English Prescribing Dataset.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051936.R1
Article Type:	Original research
Date Submitted by the Author:	31-Oct-2022
Complete List of Authors:	Barrett, Ravina; University of Brighton, School of Applied Sciences Barrett, Rob; University of Portsmouth Lin, Sharon; University of Southampton, Faculty of Health Sciences Culliford, David; University of Southampton, Faculty of Medicine Fraser, Simon; University of Southampton, Faculty of Medicine Edwards, Christopher; University Hospital Southampton NHS Foundation Trust, Rheumatology
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Immunology (including allergy), Epidemiology, Patient-centred medicine, Oncology
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, COVID-19, EPIDEMIOLOGY, GASTROENTEROLOGY, GERIATRIC MEDICINE, Rheumatology < INTERNAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Impact of the COVID-19 pandemic on prescription refill of immune mediated inflammatory disorders: A time series analysis (Jan 2019 to Jan 2021) using the English Prescribing Dataset.

Short title (40 characters): English DMARDs study.

Author:

1. corresponding author Mrs. Ravina Barrett (https://orcid.org/0000-0003-0004-2131) MPharm, FHEA, MSc Finance, Author affiliations and information:
    a. Senior Lecturer in Pharmacy Practice, School of Pharmacy and Biomolecular Sciences, Cockcroft Building, University of Brighton, Moulsecoomb, Brighton, BN2 4GJ. +44(0)1273643986, R.Barrett2@Brighton.ac.uk
2. Mr. Robert Barrett, MBA, MCSE, MCSA, MCP, ITIL, Prince 2 rob-barrett@outlook.com ; https://orcid.org/0000-0003-3402-3377 Affiliations not disclosed.
3. Dr. Sharon X Lin; research fellow at The School of Primary Care and Population Sciences, Faculty of Medicine, Southampton General Hospital, SO16 6YD, X.Lin@soton.ac.uk
4. Dr. David Culliford, Principal Medical Statistician, NIHR Applied Research Collaboration Wessex, Faculty of Environmental and Life Sciences, University of Southampton, Southampton General Hospital (Room AA71, MP11), Southampton SO16 6YD, Tel + 44 (0) 23 8120 3374, d.j.culliford@soton.ac.uk
5. Dr. Simon Fraser BM. MSc, DM, DRCOG, DCH, MRCGP. Dip, FHEA, MFPH, FFPH. Associate Professor of Public Health; School of Primary Care and Population Sciences, Faculty of Medicine, Southampton General Hospital, SO16 6YD, Tel: 023 81206138 (https://orcid.org/) S.Fraser@soton.ac.uk.
6. Professor Christopher J Edwards BSc, MBBS, MD, FRCP, Consultant Rheumatologist, University Hospital Southampton NHS Foundation Trust, Honorary Chair of Clinical Rheumatology, Professor in Rheumatology, Faculty of Medicine, University of Southampton, Associate Director, Southampton NIHR Wellcome Trust Clinical Research Facility, cedwards@soton.ac.uk

Word count (excluding abstract, references, tables, and figures):

Introduction. 607
Materials and methods. 785
Results. 1470
Discussion.891
Total 3753

Supplementary Table 1 - ARIMA Syntax (Mar20-1) Jan 19 to Jan 21
Supplementary Table 2 - Sensitivity analysis (Mar20-1) Jan 19 to Jan 21
Supplementary Table 3 - Quantity & Cost
Supplementary Table 4 - Region
Supplementary Table 5 - Methotrexate Quantity

Abstract

Objective:

To investigate monthly prescription refills for common immunosuppressive/immunomodulatory therapies: sulfasalazine, hydroxychloroquine sulfate, azathioprine, methotrexate, leflunomide prescriptions in England during the complete first wave of COVID-19 pandemic. Secondary analysis examined unit cost analysis, social media impact and regional use variance.

Design & Setting:

A national cohort of community based, primary care patients who anonymously contribute data to the English Prescribing Dataset Data, dispensed in the community in England were included.

Descriptive statistics and interrupted time series analysis over 25-months (14-months before, 11-months after first lockdown) were evaluated (January-2019 to January-2021, with March-2020 as the cut-off point).

Main Outcome Measures:

Prescription reimbursement variance in period before the pandemic as compared to after the first lockdown.

Results:

Fluctuation in monthly quantity of medicines used are noted in March 2020, where a jump in volume is observed for hydroxychloroquine (p=0.075) and azathioprine (p=0.047). After the first lockdown, medicines use further declined, with wide confidence intervals.

Unit-cost price changed substantially: sulfasalazine 33% increase, hydroxychloroquine 98% increase, azathioprine 41% increase, methotrexate 41% increase, leflunomide 20% decrease. London showed the least variance, suggesting more homogeneous prescribing and patient experiences as compared to the 'Midlands and East of England', suggesting that some patients may have received medication that are substantially over/under requirement, representing a potential misallocation of resources and maybe a proxy for rates of adherence.

Conclusions:

Findings potentially present lower rates of adherence because of the pandemic, suggesting restrictions-imposed barriers to care access.

Unit price increases are likely to have severe budget impacts in the UK and potentially globally. We recommend timely prescription refills for patients taking immunosuppressive/immunomodulatory therapies. Healthcare professionals should identify patients on these medicines and assess their prescription-day coverage, with planned actions to flag and follow-up adherence concerns in patients.

Keywords.

COVID-19; severe acute respiratory syndrome coronavirus 2. COVID-19/SARS-CoV-2 Pandemic; Disparities, rheumatoid arthritis, medicines, pharmacy services, prescriptions

Strengths and limitations of this study.

1. This is a first of its kind work using ARIMA modelling to conduct an interrupted time series analysis on prescription reimbursement data on immunosuppressive/immunomodulatory medicines like sulfasalazine, hydroxychloroquine sulfate, azathioprine, methotrexate, leflunomide between January 2019 to January 2021 using the English Prescribing Dataset.
2. The methodological novelty of this technique during this initial phase of the pandemic provides valuable insights for clinicians, healthcare professionals, policy decision makers and budget holders for crisis humanitarian response.
3. Regional analysis is provided, that examines the variance in the use of selected medications across England.
4. Cost analysis was done to examine underlying unit price changes across time.

Introduction.

In England, all people above the age of 60 years, receive prescription medications free of charge through universal care provisions[1]. The National Health Service (NHS) has been publicly funded since 1948[2] and reimburses primary-care contractors (e.g., general practitioners (GPs), pharmacies, dentists, etc.) through central and local budgets[3]. Consequently, NHS datasets provide a valuable and accurate insight into current practice and the ongoing management of many chronic long-term conditions[4].

Immunosuppressive and immunomodulatory (IMIDs) medicines like sulfasalazine, hydroxychloroquine sulfate, azathioprine, methotrexate, leflunomide are the mainstay for the treatment of many painful conditions of the joints e.g., Rheumatoid arthritis, Psoriatic arthritis, Systemic lupus erythematosus, Spondyloarthritis and related arthritic conditions[5–9]. Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that primarily targets synovial joints, resulting in pain and functional limitations[10] and is an example of a disease in which delays to treatment can lead to considerable damage. It is the most common inflammatory arthritis, and a significant cause of morbidity and mortality[11]. From a primary care perspective, early recognition, along with its extra-articular manifestations, can lead to faster time to treatment and better health outcomes, in addition to preserved joint functionality[12–14].

IMIDs are also used in chronic conditions of the bowels[15–17] (e.g., Crohn's disease, ulcerated colitis, diverticulitis) as well as for anti-rejection therapy[18] when organ transplants or grafts have been used as they supress the autoimmune destruction. These medicines are important because they provide a lifeline towards functional mobility and improves the quality of life[19,20] for patients by relieving their pain as well as retarding disease progression. Other medicines include alkylating agents (e.g., cyclophosphamide), Janus kinase (JAK) inhibitors (e.g., Baricitinib), Phosphodiesterase type-4 (PDE4) inhibitor (e.g., apremilast) and Tumor Necrosis Factor (TNF) - alpha inhibitor (e.g., Adalimumab (Humira®), Etanercept (Enbrel®)) are used for RA.

These medicines are usually taken as chronic long-term medications for the management of such relapsing-remitting autoimmune conditions. Their consistent use provides optimal pain relief and their mechanisms of action mean long-term use dampens the inflammatory cascade response[21–23]. Collectively, this reduces pain, reduces the inflammatory mediators that recruit towards ongoing inflammatory cascades and arrests the autoimmune response. These medications, if not taken properly, can cause loss of disease control and progressing joint destruction with resultant loss of mobility, poorer mental health, and diminished quality of life.

Given increasing life expectancies worldwide, the number of elderly IMIDs patients aregrowing.[24] Comorbidities in elderly patients with RA often include cardiovascular disease, cancer, infections, venous and arterial insufficiency amongst others.[24] From a public health perspective, people with RA have been found to be significantly more likely to have reduced their work hours or stopped working; they are more likely to have lost their job or to have retired early; and are 3 times more likely to have had a reduction in household family income than either individuals with osteoarthritis (OA) or those without arthritis.[25–29] In this way, the economic effects of RA are staggering and emphasize the importance of early recognition and treatment.[30] A study from Egypt suggests that patients with RA faced remarkable difficulty to obtain their medications with subsequent change in their disease status.[31]

The COVID-19 pandemic has meant that many patients in the middle to elderly age category who may suffer from arthritis like conditions may be at higher risk of contracting the virus because of their advanced age, comorbidities, and their dampened immune function. In the United Kingdom

(UK), during the pandemic, patients could not see healthcare professionals in a timely fashion, leading to backlogs even today including operations, cancer waiting, GP referrals and casualty waiting times, with some people waiting over one year for minor operations[32]. The government has outlined how it has learned from mistakes made during the pandemic[33]. However, an independent inquiry into the government's handling of the pandemic is currently underway[34]. Normal care for patients has been affected, as reflected in urgently developed pandemic-guidelines.[35] We also know that there have been supply shortages across the UK[36], Europe and many parts of the world before [37–39] the pandemic and after for many medications during the pandemic (e.g. ibuprofen and paracetamol). The European Medicines Agency (EMA) acknowledges shortage of etanercept (Enbrel®) in pre-filled pens and syringes.[40] The study objective was to examine the effect of the pandemic on prescription prescribing patterns and costs for RA patients in England.

Materials and methods

Data and Resources

The 'English Prescribing Dataset' (EPD)[41] provided anonymised prescription data in England covered by Open Government Licence (OGL). The EPD comprises detailed information on community-issued prescriptions (not hospital) issued in England but dispensed across the UK (England, Wales, Scotland, Guernsey, Alderney, Jersey, and the Isle of Man). It holds detailed prescribing information at practice level, aggregated by British National Formulary (BNF) code e.g., 0105010E0AAABAB for 'Sulfasalazine 500mg gastro-resistant tablets' to maintain patient confidentiality. This data set contains the following variables, amongst others: ,"YEAR_MONTH" e.g., presented as 201901 to represent Jan-19,"CHEMICAL_SUBSTANCE" e.g., Methotrexate, Sulfasalazine, "Chemical Substance" by code e.g., 1001030U0,"BNF_DESCRIPTION" e.g., Metoject PEN 20mg/0.4ml inj pre-filled pens; Sulazine EC 500mg tablets (Genesis Pharm),Related "BNF_CODE" e.g., 1001030U0BEARBW,"REGIONAL_OFFICE_NAME" e.g., East Anglia Area, Wessex Area, North Of England, "STP_NAME" e.g., Greater Manchester Area, "Total Quantity" (in solid dosage),"Actual Cost" (in Great British pounds),"No Items" (representing number of items which provides information on the number of time an item appeared on a prescription entry, which is not to be confused with the total quantity). Therefore, each row of data does not represent individual patients or prescriptions. The data includes total quantity of unit-doses (e.g., tablets, prefilled insulin pens), and 'actual cost' for reimbursement. In the EPD, there is approximately a latency of released data by two months.

The data excludes prescriptions issued outside England (Wales, Scotland, Guernsey, Alderney, Jersey, and the Isle of Man); items not dispensed, disallowed and those returned for further clarification; prescriptions prescribed and dispensed in prisons, hospitals, and private prescriptions; items prescribed but not presented for dispensing or not submitted to NHS prescription services by the dispenser. This dataset included small (487 out of 2,555,396 rows) operational irregularities (e.g., 17 rows in January 2019 of 'unidentified practice data', 470 rows of 'NULL' chemical substance codes, where accurate BNF codes were given to permit extraction of the missing data). The study population represents English residents who were issued a prescription and had it dispensed.

Monthly-data from January 2019 to January 2021were compared for sulfasalazine; hydroxychloroquine sulfate; azathioprine; methotrexate and leflunomide. Sodium aurothiomalate; Anakinra; Baricitinib; Apremilast; Infliximab; Golimumab; Etanercept; Certolizumab pegol abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, Rituximab, sarilumab, tocilizumab, tofacitinib, penicillamine and cyclophosphamide were excluded because they are marginally important (normally used under specialist care and are of small volumes, less than a 1000 units per month).

Formulations not normally be used in RA (E.g., Sulfasalazine suppositories) were excluded as well as all cutaneous products (e.g., creams, gels, medicated plasters, sprays, cutaneous solutions, transdermal patches, topical solutions). Hence, the data contains tablets, oral liquids and injectables (pre-filled syringes, ampoules, vials).

All prescribed medication across the whole of the primary care interface during this period were extracted which included every single prescription item for the related variable indications i.e., 333,459,762 rows of data (99 gigabytes of data) were extracted using Structured Query Language (SQL). Then, these were filtered down to the specific medications under study. Each row represents an aggregated amount of that medication supplied at the general practitioners' practice level and does not represent individual patients, to maintain anonymity. The excluded rows were for all other medications other than the specific medications under study. After excluding unnecessary rows, 8,186,699 relevant rows (2.6 gigabytes of data) were filtered. In total, we imported 25 comma-separated values (CSV) file into a Microsoft SQL® server table labelled EPD. As each one was imported, it was validated and assigned an exact datatype (e.g., 'Total quantity' is a 'floating' data point, 'regional office name' is a textfield) to each field of data. We removed spaces, blanks, checked for wrong kinds of data (e.g., that text characters weren't in a numeric field or purely numeric characters in a textfield). We used Microsoft Visual Studio® to create and edit SQL Server Integration Services® (SSIS) packages that imported, validated and consolidated the data within an automated import routine. Detailed methods have been previously published[42] (in supplemental). Data were aggregated by month, chemical substance, regional office name and BNF code, to allow for human analysis.

The reliable, consistent EDP data allowed for direct monthly comparison. We did not conduct detailed population analysis, and these were assumed to be constant. Patient's diagnoses were unknown. Lockdown commenced on 23rd of March 2020, a second lockdown commenced on 5th November 2020.

Analysis

Analysis was carried out in Excel® v. 2007 and SPSS® v. 26. Results are presented as nominal values, descriptive statistics, and Mann-Whitney U test. Interrupted time series (ITS) analysis was used to fit time trends[43] at the 95% confidence level.

We employed a commonly used time series modelling framework (autoregressive integrated moving average, or ARIMA) to analyse the monthly total-quantity of prescription data. ARIMA is a flexible modelling construct[44–46], allowing lagged correlations and seasonal differences to be modelled, but we used only a simple model with no allowance for serial correlation nor seasonality, mainly due to the lack of data points after the interrupt time point. We had available 25 consecutive monthly data points with the interrupt time set at the 14th month (March 2020), and 14 data points before and 11 data points after March 2020 (estimating regression model with unknown breakpoints was done but minimally, because we were using the first lockdown as our clinically important cut-off point[47]). We estimated the difference in prescription total-quantity as at March 2020, and also the difference in the linear trend (i.e. between the slopes of the lines) before and after the interrupt time point. The observed temporal trend in prescription total-quantity was explored visually in advance of performing the main time series analysis. See ARIMA Syntax in Supplementary Table 1. See Sensitivity Analysis in Supplementary Table 2 which also includes log transformation[46,48,49]. Reporting is in line with the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement/RECORD Checklist[50]. Favourable institutional ethical approval was not needed due to the anonymised nature of this dataset analysis because it does not identify any individual patient and this study followed the declaration of Helsinki principles . This data set is covered by the open government licence such that permit the free analysis and reporting of such analysis.

Patient and Public Involvement: patients and members of the public were not involved in the study.

Results

Descriptive statistics can be visualised in Table 1 and Figure 1 for the entire period of study.

[Insert Figure 1 here]

Table 1 Descriptive statistics of the total quantities, presented in millions. The total quantity and actual cost in great British pounds are presented for the whole study duration from January 2019 to January 2021. Standard Deviation (SD).

	Before pandemic				After Pandemic's Onset				Total Quantity		Actual Cost (£)	
Medicine	Mean	SD	UCI	LCI	Mean	SD	UCI	LCI	Mean	SD	Mean	SD
Sulfasalazine	9.303	0.384	9.504	9.102	9.267	0.468	9.544	8.991	9.28	0.422	0.628	0.039
Hydroxychloroquine sulfate	4.645	0.190	4.745	4.545	4.835	0.260	4.989	4.681	4.721	0.247	0.448	0.122
Azathioprine	4.488	0.178	4.581	4.394	4.497	0.234	4.635	4.359	4.505	0.202	0.273	0.123
Methotrexate	4.136	0.169	4.225	4.047	4.272	0.177	4.377	4.168	4.182	0.179	4.046	0.482
Leflunomide	.545	0.025	0.558	0.532	.559	0.023	.573	.545	0.55	0.025	0.111	0.009

By total quantities of medicines

Since the March-lockdown, fluctuations in monthly volumes are observed. See Supplementary Table 3 for Fluctuating total quantities of anti-rheumatics' medicines in millions by quantity and associated price. Hydroxychloroquine use shows great variance, which is supported by the Mann-Whitney two-tailed test (test statistics 84, standard error 14.652, standardised test statistic 1.911, p-value = 0.059) over the study period.

By price of medicines

Costs are presented as nominal pound sterling (GBP) values. Examining the actual cost of medicines shows variation. Mann-Whitney U test for prices of hydroxychloroquine (p-value < 0.001), azathioprine (p-value < 0.001), methotrexate (p-value < 0.001) and leflunomide (p-value = 0.004) reject the null hypothesis that price is same before and after March 2020.

Supplemental material (Supplementary Table 3 - Quantity & Cost) shows that there was a substantial increase in unit cost of medication during this study period as indicated by the analysis below:

1. Sulfasalazine cost the NHS £0.62 million in January 2019 for 9.54 million doses (=£0.065/dose), while it cost £0.81 million in January 2021 for 9.38 million doses (=£0.086 dose), reflecting a 33% unitary cost increase.
2. Hydroxychloroquine sulfate cost the NHS £0.30 million in January 2019 for 4.89 million doses (=£0.062/dose), while it cost £0.57 million in January 2021 for 4.68 million doses (=£0.122/dose), reflecting a 98% unitary cost increase.
3. Azathioprine cost the NHS £0.19 million in January 2019 for 4.69 doses (=£0.041/dose), while it cost £0.25 million in January 2021 for 4.30 million doses (=£0.058/dose), reflecting a 41% unitary cost increase.
4. Methotrexate cost the NHS £3.27 million in January 2019 for 4.19 doses (=£0.781/dose), while it cost £4.63 million in January 2021 for 4.17 million doses (=£1.110/dose), reflecting a 42% unitary cost increase.
5. Leflunomide cost the NHS £0.12 million in January 2019 for 0.56 doses (=£0.205/dose), while it cost £0.09 million in January 2021 for 0.55 million doses (=£0.164/dose), reflecting a 20% unitary cost decrease.

It is presumed that this unit price fluctuation is not consequent to rising inflation (consumer price index, retail price index and central bank base rates were extremely/historically low and stable globally during this period).

Interrupted Time Series (ARIMA Modelling)

Sulfasalazine; Hydroxychloroquine; Azathioprine; Methotrexate; and Leflunomide are the anti-rheumatics medicines most used by total quantity in the study period. ARIMA model can be visualised in Table 2 and Figure 2.

[Insert Figure 2 here]

None of the five medicines showed evidence of a significant difference in the linear trend for monthly prescription statistics before the chosen interrupt time-point (March 2020) when modelled without any seasonal, moving average or autoregressive components, see table 2.

Table 2 Estimated change in prescription volumes at March 2020 without auto-regression ARIMA (0,0,0), Confidence intervals (CI)

Estimated slope (per month) BEFORE March 2020	**Parameter Estimate**	**Standard Error**	**T-statistic**	**P-value**	**Lower CI**	**Upper CI**
Sulfasalazine-Model_1	5435	28871	0.188	0.852	-54151	65021
Hydroxychloroquine sulfate-Model_2	-10955	14336	-0.764	0.453	-40543	18632
Azathioprine-Model_3	-12052	12273	-0.982	0.337	-37382	13278
Methotrexate-Model_4	7966	11836	0.673	0.508	-16462	32395
Leflunomide-Model_5	561	1662	0.338	0.739	-2870	3992
Post vs Pre effect (Step-change)	**Parameter Estimate**	**Standard Error**	**T-statistic**	**P-value**		
Sulfasalazine-Model_1	659017	875894	0.752	0.46	-1148740	2466774
Hydroxychloroquine sulfate-Model_2	814729	434936	1.873	0.075	-82935	1712394
Azathioprine-Model_3	786705	372342	2.113	0.047	18229	1555182
Methotrexate-Model_4	249614	359099	0.695	0.495	-491531	990758
Leflunomide-Model_5	30388	50436	0.603	0.553	-73706	134482
Estimated slope (per month) AFTER February 2020	**Parameter Estimate**	**Standard Error**	**T-statistic**	**P-value**		
Sulfasalazine-Model_1	-38151	50570	-0.754	0.459	-142522	66220
Hydroxychloroquine sulfate-Model_2	-24392	25111	-0.971	0.342	-76219	27434
Azathioprine-Model_3	-31340	21497	-1.458	0.16	-75708	13028
Methotrexate-Model_4	-10634	20733	-0.513	0.613	-53424	32156
Leflunomide-Model_5	-1188	2912	-0.408	0.687	-7198	4822

Step change (also called a level shift) is a sudden, sustained change where the time series is shifted either up or down by a given value immediately following the intervention. The step change variable takes the value of '0' prior to the start of the intervention, and '1' afterwards. From Table 2, there was evidence of a step change for azathioprine (p-value 0.047), which was statistically significant after March 2020. The confidence intervals representing the degree of uncertainty around these numbers have also widened indicating a much wider variability across the country after the pandemic's onset as compared to the prior period. There was also a change in linearity of the regression slope after March 2020.

It should be stressed that these p-values only represent a suggestion of an association between temporal change and total prescription quantities, since we are estimating several interrupted time series models within a general hypothesis of temporal change, and any estimates of effect have not been adjusted for multiplicity. It should be cautiously interrupted along with the confidence interval bounds that do definitely show a shift downwards after the March 2020 interrupt point with confidence intervals becoming more negative than before.

Supplementary Table 2 on sensitivity analysis, where log transformation continues to show interesting findings for step/phase-changes in hydroxychloroquine and azathioprine. We also modelled March and April as the point of interruption here.

By location

Nomenclature for regional territories except London was modified in April 2020, making it difficult to make direct comparisons across regions before and after this period. However sufficient clarity is provided to permit the re-aggregation of the data (April -July 20) to allow for direct comparison (Northwest + North East and Yorkshire= North of England, Midlands = Midlands and East of England, South East + South West= South of England and London).

See Supplementary Table 4 for regional analysis by quantity and cost. Figure 3 summarises the regional prescription volumes.

[Insert Figure 3 here]

Some entries were unidentified by location. Regional descriptive statistics in millions with (Mean, Std. Deviation) convention are presented: North England (6.675, 0.279), Midlands and East of England (7.586, 0.313), South England (6.498, 0.29), London (2.494, 0.122), unidentified (0.003, 0.0012). No significant differences were found. Up-to-date population denominators are unavailable (these could have changed during the pandemic), so total quantity reflects differing prevalence in different regions.
More granular analysis was conducted to examine changes to Methotrexate Quantity (Supplementary Table 5 - shows unique codes that were examined, to improve clarity and transparency and helps other researchers investigate by product code) due to its crucial importance in the management and maintenance of disease remission.

Discussion

Our results are concerning and tell us that a significant number of IMIDs patients may have not used their chronic long-term condition's medicines as they should have, for a variety of reasons. While we cannot be certain, the results of interrupted time series suggest the possibility of a causal relation between the pandemic and that changes to IMIDs prescription volumes. Our analysis cannot rule out other possible causal explanatory factors, but our results are consistent with possibility that the pandemic may have directly contributed the changes we observe. This provides an early signal for potentially deteriorating medium to longer term health in IMIDs patients. The results demonstrate a

statistically significant level of fluctuation for hydroxychloroquine and azathioprine. There are also worrying trend changes in sulfasalazine, as it has high circulating volume (approximately 9 million doses per month). In the broader sense, this data may suggest lower rates of medicines adherence by IMIDs patients who may not have received adequate clinical care.

The cost analysis presented shows that a unitary cost of medicine also jumped substantially in the study period. This has budget impact concerns for the NHS (universal health coverage provider) but has transferable realities for international audiences in their countries because of the level of insurance coverage and out of pocket expenses this would represent for their patients. These types of prices-impacts have the potential to lead to 'out of stock' shortages for patients and alter/raise 'out of pocket' price-levels for insurers. It is reasonable to expect that prescription medication coverage for IMIDs may fall consequently because of the high out of pocket expenses that patients must incur before insurance coverage commences e.g. Medicare, Medicaid. This analysis presents a fraction of the directly attributable costs of IMID patients management. It does not cover the cost of complications, surgery and onward care including the health-burden borne by family or carers or financial distress it may cause through lack of income due to disease progression. Regional variations also mean that certain categories of IMIDs patients are disproportionately affected, having further implications for health inequality. From a perspective of equity, cost increases may fuel geographical inequity potentially perpetuating post code lotteries. This analysis also provides data on the quality of initial humanitarian crisis response, to aid better future preparedness.

This analysis represents the first wave of restrictions due to the pandemic and its handling, including the effects on the supply chain shortages, governmental or policy guidance that was enacted by clinicians at the hospital level, later at a national and even supranational level, alongside emerging global data and pressures on the primary care interface mean that subsequent periods of time are not necessarily comparable to this initial phase. Subsequent lockdowns would be influenced by policy decisions in the first wave. While we recognise that a longer continuous period of time would be interesting to study to provide a contemporary narrative, it would also be confounded by a variety of policy changes, making it difficult to tease out unexplainable variables.

Health systems globally were least prepared to handle this pandemic and this performance is likely to improve overtime. However, IMIDs patients directly affected in this initial phase may potentially still have unaddressed healthcare needs due to clinical availability or capacity for providing this care. Data suggest that roughly 2.3 million people are currently waiting for surgical care, including in orthopaedics[51]. People in the most deprived communities are 1.8 times more likely to wait over one year for treatment compared to the least deprived areas[52]. Consequently, we argue, that IMIDs patients maybe especially more disadvantaged and may need additional support.

Why do we use these medicines?

Clinical treatment is intended to relieve symptoms, achieve disease remission or low disease activity if remission cannot be achieved, and to improve the patient's ability to perform daily activities. From a public health, primary care perspective, it is important that IMIDs patients continue to get their medicines regularly and adhere to the treatment plans to ensure disease progression is as delayed as feasibly possible.

For the first time, we present data on prescription and regional variations during this pandemic for licensed IMID medicines. We demonstrate that there is more variability after the onset of the pandemic in treating IMIDs patients across the country, with the potential for extremely poor drug coverage for some individuals versus excessive drug coverage for others indicating a misallocation of resources and as a proxy for clinical care coverage. These medicines also carry other licenced use (e.g., pain), so our analysis is more generalised for the IMIDs patient populations we describe.

Adherence and the patient story

Adherence concerns and access to timely prescription refills may or may not occur for a variety of reasons including not being able to go to the doctor's surgery or pharmacies because of shielding or self-isolation during the pandemic. Also, many surgeries stopped seeing patient face-to-face and substituted these with digital services. The first point of patient contact was the 111 telephone triage services (run by allied professionals) which became overwhelmed.[53,54] Telephone triage may have substituted for the standard practice of a physical examination, bloods collection or annual review. In such events, patients may have had limited access to services, either because of not knowing how to access them digitally or failing to prioritise them.

While the pandemic has provided an opportunity for digital consultations and remote supervision, they have come with added uncertainty and anxiety for patients. Changes to routine has the potential for negative consequences on chronic long-term condition sufferers. Digital consultations have the potential to create digital barriers to care. This may be especially problematic for elderly IMIDs patients who can be frail or infirm because of their condition as well as the immunosuppressant's that they use. As a result, there may be instances across the country where patients have inadequate disease control, where underlying complications may escalate. Strengths and weaknesses

There are several strengths and limitations to this observational study. For the first time, we report the impact on prescription volumes of medicines licenced for RA in England during a global pandemic. Strengths of this study include being evidence-based on real world data. One of the strengths of ITS studies is that they are generally unaffected by typical confounding variables which remain fairly constant, such as population age distribution or socioeconomic status, as these only change relatively slowly over time. Nevertheless, ITS can be affected by time-varying confounders that change more rapidly.[55] Confirmed diagnoses or prescription indications as well as linked data were unavailable to us. We rely heavily on P values to justify significance, which has its limitations[56–59]. While this analysis provides important insight, it can only be descriptive and further work is needed to explore the underlying reasons for the trends observed and the implications for patients.

Limitations pertain to the timeframe, completeness, and quality of the data. We have extracted government data however, they have not been independently verified as complete, accurate and subject to revision. The analysis is descriptive with no adjustments, for changes in population structure (age, disease prevalence, social deprivation scores) which could impact prescriptions between periods and within regions. Hospital statistics are not represented in our analysis.

Future studies

This study generates an early warning signal from real-world data on patients' lives. Future studies must consider the impact on patients' lives with respect to disease progression, including over the life course of this pandemic at the individual level by studying electronic health data records. It is important to consider subsequent periods and interval between lockdowns to fully assess the potential impact to patients. Future studies may also look to examine statistics of routine safety blood tests to check for bone marrow suppression, if they have been done and at what frequency. Similarly, markers of disease progression should be examined.

Conclusion

A worrying change in trend is observed for all medicines that were studied. The trend overall is downwards which raises concerns for the longer-term care of IMIDs patients. We know that not taking medication is likely to result in increased morbidity and mortality in this patient group. Extra effort may be needed to help these patients. In conclusion, this study illustrates the risk of

interrupted provision of timely prescription refills for patients taking sulfasalazine; hydroxychloroquine; azathioprine; methotrexate and leflunomide. Health care professionals need to identify patients on these medicines and assess their prescription days coverage, with planned actions to flag and follow-up patients where there are concerns about adherence.

Acknowledgments.

We thank the NHS business services authority staff who helped with the several information requests.

Contributors:

Lead author conducted the literature search, study conception and design data analysis, statistical analysis and interpretation of data, manuscript preparation, editing and revision and submitted the final version of the paper. RB provided technical expertise with data extraction, cleaning, manipulation and data for final analysis. DC acted as the principal medical statistician on the study and was the statistical analysis lead. SL advised on statistical techniques. SF provided a public health perspective of the likely impact and considered ways to improve community public health. CE considered the clinical impact and consequences of our findings on this patient population.

Funding: no special funding was provided for the study.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf

Declaration: no financial relationships or activities have influenced the submitted work.

Ethical approval: Not required.

Data sharing: Original data are available from[60] https://www.nhsbsa.nhs.uk/prescription-data/prescribing-data/english-prescribing-data-epd No additional data available.

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

References

1 NHS services. Who can get free prescriptions. nhs.uk. 2020.https://www.nhs.uk/nhs-services/prescriptions-and-pharmacies/who-can-get-free-prescriptions/ (accessed 12 Oct 2022).

2 Office for National Statistics. NHS70: Marking 70 years of the National Health Service. 2018.https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandwellbeing/articles/nhs70marking70yearsofthenationalhealthservice/2018-06-26 (accessed 12 Oct 2022).

3 NHS England. Primary Care Support England. 2022.https://pcse.england.nhs.uk/organisations/icb-hub/ (accessed 12 Oct 2022).

4 NHS Digital. Innovative uses of data and data science. NHS Digit. 2022.https://digital.nhs.uk/data-and-information/data-insights-and-statistics/innovative-uses-of-data-and-data-science (accessed 12 Oct 2022).

5 Ogdie A, Coates LC, Gladman DD. Treatment guidelines in psoriatic arthritis. *Rheumatol Oxf Engl* 2020;**59**:i37–46. doi:10.1093/rheumatology/kez383

6 Smolen JS, Landewé RBM, Bijlsma JWJ, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020;**79**:685–99. doi:10.1136/annrheumdis-2019-216655

7 Gossec L, Baraliakos X, Kerschbaumer A, *et al.* EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis* 2020;**79**:700–12. doi:10.1136/annrheumdis-2020-217159

8 Kerschbaumer A, Sepriano A, Smolen JS, *et al.* Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2020;**79**:744–59. doi:10.1136/annrheumdis-2019-216656

9 Ledingham J, Gullick N, Irving K, *et al.* BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. *Rheumatology* 2017;**56**:865–8. doi:10.1093/rheumatology/kew479

10 Guo Q, Wang Y, Xu D, *et al.* Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. *Bone Res* 2018;**6**:15. doi:10.1038/s41413-018-0016-9

11 Løppenthin K, Esbensen BA, Østergaard M, *et al.* Morbidity and mortality in patients with rheumatoid arthritis compared with an age- and sex-matched control population: A nationwide register study. *J Comorbidity* 2019;**9**:2235042X19853484. doi:10.1177/2235042X19853484

12 Elewaut D, Matucci-Cerinic M. Treatment of ankylosing spondylitis and extra-articular manifestations in everyday rheumatology practice. *Rheumatology* 2009;**48**:1029–35. doi:10.1093/rheumatology/kep146

13 Raza K, Buckley CE, Salmon M, *et al.* Treating very early rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2006;**20**:849–63. doi:10.1016/j.berh.2006.05.005

14 Cojocaru M, Cojocaru IM, Silosi I, *et al.* Extra-articular Manifestations in Rheumatoid Arthritis. *Maedica* 2010;**5**:286–91.

15 Lamb CA, Kennedy NA, Raine T, *et al.* British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019;**68**:s1–106. doi:10.1136/gutjnl-2019-318484

16 Sawayama H, Miyamoto Y, Yoshida N, *et al.* Essential updates 2020/2021: Colorectal diseases (benign)—Current topics in the surgical and medical treatment of benign colorectal diseases. *Ann Gastroenterol Surg* 2022;**6**:321–35. doi:10.1002/ags3.12548

17 Di Jiang C, Raine T. IBD considerations in spondyloarthritis. *Ther Adv Musculoskelet Dis* 2020;**12**:1759720X2093941. doi:10.1177/1759720X20939410

18 Mysler E, Caubet M, Lizarraga A. Current and Emerging DMARDs for the Treatment of Rheumatoid Arthritis. *Open Access Rheumatol Res Rev* 2021;**13**:139–52. doi:10.2147/OARRR.S282627

19 Keskin Y, Nas K, Kiliç E, *et al.* Clinical characteristics, disease activity, functional status, and quality of life results of patients with psoriatic arthritis using biological and conventional synthetic disease-modifying antirheumatic drugs. *Arch Rheumatol* 2021;**36**:1–9. doi:10.46497/ArchRheumatol.2021.7874

20 Alves de Oliveira Junior H, Pereira da Veiga T, Acurcio FDA, *et al.* Impact of biologic DMARDs on quality of life: 12-month results of a rheumatic diseases cohort using the Brazilian EQ-5D tariff. *Hosp Pract* 2020;**48**:213–22. doi:10.1080/21548331.2020.1785212

21 Shams S, Martinez JM, Dawson JRD, *et al.* The Therapeutic Landscape of Rheumatoid Arthritis: Current State and Future Directions. *Front Pharmacol* 2021;**12**:680043. doi:10.3389/fphar.2021.680043

22 Köhler BM, Günther J, Kaudewitz D, *et al.* Current Therapeutic Options in the Treatment of Rheumatoid Arthritis. *J Clin Med* 2019;**8**:E938. doi:10.3390/jcm8070938

23 Cutolo M, Spies CM, Buttgereit F, *et al.* The supplementary therapeutic DMARD role of low-dose glucocorticoids in rheumatoid arthritis. *Arthritis Res Ther* 2014;**16**:S1. doi:10.1186/ar4685

24 Boots AMH, Maier AB, Stinissen P, *et al.* The influence of ageing on the development and management of rheumatoid arthritis. *Nat Rev Rheumatol* 2013;**9**:604–13. doi:10.1038/nrrheum.2013.92

25 Gabriel SE, Crowson CS, Campion ME, *et al.* Indirect and nonmedical costs among people with rheumatoid arthritis and osteoarthritis compared with nonarthritic controls. *J Rheumatol* 1997;**24**:43–8.

26 Gabriel SE, Crowson CS, Campion ME, *et al.* Direct medical costs unique to people with arthritis. *J Rheumatol* 1997;**24**:719–25.

27 Cross MJ, March LM, Lapsley HM, *et al.* Patient self-efficacy and health locus of control: relationships with health status and arthritis-related expenditure. *Rheumatol Oxf Engl* 2006;**45**:92–6. doi:10.1093/rheumatology/kei114

28 Callahan LF. The burden of rheumatoid arthritis: facts and figures. *J Rheumatol Suppl* 1998;**53**:8–12.

29 Yelin E. The costs of rheumatoid arthritis: absolute, incremental, and marginal estimates. *J Rheumatol Suppl* 1996;**44**:47–51.

30 Littlejohn EA, Monrad SU. Early Diagnosis and Treatment of Rheumatoid Arthritis. *Prim Care Clin Off Pract* 2018;**45**:237–55. doi:10.1016/j.pop.2018.02.010

31 Abualfadl E, Ismail F, Shereef RRE, *et al.* Impact of COVID-19 pandemic on rheumatoid arthritis from a Multi-Centre patient-reported questionnaire survey: influence of gender, rural-urban gap and north-south gradient. *Rheumatol Int* Published Online First: 1 November 2020. doi:10.1007/s00296-020-04736-9

32 British Medical Association. NHS backlog data analysis. Br. Med. Assoc. Trade Union Prof. Body Dr. UK. 2022.https://www.bma.org.uk/advice-and-support/nhs-delivery-and-workforce/pressures/nhs-backlog-data-analysis (accessed 12 Oct 2022).

33 Department of Health & Social Care. The government's response to the Health and Social Care Committee and Science and Technology Committee joint report: Coronavirus: lessons learned to date. GOV.UK. 2022.https://www.gov.uk/government/publications/coronavirus-lessons-learned-to-date-report-government-response/the-governments-response-to-the-health-and-social-care-committee-and-science-and-technology-committee-joint-report-coronavirus-lessons-learned-to-d (accessed 12 Oct 2022).

34 Dyer C. Covid-19: Government was "grossly negligent" in its handling of pandemic, says people's inquiry. *BMJ* 2021;:n2955. doi:10.1136/bmj.n2955

35 National Institute for Health and Care Excellence. COVID-19 rapid guideline: rheumatological autoimmune, inflammatory and metabolic bone disorders Guidance. https://www.nice.org.uk/guidance/ng167 (accessed 10 Aug 2020).

36 Hughes DA. Medicines Shortages in the United Kingdom. *Clin Pharmacol Ther* 2019;**106**:712–712. doi:10.1002/cpt.1495

37 Batista A, Miljković N, Polidori P, *et al.* Medicines shortages. *Eur J Hosp Pharm* 2019;**26**:290–1. doi:10.1136/ejhpharm-2019-001911

38 Miljković N, Gibbons N, Batista A, *et al.* Results of EAHP's 2018 Survey on Medicines Shortages. *Eur J Hosp Pharm Sci Pract* 2019;**26**:60–5. doi:10.1136/ejhpharm-2018-001835

39 Acosta A, Vanegas EP, Rovira J, *et al.* Medicine Shortages: Gaps Between Countries and Global Perspectives. *Front Pharmacol* 2019;**10**:763. doi:10.3389/fphar.2019.00763

40 European Medicines Agency. Medicines - Shortages. Eur. Med. Agency. https://www.ema.europa.eu/en/medicines/ema_group_types/ema_document-supply_shortage/field_ema_shortage_status/1/field_ema_shortage_status/0 (accessed 10 Aug 2020).

41 English Prescribing Dataset (EPD) - Open Data Portal BETA. https://opendata.nhsbsa.net/dataset/english-prescribing-data-epd (accessed 25 Apr 2020).

42 Barrett R, Barrett R, Dhar K, *et al.* Gonadorelins adherence in prostate cancer: A time-series analysis of England's national prescriptions during the COVID-19 pandemic (from Jan 2019 to Oct 2020). *BJUI Compass* Published Online First: 19 August 2021. doi:10.1002/bco2.101

43 Cochrane Effective Practice and Organisation of Care (EPOC). Interrupted time series (ITS) analyses. EPOC Resources for review authors. 2017.epoc.cochrane.org/resources/epoc-specific-resources-review-authors

44 Helfenstein U. Box-Jenkins modelling in medical research. *Stat Methods Med Res* 1996;**5**:3–22. doi:10.1177/096228029600500102

45 Sato RC. Disease management with ARIMA model in time series. *Einstein Sao Paulo Braz* 2013;**11**:128–31. doi:10.1590/s1679-45082013000100024

46 Schaffer AL, Dobbins TA, Pearson S-A. Interrupted time series analysis using autoregressive integrated moving average (ARIMA) models: a guide for evaluating large-scale health interventions. *BMC Med Res Methodol* 2021;**21**:58. doi:10.1186/s12874-021-01235-8

47 Muggeo VMR. Estimating regression models with unknown break-points. *Stat Med* 2003;**22**:3055–71. doi:10.1002/sim.1545

48 Benoit K. Linear regression models with logarithmic transformations. *Lond Sch Econ* 2011;**22**:23–36.

49 Feng C, Wang H, Lu N, *et al.* Log-transformation and its implications for data analysis. *Shanghai Arch Psychiatry* 2014;**26**:105–9. doi:10.3969/j.issn.1002-0829.2014.02.009

50 Benchimol EI, Smeeth L, Guttmann A, *et al.* The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015;**12**:e1001885. doi:10.1371/journal.pmed.1001885

51 Carr A, Smith JA, Camaradou J, *et al.* Growing backlog of planned surgery due to covid-19. *BMJ* 2021;:n339. doi:10.1136/bmj.n339

52 Holmes J, Jefferies D. Health inequalities and the elective backlog—understanding the problem and how to resolve it. *BMJ* 2021;:n2574. doi:10.1136/bmj.n2574

53 Without more nurses, NHS 111 staff could be 'overwhelmed.' *Emerg Nurse* 2015;**23**:6–6. doi:10.7748/en.23.7.6.s2

54 Osamor K. I warned parliament that NHS 111 would never be able to cope. The Guardian. 2020.https://www.theguardian.com/commentisfree/2020/apr/23/nhs-111-crisis-coronavirus-pandemic (accessed 9 Jun 2020).

55 Lopez Bernal J, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol* 2016;:dyw098. doi:10.1093/ije/dyw098

56 Wasserstein RL, Schirm AL, Lazar NA. Moving to a World Beyond " $p < 0.05$." *Am Stat* 2019;**73**:1–19. doi:10.1080/00031305.2019.1583913

57 Altman DG, Bland JM. Statistics Notes: Presentation of numerical data. *BMJ* 1996;**312**:572–572. doi:10.1136/bmj.312.7030.572

58 Bland JM, Altman DG. Statistics Notes: Logarithms. *BMJ* 1996;**312**:700–700. doi:10.1136/bmj.312.7032.700

59 Altman DG, Bland JM. Standard deviations and standard errors. *BMJ* 2005;**331**:903. doi:10.1136/bmj.331.7521.903

60 [dataset] NHS Business Services Authority. English prescribing data (EPD). https://www.nhsbsa.nhs.uk/prescription-data/prescribing-data/english-prescribing-data-epd (accessed 31 Oct 2022).

Figure 1 Box plot representing mean values before the pandemic and after its onset. Quantities are presented in absolute numbers.

Figure 2 ARIMA (0,0,0)(0,0,0) Prescription volumes for individual medicines (a)Sulfasalazine; (b)Hydroxychloroquine sulfate; (c)Azathioprine; (d)Methotrexate; (e)Leflunomide.

Figure 3 Monthly regional distribution (higher March and lower May 2020 quantities of RA medicines are presented in the callouts).

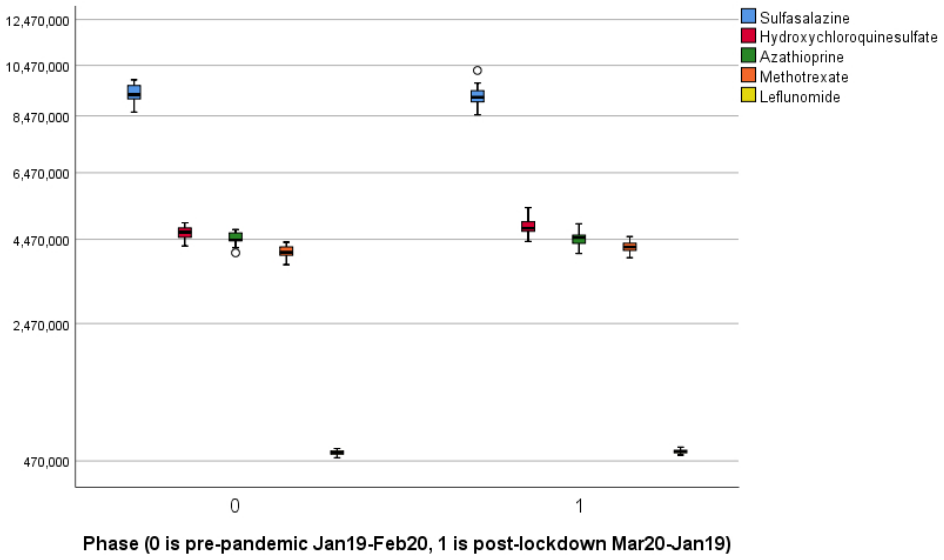

Figure 1 Box plot representing mean values before the pandemic and after its onset. Quantities are presented in absolute numbers.

300x176mm (72 x 72 DPI)

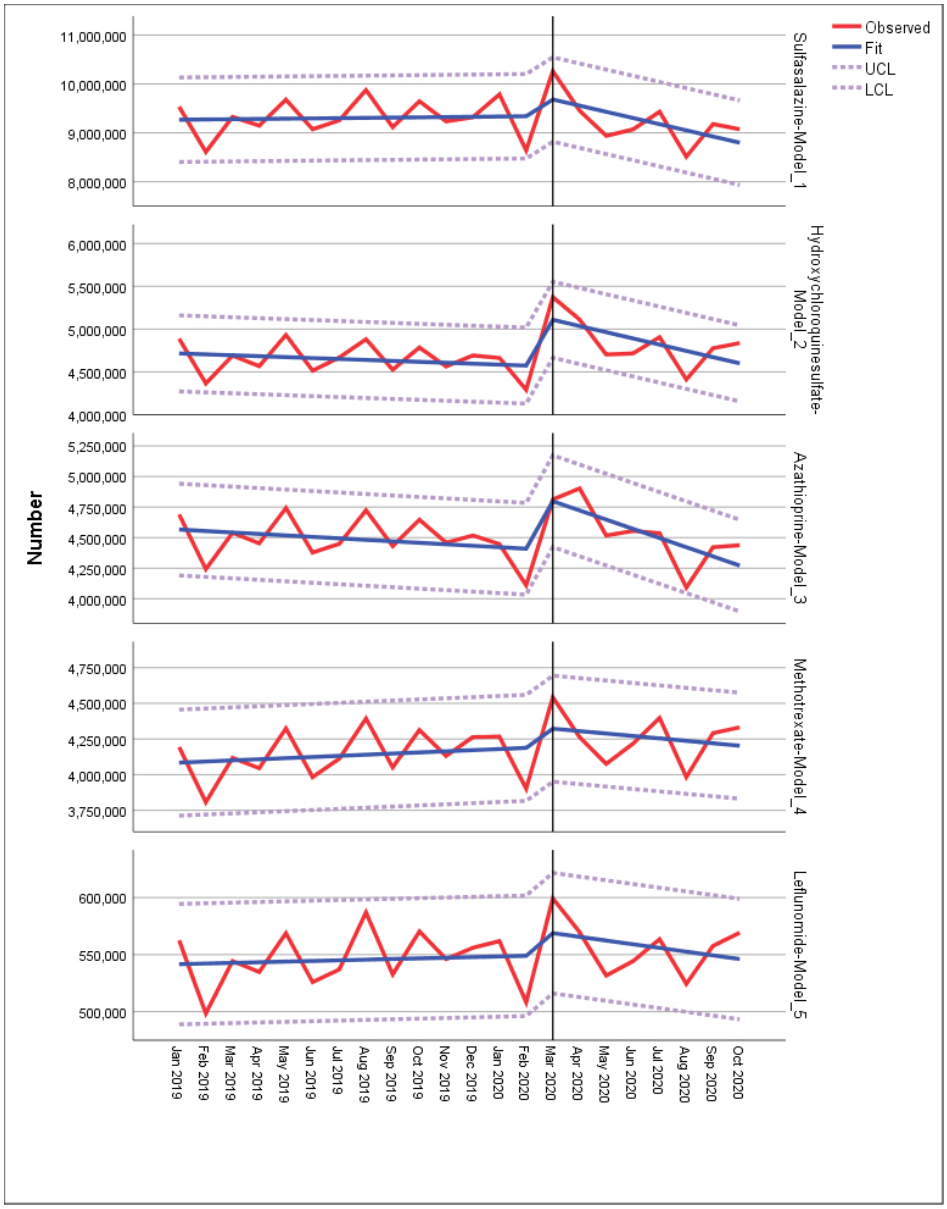

Figure 2 ARIMA (0,0,0)(0,0,0) Prescription volumes for individual medicines (a)Sulfasalazine; (b)Hydroxychloroquine sulfate; (c)Azathioprine; (d)Methotrexate; (e)Leflunomide.

272x347mm (72 x 72 DPI)

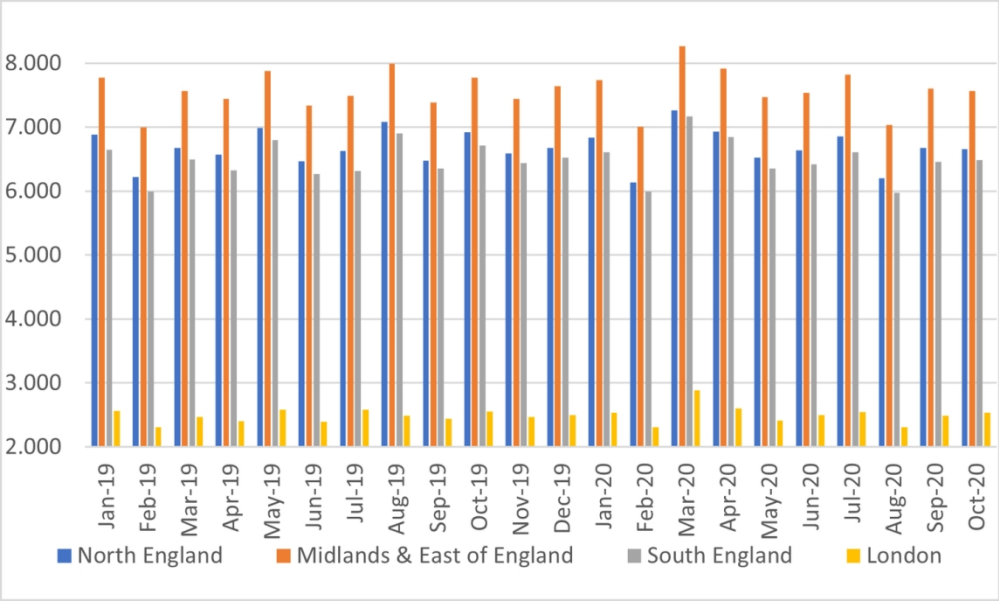

Figure 3 Monthly regional distribution (higher March and lower May 2020 quantities of RA medicines are presented in the callouts).

127x76mm (300 x 300 DPI)

Supplementary Table 1 - ARIMA Syntax (Mar20-1) Jan 19 to Jan 21

```
* Encoding: UTF-8.

DATASET ACTIVATE DataSet3.
PREDICT THRU END.
* Time Series Modeler.
TSMODEL
  /MODELSUMMARY  PRINT=[MODELFIT]
  /MODELSTATISTICS  DISPLAY=YES MODELFIT=[ SRSQUARE]
  /MODELDETAILS  PRINT=[ PARAMETERS]
  /SERIESPLOT OBSERVED FIT FORECASTCI FITCI
  /OUTPUTFILTER DISPLAY=ALLMODELS
  /SAVE  PREDICTED(Predicted) LCL(LCL) UCL(UCL)
  /AUXILIARY  CILEVEL=95 MAXACFLAGS=24
  /MISSING USERMISSING=EXCLUDE
  /MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
e
   INDEPENDENT=TimePeriod Phase Interact
    PREFIX='Model'
  /ARIMA AR=[1]  DIFF=0  MA=[0]
    TRANSFORM=NONE  CONSTANT=YES
  /AUTOOUTLIER DETECT=OFF.

PREDICT THRU END.
* Time Series Modeler.
TSMODEL
  /MODELSUMMARY  PRINT=[MODELFIT]
  /MODELSTATISTICS  DISPLAY=YES MODELFIT=[ SRSQUARE]
  /MODELDETAILS  PRINT=[ PARAMETERS]
  /SERIESPLOT OBSERVED FIT FORECASTCI FITCI
  /OUTPUTFILTER DISPLAY=ALLMODELS
  /SAVE  PREDICTED(Predicted) LCL(LCL) UCL(UCL)
  /AUXILIARY  CILEVEL=95 MAXACFLAGS=24
  /MISSING USERMISSING=EXCLUDE
  /MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
e
   INDEPENDENT=TimePeriod Phase Interact
    PREFIX='Model'
  /ARIMA AR=[0]  DIFF=1  MA=[0]
    TRANSFORM=NONE  CONSTANT=YES
  /AUTOOUTLIER DETECT=OFF.

PREDICT THRU END.
* Time Series Modeler.
TSMODEL
  /MODELSUMMARY  PRINT=[MODELFIT]
  /MODELSTATISTICS  DISPLAY=YES MODELFIT=[ SRSQUARE]
  /MODELDETAILS  PRINT=[ PARAMETERS]
  /SERIESPLOT OBSERVED FIT FORECASTCI FITCI
  /OUTPUTFILTER DISPLAY=ALLMODELS
  /AUXILIARY  CILEVEL=95 MAXACFLAGS=24
  /MISSING USERMISSING=EXCLUDE
```

```
  /MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
e
   INDEPENDENT=TimePeriod Phase Interact
    PREFIX='Model'
  /ARIMA AR=[0]  DIFF=0  MA=[1]
    TRANSFORM=NONE  CONSTANT=YES
  /AUTOOUTLIER DETECT=OFF.

PREDICT THRU END.
* Time Series Modeler.
TSMODEL
  /MODELSUMMARY  PRINT=[MODELFIT]
  /MODELSTATISTICS  DISPLAY=YES MODELFIT=[ SRSQUARE]
  /MODELDETAILS  PRINT=[ PARAMETERS]
  /SERIESPLOT OBSERVED FIT FORECASTCI FITCI
  /OUTPUTFILTER DISPLAY=ALLMODELS
  /AUXILIARY  CILEVEL=95 MAXACFLAGS=24
  /MISSING USERMISSING=EXCLUDE
  /MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
e
   INDEPENDENT=TimePeriod Phase Interact
    PREFIX='Model'
  /ARIMA AR=[0]  DIFF=0  MA=[0]
    TRANSFORM=LN  CONSTANT=YES
  /AUTOOUTLIER DETECT=OFF.
```

ARIMA Model Parameters **ARIMA (March20+ is a '1')** Total Quantities

14 months (Jan-19 to Feb-20) before the COVID-19 first lockdown in England (23rd Mar-20) until 11 months after this date (Mar-20 to Jan-21)

ARIMA(0,0,0), No Transformation	TimePeriod (Before); Phase (Step); Interact (After)	Parameter Estimate	Standard Error	T-stat	P-value	UCI	LCI
Sulfasalazine-Model_1	TimePeriod	5435	28871	0.188	0.852	65021	-54151
Sulfasalazine-Model_1	Phase	659017	875894	0.752	0.46	2466774	-1148740
Sulfasalazine-Model_1	Interact	-38151	50570	-0.754	0.459	66220	-142522
Hydroxychloroquinesulfate-Model_2	TimePeriod	-10955	14336	-0.764	0.453	18632	-40543
Hydroxychloroquinesulfate-Model_2	Phase	814729	434936	1.873	0.075	1712394	-82935
Hydroxychloroquinesulfate-Model_2	Interact	-24392	25111	-0.971	0.342	27434	-76219
Azathioprine-Model_3	TimePeriod	-12052	12273	-0.982	0.337	13278	-37382
Azathioprine-Model_3	Phase	786705	372342	2.113	0.047	1555182	18229
Azathioprine-Model_3	Interact	-31340	21497	-1.458	0.16	13028	-75708
Methotrexate-Model_4	TimePeriod	7966	11836	0.673	0.508	32395	-16462
Methotrexate-Model_4	Phase	249614	359099	0.695	0.495	990758	-491531
Methotrexate-Model_4	Interact	-10634	20733	-0.513	0.613	32156	-53424
Leflunomide-Model_5	TimePeriod	561	1662	0.338	0.739	3992	-2870
Leflunomide-Model_5	Phase	30388	50436	0.603	0.553	134482	-73706
Leflunomide-Model_5	Interact	-1188	2912	-0.408	0.687	4822	-7198

Confidence intervals were calculated as (24df):
CI=parameter+/-tinv(0.05, df)*SE

ARIMA(1,0,0), AR	TimePeriod (Before); Phase (Step); Interact (After)	Parameter Estimate	Standard Error	T-stat	P-value	UCI	LCI
Sulfasalazine-Model_1	TimePeriod	19759	20233	0.977	0.34	61517	-21999
Sulfasalazine-Model_1	Phase	417103	614888	0.678	0.505	1686169	-851964
Sulfasalazine-Model_1	Interact	-37930	34973	-1.085	0.291	34250	-110110
Hydroxychloroquinesulfate-Model_2	TimePeriod	-5175	11041	-0.469	0.644	17613	-27962
Hydroxychloroquinesulfate-Model_2	Phase	700712	335790	2.087	0.05	1393748	7675
Hydroxychloroquinesulfate-Model_2	Interact	-23233	19100	-1.216	0.238	16188	-62654
Azathioprine-Model_3	TimePeriod	-9123	10465	-0.872	0.394	12476	-30722
Azathioprine-Model_3	Phase	738472	317473	2.326	0.031	1393704	83240
Azathioprine-Model_3	Interact	-31213	18041	-1.73	0.099	6021	-68447
Methotrexate-Model_4	TimePeriod	14064	7165	1.963	0.064	28852	-724
Methotrexate-Model_4	Phase	86932	218834	0.397	0.695	538582	-364718
Methotrexate-Model_4	Interact	-7128	12399	-0.575	0.572	18463	-32718
Leflunomide-Model_5	TimePeriod	1432	1106	1.295	0.21	3714	-850
Leflunomide-Model_5	Phase	11071	33718	0.328	0.746	80661	-58520
Leflunomide-Model_5	Interact	-882	1912	-0.461	0.649	3063	-4827

the coefficient for 'time' gives us the slope of the regression line pre-intervention
the coefficient for 'phase' gives us the change in intercept
the coefficient for 'interact' gives us the change in slope post intervention

If the coefficient for time is β1, for phase is β2 and for interact is β3 then the regression model is:

Therefore, pre intervention becomes:

Outcome = constant + β1time

Outcome= constant + β1time + β2 + β3interact = (constant + β2) + (β1 + β3) time
(as time and interact are the same post intervention)

ARIMA(0,1,0), Difference	TimePeriod (Before); Phase (Step); Interact (After)	Parameter Estimate	Standard Error	T-stat	P-value	UCI	LCI
Sulfasalazine-Model_1	TimePeriod	-16503	54217	-0.304	0.764	95395	-128402
Sulfasalazine-Model_1	Phase	446642	1491083	0.3	0.768	3524086	-2630801
Sulfasalazine-Model_1	Interact	-5626	88335	-0.064	0.95	176688	-187940
Hydroxychloroquinesulfate-Model_2	TimePeriod	-4262	29227	-0.146	0.886	56059	-64583
Hydroxychloroquinesulfate-Model_2	Phase	712710	803796	0.887	0.386	2371664	-946244
Hydroxychloroquinesulfate-Model_2	Interact	-29016	47618	-0.609	0.549	69263	-127296
Azathioprine-Model_3	TimePeriod	-6734	23232	-0.29	0.775	41214	-54683
Azathioprine-Model_3	Phase	573262	638927	0.897	0.38	1891942	-745419
Azathioprine-Model_3	Interact	-21531	37851	-0.569	0.576	56590	-99652
Methotrexate-Model_4	TimePeriod	-6809	23305	-0.292	0.773	41292	-54909
Methotrexate-Model_4	Phase	439338	640948	0.685	0.501	1762190	-883514
Methotrexate-Model_4	Interact	-15532	37971	-0.409	0.687	62837	-93900
Leflunomide-Model_5	TimePeriod	-753	3188	-0.236	0.816	5828	-7333
Leflunomide-Model_5	Phase	58732	87689	0.67	0.511	239712	-122249
Leflunomide-Model_5	Interact	-2093	5195	-0.403	0.691	8629	-12814

ARIMA(0,0,1), MA	TimePeriod (Before); Phase (Step); Interact (After)	Parameter Estimate	Standard Error	T-stat	P-value	UCI	LCI
Sulfasalazine-Model_1	TimePeriod	27834	9982	2.788	0.011	48437	7231
Sulfasalazine-Model_1	Phase	459301	421006	1.091	0.288	1328214	-409613
Sulfasalazine-Model_1	Interact	-50867	21544	-2.361	0.028	-6402	-95332
Hydroxychloroquinesulfate-Model_2	TimePeriod	1157	5185	0.223	0.826	11859	-9545
Hydroxychloroquinesulfate-Model_2	Phase	637368	207951	3.065	0.006	1066559	208178
Hydroxychloroquinesulfate-Model_2	Interact	-26929	10730	-2.51	0.021	-4783	-49075
Azathioprine-Model_3	TimePeriod	-2278	4740	-0.481	0.636	7505	-12062
Azathioprine-Model_3	Phase	660176	167979	3.93	0.001	1006868	313483
Azathioprine-Model_3	Interact	-34495	8907	-3.873	0.001	-16113	-52878
Methotrexate-Model_4	TimePeriod	18549	3714	4.994	0.00007	26214	10884
Methotrexate-Model_4	Phase	27587	116695	0.236	0.816	268434	-213260
Methotrexate-Model_4	Interact	-8773	5851	-1.499	0.149	3304	-20850
Leflunomide-Model_5	TimePeriod	2037	543	3.754	0.001	3157	917
Leflunomide-Model_5	Phase	-1004	18464	-0.054	0.957	37104	-39112
Leflunomide-Model_5	Interact	-931	985	-0.945	0.356	1102	-2965

ARIMA(0,0,0) Natural Logarithm, No Transformation	TimePeriod (Before); Phase (Step); Interact (After)	Parameter Estimate	Standard Error	T-stat	P-value	UCI	LCI
Sulfasalazine-Model_1	Sulfasalazine	16.041	0.026	606.083	0	16.09466	15.987339
Sulfasalazine-Model_1	TimePeriod	0.001	0.003	0.179	0.86	0.007	-0.005
Sulfasalazine-Model_1	Phase	0.067	0.094	0.707	0.488	0.261	-0.127
Sulfasalazine-Model_1	Interact	-0.004	0.005	-0.715	0.483	0.006	-0.014
Hydroxychloroquinesulfate-Model_2	Hydroxychloroquinesulfate	15.368	0.026	597.458	0	15.422	15.314
Hydroxychloroquinesulfate-Model_2	TimePeriod	-0.002	0.003	-0.778	0.445	0.004	-0.008
Hydroxychloroquinesulfate-Model_2	Phase	0.163	0.092	1.776	0.09	0.353	-0.027
Hydroxychloroquinesulfate-Model_2	Interact	-0.005	0.005	-0.887	0.385	0.005	-0.015
Azathioprine-Model_3	Azathioprine	15.336	0.023	653.382	0	15.383	15.289
Azathioprine-Model_3	TimePeriod	-0.003	0.003	-0.986	0.335	0.003	-0.009
Azathioprine-Model_3	Phase	0.171	0.084	2.046	0.053	0.344	-0.002
Azathioprine-Model_3	Interact	-0.007	0.005	-1.404	0.175	0.003	-0.017
Methotrexate-Model_4	Methotrexate	15.22	0.024	631.677	0	15.270	15.170
Methotrexate-Model_4	TimePeriod	0.002	0.003	0.687	0.499	0.008	-0.004
Methotrexate-Model_4	Phase	0.059	0.086	0.687	0.5	0.236	-0.118
Methotrexate-Model_4	Interact	-0.003	0.005	-0.512	0.614	0.007	-0.013
Leflunomide-Model_5	Leflunomide	13.2	0.026	512.174	0	13.254	13.146
Leflunomide-Model_5	TimePeriod	0.001	0.003	0.348	0.731	0.007	-0.005
Leflunomide-Model_5	Phase	0.054	0.092	0.584	0.565	0.244	-0.136
Leflunomide-Model_5	Interact	-0.002	0.005	-0.396	0.696	0.008	-0.012

We considered monthly quantities in the time period defined by 14 months (Jan-19 to Feb-20) before the COVID-19 first lockdown in England (23rd Mar-20) until 11 months after this date (Mar-20 to Jan-21).

ARIMA Model Parameters ARIMA (March20+ is a '0')

ARIMA(0,0,0), No Transformation		Estimate	Standard Error	t	P-value	UCI	LCI
Sulfasalazine-Model_1	TimePeriod	0.003	0.003	1.091	0.288	0.009192	-0.00319
Sulfasalazine-Model_1	Phase	-0.047	0.105	-0.449	0.658	0.169709	-0.26371
Sulfasalazine-Model_1	Interact	-0.001	0.006	-0.091	0.929	0.011383	-0.01338
Hydroxychloroquinesulfate-Model_2	TimePeriod	0.002	0.003	0.565	0.578	0.008192	-0.00419
Hydroxychloroquinesulfate-Model_2	Phase	0.08	0.122	0.655	0.52	0.331796	-0.1718
Hydroxychloroquinesulfate-Model_2	Interact	-0.004	0.006	-0.618	0.543	0.008383	-0.01638
Azathioprine-Model_3	TimePeriod	0	0.003	-0.167	0.869	0.006192	-0.00619
Azathioprine-Model_3	Phase	0.152	0.105	1.451	0.162	0.368709	-0.06471
Azathioprine-Model_3	Interact	-0.008	0.006	-1.362	0.188	0.004383	-0.02038
Methotrexate-Model_4	TimePeriod	0.004	0.003	1.552	0.136	0.010192	-0.00219
Methotrexate-Model_4	Phase	-0.017	0.1	-0.171	0.866	0.18939	-0.22339
Methotrexate-Model_4	Interact	-0.001	0.005	-0.113	0.911	0.009319	-0.01132
Leflunomide-Model_5	TimePeriod	0.003	0.003	1.193	0.246	0.009192	-0.00319
Leflunomide-Model_5	Phase	-0.03	0.106	-0.285	0.778	0.188773	-0.24877
Leflunomide-Model_5	Interact	0.00006631	0.006	0.012	0.991	0.01245	-0.01232

ARIMA(1,0,0), AR		Estimate	Standard Error	t	P-value	UCI	LCI
Sulfasalazine-Model_1	TimePeriod	0.003	0.002	1.716	0.102	0.007128	-0.00113
Sulfasalazine-Model_1	Phase	-0.033	0.071	-0.459	0.651	0.113537	-0.17954
Sulfasalazine-Model_1	Interact	-0.001	0.004	-0.328	0.746	0.007256	-0.00926
Hydroxychloroquinesulfate-Model_2	TimePeriod	0.002	0.002	0.722	0.478	0.006128	-0.00213
Hydroxychloroquinesulfate-Model_2	Phase	0.092	0.094	0.983	0.337	0.286006	-0.10201
Hydroxychloroquinesulfate-Model_2	Interact	-0.004	0.005	-0.907	0.375	0.006319	-0.01432
Azathioprine-Model_3	TimePeriod	0	0.002	-0.143	0.888	0.004128	-0.00413
Azathioprine-Model_3	Phase	0.153	0.088	1.744	0.096	0.334623	-0.02862
Azathioprine-Model_3	Interact	-0.008	0.005	-1.677	0.109	0.002319	-0.01832
Methotrexate-Model_4	TimePeriod	0.004	0.001	2.719	0.013	0.006064	0.001936
Methotrexate-Model_4	Phase	-0.019	0.059	-0.323	0.75	0.10277	-0.14077
Methotrexate-Model_4	Interact	0	0.003	-0.117	0.908	0.006192	-0.00619
Leflunomide-Model_5	TimePeriod	0.004	0.002	2.073	0.051	0.008128	-0.00013
Leflunomide-Model_5	Phase	-0.034	0.068	-0.498	0.624	0.106345	-0.17435
Leflunomide-Model_5	Interact	0	0.004	0.056	0.956	0.008256	-0.00826

ARIMA(0,1,0), Difference		Estimate	Standard Error	t	P-value	UCI	LCI
Sulfasalazine-Model_1	TimePeriod	0.004	0.005	0.721	0.48	0.014319	-0.00632
Sulfasalazine-Model_1	Phase	-0.142	0.181	-0.786	0.441	0.231566	-0.51557
Sulfasalazine-Model_1	Interact	0.004	0.01	0.417	0.681	0.024639	-0.01664
Hydroxychloroquinesulfate-Model_2	TimePeriod	0.006	0.005	1.089	0.289	0.016319	-0.00432
Hydroxychloroquinesulfate-Model_2	Phase	-0.073	0.193	-0.38	0.708	0.325332	-0.47133
Hydroxychloroquinesulfate-Model_2	Interact	-0.001	0.01	-0.084	0.934	0.019639	-0.02164
Azathioprine-Model_3	TimePeriod	0.003	0.005	0.741	0.467	0.013319	-0.00732
Azathioprine-Model_3	Phase	-0.018	0.168	-0.109	0.914	0.328735	-0.36473
Azathioprine-Model_3	Interact	-0.002	0.009	-0.196	0.847	0.016575	-0.02058
Methotrexate-Model_4	TimePeriod	0.003	0.005	0.638	0.531	0.013319	-0.00732
Methotrexate-Model_4	Phase	-0.041	0.178	-0.228	0.822	0.326374	-0.40837
Methotrexate-Model_4	Interact	-0.001	0.01	-0.06	0.953	0.019639	-0.02164
Leflunomide-Model_5	TimePeriod	0.004	0.005	0.731	0.473	0.014319	-0.00632
Leflunomide-Model_5	Phase	-0.054	0.184	-0.291	0.774	0.325757	-0.43376
Leflunomide-Model_5	Interact	0	0.01	-0.025	0.981	0.020639	-0.02064

ARIMA(0,0,1), MA, Natural Log		Estimate	Standard Error	t	P-value	UCI	LCI
Sulfasalazine-Model_1	TimePeriod	0.003	0.001	3.399	0.003	0.005064	0.000936
Sulfasalazine-Model_1	Phase	0.001	0.054	0.015	0.989	0.112451	-0.11045
Sulfasalazine-Model_1	Interact	-0.003	0.003	-1.114	0.278	0.003192	-0.00919
Hydroxychloroquinesulfate-Model_2	TimePeriod	0.001	0.001	0.987	0.336	0.003064	-0.00106
Hydroxychloroquinesulfate-Model_2	Phase	0.128	0.066	1.949	0.065	0.264217	-0.00822
Hydroxychloroquinesulfate-Model_2	Interact	-0.006	0.003	-1.952	0.065	0.000192	-0.01219
Azathioprine-Model_3	TimePeriod	-0.00002175	0.001	-0.023	0.982	0.002042	-0.00209
Azathioprine-Model_3	Phase	0.161	0.053	3.059	0.006	0.270387	0.051613
Azathioprine-Model_3	Interact	-0.009	0.003	-3.398	0.003	-0.00281	-0.01519
Methotrexate-Model_4	TimePeriod	0.004	0.001	5.374	0	0.006064	0.001936
Methotrexate-Model_4	Phase	-0.017	0.034	-0.509	0.616	0.053173	-0.08717
Methotrexate-Model_4	Interact	-0.001	0.002	-0.377	0.71	0.003128	-0.00513
Leflunomide-Model_5	TimePeriod	0.004	0.001	4.722	0	0.006064	0.001936
Leflunomide-Model_5	Phase	-0.04	0.038	-1.044	0.309	0.038428	-0.11843
Leflunomide-Model_5	Interact	0	0.002	0.058	0.954	0.004128	-0.00413

ARIMA(0,0,1), MA, No Transformation		Estimate	Standard Error	t	P-value	UCI	LCI
Sulfasalazine-Model_1	TimePeriod	26528.53	7721.626	3.436	0.003	42465.18	10591.88
Sulfasalazine-Model_1	Phase	44198.442	489757.264	0.09	0.929	1055008	-966611
Sulfasalazine-Model_1	Interact	-29893.865	24000.178	-1.246	0.227	19640.07	-79427.8
Hydroxychloroquinesulfate-Model_2	TimePeriod	5769.508	5354.787	1.077	0.294	16821.25	-5282.23
Hydroxychloroquinesulfate-Model_2	Phase	687248.921	320491.407	2.144	0.044	1348711	25787.17
Hydroxychloroquinesulfate-Model_2	Interact	-32332.165	14877.977	-2.173	0.042	-1625.53	-63038.8
Azathioprine-Model_3	TimePeriod	83.53	4192.71	0.02	0.984	8736.858	-8569.8
Azathioprine-Model_3	Phase	733233.954	243803.562	3.007	0.007	1236420	230048.1
Azathioprine-Model_3	Interact	-39498.697	11810.828	-3.344	0.003	-15122.3	-63875
Methotrexate-Model_4	TimePeriod	16630.548	2992.036	5.558	0.00002	22805.81	10455.29
Methotrexate-Model_4	Phase	-80776.956	140567.625	-0.575	0.572	209340.4	-370894
Methotrexate-Model_4	Interact	-2192.432	6725.045	-0.326	0.748	11687.38	-16072.2
Leflunomide-Model_5	TimePeriod	2041.806	432.517	4.721	0.0001	2934.477	1149.135
Leflunomide-Model_5	Phase	-21148.135	20831.545	-1.015	0.322	21846.06	-64142.3
Leflunomide-Model_5	Interact	28.158	1010.937	0.028	0.978	2114.629	-2058.31

Supplementary Table 3 - Quantity & Cost

Supplemental Results (Total Quantity)

CHEMICAL_SUBSTANCE	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Trend
Sulfasalazine	9.54	8.61	9.33	9.15	9.68	9.07	9.26	9.88	9.12	9.65	9.23	9.32	9.79	8.64	10.26	9.45	8.94	9.08	9.43	8.51	9.18	9.07	8.89	9.75	9.38	
Hydroxychloroquine sulfate	4.89	4.37	4.69	4.57	4.93	4.51	4.67	4.88	4.52	4.79	4.56	4.69	4.66	4.29	5.37	5.11	4.70	4.78	4.91	4.41	4.78	4.84	4.66	5.02	4.68	
Azathioprine	4.69	4.24	4.54	4.45	4.74	4.38	4.45	4.72	4.43	4.65	4.46	4.52	4.45	4.11	4.81	4.90	4.52	4.52	4.54	4.09	4.42	4.44	4.27	4.62	4.30	
Methotrexate	4.19	3.81	4.12	4.05	4.32	3.98	4.11	4.39	4.05	4.31	4.13	4.26	4.27	3.90	4.54	4.26	4.08	4.21	4.40	3.98	4.29	4.33	4.18	4.55	4.17	
Leflunomide	0.56	0.50	0.54	0.53	0.57	0.53	0.54	0.59	0.53	0.57	0.55	0.56	0.56	0.51	0.60	0.57	0.53	0.53	0.56	0.52	0.56	0.57	0.55	0.59	0.55	

Table 1 Total Quantity; Monthly Subtotal (in millions)

Supplemental Results (Actual Cost)

Medicine	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Trend
Sulfasalazine	0.62	0.56	0.61	0.60	0.64	0.60	0.60	0.66	0.61	0.64	0.62	0.62	0.65	0.58	0.68	0.61	0.57	0.60	0.70	0.64	0.69	0.69	0.73	0.82	0.81	
Hydroxychloroquine sulfate	0.30	0.27	0.29	0.28	0.39	0.49	0.45	0.45	0.38	0.37	0.35	0.36	0.54	0.50	0.62	0.77	0.55	0.49	0.51	0.46	0.50	0.54	0.53	0.56	0.57	
Azathioprine	0.19	0.17	0.18	0.20	0.21	0.19	0.20	0.23	0.21	0.22	0.21	0.22	0.32	0.20	0.56	0.59	0.47	0.43	0.27	0.24	0.26	0.24	0.23	0.24	0.25	
Methotrexate	3.27	3.12	3.45	3.43	3.73	3.52	3.75	4.01	3.85	4.15	4.02	4.21	4.29	3.96	4.70	4.47	4.26	4.14	4.67	4.33	4.65	4.68	4.56	4.94	4.63	
Leflunomide	0.12	0.10	0.11	0.11	0.12	0.11	0.11	0.13	0.12	0.12	0.12	0.12	0.12	0.11	0.12	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.09	0.10	0.09	

Table 2 Actual Cost; Monthly Subtotal (in £millions)

Supplementary Table 4 - Region

Total Quantity by region	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Trend
North West + North East and Yorkshire,	6.88	6.22	6.68	6.57	6.99	6.47	6.63	7.08	6.47	6.92	6.59	6.68	6.84	6.13	7.26	6.93	6.53	6.64	6.86	6.2	6.68	6.66	6.43	7.01	6.54	
Midlands + East of England,	7.77	7.	7.57	7.44	7.87	7.34	7.49	7.99	7.39	7.78	7.45	7.64	7.74	7.01	8.27	7.92	7.47	7.54	7.82	7.04	7.6	7.56	7.36	8.03	7.57	
South East + South West	6.65	6.	6.5	6.33	6.79	6.27	6.32	6.9	6.36	6.71	6.44	6.53	6.61	6.	7.17	6.84	6.35	6.42	6.61	5.98	6.46	6.49	6.35	6.88	6.5	
London	2.57	2.3	2.47	2.41	2.59	2.39	2.58	2.49	2.44	2.55	2.46	2.5	2.54	2.31	2.89	2.61	2.42	2.5	2.55	2.31	2.49	2.54	2.4	2.6	2.47	
UNIDENTIFIED	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.01	0.	
Monthly Subtotal	23.87	21.52	23.22	22.75	24.25	22.48	23.02	24.46	22.66	23.96	22.94	23.35	23.73	21.45	25.59	24.3	22.77	23.1	23.84	21.52	23.23	23.25	22.54	24.52	23.08	

Table 3 Total Quantity in millions by region

Actual Cost by region	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Trend		t-test (North vs. Total)
North West + North East and Yorkshire,	1.11	1.03	1.12	1.12	1.23	1.2	1.24	1.33	1.25	1.32	1.25	1.3	1.4	1.25	1.57	1.53	1.39	1.42	0.82	0.74	0.79	0.79	0.77	0.84	0.8		P-value	9.99E-35
Midlands + East of England,	1.49	1.41	1.56	1.55	1.7	1.64	1.73	1.84	1.76	1.9	1.83	1.92	2.06	1.88	2.3	2.29	2.09	2.15	2.19	2.01	2.17	2.17	2.16	2.31	2.23			
South East + South West	1.68	1.59	1.75	1.73	1.91	1.81	1.86	2.04	1.91	2.03	1.98	2.05	2.15	1.95	2.44	2.34	2.15	2.24	2.28	2.13	2.26	2.32	2.26	2.48	2.33			
London	0.22	0.2	0.22	0.22	0.25	0.26	0.27	0.26	0.25	0.27	0.25	0.26	0.31	0.27	0.38	0.38	0.31	0.32	0.31	0.29	0.31	0.32	0.31	0.33	0.33			
UNIDENTIFIED	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.			
Monthly Subtotal	4.51	4.23	4.64	4.62	5.09	4.91	5.11	5.47	5.17	5.51	5.32	5.53	5.91	5.35	6.69	6.54	5.95	6.13	5.6	5.17	5.54	5.59	5.5	5.96	5.68			

Table 4 Actual Cost in £millions by region

Supplementary Table 5 - Methotrexate Quantity (in millions)

BNF DESCRIPTION	BNF_CODE	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21
Methotrexate 5mg/2ml solution for injection vials	1001030U0AAABAB	3.928	3.556	3.842	3.776	4.03	3.709	3.821	4.087	3.757	4.	3.828	3.948	3.949	3.608	4.195	3.934	3.763	3.89	4.059	3.67	3.958	3.993	3.851	4.191	3.84
Methotrexate 50mg/2ml solution for injection vials	1001030U0BEARBW	0.055	0.053	0.059	0.058	0.064	0.06	0.065	0.069	0.067	0.072	0.07	0.074	0.075	0.07	0.083	0.079	0.076	0.078	0.082	0.077	0.082	0.084	0.081	0.088	0.082
Methotrexate 1g/10ml solution for injection vials	1001030U0BEARBW	0.055	0.053	0.059	0.058	0.064	0.06	0.065	0.069	0.067	0.072	0.07	0.074	0.075	0.07	0.083	0.079	0.076	0.078	0.082	0.077	0.082	0.084	0.081	0.088	0.082
Methotrexate 20mg/0.8ml inj pre-filled syringes	1001030U0BEAWCB	0.037	0.036	0.041	0.04	0.044	0.042	0.045	0.048	0.048	0.051	0.05	0.054	0.053	0.049	0.06	0.056	0.054	0.056	0.06	0.055	0.06	0.06	0.059	0.064	0.06
Methotrexate 22.5mg/0.9ml inj pre-filled syringes	1001030U0BEAWCB	0.037	0.036	0.041	0.04	0.044	0.042	0.045	0.048	0.048	0.051	0.05	0.054	0.053	0.049	0.06	0.056	0.054	0.056	0.06	0.055	0.06	0.06	0.059	0.064	0.06
Methotrexate 25mg/1ml inj pre-filled syringes	1001030U0BEAXCC	0.036	0.035	0.04	0.04	0.043	0.04	0.044	0.046	0.044	0.049	0.045	0.048	0.048	0.046	0.054	0.052	0.049	0.052	0.054	0.051	0.054	0.056	0.053	0.058	0.055
Methotrexate 10mg/0.4ml inj pre-filled syringes	1001030U0BEAXCC	0.036	0.035	0.04	0.04	0.043	0.04	0.044	0.046	0.044	0.049	0.045	0.048	0.048	0.046	0.054	0.052	0.049	0.052	0.054	0.051	0.054	0.056	0.053	0.058	0.055
Methotrexate 7.5mg/0.3ml inj pre-filled syringes	1001030U0BEAZCE	0.016	0.017	0.018	0.017	0.02	0.019	0.02	0.021	0.021	0.022	0.022	0.022	0.023	0.021	0.025	0.023	0.023	0.023	0.024	0.022	0.024	0.024	0.023	0.025	0.024
Methotrexate 12.5mg/0.5ml inj pre-filled syringes	1001030U0BEAZCE	0.016	0.017	0.018	0.017	0.02	0.019	0.02	0.021	0.021	0.022	0.022	0.022	0.023	0.021	0.025	0.023	0.023	0.023	0.024	0.022	0.024	0.024	0.023	0.025	0.024
Methotrexate 15mg/0.6ml inj pre-filled syringes	1001030U0AAACAC	0.035	0.031	0.032	0.03	0.032	0.029	0.029	0.029	0.027	0.028	0.026	0.026	0.025	0.022	0.025	0.023	0.021	0.022	0.021	0.019	0.019	0.019	0.017	0.02	0.016
Methotrexate 17.5mg/0.7ml inj pre-filled syringes	1001030U0BEAQBV	0.01	0.009	0.01	0.011	0.011	0.011	0.011	0.013	0.012	0.012	0.013	0.013	0.013	0.012	0.015	0.014	0.013	0.014	0.014	0.013	0.015	0.015	0.014	0.016	0.015
Methotrexate 7.5mg/0.3ml inj pre-filled disposable	1001030U0BEAQBV	0.01	0.009	0.01	0.011	0.011	0.011	0.011	0.013	0.012	0.012	0.013	0.013	0.013	0.012	0.015	0.014	0.013	0.014	0.014	0.013	0.015	0.015	0.014	0.016	0.015
Methotrexate 10mg/0.4ml inj pre-filled disposable	1001030U0BEAYCD	0.008	0.009	0.009	0.009	0.01	0.009	0.01	0.01	0.01	0.011	0.011	0.011	0.011	0.011	0.013	0.012	0.011	0.012	0.013	0.012	0.013	0.013	0.013	0.014	0.013
Methotrexate 12.5mg/0.5ml inj pre-filled disposabl	1001030U0BEAYCD	0.008	0.009	0.009	0.009	0.01	0.009	0.01	0.01	0.01	0.011	0.011	0.011	0.011	0.011	0.013	0.012	0.011	0.012	0.013	0.012	0.013	0.013	0.013	0.014	0.013
Methotrexate 15mg/0.6ml inj pre-filled disposable	1001030U0BDAAAB	0.013	0.011	0.012	0.012	0.013	0.011	0.012	0.013	0.012	0.012	0.011	0.012	0.011	0.011	0.013	0.011	0.011	0.011	0.012	0.01	0.01	0.011	0.01	0.011	0.01
Methotrexate 17.5mg/0.7ml inj pre-filled disposabl	1001030U0BEASBX	0.005	0.005	0.006	0.006	0.007	0.006	0.006	0.007	0.006	0.007	0.007	0.007	0.008	0.007	0.009	0.009	0.008	0.008	0.009	0.008	0.009	0.009	0.009	0.009	0.009
Methotrexate 20mg/0.8ml inj pre-filled disposable	1001030U0BEASBX	0.005	0.005	0.006	0.006	0.007	0.006	0.006	0.007	0.006	0.007	0.007	0.007	0.008	0.007	0.009	0.009	0.008	0.008	0.009	0.008	0.009	0.009	0.009	0.009	0.009
Methotrexate 22.5mg/0.9ml inj pre-filled disposabl	1001030U0BEATBY	0.006	0.005	0.006	0.006	0.007	0.006	0.007	0.007	0.007	0.008	0.007	0.008	0.007	0.007	0.008	0.008	0.007	0.008	0.008	0.008	0.008	0.008	0.008	0.009	0.008
Methotrexate 25mg/1ml inj pre-filled disposable de	1001030U0BEATBY	0.006	0.005	0.006	0.006	0.007	0.006	0.007	0.007	0.007	0.008	0.007	0.008	0.007	0.007	0.008	0.008	0.007	0.008	0.008	0.008	0.008	0.008	0.008	0.009	0.008
Zlatal 20mg/0.8ml solution for injection pre-fille	1001030U0AABWBW	0.01	0.009	0.009	0.009	0.01	0.009	0.009	0.009	0.008	0.009	0.008	0.008	0.008	0.007	0.008	0.008	0.007	0.007	0.007	0.006	0.007	0.006	0.006	0.006	0.006
Zlatal 22.5mg/0.9ml inj pre-filled syringes	1001030U0AACCCC	0.006	0.006	0.006	0.006	0.006	0.006	0.006	0.006	0.005	0.006	0.005	0.006	0.005	0.005	0.006	0.005	0.005	0.005	0.005	0.004	0.005	0.004	0.004	0.004	0.004
Zlatal 25mg/1ml solution for injection pre-filled	1001030U0AACBCB	0.006	0.005	0.006	0.006	0.006	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.004	0.005	0.005	0.005	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.004
Zlatal 10mg/0.4ml solution for injection pre-fille	1001030U0AACFCF	0.003	0.003	0.003	0.002	0.002	0.002	0.002	0.002	0.003	0.002	0.003	0.002	0.003	0.003	0.003	0.002	0.003	0.003	0.003	0.002	0.002	0.003	0.003	0.003	0.003
Zlatal 7.5mg/0.3ml inj pre-filled syringes	0801030P0BFAFFS	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.002	0.001	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
Zlatal 12.5mg/0.5ml inj pre-filled syringes	0801030P0BFADFQ	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
Zlatal 15mg/0.6ml solution for injection pre-fille	1001030U0AACECE	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.002	0.003	0.003	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
Zlatal 17.5mg/0.7ml inj pre-filled syringes	0801030P0BFAHFU	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 7.5mg/0.3ml solution for injection pre-fi	1001030U0AABVBV	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.001	0.002	0.001	0.002	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 10mg/0.4ml solution for injection pre-fil	1001030U0AABHBH	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 12.5mg/0.5ml solution for injection pre-f	1001030U0AACDCD	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 15mg/0.6ml solution for injection pre-fil	1001030U0AABXBX	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 17.5mg/0.7ml solution for injection pre-f	1001030U0AABYBY	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 20mg/0.8ml solution for injection pre-fil	1001030U0AABGBG	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.001	0.	0.001	0.001	0.001	0.001	0.001
Nordimet 22.5mg/0.9ml solution for injection pre-f	0801030P0BFABFN	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.001	0.001	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 25mg/1ml solution for injection pre-fille	0801030P0AAFSFS	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Methotrexate 2.5mg tablets	1001030U0AAAEAE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.001	0.	0.	0.	0.	0.001	0.	0.	0.001	0.	0.	0.	0.	0.	0.	0.001
Methotrexate 10mg tablets	1001030U0BGAFBW	0.	0.	0.	0.	0.	0.	0.001	0.	0.	0.001	0.001	0.001	0.	0.	0.001	0.	0.	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Methotrexate 2.5mg/5ml oral liquid	1001030U0BEAVCA	0.	0.	0.	0.	0.	0.	0.	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.
Methotrexate 5mg/5ml oral liquid	1001030U0BEAVCA	0.	0.	0.	0.	0.	0.	0.	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.
Methotrexate 10mg/5ml oral liquid	0801030P0AAFUFU	0.	0.	0.	0.001	0.001	0.001	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.
Methotrexate 7.5mg/5ml oral liquid	0801030P0AAFQFQ	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.	0.001	0.	0.	0.001	0.	0.	0.	0.
Methotrexate 12.5mg/5ml oral liquid	1001030U0AABIBI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 15mg/5ml oral liquid	1001030U0AABFBF	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 20mg/2ml inj pre-filled syringes	0801030P0BFAEFR	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 15mg/1.5ml inj pre-filled syringes	1001030U0BGADCC	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 7.5mg/0.15ml inj pre-filled syringes	1001030U0BGAHCB	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 10mg/0.2ml inj pre-filled syringes	0801030P0AAFEFE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 15mg/0.3ml inj pre-filled syringes	0801030P0BFACFP	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 20mg/0.4ml inj pre-filled syringes	1001030U0AABKBK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 25mg/0.5ml inj pre-filled syringes	0801030P0AAFGFG	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 30mg/0.6ml inj pre-filled syringes	0801030P0AAFNFN	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 12.5mg/0.25ml inj pre-filled syringes	0801030P0BFAAFM	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 17.5mg/0.35ml inj pre-filled syringes	0801030P0AAFKFK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 22.5mg/0.45ml inj pre-filled syringes	1001030U0AABLBL	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 17.5mg/0.35ml inj pre-filled disposab	1001030U0BDABAC	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 20mg/0.4ml inj pre-filled disposable	0801030P0BFAGFT	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 22.5mg/0.45ml inj pre-filled disposab	1001030U0BGABCE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 7.5mg/0.15ml inj pre-filled disposabl	0801030P0AAFRFR	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 27.5mg/0.55ml inj pre-filled disposab	0801030P0BEAAFE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 30mg/0.6ml inj pre-filled disposable	0801030P0AAFPFP	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 25mg/0.5ml inj pre-filled disposable	1001030U0AABEBE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 15mg/0.3ml inj pre-filled disposable	0801030P0BEAGFK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 12.5mg/0.25ml inj pre-filled disposab	1001030U0BEAUBZ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 10mg/0.2ml inj pre-filled disposable	1001030U0BEAUBZ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 2mg/ml oral solution sugar free	0801030P0AAFHFH	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Maxtrex 2.5mg tablets	1001030U0BGAEBV	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Maxtrex 10mg tablets	1001030U0AABMBM	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 20mg/2ml solution for injection pre-fille	0801030P0AAFMFM	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 10mg/1ml solution for injection pre-fille	1001030U0BGACCD	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 15mg/1.5ml inj pre-filled syringes	0801030P0BEACFG	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 25mg/2.5ml inj pre-filled syringes	0801030P0AAFTFT	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 7.5mg/0.15ml inj pre-filled syringes	1001030U0AAAHAH	0.	0.	0.	0.	0.001	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 10mg/0.2ml inj pre-filled syringes	1001030U0BGAPBH	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 15mg/0.3ml inj pre-filled syringes	0801030P0AAFLFL	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 20mg/0.4ml inj pre-filled syringes	1001030U0BGAGBX	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 25mg/0.5ml inj pre-filled syringes	0801030P0AAFFFF	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 12.5mg/0.25ml inj pre-filled syringes	1001030U0BGAABY	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 17.5mg/0.35ml inj pre-filled syringes	0801030P0AAFIFI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 22.5mg/0.45ml inj pre-filled syringes	1001030U0BGARBI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 17.5mg/0.35ml inj pre-filled pens	1001030U0BGAMBG	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 17.5mg/0.35ml inj pre-filled pen	0801030P0AAFJFJ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 20mg/0.4ml inj pre-filled pens	1001030U0AACACA	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 20mg/0.4ml inj pre-filled pen	0801030P0BEADFH	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 22.5mg/0.45ml inj pre-filled pens	0801030P0BEAEFI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 22.5mg/0.45ml inj pre-filled pen	1001030U0AABZBZ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 7.5mg/0.15ml inj pre-filled pen	0801030P0BEAHFL	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 7.5mg/0.15ml inj pre-filled pens	1001030U0BEACBB	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 27.5mg/0.55ml inj pre-filled pens	1001030U0BGAQBM	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 27.5mg/0.55ml inj pre-filled pen	1001030U0BGAUBK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 30mg/0.6ml inj pre-filled pens	0801030P0BEABFF	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 30mg/0.6ml inj pre-filled pen	1001030U0BEAMBL	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 25mg/0.5ml inj pre-filled pens	0801030P0BEAFFJ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 25mg/0.5ml inj pre-filled pen	1001030U0BEAIBH	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 15mg/0.3ml inj pre-filled pen	1001030U0BEAGBF	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 15mg/0.3ml inj pre-filled pens	1001030U0BEAHBG	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 12.5mg/0.25ml inj pre-filled pens	1001030U0BEAJBI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 12.5mg/0.25ml inj pre-filled pen	1001030U0BEALBK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 10mg/0.2ml inj pre-filled pens	1001030U0BGAKBE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 10mg/0.2ml inj pre-filled pen	1001030U0BGANBL	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 7.5mg/0.15ml inj pre-filled injector	1001030U0BEADBC	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill10mg/0.2ml inj pre-filled injector	0801030P0AAAIAI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 12.5mg/0.25ml inj pre-filled injector	0801030P0AAANAN	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 15mg/0.3ml inj pre-filled injector	0801030P0AACKCK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 17.5mg/0.35ml inj pre-filled injector	1001030U0AAAFAF	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 20mg/0.4ml inj pre-filled injector	1001030U0AAAIAI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 22.5mg/0.45ml inj pre-filled injector	1001030U0AAAKAK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 25mg/0.5ml inj pre-filled injector	1001030U0AAARAR	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 27.5mg/0.55ml inj pre-filled injector	1001030U0AABABA	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 7.5mg/0.15ml inj pre-filled syringes	1001030U0AABCBC	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 10mg/0.2ml inj pre-filled syringes	1001030U0AABJBJ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 15mg/0.3ml inj pre-filled syringes	1001030U0BEABBA	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 17.5mg/0.35ml inj pre-filled syringes	1001030U0BEAEBD	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 20mg/0.4ml inj pre-filled syringes	1001030U0BEAFBE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 22.5mg/0.45ml inj pre-filled syringes	1001030U0BEANBM	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 25mg/0.5ml inj pre-filled syringes	1001030U0BGAIBZ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 12.5mg/0.25ml inj pre-filled syringes	1001030U0BGALBF	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
	Sum Total (Methotrexate)	4.368	3.977	4.306	4.232	4.529	4.177	4.321	4.615	4.267	4.546	4.357	4.502	4.508	4.125	4.81	4.516	4.318	4.47	4.661	4.229	4.557	4.6	4.438	4.829	4.439
	Sum of top ten rows (10010	4.253	3.868	4.187	4.116	4.402	4.061	4.197	4.484	4.143	4.415	4.228	4.37	4.374	4.001	4.662	4.378	4.187	4.332	4.52	4.098	4.416	4.459	4.299	4.68	4.299
	% Sum of top ten rows	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title and abstract PG 2 Title and abstract PG 2 N/A
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			In Introduction section
Objectives	3	State specific objectives, including any prespecified hypotheses			End of Introduction section (pg 5)
Methods					

Study Design	4	Present key elements of study design early in the paper			Materials and methods section
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Materials and methods section
Participants	6	*(a) Cohort study*- Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*- Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*- Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study*- For matched studies, give matching criteria and number of exposed and unexposed		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Materials and methods section

		Case-control study- For matched studies, give matching criteria and the number of controls per case			
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Materials and methods section, See Supplementary (Quantity & Cost), Supplementary (Region), Supplementary (Methotrexate Quantity)
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			Materials and methods section. Original data are available from https://www.nhsbsa.nhs.uk/prescription-data/prescribing-data/english-prescribing-data-epd
Bias	9	Describe any efforts to address potential sources of bias			N/A

Study size	10	Explain how the study size was arrived at			Materials and methods section
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Materials and methods section
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study*- If applicable, explain how loss to follow-up was addressed *Case-control study*- If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*- If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			Materials and methods section
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Materials and methods section

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Materials and methods section
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	None, N/A. Data Source.
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	N/A

Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study*- summarise follow-up time (*e.g.*, average and total amount)			Results, Table 1
Outcome data	15	*Cohort study*- Report numbers of outcome events or summary measures over time *Case-control study*- Report numbers in each exposure			Results, Table 1
		category, or summary measures of exposure *Cross-sectional study*- Report numbers of outcome events or summary measures			

Main results	16	(a) Give unadjusted estimates and, if applicable, confounder- adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (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			Results section. Supplementary - Quantity & Cost Supplementary - Region Supplementary - Methotrexate Quantity
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			Results section. Supplementary - ARIMA Syntax Supplementary - Sensitivity analysis
Discussion					
Key results	18	Summarise key results with reference to study objectives			Discussion section

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion section
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			Discussion section
Generalisability	21	Discuss the generalisability (external validity) of the study results			Discussion section
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			Acknowledgment section

Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Supplementary ARIMA Syntax Supplementary Sensitivity analysis

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

Impact of the COVID-19 pandemic on prescription refills for immune-mediated inflammatory disorders: a time series analysis (Jan 2019 to Jan 2021) using the English Prescribing Dataset

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051936.R2
Article Type:	Original research
Date Submitted by the Author:	12-Dec-2022
Complete List of Authors:	Barrett, Ravina; University of Brighton, School of Applied Sciences Barrett, Rob; University of Portsmouth Lin, Sharon; University of Southampton, Faculty of Health Sciences Culliford, David; University of Southampton, Faculty of Medicine Fraser, Simon; University of Southampton, Faculty of Medicine Edwards, Christopher; University Hospital Southampton NHS Foundation Trust, Rheumatology
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Immunology (including allergy), Epidemiology, Patient-centred medicine, Oncology
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, COVID-19, EPIDEMIOLOGY, GASTROENTEROLOGY, Rheumatology < INTERNAL MEDICINE, RHEUMATOLOGY

Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.

25 November 2022 at 17_24_51_default_f4b41e4e.mp4

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Impact of the COVID-19 pandemic on prescription refills for immune-mediated inflammatory disorders: a time series analysis (Jan 2019 to Jan 2021) using the English Prescribing Dataset

Authors and affiliations:

1. Mrs. Ravina Barrett (https://orcid.org/0000-0003-0004-2131) MPharm, FHEA, MSc Finance, Senior Lecturer in Pharmacy Practice, Course Leader (MSc Clinical Pharmacy), School of Applied Sciences, Cockcroft Building, University of Brighton, Moulsecoomb, Brighton, BN2 4GJ. +44(0)1273643986, R.Barrett2@Brighton.ac.uk
2. Mr. Robert Barrett, MBA, MCSE, MCSA, MCP, ITIL, Prince 2 rob-barrett@outlook.com ; https://orcid.org/0000-0003-3402-3377 Affiliations not disclosed.
3. Dr. Sharon X Lin; research fellow at The School of Primary Care and Population Sciences, Faculty of Medicine, Southampton General Hospital, SO16 6YD, X.Lin@soton.ac.uk
4. Dr. David Culliford, Principal Medical Statistician, NIHR Applied Research Collaboration Wessex, Faculty of Environmental and Life Sciences, University of Southampton, Southampton General Hospital (Room AA71, MP11), Southampton SO16 6YD, Tel + 44 (0) 23 8120 3374, d.j.culliford@soton.ac.uk
5. Dr. Simon Fraser BM. MSc, DM, DRCOG, DCH, MRCGP. Dip, FHEA, MFPH, FFPH. Associate Professor of Public Health; School of Primary Care and Population Sciences, Faculty of Medicine, Southampton General Hospital, SO16 6YD, Tel: 023 81206138 (https://orcid.org/) S.Fraser@soton.ac.uk.
6. Professor Christopher J Edwards BSc, MBBS, MD, FRCP, Consultant Rheumatologist, University Hospital Southampton NHS Foundation Trust, Honorary Chair of Clinical Rheumatology, Faculty of Medicine, University of Southampton, Co- Director, NIHR Southampton Clinical Research Facility, cedwards@soton.ac.uk

Correspondence to:
Mrs. Ravina Barrett
School of Applied Sciences, Cockcroft Building, University of Brighton, Moulsecoomb, Brighton, BN2 4GJ
R.Barrett2@Brighton.ac.uk

Supplementary Table 1 - ARIMA Syntax (Mar20-1) Jan 19 to Jan 21
Supplementary Table 2 - Sensitivity analysis (Mar20-1) Jan 19 to Jan 21 (including changepoint sensitivity analysis)
Supplementary Table 3 - Quantity & Cost
Supplementary Table 4 - Region
Supplementary Table 5 - Methotrexate Quantity

Abstract

Objective

To investigate monthly prescription refills for common immunosuppressive/immunomodulatory therapy (sulfasalazine, hydroxychloroquine, azathioprine, methotrexate, leflunomide) prescriptions in England during the complete first wave of the COVID-19 pandemic. Secondary analysis examined unit cost analysis, and regional use.

Design and setting

A national cohort of community based, primary care patients who anonymously contribute data to the English Prescribing Dataset, dispensed in the community in England were included. Descriptive statistics and interrupted time series analysis over 25 months (14 months before, 11 months after first lockdown) were evaluated (January 2019 to January 2021, with March 2020 as the cut-off point).

Outcome measures

Prescription reimbursement variance in period before the pandemic as compared to after the first lockdown.

Results

Fluctuation in monthly medicines use is noted in March 2020: a jump is observed for hydroxychloroquine (Mann-Whitney, standard error 14.652, standardised test statistic 1.911, p-value = 0.059) over the study period. After the first lockdown, medicines use fluctuated, with wide confidence intervals. Unit-cost prices changed substantially: sulfasalazine 33% increase, hydroxychloroquine 98% increase, azathioprine 41% increase, methotrexate 41% increase, leflunomide 20% decrease. London showed the least quantity variance, suggesting more homogeneous prescribing and patient access compared to Midlands and East of England, suggesting that some patients may have received medication over/under requirement, representing potential resource misallocation and a proxy for adherence rates. Changepoint detection revealed four out of the five medicines' use patterns changed with a strong signal only for sulfasalazine in March/April 2020.

Conclusions

Findings potentially present lower rates of adherence because of the pandemic, suggesting barriers to care access. Unit price increases are likely to have severe budget impacts in the UK and potentially globally. Timely prescription refills for patients taking immunosuppressive/immunomodulatory therapies are recommended. Healthcare professionals should identify patients on these medicines and assess their prescription-day coverage, with planned actions to flag and follow-up adherence concerns in patients.

Keywords

COVID-19; severe acute respiratory syndrome coronavirus 2. COVID-19/SARS-CoV-2 Pandemic; Disparities, rheumatoid arthritis, medicines, pharmacy services, prescriptions

Strengths and limitations of this study.

- This is a first of its kind work using ARIMA modelling to conduct an interrupted time series analysis on prescription reimbursement data on immunosuppressive/immunomodulatory medicines (sulfasalazine, hydroxychloroquine sulfate, azathioprine, methotrexate, leflunomide) between January 2019 and January 2021 using the English Prescribing Dataset.
- The methodological novelty of this technique during this initial phase of the pandemic provides valuable insights for clinicians, healthcare professionals, policy decision makers and budget holders for crisis humanitarian response.
- Regional and cost analysis is provided, that examines the variance in the use of selected medications across England and underlying unit price changes across time.
- Unfortunately, this rich database does not provide the exact prescription date, which is the most severe limitation of the study as it impedes more complex models.
- A key methodological limitation of the study is that while robust mathematical modelling techniques are used alongside extensive sensitivity analysis, there is only some support for a changepoint at March 2020, without stronger evidence.

Introduction

In England, all people above the age of 60 years, receive prescription medications free of charge through universal care provisions [1]. The National Health Service (NHS) has been publicly funded since 1948 [2] and reimburses primary-care contractors (e.g., general practitioners (GPs), pharmacies, dentists, etc.) through central and local budgets [3]. Consequently, NHS datasets provide a valuable and accurate insight into current practice and the ongoing management of many chronic long-term conditions [4].

Immunosuppressive and immunomodulatory (IIDs) medicines like sulfasalazine, hydroxychloroquine sulfate, azathioprine, methotrexate, leflunomide are the mainstay for the treatment of many painful conditions of the joints e.g., Rheumatoid arthritis, Psoriatic arthritis, Systemic lupus erythematosus, Spondyloarthritis and related arthritic conditions [5–9]. Amongst the most common are rheumatoid arthritis, Crohn's disease and psoriasis that affect 0.8% [10], 0.395% (overall adult prevalence of 403 per 100 000 population in 2017 [11]) and 2.8% [12] of the UK population, respectively. Study by Yue et al.[13] describes the adjusted risk ratio [aRR] of patients with COVID-19 and immune-mediated inflammatory diseases (IMIDs) as having a significantly higher risk of severe COVID-19 compared to the general population: rheumatoid arthritis (aRR 1.2, 1.1–1.3). While, other IMIDs like systemic lupus erythematosus (aRR 1.1, 0.9–1.2), psoriasis (aRR 1.0, 0.7–1.2), ulcerative colitis (aRR 0.9, 0.8–1.1), Crohn's disease (aRR 0.9, 0.7–1.0), or ankylosing spondylitis (aRR 0.8, 0.5–1.0) showed a comparable risk of severe COVID-19. Patients with atopic dermatitis (aRR 0.8, 0.7–0.9) or psoriatic arthritis (aRR 0.8, 0.6–1.0) showed a lower risk of severe COVID-19.

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that primarily targets synovial joints, resulting in pain and functional limitations [14] and is an example of a disease in which delays to treatment can lead to considerable damage. It is the most common inflammatory arthritis, and a significant cause of morbidity and mortality [15]. From a primary care perspective, early recognition, along with its extra-articular manifestations, can lead to faster time to treatment and better health outcomes, in addition to preserved joint functionality [16–18].

IIDs are also used in chronic conditions of the bowels [19–21] (e.g., Crohn's disease, ulcerated colitis, diverticulitis) as well as for anti-rejection therapy [22] when organ transplants or grafts have been used as they supress the autoimmune destruction. These medicines are important because they provide a lifeline towards functional mobility and improves the quality of life [23,24] for patients by relieving their pain as well as retarding disease progression. Other medicines include alkylating agents (e.g., cyclophosphamide), Janus kinase (JAK) inhibitors (e.g., Baricitinib), Phosphodiesterase type-4 (PDE4) inhibitor (e.g., apremilast) and Tumor Necrosis Factor (TNF) - alpha inhibitor (e.g., Adalimumab (Humira®), Etanercept (Enbrel®)) are used for RA.

These medicines are usually taken as chronic long-term medications for the management of such relapsing-remitting autoimmune conditions. Their consistent use provides optimal pain relief and their mechanisms of action mean long-term use dampens the inflammatory cascade response [25–27]. Collectively, this reduces pain, reduces the inflammatory mediators that recruit towards ongoing inflammatory cascades and arrests the autoimmune response. These medications, if not taken properly, can cause loss of disease control and progressing joint destruction with resultant loss of mobility, poorer mental health, and diminished quality of life.

Given increasing life expectancies worldwide, the number of elderly IMIDs patients are growing [28]. Comorbidities in elderly patients with RA often include cardiovascular disease, cancer, infections, venous and arterial insufficiency amongst others [28]. From a public health perspective, people with RA have been found to be significantly more likely to have reduced their work hours or stopped

working; they are more likely to have lost their job or to have retired early; and are 3 times more likely to have had a reduction in household family income than either individuals with osteoarthritis (OA) or those without arthritis [29–33]. In this way, the economic effects of RA are staggering and emphasize the importance of early recognition and treatment [34]. A study from Egypt suggests that patients with RA faced remarkable difficulty to obtain their medications with subsequent change in their disease status [35].

The COVID-19 pandemic has meant that many patients in the middle to elderly age category who may suffer from arthritis-like conditions may be at higher risk of contracting the virus because of their advanced age, comorbidities, and their dampened immune function. In the United Kingdom (UK), during the pandemic, patients could not see healthcare professionals in a timely fashion, leading to backlogs even today including operations, cancer waiting, GP referrals and casualty waiting times, with some people waiting over one year for minor operations [36]. The government has outlined how it has learned from mistakes made during the pandemic [37]. However, an independent inquiry into the government's handling of the pandemic is currently underway [38]. Normal care for patients has been affected, as reflected in urgently developed pandemic-guidelines [39]. There have been supply shortages across the UK [40], Europe and many parts of the world before [41–43] the pandemic and after for many medications during the pandemic (e.g. ibuprofen and paracetamol). The European Medicines Agency (EMA) acknowledges shortage of etanercept (Enbrel®) in pre-filled pens and syringes [44].

The objective of the present study was to examine the effect of the pandemic on prescription prescribing patterns and costs for immunosuppressive/immunomodulatory medicines in England.

Methods

Data and resources

The 'English Prescribing Dataset' (EPD) [45] provided anonymised prescription data in England covered by Open Government Licence (OGL). The EPD comprises detailed information on community-issued prescriptions (not hospital) issued in England but dispensed across the UK (England, Wales, Scotland, Guernsey, Alderney, Jersey, and the Isle of Man). It holds detailed prescribing information at practice level, aggregated by British National Formulary (BNF) code e.g., 0105010E0AAABAB for 'Sulfasalazine 500mg gastro-resistant tablets' to maintain patient confidentiality. This data set contains the following variables, amongst others: ,"YEAR_MONTH" e.g., presented as 201901 to represent Jan-19,"CHEMICAL_SUBSTANCE" e.g., Methotrexate, Sulfasalazine, "Chemical Substance" by code e.g., 1001030U0,"BNF_DESCRIPTION" e.g., Metoject PEN 20mg/0.4ml inj pre-filled pens; Sulazine EC 500mg tablets (Genesis Pharm),Related "BNF_CODE" e.g., 1001030U0BEARBW,"REGIONAL_OFFICE_NAME" e.g., East Anglia Area, Wessex Area, North Of England, "STP_NAME" e.g., Greater Manchester Area, "Total Quantity" (in solid dosage),"Actual Cost" (in Great British pounds),"No Items" (representing number of items which provides information on the number of time an item appeared on a prescription entry, which is not to be confused with the total quantity). Therefore, each row of data does not represent individual patients or prescriptions. The data includes total quantity of unit-doses (e.g., tablets, prefilled insulin pens), and 'actual cost' for reimbursement. In the EPD, there is approximately a latency of released data by two months.

The data excludes prescriptions issued outside England (Wales, Scotland, Guernsey, Alderney, Jersey, and the Isle of Man); items not dispensed, disallowed and those returned for further clarification; prescriptions prescribed and dispensed in prisons, hospitals, and private prescriptions; items prescribed but not presented for dispensing or not submitted to NHS prescription services by the dispenser. This dataset included small (487 out of 2,555,396 rows) operational irregularities (e.g., 17 rows in January 2019 of 'unidentified practice data', 470 rows of 'NULL' chemical substance

codes, where accurate BNF codes were given to permit extraction of the missing data). The study population represents English residents who were issued a prescription and had it dispensed.

Monthly data from January 2019 to January 2021 were compared for sulfasalazine; hydroxychloroquine sulfate; azathioprine; methotrexate and leflunomide. Sodium aurothiomalate; Anakinra; Baricitinib; Apremilast; Infliximab; Golimumab; Etanercept; Certolizumab pegol abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, Rituximab, sarilumab, tocilizumab, tofacitinib, penicillamine and cyclophosphamide were excluded because they are marginally important (normally used under specialist care and are of small volumes, less than a 1000 units per month).

Formulations not normally used in RA (E.g., Sulfasalazine suppositories) were excluded as well as all cutaneous products (e.g., creams, gels, medicated plasters, sprays, cutaneous solutions, transdermal patches, topical solutions). Hence, the data contains tablets, oral liquids and injectables (pre-filled syringes, ampoules, vials).

All prescribed medication across the whole of the primary care interface during this period were extracted which included every single prescription item for the related variable indications i.e., 333,459,762 rows of data (99 gigabytes of data) were extracted using Structured Query Language (SQL). Then, these were filtered down to the specific medications under study. Each row represents an aggregated amount of that medication supplied at the general practitioners' practice level and does not represent individual patients, to maintain anonymity. The excluded rows were for all other medications other than the specific medications under study. After excluding unnecessary rows, 8,186,699 relevant rows (2.6 gigabytes of data) were filtered. In total, 25 comma-separated values (CSV) file were imported into a Microsoft SQL® server table labelled EPD. As each one was imported, it was validated and assigned an exact datatype (e.g., 'Total quantity' is a 'floating' data point, 'regional office name' is a text-field) to each field of data. We removed spaces, blanks, checked for wrong kinds of data (e.g., that text characters weren't in a numeric field or purely numeric characters in a text-field). Microsoft Visual Studio® was used to create and edit SQL Server Integration Services® (SSIS) packages that imported, validated and consolidated the data within an automated import routine. Detailed methods have been previously published [46] in supplemental. Data were aggregated by month, chemical substance, regional office name and BNF code, to allow for human analysis.

The reliable, consistent EDP data allowed for direct monthly comparison. Detailed population analysis was not conduct, and these were assumed to be constant. Patient's diagnoses were unknown. Lockdown commenced on 23rd of March 2020, a second lockdown commenced on 5th November 2020.

Analysis

Analysis was carried out in Excel® v. 2007, SPSS® v. 26 and in RStudio. Results are presented as nominal values, descriptive statistics, and Mann-Whitney U test. Interrupted time series (ITS) analysis was used to fit time trends [47] at the 95% confidence level.

A commonly used time series modelling framework (autoregressive integrated moving average, or ARIMA) was employed to analyse the monthly total-quantity of prescription data. ARIMA is a flexible modelling construct [48–50], allowing lagged correlations and seasonal differences to be modelled. Only a simple model with no allowance for serial correlation nor seasonality was used, mainly due to the lack of data points after the interrupt time point. We had available 25 consecutive monthly data points with the interrupt time set at the 14th month (March 2020), and 14 data points before and 11 data points after March 2020 (estimating regression model with unknown breakpoints was done but minimally, because the first lockdown as our clinically important cut-off point [51] was used). The

estimates for the difference in prescription total-quantity as at March 2020, and also the difference in the linear trend (i.e. between the slopes of the lines) before and after the interrupt time point were calculated. The observed temporal trend in prescription total-quantity was explored visually in advance of performing the main time series analysis. Further sensitivity analysis was conducted using changepoint [52,53] and binary segmentation analysis [51]. See ARIMA Syntax in Supplementary Table 1. See Sensitivity Analysis in Supplementary Table 2 which includes log transformation [50,54,55] and the R-code and analysis for changepoint detection.

Reporting is in line with the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement/RECORD Checklist [56]. Favourable institutional ethical approval was not needed due to the anonymised nature of this dataset analysis because it does not identify any individual patient and this study followed the declaration of Helsinki principles . This data set is covered by the open government licence such that permit the free analysis and reporting of such analysis.

Patient and public involvement

None.

Results

Descriptive statistics can be visualised in Table 1 and Figure 1 for the entire period of study.

Table 1. Descriptive statistics of the total quantities, presented in millions

The total quantity and actual cost in great British pounds are presented for the whole study duration from January 2019 to January 2021. Standard Deviation (SD).

	Before pandemic				After Pandemic's Onset				Total Quantity		Actual Cost (£)	
Medicine	Mean	SD	UCI	LCI	Mean	SD	UCI	LCI	Mean	SD	Mean	SD
Sulfasalazine	9.303	0.384	9.504	9.102	9.267	0.468	9.544	8.991	9.28	0.422	0.628	0.039
Hydroxychloroquine sulfate	4.645	0.190	4.745	4.545	4.835	0.260	4.989	4.681	4.721	0.247	0.448	0.122
Azathioprine	4.488	0.178	4.581	4.394	4.497	0.234	4.635	4.359	4.505	0.202	0.273	0.123
Methotrexate	4.136	0.169	4.225	4.047	4.272	0.177	4.377	4.168	4.182	0.179	4.046	0.482
Leflunomide	0.545	0.025	0.558	0.532	0.559	0.023	0.573	0.545	0.55	0.025	0.111	0.009

By total quantities of medicines

Since the March-lockdown, fluctuations in monthly volumes are observed. See Supplementary Table 3 for Fluctuating total quantities of anti-rheumatics' medicines in millions by quantity and associated price. Hydroxychloroquine use shows great variance, which is supported by the Mann-Whitney two-tailed test (test statistics 84, standard error 14.652, standardised test statistic 1.911, p-value = 0.059) over the study period.

By price of medicines

Costs are presented as nominal pound sterling (GBP) values. Examining the actual cost of medicines shows variation. Mann-Whitney U test for prices of hydroxychloroquine (p-value < 0.001), azathioprine (p-value < 0.001), methotrexate (p-value < 0.001) and leflunomide (p-value = 0.004) reject the null hypothesis that price continue to remain consistent after March 2020.

Supplemental material (Supplementary Table 3 - Quantity & Cost) shows that there was a substantial increase in unit cost of medication during this study period as indicated by the analysis below:

1. Sulfasalazine cost the NHS £0.62 million in January 2019 for 9.54 million doses (=£0.065/dose), while it cost £0.81 million in January 2021 for 9.38 million doses (=£0.086 dose), reflecting a 33% unitary cost increase.
2. Hydroxychloroquine sulfate cost the NHS £0.30 million in January 2019 for 4.89 million doses (=£0.062/dose), while it cost £0.57 million in January 2021 for 4.68 million doses (=£0.122/dose), reflecting a 98% unitary cost increase.
3. Azathioprine cost the NHS £0.19 million in January 2019 for 4.69 doses (=£0.041/dose), while it cost £0.25 million in January 2021 for 4.30 million doses (=£0.058/dose), reflecting a 41% unitary cost increase.
4. Methotrexate cost the NHS £3.27 million in January 2019 for 4.19 doses (=£0.781/dose), while it cost £4.63 million in January 2021 for 4.17 million doses (=£1.110/dose), reflecting a 42% unitary cost increase.
5. Leflunomide cost the NHS £0.12 million in January 2019 for 0.56 doses (=£0.205/dose), while it cost £0.09 million in January 2021 for 0.55 million doses (=£0.164/dose), reflecting a 20% unitary cost decrease.

It is presumed that this unit price fluctuation is not consequent to rising inflation (consumer price index, retail price index and central bank base rates were extremely/historically low and stable globally during this period), though these have moved substantially at the point of publication.

Interrupted time series (ARIMA modelling; changepoint detection)

Sulfasalazine; Hydroxychloroquine; Azathioprine; Methotrexate; and Leflunomide are the anti-rheumatics medicines most used by total quantity in the study period. ARIMA model can be visualised in Table 2 and Figure 2.

None of the five medicines showed evidence of a significant difference in the linear trend for monthly prescription statistics before the chosen interrupt time-point (March 2020) when modelled without any seasonal, moving average or autoregressive components, see table 2.

Table 2. Estimated change in prescription volumes at March 2020 without auto-regression ARIMA (0,0,0)

Estimated slope (per month) BEFORE March 2020	**Parameter Estimate**	**Standard Error**	**T-statistic**	**P-value**	**Lower CI**	**Upper CI**
Sulfasalazine-Model_1	5435	28871	0.188	0.852	-54151	65021
Hydroxychloroquine sulfate-Model_2	-10955	14336	-0.764	0.453	-40543	18632
Azathioprine-Model_3	-12052	12273	-0.982	0.337	-37382	13278
Methotrexate-Model_4	7966	11836	0.673	0.508	-16462	32395
Leflunomide-Model_5	561	1662	0.338	0.739	-2870	3992
Post vs Pre effect (Step-change)	**Parameter Estimate**	**Standard Error**	**T-statistic**	**P-value**		
Sulfasalazine-Model_1	659017	875894	0.752	0.46	-1148740	2466774
Hydroxychloroquine sulfate-Model_2	814729	434936	1.873	0.075	-82935	1712394
Azathioprine-Model_3	786705	372342	2.113	0.047	18229	1555182
Methotrexate-Model_4	249614	359099	0.695	0.495	-491531	990758
Leflunomide-Model_5	30388	50436	0.603	0.553	-73706	134482

Estimated slope (per month) AFTER February 2020	Parameter Estimate	Standard Error	T-statistic	P-value		
Sulfasalazine-Model_1	-38151	50570	-0.754	0.459	-142522	66220
Hydroxychloroquine sulfate-Model_2	-24392	25111	-0.971	0.342	-76219	27434
Azathioprine-Model_3	-31340	21497	-1.458	0.16	-75708	13028
Methotrexate-Model_4	-10634	20733	-0.513	0.613	-53424	32156
Leflunomide-Model_5	-1188	2912	-0.408	0.687	-7198	4822

Step change (also called a level shift) is a sudden, sustained change where the time series is shifted either up or down by a given value immediately following the intervention. The step change variable takes the value of '0' prior to the start of the intervention, and '1' afterwards. From Table 2, there was evidence of a step change for azathioprine (p-value 0.047), which was statistically significant after March 2020. The confidence intervals representing the degree of uncertainty around these numbers have also widened indicating a much wider variability across the country after the pandemic's onset as compared to the prior period. There was also some evidence of change in linearity of the regression slope after March 2020.

It should be stressed that these p-values only represent a suggestion of an association between temporal change and total prescription quantities, since several interrupted time series models within a general hypothesis of temporal change were estimated, and any estimates of effect have not been adjusted for multiplicity. It should be cautiously interrupted along with the confidence interval bounds that do definitely show a shift downwards after the March 2020 interrupt point with confidence intervals becoming more negative than before.

Supplementary Table 2 on sensitivity analysis, where log transformation continues to show interesting findings for step/phase-changes in hydroxychloroquine and azathioprine. March and April were also modelled as the point of interruption.

Further changepoint detection analysis revealed four out of the five medicines do feature at time point number 16 (i.e. March/April 2020) in the list of (up to) 5 possible changepoints. However, only sulfasalazine shows a strong changepoint at March/April 2020. In azathioprine it was the second strongest, but in methotrexate and leflunomide it was the fifth changepoint detected. In hydroxychloroquine it did not feature in the top 5. Hence, the results do not conclusively point to a jump at March/April 2020 for hydroxychloroquine, although for the other medicines there is some signal of a change, especially for sulfasalazine and azathioprine.

By location

Nomenclature for regional territories except London was modified in April 2020, making it difficult to make direct comparisons across regions before and after this period. However sufficient clarity is provided to permit the re-aggregation of the data (April -July 20) to allow for direct comparison (Northwest + North East and Yorkshire= North of England, Midlands = Midlands and East of England, South East + South West= South of England and London).

See Supplementary Table 4 for regional analysis by quantity and cost. Figure 3 summarises the regional prescription volumes.

Some entries were unidentified by location. Regional descriptive statistics in millions with (Mean, Std. Deviation) convention are presented: North England (6.675, 0.279), Midlands and East of England (7.586, 0.313), South England (6.498, 0.29), London (2.494, 0.122), unidentified (0.003, 0.0012). No significant differences were found. Up-to-date population denominators are unavailable (these could have changed during the pandemic), so total quantity reflects differing prevalence in different regions.
More granular analysis was conducted to examine changes to Methotrexate Quantity (Supplementary Table 5 - shows unique codes that were examined, to improve clarity and transparency and helps other researchers investigate by product code) due to its crucial importance in the management and maintenance of disease remission.

Discussion

Results are concerning and tell us that a significant number of IMIDs patients specifically on sulfasalazine and azathioprine may have not used their chronic long-term condition's medicines as they should have, for a variety of reasons. While the research suggests some degree of inconclusiveness, the results of interrupted time series suggest the possibility of a causal relation between the pandemic and that changes to IIDs prescription volumes. As the sensitivity analysis changepoint results show different potential breakpoints, this may imply that fluctuations in prescriptions before or after our selected interrupt point were higher in magnitude, than necessarily caused by the pandemic itself. Hence, this analysis cannot rule out other possible causal explanatory factors, but results are consistent with possibility that the pandemic may have directly contributed the changes observed. This provides an early signal for potentially deteriorating medium to longer term health in IMIDs patients. The results demonstrate a statistically significant level of fluctuation for hydroxychloroquine and azathioprine. There are also worrying trend changes in sulfasalazine, as it has the highest circulating volume (approximately 9 million doses per month). In the broader sense, this data may suggest lower rates of medicines adherence by IMIDs patients who may not have received adequate clinical care.

The cost analysis presented shows that a unitary cost of medicine also jumped substantially in the study period. This has budget impact concerns for the NHS (universal health coverage provider) but has transferable realities for international audiences in their countries because of the level of insurance coverage and out of pocket expenses this would represent for their patients. These types of prices-impacts have the potential to lead to 'out of stock' shortages for patients and alter/raise 'out of pocket' price-levels for insurers. It is reasonable to expect that prescription medication coverage for IMIDs may fall consequently because of the high out of pocket expenses that patients must incur before insurance coverage commences e.g., Medicare, Medicaid. This analysis presents a fraction of the directly attributable costs of IMID patients management. It does not cover the cost of complications, surgery and onward care including the health-burden borne by family or carers or financial distress it may cause through lack of income due to disease progression. Regional variations also mean that certain categories of IMIDs patients are disproportionately affected, having further implications for health inequality. From a perspective of equity, cost increases may fuel geographical inequity potentially perpetuating post code lotteries. This analysis also provides data on the quality of initial humanitarian crisis response, to aid better future preparedness.

The study captures analysis representing the first wave of restrictions due to the pandemic and its handling, including the effects on the supply chain shortages, governmental or policy guidance that was enacted by clinicians at the hospital level, later at a national and even supranational level, alongside emerging global data and pressures on the primary care interface. This means that subsequent periods of time are not necessarily comparable to this initial phase, presenting an early and unique opportunity to assess risk for patients. Subsequent lockdowns would be influenced by

policy decisions in the first wave. While a longer continuous period of time would be interesting to study to provide a contemporary narrative, it would also be confounded by a variety of policy changes, making it difficult to tease out unexplainable variables.

Health systems globally were least prepared to handle this pandemic and this performance is likely to improve overtime. However, IMIDs patients directly affected in this initial phase may potentially still have unaddressed healthcare needs due to clinical availability or capacity for providing needed care. Data suggest that roughly 2.3 million people are currently waiting for surgical care, including in orthopaedics [57]. People in the most deprived communities are 1.8 times more likely to wait over one year for treatment compared to the least deprived areas [58]. Consequently, IMIDs patients maybe especially more disadvantaged and may need additional support.

Why use these medicines?

Clinical treatment is intended to relieve symptoms, achieve disease remission or low disease activity if remission cannot be achieved, and to improve the patient's ability to perform daily activities. From a public health, primary care perspective, it is important that IMIDs patients continue to get their medicines regularly and adhere to the treatment plans to ensure disease progression is as delayed as feasibly possible.

For the first time, this study presents data on prescription and regional variations during the pandemic for licensed IID medicines. More variability after the onset of the pandemic in treating IMIDs patients across the country is observed, with the potential for extremely poor drug coverage for some individuals versus excessive drug coverage for others indicating a misallocation of resources and as a proxy for clinical care coverage. These medicines also carry other licenced use (e.g., pain), so the analysis is more generalised for the IMIDs patient populations described.

Adherence and the patient story

Adherence concerns and access to timely prescription refills may or may not occur for a variety of reasons including not being able to go to the doctor's surgery or pharmacies because of shielding or self-isolation during the pandemic. Also, many surgeries stopped seeing patient face-to-face and substituted these with digital services. The first point of patient contact was the 111 telephone triage services (run by allied professionals) which became overwhelmed [59,60]. Telephone triage may have substituted for the standard practice of a physical examination, bloods collection or annual review. In such events, patients may have had limited access to services, either because of not knowing how to access them digitally or failing to prioritise them.

While the pandemic has provided an opportunity for digital consultations and remote supervision, they have come with added uncertainty and anxiety for patients. Changes to routine have the potential for negative consequences on chronic long-term condition sufferers. Digital consultations have the potential to create digital barriers to care. This may be especially problematic for elderly IMIDs patients who can be frail or infirm because of their condition as well as the immunosuppressant's they use. As a result, there may be instances across the country where patients have inadequate disease control, where underlying complications may escalate.

Strengths and weaknesses

There are several strengths and limitations to this observational study. For the first time, the impact on prescription volumes of medicines licenced for IMIDs patients in England are reported during a global pandemic. Strengths of this study include being evidence-based on real world data. One of the strengths of ITS studies is that they are generally unaffected by typical confounding variables which remain fairly constant, such as population age distribution or socioeconomic status, as these only

change relatively slowly over time. Nevertheless, ITS can be affected by time-varying confounders that change more rapidly [61]. Confirmed diagnoses or prescription indications as well as linked data were unavailable to us. Findings rely heavily on P-values to justify significance, which has its own limitations [62–65]. While this analysis provides important insight, it can only be descriptive and further work is needed to explore the underlying reasons for the trends observed and the implications for patients.

Limitations pertain to the timeframe, completeness, and quality of the data. Government data was used in this study; however, these have not been independently verified as complete, accurate and are subject to revision. The analysis is descriptive with no adjustments, for changes in population structure (age, disease prevalence, social deprivation scores) which could impact prescriptions between periods and within regions. Hospital statistics are not represented in our analysis. Unfortunately, this rich database does not provide the exact prescription date which is the most severe limitation of the study as it impedes more complex models. Finally, a key methodological limitation of the study is that while robust mathematical modelling techniques are used alongside extensive sensitivity analysis, there is only some support for a changepoint at March 2020, without stronger evidence.

Future work

This study generates an early warning signal from real-world data on patients' lives. Future studies must consider the impact on patients' lives with respect to disease progression, including over the life course of this pandemic at the individual level by studying electronic health data records. It is important to consider subsequent periods and interval between lockdowns to fully assess the potential impact to patients. Future studies may also look to examine statistics of routine safety blood tests to check for bone marrow suppression, if they have been done and at what frequency. Similarly, markers of disease progression should be examined. Further cost effectiveness analysis needs to be conducted in light of the changing medicines prices with inflationary adjustments.

Conclusion

A worrying change in trend is observed for sulfasalazine and azathioprine, but not all medicines that were studied, which has the potential to impact longer-term care of some IMIDs patients. Clinicians know that not taking medication is likely to result in increased morbidity and mortality in these patient populations. Hence, perhaps extra clinical consideration may be needed to help these patients. In conclusion, this study illustrates the risk of interrupted provision of timely prescription refills. Health care professionals need to identify patients on IIDs medicines and assess their prescription day-coverage, with planned actions to flag and follow-up patients where there are concerns about adherence.

Acknowledgements: We thank the NHS business services authority staff who helped with the several information requests.

Contributors: Lead author (RaB) conducted the literature search, study conception and design data analysis, statistical analysis and interpretation of data, manuscript preparation, editing and revision and submitted the final version of the paper. RoB provided technical expertise with data extraction, cleaning, manipulation and data for final analysis. DC acted as the principal medical statistician on the study and was the statistical analysis lead. SXL advised on statistical techniques. SF provided a public health perspective of the likely impact and considered ways to improve community public health. CJE considered the clinical impact and consequences of our findings on this patient population.

Funding: No specific funding was provided for the study.

Competing interests: All authors have completed the ICMJE uniform disclosure form. No financial relationships or activities have influenced the submitted work.

Ethical approval: Not required.

Data availability statement: The original data are available from [45] https://www.nhsbsa.nhs.uk/prescription-data/prescribing-data/english-prescribing-data-epd. No additional data are available.

Transparency: The lead author (RaB) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

References

1 NHS services. Who can get free prescriptions. nhs.uk. 2020.https://www.nhs.uk/nhs-services/prescriptions-and-pharmacies/who-can-get-free-prescriptions/ (accessed 12 Oct 2022).

2 Office for National Statistics. NHS70: Marking 70 years of the National Health Service. 2018.https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandwellbeing/articles/nhs70marking70yearsofthenationalhealthservice/2018-06-26 (accessed 12 Oct 2022).

3 NHS England. Primary Care Support England. 2022.https://pcse.england.nhs.uk/organisations/icb-hub/ (accessed 12 Oct 2022).

4 NHS Digital. Innovative uses of data and data science. NHS Digit. 2022.https://digital.nhs.uk/data-and-information/data-insights-and-statistics/innovative-uses-of-data-and-data-science (accessed 12 Oct 2022).

5 Ogdie A, Coates LC, Gladman DD. Treatment guidelines in psoriatic arthritis. *Rheumatol Oxf Engl* 2020;**59**:i37–46. doi:10.1093/rheumatology/kez383

6 Smolen JS, Landewé RBM, Bijlsma JWJ, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020;**79**:685–99. doi:10.1136/annrheumdis-2019-216655

7 Gossec L, Baraliakos X, Kerschbaumer A, *et al.* EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis* 2020;**79**:700–12. doi:10.1136/annrheumdis-2020-217159

8 Kerschbaumer A, Sepriano A, Smolen JS, *et al.* Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2020;**79**:744–59. doi:10.1136/annrheumdis-2019-216656

9 Ledingham J, Gullick N, Irving K, *et al.* BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. *Rheumatology* 2017;**56**:865–8. doi:10.1093/rheumatology/kew479

10 Symmons D, Turner G, Webb R, *et al.* The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. *Rheumatology* 2002;**41**:793–800. doi:10.1093/rheumatology/41.7.793

11 King D, Reulen RC, Thomas T, *et al.* Changing patterns in the epidemiology and outcomes of inflammatory bowel disease in the United Kingdom: 2000-2018. *Aliment Pharmacol Ther* 2020;**51**:922–34. doi:10.1111/apt.15701

12 Springate DA, Parisi R, Kontopantelis E, *et al.* Incidence, prevalence and mortality of patients with psoriasis: a U.K. population-based cohort study. *Br J Dermatol* 2017;**176**:650–8. doi:10.1111/bjd.15021

13 Yue X, Ye Y, Choi YC, *et al.* Risk of Severe COVID-19 Outcomes Among Patients with Immune-Mediated Inflammatory Diseases or Malignancies: A Retrospective Analysis of Real-World Data in the United States. *Adv Ther* 2022;**39**:5413–32. doi:10.1007/s12325-022-02293-0

14 Guo Q, Wang Y, Xu D, *et al.* Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. *Bone Res* 2018;**6**:15. doi:10.1038/s41413-018-0016-9

15 Løppenthin K, Esbensen BA, Østergaard M, *et al.* Morbidity and mortality in patients with rheumatoid arthritis compared with an age- and sex-matched control population: A nationwide register study. *J Comorbidity* 2019;**9**:2235042X19853484. doi:10.1177/2235042X19853484

16 Elewaut D, Matucci-Cerinic M. Treatment of ankylosing spondylitis and extra-articular manifestations in everyday rheumatology practice. *Rheumatology* 2009;**48**:1029–35. doi:10.1093/rheumatology/kep146

17 Raza K, Buckley CE, Salmon M, *et al.* Treating very early rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2006;**20**:849–63. doi:10.1016/j.berh.2006.05.005

18 Cojocaru M, Cojocaru IM, Silosi I, *et al.* Extra-articular Manifestations in Rheumatoid Arthritis. *Maedica* 2010;**5**:286–91.

19 Lamb CA, Kennedy NA, Raine T, *et al.* British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019;**68**:s1–106. doi:10.1136/gutjnl-2019-318484

20 Sawayama H, Miyamoto Y, Yoshida N, *et al.* Essential updates 2020/2021: Colorectal diseases (benign)—Current topics in the surgical and medical treatment of benign colorectal diseases. *Ann Gastroenterol Surg* 2022;**6**:321–35. doi:10.1002/ags3.12548

21 Di Jiang C, Raine T. IBD considerations in spondyloarthritis. *Ther Adv Musculoskelet Dis* 2020;**12**:1759720X2093941. doi:10.1177/1759720X20939410

22 Mysler E, Caubet M, Lizarraga A. Current and Emerging DMARDs for the Treatment of Rheumatoid Arthritis. *Open Access Rheumatol Res Rev* 2021;**13**:139–52. doi:10.2147/OARRR.S282627

23 Keskin Y, Nas K, Kiliç E, *et al.* Clinical characteristics, disease activity, functional status, and quality of life results of patients with psoriatic arthritis using biological and conventional synthetic disease-modifying antirheumatic drugs. *Arch Rheumatol* 2021;**36**:1–9. doi:10.46497/ArchRheumatol.2021.7874

24 Alves de Oliveira Junior H, Pereira da Veiga T, Acurcio FDA, *et al.* Impact of biologic DMARDs on quality of life: 12-month results of a rheumatic diseases cohort using the Brazilian EQ-5D tariff. *Hosp Pract* 2020;**48**:213–22. doi:10.1080/21548331.2020.1785212

25 Shams S, Martinez JM, Dawson JRD, *et al.* The Therapeutic Landscape of Rheumatoid Arthritis: Current State and Future Directions. *Front Pharmacol* 2021;**12**:680043. doi:10.3389/fphar.2021.680043

26 Köhler BM, Günther J, Kaudewitz D, *et al.* Current Therapeutic Options in the Treatment of Rheumatoid Arthritis. *J Clin Med* 2019;**8**:E938. doi:10.3390/jcm8070938

27 Cutolo M, Spies CM, Buttgereit F, *et al.* The supplementary therapeutic DMARD role of low-dose glucocorticoids in rheumatoid arthritis. *Arthritis Res Ther* 2014;**16**:S1. doi:10.1186/ar4685

28 Boots AMH, Maier AB, Stinissen P, *et al.* The influence of ageing on the development and management of rheumatoid arthritis. *Nat Rev Rheumatol* 2013;**9**:604–13. doi:10.1038/nrrheum.2013.92

29 Gabriel SE, Crowson CS, Campion ME, *et al.* Indirect and nonmedical costs among people with rheumatoid arthritis and osteoarthritis compared with nonarthritic controls. *J Rheumatol* 1997;**24**:43–8.

30 Gabriel SE, Crowson CS, Campion ME, *et al.* Direct medical costs unique to people with arthritis. *J Rheumatol* 1997;**24**:719–25.

31 Cross MJ, March LM, Lapsley HM, *et al.* Patient self-efficacy and health locus of control: relationships with health status and arthritis-related expenditure. *Rheumatol Oxf Engl* 2006;**45**:92–6. doi:10.1093/rheumatology/kei114

32 Callahan LF. The burden of rheumatoid arthritis: facts and figures. *J Rheumatol Suppl* 1998;**53**:8–12.

33 Yelin E. The costs of rheumatoid arthritis: absolute, incremental, and marginal estimates. *J Rheumatol Suppl* 1996;**44**:47–51.

34 Littlejohn EA, Monrad SU. Early Diagnosis and Treatment of Rheumatoid Arthritis. *Prim Care Clin Off Pract* 2018;**45**:237–55. doi:10.1016/j.pop.2018.02.010

35 Abualfadl E, Ismail F, Shereef RRE, *et al.* Impact of COVID-19 pandemic on rheumatoid arthritis from a Multi-Centre patient-reported questionnaire survey: influence of gender, rural-urban gap and north-south gradient. *Rheumatol Int* Published Online First: 1 November 2020. doi:10.1007/s00296-020-04736-9

36 British Medical Association. NHS backlog data analysis. Br. Med. Assoc. Trade Union Prof. Body Dr. UK. 2022.https://www.bma.org.uk/advice-and-support/nhs-delivery-and-workforce/pressures/nhs-backlog-data-analysis (accessed 12 Oct 2022).

37 Department of Health & Social Care. The government's response to the Health and Social Care Committee and Science and Technology Committee joint report: Coronavirus: lessons learned to date. GOV.UK. 2022.https://www.gov.uk/government/publications/coronavirus-lessons-learned-to-date-report-government-response/the-governments-response-to-the-health-and-social-care-committee-and-science-and-technology-committee-joint-report-coronavirus-lessons-learned-to-d (accessed 12 Oct 2022).

38 Dyer C. Covid-19: Government was "grossly negligent" in its handling of pandemic, says people's inquiry. *BMJ* 2021;:n2955. doi:10.1136/bmj.n2955

39 National Institute for Health and Care Excellence. COVID-19 rapid guideline: rheumatological autoimmune, inflammatory and metabolic bone disorders Guidance. https://www.nice.org.uk/guidance/ng167 (accessed 10 Aug 2020).

40 Hughes DA. Medicines Shortages in the United Kingdom. *Clin Pharmacol Ther* 2019;**106**:712–712. doi:10.1002/cpt.1495

41 Batista A, Miljković N, Polidori P, *et al.* Medicines shortages. *Eur J Hosp Pharm* 2019;**26**:290–1. doi:10.1136/ejhpharm-2019-001911

42 Miljković N, Gibbons N, Batista A, *et al.* Results of EAHP's 2018 Survey on Medicines Shortages. *Eur J Hosp Pharm Sci Pract* 2019;**26**:60–5. doi:10.1136/ejhpharm-2018-001835

43 Acosta A, Vanegas EP, Rovira J, *et al.* Medicine Shortages: Gaps Between Countries and Global Perspectives. *Front Pharmacol* 2019;**10**:763. doi:10.3389/fphar.2019.00763

44 European Medicines Agency. Medicines - Shortages. Eur. Med. Agency. https://www.ema.europa.eu/en/medicines/ema_group_types/ema_document-supply_shortage/field_ema_shortage_status/1/field_ema_shortage_status/0 (accessed 10 Aug 2020).

45 [Dataset] English Prescribing Dataset (EPD) - Open Data Portal BETA. https://opendata.nhsbsa.net/dataset/english-prescribing-data-epd (accessed 25 Apr 2020).

46 Barrett R, Barrett R, Dhar K, *et al.* Gonadorelins adherence in prostate cancer: A time-series analysis of England's national prescriptions during the COVID-19 pandemic (from Jan 2019 to Oct 2020). *BJUI Compass* Published Online First: 19 August 2021. doi:10.1002/bco2.101

47 Cochrane Effective Practice and Organisation of Care (EPOC). Interrupted time series (ITS) analyses. EPOC Resources for review authors. 2017.epoc.cochrane.org/resources/epoc-specific-resources-review-authors

48 Helfenstein U. Box-Jenkins modelling in medical research. *Stat Methods Med Res* 1996;**5**:3–22. doi:10.1177/096228029600500102

49 Sato RC. Disease management with ARIMA model in time series. *Einstein Sao Paulo Braz* 2013;**11**:128–31. doi:10.1590/s1679-45082013000100024

50 Schaffer AL, Dobbins TA, Pearson S-A. Interrupted time series analysis using autoregressive integrated moving average (ARIMA) models: a guide for evaluating large-scale health interventions. *BMC Med Res Methodol* 2021;**21**:58. doi:10.1186/s12874-021-01235-8

51 Muggeo VMR. Estimating regression models with unknown break-points. *Stat Med* 2003;**22**:3055–71. doi:10.1002/sim.1545

52 Killick R, Eckley IA. **changepoint** : An *R* Package for Changepoint Analysis. *J Stat Softw* 2014;**58**. doi:10.18637/jss.v058.i03

53 Killick R, Haynes K, Eckley I, *et al. changepoint: Methods for Changepoint Detection*. 2022. https://CRAN.R-project.org/package=changepoint (accessed 24 Nov 2022).

54 Benoit K. Linear regression models with logarithmic transformations. *Lond Sch Econ* 2011;**22**:23–36.

55 Feng C, Wang H, Lu N, *et al.* Log-transformation and its implications for data analysis. *Shanghai Arch Psychiatry* 2014;**26**:105–9. doi:10.3969/j.issn.1002-0829.2014.02.009

56 Benchimol EI, Smeeth L, Guttmann A, *et al.* The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015;**12**:e1001885. doi:10.1371/journal.pmed.1001885

57 Carr A, Smith JA, Camaradou J, *et al.* Growing backlog of planned surgery due to covid-19. *BMJ* 2021;:n339. doi:10.1136/bmj.n339

58 Holmes J, Jefferies D. Health inequalities and the elective backlog—understanding the problem and how to resolve it. *BMJ* 2021;:n2574. doi:10.1136/bmj.n2574

59 Without more nurses, NHS 111 staff could be 'overwhelmed.' *Emerg Nurse* 2015;**23**:6–6. doi:10.7748/en.23.7.6.s2

60 Osamor K. I warned parliament that NHS 111 would never be able to cope. The Guardian. 2020.https://www.theguardian.com/commentisfree/2020/apr/23/nhs-111-crisis-coronavirus-pandemic (accessed 9 Jun 2020).

61 Lopez Bernal J, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol* 2016;:dyw098. doi:10.1093/ije/dyw098

62 Wasserstein RL, Schirm AL, Lazar NA. Moving to a World Beyond " $p < 0.05$." *Am Stat* 2019;**73**:1–19. doi:10.1080/00031305.2019.1583913

63 Altman DG, Bland JM. Statistics Notes: Presentation of numerical data. *BMJ* 1996;**312**:572–572. doi:10.1136/bmj.312.7030.572

64 Bland JM, Altman DG. Statistics Notes: Logarithms. *BMJ* 1996;**312**:700–700. doi:10.1136/bmj.312.7032.700

65 Altman DG, Bland JM. Standard deviations and standard errors. *BMJ* 2005;**331**:903. doi:10.1136/bmj.331.7521.903

FIGURE TITLES AND LEGENDS

Figure 1. Box plot representing mean values before the pandemic and after its onset
Quantities are presented in absolute numbers.

Figure 2. ARIMA (0,0,0)(0,0,0) Prescription volumes for individual medicines: (a)Sulfasalazine; (b)Hydroxychloroquine sulfate; (c)Azathioprine; (d)Methotrexate; (e)Leflunomide

Figure 3. Monthly regional distribution (higher March and lower May 2020 quantities of RA medicines are presented in the callouts)

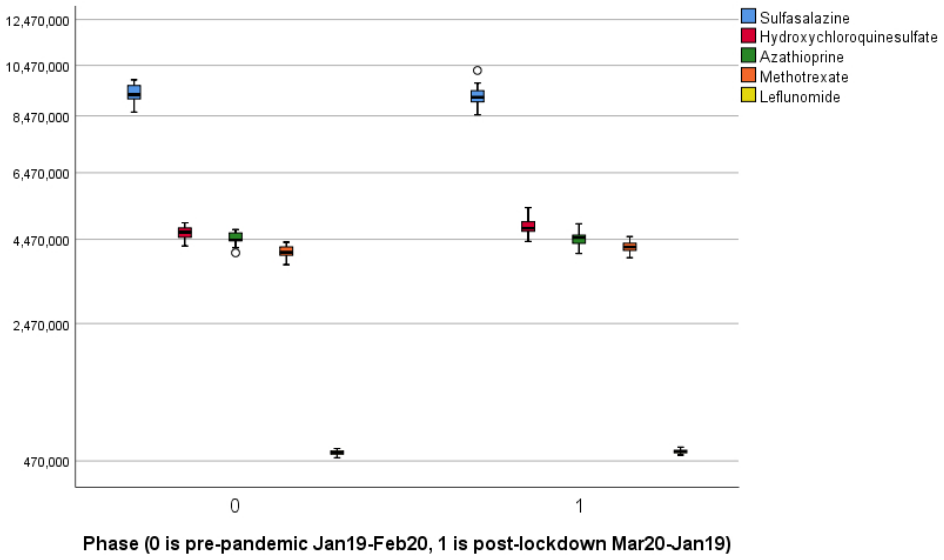

Figure 1 Box plot representing mean values before the pandemic and after its onset. Quantities are presented in absolute numbers.

300x176mm (72 x 72 DPI)

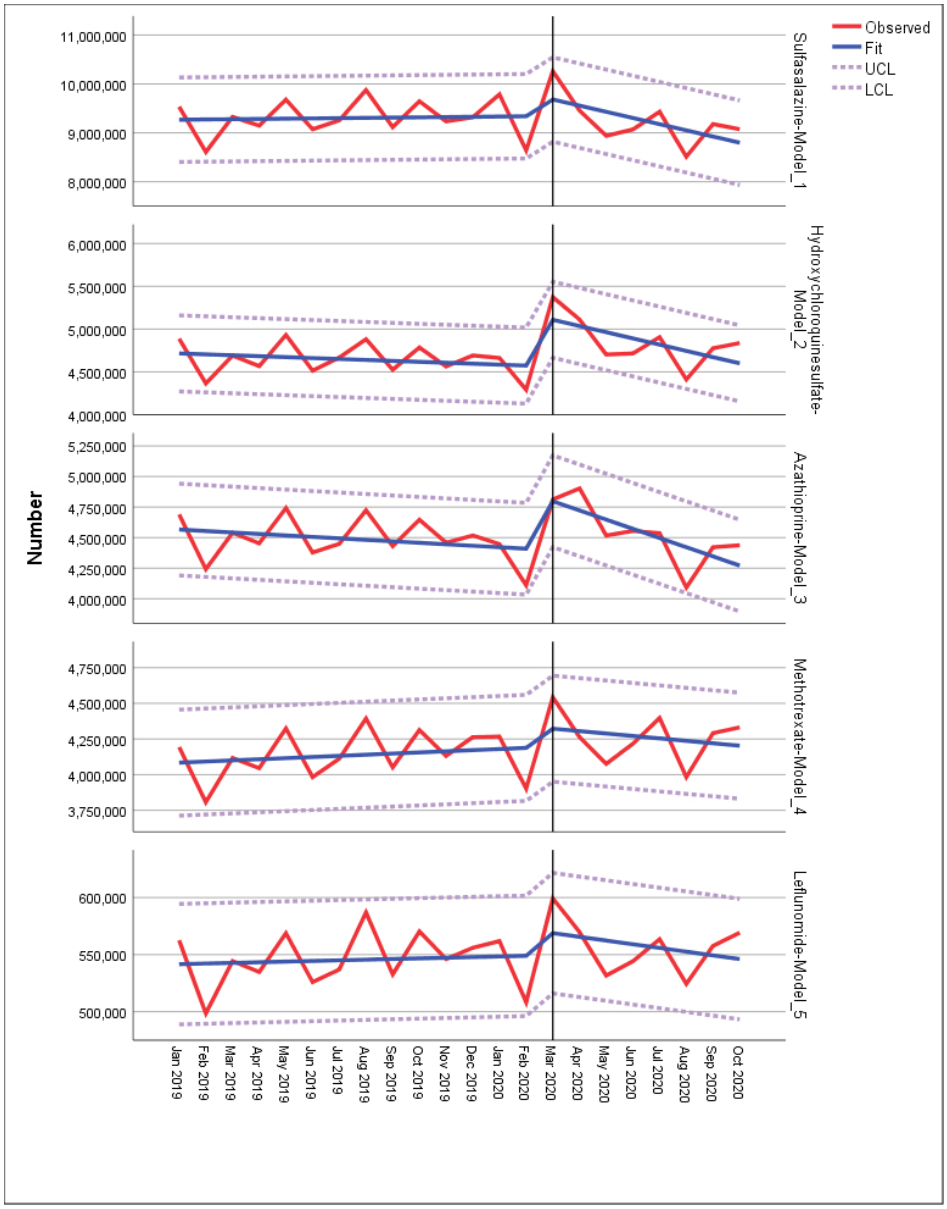

Figure 2 ARIMA (0,0,0)(0,0,0) Prescription volumes for individual medicines (a)Sulfasalazine; (b)Hydroxychloroquine sulfate; (c)Azathioprine; (d)Methotrexate; (e)Leflunomide.

272x347mm (72 x 72 DPI)

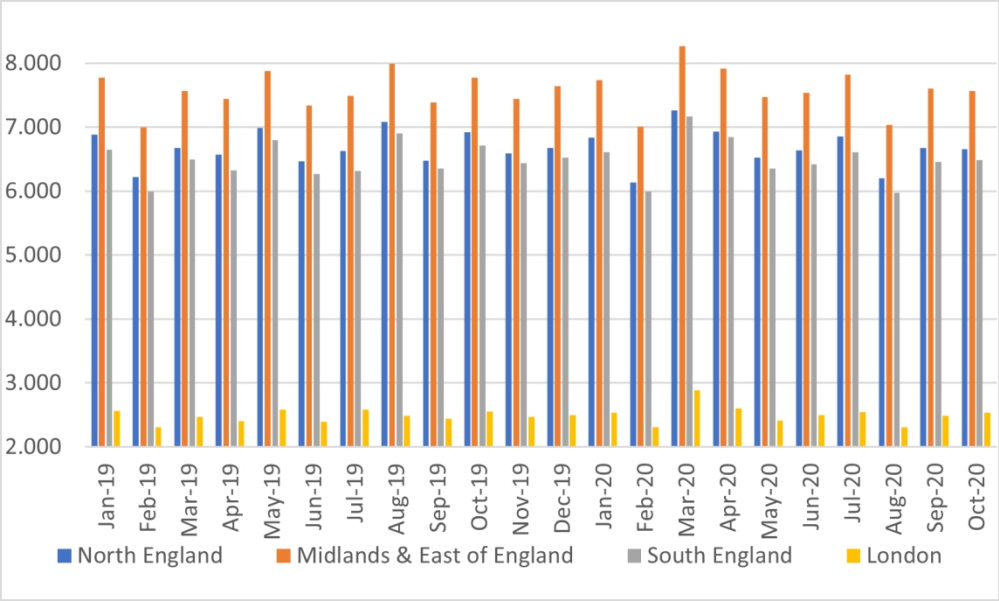

Figure 3 Monthly regional distribution (higher March and lower May 2020 quantities of RA medicines are presented in the callouts).

127x76mm (330 x 330 DPI)

Supplementary Table 1 - ARIMA Syntax (Mar20-1) Jan 19 to Jan 21

```
* Encoding: UTF-8.

DATASET ACTIVATE DataSet3.
PREDICT THRU END.
* Time Series Modeler.
TSMODEL
  /MODELSUMMARY  PRINT=[MODELFIT]
  /MODELSTATISTICS  DISPLAY=YES MODELFIT=[ SRSQUARE]
  /MODELDETAILS  PRINT=[ PARAMETERS]
  /SERIESPLOT OBSERVED FIT FORECASTCI FITCI
  /OUTPUTFILTER DISPLAY=ALLMODELS
  /SAVE  PREDICTED(Predicted) LCL(LCL) UCL(UCL)
  /AUXILIARY  CILEVEL=95 MAXACFLAGS=24
  /MISSING USERMISSING=EXCLUDE
  /MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
e
   INDEPENDENT=TimePeriod Phase Interact
    PREFIX='Model'
  /ARIMA AR=[1]  DIFF=0  MA=[0]
    TRANSFORM=NONE  CONSTANT=YES
  /AUTOOUTLIER DETECT=OFF.

PREDICT THRU END.
* Time Series Modeler.
TSMODEL
  /MODELSUMMARY  PRINT=[MODELFIT]
  /MODELSTATISTICS  DISPLAY=YES MODELFIT=[ SRSQUARE]
  /MODELDETAILS  PRINT=[ PARAMETERS]
  /SERIESPLOT OBSERVED FIT FORECASTCI FITCI
  /OUTPUTFILTER DISPLAY=ALLMODELS
  /SAVE  PREDICTED(Predicted) LCL(LCL) UCL(UCL)
  /AUXILIARY  CILEVEL=95 MAXACFLAGS=24
  /MISSING USERMISSING=EXCLUDE
  /MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
e
   INDEPENDENT=TimePeriod Phase Interact
    PREFIX='Model'
  /ARIMA AR=[0]  DIFF=1  MA=[0]
    TRANSFORM=NONE  CONSTANT=YES
  /AUTOOUTLIER DETECT=OFF.

PREDICT THRU END.
* Time Series Modeler.
TSMODEL
  /MODELSUMMARY  PRINT=[MODELFIT]
  /MODELSTATISTICS  DISPLAY=YES MODELFIT=[ SRSQUARE]
  /MODELDETAILS  PRINT=[ PARAMETERS]
  /SERIESPLOT OBSERVED FIT FORECASTCI FITCI
  /OUTPUTFILTER DISPLAY=ALLMODELS
  /AUXILIARY  CILEVEL=95 MAXACFLAGS=24
  /MISSING USERMISSING=EXCLUDE
```

```
  /MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
e
   INDEPENDENT=TimePeriod Phase Interact
    PREFIX='Model'
  /ARIMA AR=[0]  DIFF=0  MA=[1]
    TRANSFORM=NONE  CONSTANT=YES
  /AUTOOUTLIER DETECT=OFF.

PREDICT THRU END.
* Time Series Modeler.
TSMODEL
  /MODELSUMMARY  PRINT=[MODELFIT]
  /MODELSTATISTICS  DISPLAY=YES MODELFIT=[ SRSQUARE]
  /MODELDETAILS  PRINT=[ PARAMETERS]
  /SERIESPLOT OBSERVED FIT FORECASTCI FITCI
  /OUTPUTFILTER DISPLAY=ALLMODELS
  /AUXILIARY  CILEVEL=95 MAXACFLAGS=24
  /MISSING USERMISSING=EXCLUDE
  /MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
e
   INDEPENDENT=TimePeriod Phase Interact
    PREFIX='Model'
  /ARIMA AR=[0]  DIFF=0  MA=[0]
    TRANSFORM=LN  CONSTANT=YES
  /AUTOOUTLIER DETECT=OFF.
```

ARIMA Model Parameters **ARIMA (March20+ is a '1')** Total Quantities

14 months (Jan-19 to Feb-20) before the COVID-19 first lockdown in England (23rd Mar-20) until 11 months after this date (Mar-20 to Jan-21)

ARIMA(0,0,0), No Transformation	TimePeriod (Before); Phase (Step); Interact (After)	Parameter Estimate	Standard Error	T-stat	P-value	UCI	LCI
Sulfasalazine-Model_1	TimePeriod	5435	28871	0.188	0.852	65021	-54151
Sulfasalazine-Model_1	Phase	659017	875894	0.752	0.46	2466774	-1148740
Sulfasalazine-Model_1	Interact	-38151	50570	-0.754	0.459	66220	-142522
Hydroxychloroquinesulfate-Model_2	TimePeriod	-10955	14336	-0.764	0.453	18632	-40543
Hydroxychloroquinesulfate-Model_2	Phase	814729	434936	1.873	0.075	1712394	-82935
Hydroxychloroquinesulfate-Model_2	Interact	-24392	25111	-0.971	0.342	27434	-76219
Azathioprine-Model_3	TimePeriod	-12052	12273	-0.982	0.337	13278	-37382
Azathioprine-Model_3	Phase	786705	372342	2.113	0.047	1555182	18229
Azathioprine-Model_3	Interact	-31340	21497	-1.458	0.16	13028	-75708
Methotrexate-Model_4	TimePeriod	7966	11836	0.673	0.508	32395	-16462
Methotrexate-Model_4	Phase	249614	359099	0.695	0.495	990758	-491531
Methotrexate-Model_4	Interact	-10634	20733	-0.513	0.613	32156	-53424
Leflunomide-Model_5	TimePeriod	561	1662	0.338	0.739	3992	-2870
Leflunomide-Model_5	Phase	30388	50436	0.603	0.553	134482	-73706
Leflunomide-Model_5	Interact	-1188	2912	-0.408	0.687	4822	-7198

Confidence intervals were calculated as (24df):
CI=parameter+/-tinv(0.05, df)*SE

ARIMA(1,0,0), AR	TimePeriod (Before); Phase (Step); Interact (After)	Parameter Estimate	Standard Errc	T-stat	P-value	UCI	LCI
Sulfasalazine-Model_1	TimePeriod	19759	20233	0.977	0.34	61517	-21999
Sulfasalazine-Model_1	Phase	417103	614888	0.678	0.505	1686169	-851964
Sulfasalazine-Model_1	Interact	-37930	34973	-1.085	0.291	34250	-110110
Hydroxychloroquinesulfate-Model_2	TimePeriod	-5175	11041	-0.469	0.644	17613	-27962
Hydroxychloroquinesulfate-Model_2	Phase	700712	335790	2.087	0.05	1393748	7675
Hydroxychloroquinesulfate-Model_2	Interact	-23233	19100	-1.216	0.238	16188	-62654
Azathioprine-Model_3	TimePeriod	-9123	10465	-0.872	0.394	12476	-30722
Azathioprine-Model_3	Phase	738472	317473	2.326	0.031	1393704	83240
Azathioprine-Model_3	Interact	-31213	18041	-1.73	0.099	6021	-68447
Methotrexate-Model_4	TimePeriod	14064	7165	1.963	0.064	28852	-724
Methotrexate-Model_4	Phase	86932	218834	0.397	0.695	538582	-364718
Methotrexate-Model_4	Interact	-7128	12399	-0.575	0.572	18463	-32718
Leflunomide-Model_5	TimePeriod	1432	1106	1.295	0.21	3714	-850
Leflunomide-Model_5	Phase	11071	33718	0.328	0.746	80661	-58520
Leflunomide-Model_5	Interact	-882	1912	-0.461	0.649	3063	-4827

the coefficient for 'time' gives us the slope of the regression line pre-intervention
the coefficient for 'phase' gives us the change in intercept
the coefficient for 'interact' gives us the change in slope post intervention

If the coefficient for time is β1, for phase is β2 and for interact is β3 then the regression model is:

Therefore, pre intervention becomes:

Outcome = constant + β1time

Outcome= constant + β1time + β2 + β3interact = (constant + β2) + (β1 + β3) time
(as time and interact are the same post intervention)

ARIMA(0,1,0), Difference	TimePeriod (Before); Phase (Step); Interact (After)	Parameter Estimate	Standard Errc	T-stat	P-value	UCI	LCI
Sulfasalazine-Model_1	TimePeriod	-16503	54217	-0.304	0.764	95395	-128402
Sulfasalazine-Model_1	Phase	446642	1491083	0.3	0.768	3524086	-2630801
Sulfasalazine-Model_1	Interact	-5626	88335	-0.064	0.95	176688	-187940
Hydroxychloroquinesulfate-Model_2	TimePeriod	-4262	29227	-0.146	0.886	56059	-64583
Hydroxychloroquinesulfate-Model_2	Phase	712710	803796	0.887	0.386	2371664	-946244
Hydroxychloroquinesulfate-Model_2	Interact	-29016	47618	-0.609	0.549	69263	-127296
Azathioprine-Model_3	TimePeriod	-6734	23232	-0.29	0.775	41214	-54683
Azathioprine-Model_3	Phase	573262	638927	0.897	0.38	1891942	-745419
Azathioprine-Model_3	Interact	-21531	37851	-0.569	0.576	56590	-99652
Methotrexate-Model_4	TimePeriod	-6809	23305	-0.292	0.773	41292	-54909
Methotrexate-Model_4	Phase	439338	640948	0.685	0.501	1762190	-883514
Methotrexate-Model_4	Interact	-15532	37971	-0.409	0.687	62837	-93900
Leflunomide-Model_5	TimePeriod	-753	3188	-0.236	0.816	5828	-7333
Leflunomide-Model_5	Phase	58732	87689	0.67	0.511	239712	-122249
Leflunomide-Model_5	Interact	-2093	5195	-0.403	0.691	8629	-12814

ARIMA(0,0,1), MA	TimePeriod (Before); Phase (Step); Interact (After)	Parameter Estimate	Standard Errc	T-stat	P-value	UCI	LCI
Sulfasalazine-Model_1	TimePeriod	27834	9982	2.788	0.011	48437	7231
Sulfasalazine-Model_1	Phase	459301	421006	1.091	0.288	1328214	-409613
Sulfasalazine-Model_1	Interact	-50867	21544	-2.361	0.028	-6402	-95332
Hydroxychloroquinesulfate-Model_2	TimePeriod	1157	5185	0.223	0.826	11859	-9545
Hydroxychloroquinesulfate-Model_2	Phase	637368	207951	3.065	0.006	1066559	208178
Hydroxychloroquinesulfate-Model_2	Interact	-26929	10730	-2.51	0.021	-4783	-49075
Azathioprine-Model_3	TimePeriod	-2278	4740	-0.481	0.636	7505	-12062
Azathioprine-Model_3	Phase	660176	167979	3.93	0.001	1006868	313483
Azathioprine-Model_3	Interact	-34495	8907	-3.873	0.001	-16113	-52878
Methotrexate-Model_4	TimePeriod	18549	3714	4.994	0.00007	26214	10884
Methotrexate-Model_4	Phase	27587	116695	0.236	0.816	268434	-213260
Methotrexate-Model_4	Interact	-8773	5851	-1.499	0.149	3304	-20850
Leflunomide-Model_5	TimePeriod	2037	543	3.754	0.001	3157	917
Leflunomide-Model_5	Phase	-1004	18464	-0.054	0.957	37104	-39112
Leflunomide-Model_5	Interact	-931	985	-0.945	0.356	1102	-2965

ARIMA(0,0,0) Natural Logarithm, No Transformation	TimePeriod (Before); Phase (Step); Interact (After)	Parameter Estimate	Standard Error	T-stat	P-value	UCI	LCI
Sulfasalazine-Model_1	Sulfasalazine	16.041	0.026	606.083	0	16.09466	15.987339
Sulfasalazine-Model_1	TimePeriod	0.001	0.003	0.179	0.86	0.007	-0.005
Sulfasalazine-Model_1	Phase	0.067	0.094	0.707	0.488	0.261	-0.127
Sulfasalazine-Model_1	Interact	-0.004	0.005	-0.715	0.483	0.006	-0.014
Hydroxychloroquinesulfate-Model_2	Hydroxychloroquinesulfate	15.368	0.026	597.458	0	15.422	15.314
Hydroxychloroquinesulfate-Model_2	TimePeriod	-0.002	0.003	-0.778	0.445	0.004	-0.008
Hydroxychloroquinesulfate-Model_2	Phase	0.163	0.092	1.776	0.09	0.353	-0.027
Hydroxychloroquinesulfate-Model_2	Interact	-0.005	0.005	-0.887	0.385	0.005	-0.015
Azathioprine-Model_3	Azathioprine	15.336	0.023	653.382	0	15.383	15.289
Azathioprine-Model_3	TimePeriod	-0.003	0.003	-0.986	0.335	0.003	-0.009
Azathioprine-Model_3	Phase	0.171	0.084	2.046	0.053	0.344	-0.002
Azathioprine-Model_3	Interact	-0.007	0.005	-1.404	0.175	0.003	-0.017
Methotrexate-Model_4	Methotrexate	15.22	0.024	631.677	0	15.270	15.170
Methotrexate-Model_4	TimePeriod	0.002	0.003	0.687	0.499	0.008	-0.004
Methotrexate-Model_4	Phase	0.059	0.086	0.687	0.5	0.236	-0.118
Methotrexate-Model_4	Interact	-0.003	0.005	-0.512	0.614	0.007	-0.013
Leflunomide-Model_5	Leflunomide	13.2	0.026	512.174	0	13.254	13.146
Leflunomide-Model_5	TimePeriod	0.001	0.003	0.348	0.731	0.007	-0.005
Leflunomide-Model_5	Phase	0.054	0.092	0.584	0.565	0.244	-0.136
Leflunomide-Model_5	Interact	-0.002	0.005	-0.396	0.696	0.008	-0.012

We considered monthly quantities in the time period defined by 14 months (Jan-19 to Feb-20) before the COVID-19 first lockdown in England (23rd Mar-20) until 11 months after this date (Mar-20 to Jan-21).

ARIMA Model Parameters ARIMA (March20+ is a '0')

ARIMA(0,0,0), No Transformation		Estimate	Standard Error	t	P-value	UCI	LCI
Sulfasalazine-Model_1	TimePeriod	0.003	0.003	1.091	0.288	0.009192	-0.00319
Sulfasalazine-Model_1	Phase	-0.047	0.105	-0.449	0.658	0.169709	-0.26371
Sulfasalazine-Model_1	Interact	-0.001	0.006	-0.091	0.929	0.011383	-0.01338
Hydroxychloroquinesulfate-Model_2	TimePeriod	0.002	0.003	0.565	0.578	0.008192	-0.00419
Hydroxychloroquinesulfate-Model_2	Phase	0.08	0.122	0.655	0.52	0.331796	-0.1718
Hydroxychloroquinesulfate-Model_2	Interact	-0.004	0.006	-0.618	0.543	0.008383	-0.01638
Azathioprine-Model_3	TimePeriod	0	0.003	-0.167	0.869	0.006192	-0.00619
Azathioprine-Model_3	Phase	0.152	0.105	1.451	0.162	0.368709	-0.06471
Azathioprine-Model_3	Interact	-0.008	0.006	-1.362	0.188	0.004383	-0.02038
Methotrexate-Model_4	TimePeriod	0.004	0.003	1.552	0.136	0.010192	-0.00219
Methotrexate-Model_4	Phase	-0.017	0.1	-0.171	0.866	0.18939	-0.22339
Methotrexate-Model_4	Interact	-0.001	0.005	-0.113	0.911	0.009319	-0.01132
Leflunomide-Model_5	TimePeriod	0.003	0.003	1.193	0.246	0.009192	-0.00319
Leflunomide-Model_5	Phase	-0.03	0.106	-0.285	0.778	0.188773	-0.24877
Leflunomide-Model_5	Interact	0.00006631	0.006	0.012	0.991	0.01245	-0.01232

ARIMA(1,0,0), AR		Estimate	Standard Error	t	P-value	UCI	LCI
Sulfasalazine-Model_1	TimePeriod	0.003	0.002	1.716	0.102	0.007128	-0.00113
Sulfasalazine-Model_1	Phase	-0.033	0.071	-0.459	0.651	0.113537	-0.17954
Sulfasalazine-Model_1	Interact	-0.001	0.004	-0.328	0.746	0.007256	-0.00926
Hydroxychloroquinesulfate-Model_2	TimePeriod	0.002	0.002	0.722	0.478	0.006128	-0.00213
Hydroxychloroquinesulfate-Model_2	Phase	0.092	0.094	0.983	0.337	0.286006	-0.10201
Hydroxychloroquinesulfate-Model_2	Interact	-0.004	0.005	-0.907	0.375	0.006319	-0.01432
Azathioprine-Model_3	TimePeriod	0	0.002	-0.143	0.888	0.004128	-0.00413
Azathioprine-Model_3	Phase	0.153	0.088	1.744	0.096	0.334623	-0.02862
Azathioprine-Model_3	Interact	-0.008	0.005	-1.677	0.109	0.002319	-0.01832
Methotrexate-Model_4	TimePeriod	0.004	0.001	2.719	0.013	0.006064	0.001936
Methotrexate-Model_4	Phase	-0.019	0.059	-0.323	0.75	0.10277	-0.14077
Methotrexate-Model_4	Interact	0	0.003	-0.117	0.908	0.006192	-0.00619
Leflunomide-Model_5	TimePeriod	0.004	0.002	2.073	0.051	0.008128	-0.00013
Leflunomide-Model_5	Phase	-0.034	0.068	-0.498	0.624	0.106345	-0.17435
Leflunomide-Model_5	Interact	0	0.004	0.056	0.956	0.008256	-0.00826

ARIMA(0,1,0), Difference		Estimate	Standard Error	t	P-value	UCI	LCI
Sulfasalazine-Model_1	TimePeriod	0.004	0.005	0.721	0.48	0.014319	-0.00632
Sulfasalazine-Model_1	Phase	-0.142	0.181	-0.786	0.441	0.231566	-0.51557
Sulfasalazine-Model_1	Interact	0.004	0.01	0.417	0.681	0.024639	-0.01664
Hydroxychloroquinesulfate-Model_2	TimePeriod	0.006	0.005	1.089	0.289	0.016319	-0.00432
Hydroxychloroquinesulfate-Model_2	Phase	-0.073	0.193	-0.38	0.708	0.325332	-0.47133
Hydroxychloroquinesulfate-Model_2	Interact	-0.001	0.01	-0.084	0.934	0.019639	-0.02164
Azathioprine-Model_3	TimePeriod	0.003	0.005	0.741	0.467	0.013319	-0.00732
Azathioprine-Model_3	Phase	-0.018	0.168	-0.109	0.914	0.328735	-0.36473
Azathioprine-Model_3	Interact	-0.002	0.009	-0.196	0.847	0.016575	-0.02058
Methotrexate-Model_4	TimePeriod	0.003	0.005	0.638	0.531	0.013319	-0.00732
Methotrexate-Model_4	Phase	-0.041	0.178	-0.228	0.822	0.326374	-0.40837
Methotrexate-Model_4	Interact	-0.001	0.01	-0.06	0.953	0.019639	-0.02164
Leflunomide-Model_5	TimePeriod	0.004	0.005	0.731	0.473	0.014319	-0.00632
Leflunomide-Model_5	Phase	-0.054	0.184	-0.291	0.774	0.325757	-0.43376
Leflunomide-Model_5	Interact	0	0.01	-0.025	0.981	0.020639	-0.02064

ARIMA(0,0,1), MA, Natural Log		Estimate	Standard Error	t	P-value	UCI	LCI
Sulfasalazine-Model_1	TimePeriod	0.003	0.001	3.399	0.003	0.005064	0.000936
Sulfasalazine-Model_1	Phase	0.001	0.054	0.015	0.989	0.112451	-0.11045
Sulfasalazine-Model_1	Interact	-0.003	0.003	-1.114	0.278	0.003192	-0.00919
Hydroxychloroquinesulfate-Model_2	TimePeriod	0.001	0.001	0.987	0.336	0.003064	-0.00106
Hydroxychloroquinesulfate-Model_2	Phase	0.128	0.066	1.949	0.065	0.264217	-0.00822
Hydroxychloroquinesulfate-Model_2	Interact	-0.006	0.003	-1.952	0.065	0.000192	-0.01219
Azathioprine-Model_3	TimePeriod	-0.00002175	0.001	-0.023	0.982	0.002042	-0.00209
Azathioprine-Model_3	Phase	0.161	0.053	3.059	0.006	0.270387	0.051613
Azathioprine-Model_3	Interact	-0.009	0.003	-3.398	0.003	-0.00281	-0.01519
Methotrexate-Model_4	TimePeriod	0.004	0.001	5.374	0	0.006064	0.001936
Methotrexate-Model_4	Phase	-0.017	0.034	-0.509	0.616	0.053173	-0.08717
Methotrexate-Model_4	Interact	-0.001	0.002	-0.377	0.71	0.003128	-0.00513
Leflunomide-Model_5	TimePeriod	0.004	0.001	4.722	0	0.006064	0.001936
Leflunomide-Model_5	Phase	-0.04	0.038	-1.044	0.309	0.038428	-0.11843
Leflunomide-Model_5	Interact	0	0.002	0.058	0.954	0.004128	-0.00413

ARIMA(0,0,1), MA, No Transformation		Estimate	Standard Error	t	P-value	UCI	LCI
Sulfasalazine-Model_1	TimePeriod	26528.53	7721.626	3.436	0.003	42465.18	10591.88
Sulfasalazine-Model_1	Phase	44198.442	489757.264	0.09	0.929	1055008	-966611
Sulfasalazine-Model_1	Interact	-29893.865	24000.178	-1.246	0.227	19640.07	-79427.8
Hydroxychloroquinesulfate-Model_2	TimePeriod	5769.508	5354.787	1.077	0.294	16821.25	-5282.23
Hydroxychloroquinesulfate-Model_2	Phase	687248.921	320491.407	2.144	0.044	1348711	25787.17
Hydroxychloroquinesulfate-Model_2	Interact	-32332.165	14877.977	-2.173	0.042	-1625.53	-63038.8
Azathioprine-Model_3	TimePeriod	83.53	4192.71	0.02	0.984	8736.858	-8569.8
Azathioprine-Model_3	Phase	733233.954	243803.562	3.007	0.007	1236420	230048.1
Azathioprine-Model_3	Interact	-39498.697	11810.828	-3.344	0.003	-15122.3	-63875
Methotrexate-Model_4	TimePeriod	16630.548	2992.036	5.558	0.00002	22805.81	10455.29
Methotrexate-Model_4	Phase	-80776.956	140567.625	-0.575	0.572	209340.4	-370894
Methotrexate-Model_4	Interact	-2192.432	6725.045	-0.326	0.748	11687.38	-16072.2
Leflunomide-Model_5	TimePeriod	2041.806	432.517	4.721	0.0001	2934.477	1149.135
Leflunomide-Model_5	Phase	-21148.135	20831.545	-1.015	0.322	21846.06	-64142.3
Leflunomide-Model_5	Interact	28.158	1010.937	0.028	0.978	2114.629	-2058.31

```r
#Changepoint Analysis
#install.packages("changepoint")
library(changepoint)
#install.packages("changepoint.np")
library(changepoint.np)
#install.packages("EnvCpt")
library(EnvCpt)
library(ggplot2)
library(lubridate)
install.packages("rmarkdown")


data <- read.delim("C:\\Users\\rb1097\\OneDrive - University of Brighton\\Chp 8, 10 RA Folder\\BMJ Open\\R3\\Data.csv",sep = ",")
data$Sulfasalazine<-as.numeric(data$Sulfasalazine)
data$Hydroxychloroquine.sulfate<-as.numeric(data$Hydroxychloroquine.sulfate)
data$Azathioprine<-as.numeric(data$Azathioprine)
data$Methotrexate<-as.numeric(data$Methotrexate)
data$Leflunomide<-as.numeric(data$Leflunomide)
class(Sulfasalazine)
class(data$ï..Month) # "character"

data$ï..Month<-as.POSIXct(strptime("01/01/2019", "%d-%m-%Y"))
class(data$ï..Month) # "POSIXct" "POSIXt"

data$ï..Month
#data
#class(object)

head(data)
View(data)
length(data)
summary(data)

ts.plot(data,xlab="Time in months",ylab="Prescription Quantity")

---------------------------------------
data.amoc=cpt.mean(data$Sulfasalazine)
means=param.est(data.amoc)$mean
data$Sulfasalazine.resid=data$Sulfasalazine-rep(means,seg.len(data.amoc))
shapiro.test(data$Sulfasalazine.resid)
#Shapiro-Wilk normality test
#data:  data$Sulfasalazine.resid
#W = 0.97663, p-value = 0.8113


ks.test(data$Sulfasalazine.resid,pnorm,mean=mean(data$Sulfasalazine.resid),sd=sd(data$Sulfasalazine.resid))
#One-sample Kolmogorov-Smirnov test
#data:  data$Sulfasalazine.resid
#D = 0.10639, p-value = 0.9114
#alternative hypothesis: two-sided

### Below, we have tried varied methods: Choice of "AMOC", "PELT", "SegNeigh" or "BinSeg"

Mean_Variance <-cpt.meanvar(data$Sulfasalazine, penalty = "MBIC",pen.value = 0,method = "AMOC",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of changepoints for data

#Created Using changepoint version 2.2.3
#Changepoint type      : Change in mean and variance
#Method of analysis    : AMOC
#Test Statistic  : Normal
#Type of penalty       : MBIC with value, 9.656627 (Minimum Bayesian information criterion)
#Minimum Segment Length : 2
#Maximum no. of cpts   : 1
#Changepoint Locations : 24   (Changepoint at Dec 2020 detected using this method)

```

```
Mean_Variance <-cpt.meanvar(data$Sulfasalazine, penalty = "MBIC",pen.value = 0,method = "PELT",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of changepoints for data
#Created Using changepoint version 2.2.3
#Changepoint type      : Change in mean and variance
#Method of analysis    : PELT
#Test Statistic  : Normal
#Type of penalty       : MBIC with value, 12.8755  (Minimum Bayesian information criterion)
#Minimum Segment Length : 2
#Maximum no. of cpts   : Inf
#Changepoint Locations :  (No Changepoint detected using this method)


Mean_Variance <-cpt.meanvar(data$Sulfasalazine, penalty = "MBIC",pen.value = 0,method = "SegNeigh",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of changepoints for data
#Created Using changepoint version 2.2.3
#Changepoint type      : Change in mean and variance
#Method of analysis    : AMOC
#Test Statistic  : Normal
#Type of penalty       : MBIC with value, 9.656627
#Minimum Segment Length : 2
#Maximum no. of cpts   : 1
#Changepoint Locations : 24  (Changepoint at Dec 2020 detected using this method)

Mean_Variance <-cpt.meanvar(data$Sulfasalazine, penalty = "MBIC",pen.value = 0,method = "BinSeg",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of changepoints for data

#Created Using changepoint version 2.2.3
#Changepoint type      : Change in mean and variance
#Method of analysis    : BinSeg
#Test Statistic  : Normal
#Type of penalty       : MBIC with value, 12.8755
#Minimum Segment Length : 2
#Maximum no. of cpts   : 5
#Changepoint Locations :
#  Range of segmentations:
#   [,1] [,2] [,3] [,4] [,5]
#[1,]   16   NA   NA   NA   NA
#[2,]   16   14   NA   NA   NA    Change points relate to:  16 (April 2020), 14 (Feb 2020),22 (Oct 2020), 20 (Aug 2020), 12 (Dec 19)
#[3,]   16   14   22   NA   NA
#[4,]   16   14   22   20   NA
#[5,]   16   14   22   20   12

#For penalty values: 0.7861357 0.7861357 0.7861357 0.7861357 0.7861357
-------------------------------------
data.amoc=cpt.mean(data$Hydroxychloroquine.sulfate)
means=param.est(data.amoc)$mean
data$Hydroxychloroquine.sulfate.resid=data$Hydroxychloroquine.sulfate-rep(means, seg.len(data.amoc))
shapiro.test(data$Hydroxychloroquine.sulfate.resid)
#Shapiro-Wilk normality test
#data:  data$Hydroxychloroquine.sulfate.resid
#W = 0.98426, p-value = 0.9545


ks.test(data$Hydroxychloroquine.sulfate.resid,pnorm,mean=mean(data$Hydroxychloroquine.sulfate.resid),sd=sd(data$Hydroxychloroquine.sulfate.resid))
#One-sample Kolmogorov-Smirnov test
#data:  data$Hydroxychloroquine.sulfate.resid
#D = 0.12088, p-value = 0.8164
#alternative hypothesis: two-sided
```

```
Mean_Variance <-cpt.meanvar(data$Hydroxychloroquine.sulfate, penalty = "MBIC", pen.value = 0,method = "AMOC",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE, shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of changepoints for data
#Created Using changepoint version 2.2.3
#Changepoint type      : Change in mean and variance
#Method of analysis    : AMOC
#Test Statistic  : Normal
#Type of penalty       : MBIC with value, 9.656627
#Minimum Segment Length : 2
#Maximum no. of cpts   : 1
#Changepoint Locations : 24

Mean_Variance <-cpt.meanvar(data$Hydroxychloroquine.sulfate, penalty = "MBIC", pen.value = 0,method = "PELT",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE, shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of changepoints for data
#   Created Using changepoint version 2.2.3
#   Changepoint type      : Change in mean and variance
#   Method of analysis    : PELT
#   Test Statistic  : Normal
#   Type of penalty       : MBIC with value, 12.8755
#   Minimum Segment Length : 2
#   Maximum no. of cpts   : Inf
#   Changepoint Locations :


Mean_Variance <-cpt.meanvar(data$Hydroxychloroquine.sulfate, penalty = "MBIC", pen.value = 0,method = "SegNeigh",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of changepoints for data
#   Created Using changepoint version 2.2.3
#   Changepoint type      : Change in mean and variance
#   Method of analysis    : PELT
#   Test Statistic  : Normal
#   Type of penalty       : MBIC with value, 12.8755
#   Minimum Segment Length : 2
#   Maximum no. of cpts   : Inf
#   Changepoint Locations :


Mean_Variance <-cpt.meanvar(data$Hydroxychloroquine.sulfate, penalty = "MBIC", pen.value = 0,method = "BinSeg",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of changepoints for data

#   Created Using changepoint version 2.2.3
#   Changepoint type      : Change in mean and variance
#   Method of analysis    : BinSeg
#   Test Statistic  : Normal
#   Type of penalty       : MBIC with value, 12.8755
#   Minimum Segment Length : 2
#   Maximum no. of cpts   : 5
#   Changepoint Locations :
#   Range of segmentations:
#         [,1] [,2] [,3] [,4] [,5]
#   [1,]   14   NA   NA   NA   NA
#   [2,]   14   17   NA   NA   NA # changepoint 14 is Feb-20,changepoint  17 May-20, changepoint 12  Dec-19, changepoint 10  Oct-19, changepoint 20  Aug-20
#   [3,]   14   17   12   NA   NA
#   [4,]   14   17   12   10   NA
#   [5,]   14   17   12   10   20
#
#    For penalty values: 9.736784 9.736784 1.611916 1.611916 1.088258

```

```
------------------------------------
data.amoc=cpt.mean(data$Azathioprine)
means=param.est(data.amoc)$mean
data$Azathioprine.resid=data$Azathioprine-rep(means,seg.len(data.amoc))
shapiro.test(data$Azathioprine.resid)
#Shapiro-Wilk normality test
#data:  data$Azathioprine.resid
#W = 0.96776, p-value = 0.5889


ks.test(data$Azathioprine.resid,pnorm,mean=mean(data$Azathioprine.resid),sd=sd(data$Azathioprine.resid))
#One-sample Kolmogorov-Smirnov test
#data:  data$Azathioprine.resid
#D = 0.1164, p-value = 0.8489
#alternative hypothesis: two-sided

Mean_Variance <-cpt.meanvar(data$Azathioprine, penalty = "MBIC",pen.value = 0,method = "AMOC",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of changepoints for data
#   Created Using changepoint version 2.2.3
#   Changepoint type      : Change in mean and variance
#   Method of analysis    : AMOC
#   Test Statistic  : Normal
#   Type of penalty       : MBIC with value, 9.656627
#   Minimum Segment Length : 2
#   Maximum no. of cpts   : 1
#   Changepoint Locations : 24


Mean_Variance <-cpt.meanvar(data$Azathioprine, penalty = "MBIC",pen.value = 0,method = "PELT",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of changepoints for data
#   Created Using changepoint version 2.2.3
#   Changepoint type      : Change in mean and variance
#   Method of analysis    : PELT
#   Test Statistic  : Normal
#   Type of penalty       : MBIC with value, 12.8755
#   Minimum Segment Length : 2
#   Maximum no. of cpts   : Inf
#   Changepoint Locations :


Mean_Variance <-cpt.meanvar(data$Azathioprine, penalty = "MBIC",pen.value = 0,method = "SegNeigh",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of changepoints for data
# SegNeigh is computationally slow, use PELT instead

Mean_Variance <-cpt.meanvar(data$Azathioprine, penalty = "MBIC",pen.value = 0,method = "BinSeg",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of changepoints for data
#   Created Using changepoint version 2.2.3
#   Changepoint type      : Change in mean and variance
#   Method of analysis    : BinSeg
#   Test Statistic  : Normal
#   Type of penalty       : MBIC with value, 12.8755
#   Minimum Segment Length : 2
#   Maximum no. of cpts   : 5
#   Changepoint Locations :
#   Range of segmentations:
#         [,1] [,2] [,3] [,4] [,5]
#   [1,]   19   NA   NA   NA   NA
#   [2,]   19   16   NA   NA   NA #Changepoint 19 (July 20), Changepoint 16 (April 20), Changepoint 14 (Feb 20), Changepoint 12 (Dec 19), Changepoint 10 (Oct 19)
#   [3,]   19   16   14   NA   NA
```

```
#    [4,]   19   16   14   12   NA
#    [5,]   19   16   14   12   10
#
#     For penalty values: 2.656231 2.656231 2.656231 2.656231 2.656231

---------------------------------------
data.amoc=cpt.mean(data$Methotrexate)
means=param.est(data.amoc)$mean
data$Methotrexate.resid=data$Methotrexate-rep(means,seg.len(data.amoc))
shapiro.test(data$Methotrexate.resid)
#Shapiro-Wilk normality test
#data:  data$Methotrexate.resid
#W = 0.99406, p-value = 0.9999


ks.test(data$Methotrexate.resid,pnorm,mean=mean(data$Methotrexate.resid),sd=sd(data$
Methotrexate.resid))
#   One-sample Kolmogorov-Smirnov test
#data:  data$Methotrexate.resid
#D = 0.070042, p-value = 0.9989
#alternative hypothesis: two-sided


Mean_Variance <-cpt.meanvar(data$Methotrexate, penalty = "MBIC",pen.value = 0,method =
 "AMOC",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of
changepoints for data
#   Created Using changepoint version 2.2.3
#   Changepoint type      : Change in mean and variance
#   Method of analysis    : AMOC
#   Test Statistic  : Normal
#   Type of penalty       : MBIC with value, 9.656627
#   Minimum Segment Length : 2
#   Maximum no. of cpts   : 1
#   Changepoint Locations : 24

Mean_Variance <-cpt.meanvar(data$Methotrexate, penalty = "MBIC",pen.value = 0,method =
 "PELT",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of
changepoints for data
#   Created Using changepoint version 2.2.3
#   Changepoint type      : Change in mean and variance
#   Method of analysis    : PELT
#   Test Statistic  : Normal
#   Type of penalty       : MBIC with value, 12.8755
#   Minimum Segment Length : 2
#   Maximum no. of cpts   : Inf
#   Changepoint Locations :


Mean_Variance <-cpt.meanvar(data$Methotrexate, penalty = "MBIC",pen.value = 0,method =
 "SegNeigh",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2
)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of
changepoints for data
#SegNeigh is computationally slow, use PELT instead (returns PELT method results)


Mean_Variance <-cpt.meanvar(data$Methotrexate, penalty = "MBIC",pen.value = 0,method =
 "BinSeg",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of
changepoints for data
#   Created Using changepoint version 2.2.3
#   Changepoint type      : Change in mean and variance
#   Method of analysis    : BinSeg
#   Test Statistic  : Normal
#   Type of penalty       : MBIC with value, 12.8755
#   Minimum Segment Length : 2
#   Maximum no. of cpts   : 5
#   Changepoint Locations :
#   Range of segmentations:
```

```
#        [,1] [,2] [,3] [,4] [,5]
#   [1,]    4   NA   NA   NA   NA
#   [2,]    4   20   NA   NA   NA #Changepoint  4   is Apr-19, Changepoint  20  Oct-19, Changepoint 13  Jan-20, Changepoint 4   Apr-19, Changepoint 11  Nov-19, Changepoint 16  Apr-20
#   [3,]    4   20   13   NA   NA
#   [4,]    4   20   13   11   NA
#   [5,]    4   20   13   11   16
#
#    For penalty values: 2.821485 0.472209 0.4089625 0.4089625 0.4089625


---------------------------------------
data.amoc=cpt.mean(data$Leflunomide)
means=param.est(data.amoc)$mean
data$Leflunomide.resid=data$Leflunomide-rep(means,seg.len(data.amoc))
shapiro.test(data$Leflunomide.resid)
#Shapiro-Wilk normality test
#data:  data$Leflunomide.resid
#W = 0.79083, p-value = 0.0001605


ks.test(data$Leflunomide.resid,pnorm,mean=mean(data$Leflunomide.resid),sd=sd(data$Leflunomide.resid))
#One-sample Kolmogorov-Smirnov test
#data:  data$Leflunomide.resid
#D = 0.26919, p-value = 0.04329
#alternative hypothesis: two-sided


Mean_Variance <-cpt.meanvar(data$Leflunomide, penalty = "MBIC",pen.value = 0,method = "AMOC",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of changepoints for data
#   Created Using changepoint version 2.2.3
#   Changepoint type      : Change in mean and variance
#   Method of analysis    : AMOC
#   Test Statistic  : Normal
#   Type of penalty       : MBIC with value, 9.656627
#   Minimum Segment Length : 2
#   Maximum no. of cpts   : 1
#   Changepoint Locations : 24


Mean_Variance <-cpt.meanvar(data$Leflunomide, penalty = "MBIC",pen.value = 0,method = "PELT",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of changepoints for data
#   Created Using changepoint version 2.2.3
#   Changepoint type      : Change in mean and variance
#   Method of analysis    : PELT
#   Test Statistic  : Normal
#   Type of penalty       : MBIC with value, 12.8755
#   Minimum Segment Length : 2
#   Maximum no. of cpts   : Inf
#   Changepoint Locations :


Mean_Variance <-cpt.meanvar(data$Leflunomide, penalty = "MBIC",pen.value = 0,method = "SegNeigh",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of changepoints for data
#   SegNeigh is computationally slow, use PELT instead (returns PELT method results)

Mean_Variance <-cpt.meanvar(data$Leflunomide, penalty = "MBIC",pen.value = 0,method = "BinSeg",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2)
Mean_Variance  # Calculates the optimal positioning and (potentially) number of changepoints for data
#   Created Using changepoint version 2.2.3
#   Changepoint type      : Change in mean and variance
#   Method of analysis    : BinSeg
```

```
#   Test Statistic  : Normal
#   Type of penalty       : MBIC with value, 12.8755
#   Minimum Segment Length : 2
#   Maximum no. of cpts   : 5
#   Changepoint Locations :
#   Range of segmentations:
#        [,1] [,2] [,3] [,4] [,5]
#   [1,]    7   NA   NA   NA   NA
#   [2,]    7    5   NA   NA   NA Changepoint 7 is Jul-19, Changepoint 5 is May-19,
Changepoint 3 is Mar-19, Changepoint 20 is Aug-20, Changepoint 16 is Apr-20
#   [3,]    7    5    3   NA   NA
#   [4,]    7    5    3   20   NA
#   [5,]    7    5    3   20   16
#
#    For penalty values: 1.181572 1.181572 0.8537313 0.2305199 0.2305199
```

Supplementary Table 3 - Quantity & Cost

Supplemental Results (Total Quantity)

CHEMICAL_SUBSTANCE	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Trend
Sulfasalazine	9.54	8.61	9.33	9.15	9.68	9.07	9.26	9.88	9.12	9.65	9.23	9.32	9.79	8.64	10.26	9.45	8.94	9.08	9.43	8.51	9.18	9.07	8.89	9.75	9.38	
Hydroxychloroquine sulfate	4.89	4.37	4.69	4.57	4.93	4.51	4.67	4.88	4.52	4.79	4.56	4.69	4.66	4.29	5.37	5.11	4.70	4.78	4.91	4.41	4.78	4.84	4.66	5.02	4.68	
Azathioprine	4.69	4.24	4.54	4.45	4.74	4.38	4.45	4.72	4.43	4.65	4.46	4.52	4.45	4.11	4.81	4.90	4.52	4.52	4.54	4.09	4.42	4.44	4.27	4.62	4.30	
Methotrexate	4.19	3.81	4.12	4.05	4.32	3.98	4.11	4.39	4.05	4.31	4.13	4.26	4.27	3.90	4.54	4.26	4.08	4.21	4.40	3.98	4.29	4.33	4.18	4.55	4.17	
Leflunomide	0.56	0.50	0.54	0.53	0.57	0.53	0.54	0.59	0.53	0.57	0.55	0.56	0.56	0.51	0.60	0.57	0.53	0.53	0.56	0.52	0.56	0.57	0.55	0.59	0.55	

Table 1 Total Quantity; Monthly Subtotal (in millions)

Supplemental Results (Actual Cost)

Medicine	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Trend
Sulfasalazine	0.62	0.56	0.61	0.60	0.64	0.60	0.60	0.66	0.61	0.64	0.62	0.62	0.65	0.58	0.68	0.61	0.57	0.60	0.70	0.64	0.69	0.69	0.73	0.82	0.81	
Hydroxychloroquine sulfate	0.30	0.27	0.29	0.28	0.39	0.49	0.45	0.45	0.38	0.37	0.35	0.36	0.54	0.50	0.62	0.77	0.55	0.49	0.51	0.46	0.50	0.54	0.53	0.56	0.57	
Azathioprine	0.19	0.17	0.18	0.20	0.21	0.19	0.20	0.23	0.21	0.22	0.21	0.22	0.32	0.20	0.56	0.59	0.47	0.43	0.27	0.24	0.26	0.24	0.23	0.24	0.25	
Methotrexate	3.27	3.12	3.45	3.43	3.73	3.52	3.75	4.01	3.85	4.15	4.02	4.21	4.29	3.96	4.70	4.47	4.26	4.04	4.67	4.33	4.65	4.68	4.56	4.94	4.63	
Leflunomide	0.12	0.10	0.11	0.11	0.12	0.11	0.11	0.13	0.12	0.12	0.12	0.12	0.12	0.11	0.12	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.09	0.10	0.09	

Table 2 Actual Cost; Monthly Subtotal (in £millions)

Supplementary Table 4 - Region

Total Quantity by region	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Trend
North West + North East and Yorkshire,	6.88	6.22	6.68	6.57	6.99	6.47	6.63	7.08	6.47	6.92	6.59	6.68	6.84	6.13	7.26	6.93	6.53	6.64	6.86	6.2	6.68	6.66	6.43	7.01	6.54	
Midlands + East of England,	7.77	7.	7.57	7.44	7.87	7.34	7.49	7.99	7.39	7.78	7.45	7.64	7.74	7.01	8.27	7.92	7.47	7.54	7.82	7.04	7.6	7.56	7.36	8.03	7.57	
South East + South West	6.65	6.	6.5	6.33	6.79	6.27	6.32	6.9	6.36	6.71	6.44	6.53	6.61	6.	7.17	6.84	6.35	6.42	6.61	5.98	6.46	6.49	6.35	6.88	6.5	
London	2.57	2.3	2.47	2.41	2.59	2.39	2.58	2.49	2.44	2.55	2.46	2.5	2.54	2.31	2.89	2.61	2.42	2.5	2.55	2.31	2.49	2.54	2.4	2.6	2.47	
UNIDENTIFIED	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.01	0.	
Monthly Subtotal	23.87	21.52	23.22	22.75	24.25	22.48	23.02	24.46	22.66	23.96	22.94	23.35	23.73	21.45	25.59	24.3	22.77	23.1	23.84	21.52	23.23	23.25	22.54	24.52	23.08	

Table 3 Total Quantity in millions by region

Actual Cost by region	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Trend	t-test (North vs. Total)
North West + North East and Yorkshire,	1.11	1.03	1.12	1.12	1.23	1.2	1.24	1.33	1.25	1.32	1.25	1.3	1.4	1.25	1.57	1.53	1.39	1.42	0.82	0.74	0.79	0.79	0.77	0.84	0.8	P-value	9.99E-35
Midlands + East of England,	1.49	1.41	1.56	1.55	1.7	1.64	1.73	1.84	1.76	1.9	1.83	1.92	2.06	1.88	2.3	2.29	2.09	2.15	2.19	2.01	2.17	2.17	2.16	2.31	2.23		
South East + South West	1.68	1.59	1.75	1.73	1.91	1.81	1.86	2.04	1.91	2.03	1.98	2.05	2.15	1.95	2.44	2.34	2.15	2.24	2.28	2.13	2.26	2.32	2.26	2.48	2.33		
London	0.22	0.2	0.22	0.22	0.25	0.26	0.27	0.26	0.25	0.27	0.25	0.26	0.31	0.27	0.38	0.38	0.31	0.32	0.31	0.29	0.31	0.32	0.31	0.33	0.33		
UNIDENTIFIED	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.		
Monthly Subtotal	4.51	4.23	4.64	4.62	5.09	4.91	5.11	5.47	5.17	5.51	5.32	5.53	5.91	5.35	6.69	6.54	5.95	6.13	5.6	5.17	5.54	5.59	5.5	5.96	5.68		

Table 4 Actual Cost in £millions by region

Supplementary Table 5 - Methotrexate Quantity (in millions)

BNF DESCRIPTION	BNF_CODE	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21
Methotrexate 5mg/2ml solution for injection vials	1001030U0AAABAB	3.928	3.556	3.842	3.776	4.03	3.709	3.821	4.087	3.757	4.	3.828	3.948	3.949	3.608	4.195	3.934	3.763	3.89	4.059	3.67	3.958	3.993	3.851	4.191	3.84
Methotrexate 50mg/2ml solution for injection vials	1001030U0BEARBW	0.055	0.053	0.059	0.058	0.064	0.06	0.065	0.069	0.067	0.072	0.07	0.074	0.075	0.07	0.083	0.079	0.076	0.078	0.082	0.077	0.082	0.084	0.081	0.088	0.082
Methotrexate 1g/10ml solution for injection vials	1001030U0BEARBW	0.055	0.053	0.059	0.058	0.064	0.06	0.065	0.069	0.067	0.072	0.07	0.074	0.075	0.07	0.083	0.079	0.076	0.078	0.082	0.077	0.082	0.084	0.081	0.088	0.082
Methotrexate 20mg/0.8ml inj pre-filled syringes	1001030U0BEAWCB	0.037	0.036	0.041	0.04	0.044	0.042	0.045	0.048	0.048	0.051	0.05	0.054	0.053	0.049	0.06	0.056	0.054	0.056	0.06	0.055	0.06	0.06	0.059	0.064	0.06
Methotrexate 22.5mg/0.9ml inj pre-filled syringes	1001030U0BEAWCB	0.037	0.036	0.041	0.04	0.044	0.042	0.045	0.048	0.048	0.051	0.05	0.054	0.053	0.049	0.06	0.056	0.054	0.056	0.06	0.055	0.06	0.06	0.059	0.064	0.06
Methotrexate 25mg/1ml inj pre-filled syringes	1001030U0BEAXCC	0.036	0.035	0.04	0.04	0.043	0.04	0.044	0.046	0.044	0.049	0.045	0.048	0.048	0.046	0.054	0.052	0.049	0.052	0.054	0.051	0.054	0.056	0.053	0.058	0.055
Methotrexate 10mg/0.4ml inj pre-filled syringes	1001030U0BEAXCC	0.036	0.035	0.04	0.04	0.043	0.04	0.044	0.046	0.044	0.049	0.045	0.048	0.048	0.046	0.054	0.052	0.049	0.052	0.054	0.051	0.054	0.056	0.053	0.058	0.055
Methotrexate 7.5mg/0.3ml inj pre-filled syringes	1001030U0BEAZCE	0.016	0.017	0.018	0.017	0.02	0.019	0.02	0.021	0.021	0.022	0.022	0.022	0.023	0.021	0.025	0.023	0.023	0.023	0.024	0.022	0.024	0.024	0.023	0.025	0.024
Methotrexate 12.5mg/0.5ml inj pre-filled syringes	1001030U0BEAZCE	0.016	0.017	0.018	0.017	0.02	0.019	0.02	0.021	0.021	0.022	0.022	0.022	0.023	0.021	0.025	0.023	0.023	0.023	0.024	0.022	0.024	0.024	0.023	0.025	0.024
Methotrexate 15mg/0.6ml inj pre-filled syringes	1001030U0AAACAC	0.035	0.031	0.032	0.03	0.032	0.029	0.029	0.029	0.027	0.028	0.026	0.026	0.025	0.022	0.025	0.023	0.021	0.022	0.021	0.019	0.019	0.019	0.017	0.02	0.016
Methotrexate 17.5mg/0.7ml inj pre-filled syringes	1001030U0BEAQBV	0.01	0.009	0.01	0.011	0.011	0.011	0.011	0.013	0.012	0.012	0.013	0.013	0.013	0.012	0.015	0.014	0.013	0.014	0.014	0.013	0.015	0.015	0.014	0.016	0.015
Methotrexate 7.5mg/0.3ml inj pre-filled disposable	1001030U0BEAQBV	0.01	0.009	0.01	0.011	0.011	0.011	0.011	0.013	0.012	0.012	0.013	0.013	0.013	0.012	0.015	0.014	0.013	0.014	0.014	0.013	0.015	0.015	0.014	0.016	0.015
Methotrexate 10mg/0.4ml inj pre-filled disposable	1001030U0BEAYCD	0.008	0.009	0.009	0.009	0.01	0.009	0.01	0.01	0.01	0.011	0.011	0.011	0.011	0.011	0.013	0.012	0.011	0.012	0.013	0.012	0.013	0.013	0.013	0.014	0.013
Methotrexate 12.5mg/0.5ml inj pre-filled disposabl	1001030U0BEAYCD	0.008	0.009	0.009	0.009	0.01	0.009	0.01	0.01	0.01	0.011	0.011	0.011	0.011	0.011	0.013	0.012	0.011	0.012	0.013	0.012	0.013	0.013	0.013	0.014	0.013
Methotrexate 15mg/0.6ml inj pre-filled disposable	1001030U0BDAAAB	0.013	0.011	0.012	0.012	0.013	0.011	0.012	0.013	0.012	0.012	0.011	0.012	0.011	0.011	0.013	0.011	0.011	0.011	0.012	0.01	0.01	0.011	0.01	0.011	0.01
Methotrexate 17.5mg/0.7ml inj pre-filled disposabl	1001030U0BEASBX	0.005	0.005	0.006	0.006	0.007	0.006	0.006	0.007	0.006	0.007	0.007	0.007	0.008	0.007	0.009	0.009	0.008	0.008	0.009	0.008	0.009	0.009	0.009	0.009	0.009
Methotrexate 20mg/0.8ml inj pre-filled disposable	1001030U0BEASBX	0.005	0.005	0.006	0.006	0.007	0.006	0.006	0.007	0.006	0.007	0.007	0.007	0.008	0.007	0.009	0.009	0.008	0.008	0.009	0.008	0.009	0.009	0.009	0.009	0.009
Methotrexate 22.5mg/0.9ml inj pre-filled disposabl	1001030U0BEATBY	0.006	0.005	0.006	0.006	0.007	0.006	0.007	0.007	0.007	0.008	0.007	0.008	0.007	0.007	0.008	0.008	0.007	0.008	0.008	0.008	0.008	0.008	0.008	0.009	0.008
Methotrexate 25mg/1ml inj pre-filled disposable de	1001030U0BEATBY	0.006	0.005	0.006	0.006	0.007	0.006	0.007	0.007	0.007	0.008	0.007	0.008	0.007	0.007	0.008	0.008	0.007	0.008	0.008	0.008	0.008	0.008	0.008	0.009	0.008
Zlatal 20mg/0.8ml solution for injection pre-fille	1001030U0AABWBW	0.01	0.009	0.009	0.009	0.01	0.009	0.009	0.009	0.008	0.009	0.008	0.008	0.008	0.007	0.008	0.008	0.007	0.007	0.007	0.006	0.007	0.006	0.006	0.006	0.006
Zlatal 22.5mg/0.9ml inj pre-filled syringes	1001030U0AACCCC	0.006	0.006	0.006	0.006	0.006	0.006	0.006	0.006	0.005	0.006	0.005	0.006	0.005	0.005	0.006	0.005	0.005	0.005	0.005	0.004	0.005	0.004	0.004	0.004	0.004
Zlatal 25mg/1ml solution for injection pre-filled	1001030U0AACBCB	0.006	0.005	0.006	0.006	0.006	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.004	0.005	0.005	0.005	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.004
Zlatal 10mg/0.4ml solution for injection pre-fille	1001030U0AACFCF	0.003	0.003	0.003	0.002	0.002	0.002	0.002	0.002	0.003	0.002	0.003	0.002	0.003	0.003	0.003	0.002	0.003	0.003	0.003	0.002	0.002	0.003	0.003	0.003	0.003
Zlatal 7.5mg/0.3ml inj pre-filled syringes	0801030P0BFAFFS	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.002	0.001	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
Zlatal 12.5mg/0.5ml inj pre-filled syringes	0801030P0BFADFQ	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
Zlatal 15mg/0.6ml solution for injection pre-fille	1001030U0AACECE	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.002	0.003	0.003	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
Zlatal 17.5mg/0.7ml inj pre-filled syringes	0801030P0BFAHFU	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 7.5mg/0.3ml solution for injection pre-fi	1001030U0AABVBV	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.001	0.002	0.001	0.002	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 10mg/0.4ml solution for injection pre-fil	1001030U0AABHBH	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 12.5mg/0.5ml solution for injection pre-f	1001030U0AACDCD	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 15mg/0.6ml solution for injection pre-fil	1001030U0AABXBX	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 17.5mg/0.7ml solution for injection pre-f	1001030U0AABYBY	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 20mg/0.8ml solution for injection pre-fil	1001030U0AABGBG	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.001	0.	0.001	0.001	0.001	0.001	0.001
Nordimet 22.5mg/0.9ml solution for injection pre-f	0801030P0BFABFN	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.001	0.001	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Nordimet 25mg/1ml solution for injection pre-fille	0801030P0AAFSFS	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Methotrexate 2.5mg tablets	1001030U0AAAEAE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.001	0.	0.	0.	0.	0.001	0.	0.	0.001	0.	0.	0.	0.	0.	0.	0.001
Methotrexate 10mg tablets	1001030U0BGAFBW	0.	0.	0.	0.	0.	0.	0.001	0.	0.	0.001	0.001	0.001	0.	0.	0.001	0.	0.	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Methotrexate 2.5mg/5ml oral liquid	1001030U0BEAVCA	0.	0.	0.	0.	0.	0.	0.	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.
Methotrexate 5mg/5ml oral liquid	1001030U0BEAVCA	0.	0.	0.	0.	0.	0.	0.	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.
Methotrexate 10mg/5ml oral liquid	0801030P0AAFUFU	0.	0.	0.	0.001	0.001	0.001	0.	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.
Methotrexate 7.5mg/5ml oral liquid	0801030P0AAFQFQ	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.	0.001	0.	0.	0.001	0.	0.	0.	0.
Methotrexate 12.5mg/5ml oral liquid	1001030U0AABIBI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 15mg/5ml oral liquid	1001030U0AABFBF	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 20mg/2ml inj pre-filled syringes	0801030P0BFAEFR	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 15mg/1.5ml inj pre-filled syringes	1001030U0BGADCC	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 7.5mg/0.15ml inj pre-filled syringes	1001030U0BGAHCB	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 10mg/0.2ml inj pre-filled syringes	0801030P0AAFEFE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 15mg/0.3ml inj pre-filled syringes	0801030P0BFACFP	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 20mg/0.4ml inj pre-filled syringes	1001030U0AABKBK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 25mg/0.5ml inj pre-filled syringes	0801030P0AAFGFG	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 30mg/0.6ml inj pre-filled syringes	0801030P0AAFNFN	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 12.5mg/0.25ml inj pre-filled syringes	0801030P0BFAAFM	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 17.5mg/0.35ml inj pre-filled syringes	0801030P0AAFKFK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 22.5mg/0.45ml inj pre-filled syringes	1001030U0AABLBL	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 17.5mg/0.35ml inj pre-filled disposab	1001030U0BDABAC	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 20mg/0.4ml inj pre-filled disposable	0801030P0BFAGFT	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 22.5mg/0.45ml inj pre-filled disposab	1001030U0BGABCE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 7.5mg/0.15ml inj pre-filled disposabl	0801030P0AAFRFR	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 27.5mg/0.55ml inj pre-filled disposab	0801030P0BEAAFE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 30mg/0.6ml inj pre-filled disposable	0801030P0AAFPFP	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 25mg/0.5ml inj pre-filled disposable	1001030U0AABEBE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 15mg/0.3ml inj pre-filled disposable	0801030P0BEAGFK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 12.5mg/0.25ml inj pre-filled disposab	1001030U0BEAUBZ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 10mg/0.2ml inj pre-filled disposable	1001030U0BEAUBZ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methotrexate 2mg/ml oral solution sugar free	0801030P0AAFHFH	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Maxtrex 2.5mg tablets	1001030U0BGAEBV	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Maxtrex 10mg tablets	1001030U0AABMBM	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 20mg/2ml solution for injection pre-fille	0801030P0AAFMFM	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 10mg/1ml solution for injection pre-fille	1001030U0BGACCD	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 15mg/1.5ml inj pre-filled syringes	0801030P0BEACFG	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 25mg/2.5ml inj pre-filled syringes	0801030P0AAFTFT	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 7.5mg/0.15ml inj pre-filled syringes	1001030U0AAAHAH	0.	0.	0.	0.	0.001	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 10mg/0.2ml inj pre-filled syringes	1001030U0BGAPBH	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 15mg/0.3ml inj pre-filled syringes	0801030P0AAFLFL	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 20mg/0.4ml inj pre-filled syringes	1001030U0BGAGBX	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 25mg/0.5ml inj pre-filled syringes	0801030P0AAFFFF	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 12.5mg/0.25ml inj pre-filled syringes	1001030U0BGAABY	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 17.5mg/0.35ml inj pre-filled syringes	0801030P0AAFIFI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject 22.5mg/0.45ml inj pre-filled syringes	1001030U0BGARBI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 17.5mg/0.35ml inj pre-filled pens	1001030U0BGAMBG	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 17.5mg/0.35ml inj pre-filled pen	0801030P0AAFJFJ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 20mg/0.4ml inj pre-filled pens	1001030U0AACACA	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 20mg/0.4ml inj pre-filled pen	0801030P0BEADFH	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 22.5mg/0.45ml inj pre-filled pens	0801030P0BEAEFI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 22.5mg/0.45ml inj pre-filled pen	1001030U0AABZBZ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 7.5mg/0.15ml inj pre-filled pen	0801030P0BEAHFL	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 7.5mg/0.15ml inj pre-filled pens	1001030U0BEACBB	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 27.5mg/0.55ml inj pre-filled pens	1001030U0BGAQBM	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 27.5mg/0.55ml inj pre-filled pen	1001030U0BGAUBK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 30mg/0.6ml inj pre-filled pens	0801030P0BEABFF	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 30mg/0.6ml inj pre-filled pen	1001030U0BEAMBL	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 25mg/0.5ml inj pre-filled pens	0801030P0BEAFFJ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 25mg/0.5ml inj pre-filled pen	1001030U0BEAIBH	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 15mg/0.3ml inj pre-filled pen	1001030U0BEAGBF	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 15mg/0.3ml inj pre-filled pens	1001030U0BEAHBG	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 12.5mg/0.25ml inj pre-filled pens	1001030U0BEAJBI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 12.5mg/0.25ml inj pre-filled pen	1001030U0BEALBK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 10mg/0.2ml inj pre-filled pens	1001030U0BGAKBE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Metoject PEN 10mg/0.2ml inj pre-filled pen	1001030U0BGANBL	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 7.5mg/0.15ml inj pre-filled injector	1001030U0BEADBC	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill10mg/0.2ml inj pre-filled injector	0801030P0AAAIAI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 12.5mg/0.25ml inj pre-filled injector	0801030P0AAANAN	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 15mg/0.3ml inj pre-filled injector	0801030P0AACKCK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 17.5mg/0.35ml inj pre-filled injector	1001030U0AAAFAF	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 20mg/0.4ml inj pre-filled injector	1001030U0AAAIAI	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 22.5mg/0.45ml inj pre-filled injector	1001030U0AAAKAK	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 25mg/0.5ml inj pre-filled injector	1001030U0AAARAR	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 27.5mg/0.55ml inj pre-filled injector	1001030U0AABABA	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 7.5mg/0.15ml inj pre-filled syringes	1001030U0AABCBC	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 10mg/0.2ml inj pre-filled syringes	1001030U0AABJBJ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 15mg/0.3ml inj pre-filled syringes	1001030U0BEABBA	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 17.5mg/0.35ml inj pre-filled syringes	1001030U0BEAEBD	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 20mg/0.4ml inj pre-filled syringes	1001030U0BEAFBE	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 22.5mg/0.45ml inj pre-filled syringes	1001030U0BEANBM	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 25mg/0.5ml inj pre-filled syringes	1001030U0BGAIBZ	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
Methofill 12.5mg/0.25ml inj pre-filled syringes	1001030U0BGALBF	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
	Sum Total (Methotrexate)	4.368	3.977	4.306	4.232	4.529	4.177	4.321	4.615	4.267	4.546	4.357	4.502	4.508	4.125	4.81	4.516	4.318	4.47	4.661	4.229	4.557	4.6	4.438	4.829	4.439
	Sum of top ten rows (10010	4.253	3.868	4.187	4.116	4.402	4.061	4.197	4.484	4.143	4.415	4.228	4.37	4.374	4.001	4.662	4.378	4.187	4.332	4.52	4.098	4.416	4.459	4.299	4.68	4.299
	% Sum of top ten rows	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title and abstract PG 2 Title and abstract PG 2 N/A
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			In Introduction section
Objectives	3	State specific objectives, including any prespecified hypotheses			End of Introduction section (pg 5)
Methods					

Study Design	4	Present key elements of study design early in the paper			Materials and methods section
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Materials and methods section
Participants	6	*(a) Cohort study*- Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*- Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*- Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study*- For matched studies, give matching criteria and number of exposed and unexposed		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Materials and methods section

		Case-control study- For matched studies, give matching criteria and the number of controls per case			
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Materials and methods section, See Supplementary (Quantity & Cost), Supplementary (Region), Supplementary (Methotrexate Quantity)
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			Materials and methods section. Original data are available from https://www.nhsbsa.nhs.uk/prescription-data/prescribing-data/english-prescribing-data-epd
Bias	9	Describe any efforts to address potential sources of bias			N/A

Study size	10	Explain how the study size was arrived at			Materials and methods section
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Materials and methods section
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study*- If applicable, explain how loss to follow-up was addressed *Case-control study*- If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*- If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			Materials and methods section
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Materials and methods section

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Materials and methods section
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	None, N/A. Data Source.
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	N/A

Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study*- summarise follow-up time (*e.g.*, average and total amount)			Results, Table 1
Outcome data	15	*Cohort study*- Report numbers of outcome events or summary measures over time *Case-control study*- Report numbers in each exposure			Results, Table 1
		category, or summary measures of exposure *Cross-sectional study*- Report numbers of outcome events or summary measures			

Main results	16	(a) Give unadjusted estimates and, if applicable, confounder- adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (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			Results section. Supplementary - Quantity & Cost Supplementary - Region Supplementary - Methotrexate Quantity
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			Results section. Supplementary - ARIMA Syntax Supplementary - Sensitivity analysis
Discussion					
Key results	18	Summarise key results with reference to study objectives			Discussion section

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion section
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			Discussion section
Generalisability	21	Discuss the generalisability (external validity) of the study results			Discussion section
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			Acknowledgment section

Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Supplementary ARIMA Syntax Supplementary Sensitivity analysis

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.